Hard wired pathways

The relation between immunological and molecular research at the Netherlands Cancer Institute

P.L. Lindenbergh

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Contents

Introduction

When I heard that the authoritative journal *Science* proclaimed cancer immunotherapy as the "Breakthrough of the Year 2013", I was stunned twice.[1] To start with, I was completely unfamiliar with the concept of immunotherapy for cancer, despite my bachelor training in the biomedical sciences at the University Medical Center Utrecht. During my studies I learned to conceive of tumour formation as the consequence of deregulated molecular processes inside cancer cells. To me, the legitimate way to study cancer was to further unravel this molecular signalling. I simply never thought of cancer as an immunological problem. However, after browsing the internet, I realised that all over the world, Utrecht included, also immunologists study cancer. This realisation provoked the second wave of surprise. How was it possible that I never learned about this branch of cancer research during my four years of bachelor training? Why was the molecular perspective dominating the university's curriculum?

Put into a larger perspective, these questions concern the relations among the various sub-disciplines of the biomedical sciences. As the plurality of its name indicates, the field of biomedical sciences harbours a variety of such sub-disciplines. In practice, the branches of the biomedical sciences are classified in two ways: on the one hand, along the axis of different clinical domains (e.g. oncology, cardiology and neurology) and, on the other hand, along the axis of the various approaches (e.g. epidemiology, immunology and molecular biology). The first classification describes the kind of clinical problems biomedical scientists aim to understand and solve, while the second classification indicates the kind of theories, methods and therapeutic interventions the scientists employ to approach these problems. Biomedical scientists often appeal to both kinds of classifications when typifying their work, resulting in combinations such as cardiac biochemistry, neuro-epidemiology, immuno-oncology or molecular oncology (see **table 1**).[2] Importantly, in most clinical domains more than one approach is employed and vice versa. For example, not every cancer researcher is a molecular biologist and not all molecular biologists study cancer. Working within the borders of the same domains, scientists can be each other's companions as well as competitors.

In this complex web of partly overlapping research interests, it is hard to pinpoint who defines the disciplinary borders and who is allowed to cross these borders. Besides the scientists themselves, local and national policy makers, funding agents, popular media and (pharmaceutical) companies may influence the disciplinary landscape. As extensively described by science sociologist Thomas Gieryn, the social processes in which these borders are constructed, result in a demarcation between in- and outsiders.[3] Despite of the apparent lack of central control, in this so-called "boundary work" the stakes are high. The marginalisation or even exclusion of a sub-discipline from a certain (clinical) domain, will be reflected in a poor ability to obtain staff positions, laboratory space and sustainable collaborations.[4] More importantly, as we will see in this thesis, the contours of the biomedical landscape determine to a large extent which therapies become available to the patient suffering from the studied pathological process.

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[1] J. Couzin-Frankel, "Cancer Immunotherapy," *Science* 342 (2013), 1432-1433.

[2] Author unknown, "Tumor Immunology," Radboud Universitair Medisch Centrum, url: https://www.radboudumc.nl/Research/Organisationofresearch/Departments/TumorImmunology/Pages/default.aspx, last update: unknown, consulted at: 17-05-2016.
Author unknown, "Cardiac Biochemistry Research," Duke University School of Medicine, url: https://medicine.duke.edu/divisions/cardiology/research/basic-research/cardiac-biochemistry/cardiac-biochemistry-research, last update: unknown, consulted at: 22-05-2016.

[3] Thomas Gieryn, "Contesting Credibility Cartographically", in *Cultural Boundaries of Science: Credibility on the line*, Chigago: The University of Chigago Press (1999), 1-36.

[4] Gieryn, "Contesting Credibility," 21-36.

	Axis of clinical domains				
Axis of approaches		**Oncology**	**Cardiology**	**Neurology**	**…**
	Molecular biology	Molecular oncology	Molecular cardiology	Molecular neurology	
	Immunology	Immuno-oncology	Cardiac immunology	Neuro-immunology	
	Epidemiology	Oncological epidemiology	Cardiac epidemiology	Neuro-epidemiology	
	…				…

Table 1. Scheme of clinical domains and biomedical approaches. The table shows an (incomplete) axis of clinical domains and an (incomplete) axis of approaches. Researchers often appeal to both axes when characterising their research.

Because of the high impact on the work of scientists, their collaborative networks and the availability of therapies to the patient, this thesis aims to provide more insight into the complex web of relations among biomedical sub-disciplines. However, to do justice to the decisive role of local circumstances and actors, such an aim demands for small-scale perspective.[5] Therefore the scope of this study is limited in three ways: thematically, spatially and temporally.

Thematically, this thesis will be limited to the relation between molecular and immunological cancer research. Although international or national data are hard to find, cancer research seems to be among the biggest branches of the biomedical sciences. For example, the main Dutch funding agent for cancer research, KWF Kankerbestrijding, is the largest of its kind. In 2014 it could award more funding than the next four largest health-related foundations together. Consistently, cancer research is performed at virtually all biomedical institutes in the Netherlands and beyond.[6]

[5] Gieryn, "Contesting Credibility," 28-30.

[6] Author unknown, "Deelnemers onderzoek 2014," in *Feiten & Cijfers Goede Doelen 2014*, Amsterdam: VFI Brancheorganisatie van goede doelen (2014), 26.
Author unknown, "Inkomsten en uitgaven," KWF Kankerbestrijding, url: https://www.kwf.nl/over-kwf/inkomsten-uitgaven, last update: unknown, consulted at: 07-02-2016.
Author unknown, "2014 in het kort," in *Het jaar 2014*, The Hague: Hartstichting (2015), 7-8.
Author unknown, "STOP AIDS NOW! in 2014 en de toekomst," STOP AIDS NOW!, url: http://jaarverslag.stopaidsnow.nl/, last update: unknown, consulted at: 07-02-2016.
Author unknown, "Financial Statements 2014," in *Overview 2014*, The Hague: KNCV Tuberculosis Foundation (year unknown), 42-45.
Author unknown, "Inkomsten en uitgaven 2014," Nierstichting, url: https://www.nierstichting.nl/jaarverslag/, last update: unknown, consulted at: 07-02-2016.

However, cancer research is not only put centre stage in this study because of its omnipresence. A closer analysis of specifically the relation between molecular and immunological cancer research has two important advantages. Firstly, due to the recent breakthroughs in immunological cancer research, the disciplinary boundaries within this clinical domain are changing rapidly.[7] Because of these current dynamics, it is possible to study the new oncological landscape *in the making*.

Secondly, this thematic focus sheds a new light on the so-called *molecularisation* of cancer research and the biomedical sciences in general. Over the past years, multiple accounts of this development were published by historians, sociologists, philosophers and biomedical scientists. Commonly these accounts depict the molecularisation of the field as a revolutionary and yet a rather smooth transition fuelled by newly developed techniques and insights. Much emphasis has been laid on the possibilities of these novel techniques and how they circulated through networks of researchers.[8] However, not so much attention is paid to the boundary work involved in the establishment of the molecular biology and the implications of this for the existing approaches in (cancer) research. To traverse this gap in the present historiography, this study does not depict molecular biology as merely a new set of techniques and ideas which was peacefully integrated into the existing approaches. Rather, this study perceives molecular biology as a new approach which had to conquer territories, not least within the oncological domain. Furthermore, this study aims to understand what this development meant for other players in the field, predominantly the immunologists.

Spatially, this study is limited to the molecular and immunological cancer research conducted at the Netherlands Cancer Institute in Amsterdam. There are four considerations that guided this spatial limitation, presented here in order of increasing importance. Firstly, the Netherlands Cancer Institute is an internationally renowned institute and thus can be expected to epitomise the state of the art in cancer research.[9] Secondly, since its establishment in 1913 the institute has been connected to the Antoni van Leeuwenhoek Hospital and therefore allows for an analysis of the interaction between the various researchers and clinicians.[10] Being the main authority in patient care, clinicians form an inevitable link between the bench and bedside and hence they can be important allies for biomedical scientists. Thirdly, having one immunological division and multiple molecular divisions, the institute

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Author unknown, "Projectendatabase," KWF Kankerbestrijding, url: http://proj.kwf.nl/, last update: unknown, consulted at: 07-02-2016.

[7] Couzin-Frankel, "Cancer Immunotherapy," 1432-1433.

[8] Olivera J. Finn, "Human Tumor Immunology at the Molecular Divide," *The Journal of Immunology* 178 (2007), 2615-2616.
Patricia J. Gearhart, "The Birth of Molecular Immunology," *The Journal of Immunology* 173 (2004), 4259-4259.
James Le Fanu, "The Brave New World of the New Genetics," in *The Rise And Fall Of Modern Medicine*, revised edition, New York: Basic Books (2012), 311-350.
I. Löwy, "Heredity," in *Preventive Strikes: Women, Precancer, and Prophylactic Surgery*, Baltimore: The John Hopkins University Press (2010), 166-197. sp. 173-175.
S. Mukherjee, *The Emperor of All Maladies*, London: Fourth Estate (2011).
Hans-Jörg Rheinberger, "Recent science and its exploration: the case of molecular biology," *Studies in History and Philosophy of Biological Sciences* 40 (2009), 6-12.
Steve Sturby, "Reflections: Molecularization, Standardization and the History of Science," in *Molecularizing Biology and Medicine: New Practices and Alliances 1910s-1970s*, ed. Soraya de Chadarevian and Harmke Kammingma, Amsterdam: Harwood Academic Publishers (1998), 273-292.

[9] Author unknown, "Institutions," EU Life, url: http://eu-life.eu/institutions, last update: unknown, consulted at: 22-05-2015. Note: It is hard underpin this statement with a reference as the reputation is of a research institute is typically discussed orally. One important indication is that the institute is part of the EU Life network.

[10] Author unknown, *Eerste Jaarverslag: 1914*, Amsterdam: Vereeniging Het Nederlands Kanker Instituut (1914).

harbours both approaches of interest.[11] Fourthly, many of the institute's employees were willing to cooperate with this study. Without the information they shared with me and the access they provided me to their laboratories and archives, this study would have been impossible.

Temporally, this study covers the period from 1980 to 2015. Although the Division of Immunology was established in 1961, it would take almost two decades before molecular biology started taking its shape at the institute. In the slipstream of the leading biomedical research centres in the United States, the first molecular research lines at the Netherlands Cancer Institute were started in the late '70s.[12] In the early '80s the first molecular division was established, which demarcated the institutionalisation of this new approach. As will be discussed elaborately, in the period between 1980 and 2015, the molecular approach would expand considerably.

To gain insight into this process of molecularisation and how it has been interfering with the work of the immunologists, I took a combined anthropological and historical approach. Part I of this thesis reports on two field studies I performed at the institute's Division of Immunology and the Division of Molecular Carcinogenesis in 2014. Based on participant observation, a survey study and semi-structured interviews (see **figure 1**), the divisions were compared in their research aims, theories, methodology and social status. As we will see, this comparison highlights a considerable overlap between the two approaches. However, also multiple dissimilarities can be identified and hence it seems reasonable to perceive immunological and molecular cancer research as two different approaches.

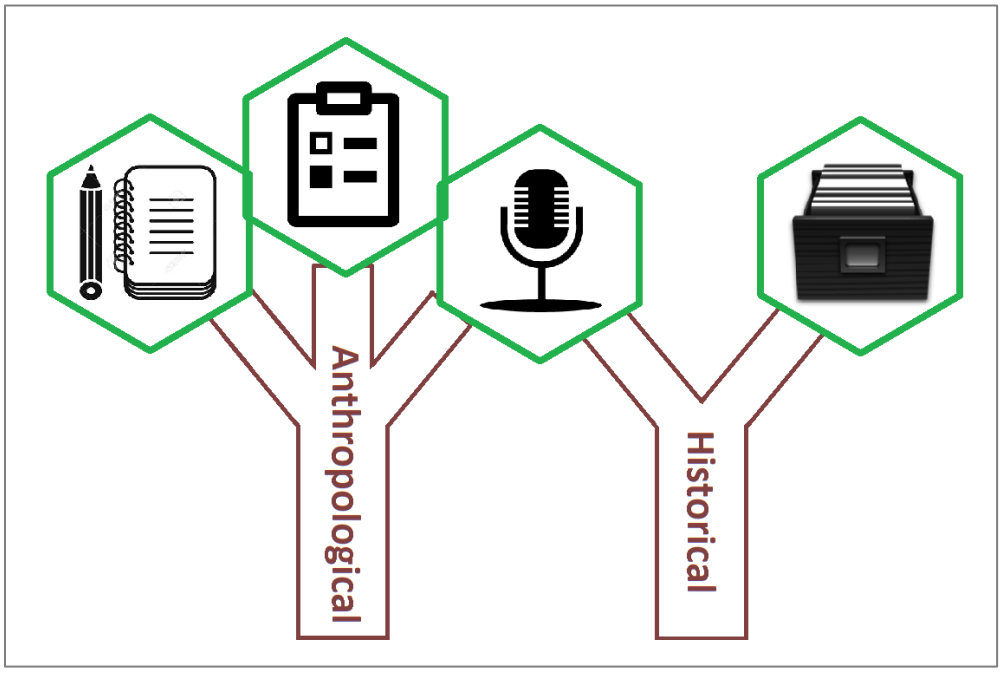

Figure 1. The methodological trunks of this study. The anthropological data discussed in Part I were obtained by participant observation, a survey study and semi-structured interviews. The historical analysis described in Part II is based on oral histories obtained in the semi-structured interviews and archival sources.

[11] Author unknown, "Divisions," The Netherlands Cancer Institute, url: http://www.nki.nl/divisions/, last update: unknown, consulted at 07-02-2016.
[12] R. Michalides, H. Daams, L. van Deemter, R. Nusse, A. Riethorst E. Wagenaar, "Molecular biology of the mouse mammary tumor virus," in *Annual Report 1978*, Amsterdam: The Netherlands Cancer Institute (year unknown), 70-71.

In Part II, these similarities and differences are put into historical perspective. Departing from several oral histories obtained in the semi-structured interviews, additional historical research was performed based on archival sources (see figure 1). In this part we will see how the establishment of the molecular approach was mediated by the formation of new collaborative networks, which united multiple, but not all, branches of the institute's research. Gradually growing into the new standard, the molecular approach served as a vehicle for inclusion and exclusion. Ultimately, Part II will show how the immunologists' historical relation to these networks explains the similarities and differences described in Part I.

Part I

Tumour immunology at the Netherlands Cancer Institute: Self or non-self?

1. Introduction and methodology of Part I

An important assumption made in this study is that it is plausible to speak of immunological and molecular cancer research as two different approaches to the same clinical domain: oncology. Especially the tumour immunologists seem to have their own departments at research institutes and universities.[13] Furthermore they often communicate their findings at distinct congresses and in specific journals and textbook chapters.[14] But is this organisational stratification enough to think of the immunological approach as different from the molecular one?

To address this, I performed an anthropological field study at the Netherlands Cancer Institute. The main goal of this field study was to investigate how immunological and molecular cancer research may

[13] Author unknown, "Welcom to tumorimmunology," UMC Utrecht, url: http://www.tumor-immunology-utrecht.nl, last update: unknown, consulted at: 17-05-2016.
Author unknown, "Department of Immunology," MD Anderson Cancer Center, url: https://www.mdanderson.org/education-and-research/departments-programs-and-labs/departments-and-divisions/immunology/index.html, last update: unknown, consulted at: 17-05-2016.
Author unknown, "Department of Cancer Immunology and Virology," Dana-Farber Cancer Institute, url: http://www.dana-farber.org/Research/Departments-and-Centers/Department-of-Cancer-Immunology-and-Virology.aspx, last update: unknown, consulted at: 17-05-2016.

[14] Author unknown, "Tumor Immunology: Multidisciplinary Science Driving Combination Therapy (J7)," Keystone Symposia, url: http://www.keystonesymposia.org/15J7, last update: unknown, consulted at: 17-05-2016.
Author unknown, "ESMO Symposium on Immuno-Oncology 2015," European Society for Medical Oncology, url: http://www.esmo.org/Conferences/Past-Conferences/Immuno-Oncology-2015, last update: unknown, consulted at: 17-05-2016.
Author unknown, "Cancer Immunology Research," AACR Journals, url: http://cancerimmunolres.aacrjournals.org/, last update: unknown, consulted at: 17-05-2016.
Author unknown, "Cancer Immunity," Cancer Immunity, url: http://cancerimmunity.org/, last update: unknown, consulted at: 17-05-2016.
R.A. Weinberg, "Crowd Control: Tumor Immunology and Immunotherapy," in *The Biology of Cancer*, second edition, New York: Garland Science (2014), 723-796.

differ in their approach and the related social status of their approach. An anthropological approach suits this goal because it provides data about the daily scientific practice. It allows for an analysis before the point that the scientific process is boiled down to the stylised articles published in scientific journals. Due to editing, peer review and most of all selection and restructuring by the authors, scientific articles do not seem to offer a reliable reconstruction of the daily scientific practice.[15] Grasping similarities and differences between the two approaches requires a closer study of the daily research routine. Such a close study was achieved by visiting and subsequently comparing the Division of Immunology (B3) and the Division of Molecular Carcinogenesis (B7).

In the upcoming chapters this comparison will be structured according to four aspects of scientific paradigms. Three of these are directly derived from Larry Laudan's *Dissecting the Holist Picture*, in which he distinguishes an axiological, theoretical and methodological level within each paradigm. The axiological level concerns the goals that the scientists try to achieve with their work, such as explaining a certain class of phenomena. The theoretical level regards the scientists' ontology and thus the kind of entities to which they refer when postulating theories. The methodological level entails the techniques and methodological rules the scientists apply to reach their aims and to underpin their theories.[16]

As we will see, the approaches differ at all these three levels, showing that indeed we could speak of two distinct sub-disciplines. However, as described by Gieryn, different sub-disciplines may not only differ in their aims, theories and methods, but also in their credibility.[17] To fully understand the relation between the immunological and molecular cancer research, we also need insight into any possible difference in their social status. Therefore, the social status will be the last point of comparison. Prior to this comparison in the upcoming chapters, the rest of this chapter describes how the field studies were performed and how data was collected.

1.1 Accessing the present: Methodological remarks

To a large extent my methodology is based on Latour and Woolgar's *Laboratory Life*. Like Latour, I studied the researchers while participating in the daily practice of their work at the laboratory, offices and seminar rooms. Resembling Latour's method, I also collected data by semi-structured interviews.[18]

However, in four important ways my study departed from Latour's. Firstly, my study had a comparative design, as I collected data at two field sites situated at different floors of the same research institute. Secondly, I collected an additional form of data by sending around questionnaires. Thirdly, whereas Latour's field visit took almost two years, mine took six weeks per field site. This difference in study time resembles the difference in scope of our studies. Whereas Latour´s work aimed at giving a comprehensive account of the scientific practice as such, my study focusses on the differences and

[15] B. Latour and S. Woolgar, *Laboratory Life: The Construction of Scientific Facts*, second edition, Princeton: Princeton University Press (1986), 28-29.
[16] L. Laudan, "Dissecting the Holist Picture of Scientific Change," in *Philosophy of Science: The Central Issues*, ed. M. Curd and J.A. Cover, London: W.W. Norton & Company (1998), 139-169.
M. Curd and J.A. Cover, "Laudan's Criticisms of Kuhn," in *Philosophy of Science: The Central Issues*, ed. M. Curd and J.A. Cover, London: W.W. Norton & Company (1998), 235-239.
[17] Thomas Gieryn, *Cultural Boundaries of Science: Credibility on the line*, Chigago: The University of Chigago Press (1999).
[18] Latour and Woolgar, *Laboratory Life*, 20-40.

similarities between two specific scientific practices. Fourthly, unlike Latour I was not a complete stranger to the laboratory life. During my bachelor studies I was trained to use biomedical concepts and instruments in a certain way. Furthermore, I have spent some weeks at the laboratories of the University Medical Center Utrecht during short internships. In other words, to some extent I am socialised in the sub-cultures I studied. Because I had not an absolute outsider perspective, it is very likely that unconscious expectations rooted in my previous experiences biased my observations.

On the other hand, my biomedical background also had advantages. Due to this background, it was easier to gain access to the field sites, to participate in the daily work, to understand the aims of the research projects and to build rapport with the field members. As we will see in the upcoming chapters, being both an anthropological observer and an interpreting biomedical scientist, has been necessary to appreciate the subtle, but important differences between the two approaches.

Gaining access to the fields

I primarily gained access to the institute via the head of the only existing immunological division of the institute. Upon explaining my intention to study the daily practice of science by participating in the laboratory work, she put me in touch with two supervisors. These supervisors would introduce me into their laboratories and research groups.

Three important factors influenced the selection of supervisors and the field sites they would introduce into. To start with, the selection must have been dependent on the network of the head of the immunological division. She only introduced me to supervisors who she expected to be appropriate and relevant for this study. In addition, the field sites were selected to be situated at the immunological division (B3) and at one of the institute's molecular divisions (B7). Lastly, the sites were selected based on the readiness of the supervisors and group leaders to provide me access to their research groups and laboratories. At B3 I was supervised by a research technician and at B7 my supervisor was one of the group leaders working at this division. Although their affiliations and thus their daily responsibilities differed, the supervisors introduced me in a similar way to the laboratory life.

During both field visits I participated in a role comparable to the students doing an internship at the divisions. Hence, I was introduced to other field members by my supervisors as an intern currently studying philosophy of science, with a special interest in "how we do science and how we think science."[19] In addition, my supervisors introduced me into the ongoing research projects of the group. As they would have done to any other student, they taught me how to perform certain experimental techniques and got me involved in the interpretation of the data produced.

Taking the role of a student had two advantages. Firstly, participating as a student suited my age (24) and educational background. Secondly, the student role is naturally close to the role of the "Earnest Novice", a role sociologist William Neuman advocates for field observers in his methodological book *Understanding Research*. According to Neuman the Earnest Novice is humble, asks questions and listens carefully to the other field members. Taking this attitude enables the observer to collect much information and to approach the field with few preconceptions. Furthermore, field members are generally more willing to share (confidential) information when approached as experts.[20] Master

[19] FI20; FM14. See "Consent of informants and institute" for more details about the disclosure of my study.
[20] W.L. Neuman, "Observing People in Natural Settings," in *Understanding Research*, Essex: Pearson (2014), 281-312.

students often have little research experience and are at the laboratories to be educated by the more experienced group members. In my role as a master student, I was expected to literally follow in the field members' footsteps, ask many "basic" questions and listen to the field members, rather than acting independently or promoting my own ideas.[21]

Like the days of the other students, mine were filled with studying and executing experimental protocols, discussing data, chatting in the coffee room, attending seminars and writing down my activities and findings in the lab books. The only difference was that the notes I took were not only about the experiments and their outcomes, but also about the social context in which they were performed and presented.

Field observations

To obtain data on the daily research routine, two field visits were performed during the late Summer and Autumn of 2014. At each field site, the first five weeks were dedicated to participant observation. In total I collected about 270 pages of field notes (see **figure 2**). The daily field visits took place on Monday to Friday, the standard working days of the field members. Although occasionally individual members of both divisions indicated to work during the weekend, no field visits were made on Saturdays and Sundays.[22]

Mainly following the rhythm of the field members, my field visits typically started between 8:30 and 9:00 at B3 and between 9:00 and 9:30 at B7. I usually left the field sites between 17:30 and 19:30. Sometimes I entered earlier or left later to observe outside the hours which were considered to be the normal working hours by the field members.[23] For some events, like "lab outings" or "cheese and wine parties", the field members and I left the institute. Nevertheless, the vast majority of the observations were made in the institute's laboratories, offices, seminar rooms, restaurant and in the corridors connecting all these places.

Throughout my time at the field sites, I collected short, jotted notes which served as reminders for the actual writing of my field notes.[24] Usually I wrote my field notes at the end of the field visit or immediately upon leaving the field. Again drawing on Neuman's methodology, in my field notes, I distinguished between descriptions of events and settings (Observational notes), my interpretations of these events (Inferential notes), strategic considerations (Analytical notes) and reflections on my emotional mood and their influence on my perception of the events (Personal notes).[25]

Although all contain relevant information, the Observation notes make up the main part of the field data and will be cited the most throughout the rest of Part I (see **table 2**). These notes contain descriptions of the everyday life at the institute, including the work at the laboratories and offices, the group meetings, seminars and chitchats at the coffee machine. Sometimes, I participated in the described events, whereas in other cases, I only observed and listened. Furthermore the Observation notes contain descriptions of what Neuman calls "field interviews": informal conversations in which I

[21] Neuman, "Observing People," 295.
[22] FI74; FM41.
[23] FI87, 108; FI74.
[24] Neuman, "Observing People," 301.
[25] Neuman, "Observing People," 301.

asked field members questions, for example about the people they collaborate with or their motives to not attend a certain seminar.[26]

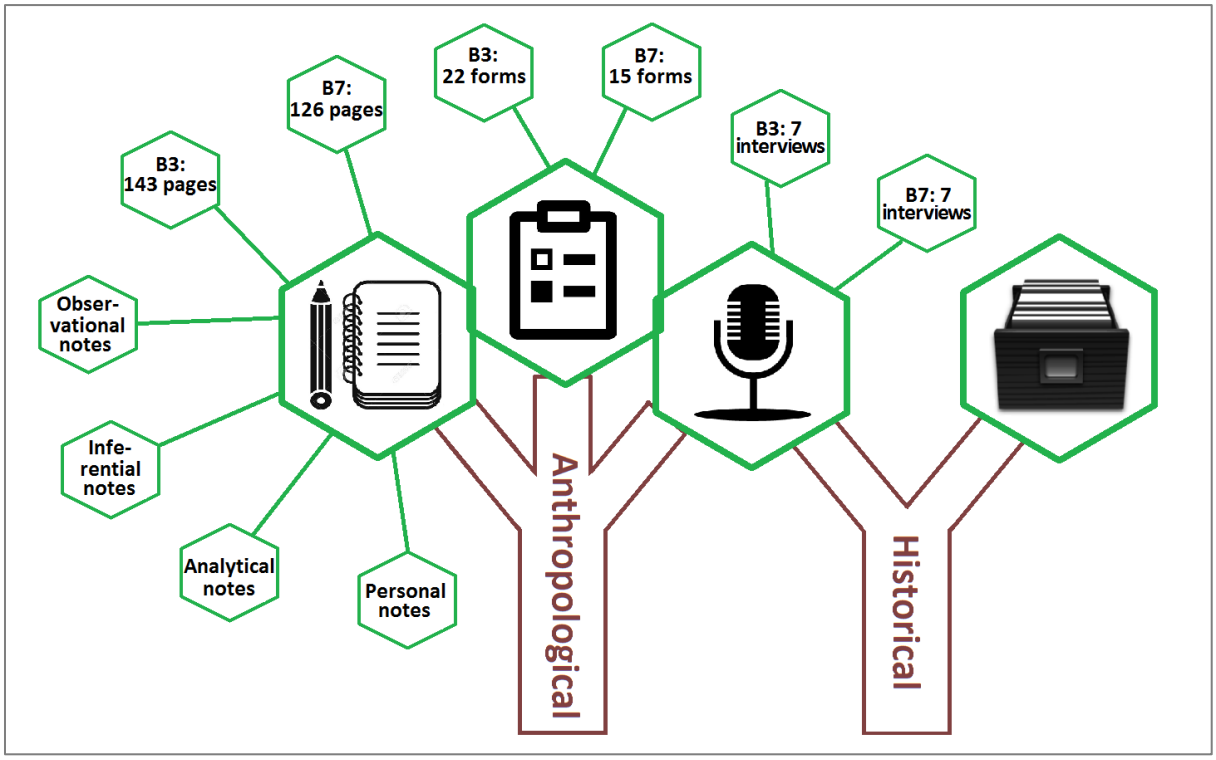

Figure 2. The forms of collected data and their quantities in Part I. Part I of this thesis is based on three forms of data collected via anthropological methods: field notes, questionnaires and interviews. The studied field sites were the Division of Immunology (B3) and the Division of Molecular Carcinogenesis (B7) of the Netherlands Cancer Institute. The figure indicates the quantities of collected data and the kinds of field notes. Historical data will take centre stage in Part II.

Semi-structured interviews

Besides the casually occurring field interviews during the phases of participant observation, I performed more extensive, semi-structured interviews in the sixth week of my stays at both divisions. To gain in-depth insight into the field member's own perception of their work, at both divisions I interviewed seven field members. As listed in Appendix 2, the interviewees were a more or less representative mixture of technicians (4), PhD students (3), postdoctoral fellows (5) and group leaders (2).[27] Furthermore, the selection of interviewees covered the variety of gender, age and nationality of the field members working at both field sites. Field members were approached for the interviews in person or via e-mail in the fifth week of my stay at the divisions. Except one, all approached field members agreed to be interviewed.

The interviews generally took between 60 to 90 minutes and were situated in unused seminar rooms, meeting rooms or offices. These locations were selected to create, simultaneously, an atmosphere of confidentiality and familiarity. These closable and thus relatively isolated locations were separated enough from the rest of the field sites to guarantee privacy. Being the common locations to discuss

[26] Neuman, "Observing People," 302-304.
[27] Appendix 2.

their experimental data and plans with other field members, these rooms were also expected to offer a familiar setting for the interviewees to talk about their work at the institute.[28]

To further normalise the setting, the opening of the interviews was dedicated to questions about the current work of the interviewee. In fact, the first question of every interview was: "What is the last experiment you performed and how did it go?" Like during the field visits, I took the role of an Earnest Novice and approached the interviewees as experts on cancer research. Besides their current work, the topics of the questions included the overarching projects of the research groups, collaborations, the reputation of the groups and the (recent) developments within cancer research. Appendix 3 shows an overview of the standard questions which guided the interviews. However, I often respected the natural flow of the conversations and frequently delved further into interesting but unexpected topics. Consequently, the order and exact formulation of the questions differed per interview. All interviews were recorded and I will refer to these records in the proceeding sections of this chapter.

Questionnaires

Besides the in-depth information the interviews provided, a more general insight into the field members' backgrounds, daily work and opinions about cancer research was obtained by sending out a questionnaire. The questionnaire contained questions about their education, previous work experience, current work, general views on cancer research and the different disciplines within it (see Appendix 4). The questionnaires were announced and distributed in the fifth week of my stays at the field sites and most of them were collected in the sixth week. At both divisions all the field members (about 50 per division) received the questionnaire. The questionnaires were filled out and returned by 23 members of B3 and 15 of B7.

In the analysis the answers were compared at divisional level. Although the questionnaire only contained open questions, the analysis did not provide merely qualitative data. By categorising and counting the given answers, qualitative patterns could be quantified. For example, it could be calculated which percentage of the division members ranked a certain experimental technique among the techniques they commonly use. Besides quoting illustrative answers of the field members, these patterns will be used throughout the rest of this part to reveal differences and similarities between the aims, methods, theories and social status of the divisions.

Form of data	Abbreviation B3	Abbreviation B7	Example	Meaning example
Field notes	FI.[page #]	FM.[page number]	FI.5-6	Field notes, made at Immunology, page 5-6
Interviews	II[interviewee#].[minute#]	IM[interviewee#].[minute#]	IM3.10-13	Interviewee 3 from Molecular Carcinogenesis, minute 10-13
Questionnaires	Q[question#]	Q[question#]	Q7	Questionnaire, question 7

Table 2. Abbreviations used for references to field data in footnotes.

[28] FI122, FM13; 73; 112; 113; 115.

2. Axiological level

As Laudan discusses in *Dissecting the Holist Picture*, the axiological level of a scientific paradigm concerns the "goals that science seeks".[29] In other words, scientists adhering to different approaches, may differ in their scientific aims. Although Laudan regularly characterises these scientific aims as "cognitive goals", here also non-cognitive goals will be considered.[30] As I will discuss below, it does not seem to be appropriate to qualify the aims of the studied cancer researchers as merely cognitive. As might be expected of biomedical research, at both divisions the aims are to a large extent of clinical nature. However, before turning to these interrelated cognitive and clinical aims, I will discuss yet another kind of non-cognitive aim: publishing in high impact journals.

2.1 Chasing *Nature*

It is about 13:30 at 6 October when a technician and I are working at the same bench in the main laboratory of B7. One student is also working in the lab and other field members are passing the space only occasionally. The technician and I are both preparing an agarose gel for the size analysis of DNA fragments. During the course of our work, which also involves some waiting, we have a conversation about the division's research groups and its members. Once the orange coloured samples are loaded onto our gels and the currents are switched on to pull our DNA fragments through the gels, he continues our conversation by evaluating various field members. About one of the division's members he is particularly positive, as he says: "X doet het heel goed. Hij denkt in figuren van papers."[31]

Not only during the chitchat I had with this technician, but also in other situations and in the interviews field members of both divisions linked scientific success to publications in scientific journals.[32]

[29] Laudan, "Dissecting the Holist Picture," 142.
[30] Laudan, "Dissecting the Holist Picture," 142-143.
[31] FM84. Translation: "X is doing very well. He thinks in figures of papers."
[32] FI122, 125; FM68; II7.31; IM4.56.

Consistently, field members identify the natural end of a scientific project often by the publication of its data.[33] In fact, at first sight a complete stranger observing the daily routine at the institute might infer that the most important goal of the field members is to publish their data in what they call "high impact journals".[34]

During the field visits I observed a couple of times the events taking place once a paper is accepted for publication in such a frequently cited journal.[35] The events that follow are notably similar at both divisions. Once a certain paper is accepted for publication in a scientific journal, the news quickly spreads by mouth throughout the offices and laboratories of the divisions.[36] To make sure no one misses the news, the authors of the accepted publications may announce the acceptance in the weekly group meetings.[37] When considering the field members' responses upon hearing the news, at least two patterns stand out at both divisions. Firstly, without exception the field members respond in a positive way to the news. The field members express their positivity by explicitly valuing the news as "good" or "great" and by congratulating the authors.[38] Secondly, most often the field members continue the conversation by discussing the journal in which the paper will appear and its impact factor.[39] For example, on 13 August at 9:30 a technician is one of the five field members who enter the office in which a postdoc and I are working to congratulate this postdoc with the acceptance of his paper. Upon congratulating the postdoc with the acceptance of his paper, the technician comments on the journal by saying: "Mooie impact ook."[40]

In terms of impact factors, the absolute top seems to be a publication in the journal *Nature*. With an impact factor above 40 it was the highest ranked general journal in the "Journal Citation Reports Science Edition" of publisher Thomson Reuters in 2014.[41] Hence, publications in *Nature* are highly valued by the field members of both divisions.[42] Furthermore, during the field visit, members reported twice that they first tried to get their most recent paper accepted by *Nature* before they submitted it to another journal.[43] Publishing experimental data in *Nature* or another high impact journal is an important aim of the members of both divisions. How could this axiological similarity be explained?

First of all, it seems to be a general conviction at the institute that the number of (high impact) publications is an indication of the quality of scientific endeavours. From 1987 onwards, the institute's *Annual Report* contains a table in which the number of publications and their impact factors are listed. These tables and the accompanying commentary appear under the telling subheading "Quality of Research".[44] In addition, the institute's library publishes annually a citation analysis, in which the average impact factor of the publications is calculated per division.[45]

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[33] FI57-58; II1.21; IM1.3; IM3.21; IM4.23; IM5.6; IM6.20.
[34] FM68.
[35] FI28, 66, 89; FM27, 42.
[36] FI66; FM27.
[37] FI28; FM42.
[38] FI66, 89, 92; FM27.
[39] FI28, 89; FM27, 42.
[40] FI89. Translation: "Nice impact as well."
[41] Author unknown, *2014 Journal Citation Report Science Edition*, New York: Thomson Reuters (2015).
[42] FI122; FM21, 112; II5.38; IM2.36.
[43] FI67, 90-91.
[44] Author unknown, *Annual Report 1986*, Amsterdam: The Netherlands Cancer Institute (year unknown).
[45] Author unknown, *Citatie analyse: Publicaties 2011*, Amsterdam: Netherlands Cancer Institute (2014).

Furthermore, the institute does not only count publications in its yearly assessment of the research quality. Also in the selection and evaluation of new staff members the number of high impact publications is taken into account.[46] At the NKI publications can be vital for beginning group leaders. According to a PhD student working at B3, in 2013 the NKI sent home two of its novice group leaders because they were unsuccessful in publishing their otherwise interesting data.[47]

In general field members of both divisions declared that the pressure to publish is high for young researchers as their future careers significantly depend on it.[48] According to them, especially funding agencies take the number of high impact publications into account when awarding research grants.[49] As one of the postdocs of B3 firmly puts it in an interview: "Because you need to have this high impact paper. Otherwise you will never get your own grants. So if you don't have high impact papers, your career is over."[50]

In other words, the field members do not form an exception to the world wide tendency to assign great importance to high impact publications, explaining why they aim for such publications. This widespread obsession with impact factors is increasingly subjected to criticism, also by one of the interviewed field members.[51] Although these critiques might be important, they are not our main concern here. What is relevant for this study is that the divisions did not differ in this respect. The members of both divisions aim for high impact publications. But let us delve a bit deeper. What kind of stories would they like to publish in *Nature*?

2.2 Clinical values

It is 28 August in the end of the morning. I am writing in my lab book in the students room of B3. The students room is also used by other field members for seminars and meetings.[52] One of the division's technicians is having a conversation with a representative of a company selling laboratory equipment. In the beginning of their conversation the representative asks for a general overview of the work done at the immunology laboratory:

> [Woman of company:]
> Ik ben het bestand natuurlijk een beetje aan het bijwerken. Kan je misschien even kort vertellen waar jullie nu mee bezig zijn?
>
> [Technician working at B3:]
> Heel veel kweekwerk, veel gen transfer, veel klinische trials met antilichaam-therapy en TIL therapie. Met TIL therapy isoleren we de T cellen uit de tumor

[46] FI75; 104.
[47] FI105.
[48] II2.65; II5.16; II6.28; IM1.13; IM5.13.
[49] FI89; II2.65.
[50] II2.65-66.
[51] II2.65-66.
Huub Dijstelbloem, Frank Huisman, Frank Miedema, Wijnand Mijnhardt, "Science in Transition: Position Paper (version 2)," Science in Transition, url: http://www.scienceintransition.nl/wp-content/uploads/2013/10/Sience-in-Transition-Position-paper-versie-2.pdf, last update: 17-10-2013, consulted at 22-05-2016.
Reinhard Werner, "The focus on bibliometrics makes papers less useful," *Nature* 517 (2015), 245.
Ruud Abma, "De lessen van Stapel," in *De Publicatiefabriek: Over de betekenis van de affaire-Stapel*, Nijmegen: Uitgeverij Vantilt (2013), 153-164.
[52] FI43, 59, 65, 120, 129.

> en kweken we die op. We bieden een veel groter leger aan van immune cellen. Het is voornamelijk om melanoma mee te bestrijden.[53]

From the technician's answer becomes clear that the focus of the research is on therapies for melanoma, cancer of certain skin cells. Comparable clinical ambitions were observed during the field visits to B7, for example at 16 September in the evening. Although most people left, a PhD student and I are still running some experiments at the laboratory of B7. It is about 19:30 when we decide to leave the institute to get dinner at the Surinamese takeaway opposite to the cancer hospital.[54] While we are passing the empty waiting room of the radio therapy department, we discuss the role of *in vitro* and *in vivo* models for cancer:

> [Observer:]
> Yes, but last week I heard X saying that the same inhibitor has a different effect in 2D cultured cells, in 3D cultured cells and in vivo. So that is really hard to understand.
>
> [PhD student:]
> Yes, we don't know how it works. But that is not my main concern. I want to do my research on lung cancer and I want to improve therapy for it. Those conceptual issues are X's concern as an older PI. Only a person like X thinks about this.[55]

Rather explicitly the PhD student states what he aims for with his research: improving cancer therapy. Although not on a daily basis, also in other situations members of both divisions overtly declared that the end of their work is improving the arsenal of therapies to treat cancer patients.[56] However, more often the aim for improved cancer therapy was expressed in a less explicit way. In the interviews field members of both divisions were asked what the most important developments or breakthroughs were in their field of research. Hardly without exceptions the interviewees mentioned examples of clinical successes, such as a high response rate in a clinical trial of a new cancer treatment.[57]

And although this emphasis on clinical successes is shared by members of both divisions, the specific kind of successes mentioned, differed remarkably per division. Most examples given by immunologists were so called "immunotherapies": anti-PD1, anti-CTLA4 and TIL therapy. [58] As I was told by several interviewees, the common characteristic of these therapies is that they stimulate the patient's immune cells to recognise and destroy tumour cells.[59] In an interview, one of the PhD students of B3 explained

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[53] FI129. Translation:
[Woman of company:] I am currently updating the database. Could you tell me shortly what you are doing now?
[Technician working at B3:] A lot of cell culture, lots of gene transfer, many clinical trials with antibody therapy and TIL therapy. With TIL we isolate the T cells from the tumour and then expand them. We administrate a much larger army of immune cells. It is mainly to treat melanoma with.
[54] FM48.
[55] FM48-49.
[56] FI80; FM13, 20, 121; II5.41.
[57] II2.28-30; II4.25; II5.41; II6.33; II7.21-23; IM1.32; IM4.55; IM6.27; IM7.58-59.
[58] II2.78; II3.49; II4.25; II5.41; II6.33; II7.21-23.
[59] II2.28; II3.19; II7.16.

why she considered the clinical successes of TIL therapy for melanoma to be important in her field of research:

> Nouja, toen heeft men eigenlijk zich gerealiseerd dat het immuunsysteem ook daadwerkelijk effect kan hebben op de controle van die tumour. En als je dat immuunsysteem maar op zo'n manier manipuleert, kan je dat effect misschien groter maken. En daarom is toen die focus gekomen op therapieën die aangrijpen op de lymfocyten.[60]

On the contrary, the members of B7 most often mentioned Herceptin, Gleevec or BRAF inhibitors, all examples of what the field members call "targeted therapy".[61] One of B7's PhD students explained in an interview what characterises these targeted therapies:

> Ja, meer, ja, meer uitzoeken wat is, wat is er mis en daar een, een drug bij vinden. In plaats van een drug vinden die werkt en je weet nog iet hoe. Nee, er zijn een aantal succesverhalen, zoals [euh]... ja weer vemurafenib, de BRAF inhibitor, die specifiek de mutante eiwit,is hét voorbeeld van targeted therapy. Je hebt hetzelfde met [euhm] Gleevec in sommige leukemie. Die gewoon heel specifiek een driver van de kanker aanpakt. Dat zijn de succesverhalen.[62]

In another interview a senior postdoc of B7 explained how such a driver is used as a therapeutic target:

> Het idee van targeted therapy is dat je puur en alleen dat product aanpakt wat misgegaan is in een kankercel. Dus wat een kankercel onderscheid van jouw lichaamseigen cellen, dat probeer je aan te pakken. Als tenminste die kankercel ook van dat genproduct afhankelijk is [voor] z'n deling, dus dat is dan de achilleshiel. Je moet wel... Je hebt heel veel verschillen tussen gewone cellen en kankercellen, maar je moet dus ook iets pakken waarvoor 'ie echt gevoelig voor is. Dus targeted in die zin betekent ook wel echt dat je iets aan probeert te pakken wat anders is in een kankercel als in een gewone cel en waar die ook van afhankelijk is.[63]

Rather than mobilising the patient's immune cells, targeted therapies are directed against a cancer cell's disrupted internal signalling networks. These networks are believed to be responsible for the cancer cell's pathogenic survival or proliferation. In the daily laboratory life, the same divide was

[60] II4.26. Translation: Well, then people actually realised that the immune system really can have an effect on the controlling of this tumour. And if you manipulate the immune system in a certain way, you might be able to increase this effect. And therefore the focus has been on therapies which target the lymphocytes.
[61] IM1.32, 4.55, 6.27, 7.64 7.58-59.
[62] IM1.31-32. Translation: Yes, trying to figure out what is wrong and to find a drug for it, instead of finding a drug that works while not yet knowing how. There are several success stories, like… yes again, Vemurafenib, the BRAF inhibitor, which specifically the mutated protein… the example of targeted therapy. The same goes for Gleevec in some leukaemia. That just targets a very specific driver of the cancer. Those are the success stories.
[63] IM6.23-24. Translation: The idea of targeted therapy is that you specifically target that product which has gone wrong in a cancer cell. So you try to target what a cancer cells distinguishes from your endogenous cell. At least, if this cancer cell is also depended on that gene product for its proliferation, so that is then the Achilles heel. You need to… There are a lot of differences between normal cells and cancer cells, but you need to target something it is really sensitive for. So targeted in that sense means that you try to target something which is different in the cancer cell compared to a normal cell, and something it is also depended on.

observed. Especially when discussing their own research activities with their colleagues and visitors in the seminar rooms or at the coffee machines, the field members explicate the kind of therapies they aim to develop. Indeed, the scientific endeavours of B3 members are to improve immunotherapies, while the members of B7 aim to develop targeted therapies.[64]

These field observations are consistent with the answers given in the questionnaire. In question 7, the field members were asked for the main question their group addresses. On the one hand, the vast majority of B3 reported that the central question of their group's work was about developing immunotherapy. On the other, hand most members of B7 formulated a question directly related to the improvement of targeted therapy.[65] Importantly, no member of B3 reported to be working on targeted therapy and, vice versa, no one from B7 reported to be working immunotherapy.[66] How the answers differed per division is exemplified by the following to answers:

> [Answer of a technician working at B3:]
> How immunotherapy can play a role in curing cancer. Mainly melanoma's, but other types of cancer in the future aswell. And why the therapy works for some patients, but not for others.

> [Answer of a PhD student working at B7:]
> Which genes are involved in resistance to targeted therapies and how can we use that knowledge to improve therapies. And identifying new mutations in tumors using new generation sequencing.[67]

Apart from studying different therapeutic strategies, comparing these two answers also highlights another axiological difference between B3 and B7. As the cited technician wrote, the work at B3 is mainly focussed on therapies for melanoma.[68] Only a small minority of the division is continuously studying another type, breast cancer.[69] By contrast, the members of B7 were observed to work on a very broad range of cancer types, including breast, colorectal, lung and ovarian cancer, to name but a few.[70] In one of the interviews a group leader of B3 explains why so many of their research efforts revolve around just one cancer type:

> Traditioneel om een paar redenen. [Euhm] Eén is dat [euh] het al heel lang bekend was dat het aantal T cellen... dat er veel T cellen zaten in melanoom [euh] laesies. En ten tweede dat [euh, euh] soms er een spontane regressie van melanoom optreedt, heel infrequent. En ook dat soms patiënten [euhm, euh] vitiligo ontwikkelen, dus [euhm, euh] ontkleuring van de huid als gevolg van destructie van melanocyten. En dat rook allemaal een beetje naar een immune

[64] FI80, 86-87, 94, 129; FM20, 33, 43, 64, 109, 111.
[65] Q7. Inclusion criteria immunotherapy: TIL, improving immunotherapy, adoptive cellular therapy, mechanism of immunotherapy. Inclusion criteria targeted therapy: targeted agents, improving targeted therapy, how to target oncogenic driver, lethal interaction with CDKi.
[66] Q6; Q7. Note: Which is not to say that no one is indeed working on the other kind of therapy. At least one of the clinicians working at the division of immunology is testing combinations of immunotherapy and targeted therapy for melanoma, as reported by a member of B7 in an interview (IM7.86). Nevertheless the general pattern remains: B3 works on immunotherapy, B7 on targeted therapy.
[67] Q7.
[68] FI26, 113, 129; II2.19; II4.02; II6.05; II7.02; II7.52; Q6; Q7.
[69] FM90, Q7.
[70] FM15, 26, 49, 57, 87, 111; IM1.04; IM3.04; IM4.04; IM6.02; Q6.

> response, [euh] die dingen bij elkaar. En daarom is er traditioneel heel veel aandacht geweest voor melanoom. En omdat er zo veel T cellen in die tumoren zaten kon je T cellen ook gaan groeien en je ze gaan bestuderen etcetera.[71]

Other members of B3 also emphasised that melanoma has been known as an "immunogenic" cancer type and hence is considered as an attractive type to develop immunotherapy for.[72] Importantly, here we see how the difference in studied therapeutic strategy is related to a difference in the studied cancer types. However, the difference in therapeutic strategy is also reflected in a difference of the cognitive values members of both divisions pursue.

2.3 Cognitive values

In the interviews I asked group leaders of both divisions what their groups study. A comparison of their answers elucidates at least one similarity and one difference between the divisions regarding the role of biomedical understanding in their work:

> [Group leader working at B3:]
> Traditioneel… [euhm]... soms zeg ik twee dingen, soms zeg ik drie dingen. Als ik twee dingen zeg, dan zeg ik [euh, euh] basaal onderzoek waarin we proberen te begrijpen hoe T cellen werken, en [euh] toegepast onderzoek waarin we begrijpen hoe immuunresponsen plaatsvinden in patiënten die worden behandeld met immuuntherapie en hoe we die immuunresponsen kunnen manipuleren, en kunnen versterken.[73]

> [Group leader working at B7:]
> De grootste algemene noemer is, is dat ik denk dat wil je in tumoren van patiënten voorspellen wat de beste therapieresponse is, dat je inzicht moet hebben hoe de genetische veranderingen in de tumor invloed kunnen hebben op de manier waarop een cel reageert op externe en interne signalen.[74]

Both group leaders declare that biomedical understanding will elucidate how to enhance or optimise clinical responses in cancer patients. To put it differently, they see biomedical knowledge as a means to the goal discussed in the preceding section: developing and improving cancer therapy. In the course of the field work and interviews I noticed that not only the group leaders adhere to the view that there

[71] II3.48-49. Translation: Traditionally for a couple of reasons. Firstly, it has been known for a long time that the number of T cells… that there are many T cells in melanoma lesions. And secondly that sometimes spontaneous regression of melanoma occurs, very infrequently. And also that sometimes patients develop vitiligo, depigmentation of the skin as a consequence of destruction of melanocytes. This all pointed in the direction of an immune response, all these things together. And therefore there has been traditionally a lot of focus on melanoma. And because there were so many T cells in the tumours, you could grow them and study them etcetera.
[72] II2.19, II7.52.
[73] II3.19-20. Translation: Traditionally… Sometimes I say two things, sometimes I say three things. If I say two things, then I say fundamental research in which we try to understand how T cells work, and applied research in which we understand how immune responses take place in patients treated with immunotherapy and how we can manipulate these immune responses, how we can enhance them.
[74] IM7.04. Translation: The biggest common denominator is that I think, if you want to predict in tumours of patients what the best therapy response is, then you need to have insight into how genetic modifications in the tumour influence the way in which the cell responds to external and internal signals.

is a direct relation between improvement of understanding and improvement of cancer therapy. When reflecting upon recent clinical successes in oncology, field members often reported that these were driven by newly gained biomedical insights.[75] And although some characterised their work (partly) as "fundamental" or "curiosity driven", most field members think that their current work is potentially beneficial for cancer patients exactly because their work aims for the understanding of certain biomedical phenomena.[76]

Interestingly, interviewees of both divisions declared that certain forms of immunotherapy and targeted therapy are currently used in the clinic while their mechanism of action is unknown or topic of scientific dispute.[77] This suggests that accurate biomedical insight is not always necessary for the development of clinically successful therapies. Nevertheless, what concerns us here is the described similarity in the aims of the field members: it is a common conviction at both divisions that the improvement of cancer therapy is to be achieved *through* biomedical understanding.

However, the desired biomedical understanding of *which* specific phenomena differs significantly per division. The group leader of B3 and his group strive to understand how T cells function and how immunotherapies influence the immunological processes taking place in cancer patients. By contrast, the understanding the group leader of B7 pursues, does not regard immune cells at all. His focus is merely on the cancer cell. According to this group leader, his group tries to understand how these modifications influence the tumour cell's response to signals in order to maximise the killing by targeted therapeutics.

During the weekly group meetings I attended at both divisions, I observed the same difference. In these meetings field members present their latest data and often they shortly introduce their current project by mentioning the research question they address. Indeed, at B3 these questions concerned immunological processes, mainly in and around tumours.[78] At B7 most questions aimed to understand the sensitivity or insensitivity of tumour cells to a certain therapeutic agent.[79]

However, the pattern was most clearly shown by the answers to question 6 of the questionnaire. In this question the field members were asked to explicate the specific question they address in their current work. 19 Out of the 22 respondents of B3 reported to address a question about immune responses. About three quarters of these questions concerned immune responses to tumours, either treated or not treated with immunotherapy. The remaining quarter addresses immune responses in general (i.e. not in the specific context of cancer).[80] These three quotations exemplify the range of answers given by members of B3:

[75] FI86; II2.28; II3.40; IM1.31; IM6.08; IM6.29.
[76] FM20, 71; II1.08-13; II2.06, 24; II3.19-20; II5.41-43, 46; II6.54; II7.16; IM1.30; IM4.04; IM5.02; IM6.12; IM7.09.
[77] II2.06; II3.37-38; II6.54; II7.43-44; IM6.04.
[78] FI30, 113, 114, 135.
[79] FM14, 43 71.
[80] Q6.

> [Answer of technician, addressing immune responses in cancer treated with immunotherapy:]
> What is the active 'active ingredient' in TIL? (what do they recognize; how can we make them more efficient?)
>
> [Answer of postdoc, addressing immune responses in cancer:]
> How do gamma delta T cells and neutrophils regulate metastasis?
>
> [Answer of PhD student, addressing immune responses in general:]
> How do skin resident memory T cells contribute to the control of local infections?[81]

While the vast majority of the members of B3 aim for an understanding of immunological processes, 10 out of 15 respondents from B7 aim to understand how processes inside the cancer cell influence its sensitivity to therapy. Most of these members try to understand "mechanisms of resistance" to a certain therapy. Only 3 out of 15 respondents reported that their work partly aims for the understanding of biomedical phenomena in a non-therapeutic context.[82] The following citations form a cross section of the kind of questions addressed at B7:

> [Answer of a postdoc, addressing sensitivity to therapy:]
> Improving targeted therapy and understanding mechanisms of resistance.
>
> [Answer of a PhD student, addressing sensitivity to therapy:]
> Can computational models of known biological mechanisms explain observed variability in drug response in cancer
>
> [Answer of a postdoc, addressing sensitivity to therapy and a mechanism in a non-therapeutic context:]
> Are there synthetic lethal interactions with CDKi? What are the mechanisms for Rb-mediated growth arrest.[83]

This difference in pursued understanding is easily linked to the difference in clinical aims discussed above. The members of B3 aim to understand the immunological processes they try to enhance in cancer patients. Meanwhile, four floors higher, the members of B7 try to understand the factors influencing sensitivity to therapy to come up with optimal (combinations of) targeted therapies.

2.4 Concluding remarks

Taken together we have seen three important axiological similarities between the two divisions. Firstly, members of both divisions aim for publications in high impact journals. Secondly, both divisions aim to develop therapies for cancer. Thirdly, members of both divisions claimed that this therapy development is to be achieved via the understanding certain biological processes. However, in this chapter also three important and interrelated differences were described. Firstly, the members of B3 aim to develop *immunotherapies* while the members of B7 aim to improve *targeted therapy*. Secondly,

[81] Q6.
[82] Q6.
[83] Q6.

the research efforts at B3 are mainly focussed on therapy development for the immunogenic *melanoma*, while at B7 therapies for *many more tumour types* are studied. Thirdly, the members of B3 aim to *understand immunological processes* while the members of B7 try to *understand the mechanisms underlying drug sensitivity*.

3. Theoretical level

In the previous chapter we have seen that both divisions aim to understand different processes. What kind of theories would satisfy their desire for understanding? And does this also differ per division? According to various members of B3 the answer to the latter is yes. In (informal) interviews I asked field members whether and how their work differs from the other divisions. Members of B3 often answered that their work is about cell-cell interactions, whereas the molecular biologists would focus on molecule-molecule interactions inside the cancer cell. [84] One of the division's PhD students put it as follows in one of the interviews:

> Ja ik denk... een verschil is dat wij vooral op celniveau kijken. Dus, wij kijken echt wat doet een... wat is de interactie tussen een T-cel en een tumorcel. En ik denk op veel afdelingen kijken ze meer... kijken ze kleiner zeg maar, meer in de cel.[85]

Notably, when members of B7 were asked to compare their own work with the work done at B3, only one member of B7 mentioned that immunology is different because "it is about interactions between cells".[86] Others members of B7 did not mention this particular difference or did not see any theoretical difference at all.[87] So who is right? Do the theories both groups employ and postulate indeed differ, or are they essentially the same?

The upcoming chapter will describe the kind of theories employed and postulated by the members of B3 and B7 respectively. These descriptions are based on the illustrations and central concepts the field

[84] FI66, 70; II1.36; II2.33; II4.38; II6.20-21; II7.15.
[85] II1.36. Translation: Yes, I think… a difference is that we mainly look at cell level. So, we really study what a… what is the interaction between a T cell and a tumour cell. And I think that at other divisions they look more… they look smaller, so to say, more inside the cell.
[86] FM54.
[87] FM68, 116; IM1.33; IM4.29; IM5.55; IM7.51-53.

members use to clarify their theoretical considerations. By comparing these illustrations and concepts, we will identify an important difference and similarity between the divisions' theoretical considerations.

3.1 Theories at B3

It is about noon at 9 October and a PhD student of B3 is one of the two researchers presenting their work in the "Research Club". The Research Club is the general seminar of the institute and is held twice a week in the "Piet Borst Auditorium". Postdocs and PhD students have to present their work about once a year in this seminar.[88] At 9 October members of both B3 and B7 are in the audience. The PhD student of B3 explains to them that she studies the role of the immune system in the metastasis of breast cancer. Among information about her research aims and data plots, her PowerPoint presentation shows a cartoon which illustrates the processes she studies. The cartoon schematically depicts various cell types, such as lung cells, tumour cells and immune cells, including "gamma delta T cells". In the cartoon, the various cell types are connected with arrows. Each arrow is labelled with a combination of letters and numbers, such as IL-17 or CLL2. The PhD student refers to these combinations as "cytokines" and in her experiments she studies how these signalling molecules mediate the interactions between the various cells.[89]

The PhD student's cartoon resembled the posters spread over the division's offices (see **figure 3**).[90] Other members of B3 also study intercellular interactions and the molecules that mediate them.[91] For example, the project my daily supervisor and I worked on, revolved around the recognition of melanoma cells by T cells. In our experiments, we manipulated the molecules involved in this recognition: the so called T cell receptors (TCRs) and the major histocompatibility complexes (MHCs) they may recognise. In other words, to understand the tumour immunological processes, we built upon theories which postulate intercellular interactions and the involved molecules.[92]

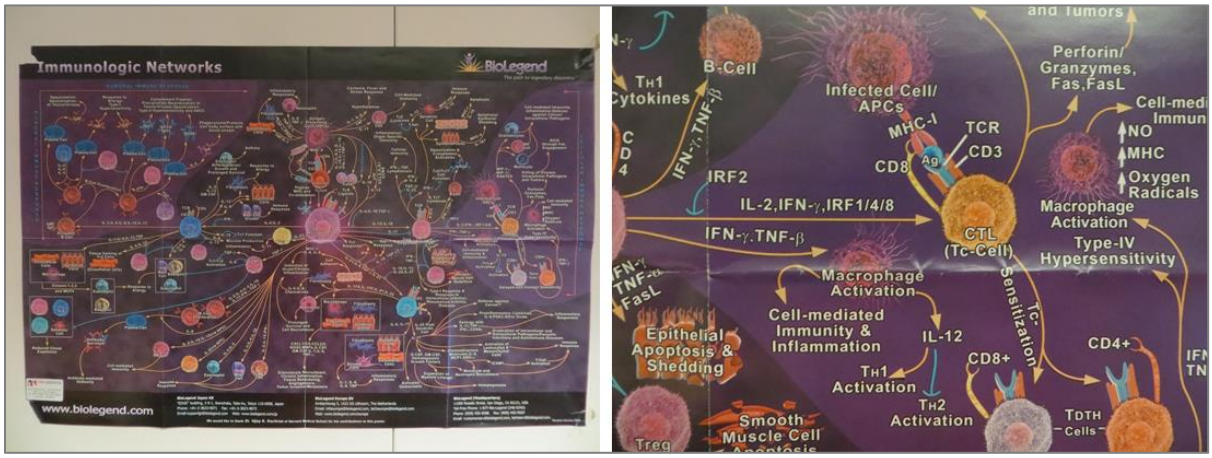

Figure 3. One of the posters at B3 and a detail of this poster. The poster shows different cell types and via which molecules (e.g. cytokines) they interact in "immunologic networks". The arrows indicate these intercellular interactions.[93]

[88] FI124; FM8; II1.16.
[89] FM89-91.
[90] FI23.
[91] FI26, 66, 70, 113.
[92] FM26, 110.
[93] Pictures were made during a later field visit in 2016.

The concept of the so called “neo-antigen” plays a central role in these theories. As one of the field members explained in the interview, MHCs present fragments of the proteins present inside the cell to the T cells. The fragments presented by healthy cells do not lead to recognition by de receptors of the T cells (see **figure 4A**). If a cell gets infected by a virus, it will present fragments of viral origin. These so called viral antigens are recognised by T cells, which in turn can kill the infected cell (see **figure 4B**). However, the members of B3 belief that cancer cells also present protein fragments which can be recognised by T cells. The field members call these fragments “neo-antigens” because they are acquired during the process of tumour formation. In this process, cancer cells accumulate DNA mutations and hence more and more abnormal proteins, from which antigens can be derived (see **figure 4C**).[94]

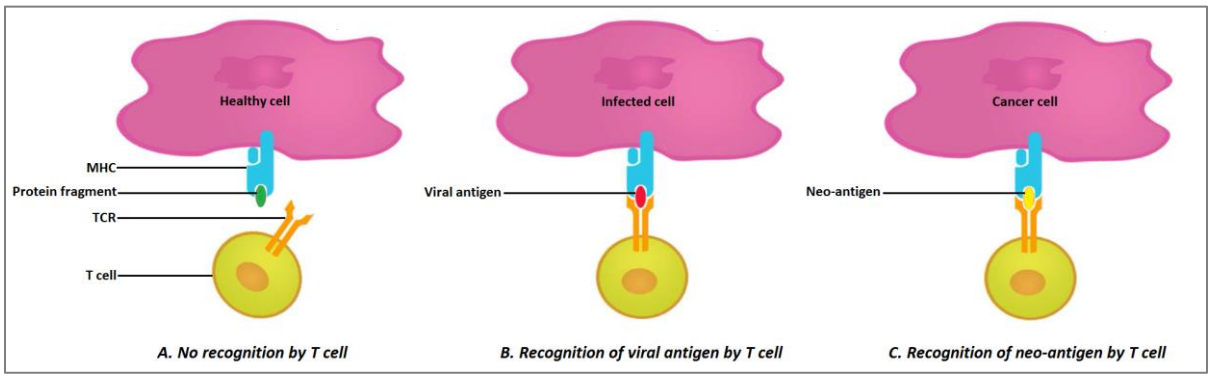

Figure 4. The interaction between the immune cell and the target cell is believed to be mediated by MHCs presenting antigens.[95]

Similar to the way viral antigens distinguish infected cells from non-infected cells, the neo-antigens are thought to distinguish cancer cells from non-cancer cells. As such, the field members consider the neo-antigens to be essential for the recognition of cancer cells by T cells and thus for a tumour specific immune response. Consequently, much of their research efforts are spent on finding these neo-antigens. The neo-antigens play an important role in the theories they postulate about the interaction between immune cells and cancer cells.[96]

Accordingly, it frequently appeared from their definition of cancers that the members of B3 conceive of tumour cells as being in constant interaction with their physiological context. In interviews and in the questionnaire, the field members were asked to give their definition of cancer. Hardly without exception, the members of B3 defined cancer as “uncontrolled cell proliferation”, sometimes adding that these cells might metastasise to other organs. However, about one third emphasised that these uncontrolled cell divisions take place in the context of a body which is unable to stop this pathological process.[97] As one of the division’s technicians put it:

> Ongeremde cellgroei, waardoor het lichaam niet meer zelf in staat is om hier weerstand tegen te bieden. Met als gevolg tumorgroei en metastasen.[98]

[94] FI103, 135; II2.2-3, 26, 47; II3.17-19; II4.16, 31.
[95] Adapted from: Andre Kunert, Trudy Straetemans, Coen Govers, Cor Lamers, Ron Mathijssen, Stefan Sleijfer, Reno Debets, “TCR-engineered T cells meet new challenges to treat solid tumors: choice of antigen, T cell fitness, and sensitization of tumor milieu,” in *Frontiers in Immunology* 363 (2013).
[96] FI103, 135; II2.2-3, 26, 47; II4.16-17, 31.
[97] Q11. Inclusion criteria: in the body, ignoring signals from environment, not kept under control by body.
[98] Q11. Translation: Unlimited cell growth, because of which the body is no longer capable to withstand it. As a consequence there is tumour growth and metastases.

3.2 Theories at B7

Let us return to the Research Club at 9 October. Today's other speaker is a PhD student of B7. He tells us that he is currently analysing "molecular data" of twenty breast cancer cell lines. Like many of his colleagues at B7, he aims "to understand the variability in drug response" in these cell lines. Similar to the first speaker of today's Research Club, he uses a cartoon to visualise the processes he studies. In his cartoon, arrows connect the names of numerous proteins present in the breast cancer cells. The word "proliferation" is projected in a big font under the cloud of protein names and arrows. Some of the arrows connect a protein with "proliferation", indicating that the activation of these proteins triggers the cell to divide. His cartoon also contains the names of drugs. Bar headed arrows pointing from these drugs are used to specify the drug targets, the particular proteins the drugs inhibit.[99]

The PhD student's attempt to understand drug sensitivity in terms of intracellular molecule interactions is exemplary for the kind of work performed at B7. Not only in PhD student's presentation in the Research Club, but also during group meetings at the division the members of B7 use this kind of cartoons to visualize the molecular "pathways" they study.[100] Furthermore, spread out on the office walls of B7, we find posters depicting this kind of schemes (see **figure 5**).[101]

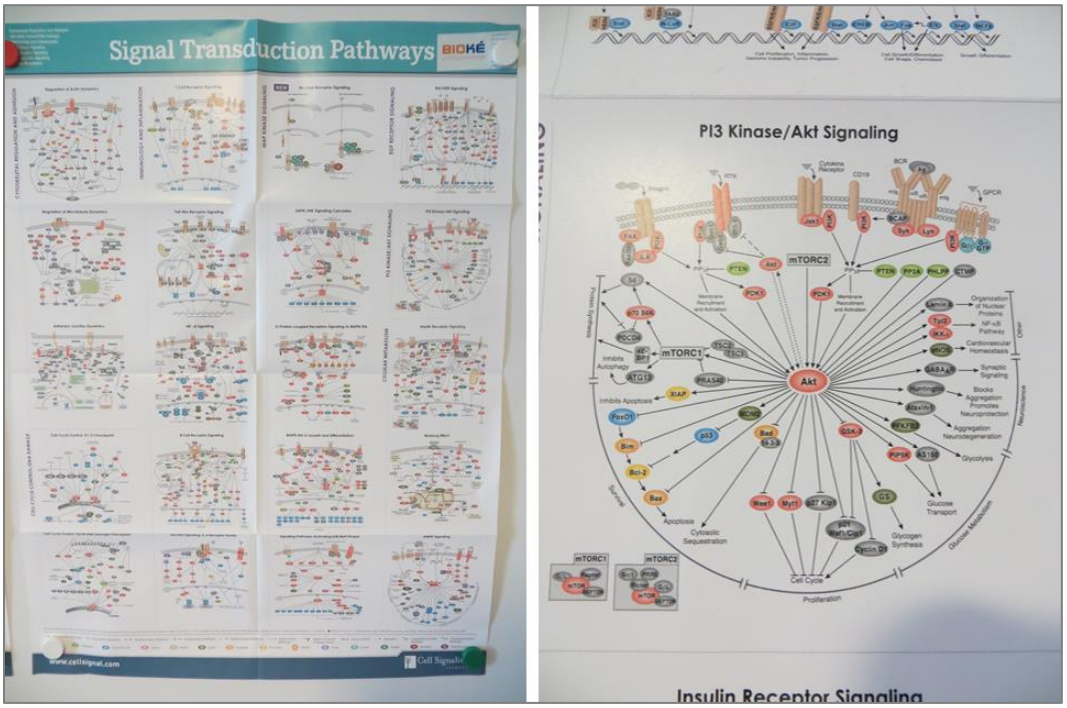

Figure 5. One of the posters at B7 and a detail of this poster. The poster shows the molecules which together constitute multiple "signal transduction pathways". The arrows indicate these intracellular molecule interactions.[102]

In the project in which I was enrolled, my supervisor and I also tried to understand sensitivity to a drug in terms of molecular interactions in the cancer cells. In collaboration with a lab in France, we worked on colorectal cells which acquired resistance to the chemotherapeutic oxaliplatin. In our experiment we tried to figure out which proteins are responsible for this resistance. If we were to understand

[99] FM87-89.
[100] FM14, 22, 42, 73, 75.
[101] Appendix 5: List of collected items, item 7.
[102] Pictures were made during a later field visit in 2016.

which molecular pathway is essential for surviving chemotherapy, we could restore sensitivity by specifically inhibiting this pathway with a targeted drug.[103]

In other words, we were looking for a "synthetic lethal". The members of B7 speak of synthetic lethality when the combination of two factors is lethal to the cell, while both factors separately do not harm it. For example, in our experiment, exposure to oxaliplatin does not kill the cancer cells. Disturbing the expression of certain genes neither is lethal to the cells. However, the combination of oxaliplatin and the disturbance of some genes may kill the cell. The members of B7 would call those genes synthetic lethals. The concept of synthetic lethality is frequently employed at B7.[104] In an informal field interview, a postdoc reported:

> Dus wat we hier nu doen is kijken naar andere genen die die Ras-tumoren ook nodig hebben. Gewoon de klassieke synthetic lethals. En daar heb ik er een van gevonden. Dus als je die outknockt dan stoppen die cellen met delen. Het is niet helemaal synthetic lethal, maar het is toch een flink effect.[105]

Indeed, in their understanding of drug sensitivity and in their search for new drug targets, the members of B7 study pathways which drive the proliferation of cancer cells. This focus on the proliferative capacity of cells is resembled by the answers they gave to question 11 of the questionnaire. Typically, the members of B7 defined cancer as "uncontrolled cell growth" and often they added that these cells might spread through the body. However, none of them emphasised the physiological context of the tumour cells and its interaction with it, resulting in definitions like:

> The uncontrolled growth of cells that eventually can invade surrounding tissue and metastasize to distant organs.[106]

3.3 Concluding remarks

On the one hand, we have seen that the members of B3 employ and postulate theories about interactions between cells. On the other hand, we have seen that the members of B7 employ and postulate theories about the interactions between molecules inside cancer cells. So indeed, the cited members of B3 were right. The difference between B3 and B7 can be summarised as: intercellular theories versus intracellular theories.

This difference is reflected in the central concepts the field members use. Perceived as the central link between the T cell and the cancer cell, the concept of the neo-antigen plays a vital role in the theories of B3 members. At B7, the members often speak of synthetic lethals, combinations of events that are detrimental to the cancer cells. Importantly, these central concepts are not only frequently used at the respective divisions, but also absolutely left unused at the other division. Other concepts neither cross over. Talking about "gamma delta T cells", "cytokines" or a tumour's "immunogenicity" is common at B3, while members of B7 were not observed to use these concepts. Vice versa, concepts like

[103] FM72.
[104] FM21, 29, 34, 72.
[105] FM34. Translation: So what we are now doing here, is searching for other genes that Ras tumours also need. Just the classic synthetic lethals. And I found one of those. So, if you knock it out, then the cells stop dividing. It is not completely synthetic lethal, but it is a considerable effect.
[106] Q11.

"oncogenic driver" or "oncogene addiction" are exclusively used by members of B7, and are not part of the day-to-day vocabulary of the members of B3.[107] Furthermore, the conceptual difference between the divisions is illustrated by their definitions of cancer. The members of B3 tend to emphasise the physiological context of the cancer cells and its failure to resist their uncontrolled growth. By contrast, no member of B7 saw this failure of the surrounding tissue or body as essential to the disease.

Given these theoretical differences, can we speak of two distinct "thought styles"? The founding father of this concept, philosopher and sociologist of science Ludwik Fleck, defined a thought style as "directed perception, with corresponding mental and objective assimilation of what has been so perceived."[108] Fleck argues that scientists that adhere to different thought styles have great difficulties understanding each other, because a thought style determines the perception by propagating a certain way of interpreting an observed event.[109] Indeed, the members of B7 think of cancer essentially as an deregulation of molecular signalling pathways, while the members of B3 perceive the tumour in constant interaction with the cells of the immune system.

However, this chapter also highlighted a similarity between these two ways of perceptions. It is too simplistic to state that B3 is merely a cell-biological division. Although the theory formation at B3 is about intercellular interactions, they fanatically study the molecular processes which guide these interactions. Like the members of B7, the members of B3 appeal to the interactions between molecules in their theories. Yet, both divisions study another class of molecules to explain another class of phenomena. The theories postulated at B3 mainly concern excreted and cell surface molecules, which mediate the interactions between immune cells and cancer cells. On the contrary, the theories employed at B7 are generally about the intracellular molecules involved in the proliferation and drug sensitivity of cancer cells. In Chapter 5 will be discussed to what extent these differences in thought style impair interdivisional communication, but first will be described how the methodologies of B3 and B7 relate to each other.

[107] FM21-22, 34, 90.
[108] Ludwik Fleck, "Epistemological Considerations Concerning the History of the Wassermann Reaction," in *Genesis and Development of a Scientific Fact*, ed. T.J. Trenn and R.K. Merton, trans. F. Bradley and T.J. Trenn, Chigago: The University of Chigago Press (1979), 82-145.
[109] Fleck, "Epistemological Considerations," 98-101.

4. Methodological level

The cartoons and theories discussed in the previous chapters are only constructed relatively late in the scientific process. Before a scientist constructs them, she must apply a series of techniques and methodological rules to reduce the studied phenomenon to a manageable set of data. In his famous account of a pedological research expedition to the Amazon rainforest, Latour describes how the pedologists translate their studied phenomenon (the border of a rainforest) into a set of highly ordered soil samples, how they apply analytic tools to assign labels and values to these samples and how this information is subsequently turned into diagrams, tables and cartoons.[110] This series of translations reflects the methodological aspect of an scientific approach, which concerns the techniques and (implicit) methodological rules a scientist has to employ.[111] The aim of this chapter is to compare the methodology of both divisions.

At a general level the methodological practices at both divisions do not diverge from Latour's account or from each other. Two parallels will be highlighted here. Firstly, like the pedologist who reduce a particular pedological situation to a set of soil samples, the field members reduce the complex body of a cancer patient to a set of cell samples. To orderly store these samples, they use so-called "well plates" (see **figure 6**).[112] These frequently used plastic items contain a variable number of wells (e.g. 24 or 96), can be covered by a lit and have the size of a human hand. These well plates resemble the highly geometrical outlook and function of the pedocomparator, one of the pedologists' central tools

[110] B. Latour, "Circulating Reference: Sampling the Soil in the Amazon Forest," *Pandora's Hope: Essays on the Reality of Science Studies*, Cambridge: Harvard University Press (1999), 24-79.
[111] Laudan, "Dissecting the Holist Picture," 142.
Curd and Cover, "Laudan's Criticisms," 235.
[112] Appendix 5: List of collected items, item 1 and 5.

discussed by Latour. The plates help the field members to simultaneously store their samples and organise their experiments.[113]

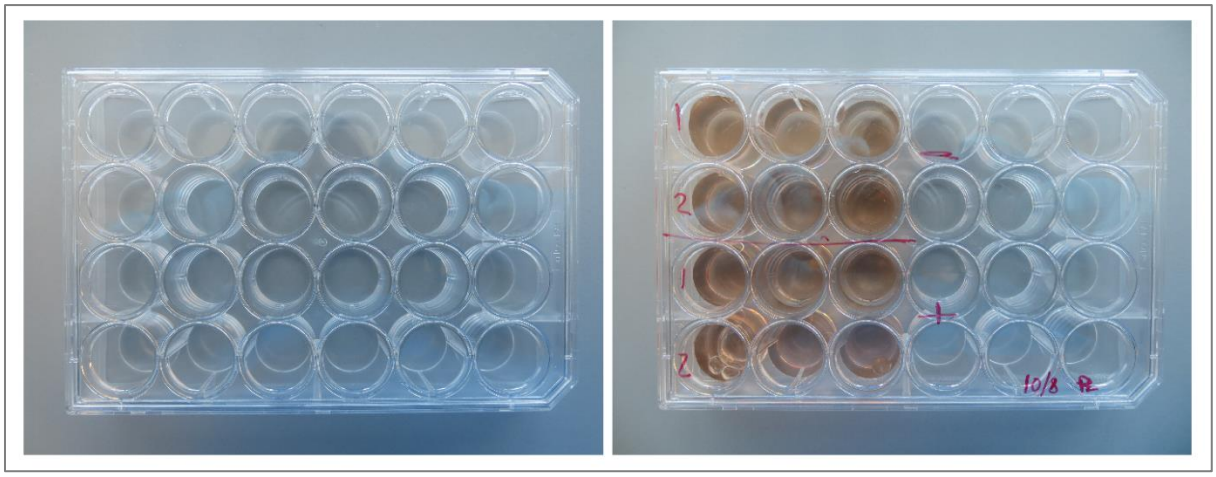

Figure 6. Pictures of an empty (left) and partly filled (right) 24 well plate. These kind of plates are used by members of both divisions. The plates help to reduce the complex body of a cancer patient to a manageable set of cell samples and to organise experiments.[114]

Secondly, once the contents of the well plates are measured in a certain way, the obtained numerical values are translated into diagrams. The particular work I did with my supervisors also resulted in such diagrams. The respective diagrams are shown in **figure 7** and show considerable similarities. Both diagrams contain a high number of individual dots, each of which represents a measurement. In addition, the diagrams contain lines that subdivide the areas of the diagrams, classifying the individual measurements. In other words, these diagrams further reduce the individual measurements to a limited number of sub-classes. This translation of numerical values into diagrams helps the cancer researchers to handle the complexity of the studied phenomenon.[115]

At this general level the divisions do not differ from each other. In fact, they do not even differ in a fundamental way from the pedologists studied by Latour. However, our aim here is not to further develop Latour's theory and to account for the scientific method as such. Rather, the main aim of this chapter is to identify to what extent the divisions give substance to this pattern in a different way. To grasp this, the upcoming two sections will give a more detailed description of the analytical tools and model systems used at B3 and B7 respectively.

[113] Latour, "Circulating Reference," 32-55.
[114] Pictures were made during a later field visit in 2016. The ussage of these plates appears from item 1 and 5 of Appendix 5: List of collected items.
[115] Latour, "Circulating Reference," 32-55.

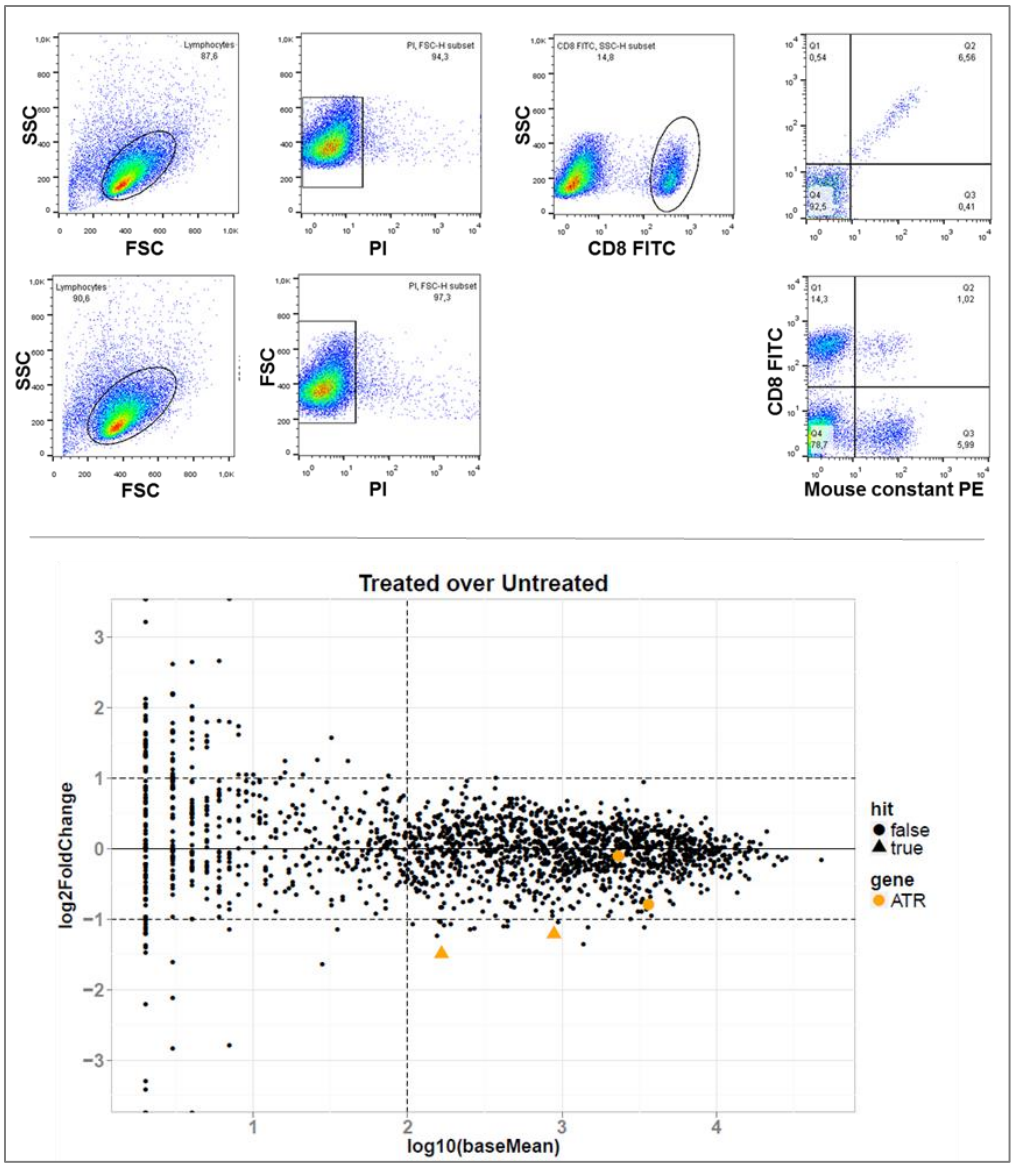

Figure 7. The diagrams that sprout from my and my supervisors' work at B3 (upper half) and B7 (lower half). The dots represent individual measurements and are classified by the lines that subdivide the diagram areas.

4.1 Analytic tools and models at B3

The protocol my supervisor and I worked with during my weeks at B3 was titled "Generation of peptide MHC class I monomers and multimers through ligand exchange". This document of 30 pages describes how to produce large amounts of MHCs *in vitro* and how to rapidly load them with a peptide fragment of choice, such as a neo-antigen. Page 2 of the protocol shows a cartoon which illustrates the principles underlying this technique (see **figure 8**). As unloaded MHCs disintegrate and hence cannot be stored, the protocol describes how to produce a large batch of MHCs loaded with so-called "conditional ligands". To exchange the conditional ligand with a peptide of choice, a sample of the produced MHCs is exposed to UV light. Upon UV exposure the conditional ligands are cleaved and subsequently dissociate from the MHCs. If this dissociation takes place in the presence of a peptide of choice, this peptide will bind the MHC before it disintegrates. Whereas the production of new MHCs takes a couple of days, this ligand exchange only takes one hour. Thus the technique enables the field members to rapidly reload MHCs with a peptide of choice, rather than producing a new batch of loaded MHCs from scratch.[116]

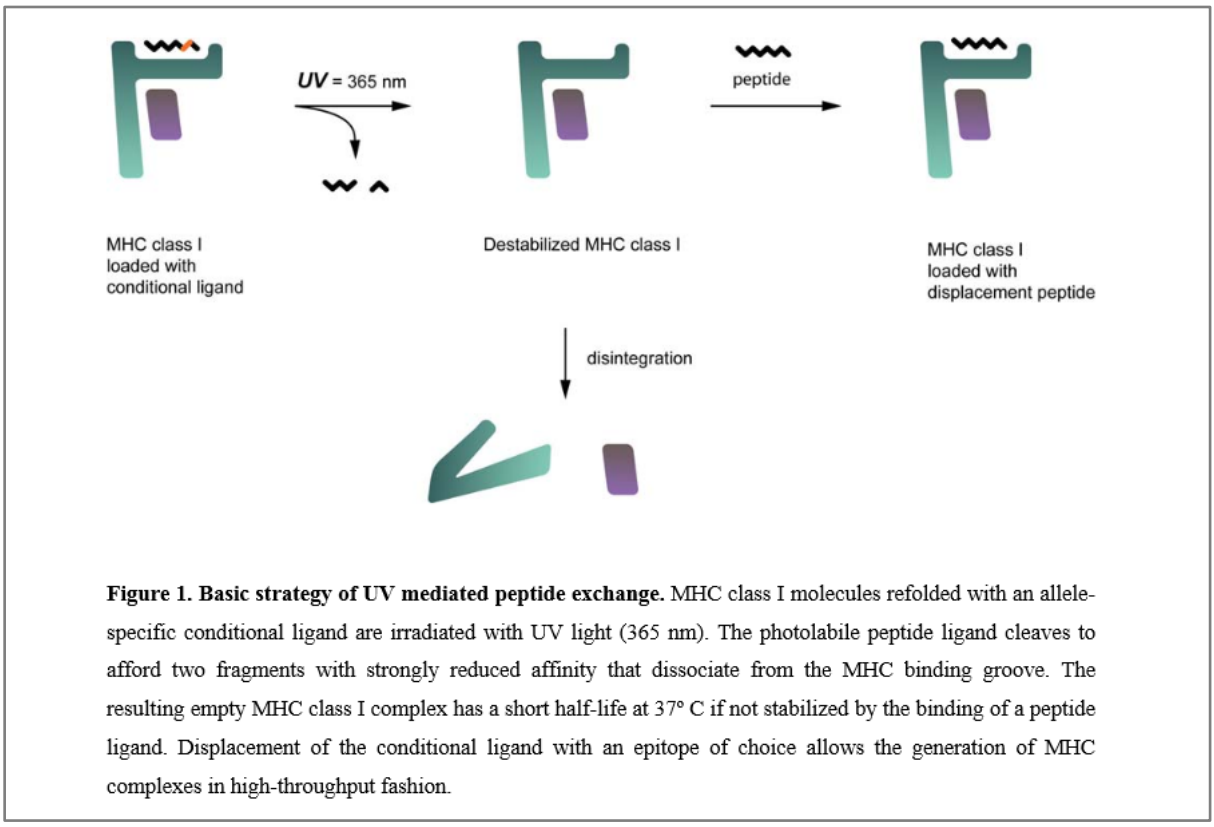

Figure 1. Basic strategy of UV mediated peptide exchange. MHC class I molecules refolded with an allele-specific conditional ligand are irradiated with UV light (365 nm). The photolabile peptide ligand cleaves to afford two fragments with strongly reduced affinity that dissociate from the MHC binding groove. The resulting empty MHC class I complex has a short half-life at 37° C if not stabilized by the binding of a peptide ligand. Displacement of the conditional ligand with an epitope of choice allows the generation of MHC complexes in high-throughput fashion.

Figure 8. An excerpt of the protocol used at B3. The cartoon shows how the loaded MHC can exchange its conditional ligand for a peptide of choice upon UV induced cleavage of the conditional ligand.

To further optimise this technique, my supervisor and I tested newly designed conditional ligands specifically for a MHC type present on mice cells. Upon determining the best candidate ligand, we made a large batch of MHCs loaded with it.[117] As the days passed by, we proceeded in the protocol. In its final methodological instructions the protocol describes how the MHCs can be used to "measure

[116] Appendix 5: List of collected items, item 1.
[117] Appendix 5: List of collected items, item 2.

antigen-specific T cell responses by MHC multimer flow cytometry".[118] For these measurements we needed to couple our neo-antigen loaded MHCs to a fluorescent molecule. Subsequently, we exposed a sample of immune cells to these fluorophore coupled MHCs. To measure whether the immune cells could recognise the presented neo-antigens, we analysed our cells using "flow cytometry".

Analytic technique: Flow cytometry

The field members use a flow cytometer to analyse cells in suspension. The machine sucks up the cell suspension and then guides every individual cell through a beam of lasers. Using laser lights of different wave lengths, it can measure the size of each cell in the sample and it can detect specific fluorescent molecules attached to the cell. In our specific experiment, my supervisor and I would measure the fraction of cells which bound the fluorescent complex of our MHCs presenting the neo-antigen.[119]

Typically the data obtained by flow cytometric analysis are plotted in what the field members call "FACS plots". Examples of such FACS plots are shown in the upper half of figure 7. In FACS plots each dot represents a cell. By placing rectangles and ovals ("gates") in the diagrams, field members further limit their analysis to a certain sub-set of cells in their sample. In our case, each cell in this sub-set was eventually classified as being positive or negative for the fluorescent MHC.[120]

FACS plots were frequently observed representations of data at B3 and hence flow cytometry seems to be an important analytical technique at this division.[121] There are three forms of evidence that further underscore the central role of flow cytometry at B3. Firstly, the members of B3 emphasised the importance of this analytic tool in the questionnaire. In question 13 the field members were asked to list four important techniques they use in their current work. Indeed, 15 out of 22 respondents included flow cytometry in this list. In fact, no other technique was named more often, suggesting it is the division's most important technique.[122]

Secondly, from the entries in the facility's "logbooks" it appeared that B3 is a frequent user of the flow cytometers. For each of the six flow cytometers there is a logbook in which every user has to register his analysis (see **figure 9**). Among others, users have to register their division and during my visits to the facility it struck me multiple times that most logbook entries were from members of B3. Hence I decided to further analyse these entries by counting the number of logbook entries per division. Although one logbook dated back to September 2013, the others only contained entries from August 2014. Members of B3 were responsible for 29 out of 73 entries (40%, see **figure 10**). This is more than twice as much as the second user (Division of Cell Biology II, 18%), indicating that B3 is indeed the main user of the flow cytometers.

[118] Appendix 5: List of collected items, item 1.
[119] FI70. See figure 7.
[120] See figure **7**.
[121] FI113; Appendix 5: List of collected items, item 3 and 4.
[122] Q13. Inclusion criteria: FACS, flow cytometry, flow, cell sorting, FACS sorting.

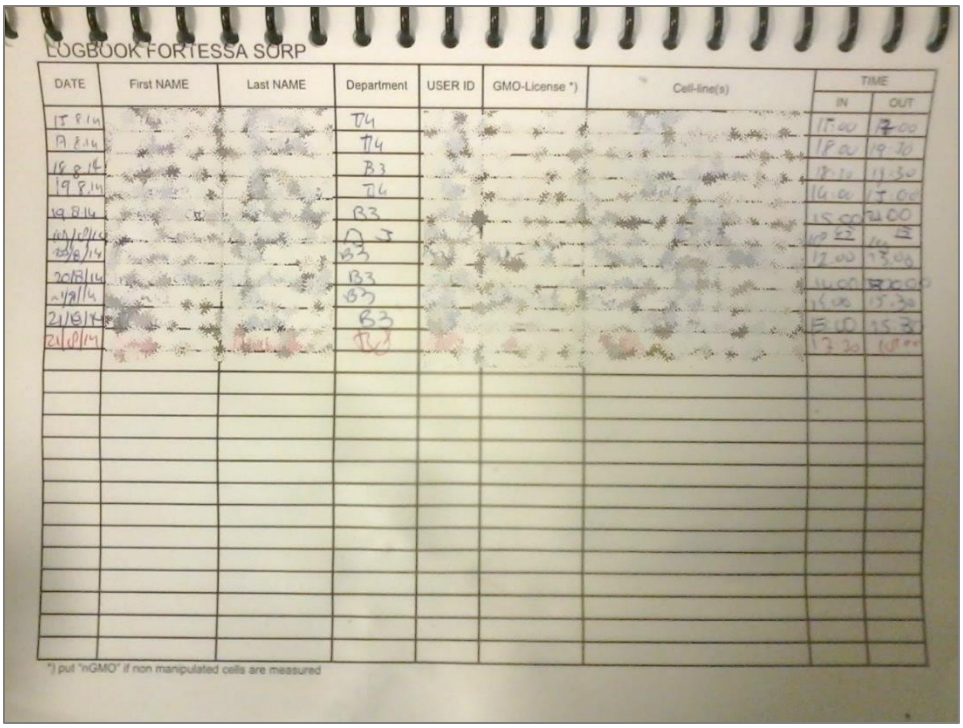

Figure 9. An example of the logbooks used to record the use of flow cytometers. Based on these logbooks could be determined which part of the entries was made by members of B3 (see figure 10). For the sake of privacy, names, user IDs and details are made unreadable.

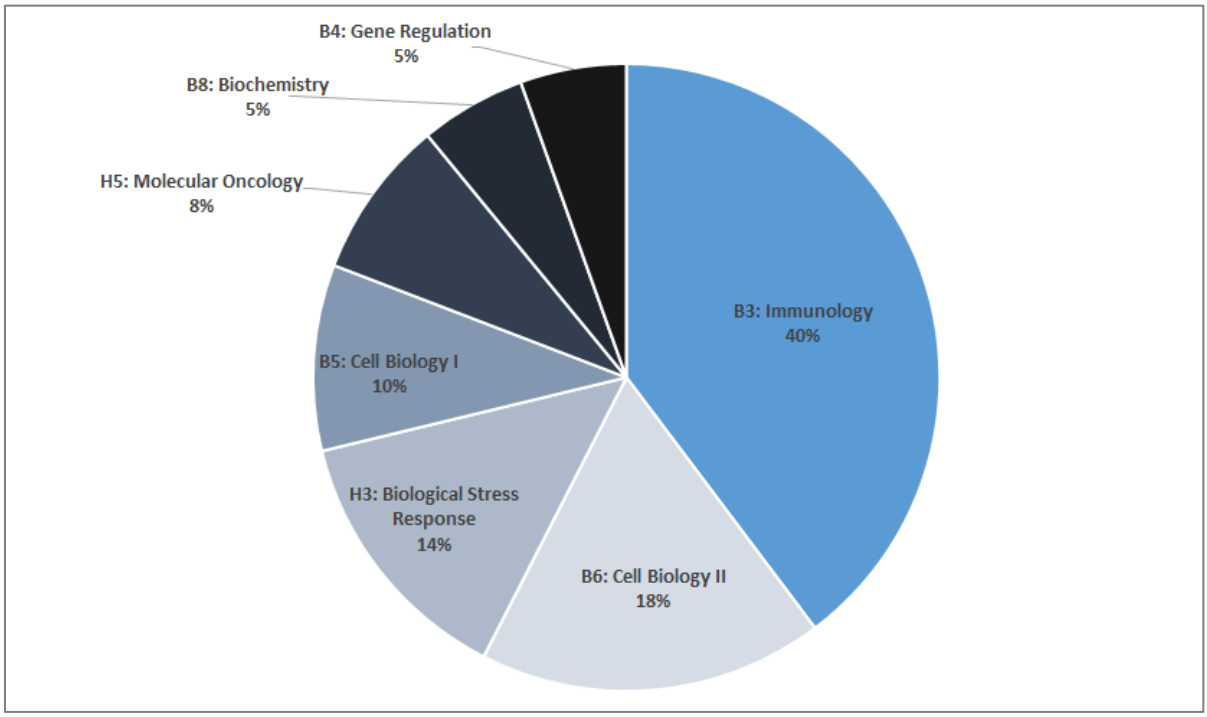

Figure 10. Analysis of logbook entries of the flow cytometers. The entries in the logbooks of the flow cytometers were analysed at 22 August 2014 (see figure 9). Most entries (40%) were from B3 members. The entry dates range from 2 September 2013 to 22 August 2014, but 77% of these entries was made between 11 and 22 August 2014. Total number of analysed entries: 73.

Thirdly, one of the facility's operators also confirmed that members of B3 are indeed frequent users of the flow cytometers. In an informal field interview I asked him who he considers to be the main users of his facility:

> [Observer:]
> Weet u wie de voornaamste gebruikers van deze faciliteit zijn?
>
> [Operator of Flow cytometry facility:]
> Deze faciliteit is beschikbaar voor alle onderzoekers van het NKI, maar eigenlijk zie [je] qua sorteringen… en eigenlijk ook qua analyse dat Immunologie het meest gebruik maakt van de flow.[123]

In the same field interview, I asked the facility's operator why members of B3 are frequent users of the flow cytometers and others are not:

> [Observer:]
> Oke. En hoe denkt u dat dat komt?
>
> [Operator of Flow cytometry facility:]
> Een aantal mensen realiseert zich niet wat er allemaal met de Flow kan. Of ze weten niet hoe het werkt. Ja, en een deel van het onderzoek vraagt niet om de Flow. Ik kan mij stellen dat als je biochemisch werk doet, of eiwitchemie, dat de flow niet zo relevant is.
>
> [Observer:]
> Dus immunologisch onderzoek leent zich goed voor de experimenten op de FACS?
>
> [Operator of Flow cytometry facility:]
> Ja, immunologie doet veel met cellen. En de apparaten zijn daar ook heel geschikt voor. Die zijn primair ontworpen voor lymfocyten. Voor tumorcellen is het toch lastiger. Die zijn onregelmatiger qua vorm.[124]

We further discuss the possibility of staining intracellular molecules rather than the membrane bound molecules such as the TCR. The operator explains that this intracellular staining is possible, but also

[123] FI99. Translation:
[Observer:] Do you know who are the main users of this facility?
[Operator of Flow cytometry facility:] This facility is available for all researchers of the NKI, but in reality, when it comes to sorting… and actually also with regards to the analysis, you see that Immunology uses the flow the most.

[124] FI99-100. Translation:
[Observer:] Okay, and how would you explain this?
[Operator of Flow cytometry facility:] A number of people does not realise the possibilities with the Flow. Or they do not know how it works. Yes, a part of the research does not require the Flow. I could imagine that, when you do biochemical work, or protein chemistry, that the flow is not relevant.
[Observer:] So immunological research suits the experiments performed with the FACS?
[Operator of Flow cytometry facility:] Yes, immunology does a lot with cells. And the machines are very suitable for this. They were primarily invented for lymphocytes. For tumour cells it is harder. Their shape is more irregular.

has multiple downsides. Intracellular staining often involves the chemical fixation of the cell's content and the disruption the cell membrane. Compared to the staining of membrane bound molecules, these procedures are highly toxic and time consuming.[125]

In sum, the operator explicated two technical reasons why B3 is the main user of the Flow cytometry facility. Firstly, members of B3 often study immune cells rather than tumour cells. Being naturally in suspension and regularly shaped, immune cells are suitable for flow cytometric analysis. Secondly, the members of B3 mainly study the membrane bound molecules, which are easier to stain and analyse than intracellular molecules.

Model systems: *In vitro*, patient material and laboratory mice

So far has been described how the members of B3 analyse their samples, but not yet where these samples are derived from. An important part of these samples are "cultured cells". After flow cytometry, "cell culture" is the most often named technique in the questionnaire. Exactly 50% of the respondents working at B3 listed it among the four important techniques.[126]

This common use of cell culture was also observed during the field visits. Following in the footsteps of my supervisor, I entered the dedicated "cell culture labs" almost on a daily basis. These laboratories are filled with multiple "flows" and "incubators" (see **figure 11**). The flows are the cabinets in which the field members can nurture and manipulate their cells in a protected environment. The cells are cultured in the earlier described plates and flasks, filled with pink coloured medium. Although the media may vary in their exact composition, they generally contain nourishment and other biochemical substances the cells need to stay alive and grow. The field members store the plates and flasks in incubators which keep the cells at about 37 Celsius degrees and the level of CO_2 at 5%, circumstances which are supposed to mimic the environment of the human body and needed to enable cell growth.[127]

Figure 11. Pictures from a cell culture lab at B3. The left picture shows "flows", cabinets in which the field members handle the cells they have in culture. The middle and right picture show the "incubators" in which the cells are kept to grow.[128]

The exact kind of cells the members of B3 culture varies highly. During the field visits they were observed to culture tumour cells, certain classes of immune cells or a mixture of several immune cells. To specifically study the interaction between immune cells and tumour cells, the field members

[125] FI99-101.
[126] Q13. Inclusion criteria: cell culture, tissue culture.
[127] FI21-23, 105.
[128] Pictures were made during a later field visit in 2016.

perform “co-cultures”, in which tumour cells and immune cells are cultured in the same plate or flask.[129] Often the cultured cells are directly derived from human material, such as blood or tumours. At B3 there is a constant influx of this material which is collected in the hospital wards of the institute or at the blood bank.[130] If this material is not stored in freezers for later usage, it is taken into culture or analysed directly upon arrival.[131]

Besides cultured cells and (cultured) patient material, the members of B3 use a third kind of model: laboratory mice. Though not as much as cell culture, about a quarter of the questionnaire respondents of B3 listed mouse models among the important techniques they currently use.[132] Although I was not allowed to enter the animal facility,[133] several field observations confirmed that the members of B3 indeed frequently use mouse models in their experiments. First of all, a significant part of my own experimental work, was to analyse the phenotype of murine immune cells. These cells were isolated from the blood of genetically transformed laboratory mice.[134] Secondly, in group discussions the members often referred to data obtained in mice experiments.[135] Thirdly, some of the field members’ (PhD) projects are entirely devoted to developing a new mouse model.[136] For example, in one of the interviews a PhD student explained what kind of mouse model she is developing and why this is needed to address her research question:

> Belangrijk voor ons is, om dit proces van hoe zo'n cytokine, hoe de response op de cytokine zich door een weefsel heen beweegt, eigenlijk. Dat is belangrijk om dat in vivo te doen. [Euhm] Omdat we willen zien hoe snel zo'n signaal verspreidt, hoe ver dat gaat, welke cellen reageren. Of d'r amplificatie zit in zo'n signaal. [Euhm] En daarvoor is het dus, ja, een in vivo model en dan kom je dus al snel bij de muis uit. [Euhm] Dus we kunnen... je, je zou mijn vraag ook wel op celniveau, in een bakje kunnen, kunnen uitzoeken, maar dan weet je natuurlijk nooit echt of dat zo ook real life gebeurd, zeg maar.[137]

Taken together, we have seen that the members of B3 employ and develop methods to manipulate the molecules which mediate cell-cell interactions. Often, these manipulations are applied on cells kept in various culture conditions, including co-cultures. In addition, intercellular interactions are manipulated and studied in mouse models. The samples derived from (cultured) patient material, cultured cells and laboratory mice are most commonly analysed by flow cytometry, which suits the focus on membrane bound molecules.

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[129] FI37, 48, 105-106, 129; II1.5; II4.2-5; II6.4-5, 10.
[130] FI128, 131, 132.
[131] FI48, 129, 131, 132, 137.
[132] Q13. Inclusion criteria: mouse models, intravital imaging, in vivo mouse experiments, mouse transgenics.
[133] To work at a Dutch animal facility, one needs to follow a course in laboratory animal science. I had not done this course at the moment of the field visits.
[134] FI97-99.
[135] FI79, 113, 119, 135-136.
[136] FI135-136; II1.5-7.
[137] II1.6. Translation: Important for us is to [study] how a cytokine, how the response to a cytokine, moves through the tissue. It is important to do this in vivo. Because we want to see how quickly such a signal spreads, how far it goes, which cells respond. Whether there is amplification of the signal. And therefore it is in an in vivo model, and then you quickly end up using the mouse. You could address my question at cellular level, in a dish, but then you never know whether it happens in the same way in real life.

4.2 Analytic tools and models at B7

At B7 my supervisor gave me a protocol which became my guide for the vast majority of the work I would perform there. The 26 pages protocol was titled "LVX ZsGreen Lentiviral pooled shRNA-mir screening libraries" and described how to perform so-called "screens" to identify gene products which influence a tumour cell's survival capacity, for example in the presence of a drug.[138] In general the strategy is to decrease ("knock down") the activity of a specific gene and to subsequently evaluate whether this knock down has a functional effect on the survival capacity of the cell. In our case the gene activity was knocked down by introducing DNA into the cells which codes for so called "shRNAs". Once present in the cell, these shRNAs are able to specifically knock down the activity of a gene by degrading the mRNA. When this knocking down is scaled up to hundreds or even thousands of genes, the experiment is typically called a screen by the field members.[139] In such a screen the target cells are treated with a large pool of different shRNAs, called a "screening library". Each cell will contain one kind of shRNA and thus only one knocked down gene. If the knock down of a certain gene gives a survival advantage, the relative occurrence of cells containing the related shRNA is enriched in the bulk population. Vice versa, if a knock down results in a survival impairment, cells containing the related shRNA are depleted and thus their relative occurrence will decrease. **Figure 12** shows an excerpt of the protocol in which the key steps of the protocol are visualised.[140]

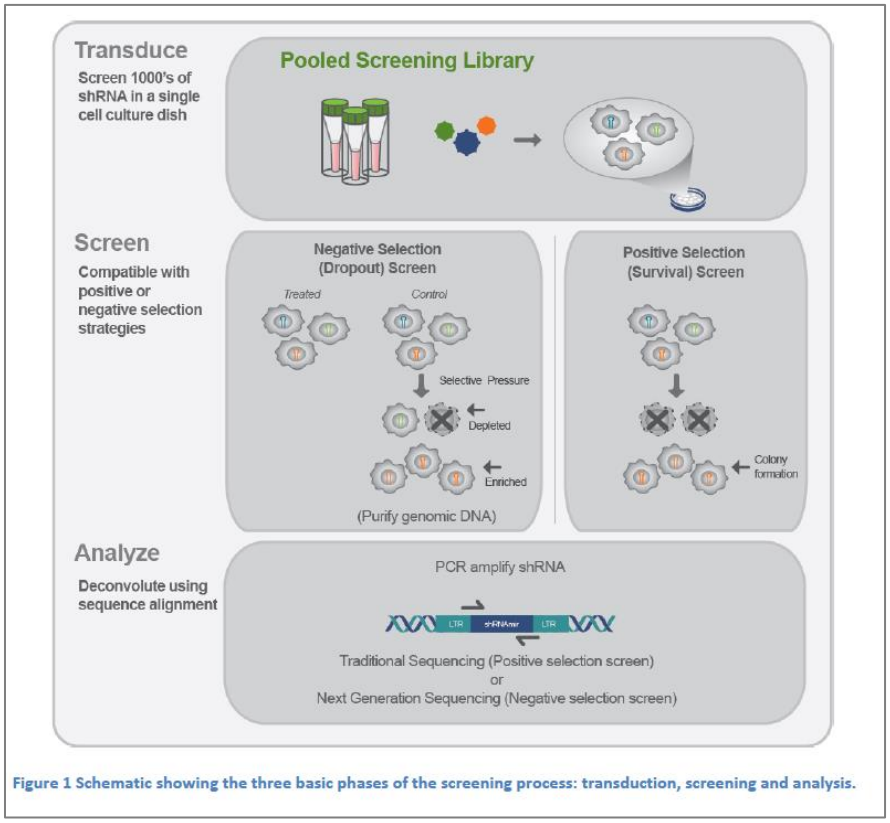

Figure 12. An excerpt from the protocol used at B7. The cartoon shows the basic steps of a "screen" in which a large set of genes is "knocked down" to identify genes involved in, for example, drug resistance.[141]

[138] FM11; Appendix 5: List of collected items, item 5.
[139] FM23-24.
[140] Appendix 5: List of collected items, item 5.
[141] Appendix 5: List of collected items, item 5.

When I entered B7, the first steps of a screen were already done. The goal of this screen was to find genes which play a role in the resistance to the chemotherapeutic oxaliplatin. A cell line resistant to this drug was treated with a screening library and subsequently exposed to oxaliplatin. Cells in which the knock down disrupted the resistance mechanism to this drug were expected to be depleted from the population.[142] My task was to amplify the genetic material coding for the shRNAs, to prepare the samples for the analysis.[143] The method the protocol described for this amplification was a series of "PCRs" (polymerase chain reactions). Subsequently the relative occurrence of each kind of shRNA was measured by a method called "sequencing".[144]

Analytic technique: Sequencing

Like flow cytometry, sequencing requires the usage of expensive and sophisticated machines, which are situated in yet another facility at the institute: the Genomics core facility.[145] In sequencing, the chemical properties of DNA molecules are translated into a sequence consisting of the letters A, T, C and G. Sequencing machines do not only detect the various sequences in a sample, but also count the relative occurrence of all these sequences. Simply, if a certain sequence is not common in a sample, the sequencing machine will detect that sequence less often. Thus, sequencing could be used to quantify the relative occurrence of each shRNA in our screening samples.[146]

Following sequencing, the large data set was processed and analysed by one of the division's bioinformaticians. The results of his analysis are shown in the lower half of figure 7. Like with flow cytometry, the data are presented in the form of a cloud of dots. However, in this case each dot does not represent an individual cell, but rather a specific shRNA targeting a certain gene. Once the relative occurrence of shRNAs targeting a certain gene meet up with defined statistical standards, the gene is called a "hit". In our case the only hit was the gene *ATR*. From this result my supervisor and I inferred that in cells in which *ATR* was knocked down, resistance to oxaliplatin was lost. In other words, the oxaliplatin resistance of the studied cells seemed to rely partly on *ATR* expression.

During the field visits it became clear that not only me and my supervisor were performing screens. Variants on the screening strategy described above are performed routinely at B7.[147] Accordingly, sequencing is an important analytic tool at this division. Besides these plain field observations, there are three forms of data that further underscore the central role sequencing plays in the work of B7.

Firstly, in the questionnaire almost half of the field members of B7 mentioned sequencing as one of the important techniques they employ in their work. No other analytic technique was mentioned more often.[148] Secondly, in the seminar room of B7 the laboratory manager put up an overview of the laboratory's spending in 2013.[149] Sequencing is by far the biggest expense at B7. The overview shows that € 417.000 was spend on this form of analysis, which makes up 42% of their total laboratory

[142] FM72.
[143] Appendix 5: List of collected items, item 6.
[144] FM72; Appendix 5: List of collected items, item 5.
[145] FM62.
[146] FM72; Appendix 5: List of collected items, item 5.
[147] FM23, 43, 64, 73, 74, 119-120.
[148] Q13. Inclusion criteria: deep sequencing, NGS, next generation sequencing, sanger sequencing, RNA sequencing.
[149] IM2.12.

costs.[150] Thirdly, there seem to exist relatively tight social links between the division and the sequencing facility, not in the last place because the current head of the facility previously worked at B7.[151] For example, when my supervisor and I went there to hand in our samples on a Friday, there was a sign on the facility's door saying "See you next week". Samples are normally only accepted on Thursdays. Nevertheless, the facility's head and one of his colleagues accepted our samples without any hassle and subsequently my supervisor had a rather long chat with them about various personal affairs.[152] A comparable sequence of events was observed when we handed in the samples of our second screen, again on a Friday.[153] That is not to say that the facility's operators would not have such contacts with members of other divisions, but surely they seem to be on good terms with B7.

Model systems: *In vitro* we trust

In general, the field members have been very willing to share important information with the observer, but in the case of their model systems the members of B7 could not have been more clear. When entering B7, one cannot miss the luminous art work which hangs next to the entrance of the division. In the brightest neon letters the visitor is acquainted with the motto of the division: "In vitro we trust" (see **figure 13**).[154]

Figure 13. The motto of B7 as shown at the entrance of the division.

However, also in another setting, the members of B7 expressed that the *in vitro* cell cultures are their main model system. In the questionnaire 60% of the B7 members indicated that cell culture is among their important research techniques, exceeding any other technique.[155] Also when asked in the interviews, the field members would stress without exception the importance of cell culture.[156] One interviewee told me that B7 is a major consumer of cell culture material, such as culture plates and flasks. When trashed, this material is collected separately and, according to this interviewee, B7

[150] Appendix 5: List of collected items, item 8.
[151] FM120. Additional note: at the facility's office there is put up a group picture taken of a lab outing of B7, in which also the facility's head joined (also at FM120).
[152] FM62-64.
[153] FM120.
[154] FM48.
[155] Q13. Inclusion criteria: cell culture, tissue culture.
[156] IM1.25; IM2.61; IM4.12; IM6:10; IM7.20-22.

produces 7-10 times as much of this waste compared to other divisions.[157] These self-reports were certainly consistent with the field observations. Besides that the input material of my own work consisted of *in vitro* cultured cells, the field members themselves were observed to frequently work with these model systems as well.[158] Consistently, also at B7 there are multiple culture labs, which contain the same equipment as the culture labs at B3 (see **figure 14**).

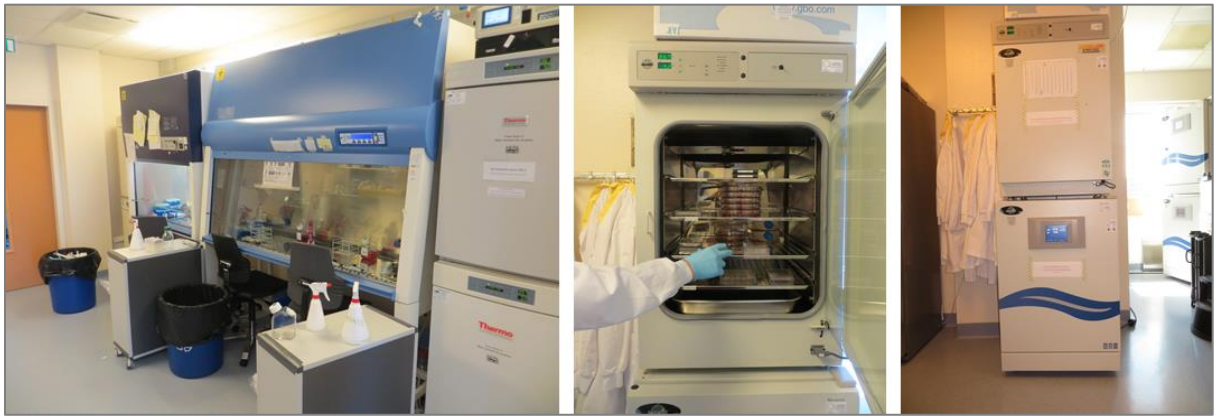

Figure 14. Pictures from a cell culture lab at B7. At face value the culture labs of B3 and B7 do not seem to differ (see figure 11), but the cell types that are cultured differ considerably.[159]

However, the spectrum of cultured material at B7 was diverse in a different way compared to B3. During the field visits the field members were not observed using patient material in their work. Only twice an interviewee told me that there is an ongoing project in which patient material was used as a model system.[160] At B7 the cultured material consists almost completely out of established tumour cell lines. The variety lies in the number of different tumour cell lines that is used, which can be up to 30 in one experiment.[161]

Additionally, B7 differed from B3 also with respect to *in vivo* experiments. At B7 the field members were not observed performing any mouse experiments. Both in the interviews and in the questionnaire, the field members did not report using mice as their experimental model.[162] Only during one of the field visits I made to B7, during which I attended a group meeting, I observed a field member discussing an *in vivo* experiment.[163] If mouse experiments are needed or requested by a peer reviewer, members of B7 mostly set up a collaborations with others, either inside or outside the institute.[164] One of the interviewed postdocs describes how and why their division depends on such collaborations, even when division members do have experience with *in vivo* studies:

> [Interviewer:]
> What kind of knowledge would people from this division need… what kind of… or knowledge, or skills do they need from their collaborators?

[157] IM2.21.
[158] FM17, 34, 43, 72, 74, 87, 95, 113, 118-119.
[159] Pictures were made during a later field visit in 2016.
[160] IM2.61; IM6.09.
[161] FM87; IM1.02; IM3.06-07; IM5.10.
[162] Q13. Inclusion criteria: mouse models, intravital imaging, in vivo mouse experiments, mouse transgenics.
[163] FM72.
[164] IM4.12, 4.25; IM5.48-49; IM6.42.

> [Interviewed postdoc:]
> One most obvious one is mouse work for follow up. Also clinical trials for follow up. We're not specialists in either one of those. You know, there are a few people in our division who have a background in mouse studies, like X and Y. They worked with mice in their PhDs. But now I guess it's a bit more of a struggle for them to do mouse work here, because we don't have the lab facilities within the animal house, for example. So they have to set it up from scratch. And most likely in collaboration with another lab that does this, to streamline the process. So, that's something that we think we cannot do ourselves. We rely on collaborators.[165]

Given these kinds of difficulties it seems convenient that the members of B7 can put their trust in their *in vitro* systems. In (informal) interviews I discussed with field members why these systems are such reliable models in their work. Frequently field members emphasised that the *in vitro* conditions rather poorly mimic the physiological conditions present in a tumour, but they still believe that their *in vitro* studies provide important, fundamental insights. The field members argued that the molecular processes they study are so fundamental or "hard wired" that they can be studied outside their normal physiological environment.[166] The following illustrative quote was given by one of B7's group leaders:

> En daarom begon ik eigenlijk ook om te zeggen dat veel van de pathways waar wij geïnteresseerd in zijn, die zijn hard wired. Dus dat betekent dat als je iets doet in weefselkweek in die pathways, dan meet je daar heel makkelijk de consequentie van, dat is veel moeilijker in de muis te meten, maar in die muis gaat het ook gebeuren.[167]

4.3 Concluding remarks

The previous two sections of this chapter do not do justice to the broad variety of techniques employed at both divisions. Nevertheless, regarding the divisions' most important techniques, we have seen two important methodological differences. To start with, the members of B3 and B7 differ in their main analytical tools. At B3 the most common form of analysis is flow cytometry, while at B7 sequencing takes centre stage. This methodological difference ties in with the differences at the axiological and theoretical level discussed in the previous chapters. The members of both divisions aim to elucidate different processes and postulate different theories to explain these processes. Flow cytometry is particularly suited for the characterisation of the molecules at the membrane of immune cells. Therefore, flow cytometry provides useful information for the members of B3, who mainly postulate theories concerning the molecules mediating intercellular interactions. Conversely, sequencing reveals the genetic information which cells harbour in their DNA. Consequently, the members of B7 use it to

[165] IM5.48-49 (at the request of the interviewee this transcript was edited to improve its readability). Note: When this quote was sent to the interviewee for approval in 2016, the interviewee noted that nowadays several members of B7 are setting up and performing mouse experiments, thanks also to the Mouse Intervention Unit being established. Thus, the situation at B7 has changed considerably in this respect over the past two years.

[166] FM48-49; FM118; IM1.24-25; IM3.07, 3.12-18; IM6.12; IM7.26.

[167] IM7.26. Translation: And therefore I started saying that many of the pathways we are interested in, are hard wired. So, if you do something with these pathways in tissue culture, than you can easily measure the consequence. That is harder to measure in the mouse, but it will happen too in the mouse.

identify relations between (experimentally induced) genetic modifications and the survival capacity of tumour cells.

However, this methodological difference is not like day and night. Members of B3 were also observed exploiting the possibilities of sequencing analysis, for example to predict what kind of neo-antigens a certain tumour will present.[168] Consistently, in the questionnaire members of B3 rather frequently list sequencing among the important techniques they use (23%).[169] On the contrary, regarding the flow cytometry there is no such methodological overlap. The data presented in figure 10 indicate that B7 is indeed not a frequent user of the flow cytometers. Additionally, during the field visits, in the interviews and in the questionnaires no indications were found that the members of B7 use flow cytometry as an analytic tool.[170]

The second methodological difference concerns the model systems in which the field members perform their experiments. On the one hand, the members of B3 use a rather broad range of model systems, including *in vitro* cultured cell lines, patient material, co-cultures and mouse models. On the other hand, the members of B7 perform virtually all their work in a broad range of *in vitro* cultured cell lines. To further understand this difference, it is useful to recall Latour's account of the scientific method.

Consistent with Latour's account, we have seen that at both divisions the members reduce their object of study (the body of the cancer patient) to manageable model systems. However, the difference between B3 and B7 is that the members of B7 go further in this reduction. At B7 the complex body of the cancer patient is boiled down to the uncontrolled proliferating cancer cell. The model systems used by B3 show higher levels of complexity, often consisting of a mixture of cell types (co-cultures and patient material) or even a complete organism (mice). Compared to the models of B3, the mono-cultured cell lines of B7 lost more multiplicity and particularity. The difference between these cell lines and the patients they were once derived from, is bigger than the difference between the patient and her tumour material that enters B3 directly from the hospital wards.[171]

As Latour points out, such highly reduced models are not necessarily disadvantageous. What the models used at B7 lost in multiplicity and particularity, they gained in terms of universality and standardisation.[172] The cell lines are a rather universal model for a certain cancer type, while the patient samples merely represent a particular patient. On top of that, the variability between two samples of the same cell line is smaller than the variability between two patient samples. Therefore the usage of cell lines helps the members of B7 to standardise their experiments. Using more complex, particular models may introduce a level of variability that impairs their view on the universal, molecular "hard wire" of cancer cells that is believed to underlie tumour formation and therapy resistance.

[168] FI93; FI106; FI141; Appendix 5: List of collected items, item 3.
[169] Q13. Inclusion criteria: deep sequencing, NGS, next generation sequencing, sanger sequencing, RNA sequencing.
[170] Q13. Inclusion criteria: FACS, flow cytometry, flow, cell sorting, FACS sorting.
[171] Latour, "Circulating Reference," 24-79.
[172] Latour, "Circulating Reference," 70-71.

5. Social level

When my six weeks at B3 came to an end, I took the elevator to start four floors higher at B7. Interestingly, I experienced my start at B7 as an introduction to a completely new field site. As discussed in the previous chapters, the members of B7 aim to develop different therapies, postulate different theories and predominantly use different methods. But most of all, it felt like I entered a new social circle. When I arrived at B7, virtually all division members were new to me. During my stays at both divisions, I predominantly had contact with the members of the respective divisions. Even when we left the division for a seminar in the auditorium, a lunch in the restaurant or a "lab outing" in the outdoors, we did this together with division mates.[173] Thus, the divisions do not only organise the experimental work performed at the institute, but also the social relations.

Many of the interviewed field members also experience a distinction between the divisions. Members of B3 often described their division as an "eilandje" or a "vreemde eend in de bijt".[174] The members of B7 came up with similar descriptions and would characterize B3 as "een eigen wereldje" or "een andere tak van sport".[175] Interestingly, B7 was never described in such terminology, indicating that B3 is seen as the exceptional case at the institute. The aim of this chapter is to verify the interviewees' perception that B3 is an isolated island. Section 5.1 will discuss field data in favour of this perception, whereas Section 5.2 will deal with the evidence against it. Subsequently, in Section 5.3, it will be discussed how the findings of this chapter tie in with the previously described differences and similarities and, as such, it will form the concluding section of Part I.

[173] FI27, 72, 32, 43, 45, 65, 77, 130, 129; FM38-39, 53-54, 114, 116.
[174] II1.24, 34-35; II2.13, 15, 33; II3.4; II4.22, 51; II7.23, 31.
[175] IM2.53; IM3.53; IM4.29; IM5.53; IM6.49.

5.1 B3 as an island

According to many of the interviewed members of B3, the other research divisions have more overlap in their work, which would be an explanation for their own perception of relative distinction from these divisions.[176] The common dominator between all the other divisions would be their focus on intracellular, molecular processes, whereas the members of B3 are mainly interested in intercellular interactions.[177] Thus the difference we have seen between B3 and B7 would be exemplary for the difference between B3 and the other research divisions in general. For example, one of the interviewees describes the difference as follows:

> So I think that, that we are very focussed on cell biology of the immune cells. So I mean it is not that we're only interested in one type of immune cells, but in general it's just the immune system and how that works during cancer. And how it interacts with the tumours. Whereas I think that a lot of other focus in the institute is on the cancer cell with molecular biology. So it's really going into the cell and understanding mechanisms within the cell, the signalling pathways, [euhm] the genetics of the cancer cell. And understanding these more [euhm] molecular mechanisms within the cancer cell.[178]

Accordingly, several field observations confirm that B7 is not an exception with its intracellular, molecular focus. Most obviously, this is reflected in the nomenclature of the institute's research divisions. Besides B7 (Molecular Carcinogenesis), the institute has multiple divisions which have the adjective "molecular" in the name, such as the Division of Molecular Genetics.[179] Conversely, there is just one division with an immunological signature: B3.

More importantly, during the Research Clubs and other institute-wide seminars, the researchers of other divisions were frequently observed to present work on intracellular molecules, including signalling proteins and DNA.[180] The jargon employed at B7 resonated in these presentations of other divisions, which would also deal with "synthetic lethality" or oncogenic "drivers".[181] On the other hand, only once a non-immunological division was observed to present work on immune cells, which happened to be in close collaboration with one of B3's research groups.[182] Other presenters would pay lip service to the importance of immunological processes,[183] but more often they did not take immunological aspects into account at all.[184]

However, these institute-wide seminars are not meant to further emphasise the disciplinary differences. Rather, several field members claim that the seminars are supposed to bridge the gaps between the various divisions and approaches the institute harbours.[185] To verify whether these seminars indeed execute this function, the attendance of field members was recorded during the field

[176] II1.35; II2.33-35; II3.4; II4.23, 38-39, 45, 51; II6.46.
[177] II1.35; II2.33-35; II4.38-39, 45; II6.46.
[178] II2.33-34.
[179] FM99.
[180] FI123; FM10, 46, 59, 80, 99, 102, 103, 112.
[181] FM59, 103.
[182] FM101-102, 104.
[183] FM10, 40, 103, 114.
[184] FI123, FM45-46, 59, 80, 87-89, 99, 103, 114-115.
[185] II2.42; II4.43; II7.33; IM2.44; IM6.69.

visits between 16 September and 16 October 2014. For a total of 14 talks the number of attendees per division was scored and analysed. These talks included Research Clubs, but also several seminars in which external researchers were invited to present their work. All these institute-wide seminars are announced in a weekly e-mail send to all researchers of the institute.[186] Typically between 40 and 70 people would attend such a seminar, while the total number of researchers at the institute is about 650.[187] The left bars of **figure 15** show that on average 7.7 and 9.6 members of respectively B3 and B7 were present, which both have about 50 members. However, between seminars the number of attendees per division differed dramatically, ranging from 0 up to 20. In other words, the field members do not randomly visit a fraction of the seminars. Instead, they are rather selective in their attendance of seminars.

The most obvious pattern in their selection is that the field members tend to visits seminars more often when a division mate is one of the speakers or the host of an external speaker (figure 15, middle and right bars). This holds especially for the members of B3, which were observed to visit 4.4 times more often a seminar in which a representative of their division is speaking or hosting. For the members of B7 this factor is less pronounced (2.4), but nevertheless their attendance shows the same tendency.

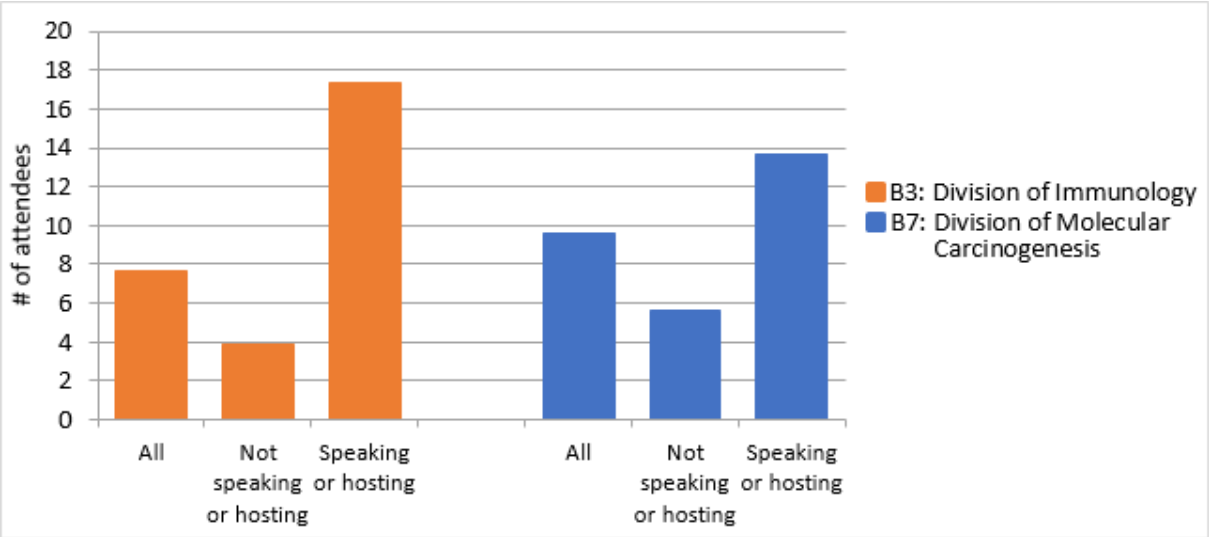

Figure 15. Attendance at seminars per division. Between 16 September and 16 October 2014 the number of attendees was scored for 14 institute-wide seminars. The left bars of both series indicate the average number of attendees per division. The middle and right bars show that members of both divisions tend to visit more often seminars in which at least one of the speakers or the host is from their own division. For B3 the difference is a factor 4.4 (17.3/3.9 = 4.4). For B7 the difference is less big; a factor 2.4 (13.7/5.6 = 2.4).

To further understand this tendency, I also collected qualitative data on the field members' motivations to attend or skip a certain seminar. Interestingly, the interviewees of both divisions reported that an important motivation to go to a seminar is to support their collaborators or befriended colleagues.[188] In one of the interviews a technician of B3 explains why she only visits the Research Club if a division mate is presenting:

[186] IM122; II2.41.
[187] FI123; FM10, 46; Nathalie Grotenhuis, *Dit was het nieuws: Populair jaarbericht 2014 Antoni van Leeuwenhoek*, Amsterdam: Antoni van Leeuwenhoek (2015), 12.
[188] II2.41; II6.37, 41-42; IM5.61, 63.

[Interviewer:]
Ga je vaak naar de wekelijkse Research Clubs?

[Technician working at B3:]
Nee. Op het begin weleens, maar ik vind het eigenlijk gewoon te veel meetings. Wij hebben op de afdeling natuurlijk wel best wel wat meetings. En dan kom je haast niet meer aan research doen toe, vind ik, als je ook daar nog twee keer in de week heen gaat. Wel weer als het inderdaad iemand is van onze afdeling, dan vaak wel, maar niet, eigenlijk anders niet. Nee.

[Interviewer:]
En waarom ga je wel als iemand van jouw afdeling…

[Technician working at B3:]
Nouja weer een beetje hetzelfde als met de stafavond. Dat je toch... Ja, ik vind het gewoon leuk om te horen hoe mensen dat dan doen en gewoon, ja, ben daar wel geïnteresseerd in. En [euh], ja, ook dat je laat weten inderdaad dat je, dat je... [euh], dat zo iemand er niet alleen of zo voor staat. Hoe zeg je dat? Zeg maar dat niet één iemand alleen van de afdeling en dan zit er vervolgens niemand van zijn afdeling. Dat is toch een beetje lullig denk ik.[189]

In his review article "Social Cohesion", sociologist Noah Friedkin classifies such an individual's expression of loyalty towards group mates as an example of "positive membership attitudes".[190] Positive membership attitudes are seen as indicators of strong cohesion in a social unit.[191] Taking into account that the divisions operate as the main social units of the institute, the social cohesion among division mates may indeed clarify the field members' tendency to visit mainly seminars of their own division. However, could this line of reasoning also explain why members of B3 have this tendency even more strongly than members of B7? In other words, is the social cohesion at B3 stronger than at B7?

Although social cohesion is harder to quantify than attendance at seminars, there are three classes of observations that point into this direction. Firstly, at B3 the field members spend a lot of time on discussing their work with their division mates. Besides the weekly group meetings, there are several sub-group meetings, such as the "TCR meeting" or the "MHC meeting".[192] Furthermore, there are

[189] II6.41-42. Translation:
[Interviewer:] Do you often visit the weekly Research Clubs?
[Technician working at B3:] No. At the beginning I did sometimes, but actually I think there are too many meetings. At our division we have quite a lot of meetings. And then there is hardly no time left for research, if you also visit that twice a week. I do go when someone of our division speaks, but otherwise I don't. No.
[Interviewer:] And why do you go if someone of your division…
[Technician working at B3:] Well, like with the staff evening. I find it just nice to hear how people do that, and I am just interested. And, yes, also to show that this person does not stand alone. How to say that? Like, that there is not just one person of our division and then nobody else of our division. That would be a bit pathetic, I think.
[190] Noah E. Friedkin, "Social Cohesion", *Annual Review of Sociology* 30 (2004), 409-425.
[191] Friedkin, "Social Cohesion", 409-425.
[192] FI28-29, 30, 37, 43-44, 59-60, 79-81, 94-95, 113-115, 119, 120, 129.

journal clubs and weekly meetings with the full division.[193] In the footsteps of my supervisor I attended three or four of these meetings per week at B3.[194] Conversely, at B7 I had to attend only the weekly "lunch meeting", in which three of the four research groups combined all their work discussions.[195]

Secondly, in addition to their work discussions, the members of B3 regularly gathered in their meeting room for other activities, such as celebrating a birthday and eating cake.[196] More than once during my stay, the field members would meet outside the institute for picnics in one of Amsterdam's parks or sportive activities during a lab outing.[197] Certainly, also at B7 the members would get together for drinks on Friday afternoons or to have a lab outing, but not as frequently as the members of B3.[198]

Thirdly, in chitchat or interviews the members of B3 would frequently state that B3 is "exceptional social" compared to other divisions or laboratories.[199] Again, such expressions could be considered as positive membership attitudes.[200] Members of B7 also have a positive attitude towards the atmosphere at their division, which they described as "wel prettig" or "relaxt".[201] However, they did not stress this as explicitly and strongly as the members of B3. Thus, compared to B7, there seems to be a higher level of social cohesion and therefore of loyalty at B3. This, in turn, may explain B3's relatively strong tendency to selectively visit seminars in which their division mates take centre stage.

However, another possible explanation could be that the members of B3 partly lack the background knowledge which is needed to fully appreciate seminars of other divisions. Two members of B3 reported that others sometimes assume too much background knowledge regarding intracellular pathways. As a consequence, they do not understand the talk and they experience their attendance as a waste of time.[202] Likewise, interviewees of B7 admitted that they have difficulties to understand the work of immunologists.[203]

This difference in background knowledge can be traced back to the educational careers of the field members. In the questionnaire 50% of the members of B3 indicated that they already specialised into immunology during their training, while only one (out of 15) respondents from B7 reported this.[204] Interestingly, the opposite pattern was found for specialisation in oncology. At B7 a majority of 64% specialised during their training in what they defined as "oncology" or "cancer", while at B3 this was only 18%. This early stratification may contribute to a lack of overlapping background knowledge between members of different divisions and thus to mutual misunderstanding.[205] For example, one of

[193] FI119; II2.38; II6.40.
[194] FI30, 37, 43-44, 59-60, 79-81, 94-95, 113-115, 119, 120, 129.
[195] FM16, 73, 83.
[196] FI43, 45, 65, 77-78.
[197] FI32-33, 143; FM59.
[198] FM38-39, 65.
[199] FI46, 67; FM59, 105; II1.14; II2.49; II6.35.
[200] Friedkin, "Social Cohesion", 409-425.
[201] IM1.13-14; IM2.42; IM3.31-32; IM4.36. Translation: "rather pleasant" or "relaxed".
[202] FI123; II2.14-5, 38.
[203] IM5.55-58; IM6.49.
[204] Q4; Q5. Inclusion criteria (including PhD training): immunology, tumour immunology, cancer immunotherapy.
[205] Q4; Q5. Inclusion criteria (including PhD training): oncology, cancer, metastasis, tumor immunology, PI3K signaling.

the interviewed postdocs of B7 explains how her educational background in "oncology" differs from the background of tumour immunologists:

> Immunology... Oncology. Well, with all my training, I can sort of follow everything that we do here at the NKI. But when it comes to immunology my background is at undergraduate level. So, I know there are different cell types, etcetera, etcetera. But I couldn't possibly tell you right now anything that would be reliable as to the functions and interactions of these immune cells. You need that in depth understanding to work out how the whole immune system works, what feedback mechanisms are there and whether modulating a certain factor makes it perform differently. So, you need a lot of background to understand how to modulate it. I think I certainly don't have it. And I don't think most people here do either. Unless they did some project before within immunology, I don't think they have this background.[206]

Interestingly this quote does not only describe how disciplinary boundaries may have their roots in educational systems, it also exemplifies a common dichotomy in the fieldmembers' perception on the disciplinary landscape: immunology *versus* oncology. (Tumour) immunology is not seen as an expertise within oncology, but as something disctinct from it. Being an expert in tumour immunology does not imply being an expert in oncology, and vice versa. However, this dichotomous perception is most clearly shown by a close analysis of the answers to question 16 of the questionnaire.

In question 16 the field members were asked to draw a schematic map of the disciplines within cancer research and their interrelations. Two exemplary answers to this question are shown in the top row of **figure 16**. To analyse the answers to this question, the individual maps were classified according to their contents. To start with, it was determined how many maps contained the word "molecular biology" or anything related, such as "genomics" or "targeted therapy".[207] As shown in the middle row of figure 16, at both divisions more than three-quarter of the answers to this question included molecular biology. The same kind of analysis was performed for the words "immunology" or "immunotherapy". Unsurprisingly, almost all members of B3 who answered this question included immunology, as shown in the bottom row of figure 16. However, the respondents from B7 included this discipline in less than a half of the cases. In an implicit way many members of B7 exclude the immunologists from the oncological domain.

In this section we have seen multiple reasons why B3 indeed could be perceived as a relatively isolated division. Firstly, because most divisions share an interest in intracellular, molecular mechanisms, the immunologists' perspective is exceptional. Secondly, members of both divisions differ in their background knowledge, which can be traced back to an early specialisation during their studies. As a consequence, the field members experience difficulties in appreciating each other's work. Thirdly, a considerable part of the members of B7 does not think of tumour immunology as a sub-discipline within cancer research. Lastly, the institute-wide seminars do not optimally function as a bridge between the various divisions, as the field members predominantly visit the seminars of their division

[206] IM5.54-56 (at the request of the interviewee this transcript was edited to improve its readability).
[207] Q16. Inclusion criteria molecular biology: molecular biology, genomics, genetics, signalling, molecular carcinogenesis, targeted therapy. Inclusion criteria immunology: immunology, immunotherapy.

mates. The latter tendency is especially strong among the members working at B3. Grouped together at their immunological island, the members of B3 show a high level of social cohesion.

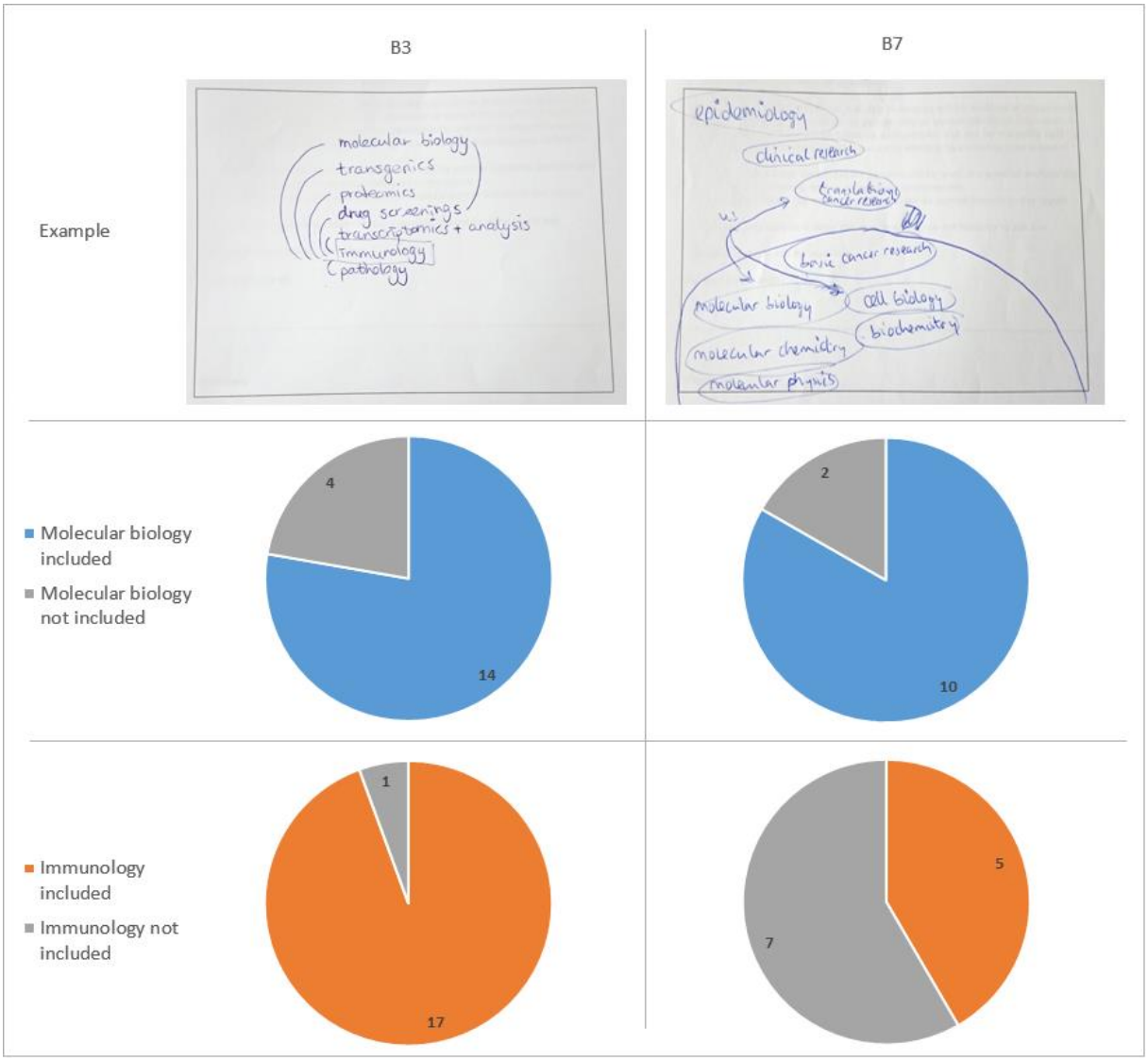

Figure 16. Analysis of schematic maps of disciplines in cancer research drawn by field members. In question 16 of the questionnaire the field members were asked to draw a schematic map in which they depict the disciplines in cancer research and their interrelations. The upper row shows two exemplary answers of a member of B3 and B7. The middle row shows that at both divisions more than three-quarter of the field members included molecular biology in the map. The lower row shows that the members of B3 almost all included immunology, while the members of B7 did this in less than half of the cases. Numbers depict absolute numbers of answers classified in a certain category. Unanswered questions were excluded from this analysis.[208]

[208] Q16. Inclusion criteria molecular biology: molecular biology, genomics, genetics, signalling, molecular carcinogenesis, targeted therapy. Inclusion criteria immunology: immunology, immunotherapy.

5.2 B3 as part of the main land

In the previous section we have seen which data we could find in support of the field members' perception that B3 is an island. However, in the preceding chapters we have seen that, in several ways, the members of B3 incorporated molecular theory and methodology. Furthermore, the field members shared a common goal: improving cancer therapy. In the upcoming section it will be assessed whether these similarities provide enough common ground to establish interdisciplinary relations with other divisions or even beyond the walls of the institute. To start with, according to one of the group leaders working at B3, there is indeed enough common ground nowadays, which he explains as follows:

> Ja, voor een deel is dat toch voortgekomen uit [euhm]. Ja, hoe zal ik het zeggen? Ik denk, als je in de tijd kijkt... Het begint allemaal uiteindelijk met, met hele brede observaties, van, van immuun responsen. Vervolgens is dat omgezet in wat nu die moleculen, wat die cellen zijn die daarvoor verantwoordelijk zijn. Hè, er zijn verschillende celsubsets gedefinieerd. Vervolgens, wat zijn nu de moleculen op die cellen die daarvoor verantwoordelijk zijn geweest? Dus niet alleen maar T cel-receptor en MHC moleculen, maar ook de co-stimulatoire en co-inhibitoire moleculen. En op het moment dat er daar een redelijke kennis over was, heeft dat geleid tot ontwikkeling van [euh] van antilichamen die vervolgens in, in allerlei proefdiermodellen getest konden worden om te kijken wat hun effect was. [Euhm] En ik denk op moment dat immunologie dat stadium had bereikt, hè, en dat je aan iemand van een ander veld kunt uitleggen: [euhm] PD1 is een negatieve regulator van T cel-activiteit, op het moment dat we die negatieve regulator blokkeren, hebben we meer actieve T cellen, kan ook iemand uit een ander onderzoeksveld moleculair begrijpen wat het proposed mechanism of action is. Hè, dus dan kom je uiteindelijk op dezelfde taal kom je uit.[209]

According to this group leader, the molecular approach provides nothing less than a lingua franca which facilitates interdisciplinary communication. In this quote he particularly describes the proposed molecular mechanism of the immunotherapeutic nivolumab, which only recently entered the clinic. The development of nivolumab is generally considered to be part of a series of clinical successes tumour immunologists have been achieving from 2010 onwards.[210] Certainly, this particular successes grabbed the attention of the members of B7. Although members of B7 frequently omitted to include immunology into their disciplinary map, most seemed to be aware of these immunologists' clinical

[209] II3.40-42. Translation: Yes, to some extent that arose from. Yeah, how to say that? I think, when you look throughout the time… It all starts with broad observations of immune responses. Then this is translated into the molecules, the cells that are responsible for this. Hè, several cell sub-sets have been defined. Then, what are the molecules on these cells that are responsible for this? So not only the T cell receptor and MHC molecules, but also the co-stimulatory and co-inhibitory molecules. And at the moment that there was a reasonable amount of knowledge about this, this led to the development of antibodies, which consequentially were tested in multiple animal models to observe their effect. And I think that at the moment that immunology reached the state in which you could explain to someone in another field: PD1 is a negative regulator of T cell activity, at the moment that we block this negative activity, we have more active T cells, then someone from another research field could understand molecularly the proposed mechanism of action. So then you end up speaking the same language.

[210] FI140; II7.21; Couzin-Frankel, "Cancer Immunotherapy," 1432-1433.

achievements in the last five years.[211] Some of them would indeed know the proposed molecular mechanism as described by the group leader of B3, which indicates that their thought styles (described in Chapter 3) overlap enough to understand each other's work.[212]

Interestingly, the members of B7 reported that these recent clinical successes surprised them and improved the visibility and reputation of B3 at the institute.[213] For example, one of the technicians working at B7 mentioned that these successes reminded her of the existence of B3. Before she was hardly aware of the activities of this division, but now she is rather optimistic about the clinical potential of immunotherapy and thus about the work done at B3.[214]

According to multiple field members, the clinical successes also translated into new collaborative relations.[215] For example, to the question whether other divisions had become more open to collaboration, the interviewed group leader of B3 answered:

> In extreme mate, ja, ja. Maar dat is ook logisch hè. Als je clinicus bent, als je ziet dat een therapie effectief kan zijn, ja dan, dan wil je daar op dat moment ook een bijdrage aan leveren. [Euhm] Hetzij om die therapieën te verbeteren, nieuwe therapieën te ontwikkelen. Hetzij simpelweg als klinische zorg. [Euhm] Ja, dus dat zien we ook… hè dat traditioneel de enige tumorsamples die hier op de afdeling kwamen, of bloedsamples, waren van patiënten met melanoom en niercelkanker, maar nu is dat ook longkanker, blaaskanker, ovarium, colorectaal, hè, hè, het gaat nu pas alle kanten.[216]

Consistently, the members of B3 and B7 seem to have a comparable number of collaborators at the institute. In question 15 the field members were asked to list their collaborators from outside their own division. On average the members of B3 listed 0.8 collaborators from other NKI divisions. For B7 this number was 0.7.[217] So on top of their improved visibility and reputation, B3 does not seem to be in shortage of (potential) cooperative colleagues. In other words, the credibility of B3 at the institute substantially increased in the past five years.

However, also outside the institute B3 and the immunological approach in general gained credibility. Four observations show that the clinical successes of immunotherapy have also been noticed by fundraisers, popular media, insurance companies and pharmaceutical companies. To start with, the main Dutch funding agent for cancer research, KWF Kankerbestrijding, put B3 in their spotlight. To support their fundraising activities, the KWF displays short educational videos on their website about

[211] IM1.34-36; IM3.57; IM4.47-48; IM5.78; IM6.46-47; IM7.77.
[212] FM35; IM1.34-36; IM7.42-43; Fleck, "Epistemological Considerations," 99.
[213] IM1.39; IM3.57; IM4.47; IM5.76; IM6.47; IM7.76.
[214] IM4.51.
[215] II2.19; II3.43-45; IM6.53.
[216] II3.45-6. Translation: To an extreme extent, yes, yes. But that makes sense, right. If you see, as a clinician, that a certain therapy can be effective, then you want to contribute to that at that moment. Either to improve those therapies, to develop new therapies. Either simply as clinical care. So, that is what we are seeing… that traditionally the only tumour samples that came to the division, or blood samples, were from patients with melanoma or kidney cell cancer, but now this also includes lung cancer, bladder cancer, ovarium, colorectal, only now is goes into all directions.
[217] Q15.

"wetenschappelijke mijlpalen".[218] One of the division's group leaders was asked to be the main character in a video about immunotherapy, which was shot during one of my field visits. During the shootings the group leader was not only asked to explain the basics of immunotherapy, but also how (KWF funded) research has been contributing to its development. In addition, the producer and the cameraman encouraged the group leader multiple times to emphasise the advantages of immunotherapy and which cancers it will cure in the future. On his own initiative the group leader also described the possible side-effects of immunotherapy, such as intestinal inflammation.[219] However, for these nuances the fundraiser's enthusiasm about immunotherapy was simply too big. The passages about the side-effects did not make it to the final version of the video.[220]

Secondly, this enthusiasm resonates in the popular media. Newspapers, news sites and magazines published multiple articles about the achieved clinical successes. In the Netherlands the journalists often write specifically about the work performed at B3 or ask one of the group leaders to give an expert view on the topic.[221] For example, in 2015 such an article made it to the cover of *Elsevier*, under the headline "Alsnog genezen: Immunotherapie tegen kanker werkt".[222] The article describes the successful application of immunotherapy at the institute's hospital and how the members of B3 are involved in this.[223] The *Elsevier* cover and other examples of media interest are shown in **figure 17**.

[218] Author unknown, "Werken aan mijlpalen," KWF Kankerbestrijding, url: https://www.kwf.nl/over-kwf/werken-aan-mijlpalen/Pages/default.aspx, last update: unknown, consulted at: 10-01-2016. Translation: "scientific milestones".
[219] FI84-87.
[220] Author unknown, "Wetenschappelijke mijlpaal: immunotherapie," KWF Kankerbestrijding, url: https://www.kwf.nl/over-kwf/geschiedenis/Pages/wetenschappelijke-mijlpaal-immunotherapie.aspx, last update: unknown, consulted at: 10-01-2016.
[221] Sarah Boseley, "Immunotherapy: the big new hope for cancer treatment," *The Guardian*, url: http://www.theguardian.com/science/2015/jun/01/immunotherapy-the-big-new-hope-for-cancer-treatment, last update: 01-06-2015, consulted at: 10-01-2016.
Andries Fluit and Annelies Delchambre, "Weg met chemo! Is immuuntherapie de toekomst van kankerbestrijding?," *De Morgen*, url: http://www.demorgen.be/wetenschap/weg-met-chemo-is-immuuntherapie-de-toekomst-van-kankerbestrijding-b79dcaaa/, last update: 02-06-2015, consulted at: 10-01-2016.
Hanneke van Houwelingen, "Artsen lyrisch over doorbraak tegen huidkanker," *Het Algemeen Dagblad*, url: http://www.ad.nl/ad/nl/4560/Gezond/article/detail/4048014/2015/06/02/Artsen-lyrisch-over-doorbraak-tegen-huidkanker.dhtml, last update: 02-06-2015, consulted at: 10-01-2016.
Simon Rozendaal, "Mens versus tumor: kunnen we toch winnen?," *Elsevier* 8 (2015), 66-70.
Ellen de Visser, "Laat lichaam zelf tumor te lijf gaan," *De Volkskrant*, url: http://www.volkskrant.nl/archief/laat-lichaam-zelf-tumor-te-lijf-gaan~a3584283/, last update: 27-01-2014, consulted at: 10-01-2016.
Author unknown, "Prijs voor immunotherapie," *De Telegraaf*, url: http://www.telegraaf.nl/gezondheid/actueel/22245677/__Prijs_voor_immunotherapie__.html, last update: 27-01-2014, consulted at: 10-01-2016.
[222] Rozendaal, "Mens versus tumor," cover. Translation: "Cured nonetheless: immunotherapy against cancer works".
[223] Rozendaal, "Mens versus tumor," 66-70.

Figure 17. **Examples of international media interest in the successful application of immunotherapy.** The left image is the cover of the Dutch magazine *Elsevier*. Like other Dutch magazines and newspapers, the *Elsevier* article describes how immunotherapy saved the life of a patient treated by one of the clinicians affiliated to B3. The two images on the right are screenshots of the websites of the British newspaper *The Guardian* and the Belgian newspaper *De Morgen*. All examples date from 2015.[224]

Thirdly, the Dutch insurance companies also recently acknowledged the clinical benefits of immunotherapeutics and consequently started to reimburse some forms of it.[225] According to one of the interviewed PhD students of B3 this has been an major step in the broader appreciation of immunotherapy:

> Echt een heel goed voorbeeld is dat de anti-CTLA4 is nu gewoon een therapie die mensen als eerste krijgen op het moment dat ze gemetastaarde melanoom hebben. En dat wordt ook vergoed door de zorgverzekeraar. Nouja en dat kost onwijs veel geld. Dus [euh]... dat, dat... ik moet eigenlijk, ik denk eigenlijk... weet je, dat, dat de zorgverzekeraars erkennen dat dit een belangrijke manier is om je te behandelen... en dat vergoeden, dat lijkt mij eigenlijk, dat is een hele grote verandering geweest.[226]

Indeed, like most new cancer therapies, the immunotherapeutics are very expensive. To stick to the example of the cited PhD student, in 2014 the anti-CTLA4 drug cost about 70.000 euros per treated patient. Consequently, the coverage by health insurers is crucial for the broad application of these treatments, as most hospitals or patients will not be able to afford it themselves.[227]

Considering the high prices our society is prepared to pay for new cancer therapies, the fourth new ally of the tumour immunologists may not come as a surprise. Since the first successful immunotherapies came to the market, multiple pharmaceutical companies radically changed course. Some even terminated all their other R&D lines and made immunotherapy their sole focus area.[228] At

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[224] Boseley, "Immunotherapy." Fluit and Delchambre, "Weg met chemo!" Rozendaal, "Mens versus tumor," 66-70.
[225] II4.27.
[226] II4.27. Translation: A very good example is that now anti-CTLA4 is therapy that people get in the first place when they have metastasised melanoma. And it is also covered by the health insurers. Well, and it costs a lot of money. So, I think it has been a big change that health insurers acknowledge that it is an important way to treat you… and cover it.
[227] S.E.M. Tax and J.J.M. van der Hoeven, *Toegankelijkheid van dure kankergeneesmiddelen: Nu en in de toekomst*, ed. J. van Reijsen and H. Karssen, Amsterdam: KWF Kankerbestrijding (2014), 34-35.
[228] Bartjens, "Beetje Oranje-gevoel," *Het Financieele Dagblad*, 26-11-2015, 13.
Karel Berkhout and Leonie van Nierop, "Big Pharma zoekt de klappers bij de kleintjes," *NRC Handelsblad*, url: http://www.nrc.nl/handelsblad/2015/11/26/big-pharma-zoekt-de-klappers-bij-de-kleintjes-1560754, last

B7 the consequences of these courses changes are not left unnoticed. Indeed, members of B7 confirmed that companies are changing their focus from targeted therapy to immunotherapy.[229]

In other words, the newly established collaborative networks in the domain of cancer research are formed partly at the expense of the traditional alliances. Not only within the institute B3 can count on much attention and collaborators, but also major players from outside the institute are seeking association. Tumour immunologists, including the members of B3, increasingly gain a pivotal position in the dynamic network of clinicians, funding agents, science journalists, insurance companies and the pharmaceutical industry.

5.3 Concluding remarks

As discussed in the introduction of this chapter, in many ways the field members perceive B3 as an island which is relatively isolated from the rest of the institute. The main aim of this chapter has been to verify to what extent other field data are consistent with this perception. Is B3 indeed an island detached from the mainland? Interestingly, we have seen field data pointing in both directions. On the one hand, B3 forms a cohesive social unit whose research focus does not only differ from B7, but also from the other, intracellular-oriented research divisions. On the other hand, B3 has recently gained much credibility, which is substantiated by a large array of (potential) allies, both within the institute and beyond.

To reconcile these two extremes, it is helpful to reconsider common grounds identified in the earlier chapters. In Chapter 3 we have seen that both approaches aim to elucidate molecule interactions, although in different kinds of processes. In this chapter we have seen that this molecular perspective operates as a lingua franca, through which members of B7 could indeed understand the mechanism of action of a new immunotherapeutic. Thus, the field members certainly differ in their day-to-day vocabulary, but they nevertheless speak the same language.

However, the members of B7 did not only appreciate nivolumab's proposed mechanism of action. They were even more aware of its beneficial activity for cancer patients. The broad optimism about the recent successful applications of immunotherapy reflects an important axiological similarity discussed in Chapter 2. In the end of the day, the members of B3, B7 and the other divisions of the institute all aim for the improvement of cancer care. This shared goal, in combination with the first successes of immunotherapy, explains why the immunologists recently gained credibility.

And yet, in a paradoxical way, the ongoing inclusion of the immunologists into collaborative networks also highlights their outsider status. The immunologists could only *become* an insider because their default state was that of an outsider. This paradoxical status of an "embraced outsider" makes it hard to classify B3 as either part of the mainland or as a detached island. Unlike B7, the members of B3 adhere to an approach that differs in crucial ways from the NKI's mainstream, molecular approach. On

update: 26-11-2015, consulted at: 10-01-2016.
Rozendaal, "Mens versus tumor," 66-70.
Thieu Vaessen, "Miljardendeal in VS zet nieuwe therapie op kaart," *Het Financieele Dagblad*, 01-07-2015, 14.
Author unknown, "Amerikaanse farmareus investeert miljoenen in Belgisch biotechbedrijf," *Het Financieele Dagblad*, 04-02-2014, 17.
Author unknown, "Belgisch biotechbedrijf tekent miljardendeal met Merck," *Het Financieele Dagblad*, 23-07-2015, 13.

[229] FM108; IM7.78-79

the contrary, with all its new allies, B3 can neither be seen as completely detached from this mainstream.

B3 has this paradoxical status not only at the social level. In the previous chapters of Part I we have seen that there are crucial similarities and differences between the immunological and molecular approach at every level. Most importantly, both 1) aim to publish high impact papers and to improve cancer therapy, 2) postulate theories in terms of molecular interactions, and 3) use *in vitro* cell culture systems and sequencing technologies in their experimental work. On the other hand, the immunologists 1) aim to develop immunotherapy instead of targeted therapies, 2) postulate theories about intercellular interactions rather than about intracellular interactions, and 3) also use *in vivo* models and flow cytometry. Thus, if B7 represents the mainland, B3 is part of this mainland nor an island detached from it. To put it differently, B3 relates to B7 like a peninsula to the mainland: distinct, but nevertheless connected.

Thus, this asymmetric relation is reflected at the theoretical and methodological level. The members of B3 integrated aspects of the molecular theory and methodology into their approach. On the contrary, the members of B7 do not take into account any immunological aspects in their daily work. In other words, the similarities between the two approaches indicate a partial *molecularisation* of the immunological approach, rather than an *immunisation* of the molecular approach. To understand how such an asymmetry could grow, Part II of this thesis will put the relation between the two approaches into historical perspective.

Part II

The “molecularisation” of the Netherlands Cancer Institute: Controlled growth or metastasis?

6. Introduction and methodology of Part II

> The action of a gene becomes evident in its protein, which is translated from a messenger RNA that is transcribed from the genomic DNA. The promotor site on the DNA serves as attachment site for the RNA polymerase which transcribes the DNA into RNA. At the end of the gene this polymerase has to recognize a terminator site. The messenger RNA is in many cases modified by eliminating various internal parts by a process called splicing and is translated into a protein. Therefore ribosomes have to attach to the messenger RNA and protein synthesis starts at the start codon of the messenger RNA (AUG-triplet) and stops at the stop codon.[230]

This basic description of the central dogma is not from a secondary school textbook on biology. Rather this is an excerpt from the introduction to the institute's *Annual Report 1980* (see **figure 18**). Apparently, in 1980 the composers of the *Annual Report* wished to provide their readers with a crash course in molecular biology. The introduction particularly celebrates the merits of recombinant DNA technology and describes "how it works and what to with it".[231] The authors depict this technology as a breakthrough which would greatly enhance our knowledge of molecular processes:

> The understanding of the molecular basis of life is influenced by the improvements of techniques in the laboratory. The latest, much discussed breakthrough in the molecular biology is the so-called recombinant-DNA technology, which encompassed the synthesis of new combinations of nucleic acids, the introduction of these synthesized nucleic acids into cells and the

[230] Author unknown, "Introduction", in *Annual Report 1980*, Amsterdam: The Netherlands Cancer Institute (year unknown), 1-7.
[231] Author unknown, "Introduction", in *Annual Report 1980*, 1.

> expression of these new recombinant DNA molecules. This technique opens a wide world of new possibilities, some of which are already being realized.[232]

In the same year the enthusiasm about this new technology was materialised by the establishment of the institute's first recombinant DNA laboratory.[233] Besides for experiments, the new lab would be used for the recruitment of new students. In an information document for prospective students, the institute promotes itself as "zeer modern en volledig uitgerust, o.a. met een laboratorium voor recombinant DNA onderzoek."[234]

Nowadays, more than three decades later, the application of molecular technology as such can no longer be seen as modern. Unlike in 1980, today an explanation of the central dogma in the *Annual Report* would be offensive or at least unnecessary to most of its readers. As we have seen in Part I, the molecular approach is incorporated at virtually all research divisions of the institute. Particularly we have seen how the immunologists have included aspects of this approach into their work, mainly at the theoretical and methodological level. Thus between 1980 and 2015 the molecular approach turned from unique and novel into the prevailing standard. This Part II aims to give a detailed description of how the *molecularisation* of the institute took place and how this explains the asymmetry identified in Part I. However, before we turn to this recent history, the upcoming sections will discuss in more detail the consulted source material and the historical context of the studied period.

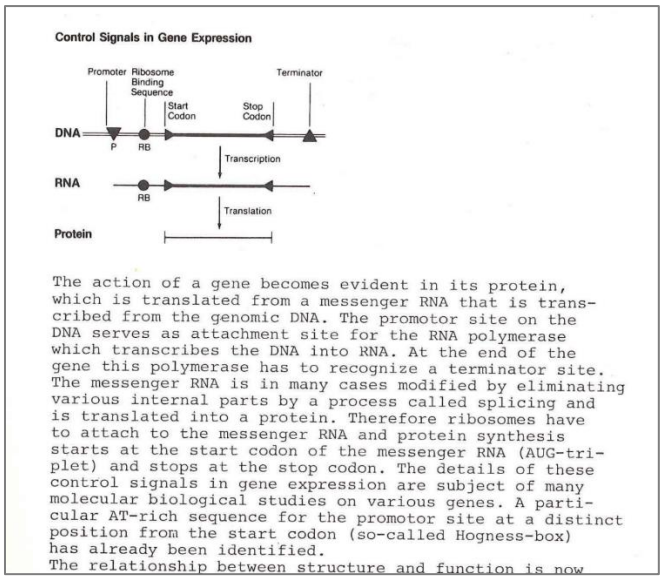

Figure 18. An excerpt of the introduction to the institute's *Annual Report 1980*. The text and illustration aim to explain the central dogma. Nowadays this is common knowledge in the field, but in 1980 the composers of the annual report considered it useful to inform the reader about this molecular theory.[235]

[232] Author unknown, "Introduction", in *Annual Report 1980*, 1.
[233] R. Michalides, L. van Deemter, L. Grijpvink-de Vries, R. Nusse. A. van Ooyen, E Wagenaar, "V.1 Moleculaire biologie van MMTV," in *Werkplannen 1982: Antoni van Leeuwenhoekhuis - Het Nederlands Kankerinstituut*, Amsterdam: The Netherlands Cancer Institute (1981), archive: Centrale Kanker Bibliotheek, 29-30.
[234] L. Smets, *Studieregeling voor hoofd- en bijvakstages*, archive: Research Raad NKI, 1983.
Translation: "very modern and fully equipped, i.a. with a laboratory for recombinant DNA research."
[235] Author unknown, "Introduction", in *Annual Report 1980*, 5.

6.1 Accessing the recent past: Methodological remarks

When studying recent history the personal memories of people who were actually involved in the developments of interest are an unique source of information. The interviews performed during the field work provided important clues for the historical analyses discussed in this part (see **figure 19**). In much of the upcoming chapters the oral sources are compared to archival sources. Are the oral and archival sources consistent? And if not, how could this be explained?

Getting access to the archival documents of the Netherlands Cancer Institute itself demanded some exploration, as the institute has no central archive. Neither there is an overarching inventory of all existing sub-archives and their contents. Nevertheless, many valuable sources were found in the depot of the institute's library. It contained a fairly complete collection of the annual reports, "werkplannen", inaugural lectures and extensive citation analyses of all the publications of the institute (see figure 19).[236] Additionally, the library's folders contained informative internal correspondence, especially concerning the citation analyses, journal subscriptions and the spread of literature throughout the institute.

Another accessible sub-archive was that of the Research Raad (in English: Research Council). The Research Raad consists of all the heads of the research divisions and is chaired by the Director of Research. Throughout the studied period this council had bi-weekly meetings in which they discussed and evaluated new policies.[237] Most of the Research Raad archive is stored at the data management company Iron Mountain. The archive contains the minutes of their meetings and a collection of the discussed documents (see figure 19). Access to this archive was provided by the current Manager of Research.

The Research Raad archive proved itself a valuable source of archival pieces because of four reasons. Firstly, the Research Raad has been an influential council because virtually all important policy plans pass it. Secondly, its members are prominent and functionally leading figures at the institute, as they are the heads of the research divisions. Thirdly, consisting of all these division heads, the Research Raad is representative for the various branches of the institute's research. Fourthly, unlike other councils, the Research Raad has had a fairly high and stable meeting frequency, providing an insightful cross section through the period of interest.[238]

Besides the Research Raad the institute harbours several other consultative or executive bodies, including the Lab Raad, the (Inter)national Scientific Advisory Board and the Beleidvoerend Orgaan.[239] However, access to their archives was limited by reasons of time and confidentiality. Especially the archive of the Beleidvoerend Orgaan could have been informative about the orchestration of the institute's molecularisation. This board consists of the director's confidants and discusses important, delicate issues, such as the long term research policies or the (mal)functioning of group leaders. Its archive contains confidential information about people who are still alive or even working at the

[236] Translation: "working plans".
[237] A. Verstraeten, *Reglement Wetenschappelijke Beleidsvoering*, archive: Research Raad NKI, RR02, date: 1985.
[238] Verstraeten, *Reglement*.
[239] Translation: Besides the Research Council the institute harbours several other consultative or executive bodies, including the Lab Council, the International Advisory Board and the Policy conducting Organ.

institute. Therefore the archive is not accessible for the vast majority of the institute's employees and it is neither for an interested student History and Philosophy of Science.[240]

Nevertheless, as we will see in the rest of this part, the combination of oral histories, the library's depot and the archive of the Research Raad provided enough source material to gain insight into the establishment of the molecular approach at the institute, its expansion and the influence on the immunologists. The contours of these developments will be sketched in the upcoming section, providing both the historical context of the studied developments and an outline of the following chapters.

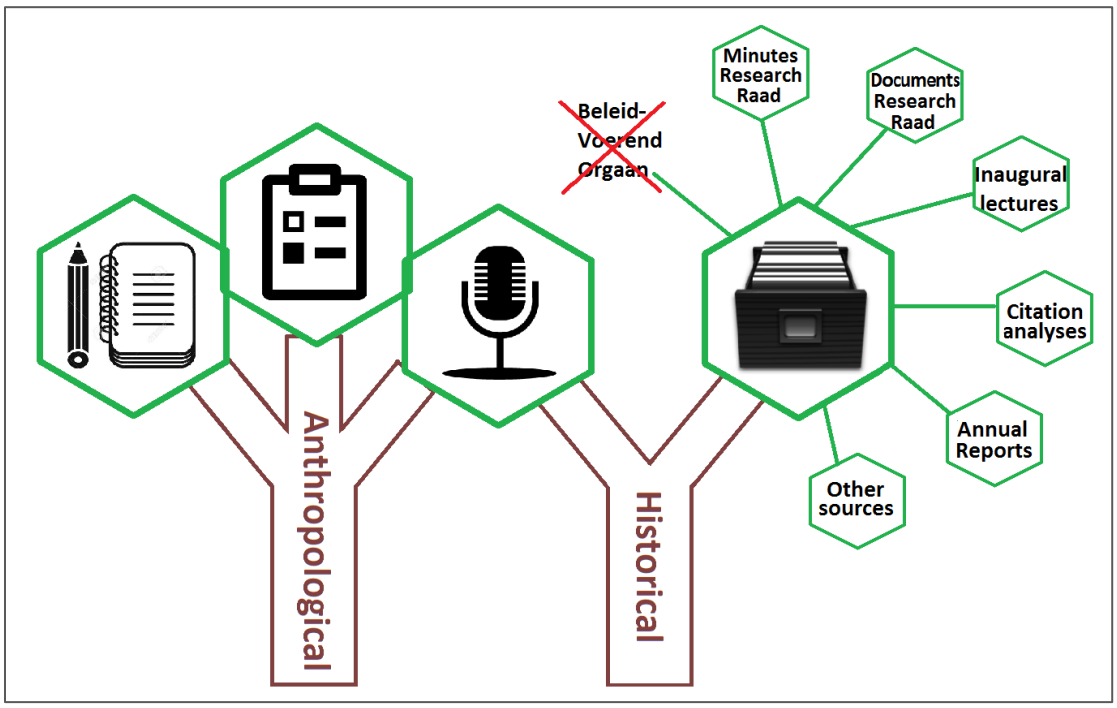

Figure 19. The sources of data used in Part II. The historical analysis described in Part II is based on oral and archival sources. The oral histories were recorded during the interviews, which were part of the field work described in Part I. The archival sources were mainly found in the library's depot and the archive of the Research Raad. Access to the archive of the Beleidvoerend Orgaan was denied for reasons of confidentiality.

6.2 Historical context and outline

From its opening in 1915 the institute has consisted of both a cancer hospital and a laboratory.[241] In the early days the two employees of the small laboratory mainly studied tumour material from exotic rats, which were killed in the ships and storehouses in the city's harbour. However, as soon as the first patients were operated, they started to study patient material. Already in this first year the laboratory labour is divided. One employee is occupied with the morphological work, while the other performs the serological work.[242]

[240] Unrecorded oral communications with Henri van Luenen, Director of Operations NKI, 06-08-2016. Verstraeten, *Reglement*.
[241] Author unknown, "Jaarverslag van den Secretaris," in *Tweede jaarverslag: 1915*, Amsterdam: Vereeniging Het Nederlands Kanker Instituut (year unknown), 13-19.
[242] Author unknown, "Laboratorium," in *Tweede jaarverslag: 1915*, Amsterdam: Vereeniging Het Nederlands Kanker Instituut (year unknown), 22-23.

Eleven years later the *Annual Report* of 1926 describes for the first time the activities employed at the "morphologische afdeeling".[243] In the following years also the "weefselkweekafdeeling" and "biologische afdeeling" are mentioned occasionally.[244] Eventually, from 1945 onwards the individual divisions separately discuss their lines of research in the *Annual Reports*, indicating that the divisions became an important organisational unit, structuring the experimental work.[245]

In the late '50s an immunological research line is started by an internist, resulting in the formal establishment of the Division of Immunology in 1960.[246] In the *Annual Report* of 1960 the institute's director qualifies the immunological research line as indispensable. Nevertheless it would take two more years before the division got its own laboratory in October 1962.[247]

In exactly the same month yet another laboratory is established, which would accommodate the new Division of Virology. In the *Annual Report* of 1962 the brand new division head J. Links summarises the aim of the virological experiments: "Wat het researchprogramma betreft, zo is het gestelde doel de tumortransformatie van een cel, geïnfecteerd met een oncogeen virus, op biochemisch niveau te bestuderen."[248] As the immunologists' research lines also included the study of oncogenic viruses, the interests of the two new divisions overlapped considerably.[249] Despite of this shared interest, we will see in the upcoming chapters that their research activities initially would not converge, but rather develop along different lines.

Most importantly, in the seventies several members of the Division of Virology would pursue the first molecular research lines at the institute. One decade later, in 1983, the Division of Virology is renamed into the Division of Molecular Biology, making it the institute's first molecular division. As we will see in Chapter 7, the establishment of the molecular approach at the institute involved the sharp demarcation of new territorial boundaries.[250]

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[243] C. Bonne, "Jaarverslag van het Laboratorium," in *Dertiende jaarverslag: 1926*, Amsterdam: Vereeniging Het Nederlands Kanker Instituut (year unknown), 13-15. Translation: "morphological division".

[244] R. Korteweg, "Jaarverslag van het Laboratorium over 1933," in *Twintigste jaarverslag: 1933,* Amsterdam: Vereeniging Het Nederlands Kanker Instituut (year unknown), 12-19

R. Korteweg, "Jaarverslag van het Laboratorium over 1940," in *Zeven en twintigste jaarverslag: 1940*, Amsterdam: Vereeniging Het Nederlands Kanker Instituut (year unknown), 9-13. Translations: "divisions of tissue culture"; "biological division".

[245] Author unknown, *Twee en dertigste jaarverslag: 1945*, Amsterdam: Vereeniging Het Nederlands Kanker Instituut (year unknown).

[246] M. Schoorl, "Jaarverslag van het Instituut," in *Zeven en veertigste jaarverslag: 1960*, Amsterdam: Het Nederlands Kanker Instituut (year unknown) 9-10.

P. Rümke, "Afdeling Immunologie," in *Zeven en veertigste jaarverslag: 1960*, Amsterdam: Het Nederlands Kanker Instituut (year unknown), 27.

[247] Schoorl, "Jaarverslag," 9.

P. Rümke, "Afdeling Immunologie," in *Negen en veertigste jaarverslag: 1962*, Amsterdam: Het Nederlands Kanker Instituut (year unknown), 37-38.

[248] J. Links, "Werkgroep virologie," in *Negenenveertigste jaarverslag: 1962*, Amsterdam: Het Nederlands Kanker Instituut (year unknown), 40.

Translation: "Concerning the research program, the aim is to study the tumour transformation of cells infected by an oncogene virus at the biochemical level."

[249] Rümke, "Afdeling Immunologie," in *Zeven en veertigste jaarverslag: 1960*, 27.

Rümke, "Afdeling Immunologie," in *Negen en veertigste jaarverslag: 1962*, 38.

[250] R. Michalides, H. Daams, L. van Deemter, R. Nusse, A. Riethorst E. Wagenaar, "Molecular biology of the mouse mammary tumor virus," in *Annual Report 1978*, Amsterdam: The Netherlands Cancer Institute (year unknown),70-71.

However, not long after its establishment, the molecular territory would start to expand. A superficial but clear illustration of this we find in the nomenclature of the institute's research divisions. As shown in **figure 20**, from the '80s onwards the number of divisions with a molecular signature increases gradually. In the slipstream of the Division of Molecular Biology, the divisions of Molecular Genetics, Molecular Carcinogenesis, Gene Regulation and Molecular Pathology were established. Consistently, an increasing number of the scarce permanent staff positions were taken by researchers working at these molecular divisions (see figure 20). Chapter 8 goes beyond these plain numbers by describing in detail how more and more of the institute's research lines were engulfed by the new approach, while Chapter 9 will discuss possible factors which drove this successful expansion.

Figure 20 also shows that no new immunological divisions were established in the studied period. Accordingly, the number of immunologists does not show an increase similar to that of the molecular biologists. That is not to say that the immunological studies were always restricted to the Division of Immunology. Indeed, occasionally immunological research projects were performed at other divisions, such as the Division of Tumour Biology.[251] However, these exceptions pale into insignificance when compared to the overwhelming and orchestrated expansion of the molecular approach. Hence Chapter 10 will describe how the molecularisation influenced the position of the immunologists. Taken together, the upcoming chapters will help us to understand the asymmetric relation identified in Part I.

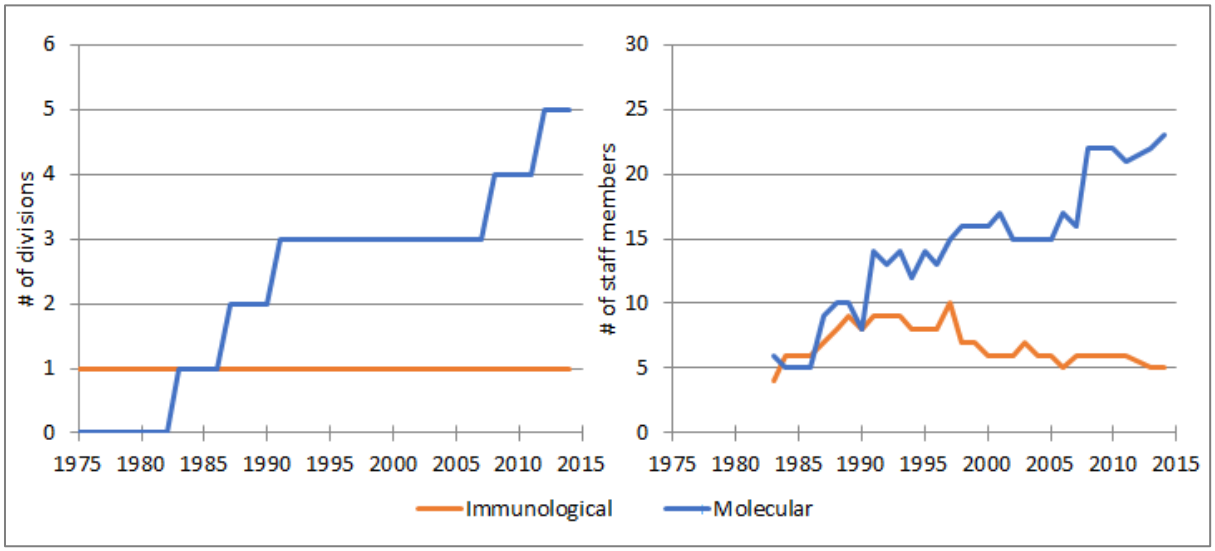

Figure 20. The number of divisions and permanent staff members per approach. The left graph shows the number of divisions with an immunological or molecular signature. The right graph shows the total number of permanent staff members working at these divisions. The data were derived from the *Annual Reports 1975-2015*.

Piet Borst, "Introduction," in *Annual Report 1983*, Amsterdam: The Netherlands Cancer Institute (year unknown), 1-2.

[251] Author unknown, "Division of Tumor Biology," in *Annual Report 1985*, Amsterdam: The Netherlands Cancer Institute (year unknown), 59.
Author unknown, "Major histocompatibility complex," in *Annual Report 1992: The Netherlands Cancer Institute Amsterdam* (year unknown), 47-49.

7. The establishment of a molecular territory

Whereas the immunologists already established themselves at the institute in the early '60s, by the early '80s the molecular biologists needed to acquire laboratories, staff and money. However, the first division dedicated to molecular biology had not to be built from scratch. As mentioned above, in 1983 the Division of Virology was renamed into the Division of Molecular Biology. Was this renaming just a superficial whim, or did it reflect a genuine shift in the division's experimental work? In this chapter we will see how this first molecular division established itself, and how both the molecular biologists and others neatly demarcated its activities.

7.1 A new director, a new division

Before the establishment of the first molecular division, one research group at the Division of Virology developed itself into the institute's pioneer of the molecular cancer research. In the '70s Roel Nusse and his colleagues were studying tumorigenic viruses and in particular their DNA and RNA.[252] Seen against the background of the general developments in the '70s, it might not be a surprise that these early molecular research lines were employed at the Division of Virology. In this period the "oncogene-theory" was postulated and it was thought that these oncogenes were to be found in viral DNA. Therefore the molecular study of tumorigenic viruses, and how they altered the patient's DNA, was an appealing angle to the study of cancer virology.[253] Accordingly, also at the NKI it were the virologists who introduced the first molecular research lines.

[252] Author unknown, "Molecular biology of the mouse mammary tumor virus (MTV)", in *Annual Report 1977*, Amsterdam: The Netherlands Cancer Institute (year unknown), 70-83.
[253] Jean-Paul Gaudillière, "The Molecularization of Cancer Etiology in the Postwar United States: Instruments, Politics and Management," in *Molecularizing Biology and Medicine: New Practices and Alliances 1910s-1970s*, ed. Soraya de Chadarevian and Harmke Kammingma, Amsterdam: Harwood Academic Publishers (1998), 139-170.

So when in February 1983 a new group with a distinct molecular signature was recruited,[254] it was located at the Division of Virology. This new group studied gene rearrangements and its leader was Piet Borst, who held the chair of Biochemistry and Molecular Biology at the University of Amsterdam. He was hired as the new Director of Research, to replace the internist-oncologist Frans Cleton.[255] In the introduction to the *Annual Report* of 1983, Borst presented his own recruitment as an important shift towards a more molecular research program at the NKI:

> Cancer research is rapidly evolving and so is the research program of our Institute. I refer to the reports that follow for details. Here I shall only mention some of the more conspicuous changes in emphasis. The arrival of a new director in 1983, together with a group of graduate students, post-docs and technicians, more than doubled the number of molecular biologists, working in the Institute.[256]

Indeed, upon Borst's arrival there was a concentration of molecular biologists at the Division of Virology. As Borst's group was studying gene rearrangements, the common dominator at the division became the adherence to the molecular approach rather than the study of tumorigenic viruses.[257] Not long after Borst's arrival, the last non-molecular research lines at the division were terminated.[258] The shift in the approach was sealed when the Research Raad in September 1983, without any documented ado, approved the renaming into the Division of Molecular Biology.[259]

Beyond studying molecules, what did it imply to adhere to this new this *molecular* approach at the NKI? To answer this question it is illuminating to read how in the early '80s the geneticists of the Division of Genetics carefully demarcated their research from that of the molecular biologists working at the Division of Virology/Molecular Biology. Although the geneticists were eager on affiliating their work to that of the molecular biologists,[260] in the *Annual Report* of 1981 they made a sharp distinction between the molecular and their own approach to the process of tumorigenesis:

> While the molecular biological techniques to approach the problem are mainly carried out within the Division of Virology, the more classical approaches are pursued within this Division. The creation and the use of particular strains, i.e. the so-called congenic and recombinant inbred strains, is the main line for these studies. However, more recently, somatic cell genetics has also been started to be used as a tool in the localization of genes involved in the tumorigenic process. The research carried out centers around two types of genes for the time being, i.e. endogenous viral genes and histocompatibility

[254] Borst, "Introduction," in *Annual Report 1983*, 1.
[255] Borst, "Introduction," in *Annual Report 1983*, 1-2.
[256] Borst, "Introduction," in *Annual Report 1983*, 2.
[257] Author unknown, "Divison of Molecular Biology," in *Annual Report 1983*, Amsterdam: The Netherlands Cancer Institute (year unknown), 71-87.
[258] Borst, "Introduction," in *Annual Report 1983*, 2.
Author unknown, "Divison of Molecular Biology," in *Annual Report 1983*, 71-87.
Author unknown, "Divison of Molecular Biology," in *Annual Report 1984*, Amsterdam: The Netherlands Cancer Institute (year unknown), 51-59.
[259] E. Kriek, *Notulen Research Raad vergadering van 16 september 1983*, archive: Research Raad NKI, RR01, date: 1983.
[260] Author unknown, "VI Genetics," in *Annual Report 1982*, Amsterdam: The Netherlands Cancer Institute (1983), 75-126,

> genes. Since many endogenous viral genes are not thought to be involved directly in the tumorigenesis process and the histocompatibility genes most likely influence growth and behavior of tumor cells, it may be necessary in the future to look for genes directly involved in tumorigenesis. Such genes are, however, not yet known although they may be located through the use of recombinant inbred strains between high and low cancer strains. Once the molecular biologists would identify them, they may be studied and located using RI strains and somatic cell hybrids using mouse hamster hybrids segregating mouse chromosomes.[261]

At least two notable observations can be made when studying this demarcation between the "classical" and molecular biological approach. The first observation regards the axiological level. According to the geneticists an important task of the molecular biologists is to identify new genes involved in tumorigenesis, the so called oncogenes.[262] Indeed, in the early '80s the molecular biologists repeatedly explicated their aim to "uncover new oncogenes" and many of their research lines centred around the study of oncogenes such as *int-1* and *myc*.[263]

Secondly, the citation given above also highlights an important methodological distinction. Only when the molecular biologists identified a new oncogene, the geneticists joined in to study these oncogenes in their mouse and hybrid models. Also in other ways the molecular biologists distinguished themselves at the methodological level in the early '80s. Unlike others, they invested most of their budget into technology needed for DNA detection and DNA transfection experiments. Other divisions hardly spent their money on these molecular techniques. Instead they would buy new centrifuges, microscopes and floppy discs.[264]

However, the new disciplinary boundaries stood out most sharply when a person tried to cross them. In the upcoming case study we will see how the molecular biologists fanatically defended their newly obtained territory against an intruder.

7.2 Case Collard: Violating boundaries

From 1981 onwards, NKI researcher John Collard pursued a research line titled "Genetic control of malignant transformation". In this project Collard studied oncogenes by combining classical karyology and flow cytometry with state of the art molecular techniques, such as recombinant DNA technology

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[261] Author unknown, "VI genetics and experimental animals," in *Annual Report 1981*, Amsterdam: The Netherlands Cancer Institute (year unknown), 73-75.

[262] Accordingly, in the next report the geneticists write: "Molecular biologists are discovering one after the other so-called oncogene, either by using retroviruses as vectors or by transfecting cells with DNA from tumor cells."
See: Author unknown, "VI Genetics," in *Annual Report 1982*, Amsterdam: The Netherlands Cancer Institute (year unknown), 75-76.

[263] Author unknown, "V Tumor viruses," in *Annual Report 1982*, Amsterdam: The Netherlands Cancer Institute (year unknown), 67-74.
Author unknown, "Divison of Molecular Biology," in *Annual Report 1983*, 72-73.
Author unknown, "Division of Molecular Biology," in *Annual Report 1984*, Amsterdam: The Netherlands Cancer Institute (year unknown), 51-59.
Author unknown, "Molecular Biology," in *Annual Report 1985*, Amsterdam: The Netherlands Cancer Institute (year unknown), 49-58.

[264] R.P. van Hoeven, *Investeringen Research 1983*, archive: Research Raad, RR01, date: 24-11-1982.

and southern blotting.[265] Such a research line perfectly tied in with the general trends in the field and in particular with the director's enthusiasm about molecular oncogene research.[266] However, there was just one difficulty. Collard did not work at the Division of Molecular Biology, but rather at the Division of Cell Biology.[267]

When in July 1983 the Beleidvoerend Orgaan sent out a proposal for a revised divisional organisation, Roel Nusse, head of Molecular Biology, seized his chance.[268] During the upcoming meetings of the Research Raad, Nusse repeatedly problematised the position of Collard at the Division of Cell Biology. According to Nusse all the molecular and oncogene research had to take place under the direct auspices of his division.[269] In the minutes of one of these meetings his view is summarised as follows: "Het risico is aanwezig dat in sectie III [Cell Biology] een oncogen onderzoek tot stand komt zonder dat van de kennis die in sectie V [Molecular Biology] aanwezig is optimaal geprofiteerd wordt. Dit mag niet gebeuren."[270] Despite of Nusse's repetitive pleas, Collard preferred to stay at Cell Biology.[271] Collard refused to move to the molecular division simply because he did not perceive himself as a molecular biologist.[272]

Nusse nor Collard could convince the Research Raad, which initially did not know how to settle this boundary conflict. Rather than making a decision, the members of the Research Raad repeatedly asked the involved parties to discuss the issue and to report any outcome.[273] This postponement of the

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[265] J.G. Collard and J.H. Hollander, "III.3a Scheiding van chromosomen en genetische controle van getransformeerde groei," in *Werkplannen 1981*, Amsterdam: Antoni van Leeuwenhoekhuis (1980), archive: Centrale Kanker Bibliotheek, 16.
J.G. Collard and J.F. Schijven, "III.3a Scheiding van chromosomen en genetische controle van getransformeerde groei," in *Werkplannen 1982*, Amsterdam: Antoni van Leeuwenhoekhuis (1981), archive: Centrale Kanker Bibliotheek, 15-16.
J.G. Collard, J.F. Schijven and J.W.G. Janssen, "III.3a Scheiding van chromosomen en genetische controle van getransformeerde groei," in *Werkplannen 1983*, Amsterdam: Antoni van Leeuwenhoekhuis (year unknown), archive: Centrale Kanker Bibliotheek, 13-14.
J.G. Collard, J.W.G. Janssen and J.F. Schijven, A.C.M. Steenvoorden, E.J. Philippus, "III.3 Genetische kontrole van getransformeerde groei," in *Werkplannen 1984*, Amsterdam: The Netherlands Cancer Institute (year unknown), archive: Centrale Kanker Bibliotheek, 18-19.
[266] S. Mukherjee, "A Risky Prediction", in *The Emperor of All Maladies*, London: Fourth Estate (2011), 370-383. Borst, "Introduction," in *Annual Report 1983*, 1.
[267] E. Kriek, "Verslag Research Raad," *Antoni van Leeuwenhoekhuis-brieven* 3 (1983), 5-10, archive: Centrale Kanker Bibliotheek.
[268] L. den Engelse, *Voorstel gewijzigde sectie-indeling*, archive: Research Raad NKI, RR01, date: 04-07-1983.
[269] Author unknown, *Notulen Research Raad vergadering van 8 juli 1983*, archive: Research Raad NKI, RR01, date: 1983.
E. Kriek, *Notulen Research Raad vergadering van 30 september 1983*, archive: Research Raad NKI, RR01, date: 1983.
E. Kriek, *Notulen Research Raad vergadering van 14 october 1983*, archive: Research Raad NKI, RR01, date: 1983.
[270] Kriek, *Notulen 30 september 1983*. Translation: "The risks exists that that at section III [Cell Biology] an oncogene study is initiated without optimal profit of the knowledge available at section V [Molecular Biology]. This cannot happen."
[271] Author unknown, *Notulen 8 juli 1983*.
E. Roos, *Reactie sektie III op het voorstel voor een gewijzigde sektie-indeling*, archive: Research Raad NKI, RR01, description: letter to Research Raad, date: 1983.
Kriek, *Notulen 30 september 1983*.
[272] Kriek, *Notulen 30 september 1983*.
[273] Roos, *Reactie sektie III*. Kriek, *Notulen 30 september 1983*.

decision gave Nusse the opportunity to gather influential allies. To start with, Nusse could count on the support of his fellow division members. They shared his view that Collard's work was similar to their own work and should therefore take place at their division.[274] In addition, the chairman of the Research Raad qualified Collard's position at Cell Biology as "niet logisch" and also proposed to move Collard to Molecular Biology.[275] Lastly, the complete Beleidvoerend Orgaan embraced Nusse's view and was keen on adding it to their reorganisational plans.[276] These three parties would all inform the Research Raad about their position in the dispute, thereby strengthening Nusse's case.

So when in November 1983 the Research Raad discussed the issue yet another time, it decided that Collard had to show his true colours.[277] The Research Raad gave Collard one year to choose between being a cell biologist or a molecular biologist, as the secretary stated in the institute's newsletter of November 1983: "Aangezien een deel van zijn werk een aanzienlijk moleculair-biologisch karakter draagt, werd hem gevraagd een keuze te maken; ofwel meer aansluiting bij ander onderzoek in sectie III [Cell Biology], of bij moleculair-biologisch werk. In dit laatste geval leek overgang naar sectie V [Molecular Biology] gewenst."[278] Until Collard choose for the first option in September 1984, he was forced to also be a member of Molecular Biology.[279] Studying oncogenes at the molecular level, while not being a member of Nusse's division was no longer option.

7.3 Concluding remarks

In this chapter we have seen how the first molecular division at the institute evolved from the Division of Virology and how its members demarcated their territory. The case of Collard shows that in the early '80s the molecular biologists themselves, but also many other influential persons, envisioned a sharp distinction between the new molecular approach and the other approaches at the institute. The molecular biologists rather successfully established a monopoly on the study of oncogenes and the application of molecular techniques. Crossing the disciplinary boundary was allowed, but only at the price of a full conversion to the new approach.

[274] Author unknown, *Verslag sektievergadering Virologie – Moleculaire Biologie 23-8-1983*, archive: Research Raad NKI, RR01, date: 1983.
[275] P. Emmelot, *Sectiewijzigingen*, archive: Research Raad NKI, RR01, description: letter from chair Research Raad to Research Raad, date: 27-09-1983.
[276] L. den Engelse, *Sectie indeling*, archive: Research Raad NKI, RR01, description: letter from secretary Beleidvoerend Orgaan tot Research Raad, date: 10-10-1983.
[277] Kriek, *Notulen 14 october 1983*. Translation: "Because a part of his work has a considerable molecular biological character, he was asked to make a decision; either more association with other research at section III [Cell Biology], or with molecular biological work. In the latter scenario a transfer to section V [Molecular Biology] seemed desirable."
[278] E. Kriek, "Verslag Research Raad," 5.
[279] L. den Engelse, "Verslag van het Beleidvoerend Orgaan over de periode mei t/m oktober 1983," *Antoni van Leeuwenhoekhuis-brieven* 3 (1983), 1-4, archive: Centrale Kanker Bibliotheek.

8. The expansion of the molecular territory

Only two years after the large divisional reorganisation of 1983, new changes took place. In the *Annual Report* of 1985 director Borst reported on the most important organisational adaptations: "A third major change in 1985 concerned the restructuring of the division of tumor biology (division VI). Dr. R. Michalides, an experienced molecular biologist with expertise in tumor biology, moved from division V to division VI and became the new head of the tumor biology division."[280]

This organisational change is remarkable because, as we have seen in the case of Collard, two years earlier many employees believed that molecular research had to be limited strictly to the Division of Molecular Biology. From the mid '80s onwards quite the opposite happened. In addition to the move of Michalides to another division, it is not hard to find other instances of the spread of the molecular approach at the NKI. Large investments in molecular technology, the establishment of new molecular divisions, the recruitment of many molecular biologists and the (institutionalised) advising or leading roles assigned to them all contributed to the *molecularisation* of the institute.[281] In the upcoming sections we will delve deeper into three illustrative examples to grasp how this transition took place.

[280] Piet Borst, "Introduction," in *Annual Report 1985*, Amsterdam: The Netherlands Cancer Institute (year unknown), 11-13.
[281] See figure 20.
L. den Engelse and P. Borst, *Beleidsplan 1985 BVO*, archive: Research Raad NKI, RR02, date: 24-06-1985.
L. den Engelse, *Nieuwe leden voor de vaste staf*, archive: Research Raad NKI, RR01, description: letter from Beleidvoerend Orgaan to Research Raad, date: 16-01-1984.
P. Borst, "Introduction," in *Annual Report 1988*, Amsterdam: The Netherlands Cancer Institute (year unknown), 9-12.
P. Borst, *Sectie en analist(e) K. Weyer*, archive: Research Raad NKI, RR01, description: letter to Research Raad, date: 04-07-1984.

8.1 Nomen est omen: Establishing the Division of Molecular genetics

Michalides would not remain the only molecular biologist put into a leading position outside the Division of Molecular Biology. In 1987 another member of Molecular Biology became head of the newly established Division of Molecular Genetics. Unlike the Division of Molecular Biology, the institute's second molecular division did not gradually evolve from an existing one. Rather, this division was built from scratch on the initiative of director Borst.[282]

The construction work for this division started in the summer of 1986 when Borst sent out a confidential memo to the Research Raad. In this memo he proposed to create a new division dedicated to molecular genetics. In addition, Borst mentioned that he already discussed his plan with molecular biologists Nusse and Michalides, who would support his plan.[283] He also reported shortly on the view of the Beleidvoerend Orgaan: "Advies BVO: doen."[284]

Already in this memo the division is informally called "sectie Berns", after its unopposed candidate head.[285] Only two years earlier Ton Berns was recruited to the Division of Molecular Biology. Before that Berns earned his spurs at the Radboud University by discovering the *pim1* oncogene, an achievement not left unnoticed when he arrived in Amsterdam.[286] The other group leader proposed in Borst's memo is Peter Démant, a classical geneticist from the Division of Tumor Biology.[287] By stimulating the collaboration between Berns and Démant, Borst aimed for nothing less than an "Integratie van klassieke en moleculaire genetica in één sectie […]".[288]

Borst's proposal was discussed in the Research Raad meeting of 29 August 1986 and the division heads unanimously supported it.[289] However, the minutes also report on some expressed concerns: "Michalides acht vorming van [e]en dergelijke sectie slechts zinvol, als in het onderzoek van Demant een accentverschuiving plaatsvindt in een meer moleculair-biologische richting."[290] No sooner said than done, Démant obeyed Michalides' heartfelt advice by planning his molecular retraining.[291]

In the upcoming meetings the Research Raad decided that the new division would be established in January 1987, to give Démant the opportunity to first have a sabbatical at the Albert Einstein School

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[282] P. Borst, *Sectie moleculaire genetica?*, archive: Research Raad NKI, RR02, description: confidential memo sent to Research Raad, date: 20-08-1986.
[283] Borst, *Sectie moleculaire genetica?*
E. Kriek, *Notulen Research Raad vergadering van 29 augustus 1986*, archive: Research Raad NKI, RR02, date: 1986.
[284] Borst, *Sectie moleculaire genetica?* Translation: "Advice BVO: do it."
[285] Borst, *Sectie moleculaire genetica?*
[286] Borst, "Introduction," in *Annual Report 1985*, 12.
[287] Borst, *Sectie moleculaire genetica?*
Author unknown, "Research Divisions," in *Annual Report 1985*, Amsterdam: The Netherlands Cancer Institute (year unknown), 4-5.
[288] Borst, *Sectie moleculaire genetica?* Translation: Borst aimed for nothing less than an "integration of classical and molecular genetics in one section […]".
[289] Kriek, *Notulen 29 augustus 1986*.
[290] Kriek, *Notulen 29 augustus 1986*. Translation of quote: Michalides considers the formation of such a division useful only if Demant shifts his research into a more molecular biological direction. It appears that Demant already planned to get familiar with the new techniques.
[291] Kriek, *Notulen 29 augustus 1986*.
E. Kriek, *Notulen Research Raad vergadering van 12 september 1986*, archive: Research Raad NKI, RR02, date: 1986.

of Medicine in New York.[292] The goal of Démants sabbatical was to familiarise him with molecular research techniques. Not only Michalides, but also the rest of the Research Raad considered this to be a "nuttig initiatief" and thus approved Démants plan and its financing.[293]

And once the new division was up and running in the spring of 1987, the members of the Research Raad kept their fingers on Démants pulse. Despite of his molecular training in New York, the Research Raad decided to intervene into his new research plans.[294] The prevailing view among the division heads was that the plans were too "classical" and needed a fundamental revision:

> Het onderzoek lijkt klassieke genetica met een modern tintje, en de vraag doet zich wederom voor of dergelijk werk nog uitgevoerd moet worden. Het voorgestelde onderzoek zal ook zeer veel kosten voor proefdieren met zich meebrengen. Opgemerkt wordt, dat het klassieke geneticawerk in het proefdierenhuis nog steeds een relatief grote plaats inneemt. Volgens sommigen gaat dit ten koste van meer slagvaardig onderzoek m.b.v. biotechnologie. Een strakkere proefdierbudgettering lijkt noodzakelijk en de proefdiercommissie wordt gevraagd zich met de budgettering bezig te houden, en prioriteiten t.a.v. de besteding aan de RR voor te leggen.[295]

This quote shows that the Research Raad did not only challenge the specific research plans of Démant, but also the classical genetic approach as such. According to the Research Raad the classical genetic research was too expensive and also less effective than the modern, molecular approach. Therefore the Research Raad decided to increase its control over the laboratory animal facility, the heart of the classical geneticists' territory. Under the guise of proper prioritisation, the Research Raad aimed to restrict the animal studies of Démant and other classical geneticists.[296]

The strength by which the Research Raad encouraged Démant to reform his research lines shows that the name of the new division was more than a lip service to the global trends in the field. Rather than integrating classical and molecular genetics, the establishment of the new division served as a vehicle for the molecularisation of Démants research. That is not to say that all the members of the Research Raad unanimously shared the view that Démant had to undergo this transition. It is reasonably possible that some members of the Research Raad had diverging (and unspoken) opinions. However, because only the discussed view made it to the minutes and was translated into concrete policy, it seems very

[292] Kriek, *Notulen 12 september 1986*.
[293] E. Kriek, *Notulen Research Raad vergadering van 26 september 1986*, archive: Research Raad NKI, RR02, date: 1986. Translation: Not only Michalides, but also the rest of the Research Raad considered this to be a "useful initiative" and thus approved Démants plan and its financing.
[294] E. Kriek, *Notulen Research Raad vergadering van vrijdag 24 april 1987*, archive: Research Raad NKI, RR02, date: 1987.
[295] Kriek, *Notulen 24 april 1987*. Translation: The research appears to be classical genetics with a modern touch, and again the question presents itself whether such work should still be carried out. The proposed study will also bring along much costs for laboratory animals. It is noted that the classical genetic work still occupies relatively a lot of space in the laboratory animal house. According to some this is at the expense of more effective research using biotechnology. A stricter laboratory animal budgeting seems to be necessary and the laboratory animal committee will be asked to concern itself with budgeting, and to submit priorities regarding the spending to the RR.
[296] Kriek, *Notulen 24 april 1987*.

likely that it was the dominant attitude among the members of the Research Raad.[297] The molecular approach gradually changed into the new standard.

8.2 Working group Molecular Biology

To help the institute's staff members to meet this new standard, they were frequently advised to consult the expertise of the molecular biologists. When the Research Raad or the Beleidvoerend Orgaan evaluated research projects, it repeatedly concluded that the input of molecular biologists was needed.[298] An example of this took place in 1987, when the Research Raad evaluated the work performed at the Division of Cell Biology. Although the Research Raad was quite positive about the division's work in general, it had one recommendation for the future: "De RR beveelt aan om de te volgen strategie voor de komende jaren te bespreken met moleculair biologen."[299]

The advising role of the molecular biologists was institutionalised in 1988 by the establishment of the "Working group Molecular biology". Like other working groups at the institute, its general function was to "increase the inter-divisional contacts".[300] The Working group Molecular Biology was meant exclusively for members of the non-molecular divisions, but was put under the auspices of prominent molecular biologists. Throughout its existence, the working group would be co-chaired by the heads of the Divisions of Molecular Biology and Molecular Genetics.[301]

The accessed sources hardly report on the bi-weekly meetings of this working party, but the exact nature of the pursued "inter-divisional contacts" is illuminated when the chairmen proposed to abolish the working group in 1992. **Figure 21** shows the respective memo that the two chairmen sent to the Research Raad and the members of the working group. According to them, the working group fulfilled its function now molecular techniques were successfully introduced at all laboratories of the institute. Hence they proposed to terminate the bi-weekly meetings, although they emphasised that their expertise could still be consulted in case of any technical questions.[302] So the molecular divisions remained the core of molecular expertise, but by 1992 researchers throughout the institute embraced the new standard and incorporated it into their work.

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[297] Kriek, *Notulen 12 september 1986*. Kriek, *Notulen 26 september 1986*. Kriek, *Notulen 24 april 1987*.

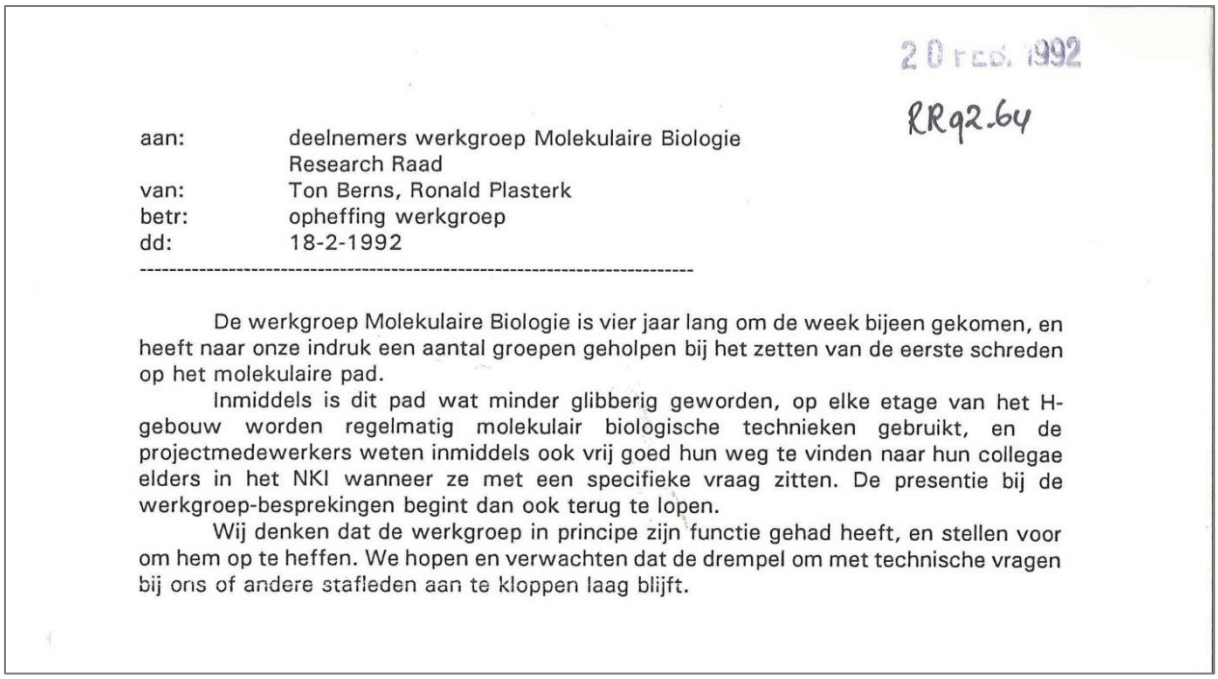
[298] E. Kriek, *Notulen Research Raad vergadering van 11 november 1983*, archive: Research Raad NKI, RR01, date: 1983.
L. den Engelse, *Werkgroep Pathomorfologie*, archive: Research Raad NKI, RR01, description: letter from Beleidvoerend Orgaan to Research Raad, date 16-01-1984.
E. Kriek, *Notulen Research Notulen Research Raad vergadering van 3 februari 1984*, archive: Research Raad NKI, RR01, date: 1984.
Author unknown, *Raad vergadering van vrijdag 25 september 1987*, 1987.

[299] Author unknown, *Notulen Research Raad vergadering van vrijdag 25 september 1987*, archive: Research Raad NKI, RR03, date: 1987. Translation: "The RR recommends to discuss the strategy for the upcoming years with molecular biologists."

[300] Borst, "Introduction," in *Annual Report 1988*, 10.

[301] Borst, "Introduction," in *Annual Report 1988*, 10.

[302] A. Berns and R. Plasterk, *Opheffing werkgroep*, archive: Research Raad NKI, RR05, description: memo to Research Raad and members of working group, date: 18-02-1992.



20 FEB. 1992

RR92.64

aan: deelnemers werkgroep Molekulaire Biologie
Research Raad
van: Ton Berns, Ronald Plasterk
betr: opheffing werkgroep
dd: 18-2-1992

De werkgroep Molekulaire Biologie is vier jaar lang om de week bijeen gekomen, en heeft naar onze indruk een aantal groepen geholpen bij het zetten van de eerste schreden op het molekulaire pad.

Inmiddels is dit pad wat minder glibberig geworden, op elke etage van het H-gebouw worden regelmatig molekulair biologische technieken gebruikt, en de projectmedewerkers weten inmiddels ook vrij goed hun weg te vinden naar hun collegae elders in het NKI wanneer ze met een specifieke vraag zitten. De presentie bij de werkgroep-besprekingen begint dan ook terug te lopen.

Wij denken dat de werkgroep in principe zijn functie gehad heeft, en stellen voor om hem op te heffen. We hopen en verwachten dat de drempel om met technische vragen bij ons of andere stafleden aan te kloppen laag blijft.

Figure 21. The memo in which the chairmen of the Working group Molecular Biology propose to abolish it. According to the chairmen, the working group successfully facilitated the introduction of molecular techniques throughout the institute and thus accomplished its task.[303]

8.3 How to convince the Ministry of Welfare, Public Health and Culture?

In the previous two sections we have seen how the research lines of the existing staff members were actively molecularised. However, also newly recruited researchers had to meet the modern standards. And although director Borst more than once emphasised that the only entry requirement was academic excellence, in practice many of these excellent recruits were molecular biologists (see figure 20).[304] Indeed, vacant positions are often at stake in boundary work. As extensively described by Gieryn, multiple parties may try to secure new staff positions for researchers belonging to their particular approach or sub-discipline.[305] Therefore this section will zoom in on one of the heated debates about the disciplinary background of new staff members that took place in the early '90s.

The provocation of this particular debate was the confidential memo titled "Toekomst van het wetenschappelijk onderzoek in het NKI: Uitbreiding van wetenschappelijke staf en faciliteiten".[306] The memo was informally called the "notitie Berns/Roos/Rodenhuis" after the staff members who wrote it, respectively from the Divisions of Molecular Genetics, Cell Biology and Medical Oncology.[307] The various versions of this memo were all written in 1992 and its aim was to support the NKI's expansion

[303] Berns and Plasterk, *Opheffing werkgroep*.
[304] P. Borst, *Nieuwe versie Knelpuntenlijst*, archive: Research Raad NKI, RR01, description: letter to Research Raad, date: 08-05-1984.
P. Borst, "Introduction," in *Annual Report 1989*, Amsterdam: The Netherlands Cancer Institute (year unknown), 11-16.
[305] Gieryn, *Cultural Boundaries*, 23.
[306] A. Berns, S. Rodenhuis, E. Roos, *Toekomst van het wetenschappelijk onderzoek in het NKI: Uitbreiding van wetenschappelijke staf en faciliteiten*, archive: Research Raad NKI, RR05, date: 20-02-1992.
A. Berns, S. Rodenhuis, E. Roos, *Toekomst van het wetenschappelijk onderzoek in het NKI: Uitbreiding van wetenschappelijke staf en faciliteiten*, archive: Research Raad NKI, RR05, date: 27-03-1992.
[307] L. den Engelse, *Notulen van de gezamenlijke Research Raad (LRR/KRR) van 20.3.92*, archive: Research Raad NKI, RR05, date: 1992.

plans by identifying the major gaps in the research repertoire. The memo describes the kind of disciplinary background new staff members had to have to cover these gaps.[308]

According to the authors, covering these gaps was essential to stay at the forefront of cancer research.[309] However, before the first version of the memo is heavily debated in the Research Raad of 20 March 1992, director Borst emphasised that the memo did not have the status of an official policy plan. Rather it had to be seen as an instrument to obtain funding from the Ministry of Welfare, Public health and Culture: "Het gaat niet om een beleidsplan maar om een plan voor de invulling van nieuwe ruimte dat onze geldgevers aan moet spreken."[310]

Not all members of the Research Raad saw this sharp distinction between policy and fund raising. For example, one member would delicately remark that "de notitie wel degelijk een soort masterplan is, dwz. een weergave van de prioriteiten die men op een bepaald moment ziet."[311] And accordingly the roaring discussions in the Research Raad did not only concern the exact status of the document, but also its contents. Multiple division heads, often backed up by their divisions, expressed deep concerns regarding the plans, whereas others saw no reason to complain.[312]

Notably the authors of the memo identified many gaps within the molecular research. In the first version of the memo they propose to recruit ten (junior[313]) group leaders, who would work in the fields of molecular genetics, molecular biology or molecular pathology. Also the cell biologists were mobilised to pursue several molecular research lines. The authors of the memo advised to recruit four cell biologists, of which three were supposed to study the functions of (onco)genes and intracellular signalling transduction.[314] Hence it is not surprising that the Divisions of Molecular Biology, Molecular Genetics and Cell Biology belonged to the firmest supporters of the memo. The members of these divisions did not take the effort to send in the requested written commentary. Predictably, their representatives in the Research Raad, who were among the authors of the memo, neither expressed any doubts concerning the proposed recruitment strategy.[315]

As mentioned, other sub-disciplines were less richly endowed by the trio Berns/Roos/Rodenhuis. Besides experimental therapy, psychosocial research and epidemiology, this also concerned immunology. Although the authors acknowledged the recently achieved successes in immunology, such as the characterisation of the MHC, they proposed to appoint only one extra junior group leader

[308] Berns, Rodenhuis and Roos, *Toekomst NKI*, date: 20-02-1992, 1-2.
Berns, Rodenhuis and Roos, *Toekomst NKI*, date: 27-03-1992, 1-2.
L. den Engelse, *Notulen van de RR-Lab-vergadering d.d. vrijdag 21 februari 1992*, archive: Research Raad NKI, RR05, date: 1992.
[309] Berns, Rodenhuis and Roos, *Toekomst NKI*, date: 20-02-1992, 2. Berns, Rodenhuis and Roos, *Toekomst NKI*, date: 27-03-1992, 2.
[310] Den Engelse, *Notulen 20.3.92*. Translation: "It does not concern a policy plan, but rather a plan for the filling of new space that must be appealing to our funders."
[311] Den Engelse, *Notulen 20.3.92*. Translation: Not all members of the Research Raad saw this sharp distinction. For example, one member would delicately remark that "the memo certainly is a kind of master plan, i.e. an expression of the priorities seen at a certain moment."
[312] Den Engelse, *Notulen 20.3.92*.
[313] Junior group leaders are called "AvL-fellows" in the memo and differ from group leaders by having less experience and group members. See: Berns, Rodenhuis and Roos, *Toekomst NKI*, date: 20-02-1992, 2.
[314] Berns, Rodenhuis and Roos, *Toekomst NKI*, date: 20-02-1992.
[315] Den Engelse, *Notulen 20.3.92*.

at the Division of Immunology. This was just enough to keep the number of staff members at the existing level, as one of the division's experienced group leaders was about to leave the division.[316]

The only possibility for expansion was seen at a new Division of Experimental Haematology. Among multiple other tasks, this division would be responsible for the evaluation of new immunotherapies. In total this full division would accommodate one group leader and two juniors, but the memo did not explicate how much of their work would be dedicated to immunotherapy. Regardless this exact quantity, the proposed expansion of immunological research was only a small fraction of the envisioned growth of molecular research.[317]

Such imbalances provoked much criticism and not in the last place from the members of Immunology.[318] In their written commentary they emphasised that the development of immunotherapy is "essentieel in toekomstig NKI", and hence they asked for "vergaande commitment" in the form of extra staff members.[319] Interestingly, they specifically pleaded for the recruitment of a molecular biologist to their division, showing that also to the immunologists the molecular approach was appealing. Nevertheless, they firmly called into question many of the proposed molecular biologists and cell biologists for the other divisions.[320]

Except of some minor compromises, the opposition of the immunologists did not have much influence on the upcoming versions of the memo. Certainly, the molecular biologists had to give up two junior positions, but these were replaced by a clinical researcher and an epidemiologist. The marginal improvement for the immunologists was the permission to recruit an experienced group leader, instead of a junior group leader.[321] The immunologists did not have enough power to overrule the prominent position of the molecular biologists. Thus, also in the final version of the memo, the institute's staff members mainly emphasised deficiencies in molecular research to support the expansion plans. An equal investment in immunology was not considered to be essential for the future position of the NKI or the persuasion of the governmental funder.

8.4 Concluding remarks

In contrast to the early '80s, we have seen in this chapter that from the mid '80s onwards the expansion of molecular biology throughout the divisions was actively promoted by the Research Raad, the Beleidvoerend Orgaan and the director. This promotion was not in the last place initiated by the

[316] Berns, Rodenhuis and Roos, *Toekomst NKI*, date: 20-02-1992.
[317] Berns, Rodenhuis and Roos, *Toekomst NKI*, date: 20-02-1992.
[318] L. den Engelse, *Notulen van de gezamenlijke Research Raad (LRR/KRR) op 6.3.92*, archive: Research Raad NKI, RR05, date: 1992.
Den Engelse, *Notulen 20.3.92*.
A. Begg, *Comments on "Toekomst van het wetenschappelijk onderzoek in het NKI"*, archive: Research Raad NKI, RR05, description: letter to secretary of Beleidvoerend Orgaan, Ed Roos, date: 26-02-1992.
C. Figdor, K. Weijer, E. Ranklin, F. Vyth and J. Borst, *Rapport "Toekomst van het wetenschappelijk onderzoek NKI"*, archive: Research Raad NKI, RR05, description: letter to Berns, Roos and Rodenhuis, date: 09-03-1992.
L. den Engelse, *Toekomst wetenschappelijk onderzoek NKI*, archive: Research Raad NKI, RR05, description: letter to secretary of Beleidvoerend Orgaan, Ed Roos, date: 17-03-1992.
[319] Figdor et al., *Rapport NKI.* Translation: In their written commentary they emphasised that the development of immunotherapy is "essential at the future NKI", and hence they asked for "extensive commitment" in the form of extra staff members.
[320] Figdor et al., *Rapport NKI.*
[321] Berns, Rodenhuis and Roos, *Toekomst NKI*, date: 27-03-1992, 2.

molecular biologists themselves, who held more and more influential positions at the institute. The number of molecular divisions was steadily increased and in the recruitment strategy much emphasis was on molecular biologists to populate these divisions. However, the molecularisation of the NKI's research programmes was not limited to the molecular divisions. Notably, researchers originally belonging to other sub-disciplines such as cell biology or classical genetics, were encouraged or even pushed to integrate the new molecular approach into their work. To go short, in the late '80s the molecular biologists exchanged their defensive and territorial attitude (described in Chapter 7) for academic imperialism, steadily expanding the molecular territory by engulfing other sub-disciplines.

As we will see later, the dominant position of the molecular biologists is an important ingredient in the explanation of the asymmetry described in Part I of this thesis. However, before we are ready to fully explicate this explanation, two more questions need to be addressed. Firstly, which factors drove the molecularisation of the NKI? And secondly, what did it mean for the immunologists to work and persevere in an institute dominated by molecular biologists? The upcoming two chapters are dedicated to the multifaceted answers to these questions.

9. Possible drivers of expansion

So far we have seen that from the late '80s onwards molecular biology was the most credible approach at the NKI and how this status resulted in the molecularisation of the institute. However, the description of this process in the previous chapters does not yet pinpoint the exact reasons why the molecular biologists became more credible than the rest. What distinguished molecular biology from other approaches, such as cell biology or immunology? To answer this question the upcoming three sections discuss respectively the role of funding agents, clinical successes and the rhetoric tools used by the molecular biologists to strengthen their position.[322]

9.1 Funding agencies

For many research institutes external research funding has been a major source of incoming money and in this respect the NKI is no exception. Hence the funding agencies possibly have had a lot of influence on the research lines pursued at the institute. Without external funding the institute's staff members cannot hire other group members, such as PhD students and technicians. As most funding is allocated on a project basis, funding agencies can influence the kind of projects executed at the institute.[323] Therefore it intersting to address to what extend funding agents contributed to the molecularisation of the NKI.

[322] Thomas Gieryn, "Home to Roost: 'Science Wars' as Baundary-Work", in *Cultural Boundaries of Science: Credibility on the line*, Chigago: The University of Chigago Press (1999), 336-362.

[323] E. Kriek, *AVR*, archive: Research Raad, RR02, description: letter from Research Raad to Ondernemingsraad, date: 08-10-1986.
Borst, "Introduction," in *Annual Report 1988*, 11.
P. Borst, "Introduction," in *Annual Report 1992*, Amsterdam: The Netherlands Cancer Institute (year unknown), 11-16.
Den Engelse, *Notulen 20.3.92*.

From 1983 onwards the *Annual Reports* contain a list of all the pending research grants, most of which are from KWF Kankerbestrijding. These lists were used to determine the number of grants per approach over the timespan of 1983 to 2015. By counting the number of *pending* grants, the analysis was corrected for the variety in the duration of grants. For example, a grant pending for four years, was counted once every year of this period. As the total number of grants allocated to NKI research groups increased from 44 in 1983 to 419 in 2014, it is useful to plot the number of grants per approach as a percentage of this total.[324] **Figure 22** shows the result of this analysis. At first sight it shows the same pattern as the two graphs discussed in Chapter 6. The molecular divisions managed to get an increasing share of the research grants, while the immunologists fluctuated around 10%. In 2014 the molecular biologists held about one third of the grants, which was in accordance with the proportion of molecular divisions (5 out of 15).

However, the difference with the immunologists was sometimes less profound than one might expect based on the growing number of molecular divisions and staff members. For example, at the turn of this century the molecular biologists had three divisions and accordingly three times more staff members than the immunologists (see figure 20). However, in 2002 these three molecular divisions managed to acquire only twice as many grants as the immunological division (29.7% versus 14.1%). In other words, the immunologists have been relatively successful in securing their financial position. In general the funding agencies did not award a disproportional number of grants to the molecular biologists.

Yet this does not imply that the funding agencies did not contribute to the expansion of the molecular biology at the institute. On the one hand it could be that the molecular biologists simply obtained a larger share of the grants because they were with more researchers and therefore could apply to more grants. On the other hand it is possible that molecular biologists were with more researchers exactly because they were awarded more grants. Furthermore, it is possible that the grants awared to the molecular biologists were relatively high. The available data at the NKI are inconclusive about these possibilities.

To fully grasp the influence of the funding agencies it might be useful to consult the archive of the KWF and other important agencies. Performing the needed analyses is beyond the scope of this thesis, but at least two suggestions can be done based on the findings in this study. To start with, a closer study of these agencies may reveal certain patterns or preferences in the granting of projects. For example, in the '90s the KWF seemed to have a fixed limit for the amount of money spent on immunological projects. According to the KWF's annual reports, it awarded every year at most 15% of its research budget to immunologists. On the contrary, no such limit existed for molecular biologists, which suggests that there was a certain strategy underlying the distribution of grants over various approaches.[325]

[324] Appendix 1, supplementary figure 1.

[325] Author unknown, "Wetenschappelijk onderzoek, onderwijs en opleiding," in *Jaarverslag 1994*, Amsterdam: Nederlandse Kankerbestrijding (year unknown), 55-71.
Author unknown, "Wetenschappelijk onderzoek, onderwijs en opleiding," in *Jaarverslag 1995*, Amsterdam: Nederlandse Kankerbestrijding, (year unknown), 51-68.
Author unknown, "Wetenschappelijk onderzoek, onderwijs en opleiding," in *Jaarverslag 1996*, Amsterdam: Nederlandse Kankerbestrijding, (year unknown), 49-62.

Secondly, the agencies' archives might contain overviews of all the submitted proposals. The sources of the NKI only provide complete overviews of the successful submissions, but not of the unsuccessful ones. Comparing the lists of submitted and actually granted proposals will give insight into the relative success rates of various types of projects and researchers. Describing these kind of patterns and the underlying policies may illuminate to what extent funding agencies indeed control(led) scientific developments.

Until these additional studies are performed, we cannot know whether the funding agencies indeed actively promoted the molecularisation of the NKI. However, we can conclude that their role was at least permissive. The molecular biologists got the grants they needed to expand, while this was certainly not the case for the immunologists.

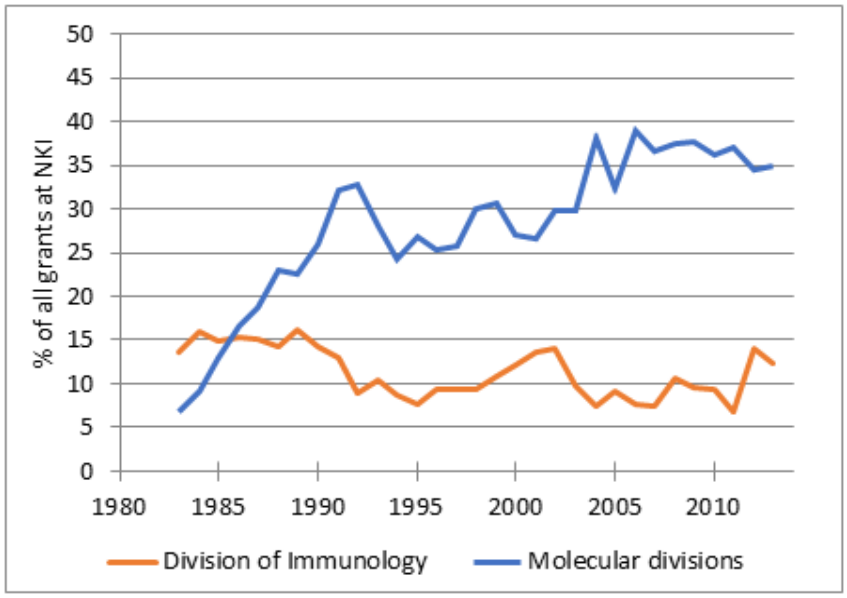


Figure 22. Pending grants per approach (100% = all grants at NKI). The presented data were derived from the NKI's *Annual Reports*, which from 1983 onwards contain an overview of all the pending research grants. Grants were classified as "immunological" or "molecular" according to the divisions of the grant holder. The number of grants is plotted as the percentage of the total number of grants at the NKI.

9.2 Clinical success: The final arbiter?

In Part I of this thesis we have seen that both immunologists and molecular biologists aim to improve cancer therapy. Furthermore, it were the clinical successes of immunotherapy that recently got the immunologists off the blacklist. Curing cancer patients seems to be the final arbiter in cancer research. Hence it is interesting to verify whether any clinical successes related to molecular biology drove its

Author unknown, "Wetenschappelijk onderzoek, onderwijs en opleiding," in *Jaarverslag 1997*, Amsterdam: Nederlandse Kankerbestrijding, (year unknown), 47-63.
Author unknown, "Wetenschappelijk onderzoek, onderwijs en opleiding," in *Jaarverslag 1998*, Amsterdam: Nederlandse Kankerbestrijding, (year unknown), 51-71.
Author unknown, "Wetenschappelijk onderzoek, onderwijs en opleiding," in *Jaarverslag 1999*, Amsterdam: Nederlandse Kankerbestrijding, (year unknown), 57-77.
Author unknown, "Wetenschappelijk onderzoek, onderwijs en opleiding," in *Jaarverslag 2001*, Amsterdam: Nederlandse Kankerbestrijding, (year unknown), 33-53.

expansion from the '80s onwards. Did the molecular approach distinguish itself from others by yielding more convincing clinical results?

To answer this question we need to focus on the earliest examples of targeted therapies. As discussed in Chapter 2, interviewees of B7 saw the development of Herceptin (for breast cancer) and Gleevec (for leukaemia) as important clinical breakthroughs in molecular cancer research.[326] The oncogenic targets of these early paradigms of targeted therapy were already identified in the early '80s. About one decade later these drugs showed promising results in *in vitro* and mice experiments. Phase I studies in patients were started earlier for Herceptin than for Gleevec (1992 versus 1998), but both drugs were only approved by the European Medicines Agency in 2000 and 2001 respectively.[327]

This short summary does not do justice to the ever complex histories of drug development, but the bottom line is of chronological nature: in the '80s and early '90s these targeted therapeutics were not yet introduced into the clinic, let alone standard of care. In this respect the targeted therapies were not ahead of the former immunotherapies, such as IL-2 infusion.[328] Both showed promising results in laboratory experiments and small clinical trials, but their efficiency was not shown yet in large patient populations.[329] It is very likely that the clinical successes of Herceptin and Gleevec further improved the credibility of the molecular approach around the year 2000, but they came simply too late to function as the drivers of the NKI's molecularisation. Apparently, clinical successes are not always the final arbiter in cancer research. So if the molecular biologists could not yet appeal to superior clinical achievements, then the question remains: why were they so credible?

9.3 Rationality at stake: The promise of the molecular approach

A preliminary, general answer to the previous question is provided by science journalist Robert Bazell in the rather heroic work *Her-2: The Making of Herceptin, a Revolutionary Treatment for Breast Cancer*. In this book Bazell describes the high expectations of targeted therapies and how these expectations were fuelled by the discovery of oncogenes:

> No matter who got the credit, the discovery of oncogenes and the growing understanding of how they work revolutionized cancer research by providing

[326] IM1.31; IM6.27; IM7.58-59, 7.64.

[327] H.M. Shepard, P. Jin, D.J. Slamon, Z. Pirot, D.C. Maneval, "Herceptin," in *Handbook of Experimental Pharmacology*, ed. Yuti Chernajovsky and Ahuva Nissim, Berlin: Springer (2008), 183-219.
Tony Hunter, "Treatment for chronic myelogenous leukemia: the long road to imatinib," *The Journal of Clinical Investigation* 117 (2007), 2036-2043.
Author unknown, "Herceptin," European Medicines Agency, url: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000278/human_med_000818.jsp&mid=WC0b01ac058001d124, last update: 12-11-2015, consulted at: 15-11-2015.
Author unknown, "Glivec," European Medicines Agency, url: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000406/human_med_000808.jsp&mid=WC0b01ac058001d124, last update: 09-06-2015, consulted at: 15-11-2015.
Note: In the USA Herceptin was approved by the Food and Drug Administration two years earlier in 1998.

[328] Author unknown, "Division of Immunology," in *Annual Report 1991*, Amsterdam: The Netherlands Cancer Institute (year unknown), 49-62.

[329] Shepard et al., "Herceptin." Hunter, "Imatinib."
Author unknown, "Division of Immunology," in *Annual Report 1988*, Amsterdam: The Netherlands Cancer Institute (year unknown), 49-60.
Author unknown, "Division of Immunology," in *Annual Report 1991*, Amsterdam: The Netherlands Cancer Institute (year unknown), 49-62.

> the first understanding of the fundamental biology of the disease. A "magic bullet" therapy that would attack the disease at its root and halt its growth without inflicting any damage to healthy tissue had long been a dream in cancer treatment. But science needed a target. Now, finally, it had one. Researchers knew what they were looking for; they knew where to train their sights. In the late '70s and early '80s, scientists found dozens of oncogenes, along with a related class of genes called tumor suppressors that can give rise to cancer. The neu oncogene, once bypassed by Weinberg, would play a key part in the struggle to bring the new genetic understanding of cancer out of the laboratory and to the patient's bedside.[330]

To go short, the high clinical expectations of the molecular approach were justified by its theoretical merits. The molecular approach was generally considered to provide fundamental insight into the aetiology of cancer.[331] This fundamental insight was expected to teach us how to target cancer cells in a precise way. Rather than the unspecific chemotherapeutics, the new molecular understanding would enable a highly specific form of cancer treatment.[332] Scientifically this approach must have been very appealing: not fighting cancer with high doses of cytotoxic chemotherapy, but through fundamental understanding of its biology. For this reason targeted therapies have been alternatively named "rational drugs".[333] The latter exemplifies Gieryn's claim that in boundary work not only laboratory space and staff positions are at stake, but also epistemic authority and rationality.[334] In cancer research it has been considered literally rational to specifically target the products of oncogenes.

This widely held interpretation of rationality resonated at the NKI in the '80s and '90s. Especially in documents meant for communication with external parties, the promise is made that the newly gained knowledge would drastically improve cancer therapy.[335] An illustrative example of this stems from the earlier discussed expansion plans in the early '90s. In this period the institute tries to convince the Dutch state to financially support its expansion plans.[336] Multiple documents were made in which the

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[330] Robert Bazell, *Her-2: The Making of Herceptin, a Revolutionary Treatment for Breast Cancer*, New York: Random House (1998).

[331] James Le Fanu, "The Brave New World of the New Genetics," in *The Rise And Fall Of Modern Medicine*, revised edition, New York: Basic Books (2012), 311-350.

[332] Bazell, *Her-2*, 18-28.

[333] B.V. Madhukar and J.E. Trosko, "The causes of cancer: implications for prevention and treatment," *Indian Journal of Pediatrics* 64 (1997), 131-141
G.N. Hortobagyi, "Developments in chemotherapy of breast cancer," *Cancer* 88 (2000), 3073-3079.
N. Sharifi and R.A. Steinman, "Targeted chemotherapy: chronic myelogenous leukemia as a model," *Journal of Molecular Medicine* 80 (2002), 219-232.
K.L. Gorringe and I.G. Campbell, "A rational approach to cancer therapy," *Genome Biology* 306 (2008), 5.

[334] Gieryn, *Cultural Boundaries*, 362.

[335] Borst, "Introduction," in *Annual Report 1983*, 1.
Author unknown, "Over het verenigingsjaar," in *78e jaarverslag 1991*, Amsterdam: The Netherlands Cancer Institute (year unknown), 7-12.
Piet Borst, "Ten geleide," in *Werkplannen 1991*, Amsterdam: The Netherlands Cancer Institute (year unknown), archive: Centrale Kanker Bibliotheek, 1-3.
Piet Borst, "Introduction," in *Annual Report 1995*, Amsterdam: The Netherlands Cancer Institute (year unknown), 13-18.

[336] Author unknown, "Over het verenigingsjaar," in *77e jaarverslag 1990*, Amsterdam: The Netherlands Cancer Institute (year unknown), 7-12.

expansion was propagated, including the document *Werkplannen 1991*.[337] In the introduction to the *Werkplannen 1991*, director Borst highlights the most important arguments for this expansion:

> Daarnaast zijn er belangrijke incidentele argumenten voor uitbreiding: Het kankeronderzoek is nu in een zeer productieve fase gekomen. Het oncogen onderzoek heeft globaal laten zien hoe kanker ontstaat. Het is nu mogelijk om het oncogene proces meer in detail op te helderen; de verwachting bestaat alom dat deze nieuwe kennis ook zal leiden tot substantiële verbeteringen bij de diagnostiek en therapie van kanker.[338]

However, the new etiological insight emanating from the discovery of oncogenes did not only provoke high clinical expectations. It also was considered to put cancer research as such centre stage and thereby boosted the self-confidence of the institute's researchers. This increased self-confidence is exemplified by a letter the Research Raad sent to the institute's Ondernemingsraad (in English: Works Council) in the autumn of 1986.[339] In this letter the Research Raad aimed to inform the Ondernemingsraad about the current situation of cancer research, which displays the self-confidence the molecular approach brought along:

> Sinds het eind van de 70'er jaren is het kankeronderzoek verschoven van de zijlijn naar het middenveld. Waar voor die tijd kankeronderzoekers ontwikkelingen op meer algemeen biologisch/biochemisch gebied in de gaten hielden, en, waar opportuun, op de eigen problematiek toepasten, zo zijn nu de rollen omgedraaid. Het moleculair-genetisch en celbiologisch onderzoek van tumorcellen legt processen bloot die onderwerp zijn van de fundamentele vraagstellingen van de biologie in het algemeen. Het is ons nu duidelijk, dat begrip van celproliferatie en de kwaadaardige afwijkingen van het normale patroon, onlosmakelijk verbonden is met gedetailleerde studies van oncogenen en al wat daarmee samenhangt. Slechts een tiental jaren geleden nog had een dergelijke opmerking waarschijnlijk grote verbazing gewekt.[340]

[337] Author unknown, "Over het verenigingsjaar," in *77e jaarverslag 1990*, 7-8. Borst, "Ten geleide," 1-3. Berns, Rodenhuis and Roos, *Toekomst NKI*, date: 20-02-1992.

[338] Borst, "Ten geleide," 2. Translation: In addition there are important, incidental arguments for expansion: nowadays cancer research got into a very productive phase. The study of oncogenes has shown generally how cancer arises. Now it is possible to elucidate the oncogenic process in more detail; is it broadly expected that this new knowledge will result in substantial improvements in the diagnosis and therapy of cancer.

[339] Kriek, *AVR*.

[340] Kriek, *AVR*. Translation: From the late '70s onwards cancer research has taken centre stage. Whereas previously cancer researchers followed the developments in the more general biological/biochemical fields, and, if appropriate, applied to their own problems, now the roles are reversed. The molecular-genetic and cell biological study of cancer cells elucidates fundamental biological processes. It is clear now, that the understanding of cell proliferation and malignant deviations from the normal pattern are closely linked with detailed studies of oncogenes and that comes with it. Only ten years ago such a remark would have probably caused great surprise.

9.4 Concluding remarks

In this chapter we discussed three factors that possibly drove the molecularisation of the NKI. At first we have seen that the role of the funding agencies was at least permissive. Unlike the immunologists, the molecular biologists were awarded an increasing number of research grants which enabled their expansion. However, additional studies are needed to pin down whether the funding agencies actively promoted this process by favouring molecular projects.

A sharper conclusion can be drawn about the role of clinical achievements, discussed in Section 9.2. The approval of Herceptin and Gleevec at the turn of this century may have enhanced the process of molecularisation, but certainly did not initiate it. In the '80s and early '90s the targeted therapies were not developed further than immunotherapies: both strategies yielded positive but preliminary results in preclinical experiments and small-scale trials.

Nevertheless, in the third section of this chapter we saw that the molecular approach was continuously presented as the most promising one. At the NKI and beyond the molecular biologists successfully framed their approach as the *rational* approach. A closer study of a tumour's oncogenic drivers would reveal its Achilles heel. The molecular approach held the promise to unite two ideals: fundamental understanding of tumour formation and the development of highly specific cancer drugs. This combination distinguished the molecular biologists from others such as the immunologists. With their focus on immune cells, the studies of the immunologists were not expected to yield fundamental insight into the molecular drivers of oncogenesis.

10. Scattered alliances in the war on cancer

Thusfar we have discussed how molecular biology developed into the prevailing approach at the NKI. This chapter will shift the attention more towards the implications of this development for the immunologists. What did it mean for the immunologists to work in an institute in which the molecular biologists set the standards? A first clue comes from a number of old jokes which field members shared with me during the (informal) interviews. For example, one of the institute's group leaders came up with a riddle that circulated at the institute in the time that the Division of Immunology was situated at floor 7 of the H building: "Een tijd geleden was er een grap. Waarom bestaat H7? Zodat H8 niet op H6 dondert."[341] Furthermore, one of the group leaders working at B3 told an anecdote to illustrate the reputation of some members of Immunology in the mid '90s:

> Als misschien als mooi voorbeeld, toen ik hier net [euhm] mijn lab was begonnen, toen was [eh] mijn [eh] voormalige [eh, eh] PhD advisor X was hier op een sabbatical. [eh] In die tijd werkte hier nog een medisch oncoloog, een beetje van... ja, de vorige generatie, die immuuntherapie... ja, nog een beetje deed op een meer soort van... ja, holistisch idee, he, van we geven patiënten een combinatie van cytokines and dan, then we keep our fingers crossed. [euhm] En X had dus een beetje de kans gezien om dat een beetje van de zijlijn [euh] aan te zien terwijl die hier sabbatical deed. En zijn uitspraak was: "ik laat me nog liever door Jomanda behandelen dan [eh] door deze clinicus." Dus dat, dat geeft een beetje aan hoeveel twijfel er was, in ieder geval bij sommige mensen, [eh, euhm] bij de immuuntherapie zoals die op dat moment [eh, eh] was ontwikkeld.[342]

[341] FI123. Translation: "Some time ago there was a joke. Why does H7 exist? To avoid H8 from booming on H6."
[342] II3.33-35. Translation: Maybe as a nice example, when I just started my lab here, my former PhD advisor X was here for a sabbatical. In that time there was still a medical oncologist working here, who was a bit of the

Also other interviewed field members indicated that the immunologists were object of derision and more serious accusations. Both members of B3 and B7 affirm that the immunologists were often seen as the opposite of the molecular biologists: descriptive, holist, vague, unpromising, suspect and even pseudoscientific.[343] Unsurprisingly, the existing concerns about the immunological approach also influenced decisions when new staff positions or laboratory space were at stake. According to one of the group leaders of B7, who started his career at the NKI in the early '90s, the credibility of the immunologists was low and hence they were impaired in the competition for human and material resources:

> [Interviewer:]
> En [eh], dus toen jij hier met je stage bezig was, en ook uiteindelijk bent gaan promoveren, [euhm] wat, wat was toen de heersende opvatting over immunotherapie? Dacht men, nou dat gaat het worden? Of dat [eh]…
>
> [Interviewed group leader:]
> Nee, toen ik dus als student hier was, toen ging het niks worden. Nee, het was dus zelfs hier in het instituut, binnen het NKI, was er een soort... nou niet tweestrijd, maar er was wel wat, wat meningsverschil of we wel of niet meer moesten investeren in de immunologie of dat we dachten van nou... dat gaat hem niet worden.
>
> [Interviewer:]
> En hoe merkte je dat dan? Dat soort…
>
> [Interviewed group leader:]
> Nou, er was een discussie natuurlijk over, van welke nieuwe groepsleiders aangetrokken moesten worden, of ze meer ruimte moesten krijgen, of ze… hè, dat soort dingen allemaal. En daar werd, werd over gesproken, ook.
>
> [Interviewer:]
> En dat kreeg je mee als student?
>
> [Interviewed group leader:]
> Ja.
>
> [Interviewer:]
> Echt?
>
> [Interviewed group leader:]
> Ja.

previous generation, who did immunotherapy on a more holist base, like we give patients a combination of cytokines and then we keep our finger crossed. And X had the chance to observe all this during his sabbatical. And his quote was: "I'd rather be treated by Jomanda [a controversial, Dutch alternative healer] than by this clinician." So that shows how much doubt there was, at least among some, about the state of immunotherapy in those days.

[343] FI139, 143; FM122; II3.8, 9-11; IM6.48; IM7.42.

[Interviewer:]
Kan je je nog concrete situaties herinneren?

[Interviewed group leader:]
[Euh] Nou ja dat ene, nou echt concreet niet, maar, maar inderdaad wel dat echt er gediscussieerd werd over als er dan nieuwe faculty of nieuwe groepsleiders gezocht moeten worden, van waar, in welk gebied die dan gezocht werden. Hè, is dat dan in de moleculaire biologie, in de oncogene cell cycle control of is dat in de immunologie. En dat er dan wel discussies waren, van dat we zeiden van die immunologie, dat moesten we maar een beetje op een laag pitje zetten, want dat zien we niet [eh] een grote bijdrage leveren aan [eh] kanker.[344]

The personal experience of this group leader is consistent with the patterns discussed in the previous chapters: the molecular biologists were allowed to expand, at the expense of others such as the immunologists. In fact, when Borst started as the institute's director in 1983, he was advised to completely abolish the Division of Immunology. In one of his columns in the Dutch newspaper *NRC Handelsblad* he describes the former scepticism about immunotherapy, and thus about the Division of Immunology, among his colleagues.[345] In unrecorded oral communication Borst confirmed that multiple of his advisers saw the abolishment of Immunology as the easiest way to save resources.[346] Although Borst never followed this advice, it shows that the jokes mentioned above were not meaningless. Insofar we can judge from the oral histories articulated by the field members, the immunologists seemed to have been outsiders with a low social status in the '80s and '90s.

On this note it is useful to consider the account of Steve Sturdy from the volume *Molecularizing Biology and Medicine*. Building upon various case studies, Sturby concludes that the molecularisation of the biomedical sciences was not merely a technical transformation. Rather, he argues, we should study

[344] IM7.49-51. Translation:
[Interviewer:] And when you were doing your internship here, and eventually also your PhD, what was the general opinion about immunotherapy? Did people think, well, this is going to make it? Or that…
[Interviewed group leader:] No, when I was here as a student, it would not make it. No, it was even that case that here at the institute, at the NKI, there was a sort of… well, not a struggle, but there was disagreement about whether or not we had to invest more in immunology, or whether we thought well… this will not make it.
[Interviewer:] And how did you notice this?
[Interviewed group leader:] Well, there was a discussion about what kind of group leaders needed to be recruited, whether they had to get more space, or… Those kind of things. And this was discussed.
[Interviewer:] And you heard about this, as a student?
[Interviewed group leader:] Yes.
[Interviewer:] Really?
[Interviewed group leader:] Yes.
[Interviewer:] Can you remember concrete situations?
[Interviewed group leader:] Well, not really concrete, but indeed, there were discussions when new group leaders had to be recruited, about the field they had to come from. Is that molecular biology, in the oncogenic cell cycle control, or is that in immunology. And there were discussions, in which we said that immunology had to be put on the back burner, because we think that it will not contribute a lot to cancer.
[345] Piet Borst, "Kankerimmunotherapie," *NRC Handelsblad*, url: http://www.nrc.nl/handelsblad/2013/06/01/kankerimmunotherapie-12664373, last update: 10-06-2013, consulted at: 10-01-2016.
[346] Unrecorded oral communication with Piet Borst, 06-08-2015.

the circulation of molecular technologies within the context of newly formed networks, which allied researchers from various fields.[347]

However, in this study concerning the NKI it seems like not everyone was equally welcome to join these molecular networks. As discussed in Chapter 8, among others the classical geneticists and cell biologists were (strongly) stimulated to integrate their work with that of the molecular biologists. On the contrary, the immunologists were virtually never encouraged to use molecular techniques or to consult the expertise of molecular biologists.

Were the immunologists indeed excluded from the newly formed molecular networks? To answer this question, the upcoming chapter will discuss to what extent the immunologists had an outsider status. To start with, Section 1 will describe the collaborative networks in which the immunologists and the molecular biologists were embedded. Subsequently, in Section 2 will be discussed whether the immunologists and molecular biologists shared a disciplinary identity, based on the journals they read and they published in. Lastly, in Section 3 will be discussed how the immunologists related their own work to the molecular approach to avoid (further) isolation.

10.1 Networks of collaboration: Shared grants and publications

To gain insight into the networks of collaboration in which the immunologists and molecular biologists were enrolled, data about shared research grants and publications were collected. As described in Chapter 9, the *Annual Reports* contain overviews of the pending research grants since 1983. Besides the title of the project and the name of the main applicant, up to 2006 these overviews also list the divisions involved in each project. Thus, it could be analysed how often and with whom research grants were shared between divisions for the period between 1983 and 2006. The left panel of **figure 23** shows that the relative importance of shared grants increased considerably over the years. While in the early '80s none of the NKI grants was shared between divisions, this gradually increased to about 15% of the total number of grants in the late '90s. Constituting an important part of the research budget, the shared grants can be used as a measure to identify patterns in collaboration.

Notably, a deeper focus on our groups of interest shows that both the immunologists and the molecular biologists descend from the institute-wide pattern (see figure 23, right panel). The proportion of shared grants involving immunologists rather abruptly jumps to about 15% in the early '90s. On the contrary, the molecular biologists increase very gradually up to only 10%. Possibly the molecular biologists were more successful in acquiring grants independently, whereas the immunologists had to associate with others to convince the funding agencies. Nonetheless, the immunologists, and to a lesser extent also the molecular biologists, associated with others to acquire funding.

[347] Sturby, "Reflections: Molecularization," 288.

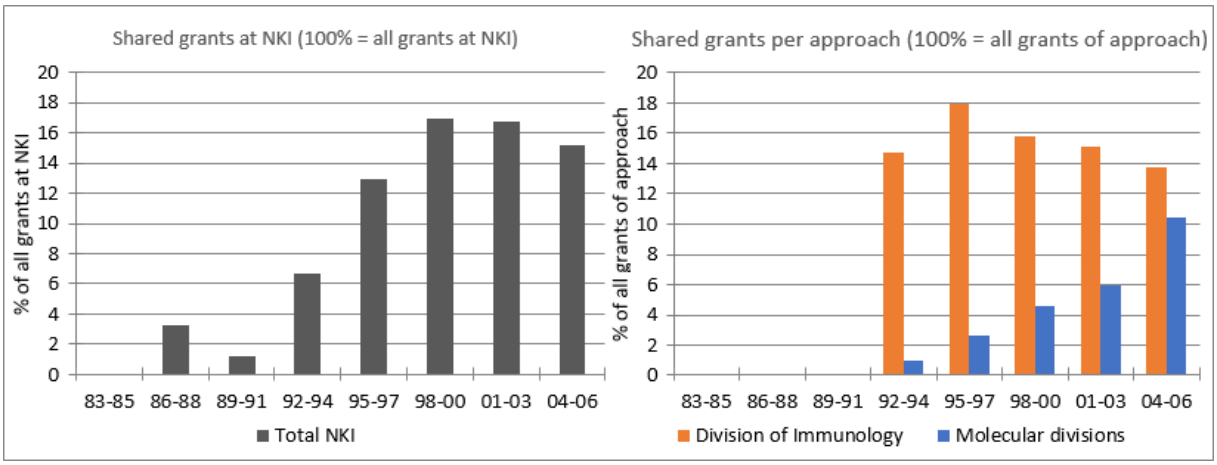

Figure 23. Percentage of shared grants for the full NKI (left) and for the approaches of interest (right) from 1983-2006. Sharing research grants became more common over the analysed period, although the immunologists shared relatively more grants than the molecular biologists. Data were derived from the *Annual Reports 1983-2006*. The total numbers of analysed pending grants are 3249 (NKI), 357 (Immunology) and 917 (molecular divisions).

So at first sight these data seem to suggest that the immunologists were not isolated from the other divisions. However, a closer analysis of the collaborative partners of the immunologists and molecular biologists reveals an important pattern. The pie charts in the upper half of **figure 24** show the type of divisions they shared their grants with. Firstly, the immunologists collaborated in more than three-quarters (77%) of the cases with "clinical" research divisions, such as Experimental Therapy or Medical Oncology. Unlike the "fundamental" research divisions (e.g. Immunology, Cell Biology or Molecular Genetics), this class of clinical divisions predominantly performs patient based research, including clinical trials.[348] For the remaining 23% the immunologists' co-applicants were from other fundamental research divisions, including the molecular divisions. With the latter the immunologists only shared a one-year grant in 2002, accounting for 3% of the grants they shared between 1983 and 2006.[349]

Likewise, this exceptional immunological-molecular grant constitutes just a minor portion of all the grants the molecular biologists shared (2%). However, concerning the other divisions, the collaborations of the molecular biologists show an opposite pattern (see figure 24). In more than three-quarters (78%) of the cases they shared a grant with the fundamental research divisions, not in the last place with the other molecular divisions (20%, see supplementary figure 2).[350] Only the remaining 22% was shared with clinical divisions. Thus, at the level of grants, the molecular biologists had more connection with the other fundamental researchers, while the immunologists allied themselves with clinicians. In supplementary figure 3 is shown that particular alliance between the immunologists and the clinicians was fairly stable over the years.[351]

[348] A. Berns, "Wetenschappelijk onderzoek," in *82e Jaarverslag 1995*, Amsterdam: The Netherlands Cancer Institute (year unknown), 6-7.
[349] Appendix 1, supplementary figure 2.
[350] Appendix 1, supplementary figure 2.
[351] Appendix 1, supplementary figure 3.

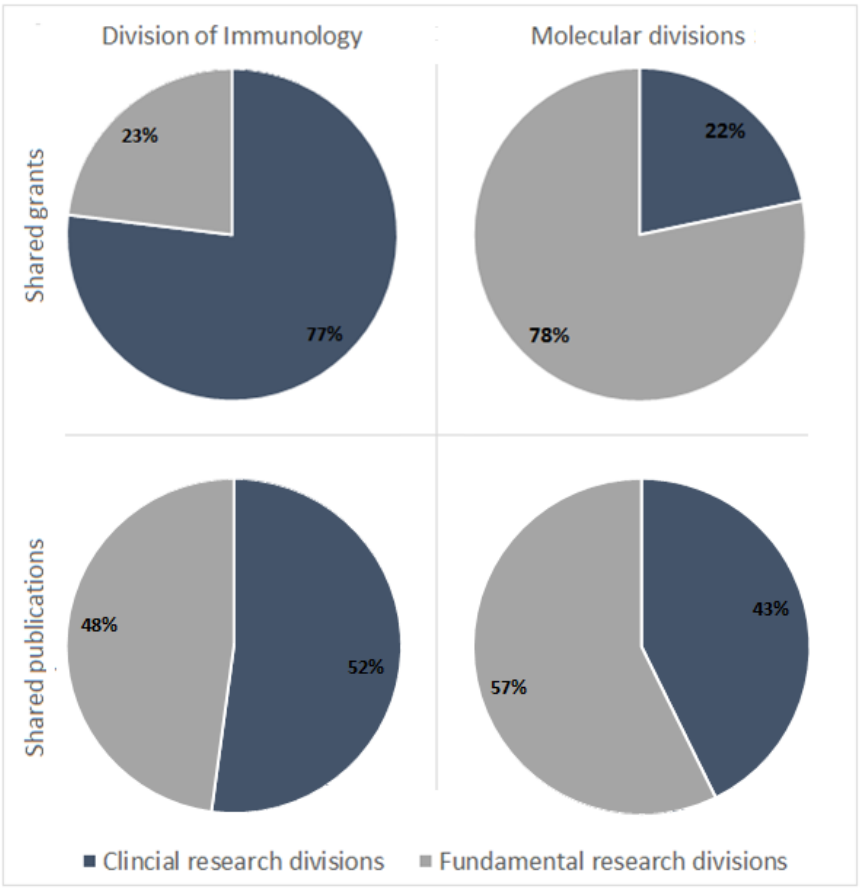

Figure 24. Collaborative partners in the sharing of grants and publications per approach from 1983-2006. The immunologists shared more often grants with clinical research divisions, while the molecular biologists shared more grants with fundamental research divisions. At the level op publications the tendency is the same, although the difference is less profound. Data were derived from the *Annual Reports 1983-2006*. Total numbers of analysed pending grants are 357 (Immunology) and 917 (molecular divisions). Total numbers of analysed publications are 444 (Immunology) and 1075 (molecular divisions).

If the acquirement of a shared grant is the starting signal for collaboration, a shared publication demarcates its finish line. As we have seen in Chapter 2, a scientific publication is often considered to be the endpoint of a successful project. Further highlighting the importance attached to publications, the institute's library publishes yearly a *Citation analysis* since 1983. These extensive documents contain lists of all the publications per division, their authors and the impact factors.[352] As a result, the relative occurrence of inter-divisional collaborations could also be analysed at the level of publications.

Unlike the grants, the sharing of publications is already a common practice at both the immunological and molecular divisions in the early '80s, as shown in **figure 25**. Neglecting an exceptional high number of shared publications for the immunologists between 1983-1985, there is an upward trend in the number of shared publications until the mid '90s. From then on the percentage of shared publications seems to stabilise for both approaches around the 30%, which is remarkably higher than the proportion of shared grants in the same period (see figure 23).

[352] Irene Benne and Miebet Wilhelm, *Citatie-analyse van publicaties uit het Annual Report 1995*, Amsterdam: The Netherlands Cancer Institute (1999).

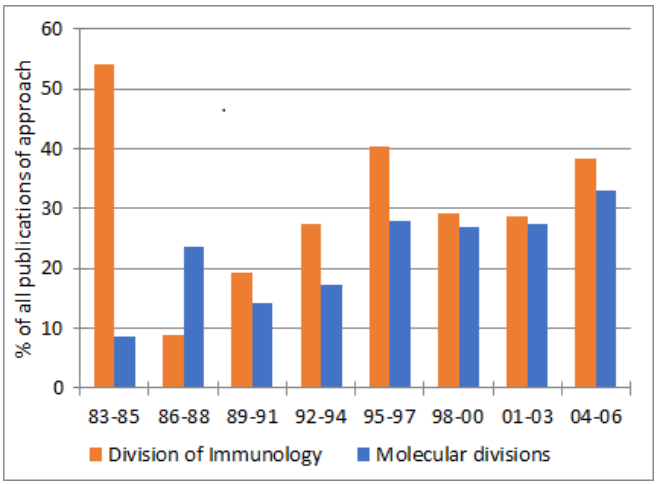

Figure 25. Percentage of shared publications per approach from 1983-2006 (100% = all publications of approach). From the mid '90s onwards the percentage of shared grants stabilises around 30% for both approaches. Data were derived from the *Citation Analyses 1983-2006*. Total numbers of analysed publications are 444 (Immunology) and 1075 (molecular divisions).

Based on the same kind of analysis performed for the grants, the lower half of figure 24 shows the divisions the publications were shared with. Notably, the difference we saw at the level of grants is less pronounced at the level of publications. In the period from 1983 to 2006 the immunologists shared 52% of their publications with the clinical researchers, while they shared 77% of their grants with them. Conversely, the molecular biologists shared their grants only in 22% of the cases with clinicians, but they co-published with them in 43% of the cases. In other words, the immunologists shared considerably less publications with the clinical divisions than one may expect based on the grants they shared and vice versa for the molecular biologists.

More specifically, between 1983 and 2006 the immunologists shared 21 publications with molecular divisions, constituting 14% of all publications they shared (see supplementary figure 2).[353] In other words, the molecular biologists were not uncommon publication partners for the immunologists, although they only shared one grant with them. Yet, when we take into account that the immunologists and molecular biologists published respectively 444 and 1075 papers in this period, the 21 shared papers do not seem to suggest that they shared a publication culture.

These kind of comparative analyses show that the funding agencies do not always determine the scientific output in terms of publications. Between the starting signal and the finish line, inter-divisional collaborations are partly redefined. Nevertheless the general patterns are consistent: between 1983 and 2006 the immunologists shared most grants and publications with clinicians, while the molecular biologists collaborated mainly with fundamental research divisions.

10.2 Shared disciplinary identity: Publication cultures

However, the findings discussed in the previous section are not enough to conclude that the immunologists and molecular biologists operated in isolation of each other. A common disciplinary identity is not only to be achieved by shared grants and publications. At a more general level

[353] Appendix 1, supplementary figure 2.

disciplinary boundaries are often reflected by the journals in which researchers publish their findings. As Ruud Abma puts it in *Over de grenzen van disciplines*: "Ze functioneren niet alleen als communicatiemiddelen, als platforms voor ideeën en organen voor kwaliteitstoetsing, maar hebben ook een rol in de verdeling van prestige onder vakgenoten."[354] Because scientific journal are important pillars of disciplinary identity, it is useful to analyse whether the immunologists and molecular biologists shared a publication culture. Did they published in and read through the same journals?

Production of literature

To identify any overlap or difference in publication culture, the journals in which the Divisions of Immunology and Molecular Biology published were classified. A journal was counted as immunological if the title contained words such as "immunity" or "immunotherapy". Equally, titles containing words like "molecular" or "oncogene" were classified as molecular biology journals.[355] The upper panels of **figure 26** show the results of this analysis. Perhaps unsurprisingly, in the analysed period the immunologists indeed published between 43% and 65% of their papers in immunological journals. Likewise, the papers from the Division of Molecular Biology frequently appeared in molecular journals, although they showed a somewhat higher fluctuation throughout the years (26-78%).

By contrast, the immunologists and molecular biologists published hardly in "each other's" journals, although also here an asymmetry can be observed. The molecular biologists only occasionally published in immunological journals, while the immunologists published a small but rather stable proportion in molecular journals. In order words, the overlap between their publication cultures is predominantly at the molecular side of the spectrum. However, in general the presented data show that both the immunologists and the molecular biologists tended to publish in approach-specific journals.

The same patterns are observed when the analysis is performed for two specific journals that epitomise both classes: *The Journal of Immunology* and *The European Molecular Biology Organisation Journal* (figure 26, middle panels). The patterns for these individual journals are more erratic, but the general tendency is the same. The immunologists published up to 35% of their papers in *The Journal of Immunology*, while the molecular biologists only in exceptional cases presented their work there. Vice versa the molecular biologists published considerably more often in *The European Molecular Biology Organisation Journal*.

Nonetheless, not all papers were published in these approach-specific journals. For example, both divisions published a minor fraction of their work (5-20%) in domain-specific journals for oncology.[356] Additionally, the immunologists and molecular biologists also published in less-specialist journals, including general medical and scientific journals (figure 26, lower panels). Interestingly, the immunologists published a considerable part of their work in the medical *Journal of Experimental Medicine* (3-15%). In the same period, the molecular biologists only once published their findings in

[354] Ruud Abma, "Disciplines," in *Over de grenzen van disciplines: Plaatsbepaling van de sociale wetenschappen*, Nijmegen: Uitgeverij Vantilt (2011), 25-41. Translation: "They do not only function as means of communication, as platforms for ideas and organs for quality assessment, they also play a role in the distribution of prestige among peers."

[355] Classification criteria were as follows. Immunological journals: antigens, immunity, immuno-, immunology, immunotherapy, leucocyte, lymphocyte, thymus. Molecular journals: DNA, gene, genetics, molecular, mutation, nucleic acid, oncogene, signalling.

[356] Appendix 1, supplementary figure 4.

this journal. Consistent with the earlier described collaborative networks, these data reflect the tight links between the immunologists and the clinical researchers.

However, the opposite is the case for the prestigious general science journals *Nature*, *Science* and *Cell*. The difference is certainly not like day and night, but overall the molecular biologists managed to get a larger fraction of their papers published in these high impact journals. Only in the latest analysed timeslot (2003-2006) the immunologists exceed the molecular biologists in this respect.[357] As appears from several archival sources, already in the '80s and '90s the impact factors of publications were used as an important measure for scientific productivity and quality, not in the last place by molecular biologists themselves.[358] Consequently, the relative high number of publications in *Nature*, *Science* and *Cell* may have increased the prestige and credibility of the molecular biologists.

[357] Also in absolute numbers the pattern is the same. In that case the immunologists exceed only twice the molecular biologists. See Appendix 1, supplementary figure 5.

[358] P. Borst, *Citatie-index 1981 en kosten 1983*, archive: Centrale Kanker Bibliotheek, description: letter to Beleidvoerend Orgaan and Research Raad, date: 02-10-1984.
P. Borst, *Citatie analyse 1984*, archive: Centrale Kanker Bibliotheek, description: letter to Research Raad, date: 10-11-87.
A. Berns, "Wetenschappelijk onderzoek," 6-7.

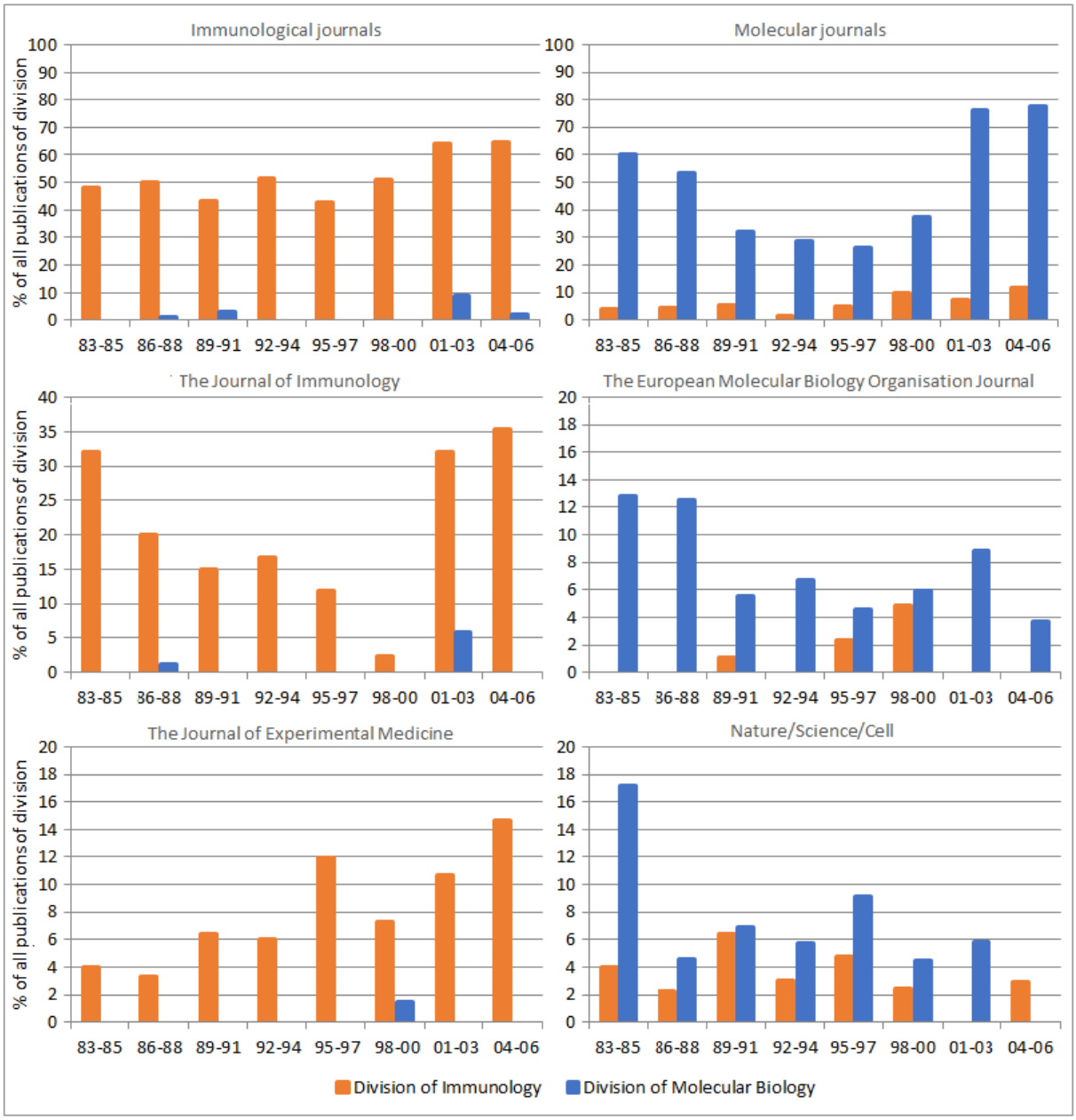

Figure 26. Publications in immunological, molecular and specific journals by the Divisions of Immunology and Molecular Biology (100% = all publications of division). The upper and middle panels show that the immunologists and molecular biologists published in approach specific journals.[359] The lower panels show that the immunologists often published in *The Journal of Experimental Medicine* and that the molecular biologists more often published in the high impact journals *Nature*, *Science* and *Cell*. Note that the range of the y-axes differs per graph. Data were derived from the *Citation Analyses 1983-2006*. Total numbers of analysed publications are 444 (Immunology) and 577 (Molecular Biology).

[359] Classification criteria were as follows. Immunological journals: antigens, immunity, immuno-, immunology, immunotherapy, leucocyte, lymphocyte, thymus. Molecular journals: DNA, gene, genetics, molecular, mutation, nucleic acid, oncogene, signalling.

Consumption of literature

So far we have focussed our attention merely to the *production* of scientific publications by the institute's researchers. However, this focus does not do justice to the ultimate function of scientific journals. Journals do not function as the graveyards of newly acquired data and insights; rather they are the medium through which these data and insights are passed on to other scientists. In other words, to fully understand to which extent the various journals demarcated and separated the sub-disciplines, we need to take into account the *consumption* of scientific literature by the institute's researchers.

Unlike the authors of a paper, the readers of it are virtually never documented. Therefore it is hard to trace back who read which papers or journals. However, one clerical sub-section in the archive of the NKI's library provides a solution. One of the folders contains a collection of 152 "literature list" subscription forms. Before the broad implementation of online literature databases, the library offered researchers the service to subscribe to a large array of literature lists. Once subscribed to such a list, a researcher would receive monthly overviews of all the new publications about a certain topic, such as "Oncogenes" or "Metastasen".[360] Interestingly, in 1991 the library revised the array of available literature lists. At least two modifications deserve our attention, as they exemplify the ongoing molecularisation of the cancer research conducted at the institute. Firstly, from 1991 on it became possible to subscribe to the list "Signal transduction". Secondly, in the same year the literature list "Immunological aspects of cancer" was replaced by "Cytokines", narrowing down the focus towards this class of immune modulating molecules.[361]

As the 152 available forms are dating from 1990 to 2002, the number of subscriptions can be used as a measure for the interest in an area of research in this period. The results of such an analysis for the lists Signal transduction and Cytokines are shown in **figure 27**. Quantitatively these lists could count on a comparable level of interest. Instead, qualitatively the subscriptions differed considerably. Although the immunologists make up about one fifth of all the subscriptions to Signal transduction, they subscribed twice as often to Cytokines. An even more profound difference was seen for the internists, a sub-group of the clinicians working at the patient wards and the clinical research divisions of the institute. Only 1 internist subscribed to Signal transduction, whereas 11 wished to stay informed about new publications on cytokines. Besides the immunologists and the internists, not that many others were interested in Cytokines, while the opposite pattern holds for Signal transduction.

[360] Author unknown, *Literature list*, archive: Centrale Kanker Bibliotheek, description: literature list request form, date: 1995.

[361] Author unknown, *Nieuwe literatuurlijsten per 01-01-1991*, archive: Centrale Kanker Bibliotheek, date: 1991.

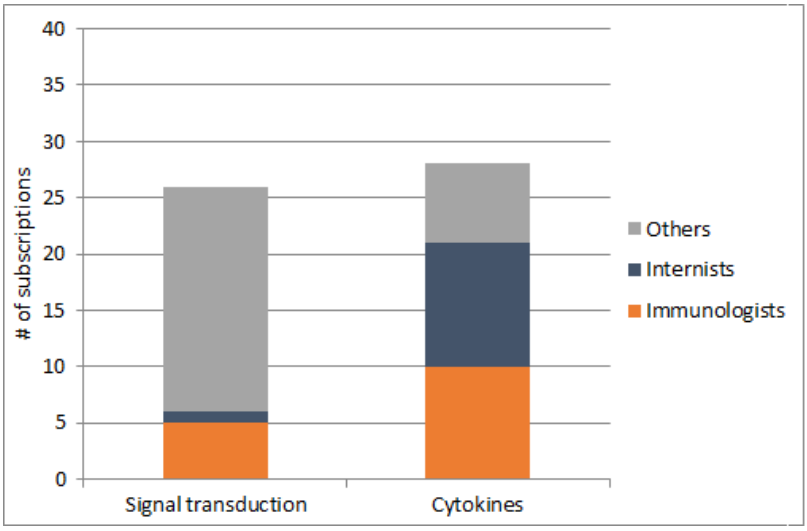

Figure 27. Subscriptions to literature lists Signal transduction and Cytokines from 1990-2002. Based on 152 subscription forms could be assessed which groups were interested in literature about signal transduction and cytokines. Both lists were new in 1991. The immunologists and internists show more interest in literature about cytokines than about signal transduction.

The immunologists: Insiders of another network

So again we see an association between the immunologists and clinicians. Not only in the acquisition of grants and in the production of publications, but also in the consumption there seem to have been tight links between these two groups. The immunologists have also held tight links with the clinicians in terms of staff members. Throughout the decades, the Division of Immunology has shared staff members with the research division of internal medicine. No other fundamental research division has maintained such long-term connections with the clinic.[362]

This unique tight link with the clinic could be explained in at least two ways. To start with, the immunologists study a system that spreads throughout the body. Unlike cell biologists or molecular geneticists, immunologist cannot limit their view to the cancer cell alone. The immunologist's systemic

[362] Author unknown, "Research Divisions," in *Annual Report 1983*, Amsterdam: The Netherlands Cancer Institute, (year unknown), iii-iv.
Author unknown, "Research Divisions," in *Annual Report 1986*, Amsterdam: The Netherlands Cancer Institute, (year unknown), 4-5.
Author unknown, "Research and Hospital Divisions," in *Annual Report 1989*, Amsterdam: The Netherlands Cancer Institute, (year unknown), 8-10.
Author unknown, "Research and Hospital Divisions," in *Annual Report 1992*, Amsterdam: The Netherlands Cancer Institute, (year unknown), 8-9.
Author unknown, "Research and Hospital Divisions," in *Annual Report 1995*, Amsterdam: The Netherlands Cancer Institute, (year unknown), 8-11.
Author unknown, "Research Divisions," in *Scientific Report 1998*, Amsterdam: The Netherlands Cancer Institute, (year unknown), 9-12.
Author unknown, "Research Divisions," in *Scientific Annual Report 2004*, Amsterdam: The Netherlands Cancer Institute, (year unknown), 9-10.

perspective may be relatively close to the more holist perspective of clinicians, who face in their daily work whole patients rather than isolated tumour cells.[363]

Another, more practical explanation concerns the model systems in which the immunologists have been performing their experimental work. Compared to molecular biologists, the immunologists needed considerably more patient material for their experiments (see supplementary figure 6).[364] Because tumour cells are inherently prone to grow aggressively outside their original physiological context, they are easier to culture continuously *in vitro* than immune cells. Consequently, for their study material the immunologists rely on a constant influx of fresh patient blood and tumour specimens to isolate immune cells from. Close contacts with the clinic have been necessary to maintain this influx, as clinicians provide access to these materials.

Thus, based on these data we cannot conclude that the immunologists were isolated outsiders at the institute. They certainly were part of a sustainable collaborative network, which they shared with clinical researchers. How to reconcile this finding with the oral histories discussed in the beginning of this chapter? According to the interviewed field members the immunologists were marginalised outsiders, with whom any association had to be avoided.

Notably, the interviewees endorsing this view had one thing in common: they all have been working at the fundamental research divisions. From their perspective the immunologists indeed may have been relatively marginalised. Compared to the leading molecular biologists, the immunologists collaborated less with the other fundamental research divisions. Especially in the acquisition of shared research grants, the immunologists lagged behind. Furthermore we have seen that the immunologists published their work in different journals and published less often in the prestigious high impact journals. Conversely, the molecular biologists frequently collaborated with other fundamental research divisions and not in the last place with each other. The immunologists did not share a disciplinary identity with the molecular biologists. Accordingly the immunologists did not belong to the inner circle of the molecularly orientated networks, which allied many of the other fundamental research divisions.

10.3 Thinking in molecules

On the other hand, the data discussed above do not imply that the immunologists and molecular biologists completely operated in parallel universes. We have seen that the immunologists occasionally connected with the molecular biologists in three ways. Firstly, between 1983 and 2006 the immunologists co-authored 14% of their shared publications with members of molecular divisions. Secondly, on regular basis, the immunologists published part of their publications in molecular journals throughout this period. Thirdly, one fifth of the subscriptions to the literature list Signal transduction came from the Division of Immunology. Thus, the immunologists did not turn their back on the

[363] During the field work I attended a seminar in which the Clinical Director of the hospital presented his scientific work. In this presentation he would remind the researchers to take the whole patient into account: "We sometimes forget that there is a patient around the tumour. […] This is important, it reminds us of the side effects of systematic treatement. I say this to make you realize that if we do something to normal tissue, you also get a response." FM40.

[364] Appendix 1, supplementary figure 6.

molecular biologists. Quite understandably, they sought for affiliation with the leading and credible molecular biologists.

However, not just any immunologist could successfully affiliate with the molecular biologists. An interviewed group leader of the Division of Immunology described the kind of requirements one had to meet in order to join their collaborative network:

> Dat mensen die, hè [euhm]… je hebt mensen die, die in moleculair kunnen denken, in moleculen kunnen denken en je hebt mensen die [euhm] alleen maar in een soort van groter proces [euh, euh] konden denken. En de mensen die in moleculen konden denken, dat waren de mensen [euh] die inderdaad gewoon heel veel aansluiting ook konden hebben, voor zover ze wilden, met andere groepen binnen het instituut. De mensen die alleen maar in het grote proces dachten, daarvoor was die aansluiting denk ik veel lastiger. Daar was gewoon echt een verschil in taal.[365]

According to this group leader "thinking in molecules" was the key requirement for successful connection with the molecular biologists.[366] In the remaining part of this of this chapter we discuss to what extent the immunologists indeed committed themselves to the new and dominant approach, both methodologically and theoretically.

According to Ilana Löwy's account of the molecularisation of tumour immunology at the U.S. National Cancer Institute, an important step towards the new standards has been the integration of *in vitro* model systems.[367] Indeed, also at the NKI the immunologists put an increasing effort into the establishment of functional *in vitro* model systems in the '80s.[368] Although not as fanatically as their colleagues at the Division of Molecular Biology, the immunologists integrated *in vitro* cultured cell lines into their array of model systems (see supplementary figure 7).[369]

Also when put into the brightest academic spotlights, the immunologists announced to incorporate the modern molecular technology into their experimental work. Traditionally, in their inaugural lectures newly appointed professors sketch their future research program, and in the '90s the next generation of immunological group leaders was certainly inspired by the new molecular possibilities.[370] For example, Carl Figdor announced to use recombinant DNA technology to study the interaction between cells and their surroundings:

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[365] II3.42-43. Translation: There are people that can think in molecules and there are people that could only think in a sort of bigger process. And the people that could think in molecules were the people that could have a lot of association with other groups within the institute, insofar they wanted this. For the people that only thought in terms of the bigger process, this association was way harder, I think. There was just a serious difference in language.

[366] II3.42.

[367] Ilana Löwy, "Immunotherapy of Cancer from Coley's Toxins to Interferons: Molecularization of a Therapeutic Practice," in *Molecularizing Biology and Medicine: New Practices and Alliances 1910s-1970s*, ed. Soraya de Chadarevian and Harmke Kammingma, Amsterdam: Harwood Academic Publishers (1998), 249-271.

[368] See for example: Author unknown, "Tumor immunologie," in *Werkplannen 1984*, Amsterdam: The Netherlands Cancer Institute (year unknown), 23-26.

[369] Appendix 1, supplementary figure 7.

[370] Carl Figdor, *Bloed kruipt waar het niet gaan kan*, Enschede: Universiteit Twente (1993).
H. Spits, *De thymus, een orgaan voor fijnproevers*, Amsterdam: Vossiuspers UvA (2003).
J.G. Borst, *Knappe koppen, koppige cellen*, Amsterdam: Vossiuspers UvA (2000).

> Uitdagingen liggen in het bestuderen van de adhesie-eigenschappen van cellen waarin met behulp van recombinant DNA technieken gemodificeerde integrinmoleculen tot expressie zijn gebracht. De huidige moleculair biologische technieken kunnen gebruikt worden om de cel op een klein onderdeel te modificeren en het gevolg daarvan te bestuderen onder de microscoop.[371]

Besides for an outlook at the future, inaugural lectures are often used to reflect on the recent past. In the '90s many of the institute's newly appointed professors, including biochemists, cell biologists and immunologists, celebrated the merits of the novel molecular approach in their inaugural lectures. They frequently stated that the newly available technology and insights caused nothing less than a revolution in the understanding of cancer aetiology, the biomedical sciences in general or even beyond.[372] Among them was Wouter Moolenaar, who held a research group at the Division of Cellular Biochemistry.[373] When he was appointed as a professor of Molecular Cell Biology in 1996, he declared: "Nu, aan het einde van de 20e eeuw, zijn we getuige van een ware revolutie; een revolutie in onze kennis van de natuur, vooral dankzij de spectaculaire ontwikkelingen in de moleculaire biologie."[374] Also the immunologists referred to the molecularisation of their field.[375] For example, in his inaugural lecture of 2003, Hergen Spits reflected on the developments in the early '90s: "De belangrijkste vooruitgang was de identificatie van de moleculen op kankercellen, met name op melanoomcellen die door de T-celvoelhoorns worden herkend."[376]

Thus indeed, the group leaders at the institute, including the new generation of immunologists, shared a common language. They were thinking in molecules. Consequently, in 1999 ex-director Borst could conclude in his farewell lecture that the differences between the various disciplines had disappeared:

[371] Figdor, *Bloed*, 20. Translation: Challenges lie in the study of adhesion characteristics of cells in which integrin molecules are expressed by recombinant DNA technology. The current molecular biological techniques can be used to modify a minor component of the cell and to study the effect of this by microscopy.
[372] W.H. Moolenaar, *Signaaloverdracht: een zaak van levensbelang*, Leiden: Rijks Universiteit Leiden (1996).
J. Neefjes, *Over leven en overleven*, Leiden: Universiteit Leiden (2000).
Borst, *Knappe koppen*, 8.
[373] Author unknown, "Research Divisions," in *Scientific Annual Report 1996*, Amsterdam: The Netherlands Cancer Institute (year unknown), 9-10.
[374] Moolenaar, *Signaaloverdracht*, 4. Translation: "Now, at the turn of the twentieth century, we witness an actual revolution; a revolution in our knowledge of the nature, mainly because of the spectacular developments in the molecular biology."
[375] Spits, *De thymus*, 11. Borst, *Knappe koppen*, 16.
[376] Spits, *De thymus*, 11. Translation: "The most important step forward was the identification of molecules on cancer cells, especially on melanoma cells, that could be recognised by T cell tentacles."

> Die integratie van verschillende basisdisciplines lijkt mij een onomkeerbare ontwikkeling. De muren in het huis van de medisch-biologische onderbouw zijn geleidelijk gesloopt en er zijn nogal wat onderzoekers die zich kriskras door dit huis bewegen. Bij jongere celbiologen en moleculair genetici in het NKI/AvL zie ik een vanzelfsprekend gemak waarmee ze morfologie, biochemie en moleculaire genetica combineren. De verschillen tussen de secties celbiologie, cellulaire biochemie, moleculaire biologie en moleculaire genetica en tumorbiologie zijn eigenlijk verdwenen.[377]

Is it coincidence that the Division of Immunology is not mentioned in this listing of interchangeable divisions? Maybe not. On the one hand, we have seen in this section that the immunologists actively embraced the molecular approach, both methodologically and theoretically. On the other hand, the analyses discussed in the earlier sections showed that even in the '90s their collaborative orientation was more often towards the clinicians than to the molecular divisions. Additionally, in Part I we have seen that the Divisions of Immunology and Molecular Carcinogenesis were not even interchangeable in 2014. In the upcoming, concluding chapter we will see how the historical analyses of Part II tie in with the conclusions of Part I.

[377] P. Borst, *Geluk in de wetenschap*, Amsterdam: Vossiuspers AUP (1999), 32. Translation: This integration of the various basic disciplines seems to me an irreversible development. The walls in the fundamental biomedical field were gradually demolished and there are many researchers who crisscross this field. I observe that young cell biologists and molecular geneticists at the NKI naturally combine morphology, biochemistry and molecular genetics. The differences between the sections cell biology, cellular biochemistry, molecular biology and molecular genetics and tumour biology are basically gone.

Conclusions and recommendations

Part I of this thesis described the outcomes of an anthropological field study performed in 2014 to gain insight into the relation between immunological and molecular cancer research. The visited field sites were the Divisions of Immunology (B3) and Molecular Carcinogenesis (B7) of the Netherlands Cancer Institute (NKI). The comparison of these divisions showed that they differ in multiple ways, but also highlighted some important similarities. Although the immunologists and molecular biologists study different biological processes, they both formulate theories in terms of interacting molecules. Methodologically the molecular biologists predominantly rely on *in vitro* studies and DNA sequencing, both of which also play a substantial role in the work of the immunologists.

Notably, these theoretical and methodological similarities reflect a partial *molecularisation* of the immunological approach, rather than a partial *immunisation* of the molecular approach. Whereas the immunologists integrated multiple aspects of molecular theory and methodology in their daily routine, no evidence was found for the opposite. In addition, an analysis of the divisions' social status revealed that the immunologists are often seen as an exceptional division, while the molecular biologists would epitomise the mainstream approach at the institute.

The programme of Part II has been to explain the asymmetric relation between the two approaches by considering the historical context of this relation. Based on a combination of archival sources and oral histories, Part II described how almost the complete institute got molecularised from the mid '80s onwards. Initially the research lines of the first molecular division were sharply demarcated from non-molecular work at other divisions, but soon the new approach would spread over most of the NKI's divisions. This general process of molecularisation was actively promoted by the policies of the Research Raad, the Beleidvoerend Orgaan and the institute's director. Besides increasing the number of molecular divisions and recruiting molecular biologists, researchers working in other disciplines were encouraged or even pushed to adopt the new approach.

This territorial expansion of the molecular biologists, at the expense of others, is an example of scientific "boundary work". Sociologist Thomas Gieryn, the founding father of this concept, described boundary work as the struggle of scientists to achieve the highest level of credibility. The most credible scientists within a scientific field will get most staff positions, laboratory space and other resources.[378] At the NKI the molecular biologists clearly won this credibility contest, which enabled them to push the boundaries of their territory.

Interestingly, the high credibility of the molecular approach was not based on achieved clinical successes. Instead, it was based on its promise to unite two important ideals in cancer research: understanding cancer and curing cancer. By providing fundamental understanding of cancer aetiology, the molecular biologists would reveal the molecular targets for highly specific anti-cancer drugs: targeted therapies. This promise was enough to initiate the molecularisation of the NKI. The paradigms of this therapeutic strategy, Gleevec and Herceptin, were only clinically tested in the (late) '90s and approved at the turn of this century. Nevertheless, it were the molecular biologists who set the standards at the NKI already from the mid '80s onwards.

In so far the immunologists did not meet these new standards, their credibility was considerably reduced. Indeed, doubts about the legitimacy of the immunological division resonated throughout the NKI. Hence, in the '90s the new generation of immunologists aimed to integrate aspects of the molecular approach into their work. The theoretical and methodological similarities found in the field study are the progeny of these integrations. Conversely, the molecular biologists could permit themselves to ignore the immunologists and their studies. No credibility was to be gained by

[378] Gieryn, "Contesting Credibility," 1-36.

integrating aspects of the immunological approach into their work, which explains the asymmetric relation between both sub-disciplines at the NKI.

Contributions to the field of science studies

This extensive case study also provides insights into the relation between biomedical sub-disciplines at a higher level of abstraction. In two ways it complements the literature about the molecularisation of the biomedical sciences. Firstly, as elaborately described in Chapter 7 and 8, the molecularisation of cancer research at the NKI involved more than the implementation of new techniques into the existing methodological arsenal. Up to date, historians of sciences have predominantly cited the availability of new, molecular technology as the driving factor of this transition.[379] However, this study shows that the broader implementation of the molecular approach was enabled by policies of influential individuals and organs, such as the Research Raad. For many researchers at the NKI this propagation of molecular technology in practice meant a full conversion to the molecular approach. In future science studies, disciplinary changes in the (biomedical) sciences should not be reduced to technological advances. Instead these kind of developments should by analysed in their social context to fully understand how and why they took place.

Secondly, the few historical studies that do take into account this social context, mainly analyse how the new technologies circulated through newly formed networks.[380] Philosopher of science Ludwik Fleck described such networks as "thought collectives", groups of scientists that share a certain way of thinking and related technologies.[381] Indeed, at the NKI the molecular biologists formed a new collective, which united former virologists, cell biologists and classical geneticists. However, the molecular approach did not only serve as a vehicle for inclusion, but also for exclusion. The immunologists were never in the esoteric (i.e. inner) circle of this collective. The immunologists published their findings in other journals and, in contrast to the molecular biologists, collaborated mainly with clinicians. As discussed before, the immunologists' outsider status and their corresponding low credibility explains the asymmetric relation between the immunologists and the molecular biologists nowadays. If a science study aims to understand the influence of a certain new sub-discipline on the field, it should not only address the newly formed collective, but also take into account the existing ones.

Although the immunologists were observed to also study molecular interactions, even in 2014 they were not at the heart of the molecular collective. The comparison in Part I showed that the divisions differ considerably at multiple levels. Firstly, they aim to develop different forms of therapy. While the immunologists try to induce an effective immune response against the tumour, the therapeutic strategy of the molecular biologists is to target the molecular pathways on which the cancer cells rely for proliferation and survival. Secondly, the immunologists postulate theories about interactions between cells, whereas the molecular biologists mainly describe intracellular processes. Thirdly, unlike the molecular biologists, the immunologists were observed to frequently use *in vivo* model systems and flow cytometry as an analytic tool. Thus, the immunologists differ from the main stream molecular approach at the three levels described by philosopher of science Larry Laudan: the axiological, theoretical and methodological level.[382]

[379] Rheinberger, "Molecular biology," 6-12. Gearhart, "Molecular Immunology," 4259-4259. Finn, "The Molecular Divide," 2615-2616. Fanu, "New Genetics," 311-350. Löwy, "Heredity," 173-175. Mukherjee, *The Emperor.*

[380] Sturby, "Reflections: Molecularization," 273-292.

[381] Fleck, "Epistemological Considerations," 82-145.

[382] Laudan, "Dissecting the Holist Picture," 142.

This outsider position is also illustrated by the observation that multiple field members did not see immunology as a part of oncology. More than half of the members of Molecular Carcinogenesis did not include immunology when they were asked to sketch a map depicting the disciplines in cancer research. In addition, members of both divisions alike described the Division of Immunology as "een vreemde eend in de bijt" or "een eigen wereldje".[383] In other words, the gap that grew between the immunologists and molecular biologists in the '80s and '90s was not yet bridged in 2014.

Unanswered questions and future studies

Unsurprisingly, this study does not only provide answers about the relation between molecular and immunological cancer research. It also generates new questions. To start with, the analyses performed in this study were inconclusive about the role of funding agencies in the molecularisation of the NKI. The funding agencies at least enabled this process by providing the molecular biologists with enough grants to expand, but it is unclear whether they actively promoted this expansion by favouring molecular grant applications. Section 9.1 describes in more detail what kind of studies could be performed to elucidate the influence of funding agencies on scientific developments.

Secondly, the clinical breakthrough of immunotherapy followed about one decade after the first clinical successes of targeted therapy. Could this difference be explained by the (former) second-class position of the immunologists? Would immunotherapies have reached the patient earlier if the immunological approach expanded as much as the molecular one did? Because the NKI is only one of the many research institutes at which tumour immunology has been studied, these questions cannot be answered by this single study. In addition, the development, clinical testing and broad-scale application of new therapeutics does not only involve cancer research institutes, but also hospitals, pharmaceutical industries, insurance companies, governmental organs and patients. Certainly, Chapter 5 describes some important developments in the attitude of these parties, but predominantly in relation to the researchers of the NKI.

Nevertheless, this study suggests that the situation at the NKI has been representative for the general tendencies in cancer research. For example, some field members reported that previously the immunologists, unlike the molecular biologists, were hardly ever keynote speakers at international oncology congresses. An analysis of the former programs of these congresses is only one of the possible studies that could show whether the low credibility of the immunologists has been a more general phenomenon. Possibly the large emphasis on molecular research has marginalised the immunologists on such a large scale that the development of immunotherapies has been impaired. On this note it will be necessary to analyse to what extent the development of these first immunotherapies relied on the partial molecularisation of immunology.

Thirdly, this study does not provide clear-cut answers to the question how the institute should organise its future research activities. Typically historical and anthropological methods yield descriptions of the past and the present, rather than normative statements about the future. Nevertheless, these descriptions provoke some speculation about the future, because they highlight discrepancies between various pursued aims at the NKI and historical parallels. An important discrepancy and a historical parallel are discussed in the upcoming paragraph.

[383] See Chapter 5.

Recommendations: Rewiring pathways

The most remarkable discrepancy can be identified between the aims of the NKI and the individual researchers. The official aim of the NKI has always been to improve the treatment of cancer patients.[384] The individual members of both Immunology and Molecular Carcinogenesis were observed to share this aim, although they work on different therapeutic strategies. Yet the most remarkable axiological similarity between the studied immunological and molecular researchers is their aim to publish in high impact journals. Obviously publications are very important instruments for communication, but at the NKI (and beyond) they are often seen as a goal in themselves. At both divisions, publishing in *Nature* seemed to be the primary concern of group leaders and their teams. Unfortunately for the cancer patient, the experiments that are necessary to stay ahead of competitors and to quickly score a *Nature* paper, are not always the experiments that yield the most insightful and clinically relevant results.

As long as the status and credibility of individual researchers will depend on the number of high impact papers they publish, it cannot be expected that they will stop aiming for this. Thus, if the NKI's primary aim is indeed to improve cancer therapy, then it should offer its researchers a working environment in which the most relevant results are seen as the endpoint of a project rather than the highest possible impact factor. Practically this suggests that the institute should stop using bibliometric parameters as indicators of scientific quality or productivity in the *Scientific Annual Reports*, in the selection of new group leaders and in the evaluation of researchers and their projects. Alternative methods for evaluation are discussed in more detail in the "Position Paper" of Science in Transition and elsewhere.[385] At a more symbolic level, the institute could decide to stop the election of the "Publication of the week" and to discourage the organisation of "paperborrels". Instead, it could highlight and celebrate insightful and clinically relevant results. Furthermore, the NKI should consider informing its major funders about these changes, because also these organisations base their decisions (partly) on the applicant's publication list.[386]

The most outstanding historical parallel can be identified between the current position of immunology (Chapter 5) and the position of molecular biology in the mid '80s (Chapter 7). Like molecular research in the mid '80s, nowadays most of the institute's immunological research is concentrated at one division. Furthermore, beyond this division there is also much enthusiasm about the immunological approach and its clinical potential. Others are keen on collaborating with the immunologists and some start hiring immunologists to integrate immunology into their own work.[387] Will every self-respecting research group soon have its own immunologist?

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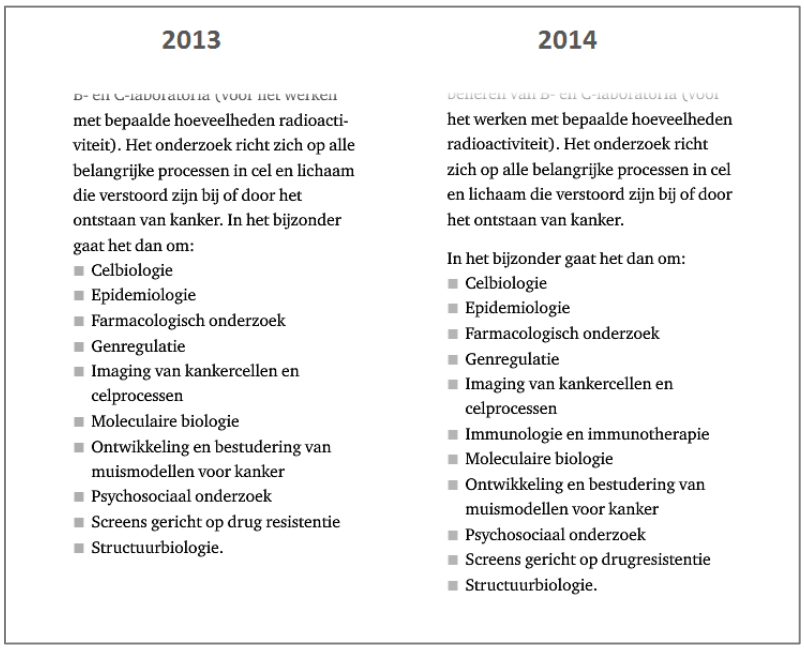
[384] W.M. de Vries, "Jaarverslag van den secretaris," in *Eerste Jaarverslag: 1914*, Amsterdam: Vereeniging Het Nederlands Kanker Instituut (1914), 3-7.
Author unknown, "Het Antoni van Leeuwenhoek," Netherlands Cancer Institute, url: http://www.avl.nl/topmenu/over-avl/, last update: unknown, consulted at 12-5-2016.

[385] Dijstelbloem et al., "Science in Transition."
Branwen Morgan, "Research impact: Income for outcome," in *Nature* 511 (2014), S72–S75.
David Dubrin, "Time to discard the metric that decides how science is rated," *The Conversation*, url: https://theconversation.com/time-to-discard-the-metric-that-decides-how-science-is-rated-27733, last update: 11-6-2014, consulted at: 14-5-2016.
Abma, "Lessen van Stapel," 153-164.
Author unknown, "List of CWTS Publications," Leiden University: Centre for Science and Technology Studies, url: https://www.cwts.nl/research/publications/list-of-cwts-publications, last update: unknown, consulted at: 22-05-2016.

[386] Dijstelbloem et al., "Science in Transition."

[387] See Chapter 5 and: Author unknown, "Vacancy Postdocs for functional genomics exploiting T cell immunity and metabolism for cancer drug target discovery," Netherlands Cancer Institute, url:

At the institutional level, this improved credibility of the immunologists is exemplified by the annually published *Jaardocument*. From 2006 onwards, these documents contain a list of the important tumorigenic processes studied at the institute and in 2014 "immunology and immunotherapy" was added to this list (see **figure 28**). Furthermore, according to its website, the institute made immunotherapy one of its three priorities (see **figure 29**). The institute flaunts its immunological research, again resembling the position of molecular biology in the '80s. Taken together, this suggests that the NKI is currently at the dawn of a process of immunisation, very much like it was at the dawn of molecularisation in the mid '80s.



2013

B- en C-laboratoria (voor het werken met bepaalde hoeveelheden radioactiviteit). Het onderzoek richt zich op alle belangrijke processen in cel en lichaam die verstoord zijn bij of door het ontstaan van kanker. In het bijzonder gaat het dan om:

- Celbiologie
- Epidemiologie
- Farmacologisch onderzoek
- Genregulatie
- Imaging van kankercellen en celprocessen
- Moleculaire biologie
- Ontwikkeling en bestudering van muismodellen voor kanker
- Psychosociaal onderzoek
- Screens gericht op drug resistentie
- Structuurbiologie.

2014

beheren van B- en C-laboratoria (voor het werken met bepaalde hoeveelheden radioactiviteit). Het onderzoek richt zich op alle belangrijke processen in cel en lichaam die verstoord zijn bij of door het ontstaan van kanker.

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- Moleculaire biologie
- Ontwikkeling en bestudering van muismodellen voor kanker
- Psychosociaal onderzoek
- Screens gericht op drugresistentie
- Structuurbiologie.

Figure 28. Two excerpts from the institute's *Jaardocument* of 2013 and 2014. From 2006 onwards these documents contain a list of "all important processes" in tumorigenesis studied at the institute. In 2014 immunology was added to this list.[388]

http://www.nki.nl/working-at-the-nki/vacancy-Postdocs-for-functional-genomics-exploiting-t-cell-immunity-and-metabolism-for-cancer-drug-target-discovery, last update: unknown, consulted at: 30-9-2015.
Author unknown, "Vacancy Postdoc Developing improved immunotherapy for melanoma using advanced antibodies," Netherlands Cancer Institute, url: http://www.nki.nl/working-at-the-nki/vacancy-postdoc-developing-improved-immunotherapy-for-melanoma-using-advanced-antibodies, last update: unknown, consulted at: 30-9-2015.

[388] Figures are excerpted from: Author unknown, "Profiel van de organisatie," in *Jaardocument 2013*, ed. A. Serrarens and N. Grotenhuis, Amsterdam: Netherlands Cancer Institute (2013), 11-18.
Author unknown, "Profiel van de organisatie," in *Jaardocument 2014*, ed. A. Serrarens and N. Grotenhuis, Amsterdam: Netherlands Cancer Institute (2015), 11-18.

Figure 29. Excerpt from the institute's website in 2016. Nowadays the further development of immunotherapy is one of the institute's priorities.[389]

If the NKI would aim to immunise its research, then this thesis might be a useful handbook to guide this transition. Specifically Chapter 8 describes the policies and strategies which led to the institute broad implementation of the molecular approach. Applied to the current situation, these policies would include increasing the number of immunological divisions; recruiting mainly immunologists as new researchers and group leaders; institutionalising the advisory role of immunological experts; appointing immunologists as heads of non-immunological divisions; and pushing non-immunologists to retrain themselves into immunologists.

Upon further reflection, an improvident application of these measures may have detrimental side effects on the existing (molecular) expertise. The enumerated measures did not lead to an *integration* of the molecular approach, but to a fairly complete conversion to it. If the NKI aims to integrate the immunological approach into other research lines rather than a complete immunisation, then it should follow a more modest strategy. In that case, it will be key to debunk the false dichotomy many researchers perceive between oncology and immunology. Most cancer researchers specialise in the study either of the molecular processes in the cancer cell or of the immune response against a tumour, while from a biological point of view these phenomena are highly interrelated. The intrinsic properties of the cancer cell determine to a large extent the immune response against it and vice versa.[390] To achieve integration, the policies should aim to change the asymmetric relation between immunological and molecular cancer research described in this study. Practically, the institute could take into account the following six considerations to facilitate this change.

Firstly, analogous to the Working group Molecular Biology, the institute can start a Working group Immunology. The Working group could have regular meetings in which non-immunologists can consult the expertise of immunologists and discuss any research plans that involve tumour immunology. In this constellation the researchers from other sub-disciplines will not only get their own questions answered, but they will also learn from the discussions of the work of others. This may help these researchers to familiarise themselves quickly with the theoretical and technical knowledge needed to

[389] Figure is excerpted from: Author unknown, "Speerpunten," Netherlands Cancer Institute, url: www.avl.nl, last update: unknown, consulted at: 14-5-2016.

[390] G.T. Motz and G. Coukos, "Deciphering and reversing tumor immune suppression," *Immunity* 39 (2013), 61-71.
C.U. Blank, J.B. Haanen, A. Ribas, T.N. Schumacher, "The 'cancer immunogram'," *Science* 352 (2016), 658-660.

study immunological aspects of cancer. In turn, the immunologists may learn how molecular biologists take another angle to tumour immunology.

Secondly, the institute could further exploit an existing platform for interdivisional and interdisciplinary exchange: the Research Clubs. This study shows that only a small minority of the researchers visits these institute wide seminars on a regular basis. Many others visit only the seminars in which one of their division mates presents. The immunologists were observed to visit 4.4 times more often seminars in which a division mate presented (or hosted), while for the molecular biologists this factor was 2.4. This tendency has a twofold explaination. On the one hand, some researchers admitted that they lack the background knowledge to appreciate the talks of colleagues working in other sub-disciplines. A possible solution is to strongly encourage or even oblige the speakers to spend 10 minutes of their talk to introducing the study. Such an extensive introduction should explain the central concepts, the current knowledge and used experimental approach in order to bridge the most important differences in background knowledge between the speaker and the audience.

On the other hand, multiple division members indicated that they visit the seminars of their division mates to express their loyalty towards them. Indeed, the divisions were observed to be the most important social units at the institute and accordingly they organise to a large extent the social relations among researchers. Due to the size of the institute, it may be impossible to cultivate an institute wide loyalty among all researchers. Therefore it will be hard to change the tendency to mainly visit the seminars of divisions mates, but one simple intervention could be a first step. Rather than announcing it in the Research Club schedule, the order of the speakers could be determined just at the start of the Research Club. This will decrease the possibilities to selectively attend the presentation of division mates.

Thirdly, a more radical way to break the social boundaries imposed by the divisional organisation, is to rearrange them. Analogous to the establishment of the Division of Molecular Genetics, the institute could create a new division which unites immunologists and molecular biologists. An obvious possibility is to establish a Division of Immuno-sensitivity, in which immunologists and molecular biologists combine their expertise to study which cancer cell properties influence a tumour's sensitivity to an immune response. Rather than dissolving divisional loyalty, the institute could exploit it to integrate immunology into other research lines.

Fourthly, if more research groups are starting immunological studies, then the usage of the needed technology will increase. This thesis describes that immunological studies typically involve flow cytometric analysis. Hence, substantial investments may be required to increase the capacity of the institute's flow cytometry facility. If the capacity of this facility becomes insufficient, this will not only impair the integration of immunology into other research lines, but also the studies of the institute's immunological flagship: the Division of Immunology.

Fifthly, on the longer term the members of Immunology should be prepared to give up this flagship position and to some extent their disciplinary identity. The molecularisation of the institute only took off when the members of the first molecular division stopped claiming their monopoly on molecular studies. The members of Immunology will have to accept that more and more immunological studies will be done independently of their expertise. In the future they will no longer be *the* immunologists, very much like the members of the Molecular Carcinogenesis are not *the* molecular biologists.

Sixthly, the institute could aim to influence biomedical education programmes in the Netherlands. This study shows that disciplinary stratification has its roots in the educational background of researchers. Members of Immunology predominantly specialised in immunology during their training, while

members of Molecular Carcinogenesis specialised in oncology. Up to date, universities and HLOs[391] continue to impose the earlier discussed dichotomy. For example, at Utrecht University tumour immunology is completely absent in the curriculum of the master "Cancer and Stem Cell Biology".[392] Via senior group leaders, who hold chairs at many Dutch universities, the institute could stimulate universities to integrate immunology into their courses on oncology.

These kinds of measures could help to stimulate the crosstalk between the two "pathways" described in this thesis. This combined anthropological and historical study of immunological and molecular research at the Netherlands Cancer Institute shows how these pathways get hardwired in organisational and social structures, such as the divisional organisation and collaborative networks. In general we have seen how disciplinary boundaries are structured by the researchers themselves, rather than being dictated by the studied phenomena. The disciplinary boundaries do not reflect distinctions between biologically unrelated processes. Instead, they reflect the human tendency to reduce a complex, multifaceted problem to manageable sub-problems. Exactly because we construct the disciplinary landscape in science ourselves, we can rewire and improve this landscape.

[391] Higher Laboratory Education (HLO) is given at universities of applied science and trains technicians.
[392] Author unknown, "Programme related courses," Utrecht University, url: http://studyguidelifesciences.nl/programme-related-courses, last update: unknown, consulted at: 16-5-2016.

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(disappeared) annual reports, citation analyses or other useful documents from the library's depot. Not in the last place because of your presence, your library served as an excellent place to store the archival files and to study them. Furthermore, I am thankful for the useful conversations I had with Piet Borst, Hein te Riele and Henri van Luenen. However, a study like this is virtually impossible without the support of an enthusiastic and incisive ally at the field site. Jannie Borst, thanks a lot for bringing me in touch with many of the people named above and for your help and discussions during the project.

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Disclosure

After I finished the analysis of the anthropological field study, but before I finished the writing of this thesis, I became a biomedical master student at the Division of Immunology of the Netherlands Cancer Institute. Both projects I am involved in, are in (technical) collaboration with a molecular division (Molecular Genetics and Molecular Carcinogenesis).

Consent of informants and the institute

Prior to the start of the field visits, the head of B3, the involved group leaders and the supervisors were informed about the purpose of the study. Upon entering the field sites, my role as an observer was mentioned during my introduction to the field members. At both divisions I further disclosed the purpose of my study and specifically my field observations to both groups of field members and to individual field members.

Prior to the start of the record, the interviewees were asked whether they agreed to be recorded. Upon starting the record, this question was repeated to record the answer. Subsequently the interviewees were informed about the purpose of the study and the interview in more detail. The interviewees were asked whether they agreed that 1) their answers would be used for an analysis at group level and/or paraphrased in the report and 2) their answers would be cited literally and anonymously in the report. For 2) it was added that the interviewee would be able to read his/her qoute(s) prior to the final version of this report was made. They were informed about their right to refuse the citation of their answers, independent on the consent given at the start of the interview.

The field members who filled out the questionnaire were informed about the study by a text above the questionnaire (see Appendix 4). They were asked to indicate whether they agreed that 1) their answers would be used for an analysis at group level and/or paraphrased in the report and 2) their answers would be cited literally and anonymously in the report. For privacy reasons, this report only contains general information about the field members, the interviewees and the responders to the questionnaire.

Access to the institute and to the archives was primarily provided by the head of B3 and the Manager of Research. Before the start of the study, we agreed that the obtained data and this report would not become publically available before the head of B3 and the Manager of Research provide permission.

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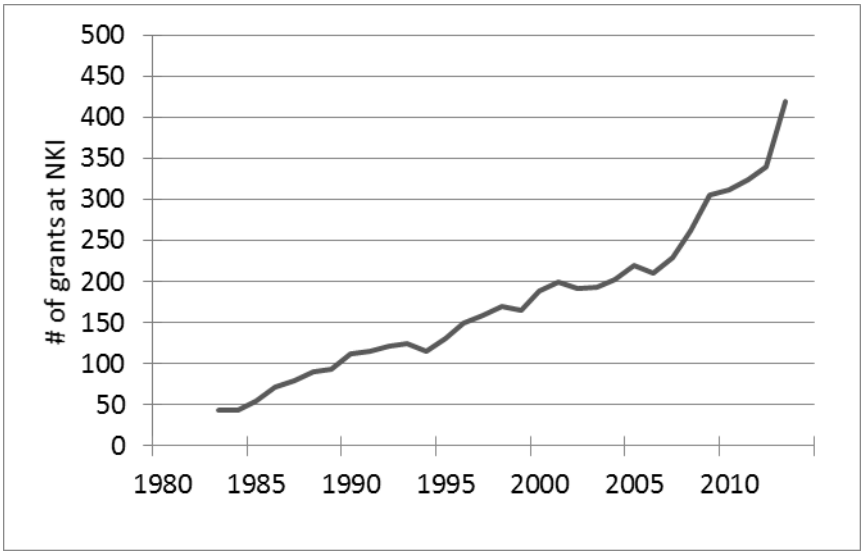
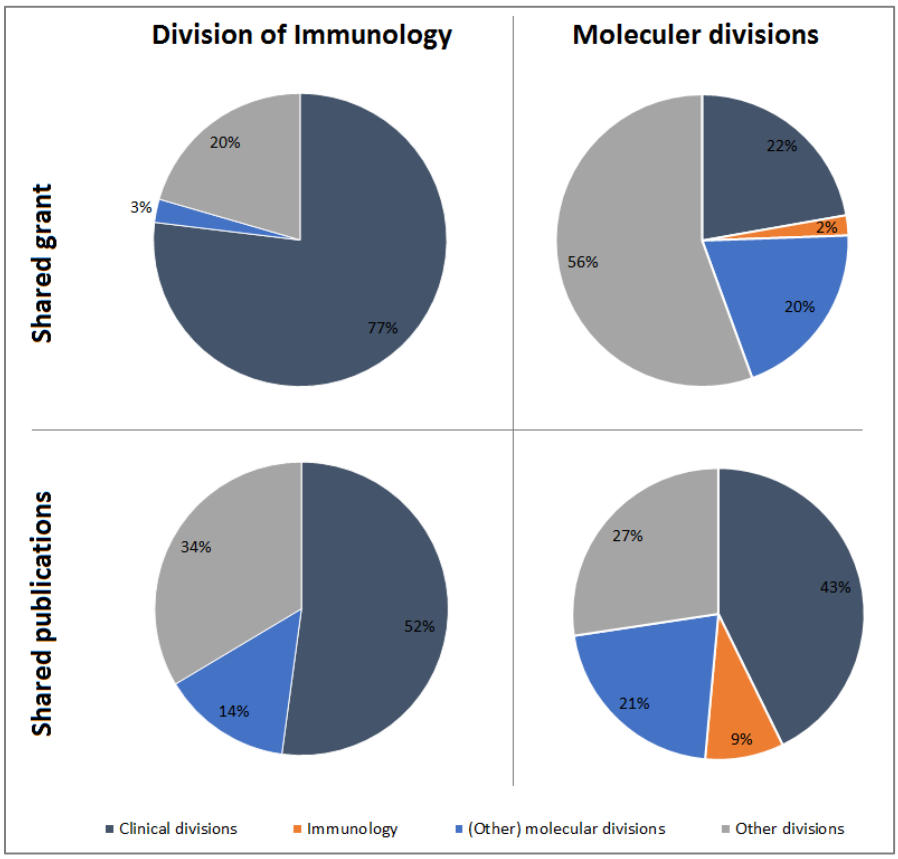
Appendices

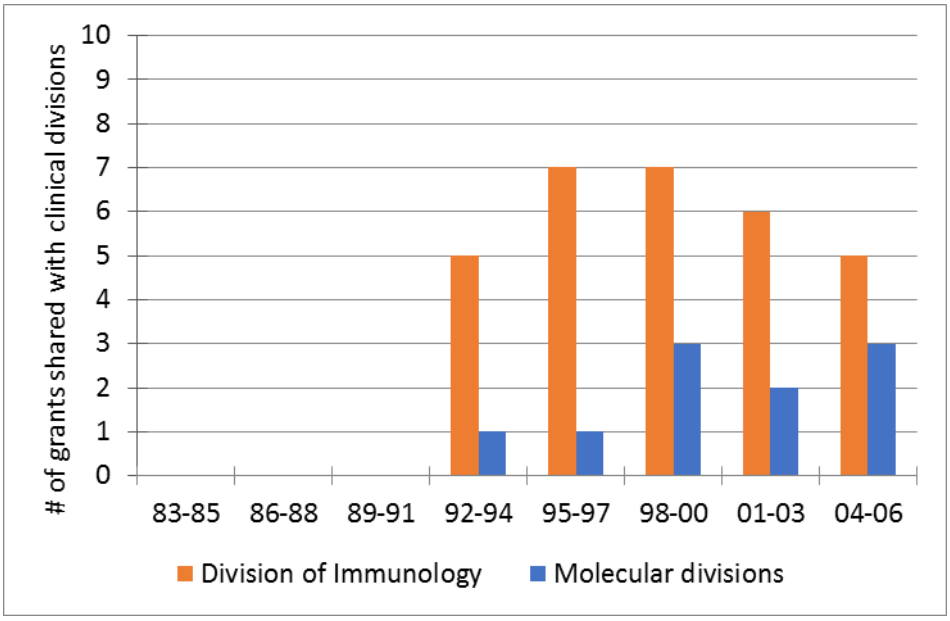
Appendix 1: Supplementary figures



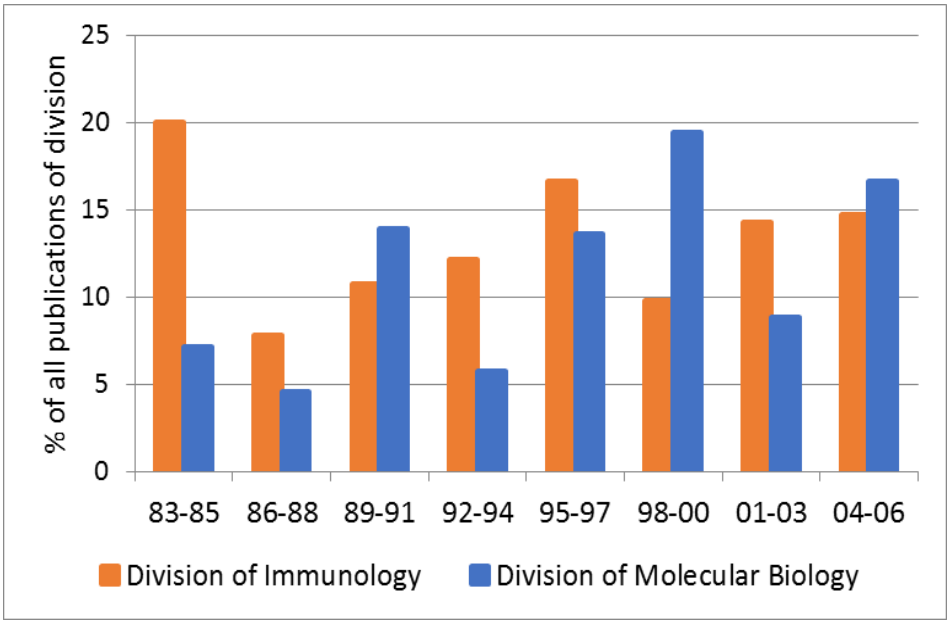
Supplementary figure 1. Total number of pending grants at the NKI. The presented data were derived from the NKI's *Annual Reports 1983-2014*, which from 1983 onwards contain an overview of all the pending research grants.



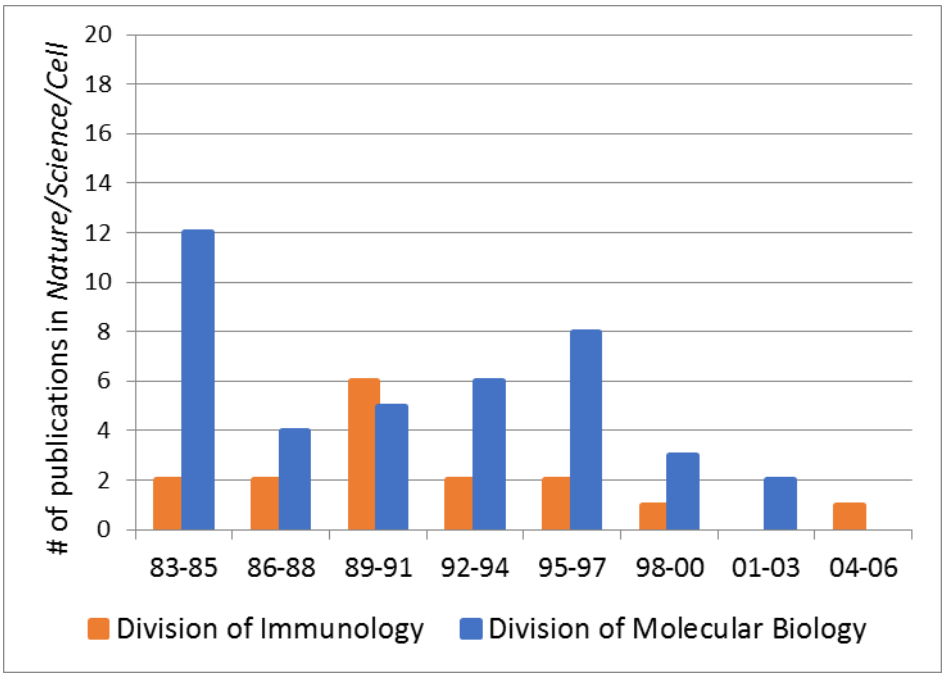
Supplementary figure 2. Collaborative partners in the sharing of grants and publications per approach from 1983-2006. Data were derived from the *Annual Reports 1983-2006*. Total numbers of analysed pending grants are 357 (Immunology) and 917 (molecular divisions). Total numbers of analysed publications are 444 (Immunology) and 1075 (molecular divisions).



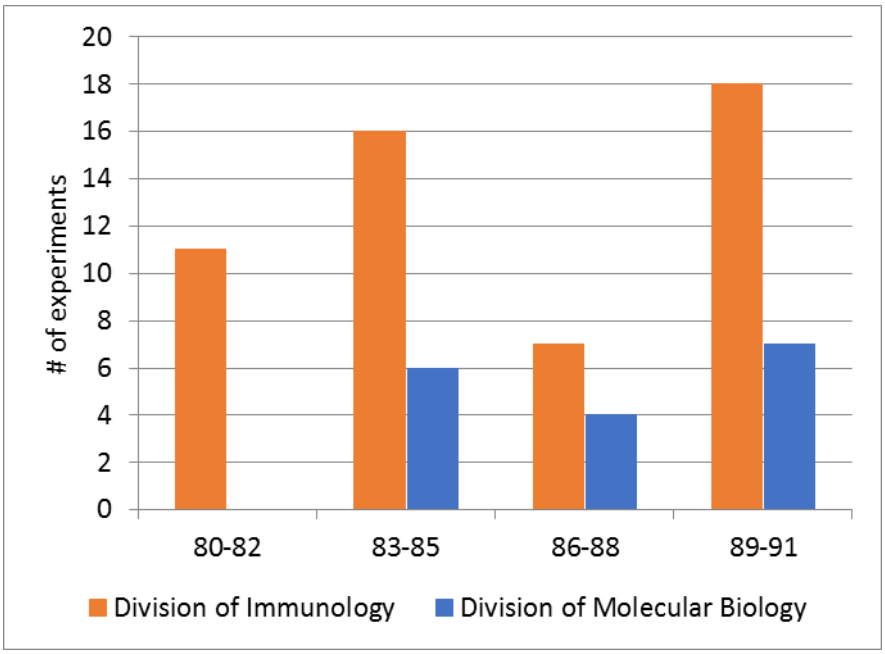
Supplementary figure 3. Grants shared with clinical divisions per approach from 1983-2006. Data were derived from the *Annual Reports 1983-2006*. The total numbers of analysed pending grants are 357 (Immunology) and 917 (molecular divisions).



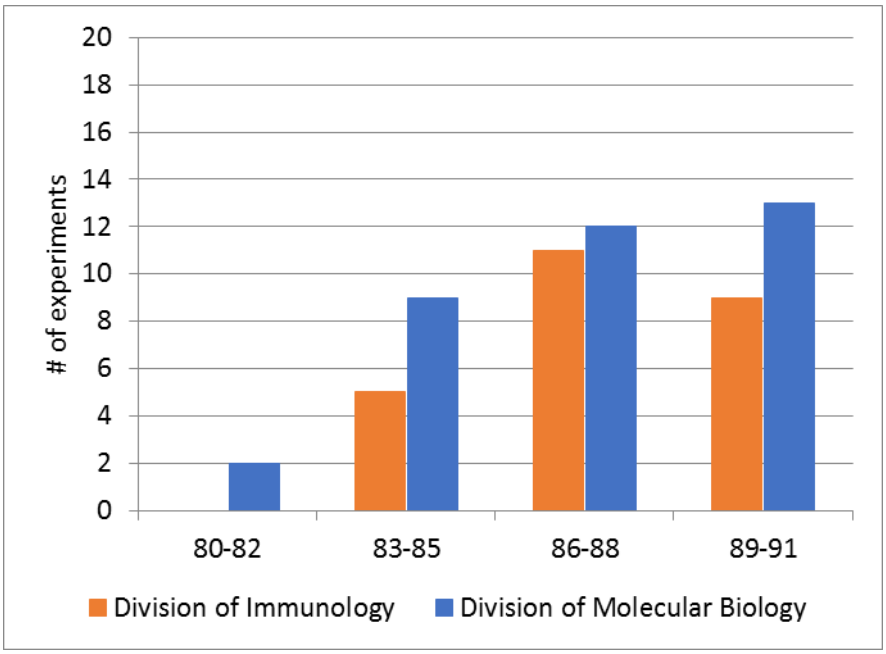
Supplementary figure 4. Publications in general oncology journals by the Divisions of Immunology and Molecular Biology (100% = all publications of division). Publications were counted as published in "general oncology journals" when the title contained the word "cancer" or "onco-", but no other specific adjective, such as "molecular". Data were derived from the *Citation Analyses 1983-2006*. Total numbers of analysed publications are 444 (Immunology) and 577 (Molecular Biology).



Supplementary figure 5. Publications in *Nature, Science* and *Cell* by the Divisions of Immunology and Molecular Biology (absolute numbers). The Division of Molecular Biology published more often in these journals than the Division of Immunology. Data were derived from the *Citation Analyses 1983-2006*. Total numbers of analysed publications are 444 (Immunology) and 577 (Molecular Biology).



Supplementary figure 6. Number of planned experiments in which patient material is needed for the Divisions of Immunology and Molecular Biology (1980-1991). At Immunology more experiments with patient material were planned in all studied timeslots. Data was derived from the *Werkplannen 1980-1991*. For time reasons, only the experiments planned by the heads of divisions were involved in this analysis.



Supplementary figure 7. Number of planned experiments in which *in vitro* cultured cell lines are used for the Divisions of Immunology and Molecular Biology (1980-1991). At Molecular Biology cell lines were introduced earlier and more compared to Immunology. Data was derived from the *Werkplannen 1980-1991*. For time reasons, only the experiments planned by the heads of divisions were involved in this analysis.

Appendix 2: Overview of interviewees

These tables list some characteristics of the interviewed field members per division.

B3: Division of Immunology

Position	**Gender**	**Nationality**	**Working > or < 5 years at NKI**
PhD student	Female	Dutch	<
Technician	Male	Dutch	>
Group leader	Male	Dutch	>
Postdoctoral fellow	Female	Non-Dutch	<
Technician	Female	Dutch	<
Postdoctoral fellow	Female	Non-Dutch	<
PhD student	Female	Dutch	<

B7: Division of Molecular Carcinogenesis

Position	**Gender**	**Nationality**	**Working > or < 5 years at NKI**
Postdoctoral fellow	Male	Dutch	<
PhD student	Male	Dutch	<
Postdoctoral fellow	Female	Dutch	>
Group leader	Male	Dutch	>
Technician	Female	Dutch	>
Postdoctoral fellow	Female	Non-Dutch	<
Technician	Male	Dutch	>

Appendix 3: Interview questions

This list of standard questions guided the semi-structured interviews.

Own work and background

- What is the last experiment you performed and how did it go?
- How does this experiment fit into your research project?
- Which model for cancer do you use the most in your current work? Why?
- Where did you work before? How does this lab compare to these other labs/companies?

The group and division

- Why did you choose to work in this particular group?
- What are the main questions your group addresses?
- For which diseases might your group's work be relevant?
- Are there any common characteristics of people working at your division?

View on cancer, cancer research and therapy

- What have been the most important breakthroughs in your field (in the last 10 years)? Which papers reported this?
- Why does the risk of cancer development increase significantly with age?
- What are the differences between a tumour cell and a healthy cell?
- What are the requirements for tumour growth?
- What do you think is the most promising strategy to treat cancer?

Collaborations and social relations at the institute

- Could you describe what typically happens at a Staff Meeting of your division?
- How important is collaboration with other groups for your project? And with which groups do you collaborate and why?
- What do you think is the reputation of your division in the NKI? Do you agree?
- Do you think the reputation of your division has changed over time? Why?
- In which settings do you get to know people from other divisions?

Other questions

- Do you like your project?
- If you were completely free to design you own project, what would it look like? How would it differ from your current work?
- What inspired you to go into research?
- Could you give a general description of the research performed at your division?
- What are the kind of grants your group applies for? Did this change over time?
- Could you please describe and explain your answer to question 16 of the questionnaire?
- Do you attend all weekly seminars? If so, why? If not, how do you select the ones you attend?
- What kind of social events do you attend here at the NKI?

Appendix 4: Questionnaire

The questionnaire distributed at both divisions is shown below.

Questionnaire - The disciplines in cancer research

The goal of this questionnaire is to get a broad impression of your background, current work and view on cancer research. I also ask you to fill in your name, because I would like to identify the networks of collaboration. However, in the report no specific names will be mentioned.

In my report the answers of you and your colleagues will be analyzed at group level. Furthermore your answers might be paraphrased or quoted literally in this report. In any case your answers will be taken up anonymously and not be traceable back to you. Please indicate below whether you agree with this by encircling your answers.

- ➔ I **do / do not** agree that my answers will be used in a general analysis and that my answers may be paraphrased in the report.
- ➔ I **do / do not** agree that my answers may be quoted literally in the report.

If you have any questions about this questionnaire, do not hesitate to ask me.

Thank you very much for your help.

Pieter Lindenbergh

Questions

1. What is your name?

2. In which group are you?

3. What is your function?

4. Please describe your educational background.

Name of program and degree	**Specialization**	**Institute**

5. Please describe your professional background.

Function	**Topic of work**	**Institute/company**

6. What is/are the main question(s) you address in your current work?

7. What is/are the main question(s) addressed by your group?

8. What are, according to you, the main questions to be addressed in cancer research in general?

9. What do you think is the bottle neck refraining us from answering these questions?

10. What do you think is the most promising strategy to overcome this bottle neck?

11. How would you define cancer?

12. What causes cancer?

13. Please list four important techniques you use in your current work.

14. Please list the members of your division you collaborated with the most in the last 12 months.

Name

15. Please list the people from outside your division you collaborated with the most in the last 12 months (including persons not working at the NKI).

Name	**Division**	**Institute**

16. Could you quickly sketch a schematic “map” of the disciplines within cancer research? Please indicate the relations among them. Which ones are close to each other? Which ones overlap? Please also indicate where you locate your group’s work.
You are free to choose which disciplines you want to include. In fact, you are free to interpret this question however you like.

17. If you have any suggestions or comments, you may write them down here.

Thank you very much for completing this questionnaire. Please hand it in at the mailboxes next to the coffee machine.

Appendix 5: List of collected items

The table below lists items I collected during the field work and I referred to in this thesis.

#	Item	Description	Source	Hard copy	Digital copy
1.	Protocol "Generation of peptide MHC"	Protocol followed at B3	B3	Yes	Yes
2.	Lab book	Describes experiments and purpose I performed	B3	Yes	No
3.	Powerpoint slides	(Visual) representation of experiments and theories; of a technician	B3	Yes	No
4.	Powerpoint slides	(Visual) representation of experiments and theories; of a student	B3	Yes	No
5.	Protocol "LVX ZsGreen Lentiviral pooled shRNA-mir screening libraries"	Protocol followed at B7	B7	Yes	Yes
6.	Lab book	Describes experiments I performed	B7	Yes	No
7.	Photo	Photo of poster showing molecular pathways	B7	No	Yes
8.	Photo	Photo of poster showing laboratory costs of B7	B7	No	Yes