Utrecht University

Institutional Readiness of Novel Advanced Therapy Medicinal Product Systems

A Study of the Interactions Between the Technological Innovation System and Institutional Readiness Concerning Chimeric Antigen Receptor for T-Cells Technology in Belgium, the Netherlands and Luxembourg.

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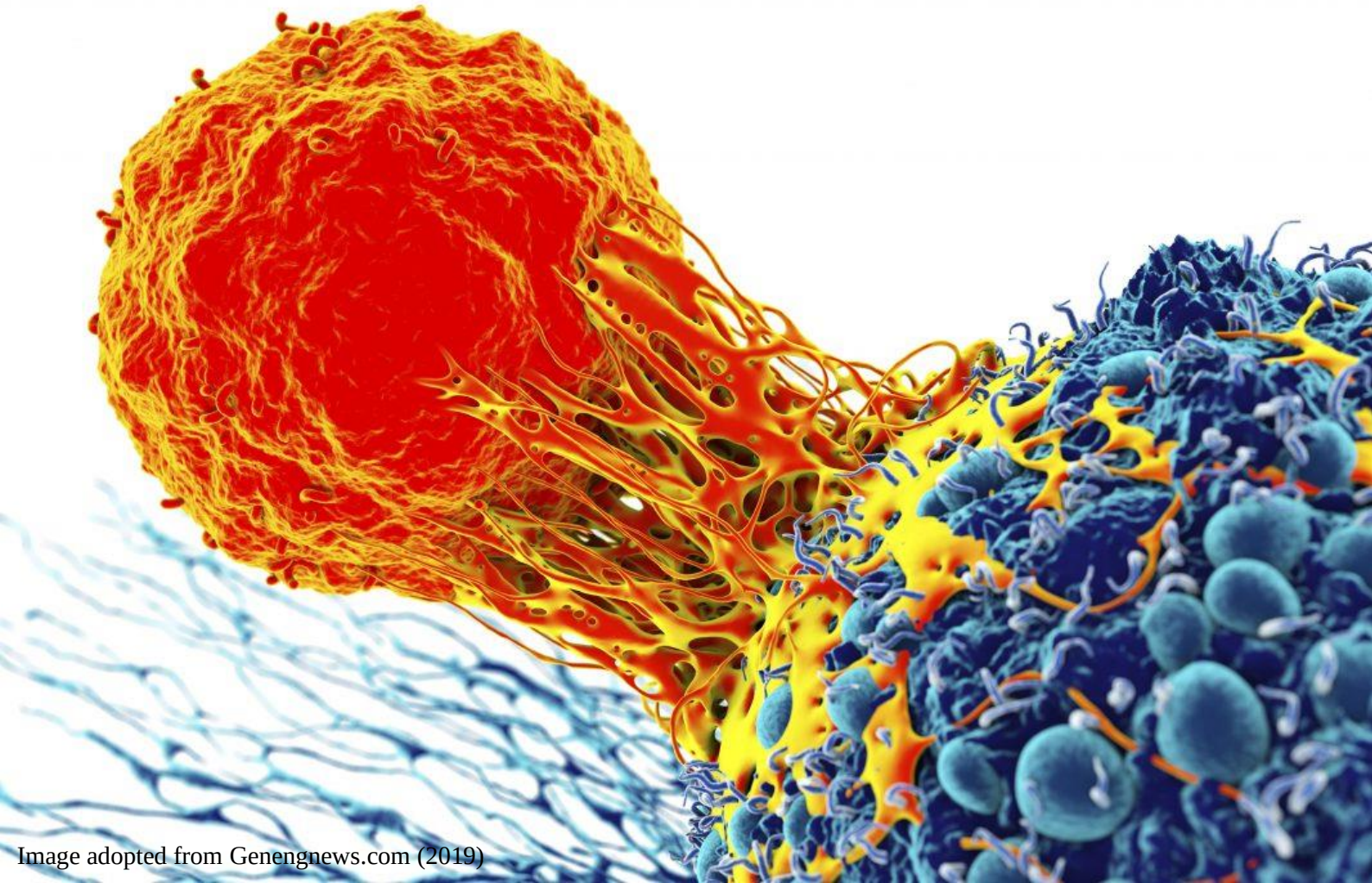

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Abstract

Chimeric Antigen Receptors for T-cells (CAR-T) technology can be used as a new innovative form of cell therapy treatment with the potential to cure diseases which as of now are considered incurable, like multiple myeloma. However, there are barriers that hamper the development, diffusion and the availability of CAR-T treatments. These barriers arise because the technology and manufacturing processes needed for autologous CAR-T treatments are subjected to a variety of barriers that are not applicable to conventional drugs, such as small molecules. The research is conducted based on the research question *"What are the most important barriers in CAR-T's innovation system in Belgium, the Netherlands and Luxembourg and how can these barriers be overcome especially regarding the institutional readiness for CAR-T cell therapy?"* The innovation process of CAR-T is analysed using two different frameworks. First, an event analysis based on the functions of the Technological Innovation System (TIS) framework is performed to map the development of the CAR-T innovation system in the Netherlands, Belgium and Luxembourg from 2011 to 2020. Second, the TIS framework only analyses innovation on a systemic level, while for complex innovative medical technologies barriers also arise on the organisational level. Webster and Gardner's institutional readiness (IR) framework is applied to cover the barriers of CAR-T innovations on the organisational level. This thesis has an explorative nature, because both CAR-T technology and the IR framework, and its categories, are relatively new and underexplored concepts. To accommodate the explorative character of the thesis, data was collected by desk research on CAR-T innovation. The desk research is complemented with 16 interviews with experts in CAR-T development, including experts from academic hospitals, the pharmaceutical industry, universities and governmental agencies. The event analysis shows that the CAR-T innovation system is currently at the end of its development phase and the beginning of the take-off phase. The main barriers on a systemic level are hampering regulations, unharmonized policies on a European level and a lack of consensus between the pharmaceutical industry and governmental agencies about what constitutes cost-effectiveness for CAR-T treatments. Barriers on the organisational level concern the lack of resources and vein-to-vein infrastructure needed to manufacture autologous CAR-T cells. This research suggests several interactions between the functions of TIS and the categories of IR, such as the interactions between; knowledge development and relative need, strategic focus and guidance of the search and between guidance of the search and evaluation processes. The thesis concludes by providing policy recommendations which are 1) pharmaceutical firms should invest in vein-to-vein infrastructure to perform the manufacturing process. 2) governments and pharmaceutical organisations are advised to find a drug reimbursement system to find consensus about cost-effectiveness of CAR-T while still providing access to treatment for patients. 3) Policy and application of policy on a European level should be actively harmonised by the EMA.

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Gijs Lunenborg

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Abbreviations

ATMP	Advanced Therapy Medicinal Product
ATTC	Advanced Therapy Treatment Centre
Benelux	Belgium, the Netherlands and Luxembourg
CAR-T	Chimeric Antigen Receptor for T cells
CBG	College ter Beoordeling van Geneesmiddelen
EC	European Commission
ERA	Environmental Risk Assessment
EU	European Union
FAGG	Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten
GCP	Good Clinical Practices
GCT	Gene and Cell Therapy
GDP	Good Distribution Practices
GMP	Good Manufacturing Practices
HTA	Health Technology Assessment
IR	Institutional Readiness
IS	Innovation System
IV	Interviewee
MM	Multiple Myeloma
MEB	Medical Evaluation Board
NIH&DI	National Institute Health and Disability Insurance
NSI	National Systems of Innovation
PM	Personalised Medicine
RSI	Regional Systems of Innovation
R&D	Research and Development
SSI	Sectoral Systems of Innovation
TIS	Technological Innovation System
TSIS	Technological Specific Innovation Systems
UNSDG	United Nations Sustainable Development Goal
US	United States
WoS	Web of Science

1. Introduction

The United Nations sustainable development goal (UNSDG) number three is to “Ensure healthy lives and promote well-being for all at all ages” (United Nations, 2019). Non-communicable diseases, like cancers and cardiovascular diseases, are the cause of death for 18 percent of the population between the ages of 30 and 70. New treatments need to be made available and accessible to decrease the number of deaths from non-communicable diseases (United Nations, 2019).

Advanced Therapy Medicinal Products (ATMPs) is a class of treatments, which shows promising results for multiple non-communicable diseases (ASCO, 2018; Hartmann et al., 2017). One rather novel promising ATMP uses Chimeric Antigen Receptors for T-cells (CAR-T) technology. CAR-T technology is the frontrunner in a class of treatments that insert chimeric antigen receptors in T-cells with the potential to treat cancers and autoimmune diseases (ASCO, 2018; Hartmann et al., 2017; National Cancer Institute, 2019; Raje et al., 2018). Currently, over 500 clinical trials are actively investigating CAR-T for all indications. The number of clinical trials on CAR-T is has been rising in the past decade (Clinicaltrials.gov, n.d.; Hartman et al., 2017).

However, there are barriers which slow down the development and diffusion of CAR-T technology. The cellular nature of ATMPs, such as CAR-T, causes several problems during development and manufacturing, including uncertainties regarding efficacy and scalability (Coppens et al., 2020; Nam et al., 2019). Treatment based on CAR-T technology is a highly personalised therapy, which requires multiple technological, operational and logistical steps and a well organised, reliable and predictable infrastructure. (Wang & Riviere, 2016). The CAR-T operational system needs GMP manufacturing sites for the genetic modification, expansion and formulation of the T-cells, qualified personnel, certified equipment, organised operations and quality control (Nam et al., 2019; Wang & Riviere, 2016). Furthermore, the CAR-T therapy needs to fit within the current medical treatment practices and organisational context of the treatment centres. Medical treatment centres need to be prepared for the uptake of CAR-T. Previously mentioned barriers can hamper the adoption of CAR-T within organisations (Webster and Gardner, 2019).

Besides the barriers that arise directly from the technological complexity of CAR-T, other barriers arise during its development. Current regulatory frameworks and guidelines are not tailored for manufacturing, distributing and use of such a complex technology as CAR-T technology. The fast-moving nature of the development of CAR-T has caused the regulations and GMP guidelines to lack behind on a European level (Hartmann et al., 2017). Other barriers in the development of CAR-T are the complexity of the clinical trials and reimbursement of treatments (Nam et al., 2019). An additional barrier is the knowledge gap between CAR-T science and application as treatments, which in general is regarded significant for personalised medicine (PM), which include CAR-Ts (Weda et al., 2017). Evidently, not enough research has been performed on the diffusion and implementation of CAR-T.

Furthermore, feedback between research on CAR-T and clinical practice is not always present (Weda et al., 2017). Finally, laws and regulations concerning CAR-T are insufficiently coherent and attuned to the technology. These barriers need to be understood and overcome in order to increase the availability and accessibility of CAR-T (Weda et al, 2017).

Barriers in the development of a novel technology like CAR-T arise from the interactions between stakeholders, laws, regulations and culture in the innovation system, called actors and institutions in the literature. Innovations Systems (IS) literature is used to assess the interactions of these actors and institutions (Hekkert et al., 2007). In this thesis an innovation system approach is used to understand the barriers for the development of CAR-T, because an innovation system approach provides insides in different aspects of the development of a technology. Because this research focusses on the development of a technology (CAR-T), the Technological Innovation Systems (TIS) framework is most applicable. In addition to TIS, this thesis incorporates the Institutional Readiness (IR) framework of Webster and Gardner (2019), because IR can assess the barriers of the development of CAR-T on an organisational level, whereas TIS only assesses the barriers on a systemic level. For complex technologies like CAR-T it is important that actors like Advanced Therapy Treatment Centres (ATTCs) are ready for the new technology. If they are not ready, it might slow down the development and adoption of that technology (Webster and Gardner, 2019).

The practical relevance of this thesis is its contribution to further the understanding of the barriers for development of CAR-T. Understanding the barriers in the innovation system surrounding CAR-T enables actors like biotech companies, policymakers and treatment centres in the CAR-T innovation system to tackle them and enhance and facilitate the availability and accessibility of CAR-T (Nam et al., 2019). The availability and accessibility of CAR-T therapies then increases, thus increasing human health and wellbeing in line with UNSDGs (United Nations, 2019).

The theoretical contribution of this thesis is that the results contribute to the further development of TIS theory surrounding novel medical innovations such as advanced cell therapies like CAR-T. TIS was developed and first used for sustainable technologies in the energy sector, only later has it been applied to technologies in healthcare (Hekkert et al., 2007; Kukk, 2016). Within the development of healthcare technologies, research deals with different actors and institutions that might not be covered by the functions of TIS. Examples of actors involved in the development of technologies in the health care sector are advanced therapy treatment centres (ATTCs) and market approval agencies. Examples of different institutions are complex supply chains within CAR-T manufacturing companies and insurances that pay for the technology instead of the user. The processes taking place on an organisational level of these actors and institutions are not incorporated in the TIS framework.

Barriers for ATMP development on an organisational level are complex and cannot be ignored when assessing the development of ATMPs. The use of the institutional readiness (IR) framework for CAR-

T development is the second addition to the theoretical relevance. IR was developed and used to assess whether ATTCs are receptive for the development of ATMPs (Webster and Gardner, 2019). IR uses categories to assess barriers on an organisational level that are designed for ATMPs. If important actors in ATMP development are not ready on an organisational level, these actors may not be able to adopt the technology. If important actors cannot adopt ATMPs because they are unreceptive, challenges arise in a wider diffusion and regulatory context (Webster and Gardner, 2019). This causes the development of ATMP technologies to slow down. TIS approach is further developed in this research by assessing which actors and IR categories of the IR framework are most important to include in the TIS framework for ATMPs. Being able to assess which actors and institutions are (not) ready on an organisational level for a complex technology like CAR-T expands the understanding of the barriers on all levels of development of such a technology. This solves the knowledge gap that TIS lacks an understanding of the barriers of technology development on an organisational level for complex technologies like CAR-T.

European countries are interesting for researching CAR-T development because, technological breakthroughs are present in Europe. However, there are only few developments and improvements made in the institutions and actors of the technological innovation system regarding the development of technological breakthroughs like CAR-T in Europe (Maciulaitis et al., 2012). This research focusses on the Benelux (Belgium, the Netherlands and Luxembourg), because 1) Janssen, one of the larger pharmaceutical companies is performing research for CAR-T in the Benelux, and 2) the Benelux are the founding countries of the Beneluxa initiative, which is an intergovernmental initiative that creates a supportive environment for the development of CAR-T. This is further explained in the methods chapter (Beneluxa, n.d.). The temporal scope of the research is from 2011 up to 2020, because in 2011 the first successful CAR-T clinical trial results were published (Rodriguez-Cartagena, Bowles, Kurani, Windebank, Kenderian & Greenberg-Worisek, 2018).

This leads to the following research question:

"*What are the most important barriers in CAR-T's innovation system in Belgium, the Netherlands and Luxembourg and how can these barriers be overcome especially regarding the institutional readiness for CAR-T cell therapy?*"

This thesis will be structured as follows; First, chapter 2 discusses the theoretical framework. It contains a background section on CAR-T technology and CAR-T treatment and comprehensive explanation of innovation systems (IS) and institutional readiness (IR) literature. Chapter 2 ends with the integration of IR in TIS in a conceptual framework. Chapter 3 presents the methodology used in this research. It describes the research design data gathering, data analysis and validity and reliability of the research. After the methods the results are presented in chapter 4. The results are analysed and discussed in chapter 5. Chapter 6. and 7 respectively provide the conclusion and discussion of the thesis.

2. Theoretical framework

This chapter presents the theoretical approaches on which the thesis is based. First, a general description of problems in ATMP development and the relevance of an innovation system approach are presented. After that, CAR-T technology and processes needed to administer CAR-T treatments to patients are explained in 2.1., this provides more context on specific problems that may form barriers in the development of CAR-T. Then, in chapters 2.2. to 2.5., innovation systems literature is explained. After that institutional readiness is explained in chapter 2.6. and 2.7. combines the two theoretical approaches in one conceptual framework.

This research uses Innovation System (IS) theory to assess the barriers CAR-T encounters during its development. The success of technological innovation processes is determined by actors, institutions and interactions between them. IS frameworks can be used to analyse the development of an innovation in a structured manner (Edquist, 2005; Hekkert et al., 2007; 2011). However, the development of healthcare technologies, like Advanced Therapy Medicinal Products (ATMPs) and especially Gene and Cell Therapies (GCTs), like CAR-T, encounter specific challenges because they have different characteristics than regular medicine. The challenges related to GCTs, as described by Coppens (2020), are:

1) GCTs are based on cellular source material, which can lead to contamination, inconsistencies and incorrect differentiation of batches. This does not line up with the current model of large-scale production in the pharmaceutical industry (Coppens, 2020).
2) GCTs do not interact with the body as normal pharmaceuticals do, which causes uncertainties and risks that need to be overcome by researchers, developers and regulators (Coppens, 2020).
3) GCTs are rarely used for a single drug-target, but rather offer treatment for several underlying defects. These new treatments shift from a one-size-fits-many drug to more individualistic approaches (Coppens, 2020).

The problems that arise during CAR-T development might cause a gap between the usability of an IS approach and the actual development of CAR-Ts. TIS might not cover all the barriers that arise with the development of such complex novel technologies. Therefore, an addition to the TIS framework is made. Institutional Readiness (IR) theory focuses on how new technologies are received within an organisation (Webster and Gardner, 2019). Gardner et al. (2018) studied IR from the point of view of Advanced Therapy Treatment Centres (ATTCs). As such, the categories of IR could be a useful addition to TIS regarding CAR-Ts, because IR could fill the knowledge gap TIS has on an organisational level regarding the development of complex new technologies like CAR-Ts. This thesis attempts to combine TIS and the IR literature to form a more holistic view of novel advanced cell therapies, such as CAR-Ts developments.

2.1. CAR-T technology and treatment process

Before addressing the TIS and IR theoretical approaches regarding the development of CAR-T in more depth, it is necessary to understand what CAR-T technology actually entails and how autologous CAR-T treatments are used in medical practice.

The basic concept of CAR-T treatments is to use altered human T-cells in a way that benefits the patient. CAR-T cells are ex vivo engineered T-cells that combine the functions of a white blood cell, which is to eliminate alien structures (cells and viruses) in the body, with a chimeric antigen receptor (CAR), which is to recognize specific alien structures (tumour cells in this case) and activate the immune system against these structures (McGuirk et al., 2017). The combination of the CAR and the T-cell allows the technology to recognize and eliminate tumorous cells which the T-cell is normally not able to effectively recognize. Depending on the disease, the specific CAR that is used can be finetuned (McGuirk et al., 2017).

Current CAR-Ts used in treatments, are mostly autologous T-cells which means they are derived from the patient. Allogenous cell therapies use cells derived from other donors. For the treatment process with autologous T-cells, shown in figure 1, there are several steps that must be performed. The first step is testing the eligibility of a patient for CAR-T treatment. Patients have to meet criteria such as; the tumour must have an adequate CAR target, the patient must have an adequate number of T-cells to collect, organ function must be adequate and patients are not allowed to have infections or certain comorbidities like cardiovascular disorders (The leukaemia & lymphoma society, 2017). The next step, called leukapheresis, draws blood from a patient and separates the T-cells needed from the blood before the blood is reinfused in the patient. After leukapheresis the collected T cells are activated and genetically modified to express CARs at their cell surface. Introduction of genetic material (transduction) encoding for CARs often uses lentiviral vectors and results in altered DNA of the T-cells, combining the CAR with the T-cell DNA. The next step is the expansion of CAR-T cells which multiplies the number of newly formed genetically identical CAR-T cells. Thereafter, the cells are isolated and formulated in a product ready for infusion back in the patient. A lymphodepleting therapy can be administered before infusion, if required, to assure the immune system of the patient does not destroy the CAR-T cells after infusion. In this case the therapy would be rendered useless (McGuirk et al., 2017).

The above described process, called the vein-to-vein process, differentiates CAR-T therapies from traditional small molecule and biologic drug therapies. CAR-T is not a product (tablet or injection) that can be manufactured in advance for multiple patients and stocked in a pharmacy or hospital. Instead, the whole process must be performed for every single patient individually. Although the production process is similar, the drug product is different for every patient because the main starting material, the T-cells, are different for every patient. The different steps present technical and regulatory problems which may form barriers that slow down the development and adoption of the technology. Adopting the

vein-to-vein supply chain requires action from multidisciplinary teams according to McGuirk et al. (2017). Along with its technological challenges the vein-to-vein process requires constant communication and collaboration between the involved organisations. McGuirk et al. (2017) conclude that if organisations understand and are prepared for the challenges involved, availability of the product will increase.

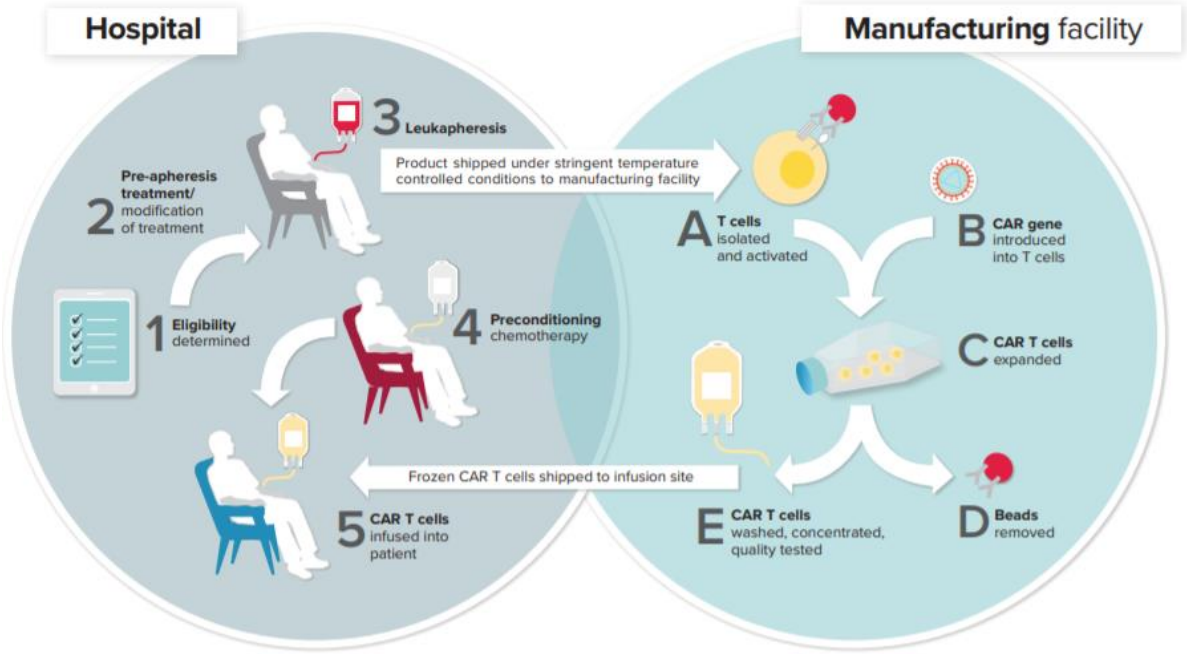


Figure 1: CAR-T vein-to-vein process, adopted from the Leukaemia & Lymphoma Society (2017).

2.2. Innovation Systems

The first innovation systems (IS) theories were developed in the past two decades (Edquist, 2005; Hekkert et al, 2007). All definitions of IS include the observation that innovation is not created in isolation by one actor. Innovation processes are a combination of all organisations and institutions within a system that can influence the development of a technology. Organisations in this context are formal structures that have clear and specific purposes. Examples are firms, universities and governments (Edquist 2005). Institutions are the norms, values, laws and regulations which dictate the relationship between all the actors in a system (Hekkert et al., 2007). Examples of institutions in the pharmaceutical sector are patent laws and the need for market approval of medical technologies by the EMA.

The systemic nature of innovation causes technological change to be a lengthy process. Innovation systems are rigid and attuned to incumbent technologies. Users are accustomed to incumbent technology and infrastructure, social norms, regulations, knowledge and production processes. This focus on incumbent technologies forms barriers for a new technology to enter the market (Hekkert et al, 2007).

Over the years, several frameworks for describing innovation systems have been developed. The most prominent are; 1) the National Systems of Innovation (NSI), which approaches innovation within a geographical area. This can be on a national level or in a regional context (Regional Systems of Innovation, RSI). 2) Sectoral Systems of Innovation (SSI) focusses on different sectors/ industries, and 3) Technological Specific innovation Systems (TSIS), which focusses on the innovation system regarding a specific technology. This thesis focusses on a particular technology, namely CAR-T, rather than the innovative capacity of a sector or nation. Therefore, the focus is on TSIS (or TIS). The definition of Bergek et al. (2015) of a technological innovation system is used in this thesis, which defines TSIS as "a set of elements, including technologies, actors, networks and institutions, which actively contribute to the development of a particular technology field" (Bergek et al., 2015, p52). The TSIS approach by Hekkert et al. (2007 & 2011) describes the interactions between these elements as seven functions.

2.3. Technological Innovation System Functions

The seven functions below are all described in Hekkert et al.'s (2007) *"Functions of innovation systems: A new approach for analysing technological change*". The functions are reformulated to fit research concerning ATMPs like CAR-T, using the operationalisation from Moors *et al.* (2018), which was used as an analytical tool for other innovative healthcare technologies.

The first function, *entrepreneurial activities*, describes the entrepreneurship activities within a system. Entrepreneurs are essential in an innovation system, because entrepreneurs transform new knowledge, networks and markets into useable business ideas (Kukk et al., 2016). For CAR-T, entrepreneurs are the companies that develop the treatment starting with performing clinical trials and eventually applying for market access. (Hekkert et al., 2007; Moors et al., 2018)

Knowledge development is necessary in an innovation system, since knowledge is one of the most essential commodities in modern day economies. In this thesis, new knowledge is defined as scientific knowledge on CAR-T, which is determined by the number of scientific publications on this technology. However, for CAR-T treatments it is not only important to develop knowledge regarding the treatment itself, but it is also important to collect knowledge regarding the manufacturing of autologous CAR-T cells. (Hekkert et al., 2007; Moors et al., 2018)

The third function, *Knowledge diffusion through networks*, indicates how much knowledge transfers take place in heterogenous networks between governments, firms and the market. This function is not very different in healthcare, because knowledge can be exchanged via the same pathways (e.g. conferences and meetings) as other technologies. (Hekkert et al., 2007; Moors et al., 2018)

Guidance of the search refers to the selection of focus points for R&D and other knowledge development. The function reflects the visibility of the demand of an innovation system. Guidance of the search can be improved by governments setting goals, implementing policies addressing problems and incentivising organisations to try to attack these problems. Just like the previous function, guidance of the search is also a result of cumulative interactions between government, organisations and the expectations of the market. It can be determined by the number of regulations and guidelines imposed by a national or international government to stimulate research and development (R&D) activities for CAR-T. (Hekkert et al., 2007; Moors et al., 2018)

New technologies must compete with existing technologies when entering a market. To make new technologies successful, they sometimes must be protected by creating (temporary) markets where the new technology can be further developed, and actors can adjust to the new technology. The latter is described by function five, *Market formation*. Drug approvals and the organisations that provide these approvals are vital in an innovation system for drugs, because medical treatments can only enter a marked after approval from a national or international agency. (Hekkert et al., 2007; Moors et al., 2018)

Every activity within an innovation system can only be performed when manufacturing resources, human and financial capital are allocated to that activity. The best indicator to measure function six *resource mobilisation* is the perception of the actors and whether they think enough resources are allocated to the right activity. In the case of CAR-T, next to financial resources and human resources, the physical infrastructure of the vein-to-vein process is important. (Hekkert et al., 2007; Moors et al., 2018)

The final functions of TIS is *creating* legitimacy. The development of a new technology could be counteracted by actors in the current system. The goal of these actors is to prevent the new technology becoming part or even overthrowing the current system. Advocacy groups that are in favour of the new technology can overthrow incumbent groups. This can cause the creative destruction of incumbent technologies. These groups include patient advocacy groups and lobby groups for or against CAR-T. (Hekkert et al., 2007; Moors et al., 2018)

2.4. Interactions

The seven functions of TIS are not isolated activities that, when performed well, form a well-functioning technological innovation system. The functions are part of a system and thus interact with each other. Interactions between different functions create feedback loops which affect the quality of the innovation system. A new technology can emerge when several functions and interactions form a positive loop. However, feedback loops of badly performed functions can also emerge, which will hamper the development of the technology. Positive feedback loops create momentum for new technology and cause creative destruction for incumbent technologies (Hekkert et al., 2007).

2.5. Phases

An innovation process has different stages or phases of development. In general, these phases are pre-development, development, take-off, acceleration and stabilization. The structure and functioning of an innovation system are different in each stage. Early stage technology requires a different supporting structure than technology that is further matured. When a technology is further developed, the TIS should be of a further maturity as well (Hekkert et al., 2011). Not all functions are equally important in each stage of development. Hence, it is important to determine in which phase CAR-T innovation is currently placed, in order to address the important functions.

2.6. Institutional readiness

TIS was developed based on sustainable technologies in the energy sector and was only later applied to healthcare technologies (Hekkert et al., 2007). Kukk (2016) used a TIS approach to analyse the development of radical personalised treatments for breast cancer. However, the functioning of the technological innovation system for the novel field of ATMPs is still rather under-explored and a TIS approach might not fully involve all institutions and actors in a system for CAR-T therapies. In addition, the TIS framework may not fully incorporate institutional challenges on a micro level. To understand innovation of ATMPs it may be important to understand the interactions between barriers on a (macro/meso) innovation systems level and the challenges on a (micro) organisational level (Webster and Gardner, 2019). As such, the institutional readiness (IR) was assessed for CAR-T in addition to performing a CAR-T TIS analysis.

Webster and Gardner (2019) and Gardner, Webster and Barry (2018) introduced the IR framework for the assessment of regenerative medicine innovation. IR was developed to determine the receptivity of a technology on an organisational level. Especially for radical technologies, such as CAR-T, institutional receptivity is low or non-existent (Webster and Gardner, 2019). Although institutional readiness was developed in the context of Advanced Therapy Treatment Centres (ATTCs), Webster and Gardner (2019) do recognize that IR can be generalized and used in other medical contexts. Based on the readiness categories for ATTCs, the IR framework should be able to recognize the need for innovation elsewhere (Webster and Gardner, 2019). This thesis attempts to find the other needs for innovation by applying the IR framework on important organisations in CAR-T development and relating institutional challenges to systemic challenges. Understanding the latter interactions should allow a greater understanding of the barriers that hamper CAR-T development.

IR is determined using the following eight categories, which can also be found in table 1; 1) *demand for new technology*, which assesses if organisations have the capacity to identify CAR-T as a novel technology; 2) *Strategic focus* determines if organisations can compare CAR-T to other technologies used to treat the same indication; 3) *Relative need and benefit of new technology* assesses the capacity of an organisation to develop CAR-T technology; 4) *(E)valuation processes in place*, assesses if the

organisation determines the value of CAR-T and if the results of these assessments are shared within the organisation and in the case of CAR-T whether there is consensus about efficacy and safety of CAR-T in and between institutions ; 5) *IR enacted through specific enablers within and outside the organisation (enacted IR)* assesses if an organisation has employees tasked with meeting regulatory requirements for CAR-T; 6) *Receptivity* assesses whether an organisation adjusts its structure to deal with challenges that are known before the adoption of the new technology; 7) *Adoptive capacity* assesses the capacity of an organisation to deal with unexpected challenges regarding the adoption of CAR-T that arise during the adoption of CAR-T; 8) *Sustainability* describes whether an organisation is able to produce, asses and distribute CAR-T for a long period of time.

Webster and Gardner (2019) applied these categories to assess the IR of ATTCs, such as academic hospitals. However, within the broader innovation system of medical technologies, the IR of other organisations and institutions may be important. This thesis identifies all actors within the CAR-T innovation system for whom IR to further develop CAR-T. Actors include, but are not limited to; the Benelux governments, biotech companies, the EMA, manufacturing plants, reimbursement agencies and hospitals. After identification of important actors this thesis assesses the institutional readiness of actors involved in CAR-T development, and the relationships between the emerging CAR-T innovation system and the institutional readiness of actors involved.

Table 1: Categories of institutional readiness adopted from Webster and Gardner (2019).

IR Category	Operationally defined
Demand for new technology	Institution has key actors engaging with and identifying new technologies that meet field/organisational needs
Strategic focus	Institution has identified potential new technologies and determined their relation to existing ones.
Relative need and benefit of new technology	Institution has key actors assessing capacity to take-on and develop new technologies within current and future contexts
(E)valuation processes in place	Assessments of the (diverse) values of new technologies are undertaken and shared
IR enacted through specific enablers within and outside of the organisation	Key individuals/groups are formally tasked to enable adoption especially in regards to meeting standards and regulatory requirements
Receptivity	Novel institutional structures are created, in anticipation of expected challenges/affordances presented by new technology. These structures reflect the need to retrain staff, the construction of new innovation spaces and new technology platforms etc
Adoptive capacity	Novel technology aligns with institutional priorities and organisational capacities. Initial problems and unanticipated challenges/affordances are identified and seen to be manageable.
Sustainability	Novel technology is routinely produced/used/assessed within institution. Current institutional arrangements and resources are sufficient for routine and ongoing production, assessment and deployment.

2.7. Conceptual Framework

The following paragraph describes the proposed links between a TIS and an IR approach, which are schematically presented in table 2.

Within the context of CAR-T the first category, *Demand for new technology*, is assessed as the ability of firms to identify existing unmet medical needs. In the context of TIS, the unmet medical need is expected to influence all the functions, as unmet medical need is a driver of innovation (Vennemann et al., 2019). *Demand for new technology* is therefore assumed to be related to all TIS functions.

Strategic focus describes the ability of organisations to compare different technologies in order to adopt the best technology. *Strategic focus* is therefore expected to be related to the *guidance of the search* function that describes how governments stimulate or discourage technologies through regulation and expectation management (Moors et al.,2018).

R*elative need* should be related to policies and regulations because organisations need to incorporate the current regulations and future regulations context of a technology like CAR-T (Webster and Gardner, 2019) and is therefore also related to *guidance of the search. Evaluation processes* can be stimulated by guidelines which assess the values of new technologies. Guidelines are assessed by the function *guidance of the search* (Moors et al., 2018), which is expected to influence the evaluation processes.

The *enacted IR* category focusses on how actors incentivise the adoption of CAR-T and create legitimacy within an organisation but also on how to overcome regulatory challenges (Webster and Gardner, 2019). Therefore, *enacted IR* is expected to be related to the *guidance of the search* and *creating legitimacy* functions.

Receptivity assessed the changes an organisation makes before adopting CAR-T and is therefore closely related to overcoming the *creation of legitimacy* to counteract the resistance to change to CAR-T (Hekkert et al., 2007). *Receptivity* is also expected to be influenced by guidelines because *receptivity* is about overcoming challenges that are known before the adoption of CAR-T and is therefore also related to *guidance of the search*.

Adoptive capacity is related to the *creating legitimacy*. It assesses how unexpected challenges can be overcome within an organisation. *Sustainability* in IR context is an interesting case for CAR-T, because continuous production, assessment and deployment can be difficult for cell based ATMPS, like CAR-T. These difficulties arise due to the irregularities in the developments of ATMPs (Coppens et al., 2020).

Enough resources and adequate knowledge are needed to achieve sustainable production, assessment and deployment. *Sustainability* may therefore be closely related to *resource mobilisation, knowledge development* and *knowledge diffusion*.

If these relations between the TIS functions and IR categories are understood properly, the barriers for CAR-T development can be assessed in a more holistic manner.

Table 2: Conceptual framework: Proposed relations between TIS functions and IR categories

TIS function	related IR categories
F1. Entrepreneurial Activities	Demand for new technology
F2. Knowledge development	Demand for new technology Sustainability
F3. Knowledge Diffusion	Demand for new technology Sustainability
F4. Guidance of the Search	Demand for new technology Strategic focus Relative need Enacted IR
F5. Market Formation	Demand for new technology (E)valuation processes in place Receptivity
F6. Resource Mobilisation	Demand for new technology Sustainability
F7. Creating legitimacy	Demand for new technology Enacted IR Receptivity Adoptive Capacity

3. Methodology

This chapter presents the research design in 3.1., scope of the research in 3.2., data gathering in 3.3., operationalisation of the conceptual framework in 3.4., data analysis in 3.5. and finally, the quality of the research in 3.6.

3.1. Research design

This thesis aims to answer the research question *"What are the most important barriers in CAR-T's innovation system in Belgium, the Netherlands and Luxembourg and how can these barriers be overcome especially regarding the institutional readiness for CAR-T cell therapy?"* The research has a qualitative explorative nature, because the interactions between TIS and IR are underexplored. It ultimately aims to give recommendations on how the current technological innovation system can be improved to make CAR-T more available and accessible (Bryman, 2016; Oost, 2003). A qualitative approach suits this sort of research best, because it provides means to dive deeper into certain functions and provides a detailed explanation of the barriers that define the CAR-T technological innovation system, and which relations between TIS and IR are important in the development of CAR-T.

The research consists of two parts. In the first part, the developments within the technological innovation system of CAR-T up to now are analysed by performing an event analysis using a combination of qualitative and quantitative data. An event analysis maps a consistent string of events which describe the development, diffusion, and implementation of a technology over a determined period (Negro et al., 2008; van de Ven 2017). Events are systemic level changes caused by one or several actors within that system (Kukk et al., 2016). Events in this thesis are changes in the CAR-T innovation system concerning one of the seven functions of TIS. Events that are relevant to the innovation system of CAR-T are described and analysed based on an operationalisation of the functions of TIS (table 5). The event analysis yields a comprehensive overview of the changes in all the aspects of CAR-T development when looked at from a TIS perspective. The development of the TIS functions over time for CAR-T is used to determine the phase of its development by determining the extent of the diffusion. The phase is determined by answering the following four questions in Hekkert et al. (2011). The four questions are; 1) Is there a working prototype? 2) Is there commercial application? 3) Is there a fast market growth? And finally, 4) Is there market saturation? (Hekkert et., 2011).

The second part of the research explores in detail the relationships between a TIS and an IR approach, which are proposed in the conceptual framework. Data for the second part was derived from semi-structured interviews with experts. Questions were based on the results of the event analysis and the operationalisation for IR categories (table 5). Interactions between the TIS functions and IR categories are mapped and analysed.

3.2. Scope

The unit of analysis is the development of CAR-T technology, a cellular form of AMTP, for the disease Multiple Myeloma. This chapter explains the unit of analysis and the scope of the research.

ATMPs are a fast-developing complex new class of medical products. Especially CAR-T, which is a form of ATMP, is an interesting case, because the cellular nature of CAR-T forms several problems in the development of the technologies, like uncertainties in manufacturing (Coppens, 2020). CAR-T is chosen because the technology shows promising results in clinical trials. In addition, CAR-T is developing rather quickly with over 500 clinical trials running for all indications (Clinicaltrials.gov, n.d.; Jayaraman, 2019) and several of the larger pharmaceutical companies are now developing their own CAR-T products, such as Novartis and the Janssen pharmaceutical company (Janssen, 2018; Novartis, 2018).

This research mainly focusses on CAR-T for multiple myeloma (MM), a form of haematological cancer which still requires a cure to cause remission in patients (ASCO, 2018). MM has an estimated prevalence between 0.4 and 2.1 cases per 100.000 people, which makes it and orphan disease (Blum, Bazou & O'Gorman, 2018; Lawrence, 2018; Zhang, Zhu, Jacomy, Lu, & Jegga, 2011). The disease caused over 98 thousand deaths worldwide in 2016 (Blum, Bazou & O'Gorman, 2018; Lawrence, 2018). The highest incidences were found in Australia, high income North America and in western Europe, and these incidences were rising when compared to 1990. However, the measured incidence in the rest of the world might have been lower due to the lack of diagnostic tools (Lawrence, 2018). Patients are treated but are unlikely to reach full remission with current treatments.

These current treatments for MM include Chemotherapy, Targeted therapies, and Immunotherapy (ASCO, 2018). It is important for the wellbeing of patients all over the world that more effective treatments possibly even cures, will be discovered, developed and made available. CAR -T is a relatively new form of personalised medicine and seems to be a candidate for a new more effective treatment for MM. According to Raje et al. (2018), CAR-T could potentially form a new paradigm for the treatment for MM because clinical trials show promising efficacy results. The first positive clinical trial results were published in 2011, when a patient first fully recovered from a haematological oncological disease, lymphocytic leukaemia, by CAR-T (Rodriguez-Cartagena et al., 2018), therefore the temporal scope of the event analysis is from 2011 to 2020.

The research focusses on the Benelux countries. European countries are interesting because, despite technological breakthroughs, there are few policy related innovations concerning these medical breakthroughs in Europe (Maciulaitis et al., 2012). Regulators from national to European level are advised to ensure support for implementing programmes for the developments of ATMPs (Meij, Canals, Lowery & Scott, 2019). The Benelux countries started a programme in 2015 which aims to incentivise the availability and low price of innovative treatments (Beneluxa, n.d.). Beneluxa creates a supportive

environment for ATMPs. In addition, Janssen Pharmaceuticals performs much of its CAR-T development for MM in the Benelux.

3.3. Data Gathering

The data gathering for the event analysis consisted of desk research and interviews. Firstly, the development of the CAR-T innovation system was analysed using desk research. The sources used are scientific papers from PubMed, Scholar and Web of Science as well as grey literature and news articles. Search terms were found trough the snowballing technique. For searches concerning quantitative data in databases like Pubmed, Web of Science and Lexis Nexis, the search technique and terms are explained in the results chapter. Search terms that were used to start the desk research are shown in table 3, snowballing of search terms was applied to extend the search. In addition, interviews were held to gain more in-depth information about the current state of CAR-T development and to triangulate the data found in the desk research.

Table 3: Starting set of search terms used for the desk research in alphabetical order

SEARCH TERMS		
Academic hospitals	Development	Institutions
ATMP	Drivers	Luxembourg
Barriers	Efficacy	Market approval
Belgium	EMA	Manufacturing
Benelux	Europe	Newspapers
Biotech	Events	Netherlands
CAR-T	FAGG	Policy
CBG	Financial	Readiness
Clinical trials	Funding	Regulation
Companies	GCT	Reimbursement
Conferences	Hospital exemption	Vein-to-vein

The data for the second part of the research was gathered via 16 semi-structured interviews. To enhance the explorative character of the study the interviews are semi structured, which allows for coverage of most subjects but can also provide an extensive exploration of subjects that might be more important to certain interviewees (Whiting, 2008). The interviews were structured with an interview guide (Appendix I), but the order in which the questions were asked was different per interview and the questions deviated depending on the answers of the interviewee. The interviewees were the actors that were identified during the desk research in the first part of the research. The sample of interviewees represents the population in the CAR-T innovation system found in the desk research as much as possible. Other potential interviewees were contacted, but due to time constraints and the COVID-19 situation not all were available. Table 4 shows the interview pool and how they are referred to in the results and analysis chapters.

Table 4: interviewee references

INTERVIEWEE NUMBER	ORGANISATION	FUNCTION/DEPARTMENT
IV1	University	Researcher
IV2	Advocacy group Biotech	Program manager
IV3	Government the Netherlands	Clinical assessor
IV4	Government the Netherlands	Advisor
IV5	Pharmaceutical company	Director CAR-T clinical trials
IV6	Government Belgium	Reimbursement pharmaceuticals
IV7	Pharmaceutical company	Regulatory affairs
IV8	Pharmaceutical company	Manager gene and cell therapy
IV9	Advocacy group biotech	Advisor
IV10	Academic hospital	Researcher
IV11	Pharmaceutical company	Governmental affairs
IV12	Biotech start-up/academic hospital	Researcher
IV13	Pharmaceutical company	External affairs
IV14	Pharmaceutical company	External affairs
IV15	Pharmaceutical company	Vein-to-vein manager
IV16	Pharmaceutical company	Global development

3.4. Operationalisation

To perform the event analysis, the functions on which the event analysis is based are operationalised (Table 5). The article from Hekkert et al. (2007) and Bergek et al. (2008) provide an operationalisation for these functions, but not specified for ATMP development. Moors et al. (2018) provide an operationalisation specifically for personalised medicine. The operationalisation of the functions of TIS in this research is based on the operationalisation of Moors et al. (2018) and the operationalisation of the categories of Institutional Readiness is based on Webster and Gardner (2019). The operationalisation is explained below and summarised in table 5.

Operationalisation is initially always focussed on CAR-T for MM. However, CAR-T is a relatively new technology and data might be scarcely available. If data is not sufficiently available for CAR-T for MM, CAR-Ts not specifically for MM are also measured. If the latter does not yield enough data, data for ATMPs instead of for CAR-T only is gathered. Concerning the geographical scope, if searches for Belgium, Luxembourg and the Netherlands do not yield enough data, the searches were expanded to encompass the whole of Europe.

3.4.1. Functions

Entrepreneurial activities are measured by the number of CAR-T clinical trials, CAR-T patents and new biotech start-ups working with CAR-T entering the market. The number of clinical trials is quantitatively measured per country. Each CAR-T trial results in a +1 in the data, as do all the patents concerning CAR-T that were applied for since 2011. For new entrants the operationalisation is similar. Every biotech start-up that is or was developing CAR-T since 2011 is counted as a +1. Because, as stated above, not enough data may be found, the nature of the clinical trials, patents and new entrants are also described qualitatively.

Knowledge development is measured by the number of scientific publications surrounding CAR-T for MM. A list of search terms is formed that represent the field of CAR-T. The search terms are chosen by reviewing the key words of known CAR-T articles. The number of articles is counted from Web of Science and Pubmed.

Knowledge diffusion is measured by the number of conferences, workshops and summits held where CAR-T is a subject, per country. The conferences and workshops are also qualitatively explained. Because borders in Europe are normally open, travel is relatively easy and international CAR-T events in all of Europe are counted.

Guidance of the search qualitatively discusses favourable and unfavourable regulations and guidelines for CAR-T R&D in order to get a more in depth understanding of the regulations that are in place in the Benelux.

Market formation is measured with three indicators; market approvals, initiatives that impact the availability of CAR-T treatments for patients, and reimbursement policies. Market approvals are measured quantitively, however, if market approval is not given the treatment automatically fails, so the market approval process for CAR-T is also described qualitatively. Reimbursement policies are assessed qualitatively, because an in depth understanding of these two is needed to understand its impact on CAR-T development.

Resource mobilisation qualitatively assessed the financial investments in CAR-T, because no sufficient data was found to asses it quantitatively. To describe all the barriers that arise due to the vein-to-vein process, the availability of educated human resources and adequate infrastructure for the development and manufacturing of CAR-T is assessed, this is done qualitatively.

Creation of legitimacy focuses on the lobby activities in favour of and against CAR-T technology development. This is done qualitatively by describing the lobby groups and their activities. News coverage is also a part of the creation of legitimacy. Media coverage CAR-T events and milestones, both negative and positive, are counted quantitatively. Whether a news article is stimulating of discouraging the development of CAR-T is assessed by scanning the article.

3.4.2. Institutional Readiness categories

The institutional readiness (IR) categories are all about complex processes or non-tangible ideas that are difficult to quantitively measure. Therefore, the IR of organisations for CAR-T are only assessed qualitatively. Webster and Gardner (2019) operationalised the IR framework for ATTCs. However, different organisations perform different activities for a technology and thus have different interpretations of the IR categories, so results can differ between organisations. Thus, it is important to acquire data from different perspectives in the innovations system. The general operationalisation from Webster and Gardner (2019) of the categories and the interpretation in this thesis is presented below.

Demand for new technology indicates whether an organisation has the financial, human and knowledge capabilities to detect if the market has a demand for new technologies. For CAR-T this correlates with the unmet medical need for a certain indication and whether that organisation has the means to actively identify the need. This category measures if a company has specialised teams or people for identifying new technologies, and the manner how these tasks are carried out by the specialised teams. (Webster and Gardner, 2019)

Strategic focus is a follow up on the first category. If there is an identified unmet medical need, how do organisations identify how the benefits and disadvantages of the new technology compare to other technologies that treat the same disease. This function assesses whether a firm's employees are well equipped and trained enough to perform the identification of the new technology and the comparison to other technologies. (Webster and Gardner, 2019)

Relative need and benefit of new technology describes whether an organisation is sufficiently capable of adopting the newly identified technology. This can also be assessed by asking if companies have appropriately trained employees and sufficient resources for adopting the new technology. (Webster and Gardner, 2019)

Evaluation processes in place tells if an organisation has internal institutions or actors that asses the value of new technologies. For new innovative medicine an important indicator is whether stakeholders agree what constitutes an effective treatment and whether the results of these assessments are shared within the organisation. (Webster and Gardner, 2019)

IR enacted through specific enablers within and outside of the organisation indicates whether a firm is ready for standards and the regulatory implications that are needed when CAR-T is adopted within the firm, and which specific regulations form barriers. Another indicator is whether actors within the organisation are formally tasked to enable the adoption process. (Webster and Gardner, 2019)

Receptivity is a concept that assesses whether an organisation foresees certain challenges that will arise when CAR-T is adopted. An example mentioned in Webster and Gardner (2019) is; the need to retrain employees before the new technology is adopted. But this category can also be applied to equipment and intangible assets. Interviewees were asked whether their organisations have made adjustment in their supply chain to be able to work with CAR-T. (Webster and Gardner, 2019)

Adoptive capacity is similar to the *receptivity* category but differs in how challenges for adoption of a technology arise. Adoptive capacity assesses if an organisation experienced any challenges that were not expected before the adoption of CAR-T, and if the organisation is ready for unanticipated challenges that might have arisen when CAR-T was adopted. (Webster and Gardner, 2019)

Sustainability in IR context is the ability to produce, asses or use the technology on a long term. This means that an organisation has the institutions in place be a part of innovation system of CAR-T until the technology is fully developed. It is assessed by the continued ability to provide the development of available, affordable, save and effective CAR-Ts. (Webster and Gardner, 2019)

The next chapters will provide an explanation about how the data is analysed and the quality of the research.

Table 5: Operationalisation of technological innovation systems and institutional readiness theories

TIS FUNCTION OR IR CATEGORY	INDICATOR	MEASUREMENT
Entrepreneurial activities	Number of CAR-T Clinical trials	+1
	Number of biotech and pharmaceutical firms in the CAR-T market	+1
	CAR-T patents	+1
Knowledge development	Scientific publications concerning CAR-T	+1
Knowledge diffusion	CAR-T congresses, workshops & symposia	+1 & qualitatively
Guidance of the search	Regulations and guidelines for R&D	qualitatively
	GMO regulations	qualitatively
	Hospital exemption	qualitatively
Market formation	Market approvals for CAR-T treatments	qualitatively
	Initiatives stimulating CAR-T availability	qualitatively
	Reimbursement policies	qualitatively
Resource mobilisation	Physical infrastructure	qualitatively
	Financial resources	qualitatively
	Human resources working with CAR-T	qualitatively
Creation of legitimacy	Lobbying of organisation involved in CAR-T	qualitatively
	Media coverage of CAR-T developments	-1/+1
Demand for new technology	Capabilities for detecting new technology	qualitatively
Strategic focus	Comparing CAR-T to other technologies	qualitatively
Relative need and benefit of new technology	Abilities for developing CAR-T	qualitatively
Evaluation processes in place	Sharing of evaluation results within the organisation	qualitatively
	What constitutes evidence and cost-effectiveness of CAR-T treatments	qualitatively
IR enacted through specific enablers within and outside of the organisation	People tasked with readiness for CAR-T especially regarding standards and regulations	qualitatively
Receptivity	Organisational changes before adoption of CAR-T	qualitatively
Adoptive capacity	Organisational changes during adoption of CAR-T	qualitatively
Sustainability	Ability for long term adoption of CAR-T	qualitatively

3.5. Data analysis

The grey and scientific literature was used to deductively construct an event analysis in which all CAR-T related developments are included and divided into the different functions of the innovation system (Negro et al., 2008). The events consisted of the TIS functions and IR categories at first, but new events that are not covered by those two frameworks emerged, such as learning by cooperation.

The transcribed interviews were uploaded to NVivo for coding and analysis. Interview data was used as complementary source to triangulate the desk research and to explore IR. The approach for analysing the data consists of a thematic analysis which is designed to find themes that are important according to the data (Fereday & Muir-Cochrane, 2006). All these themes are shown in the codes that were used, presented in appendix II. Every bit of data that has an influence on the development of CAR-T is divided into the themes. Some datapoints are divided into more than one function or category, showing possible connections between functions and categories. The connections between themes are inductively used to construct a framework that encompasses important interactions that were found in the data.

3.6. Quality of the research

This chapter discusses the different types of validity that are applicable to this thesis, internal and external validity.

3.6.1. Internal validity

Descriptive validity is the extent to which the gathered data is interpreted objectively (Maxwell, 1992). To increase descriptive validity, tools like NVivo help to create clear overviews of interview data. Feedback with interviewees about the results may prevent personal viewpoint to influence the data.

Interpretive validity describes how data in qualitative research is influenced by the viewpoints of the people from who data is gathered (Maxwell, 1992). To ensure that the interpretive validity is as high it can be, multiple interviewees with different kinds of actors were held and data for the event analysis is triangulated with desk research and interviews combined.

3.6.2. External validity

Generalisability indicates whether the results of this research could be applicable for 1) the whole CAR-T system and 2) systems surrounding other cell therapy technologies. The results can to a certain extent, be generalised for other CAR-T treatments, because it is expected that similar technologies run into the same kinds of barriers. (Maxwell, 1992)

Reliability describes the consistency over time and the reproducibility of a study (Golafshani, 2003). Reproducibility is ensured by providing transparent insight into the methods used in this research. Search terms for the desk research are provided. Though questions varied per interview, the research guide gives insights into which subjects the interviews discussed, ensuring reproducibility.

4. Results

Chapters 4.1. to 4.7 discuss the results of the event analysis over the period 2011 to 2020. Section 4.8. shows the results of the categories of IR concerning CAR-T development.

4.1. Entrepreneurial activities

This section discusses the different indicators that assess entrepreneurial activities. Section 4.1.1. explains the clinical trials for CAR-T in the Benelux. Section 4.1.2. elaborates on the new entrants in the CAR-T industry. Finally, 4.1.3. discusses patent application/registration in Europe for CAR-T.

4.1.1. Number of CAR-T clinical trials in the Benelux

The first indicator for *entrepreneurial activities* is *the number of clinical trials for CAR-T for MM in the Benelux*. In 2011 the number of ongoing clinical trials for CAR-T for all diseases was around 50 in the entire world (Hartmann et al., 2017). The number of clinical trials for all diseases increased to 188 in 2016, of which 14 happened in Europe (Hartmann et al., 2017). This exponential growth was mainly caused by the breakthroughs in CAR-T cells that target the CD-19 antigen in B-cell malignancies, a form of blood cancer. Most of these clinical trials use autologous T-cells. However, in 2016 both the Netherlands and Belgium had only one active CAR-T clinical trial of which the disease was not specified (Hartman et al., 2017).

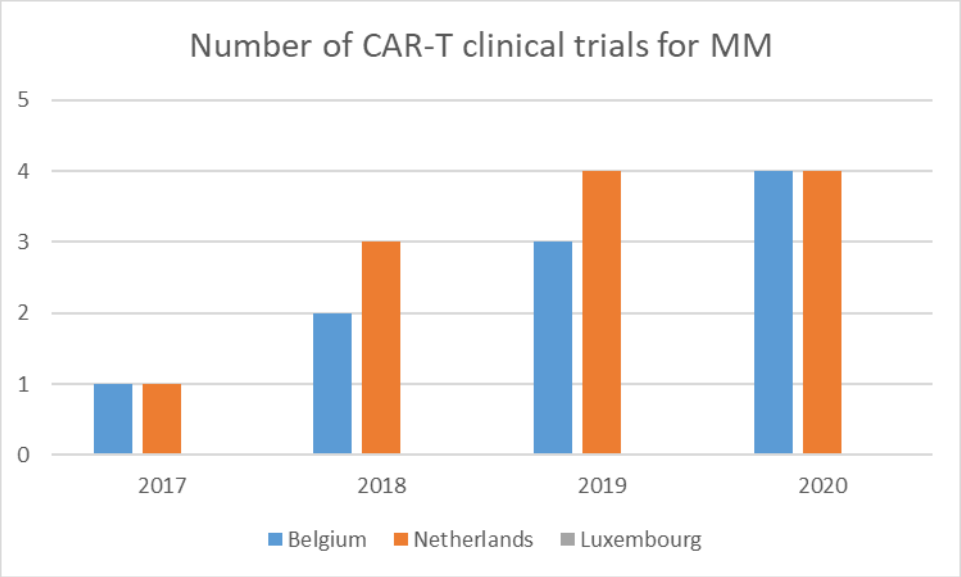


Figure 2: Active CAR-T trials for MM in the Benelux (Clinicaltrials.gov: Per country: search terms CAR-T AND multiple myeloma).

Figure 2 shows the number of *active clinical trials* in the Benelux countries from 2017 to 2020 for MM. The graph starts in 2017, because before 2017 no clinical trials for CAR-T for MM were found in the Benelux. Up to 2020 Luxembourg has no active clinical trials for MM. In Belgium and the Netherlands, the first clinical trial for CAR-T for MM was initiated in 2017. The trial in the Netherlands was a small trial, with only 12 patients and was terminated in 2019, because efficacy was not deemed high enough

to proceed with the study (Clinicaltrials.gov, n.d.). Two of the four trials for MM that are active in 2020 in Belgium are sponsored by Janssen Pharmaceuticals. These phase II and phase III trials and both study the drug designated JNJ-68284528. The other two are both multicenter studies. The multicenter trials are also phase II and III trials and researching bb2121, a form of CAR-T which recognizes a B-cell antigen and potential treatment for MM (Raje et al., 2019). Both the trials for JNJ-68284528 and the phase III trial for bb2121 include study sites in the Netherlands (Clinicaltrials.gov, n.d.). In addition, in the Netherlands another phase II study is active which investigates the long-term effects of autologous CAR-T treatment for 15 years after the first doses is given to the patient in 2018 (Clinicaltrials.gov, n.d.). Three out of four active studies in 2020 are multinational studies, which means that in the Benelux five different clinical trials are active as of 2020. Compared to the rest of the world, 92 trials were active in the whole world in 2020 for CAR-T for MM (Clinicaltrials.gov, n.d.).

Knowledge for CAR-T technologies is often created in an academic setting before it is transferred to private companies by the creation of spinoffs from university (IV3). Prior to phase I clinical trials the technologies are often (partly) transferred to biotech or pharmaceutical companies. For CAR-T development this is especially important, according to IV3, IV10 & IV15, because the academic organisations, such as the Vrije Universiteit, Utrecht University, Antwerp University, Leiden University and KU Leuven (according to the knowledge development search on WoS) are well equipped to address fundamental scientific questions but are less capable of running large scale trials with the vein-to-vein process that is needed for autologous CAR-T cell studies and MM treatments.

4.1.2. New entrants in the CAR-T industry

The second indicator of entrepreneurial activities is the *number of biotech and pharmaceutical companies* active in CAR-T development in the Benelux. Although not all are exclusively focussed on MM, an estimated 48 to 107 companies are now part of the CAR-T market worldwide (CISTON, 2019; BioInformant, n.d.). In the Benelux, Kite Pharma is a company that has a research facility in Amsterdam and a production facility in Hoofddorp near Amsterdam. Kite Pharma is the company that developed Yescarta, one of the two approved CAR-T technologies in Europe. Novartis, developer of Kymriah the other approved CAR-T technology in Europe, also has sites in the Benelux. Janssen Pharmaceuticals has major research facilities in Beerse in Belgium and Leiden in the Netherlands. Celyad is another company focussing on the development of both autologous and allogenic CAR-T cells for haematological malignancies and solid tumours (Celyad, n.d.).

Another new entrant is CARAMBA, an organisation that focusses specifically on finding innovative treatments for MM. CARAMBA was founded in January 2018 by the European Commission with 6,1 million euros and has ten partners all over Europe, including MMPE in Belgium (CARAMBA, n.d.). CARAMBA aims to achieve its mission by performing clinical trials with CAR-T technology (CARAMBA, n.d.). CARAMBA uses CARs that target the SLAMF7 antigen on myeloma cells in

combination with sleeping beauty transposition which does not require viral particles. Using the novel SLAMF7 design for the CAR-T manufacturing process and the sleeping beauty transposition CARAMBA can provide safe and high-level CAR clinical trials, which, according to their site, is a milestone for myeloma treatment (CARAMBA, n.d.). Their phase I clinical trial started recruiting patients in 2020 and the phase II trials will start in 2021 (CARAMBA, n.d.).

Another set of important new entrants within CAR-T development are manufacturers of cell and gene therapies. The first example of this is the firm Anicells in Belgium (Anicells, n.d.). The cooperation between Antwerp University Hospital, University of Antwerp and the Provincial Innovation Centre of Antwerp is a firm which specialises in support services for clinical cell therapy and manufacturing space and equipment for GMP-compliant cell therapy products, like CAR-T (Anicells, n.d.). Anicells was founded in 2017. Anicells does not directly develop new CAR-T technologies. It does provide companies that are incapable of building infrastructure the opportunity to further develop the technology and bring it to patients. Anicells does this by providing clean rooms for research and development (IV12). The second example is MaSTherCell, another firm that complements the development of GMP compliant gene and cell therapy technologies. MaSTherCell was founded in 2011 as a spinoff from the Free University of Brussels (Université libre de Bruxelles), with support from private investors. MaSTherCell obtained its license for manufacturing in 2014 and started production for clinical studies in the same year (MaSTherCell, n.d.). Next to MaSTherCell and Anicells, the University Medical Centre Groningen will start to produce their own CAR-T treatments to circumvent the production facilities in the US (‘Groningen pept kankermedicijnen op’, 2020, p. 5).

For smaller CAR-T developers adjacent industry companies like Anicells and MaSTherCell are important to be able to perform trials without having to set up the whole vein-to-vein infrastructure (IV12). This reduces the amount of resources needed and risks involved in CAR-T development (IV12). Lower risks of CAR-T development may stimulate new entrants to invest in CAR-T.

IV12 states that the entrepreneurial ecosystem in Belgium is much more suited for development of CAR-T than the Dutch ecosystem. The reason for this is that the Belgian ecosystem is more focused on cooperation between different sorts of organisations than the Dutch system. In other words, in Belgium the academic world is more connected to the private sector (IV9). However, IV3 noted that the innovation climate in the Netherlands is adequate enough for companies to perform registration studies for CAR-T. No new entrants in the CAR-T market were found in Luxembourg.

4.1.3. Patents

The last indicator for entrepreneurial activities is the *number of patents* that are granted for a certain treatment or technology. Worldwide, the number of patents for CAR-T treatments in general started to take of around the years 2012 and 2013. However, at the end of a CAR-T patent study by Jürgens & Clarke (2016) in 2016, the total number of patents for CAR-T technologies for all diseases had risen to over 600 worldwide. The same study only found one patent application for CAR-T in the whole of the Benelux, which was in Belgium.

Four patents were found in a search in Espacenet for the number of patents concerning CAR-T for multiple myeloma. These patents were published in 2018, 2019 and two in 2020. Search terms for this search were CAR-T and/or chimeric antigen receptors and myeloma. For the country codes of Belgium, Luxembourg and the Netherlands no patents could be found for myeloma. This means that according to this search on Espacenet no patents for CAR-T for MM in the Benelux were filed. The search for CAR-T patents was extended to all CAR-T technologies, not specifically for myeloma or MM. Again, no patents for the individual countries were found (note that Jürgens & Clarke (2016) found one in Belgium in 2016). A similar search for the European Patent Office yielded the results shown in figure 3. The graph shows a clear rise starting in 2016.

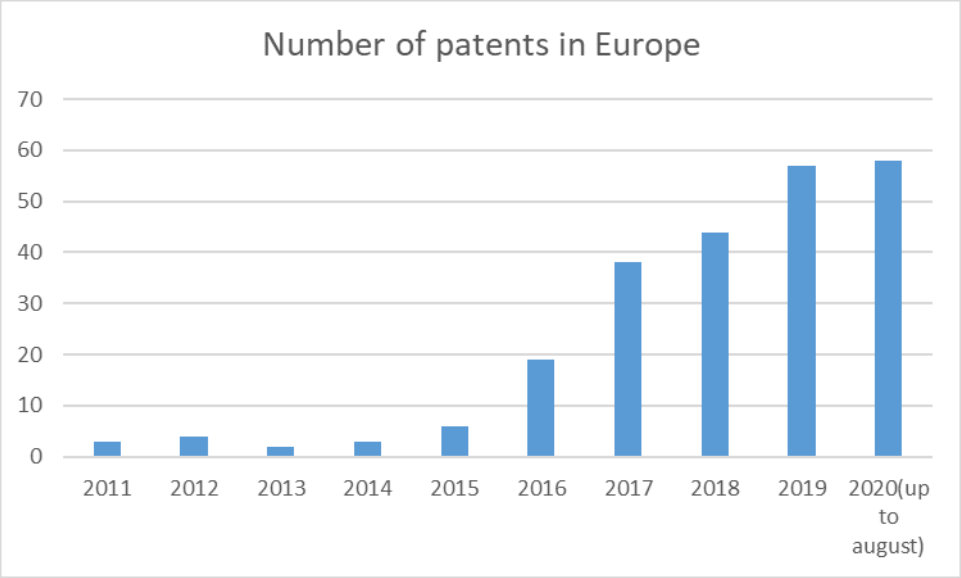


Figure 3: number of patents concerning CAR-T in Europe

Lentiviral vectors used in the CAR-T manufacturing process can also be patented and if so, cannot be used in other research in other organisations (IV8). The lentivirus intellectual property of the manufacturing process is protected. Which may prevent some organisations, like hospitals, from developing their own CAR-Ts. This may decrease CAR-T availability for patients.

4.2. Knowledge Development

This chapter shows the results of *knowledge development* in the CAR-T innovation system. Knowledge development was measured by the number of published scientific articles about CAR-T.

The number of scientific articles concerning CAR-T is determined by searching for articles in two different databases, Web of Science and Pubmed. First, articles were searched in Belgium, Luxembourg and the Netherlands on CAR-T for MM. Search terms in both databases were "chimeric antigen receptor", "T cells", "multiple myeloma" and the countries. The results of this search are presented in graphs 4A and 4B. Thereafter the search was extended to include articles about all CAR-T technologies in Belgium, Luxembourg and the Netherlands, regardless of disease. For the latter search, the search term "*multiple myeloma*" was removed. The search did not contain any other specific search terms, because the number of articles was already very low. The analysis was performed in July 2020, which partly explains the apparent drop in number of articles in that year.

The number of scientific articles found on Web of Science on CAR-T for MM before 2017 was one at the most in each of the countries. After 2017 there is a gradual increase of knowledge creation concerning CAR-T for MM in the Benelux, compared to before 2017. A similar search in the PubMed database which also included search terms "*chimeric antigen receptor*", "*T cells*", "*multiple myeloma*", yielded eight articles in Belgium, eleven in the Netherlands and zero in Luxembourg over the last five years. The latter PubMed search is shown in figure 4B. Globally, there was a total of 320 articles on CAR-T for MM from 2011 to July 2020.

To expand the results, the search term "multiple myeloma" was neglected to find articles on CAR-T for all diseases. The results of the latter search are shown in figures 4C and 4D. For CAR-T for other diseases, such as other non-Hodgkin's lymphomas ('Groningen pept kankermedicijnen op', 2020, p. 5) and chronic lymphocytic leukaemia (Kanker-actueel.nl, 2020), the knowledge development started to increase in 2014/2015 in the Netherlands and in 2016 in Belgium. Only one article CAR-T from Luxembourg was found in the year 2014.

In the Benelux the biggest contributor to CAR-T for MM knowledge development according to Web of Science is the Dutch Free University (VU) and the VU medical Centre (VUmC), which respectively co-authored 8 and 3 articles about CAR-T for MM. Other universities, such as Utrecht University, Antwerp University, Leiden University, Erasmus University and KU Leuven contributed to 2 or less articles about CAR-T for MM according to Web of Science. Knowledge for CAR-T is mainly developed in the academic world (IV1, IV3, IV5 & IV12). This is possible according to IV5, because the knowledge development is more advanced in academic environments, such as the VU.

However, CAR-T innovations are often further developed by pharmaceutical firms. This is to be expected for a biotech innovation as the costs for scaling up are too high for academia or smaller firms (IV3 & IV13). Academic hospitals such as the UMCU in Utrecht used to receive funds to develop new technologies, however this funding, called the "Academische Component", were cut by the Dutch government (IV10).

Knowledge is not strictly bound to one specific country. Research is often done by international organisations (e.g. Gilead, Janssen and Novartis) and cooperation's between organisations (e.g. CARAMBA). The knowledge that is developed is transferred between countries (IV3, IV5, IV6, IV8 & IV11).

When compared to China and the US, there is a lack of fundamental research regarding CAR-T in Europe (Hartmann et al., 2017) (IV5), which is attributed to the harsher research climate in Europe. The harsher climate can be explained by the stricter drug approval processes and stricter (GMO) regulations, according to IV9. Specific regulations that make up this regulatory framework will be discussed in the *guidance of the search* chapter (4.4.). Another reason for the discrepancy in the amount of research done in Europe versus the amount of research in China and the US (Hartmann et al., 2017) according to IV5 and IV11 is that in those countries more financial and human resources are invested in the development of technologies like CAR-T.

The knowledge needed to make CAR-T available for patients is not only knowing how to produce a batch of CAR-T, but the entire vein-to-vein process is complicated and needs to be understood and managed before organisations can adopt the technology (IV15 & IV16). IV15 noted that current systems of mass production in factories for small molecule therapeutics cannot be used for CAR-T and IV15s firm needed to discover how to implement CAR-T in the supply chain. Several experts from the pharmaceutical industry stated that in order to efficiently adopt CAR-T within a system or organisation, all the procedures, regulations, institutions and knowledge needs to build up from the very start. Simply mimicking supply chain from other organisations or countries is not regarded to be productive (IV7, IV8, IV9 & IV16).

In the previous two chapters it was determined that almost no activities regarding knowledge development and entrepreneurial activities for CAR-T are present in Luxembourg. Therefore, Luxembourg is not part of the further results and analysis, because it is unlikely a technology develops in country when no entrepreneurship and knowledge development take place for a technology in that country.

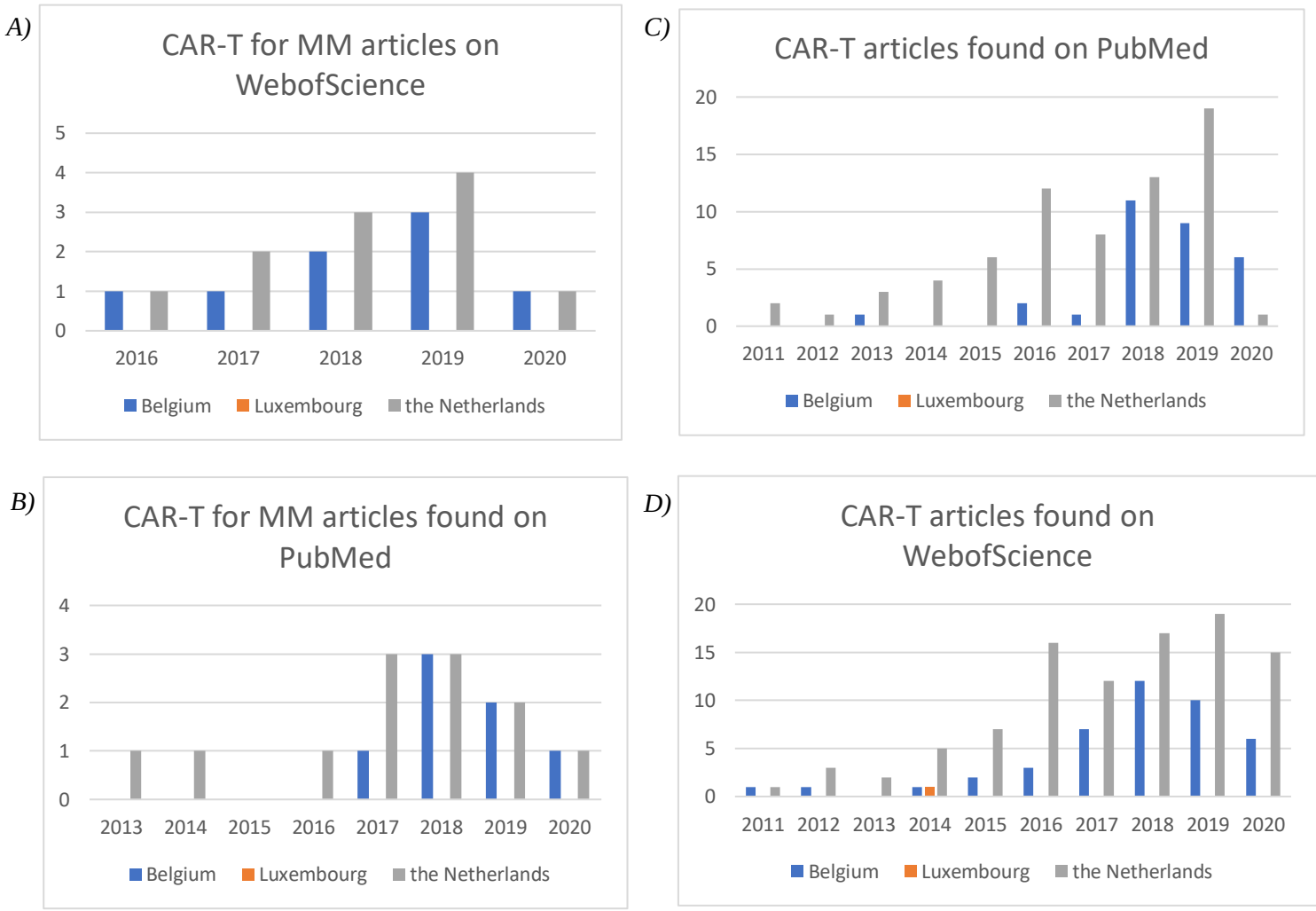


Figure 4: Knowledge development on CAR-T between 2011 and 2020 found on WebofScience and Pubmed. Graphs A and B show CAR-T knowledge development for MM in the Benelux. Graphs C and D show CAR-T knowledge development for all diseases in the Benelux. Graph 4A and 4B start in the years that the first articles were found.

4.3. Knowledge diffusion

Knowledge Diffusion is determined by the number of *conferences, symposia* and *workshops* related to CAR-T in the three Benelux countries between 2011 and 2020. In this context the content of the conferences is also important to address in order to understand whether these networks (conferences, symposia, workshops) increased the diffusion of knowledge about CAR-T treatments. From the interviews it emerged that *learning trough cooperation* is also important in CAR-T development. This is discussed as a separate indicator in chapter 4.3.2., but first CAR-T conferences, symposia and workshops are discussed in 4.3.1.

4.3.1. CAR-T conferences

There are different conferences organised for stimulating CAR-T development. Most of these meetings do not take place in the Benelux but are nonetheless relevant as will be discussed later in this chapter. Several of these meetings were not specifically aimed at CAR-T or the broader set of ATMP technologies, but they do have an impact on the development of CAR-T and are therefore discussed in this section of the results. Table 6 provides an overview of the locations of meetings.

The European Medicines Agency (EMA) hosted a multi-stakeholder workshop to foster the development of ATMPs in May 2016 (EMA, n.d.-a). The purpose of this workshop was to increase interaction and guidance from regulators, foster sharing of information, harmonise between ATMP regulation between member states and facilitate that every patient has equal access to ATMP treatments (EMA, n.d.-a). The main results of this workshop were the promise of several different guidelines for topics including GMO, GMP and scientific guidelines. The GMP guidelines and regulations regarding GMO are discussed in the *guidance of the search* chapter. Another result of the workshop was that the EMA would organise and give training sessions and workshops continuously within their European network. The stakeholders from the pharmaceutical industry, regulators, incubators, investors, patient representatives, academia and physicians identified several barriers for the development of ATMPs (EMA, n.d. -b). Barriers were divided over 14 themes and included among other topics such as the lack of ATMP related guidelines, transparency issues and the lack of awareness (EMA, n.d. -b).

The CAR-T Cell Receptor (CAR-TCR) Summit is an annual summit organised by Hanson Wade since 2019 in Europe as well as in other areas around the world. During the summit in 2019 around 120 experts discussed topics like availability, accessibility and price of CAR-T treatments. This is the largest summit with specifically CAR-T as its subject (CAR-TCR, n.d.).

The European Society for Blood and Marrow Transplantation organised their second CAR-T conference (The 2nd European CAR-T Conference) on the first of February 2020 in Barcelona. The first conference, one year earlier, featured speakers that focussed specifically on MM (e.g. the CARAMBA project) (EBMT, n.d.).

The CAR-T Congress EU is an event that takes place in London and was organised for the second time in 2020, with a specific focus on oncology. The line-up of speakers was a combination of experts from biotech firms, clinicians, academics and professionals from logistics, process standardisation and service companies with regard to CAR-T treatment (CAR-TcongressEU, n.d.).

The European Haematology Association (EHA) hosts a yearly congress. The "Annual congress of EHA" was hosted for the 25th time in 2020. Due to the Covid-19 pandemic, the 2020 conference was held digitally (EHA, 2020). As the name suggests, the topics of the Annual congress of EHA is not only focussed on CAR-T, but (poster) presentations about clinical practice and efficacy of CAR-T were held. However, these were not specifically focussed on MM. Next to CAR-T technologies, presentations for other cell and gene therapies against Haematological diseases were held.

The American Society of Haematology (ASH) is a haematology advocacy group that organises the ASH annual meeting & exposition which is world's most comprehensive event concerning haematology according to the website (ASH, 2020). ASH's annual meeting & exposition will be held for the 62nd time in December 2020 in San Diego (ASH, 2020). Like the EHA congress, the ASH annual meeting is not specifically focussed on CAR-T. As of now, no specific CAR-T presentations or discussions can be found, but the full program is not announced yet.

The International Society of Cell and gene Therapy (ISCT) hosts an annual conference since 1993. It is hosted in a different city every year (ISCT, n.d. -a). The Society is comprised of 2300 cell and gene therapy experts from over 60 countries. Building on their long-term relationships, the ISCT strives to promote collaboration between academical, regulatory and commercial organisations for the benefit of the patient (ISCT, n.d. -b).

Table 6: Locations of CAR-T meetings

Congress	Benelux yes/no/sometimes
CAR-TCR	No
ASH	No
EHA	Sometimes
ISCT	Sometimes
CAR-T congress EU	No
European CAR-T Conference	No

Interviewees IV3, IV5, IV6, IV8, IV11 stated that they attend conferences for either CAR-T or haematology. The two most mentioned conferences are organised by the European Haematology Association (EHA) and the American Society of Haematology (ASH). Conferences, workshops and symposia are deemed useful (IV3), important (IV5, IV6 and IV11) and by one interviewee even crucial for development and availability of CAR-T, saying:

"*calling it important is an understatement*" (IV8, 2020)

Especially ASH, a conference in the United States, was considered to be valuable for obtaining new insights about CAR-T. One interviewee (IV5) stated that congresses in the Benelux often repeat results on new CAR-T developments already presented at the ASH conference. Smaller gatherings in Europe are not considered innovative enough (IV5). Often, identification of new innovative CAR-T technologies happens at the worldwide conferences (IV5). Conferences can be used as a market scan for smaller biotech firms developing innovative CAR-T technologies. This mechanism may help foster CAR-T innovation by sharing knowledge on which other organisations can further develop CAR-T, according to IV11.

For regulatory agencies there are two main reasons to attend conferences and symposia. First, symposia help to identify how many and what kind of haematological treatments are in the pipeline of biotech and pharmaceutical companies (IV6) as pharmaceutical companies do reveal the key outcomes from clinical trials at congresses like ASH and EHA (IV8). And second, it is thought to be important to already get to know the CAR-T technologies that the regulatory bodies have to assess in the future (IV6). IV3 stated that oncology conferences with CAR-T workshops are useful to update personal general knowledge. However, for a regulatory agency, part of the information presented may be information that is already known from recent or ongoing regulatory procedures.

4.3.2. Learning through cooperation

This aspect of knowledge diffusion did not appear in the operationalisation but was mentioned in the interviews as part of knowledge diffusion. Examples of cooperation's that foster knowledge diffusion are the acquisitions (e.g. Kite Pharma and Gilead Sciences, Juno Therapeutics and Celgene Corporation) and co-development agreements (e.g. Legend Biotech and Janssen) between biotech companies and larger pharmaceutical companies (IV9).

According to IV5, collaborations, like spin-offs between academic hospitals in Belgium and pharmaceutical firms, such as Janssen, are useful to share knowhow about how to deal with complex technologies like CAR-T from hospitals with the pharmaceutical firms. Using the technological know-how, the pharmaceutical firms can then use their large pool of financial and human resources to scale up processes needed for CAR-T development. Hospitals can also learn from each other about adopting processes to provide CAR-T treatments for patients and to do CAR-T studies. Medical doctors from other countries come to academic hospitals in the Netherlands to view procedures surrounding CAR-T treatment in hospitals (IV10).

4.4. Guidance of the search

In the chapters below the regulations and guidelines affecting the research and development of CAR-T are discussed. Chapter 4.4.1. discusses regulations and guidelines that affect the development of CAR-T on a European level. 4.4.2. and 4.4.3. present the results about respectively GMO regulations and hospital exemptions in the Benelux. No relevant information was found for Luxembourg; therefore, Luxembourgish regulations and guidelines are not presented in this chapter.

4.4.1. European regulations and guidelines influencing CAR-T development

In 2016 Hartman et al. (2017) noted that regulatory requirements for ATMPs still posed a challenge for developers of ATMPs in Europe. Examples are the unharmonized regulations between member states, GMP compliances and certification for GMO manufacturing. These challenges may cause delays in research and development (Hartman et al., 2017).

Different countries have different application forms for approval to perform clinical trials. In the year 2014 the Clinical Trials Regulation (Regulation (EU) No 536/2014) was adopted. But until this comes into effect, only voluntary harmonization efforts are used to counter this problem (Hartman et al., 2017). Harmonization of application forms is vital for ATMPs because cell-based trials are highly irregular. Harmonisation can prevent miscommunication about clinical trials. Clinical Trials Regulation (Regulation (EU) No 536/2014) was scheduled to come into effect in 2019. This would harmonize the clinical trial reporting in Europe (Buechner et al., 2018). However, due to technical difficulties the regulation still did not come into effect (EMA, n.d.-c). Furthermore, the environmental risk assessments (ERA) for CAR-T technology are assessed different in different countries, because there or two different strategies of approaching ERA, deliberate release and contained use. In regulation 536 harmonisation is not considered which makes the submission of clinical trials with GMOs after the regulation virtually impossible (Buechner et al., 2018).

The Committee for Advanced Therapies (CAT) is a committee hosted by the EMA. CAT provides certification for quality and non-clinical data for ATMPs developed by small and medium-sized enterprises. CAT also provides recommendations for ATMP classification, advice on efficacy follow-up, pharmacovigilance and regulation, giving scientific advice with Scientific Advice Working Party as a partner and giving scientific advice about innovative medicine in general (EMA, n.d.-d).

IV2, IV3, IV7, IV11 & IV12 notice that even though there are European regulations that should work in all countries, some regulations are interpreted differently in the different member states of the EU. The fact that member states of the EU handle regulations concerning CAR-T development differently is seen as a hurdle by pharmaceutical firms. Unharmonized regulations cause delays in development because international organisations must go through slightly different procedures in every country. Harmonisation of regulation and the execution of regulation would be a major step toward widely available CAR-T treatments (IV5 & IV13).

IV9 suggests that development of CAR-T technology in Europe stays behind in CAR-T knowledge development and clinical trials when compared to China and the US (Hartmann et al., 2017) mainly due to the stricter GMO regulations. For example, stricter GMO regulation makes Europe less attractive for organisations such as biotech firms to perform research in because the research has to meet higher standards (IV9).

Another way the EU wants to combat barriers in CAR-T development are guidelines for good practices. However, due to the fastmoving development of ATMPs, these guidelines were not available as of 2016 (Hartman et al., 2017). The EMA also provides scientific advice and protocol assistance for manufacturing and distribution; Orphan designation; the micro, small and medium-sized enterprise (SME) office; Classification of advanced therapy medicinal products (ATMPs); Certification of quality and non-clinical data for SMEs (EMA, n.d. -f). In 2018 the European Commission provided good manufacturing practices guidelines for ATMPs and in 2019 the good clinical practice guideline for ATMPs was released (European Commission, 2019). The European Commission also launched a joint program in order to stimulate ATMP development by streamlining the procedures and making sure the needs of ATMP manufactures are met (European Commission, 2017). In addition to the latter, the European commission also formalizes classification of ATMPs which is provided by the CAT. Scientific advice and protocol assistance are provided by the scientific advice working party with help of the CAT. CAT also provides certification of quality and non-clinical data for SMEs (European Commission, 2017). IV3 & IV7 stated that scientific guidance during clinical trials helps to accelerate the development of CAR-T.

4.4.2. Impact of GMO regulation on CAR-T development

Regulations concerning the use of genetically modified organisms in treatments is the most discussed type of regulation in the acquired data in this research. To understand the impact of GMO regulation on the development of CAR-T, the regulatory agencies and the two main types of GMO regulation, *deliberate release* and *contained use,* are shortly explained below.

In Belgium the Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten (FAGG) is responsible for regulating the use of GMOs in clinical trials and as a therapy. However, the administrative procedures, inspections and the admission are the responsibility of the governing bodies of the three main regions of Belgium (Flanders, Wallonia and Brussels). This means organisations that develop GMOs like CAR-T have to be familiar with the approval processes of different governmental institutions. More resources have to be allocated to these different approval processes and may cause delays in development (IV7 & IV12).

In the Netherlands the responsibility for GMO regulation is in the hands of three different ministries, *Ministerie van Infrastructuur en Waterstaat*, *Ministerie van Volksgezondheid, Welzijn en Sport* and *Ministerie van Landbouw, Natuur en Voedselkwaliteit*. However, policy is mainly based on two main advisory bodies. First, the Bureau Genetisch Gemodifischeerde Organismen (BGGO) judges the use of GMOs and provides permits to the users of GMOs (Rijksoverheid, n.d.-a). Second, the Netherlands also has an additional advisory body called the Commissie Genetische Modificatie (COGEM). The COGEM advises the government about the risks involving the use of GMOs (Rijksoverheid, n.d.-b).

Regulatory agencies can assess the use and risks of GMOs in two ways, *deliberate relea*se and *contained use* (IV3). Deliberate release, which is used in the Netherlands (IV3 & IV7), follows the principle that if a gene or cell therapy is injected in a patient, it will be excreted into the environment (Lake, 1991). Once in the environment it may pose risks that should be assessed before the treatment is used. Contained use, which is used in Belgium, does not consider the excretion of GMOs into the environment (Lake, 1991; IV7). In Belgium, that risk does not have to be assessed. The Netherlands and other countries that use(d) deliberate release require more documentation with proof that the CAR-T does not impact the environment compared to countries that use the contained use strategy (IV3 & IV7). IV3 stated that the due to recent harmonisation efforts lately the burden of proof in the Netherlands also declined. GMOs are still assessed according to the deliberate release strategy, but because GMOs and their effect on the environment have been rigorously tested, the amount of documentation for each individual GMO is less than it was before this harmonisation (IV3). IV5 commented that getting GMO approval in Belgium is still a faster process than it is in the Netherlands. IV2 explains the lack of speed for GMO application in the Netherlands through the fact that the Ministerie van Infrastructuur en Waterstaat is responsible for approvals (Rijksoverheid, n.d.-a). Its job is to minimize risks and a consequence of trying to minimize risks is that procedures take longer. Another explanation given for the longer GMO approval procedures in the Netherlands is that GMO regulation is based on agricultural regulations (IV3 & IV16), which is deliberate release into the environment.

IV10 states that the Netherlands has accelerated its approval process for GMO use in clinical studies. First, to get approved, organisations had to wait for six weeks twice. In those six weeks the public could file concerns about the use of GMO in studies in that specific organisation. However, nowadays there is only one six week waiting period for approval, due to lobbying efforts from advocacy groups and talks between medical doctors and politicians. The second six weeks were dropped in 2019 (Loketgentherapie, 2019).

During development, certain technologies can be approved faster in the Netherlands in exceptional situations. During the COVID-19 crisis in 2020 the Dutch government drafted an exemption that resulted in the faster approval of gene and cell therapies against COVID-19. The time for approval for research with GMOs for COVID-19, is adjusted to a maximum of 28 days (Rijksoverheid, 2020). Normally this could take 56 days in the Netherlands. Later that year, in July, the European Commission (EC) published a new temporary regulation that completely neglects the need to apply for approval if GMO research is aimed to find a curative solution for COVID-19. However, this regulation is only applicable for COVID-19, so not for other diseases and will disappear when the WHO no longer marks COVID-19 as a pandemic (Bureau GGO, 2020).

In January of 2020 the COGEM released a new report entitled "*Assessment of risks for third parties with gene therapy studies with replication deficient GMOs and Genetically modified T cells*" (Beoordeling van risicos voor derden bij gentherapiestudies met replicatie deficiente ggos en gg-t cellen; COGEM, 2020) with advice on how to implement policy regarding the safety and risks involving the use of genetically modified T cells, including CAR-T cells. The report mentions specific cases for which, out of pragmatic and efficiency reasons, GMO regulation does not apply (COGEM, 2020). The main example given in de recommendations is on the risk that traces of genetically modified T-cells for cancer are transmitted when those patients donate tissue or organs. In that case GMO can be neglected, if the technology is already reviewed and no further assessments have to be performed for the safety during the tissue or organ donation procedure (COGEM, 2020).

4.4.3. Hospital exemption and CAR-T

Hospital Exemption (HE) was implemented in the Netherlands in 2008 by the Inspectie Gezondheidszorg en Jeugd (IGJ) (Hegger et al., 2017). In January 2017 the Belgian FAGG, the agency that monitors medicine development in Belgium accepted a law that allows hospital exemptions (HEs) for ATMPs (FAGG, 2017).

HE allows the use of advanced therapies that are made for only a few patients. The goal of HE is to provide new innovative treatments for patients with rare conditions who cannot be treated by approved technologies (FAGG, 2017; IGJ, n.d.). HE treatments are not developed according to routine and specific quality norms but are allowed to be used in Belgian and Dutch hospitals under the exclusive professional responsibility of medical doctors. Gene therapies, somatic cell therapies, tissue manipulation and advanced therapy are defined as ATMPs under Dutch regulation. Despite this regulation being in place for over three years in Belgium in 2020 only one case of hospital exemption has been granted. It was not a CAR-T related treatment that received the grant (FAGG, 2017). According to IV1, because the requirements to be allowed to perform HE are too strict for hospitals to meet. IV1 adds to this that in the Netherlands the HE works better because the IGJ and CBG developed the HE in

the Netherlands in cooperation with the hospitals. Two of the eleven academic hospitals in the Netherlands use hospital exemptions.

HE treatments are created by hospitals and/or universities for a small number of patients (IV1). The provision of otherwise inaccessible treatments is the main benefit for patients with orphan diseases. Academic hospitals have the flexibility and knowledge to create these CAR-Ts in small batches, but hardly possess the financial resources to perform HE (IV1). While pharmaceutical companies have the resources to create CAR-Ts in larger batches for larger groups of patients, but HE treatments are often not commercially viable (IV1). Forming a strategy that exploits the benefits of both HE and regular production of CAR-T should yield the highest accessibility (IV8 & IV9). Another benefit that is mentioned is that HE CAR-Ts will be cheaper per treatment, because they are not as heavily scrutinised by regulators as treatments that are developed and approved normally (IV3 & IV9).

IV3 and IV6 would like to see the HE CAR-Ts to be registered just like normal CAR-T products or other treatments. Unapproved medicine, especially a complex product like CAR-T, can be problematic, because small changes in the technology can cause large variations in the clinical effect produced by the final product. (IV3 & IV6). IV3 adds that HE can lead to inequality between patients because HE CAR-Ts might only be used for individual cases without a formal market authorization, thus hampering the widespread use. Finding a balance between registration and HE is a solution for making CAR-T more widely available for patients (IV3, IV8 & IV9). Furthermore, HE is arranged on a national level which can cause inequality between member states of the EU (IV3).

4.5. Market formation

Market formation discusses the CAR-T market approvals provided by national and international agencies (4.5.1). This chapter also discusses the Priority Medicine Initiative (PRIME) which is initiated to guide organisations through the approval process, which makes market approvals easier to acquire. Finally, reimbursements are discussed (4.5.3.).

4.5.1. CAR-T market authorizations

Market authorization of drugs on a European level is provided by the EMA and market authorisation on a national level is provided by the CBG and FAGG in the Netherlands and Belgium respectively. For regular treatments these organisations perform these tasks for their respective area of authority, however, for therapies like CAR-T a centralized procedure is in place. This process starts with two European countries that lead the reviewing process. These two countries, different for every application, evaluate the application of the treatment and write an extensive assessment report which is then commented on by agencies of all member states (IV3). This means that once it is approved, it is approved in all European member states (IV3).

The first and only two CAR-T technologies approved in Europe to enter the market as of 2018 are Kymriah from Novartis and Yescarta from a collaboration between Kite Pharma and Gilead.

4.5.2. Priority Medicine Initiative

In March 2016 the Priority Medicine initiative (PRIME) was initiated by the EMA. This programme aims to support the development of treatments that target conditions with an unmet medical need, such as MM. PRIME consists of two main features: accelerated assessment and fostering dialogue between industry organisations and the EMA. Accelerated assessment provides faster market authorisation for technologies that are designated as PRIME treatment. Fostering dialogue focusses on providing early scientific advice during the clinical development program to enable accelerated assessment of medicine applications for market authorization. Improved clinical trial design makes sure that patients only participate in trials that lead to marketing authorization (EMA, n.d.-c; EMA, n.d.-e). Four CAR-T trials were part of the initial nineteen PRIME technologies, none of those CAR-T trials were performed in the Benelux. Kite and Novartis both performing one and Juno Therapeutics performing two of those trials. In April 2019 Janssen Pharmaceuticals received its first PRIME status for JNJ-4528 for MM (Pharmatimes, 2019). As of April 2020, five CAR-T clinical trials were deemed eligible for the programme. IV3 stated that PRIME does help accelerate the availability of CAR-T through the dialogue between firms and the approval agency.

4.5.3. Reimbursement policies for CAR-T

Estimates of the cost of CAR-T treatments are between 200.000 and 500.000 euros per patient for a one-time treatment (IV6 & IV13). Because of the high costs, most patients would not be able to pay for the treatment (IV6).

Thus, this chapter is mainly focussed on how much and when governmental agencies reimburse CAR-T treatments. Governmental agencies responsible for reimbursements are the Zorginstituut (ZIN) in the Netherlands and the National Institute Health & Disability Insurance (NIH&DI) in Belgium.

Difficulties in addressing this problem are the following. Firstly, unlike current MM or other oncological treatments, CAR-T is administered once. CAR-T treatment costs are relatively high to reimburse compared to treatments where the costs are spread over several injections or hospital visits (IV4 & IV6). Secondly, CAR-T treatments are mostly applicable to smaller patient populations than conventional treatments. This results in the problem of what metrics are to be used measuring the effectiveness and safety of the treatment (IV4 & IV6). How can effectiveness be assured when patient populations and the amount of data are low?

Governments need a high degree of certainty before they provide the funds to adopt the technology or before providing reimbursements. If that data is not present, governments will choose cheaper treatments that are already proven to be effective with a sufficient amount of data. In order to study long term gains and losses of CAR-T, follow-up studies are needed to determine the efficacy and side effects (IV4 & IV6). As of now, according to IV6, there is not much experience with CAR-T within the Belgian governmental reimbursement organisation and until further follow-up results are acquired within the organisation, it will follow the current result for CAR-T clinical trials. Price negotiations halted in Belgium for one of the two approved treatments in 2019 (IV6). The reason why one of the price negotiations halted could not be disclosed because that information is classified (IV6).

Another factor to consider is that at the moment, CAR-T treatments are a last resort for MM patients and often the fourth or fifth treatment that is used after the other treatments failed or stopped working (IV6, IV13 & IV14). It is the hope of experts like IV6 that that will change. But until that changes, governments are not always likely to reimburse the fifth treatment a patient receives if a treatments cost between two and five hundred thousand euros (IV6).

It is suggested, by IV9 & IV12 from the pharmaceutical industry, that CAR-T treatments need other models to calculate the amount of money the government should pay per cure. IV4 stated that CAR-T is for the most part treated the same as any other treatment that is assessed by the Zorginstituut in the Netherlands (IV4). IV11 stated that current health technology assessments (HTAs) are adequate to calculate the value of CAR-T treatments, because these models are already in development since before 2000 and are adopted to fit more complex technologies.

Delays in the negotiation process between pharmaceutical firms and governmental insurance organisations are in the interest of none of the actors impacted by the delays, least of which are patients (IV9 & IV10). There are systems elsewhere that simultaneously provide patients with a treatment and allow organisations involved to negotiate the price of a treatment. Germany, for example, has a reimbursement system in place, that provides a treatment for the patient, data for the governmental agencies and ensures financial reimbursements for the manufacturer of a treatment if the treatment has proven its efficacy (OECD, 2018) (IV9, IV10 & IV11). This sort of value for money systems based on real world evidence ensures availability during price negotiations (OECD, 2018) (IV9, IV10 & IV11).

4.6. Resource mobilisation

Different kinds of resources were marked as important by the literature and the interviewees. The physical infrastructure, financial resources and human resources. The impact of the different resources on CAR-T development will be discussed below. Chapter 4.6.1. discusses the physical infrastructure that is needed for CAR-T production. 4.6.2. presents the results found for financial resources for CAR-T development and the reimbursements for CAR-T treatments. Finally, in 4.6.3., human resources that are needed in CAR-T development and manufacturing are discussed.

4.6.1. Physical infrastructure for CAR-T production

A lack of compatible physical infrastructure between hospitals and GMP facilities for manufacturing high quality CAR-T cells consistently forms problems (Hartman et al., 2017). Coming years, manufacturing capabilities for CAR-T need to be scaled up to meet the growing market and different CAR-Ts that are currently being developed (IV3 & IV5). The large pharmaceutical companies are looking to build their own manufacturing plants. Kite and Gilead already opened their new manufacturing plant for the European markets in Hoofddorp near Amsterdam (IV2). Other pharmaceutical companies are also planning to build a manufacturing plants in Europe (IV5). MaSTherCell and Anicells can provide manufacturing capacity for smaller biotech firms and academical studies in Belgium (IV12) The closer manufacturing plants are to the hospitals and patients, the faster the patients can receive the treatment. Travel time is reduced, and time spend when crossing borders is eliminated. Next to this, a solution is needed for cell therapy products that are not frozen at the end of production. Adequate infrastructure to get those technologies to the patient in time is still needed (IV12).

Another barrier for manufacturing is a shortage of lentiviral vectors (IV5 & IV12). Not all CAR-T manufacturing processes are dependent on these viral vectors (IV12). But CAR-Ts that do, like CAR-T for MM, often encounter shortages in availability (IV5 & IV12). The shortage of lentiviral vectors is a worldwide problem. Pharmaceutical firms can build production facilities, but this is seen as a major barrier because the production process of lentiviral vectors is complex and takes time (IV5, IV8 & IV13). Building a production process that is able to consistently produce stable lentiviral vectors is an

unforeseen barrier which slows down manufacturing or can even mean that a smaller number of patients can be treated (IV5 & IV8).

4.6.2. Financial resources for CAR-T development

The CARAMBA project further develops CAR-T for multiple myeloma, because although there are innovate treatments, myeloma is a disease that is still incurable (CARAMBA, n.d.) and receives 6,1 million euros over a time span of four years (i.e. 2018-2021) from the European commission (CARAMBA, n.d.).

Only 20% of CAR T cell trials are sponsored by pharmaceutical industry (Hartman et al., 2017), and its knowledge development mainly depend on knowledge institutes. Financial resources from the total R&D expenses of the 27 largest pharmaceutical companies have risen from 30 billion US dollars in 2000 to 120 billion US dollar in 2018 (SOMO, 2020). This clearly shows a rise in the total R&D expenses of the pharmaceutical industry.

One argument that was made by IV4 was that if a treatment is discovered in an academic setting and a pharmaceutical firm acquires the technology, there should be a system in place that ensures that the initial development costs invested by the government is to be taken into account during price negotiations. Such a system should ensure that the costs of development can be earned back by public organisations (IV4).

4.6.3. Human resources for CAR-T development and treatment

Human resources assess whether there are enough educated people able to work with CAR-T. About a quarter of the students that enrolled in a bachelor or master in 2017 course was in a health or technology program (Health Holland, 2018). About a third of the PhD tracks that were started in the Netherlands in 2015/2016 were in the Health and Wellbeing sector (Health Holland, 2018). In Belgium the number of people employed by biotech industry companies has grown with 23.8% in the period between 2014 and 2017 compared to an average European growth of 0.3% (Pharma.be, 2020). Next to this, one study suggested that Belgium has the highest amount of PhD in life sciences and related industries per 1000 people (McKinsey, 2019). Attracting new educated employees is important in CAR-T development but not seen as a barrier for the development of CAR-T (IV4, IV5 & IV8)

When CAR-T was adopted in the firm of IV5 & IV8, the company hired the right employees with a technological or health background for CAR-T development. Dutch governmental agencies have enough educated people to adopt CAR-T into their organisation and assessments of CAR-T technologies (IV4). For some of the specific knowledge about ATMPs, governmental agencies have contact with specialists from, for example hospitals (IV4). However, the lack of educated and experienced employees in hospitals could be a problem in the future if the number of CAR-Ts grow (IV10). Hospitals are not able to easily attract new highly educated staff due to restrains on budget.

4.7. Creating legitimacy for CAR-T treatments

Creating legitimacy for CAR-T is needed to create a sense of urgency for CAR-T developer and regulators to make the treatment available faster. Creating legitimacy is determined by two different indicators, namely: number and nature of advocacy groups, which are discussed in chapter 4.7.1. and, media coverage, the number of published news articles regarding CAR-T and these results are presented in 4.7.2.

4.7.1. Advocacy groups

A public initiative, initiated by ministers responsible for pharmaceutical policy, that supports the development of new innovative treatments for small groups of critically ill people is Beneluxa (Beneluxa, n.d.). Beneluxa is an initiative founded in 2015 by the Benelux countries, but since then more countries have joined (Beneluxa, n.d.). The mission of Beneluxa is to ensure affordability and accessibility of treatments for patients with orphan diseases (Beneluxa, n.d.). Tools that are used by Beneluxa are scanning the market for new technologies, sharing information and policies, the assessments of health technologies and negotiating about pricing and reimbursements. Beneluxa is led by a steering committee aided by technical domain task forces for the different collaborations (Beneluxa, n.d.). According to IV4 Beneluxa also creates a scientific basis on which assessments from governments can be performed. Beneluxa put out a statement in the beginning of 2020 about the pathways surrounding CAR-T (Beneluxa, 2020). The statement contains the following; patients with acute lymphoblastic leukaemia that receive CAR-T are likely to still need stem-cell transplantations. For this specific disease attention needs to be given to cost-effectiveness. The argument of Beneluxa is that developers and other actors involved in CAR-T development and treatment should be careful. Acute lymphoblastic leukaemia (ALL) patients who received a CAR-T treatment still require other expensive treatments, such as stem cell transplantation. The latter patients would have received stem cell transplantation anyway. Developing and administering the CAR-T product for ALL patients is an extra, and maybe obsolete treatment, that costs resources for developers and reimbursement agencies. For other CAR-T treatments, such as CAR-T for MM, this question of efficacy versus cost should also be considered.

Myeloma Patients Europe (MPE) is an advocacy group specifically for MM patients situated in Belgium and it strives to form connections between all MM related actors for better quality care. Through knowledge sharing, education, ensuring patient centred clinical trials and shaping policy MPE aims to give patient the best and equal care (Myeloma Patients Europe, n.d.) MPE originated in 2011 from a merger between the European Myeloma Platform and Myeloma Euronet. The headquarter of MPE is located in Brussels. MPE is also a partner within the CARAMBA project (Myeloma Patients Europe, n.d.). Members include individuals as well as other advocacy groups. MPE acts like an umbrella organisation for other advocacy groups.

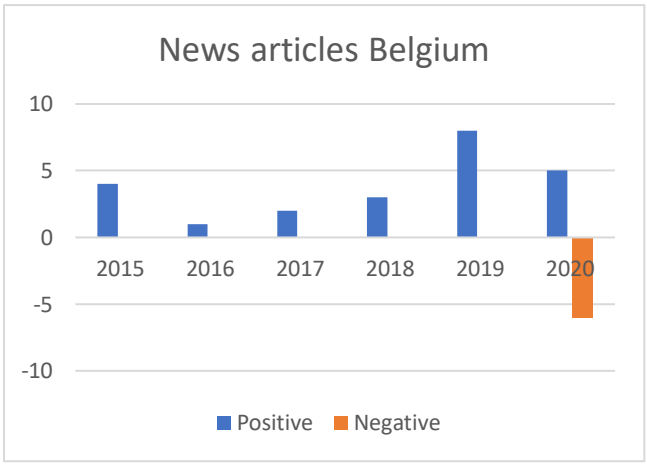
Hematon is a Dutch advocacy group for people with haematological cancers or people who underwent stem cell transplantation for such a disease (Hematon, n.d.). Hematon advocates for the availability of expensive treatments, quality of haematological care, the role of patients in scientific research and jobs for patients after cancer (Hematon, n.d.).

Stichting Hemato-Oncologie voor Volwassenen Nederland (HOVON) is an advocacy group, established in 1985, that aims to increase access to treatments for rare haematological diseases (Hovon, n.d.). Hovon helps patients access to treatments by doing research and organising a treatment network between hospitals (Hovon, n.d.).

4.7.2. Media coverage of CAR-T developments

A search for news articles regarding CAR-T development, availability and efficacy on LexisNexis was performed. Like with the search for scientific articles, a search was first done with the "multiple myeloma" as a search term. However, this yielded no result when Belgium, Luxembourg or the Netherlands were chosen as location of publication. Therefore, the search was extended to look for al CAR-T related new articles in the three separate countries. This search resulted in the positive and negative reporting regarding CAR-T shown in figures 5A and 5B. Luxembourg is not shown, because no news articles about CAR-T were found that were published in Luxembourg. The graphs start in the year 2015 instead of 2011 because in that year the first CAR-T articles were published in the Benelux.

A)



B)

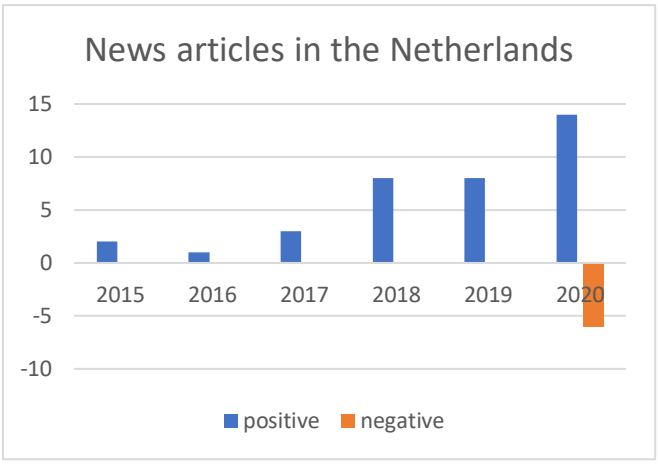


Figure 5: News articles concerning CAR-T in Belgium and the Netherlands

The news surrounding CAR-T in Belgium found in the Lexis Nexis search mainly contains information about mergers in the biotech industry of companies (mainly Celyad) that are affiliated with CAR-T. Most economic articles are positive, about increasing value of CAR-T firms. However, in the first half of 2020 some negative articles were published about the value of stock from companies developing CAR-T. For Belgium one article was found, written in 2017, which describes CAR-T as being equally ordinary in the future as biological treatments are now.

In the Netherlands the earlier news articles from 2015 and 2016 are mainly about Celgene investing in Juno Therapeutics for their CAR-T technology. Later outlets like Volkskrant, Financieel Dagblad and Dagblad van het Noorden report about milestones in the development of CAR-T technologies, all in a positive way. One way in which CAR-T treatments are portrayed positively, are the stories about patients who are cured by CAR-T treatments. Different outlets describe the story of Kees, a man diagnosed with an aggressive form of leukaemia, who's only chance for survival would be to receive CAR-T cell therapy. The news outlets describe how a crowdfunding campaign was set up to raise enough money for the treatment, updates on the treatment and how Kees is leukaemia free after the treatment. On 24 September 2020 the Volkskrant published an article about how the University Medical Centre Groningen is about to produce their own CAR-T for Lymphomas ('Groningen pept kankermedicijnen op', 2020, p. 5). The impact of publications like the latter and impact of creation of legitimacy on CAR-T development were discussed with some of the interviewees.

The importance of the creation of legitimacy was brought up several times in the interviews (IV8, IV9, IV10 & IV11). Legitimising CAR-T, in other words creating a support base is considered essential for the diffusion of the technology. A sense of urgency within the patient group needs to be created to increase this support base for expensive medical technologies. A sense of urgency among the patients of haematological diseases can incentivise governments to adjust regulation in favour of faster development of medicine (IV6 & IV9). An example of this mechanism is how the Dutch government shortened the application for GMO permits during the COVID-19 crisis. Instead of 56 days, gen and cell therapies will be assessed in 28 days (Rijksoverheid, 2020) (IV8). If the same sense of urgency can be created by patients and patient advocacy groups it might also stimulate organisations that are active in the development of CAR-T to develop treatments quicker, by stimulating pharmaceutical companies to make their treatment available cheaper and taking into account the patient perspective (IV10 & IV11) or stimulating governments to create incentives for CAR-T developments (IV6). Another addition by IV11 is that the role of patients in scientific research concerning drug development should be bigger than it is now.

However, experts fear that the COVID-19 crises will not set a precedent for orphan diseases like MM, because for MM, which is an orphan disease, there is not such a sense of urgency. Experts are divided on what effect the COVID-19 crisis and the emergency regulations will have on the further development of ATMPs for therapies not related to COVID-19. Two experts agree that the crisis provides opportunities to change regulation and policy regarding CAR-T but several of them are sceptical whether regulations and procedures will change in the future (IV7 & IV8). However, if the media and the advocacy group can create a sense of urgency for MM it might be possible to influence decision making surrounding CAR-T for MM.

Figure 6 shows the timeline for CAR-T development from 2011 to 2020. The timeline shows the most import events that were identified in the event analysis.

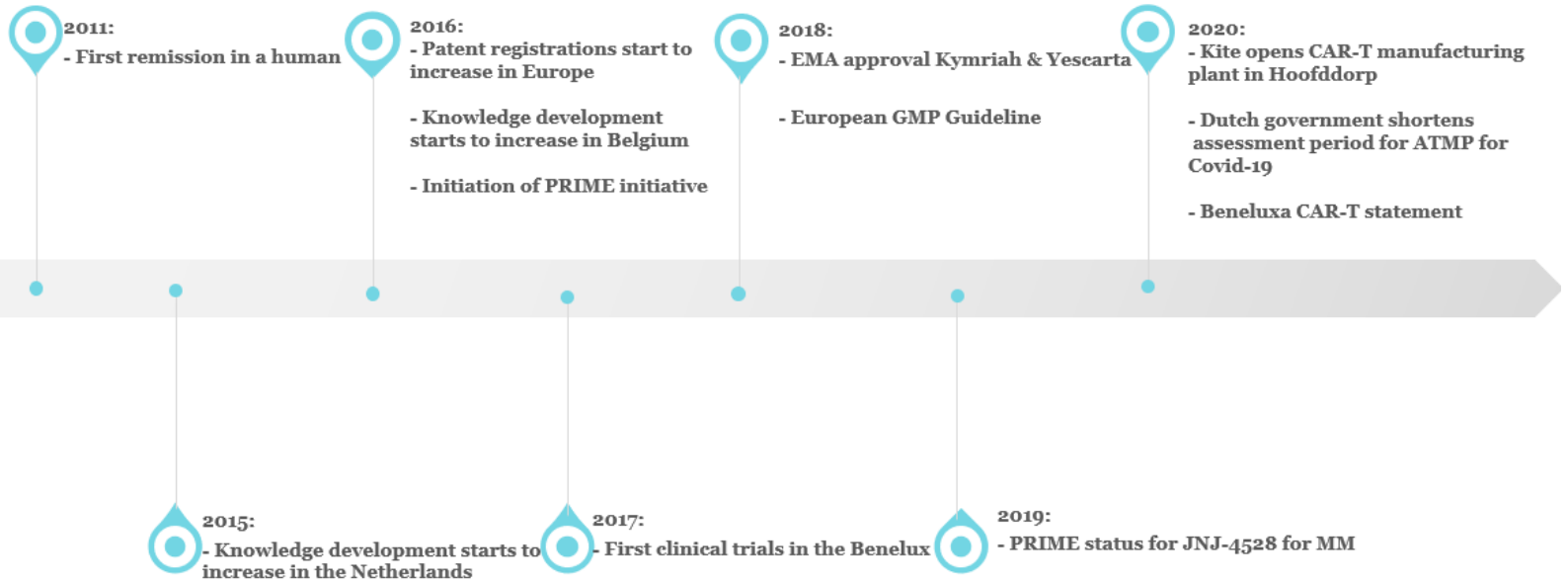


Figure 6: Schematic timeline of the most important events regarding the development of CAR-T technology.

4.8. Institutional readiness for organisation developing CAR-T

This chapter discusses the results concerning the institutional readiness of organisations involved in the development of CAR-T. Chapters 4.8.1. to 4.8.8. discuss the results of the different categories of institutional readiness concerning CAR-T in the Benelux.

4.8.1. Demand for new technology

The *demand for new technology* category assesses whether institutions, such as regulatory agencies, have the capacity and people to identify CAR-T (Webster and Gardner, 2019).

The capabilities of different governmental agencies and pharmaceutical organisations to detect new CAR-T technologies depend on internal and external factors. IV5 mentioned one internal factor in a pharmaceutical firm that increases awareness of new technologies is having separate teams of which the main job is to scout the market for new technologies (IV5). Pharmaceutical and governmental organisations like Janssen and the NIH&DI, the governmental reimbursement agency in Belgium, both noted they have special teams of employees that scout the market for new technologies like CAR-T (IV5 & IV6).

Regulatory agencies, such as the NIH&DI in Belgium, also have special teams that check the pipelines of firms in order to be prepared for new technologies. Horizon scan from the Beneluxa initiative was deemed very useful for the scouting of new innovative technologies to be prepared for the technologies of the future (IV6).

Most respondents who attended CAR-T conferences, symposia or workshops recognized that these meetings are useful for pharmaceutical firms to scout the CAR-T market. Attending congresses is also a chance for regulatory agencies to scout CAR-T pipelines of pharmaceutical companies (IV3, IV5, IV6, IV8, IV11). As already discussed in the knowledge diffusion part (Chapter 4.3.1.) these congresses increase knowledge spill overs between small biotech firms and pharmaceutical firms. Again, there is the example of J&J acquiring Legend Biotech, a small Chinese CAR-T developer. The 2017 ASH congress did play a role in that acquisition. Their codeveloped CAR-T technology is scheduled for approval in 2022 (IV8). This suggest that if governmental and pharmaceutical organisations in Belgium and the Netherlands perform the *demand for a new technology* well, by attending conferences, the development of CAR-T will be increased, because knowledge and ideas are shared between organisations.

4.8.2. Strategic focus

The *strategic focus* category discusses how institutions, such as pharmaceutical firms and reimbursement agencies, asses the value of CAR-T treatments compared to other technologies that are also used to treat MM (Webster and Gardner, 2019).

An aspect of strategic focus and the relationship of CAR-T treatment with other technologies is the line/order of treatment in which CAR-T is given. As of now people treated with CAR-T in studies and after market approval, only receive the CAR-T treatment as a last resort (IV13). First, patients receive treatments that are already used for a longer period of time. These current treatments for MM include chemotherapy, targeted therapies, and immunotherapy (IV4) (ASCO, 2018). Patients are treated but are unlikely to reach full remission with current treatments. It is therefore the goal of the pharmaceutical firms that develop CAR-T to provide CAR-T treatments as a first line treatment (IV13 & IV14). However, a barrier for CAR-T becoming a first line treatment is that there is not enough data compared to the current treatments that proof the safety of the treatment. However, being a fourth- or fifth-line treatment combined with being an expensive treatment, causes to be less approving of CAR-T treatments (IV6). If an MM patient already received chemotherapy, targeted therapies and immunotherapies the patient has already cost a lot of financial resources. The question is then whether they should receive a fourth, expensive, treatment of which the efficacy is not sufficiently proven for the governmental reimbursement agencies (IV4 & IV6).

4.8.3. Relative need

The category *relative need* assesses whether hospitals, CAR-T developers and governmental agencies have actors that identify the necessary capacity to develop and take on CAR-T now and within future contexts (Webster and Gardner, 2019). This thesis found two aspects that are important in the *relative need* for CAR-T treatments. First, a CAR-T developing firm's ability to technically execute the vein-to-vein process now and second, how the necessary capacity of hospitals, governmental agencies and pharmaceutical firms is affected if the knowledge for allogenic CAR-T cell treatments is developed.

First, biotech and pharmaceutical firms that decide to adopt CAR-T within their supply chain have to adopt or outsource the vein-to-vein process. The vein-to-vein process requires factories and a complex logistical system. A lot of knowhow about the logistical process surrounding CAR-T and resources, such as manufacturing plants and educated employees are needed to adopt the vein-to-vein process within a firm (IV15 & IV16). These changes are probably not worth the advantages of adopting only one CAR-T technology but should yield more than one treatment (IV5 & IV8). According to IV8 firms should not just create one CAR-T. Once a firm decides it wants to adopt CAR-T into its supply chain, it has to adopt the whole vein-to-vein supply chain (IV8). Large pharmaceutical firms are mostly able adopt the vein-to-vein process, due to the amount of financial resources at their disposal (IV13 & IV14),

however shortages of lentiviral vectors during the production did slow down the adoption for pharmaceutical firms according to IV5 and IV12.

Second, regarding useful future strategies for the development of CAR-T, one topic discussed by five interviewees (IV3, IV5, IV8, IV10, IV14 & IV16), was the development of allogenic CAR-T cell therapies. Allogenic cell therapies use cells from a donor instead of the patient. Allogenic cell therapies would neglect the barriers that now arise due to the vein-to-vein process. Future regulations, manufacturing processes and treatment centres should be prepared for when allogenic therapies become widely available. The pharmaceutical industry, governments and academic hospitals (IV3, IV5, IV8, IV10, IV14 & IV16) all are aware that allogenic cells will most likely be available in the future, but a lot of research is needed concerning the safety and efficacy of allogenic cells.

4.8.4. Evaluation processes

The category *evaluation processes* describes the assessments of efficacy and feasibility of CAR-T and whether they are shared within organisations. *Evaluation processes* also describes if there is consensus within and between firms on what constitutes as evidence and cost effectiveness (Webster and Gardner, 2019), as for a CAR-T treatment in our case.

Regulatory agencies collaborate a lot with the EMA for example to share information about how approval processes should be designed in the case of CAR-T (IV3). This process is normally not different from other medical technologies, besides that leading countries in development take the lead in the European drug approval process of CAR-T. The regulatory agencies of the countries that lack behind are then involved in the process. The goal of this involvement is to share the knowledge and the know-how of the approval agencies of the leading countries with the other countries (IV3). Pharmaceutical firms share their knowledge concerning CAR-T adoption within the organisation using cross functional teams (IV8 & IV16). If every segment of an organisation is present in cross functional teams, knowledge is automatically diffused within the organisation. However, sometimes external advisors are needed and besides that, interviews with patients and MDs are a good way to receive feedback about the drug.

Consensus between regulatory agencies and CAR-T developers on what constitutes evidence and cost effectiveness is not always reached for CAR-T treatments for MM. This problem arises when pharmaceutical firms apply for reimbursement at the Zorginstituut in the Netherlands and the NIH&DI in Belgium. First, for orphan diseases like MM not as much evidence for safety and effectiveness can be gathered as compared to more prevalent diseases (IV6). This forms a barrier for the Zorginstituut and the NIH&DI, because the costs cannot be calculated from meaningful averages about efficacy in the data. These meaningful averages do not exist in samples sizes that are as small as the population of patients with MM (IV6). For the calculation all individual cases have to be assessed with follow up studies to study long-term effects (IV6). The lack of data about the effectiveness results in discussion

and negotiations about costs effectiveness of CAR-T for MM, also discussed in chapter 4.6.2. As of now there is no consensus about the cost effectiveness. The latter barrier arises due to a lack of consensus about the efficacy of CAR-T, CAR-T mostly being a fourth- or fifth-line treatment, CAR-T being expensive compared to other treatments, and CAR-T being a treatment which is only administered once. The latter two reasons might make the calculations for cost effectiveness different than the same calculations for conventional treatments according to IV9 and IV12. However, IV4 and IV11 state that current HTAs are adequate for those calculations. Cost effectiveness can be improved if organisations can; 1) decrease the price during negotiations between government and pharmaceutical industry and 2) provide CAR-T treatment as a first line treatment if more data is available about the effectiveness.

4.8.5. Enacted IR

Enacted IR describes if organisations in drug development have tasked people with improving the readiness of the organisation regarding regulations (Webster and Gardner, 2019). In this thesis, *enacted IR* describes how important regulatory agencies in CAR-T development adjust to regulations specific for CAR-T.

Meeting regulatory demands is not a problem for academic hospitals. They are required to have Standard Operating Procedures (SOPs). A hospital also needs certifications for clinical studies if it wants to develop its own CAR-T technology. Academic hospitals have special teams with trial managers who take care of protocols and legal requirements (IV10).

It is suggested by IV3 that regulatory agencies should be pro-active when developing regulations for new innovative technologies like CAR-T, because it allows the agencies and people in the agencies to learn from regulation development (IV3). Experience from the few ATMP dossiers in the past ensures the quality of regulations according an interviewee from a regulatory agency (IV3). Experience can be built by letting the same employees handle ATMP dossiers (IV3).

According to IV12 the knowledge on how to develop and implement regulations concerning the adoption of CAR-T should be developed in the hospitals and the regulatory agencies (IV12). According to IV12, CAR-T developers are not familiar with the paperwork for clinical study or market approval that comes with the technology. Getting familiar with procedures is important for hospitals to smoothly develop CAR-Ts in the future (IV12).

4.8.6. Receptivity

Receptivity measures the changes organisations made in anticipation of the adoption of CAR-T (Webster and Gardner, 2019).

The lack of knowledge and know how about the logistics involved in the production and the vein-to-vein process of CAR-T is another important issue that requires changes within a pharmaceutical firm (IV13 & IV15). External production facilities had to be used in the beginning when pharmaceutical

firms did not have their own GMP facilities yet (IV13). Compared to small molecule development, there is a lack of experience in the whole supply chain and vein-to-vein process of CAR-T (IV13). IV13 states the following about the difference between small molecules and CAR-T:

"*We can just switch [the manufacturing process for small molecules] on, we can plug in one more drug into the same network. We do not have a manufacturing network for, in this case [CAR-T]. We are working on that." (IV13, 2020)*

IV15 adds to this statement by noting that a pharmaceutical company needs another set of logistical capabilities in its supply chain for the vein-to-vein process. One example given by IV15 is the need for transparency by the CAR-T developer in the supply chain. Hospitals need to be able to identify in which step of the vein-to-vein process the CAR-T treatment for each specific patient is in order to communicate properly with the patient, when they will receive the treatment. Special teams within the pharmaceutical firm and within academic hospitals were established to address all aspects of the new supply chain (IV10 & IV15).

Pharmaceutical companies invent new jobs for the adoption of CAR-T, such as vein-to-vein managers, within their firm and hire people to perform the jobs (IV5). People from universities or firms where they already have experience with certification and scheduling for example (IV5, IV7 & IV13). People with new expertise are assigned within cross functional teams, the most notable example are the teams and people that take care of the logistics of the vein-to-vein process. Budgets are no limits in the for-profit pharma industry. When a pharmaceutical company started working on CAR-T, their team existed of twenty people. A few years later in 2020 there are between five hundred and a thousand people working on CAR-T (IV5).

In an academic hospital in the Netherlands a special team of 12 people was established for CAR-T trials (IV10). The team consists of nurses, secretaries and trial managers who take care of contracting and a data manager who keeps track of the developments concerning all patients. Infrastructure for the vein-to-vein process, like a freezer that can reach minus 130 degrees Celsius, were already present in the hospital because of earlier use of cell and gene therapies (IV10).

4.8.7. Adoptive Capacity

The category *adoptive capacity* describes unexpected challenges during the adoption of CAR-T within an organisation and how an organisation manages unexpected challenges (Webster and Gardner 2019).

One unexpected complexity in the development of a CAR-T technology mentioned by a pharmaceutical company is that every time something changes in the production process of CAR-T, the treatment changes slightly (IV16). According to regulations the company must file for approval once again. This complexity was not seen upfront by pharmaceutical companies and delayed the application for clinical trials (IV16). This delays the development of CAR-T according to IV16.

Several technological problems arose during the production process of CAR-T cells. An example given is the freezing procedures of the T-cells (IV5). Every hospital has its own freezing protocols. However, due to strict regulations concerning quality, pharmaceutical firms are not allowing differences between cells from different hospitals. Some pharmaceutical firms working with Car-T cells standardised their protocol (IV5). This in turn can be a problem for hospitals in the future according to IV5 as separate pharmaceutical and biotech firms are developing their own protocols. Problems will arise if hospital lab workers must work with different protocols for freezing CAR-T cells (IV5).

Other unexpected challenges were part of the logistical system of the vein-to-vein process, in the pharmaceutical firm Janssen there was an unexpected need for special employees for patient scheduling (IV16), because patients need to be updated if the vein-to-vein process is delayed. The shortage of lentiviral vectors and standardising procedures are barriers in the vein-to-vein process some stakeholders within the pharmaceutical industry did not see coming (IV5).

Academic hospitals in Belgium and the Netherlands did not experience many barriers when adopting CAR-T as a treatment (IV10 & IV12), except for manpower and rooms for treatment (IV10). Another barrier experienced by the academic hospital, for the implementation of all new innovative technologies including CAR-T, was the lack of funding for research by the government (IV10). The hospital used to have funding, called the "*academische component*", which was used for research within the hospital. However, that funding completely disappeared due to cutbacks (IV10). IV10 also explained that the treatments within the hospital that should yield money for the academic hospital were laid off to other hospitals. The combination of the disappearance of the "*academische component*" and the treatment yielding income for the hospital, decreased the ability of the academic hospital to further invest in the development and implementation of new innovative technologies.

Governmental reimbursement organisations have not yet encountered unexpected problems regarding the adoption of CAR-T. Regulatory agencies in Belgium do not have much experience yet in working with CAR-T but will be treated the same as normal technologies (IV6). Regulatory agencies in Belgium and the Netherlands encounter roughly the same problems and working together with other regulatory agencies could be a solution to solve future barriers encountered for CAR-T (IV6).

4.8.8. Sustainability

Sustainability describes if organisations are able to produce, regulate, asses and develop CAR-T treatments in the long term (Webster and Gardner, 2019).

The ability of academic hospitals and medical approval organisations to keep assessing, approving, researching and developing CAR-T is not seen as a problem for most organisations. However, IV9 from an industry advocacy group stated that it is unclear whether regulatory organisations and hospitals keep working with CAR-T treatments if the number of different CAR-T treatments drastically increases the coming years.

Medical approval agencies in Europe should be suited to keep approving CAR-Ts even when the number of CAR-T treatment applications keeps growing. The EMA is rather large and will be able to keep up with the demand for more approval processes (IV3). The governmental reimbursement agency in Belgium expects to be understaffed in the future (IV6) and may need to hire more employees to be able to keep assessing CAR-T treatments in a sustainable way, because they might lack the human resources to perform all assessments. However, IV6 does state that the regulations are fitted for long term application for CAR-T treatments.

If in the future the number of autologous CAR-T treatments will increase drastically, academic hospitals might not be able to keep up with the burden of all the CAR-T treatments (IV10). This solution can only work in peripheral hospitals that are able to perform all technological procedures associated with CAR-T, this thesis found no data on whether peripheral hospitals are prepared for this.

After this chapter, the results of the emerging CAR-T innovation system and the institutional readiness are analysed and linked to each other in chapter 5.

5. Analysis

This chapter provides an interpretation of the results by linking the results back to the theoretical framework. This chapter mainly focusses on Belgium and the Netherlands, not on Luxembourg, because not enough data was found for Luxembourg. The theoretical aim of this research was to identify connections between barriers in the innovation system of CAR-T and the barriers in institutional readiness of the organisations involved in CAR-T development. First, the functions of TIS are analysed in chapter 5.1. Chapter 5.2. discusses the phase of the CAR-T innovation system and the identified relations between the functions. Chapter 5.3. analyses the IR categories and comments on the connections between TIS and IR that were found in the results. Finally, chapter 5.4. provides theoretical insights that are derived from the data.

5.1. Analysis of the TIS functions for CAR-T

In chapter 5.1.1. to 5.1.7. the functions for the development of CAR-T technology are analysed. Chapter 5.2. discusses the phase of the CAR-T innovation system and the interactions between the functions that were found in the results.

5.1.1. Entrepreneurial activities

This function was assessed using three indicators concerning CAR-T; clinical trials, new entrants and patents. The first CAR-T clinical trials in the Benelux started in the year 2017. Since then the number of different active CAR-T clinical trials in the Benelux has grown to five. According to the interviewees the clinical trials for all drugs, but especially for CAR-T, can only be performed when the resources of large pharmaceutical companies are invested in such a technology. However, these larger pharmaceutical companies do not always have the fundamental know how to answer fundamental scientific questions about CAR-T. An exception is CARAMBA, an organisation that performs CAR-T research and clinical trials for MM with new technologies for save and high-level manufacturing. CARAMBA exercises a multicentre study with a partner in Belgium and receives funding from the EU. Also important are companies in adjacent industries, like biotech firms that specifically focus on the manufacturing of gene- and cell therapies. The latter provide new pathways for the development of CAR-T technology. Anicells and MaSTherCell are two identified examples that help the development of CAR-T. The latter firms provide GMP facilities or entire new solutions for the manufacturing of CAR-T, which helps smaller biotech firms to overcome huge investments in GMP facilities. Smaller firms then do not have to deal with the risks of large investments and are able to perform early stage clinical trials. Patents, the last entrepreneurial activities indicator, was only be measured on a European level, because no specific data is available for patents in Belgium and the Netherlands. The data does shows that on a European level the number of patents regarding CAR-T is rising with the number of published patents in august of 2020 already exceeding the whole year 2019. This rise started in 2016. Publication of patents mostly happens 18 months after application meaning the number of applications

started in 2014 (Espacenet, n.d.). The number of patents shows that entrepreneurial activity for CAR-T started rising in 2014 in Europe. The number of clinical trials show that in 2017 the entrepreneurial activity for CAR-T for MM started in the Benelux. This means that entrepreneurial activities started to increase earlier in the rest of Europe than it did in the Benelux.

5.1.2. Knowledge development

Knowledge development for CAR-T for MM in the Netherlands and Belgium started to increase in the year 2015 and 2016 respectively. CAR-T knowledge development, not specifically for MM started increasing in 2013 in the Netherlands and in Belgium it started three years later, in 2016. Knowledge development is consistently higher in the Netherlands, possibly because the Netherlands is a larger country with more universities. Smaller numbers of population and universities is also one of the reasons why Europe lacks behind in knowledge development when compared to China and the US. One other reason for a relative lack in knowledge development in European countries are stricter (GMO) regulations that make testing and market access, needed for the development of CAR-T knowledge, more difficult than in China and the US. Next to developing the technology, it is important for the availability of CAR-T treatments that the vein-to-vein process is properly understood by the distributers of CAR-T, including CAR-T developers and hospitals. The vein-to-vein process can cause barriers for availability of the treatment, like the mentioned lack of production facilities, or that CAR-T cryofreeze procedures need to be properly managed. Sufficient knowledge about the vein-to-vein process is needed. Knowledge is mostly created in academic settings, like the VU, Leiden University, University of Antwerp, KU Leuven and Utrecht University.

5.1.3. Knowledge diffusion

Knowledge diffusion is measured by the number of conferences, symposia and workshops for CAR-T. Several different international conferences were found for either specifically CAR-T or with CAR-T as one of the subjects. Meetings are regarded useful by some interviewees and crucial by others. Especially the larger international haematology conferences were deemed important for acquire new insights concerning CAR-T. Small conferences are deemed not innovative enough, meaning that obtaining new knowledge about CAR-T will not happen at the smaller conferences. Conferences like ASH and EHA help organisations like pharmaceutical firms and regulatory agencies acquiring knowledge. Regulatory agencies get to know the technologies of the future and have the chance to scout the pipelines of biotech and pharmaceutical firms. This helps regulatory agencies to prepare for the applications and assessments regarding CAR-T approval of the future. For pharmaceutical firms, conferences turned out to be useful to scout new innovative biotech firms to collaborate with, which can foster CAR-T innovation.

5.1.4. Guidance of the search

Regulations concerning CAR-T are determined at the European level by the EMA and at the national level by cooperation's between different ministries and regulatory agencies like, the FAGG and CBG in Belgium and the Netherlands respectively. Harmonisation between member states is one of the main regulatory barriers. Even though there are efforts to harmonise regulations between member states, the interpretation of the harmonisation is still different between member states, which essentially neglects the harmonisation efforts. The other two regulations influencing the development of CAR-T are GMO regulations and hospital exemptions.

GMO regulation is considered to be less strict in Belgium. This was attributed to the use of the *deliberate release* framework of GMOs in the Netherlands opposed to the *contained use* strategy in Belgium. The burden of proof is higher in the Netherlands because of that difference in strategy. The burden of proof has recently declined in the Netherlands because of harmonisation efforts. For clinical studies in the Netherlands, the GMO approvals have also been faster due to one of two 6 weeks waiting periods being abolished. Next to regulations, guidelines, such as GMP and GDP guidelines from the EMA have a positive impact on the development of CAR-T by supporting developers in the policies and processes needed to perform R&D.

Hospital exemption's aim is to provide treatment for patients with disease that is so rare that no registered drug exists to effectively treat the disease. Some interviewees are in favour of finding a strategy to use HEs that both exploit the flexibility of a hospital to treat niche patients with CAR-Ts that are not registered and the ability of large firms to eventually mass produce CAR-Ts in order to treat patients with approved medical technologies. This increases the number of CAR-Ts that enter the market and availability for niche patients especially. However, hospital exemption should be treated with caution as small changes in a CAR-T treatment can cause large variations in the effects on a patient. These variations can be dangerous for patients. Also, hospital exemption might cause inequality between patients in different hospitals within a country and patients in different countries, which in not in line with the goal of providing effective treatments for everybody.

Guidance of the search improved over the years especially regarding regulations, although harmonisation efforts still need to be performed. Hospital exemption increases the availability of CAR-T treatments but still has some gaps that need to be addressed.

5.1.5. Market formation

Market formation is measured with two indicators, approvals for CAR-T treatments and regulations and guidelines stimulating market access for CAR-T. In 2018 the first and only two CAR-T treatments in the Benelux were approved by the EMA. Kymriah from Kite Pharma and Yescarta from Novartis. However, more CAR-T technologies are being developed and will apply for approval the coming years.

To facilitate an easier application trajectory for new innovative treatments against orphan diseases like MM, the EMA established the Priority Medicines initiative (PRIME). PRIME helps biotech and pharmaceutical firms getting market access for innovative drugs for rare disease by guiding the firms through the market approval process. This increases the speed to get market access and decreases the effort needed to achieve access. PRIME increases the market formation for innovative drugs like CAR-T and five CAR-T treatments received a PRIME designation from the EMA. Next to PRIME, the GMP and GDP guidelines also have a positive impact on the availability of CAR-T treatments by providing CAR-T developers with advice on how perform trials and treatments.

A barrier for the availability of CAR-T treatments for patients concerns reimbursement policies for CAR-T treatments. In the case of MM, an orphan disease, there are not many cases to derive data from, about the efficacy and safety of a CAR-T treatment. This is a problem for market access, because governmental reimbursement agencies need sufficient data to make a substantiated decision about which treatment for MM patients will be reimbursed. If data about efficacy for chemotherapy is more substantiated than it is for CAR-T, financial resources will go the chemotherapy. This problem is present during negotiation between pharmaceutical firms and reimbursement agencies. CAR-T developers want to earn their money back and reimbursement agencies want to keep CAR-T prices low in order to keep the costs of care low. This can lead to lengthy negotiations, during which the treatment is not available for patients.

5.1.6. Resource mobilisation

A well organised physical infrastructure for the vein-to-vein process, like manufacturing plants, is necessary to bring autologous CAR-T therapies to patients. Large pharmaceutical companies acknowledge the problem that not enough production facilities exist. These companies have built or are looking to build their own manufacturing facilities. Another problem in CAR-T production is the shortage of lentiviral vectors which are used in the T-cell production. More lentivirus manufacturing plants in or near the Benelux are required for a continuous production of CAR-T products.

According to interviewees financial resources for R&D are not a problem as larger firms have enough resources to invest in CAR-T research. Human resources for CAR-T development and assessment were not seen as a problem by the pharmaceutical firms who are able to hire qualified and educated people and the governmental agencies who have people with the right qualifications or are able to convene with external experts of CAR-T. For hospitals the lack of qualified people, like nurses and doctors, are not a barrier now, but could form a problem in the future if more CAR-T treatments become available. Hospitals cannot easily hire new employees due to budget restraints.

5.1.7. Creating legitimacy

There are several different advocacy groups supporting haematology patients or the development of CAR-T for haematological diseases. Creating a sense of urgency for curing MM is crucial for the

development of CAR-T. A sense of urgency within a large portion of the population of a country could stimulate organisations involved in CAR-T development to act. Media outlets and advocacy groups can play a significant role in the creation of this sense of urgency, which is currently not there. If more attention is given to how CAR-T can cure MM, without misleading patients with overly optimistic results, patients can pressure organisations involved in CAR-T development to make efforts to increase the availability of CAR-T treatments for MM. However, experts and actors in the industry are divided whether this sense of urgency could form for an orphan disease like MM.

5.2. Phase and interactions of the innovation system of CAR-T

After assessing the functions of the innovation system of CAR-T, the phase of the CAR-T innovation system is discussed. Hekkert et al. (2011) use four questions to determine the phase of the innovation system. Based on answers to those questions, the innovation system for CAR-T in the Benelux is at the end of the development phase or the beginning of the take-off phase, because there are commercial applications of CAR-T (Kymriah and Yescarta), but fast market growth is not yet achieved in the Benelux. The rest of 5.2. will discuss the relations between the different functions, which are shown in figure 7.

In the development and take-off phase *entrepreneurial activities* is critical according to the theory (Hekkert et al., 2011). The results show a rise in both clinical trials for CAR-T for MM in the Benelux and patent registration for CAR-T in Europe. However, results show that organisations are only able to develop CAR-T if they are able to perform the vein-to-vein process. Infrastructure like manufacturing plants and the availability of resources like lentiviral vectors are vital in this process. Large firms like Kite Pharma are able to build their own plants and smaller biotech firms can make use of infrastructure provided by firms like Anicells and MaSTherCell. This shows that for autologous CAR-T therapies in the beginning of the take-off phase *entrepreneurial activities* and *resource mobilisation* have an impact on each other.

Creating legitimacy is also critical in the take-off phase according to Hekkert et al. (2011). For CAR-T for MM the creation of legitimacy should create a sense of urgency that could stimulate organisations in CAR-T development to put more effort in making CAR-T available through investing more resources or changing regulations or policies. However as of now no real sense of urgency is created by advocacy groups. This can be seen by looking at the sense of urgency which immediately resulted in regulatory actions. These actions have not happened so swiftly for CAR-T for MM. This is impacting the *guidance of the search* function.

Knowledge diffusion is, according to Hekkert et al. (2007), a possible important supporting function in the development phase. In the case of CAR-T, knowledge diffusion like international conferences impact entrepreneurial activities, because large pharmaceutical firms learn about small biotech firms at

conferences. *Knowledge diffusion* impacts *market formation* because it lets regulatory agencies scout the pipelines of CAR-T developing firms and prepare for upcoming approvals.

Guidance of the search, *market formation* and *resource mobilisation* seen as important supporting functions in the development and take of phase (Hekkert et al., 2011). *Guidance of the search* describes the regulations regarding the development CAR-T. GMO regulations impact the ability of pharmaceutical and biotech firms to perform studies and clinical trials and therefore effect *entrepreneurial activities* and *knowledge development*. *Guidance of the search* impacts the quality of the infrastructure, *resource mobilisation*, through GMP and GDP guidelines for CAR-T. Next to this, the HE regulation also stimulates market formations because it creates possibilities for otherwise non approved drugs to be available to patients, increasing the availability of CAR-T treatments.

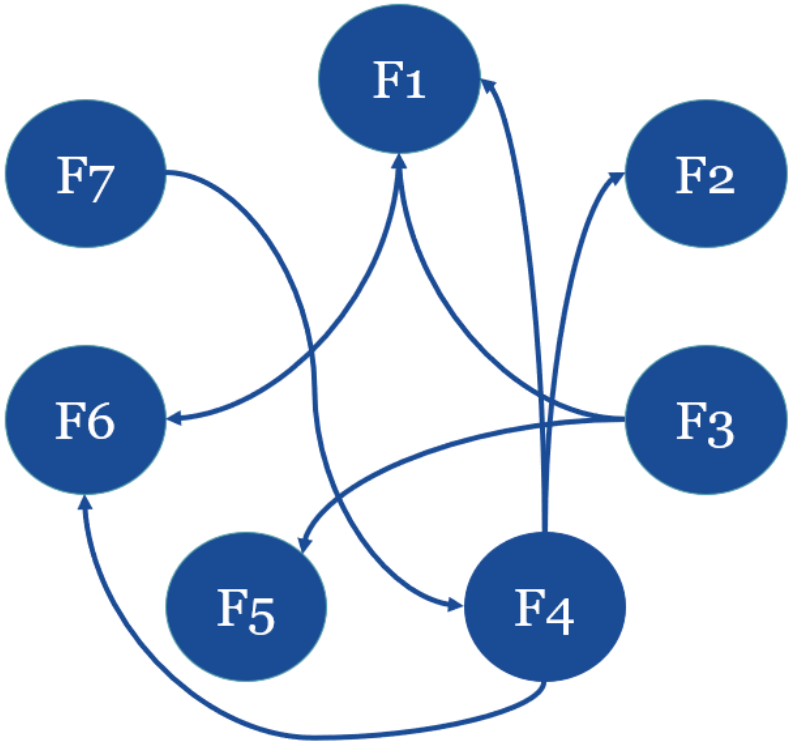


Figure 7: Assumed relations between TIS functions for CAR-T technology for MM in the end of the development and beginning of the take-off phase

5.3. Analysis of institutional readiness of CAR-T

This chapter describes the barriers for the IR categories and their interactions with each other and the TIS functions. The analysis and interactions of the IR categories, shown in figure 8, are discussed in chapter 5.3.1. to 5.3.8.

5.3.1. Demand for new technology

The *demand for new technology* is well developed in all organisations that develop CAR-T. The main aspect that provided organisations with an accurate view of the demand was attending conferences or workshops. As mentioned in the *knowledge diffusion* chapters, pharmaceutical firms scout for new technologies at large international conferences and governmental organisations can get an early look at pipelines of pharmaceutical firms, preparing them for assessments to come. External initiatives, like the horizon scan from Beneluxa, help governmental organisations to scan for upcoming CAR-T technologies. Attendance at conferences from all different sorts of organisations is thus an important factor in CAR-T development. A strong *knowledge diffusion* function is important for organisations in CAR-T development to recognize what and how many new technologies are being developed.

5.3.2. Strategic focus

Strategic focus of CAR-T compared to other treatments for MM forms a barrier when considering the line of treatment. This barrier is mainly present within reimbursement agencies like the NIH&DI and the Zorginstituut which need to choose which treatment to reimburse. Currently, CAR-T technologies are only used as a last resort for patients who have no hope of being treated with other therapies. The reason for this is that not enough data is available to make a huge financial invest in the current CAR-T therapies. This is the same reason why negotiations between pharmaceutical firms and reimbursement agencies stop or take a long time. The problem for the pharmaceutical firms is that they cannot provide the reimbursement agencies with large quantities of data to convincingly prove the cost-effectiveness of CAR-T treatments. The lack of sufficient *knowledge development* about the technology is in the case of CAR-T for MM holding back the availability of treatments. *Strategic focus* is impacted by *knowledge development* and has an impact on the reimbursements of treatments which belongs to the *market formation* function.

5.3.3. Relative need

The *relative need* category showed that pharmaceutical firms cannot just create one CAR-T as a onetime addition to their pipeline. Once a firm decides it wants to adopt CAR-T into their supply chain, it has to adopt the whole vein-to-vein supply chain. This is such a large investment that developing only one CAR-T is not feasible. Lentiviral vector shortages are a problem in the adoption of CAR-T that was not detected beforehand (*resource mobilisation* affects *adoptive capacity*) and impairs the *relative need* category.

Another aspect of *relative need* is how autologous CAR-T compares to technology that may be developed in the future. Allogenic cell therapies will neglect several of the barriers that arise during autologous cell therapies, especially those regarding the vein-to-vein process. Future strategies of hospitals, regulatory agencies and CAR-T developers should include the development of allogenic CAR-T cell therapies. Development of allogenic cell therapies should also include the regulatory framework and guidelines surrounding the technologies. Mainly *knowledge development* concerning the safety and efficacy of allogenic cell therapies is needed.

5.3.4. Evaluation processes

Within the e*valuation processes* category, it stood out how national regulatory agencies asses CAR-T technologies and share that knowledge with other national governments. This knowledge sharing trough cooperation is useful, especially on a European level. This suggests that *knowledge diffusion* interacts with *evaluation processes*.

However, a barrier in this category that directly delays the availability of CAR-T treatments was the lack of consensus about what constitutes evidence for safety, efficacy and cost-effectiveness between pharmaceutical companies and approval agencies. This aspect of *evaluation processes* is affected by regulations, about when CAR-T is considered safe and effective, from the *guidance of the search* function. Cost effectiveness is affected by the line of treatment from the *strategic focus* category.

5.3.5. Enacted IR

Enacted IR was barely a problem for academic hospitals, if a hospital can find the well-educated and experienced clinical trial managers to deal with the regulatory aspect of adopting CAR-T. Regulatory agencies need employees to develop and apply regulations for CAR-T. *Enacted IR* is impacted by *human resources*.

5.3.6. Receptivity

Barriers concerning *receptivity* are mainly related to the adoption of the vein-to-vein process within organisations. Organisations cannot simply decide to adopt CAR-T, a firm must have the knowledge, logistical infrastructure and human resources to perform the whole vein to vein process. Sufficient resources and knowledge in the innovation system is thus important for organisations to be receptive for CAR-T. To be able to adopt CAR-T, hospitals and pharmaceutical firms both have to set up special interdisciplinary teams. *Receptivity* for CAR-T is therefore mainly depended on *human resources.*

5.3.7. Adoptive capacity

Adoptive capacity describes the initial and unexpected problems of adopting CAR-T within an organisation. Unexpected problems are mostly based on or are technological problems, often based on the vein-to-vein process. Freezing protocols is an example that was mentioned. But these problems can mostly be overcome by organisations. *Adoptive capacity* was also mainly influenced by *resource mobilisation*, because the shortage of lentiviral vectors was ultimately unexpected. As discussed above, unexpected problems like the lentivirus shortages impact *relative need*. Also, better *adoptive capacity* of institutions creating resources, like lentiviral vectors has an impact on the *resource mobilisation*. Because acting adequately on the unexpected shortage of lentiviral vectors minimizes the shortage in resources.

5.3.8. Sustainability

Sustainability issues depend on the resources that are allocated to hospitals and governmental agencies and hospital's ability to perform the vein-to-vein process. Currently, *financial and human resources* are sufficient to adopt the number of CAR-T treatments available. But problems may arise in the future when the number of CAR-T treatment grows. *Sustainability* in the context is of IR can be seen as a combination of the first seven categories. Meaning, sustainability assesses whether organisations have the right people, resources and are ready for new regulations but on the long term. In other words, sustainability is the IR but in a future context and therefore needs to be approached differently than the other functions.

5.4. Interactions between institutional readiness of emerging CAR-T innovation system for MM in the Benelux

Figure 8 shows the tentative connections between several of the TIS functions and IR categories. A connection between a TIS function and an IR category or between two IR categories means that if a function is performing well in the CAR-T innovation system that the IR categories that it is linked to will be positively impacted. For example, when *knowledge diffusion* (F3) is performed well, it will be easier for organisations like hospitals, governmental agencies and pharmaceutical firms to perform the *demand for new technology* (C1) category.

The first observation is that most interactions in the tentative framework are from *function* to *category*, and not many the other way around, however this may be explained due to the structure of the research which mapped IR categories based on a TIS event analysis. The only interactions that found the other way around are *receptivity* on *resource mobilisation* and *strategic focus* on *guidance of the search*. According to Webster and Gardner (2019) an organisation should influence the development of a technology, which means more interactions from IR to TIS are expected. However, these were not found in the data collected in this research. Though this does not mean they do not exist, this framework is only tentative.

Another observation from the results is that there are similarities between categories. For example, *sustainability* can for the most part be seen as the *receptivity* and *adoptive capacity* of the future. *Receptivity* and *adoptive capacity* are also very similar with the only difference being the *adoptive capacity* describes barriers that are unexpected. Another example is the similarity between *demand for new technology* and *strategic focus*. Meaning, to find out whether a new technology is in demand, an organisation would always have to compare that novel technology to current technologies.

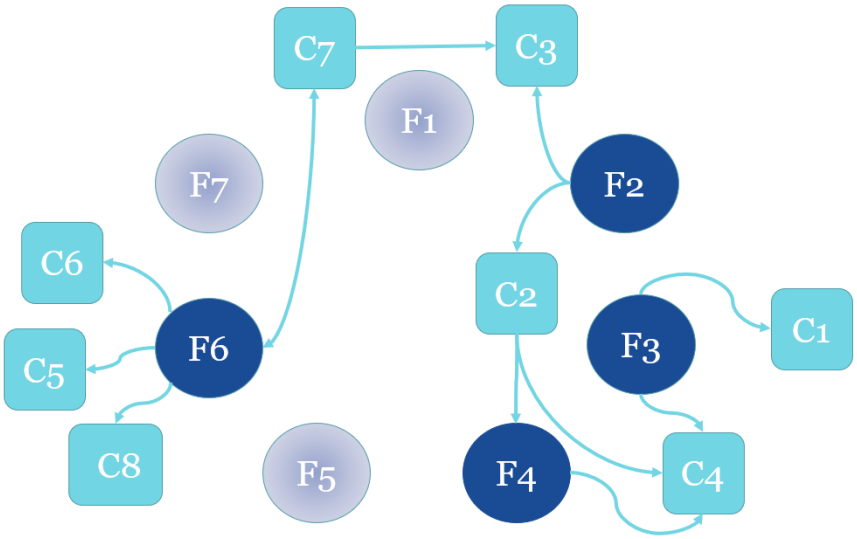


Figure 8: Tentative connections between institutional readiness and CAR-T innovation system functions. Legend: square= IR category, circle= TIS Function, transparent functions had no link with an IR category. Links between TIS functions were removed from this image to keep the image clear and concise, the links between TIS functions from figure 7 do still apply to the framework.

6. Conclusion

Chimeric Antigen Receptor for T cells (CAR-T) technology is a relatively new technology, that can provide safe and effective treatment for diseases that were not effectively treatable with other technologies. However, due to the cellular nature of CAR-T technology, it encounters barriers that decrease the availability of the treatment for patients. This thesis was performed to help increase the availability of CAR-T treatments for multiple myeloma (MM), an orphan disease for which an effective treatment is still required. This was done by answering the research question: "*What are the most important barriers in CAR-T's innovation system in Belgium, the Netherlands and Luxembourg and how can these barriers be overcome especially regarding the institutional readiness for CAR-T cell therapy?*" To answer this question, institutional readiness and technological innovation system literature were used as theoretical background and data was gathered through desk research and 16 interviews with experts and actor in CAR-T development. This chapter answers the research question first by discussing the main barriers (6.1.) and then providing policy recommendations (6.2.).

6.1. Barriers for CAR-T development

Several barriers were found in the CAR-T innovation system and institutional readiness of organizations involved in CAR-T development in Belgium and the Netherlands over the period between 2011 and 2020. The barriers mostly arise because of the complexity and resource intensive vein-to-vein process of autologous CAR-T cells, which requires manufacturing capacity, protocols, proper human resources and is subjected to genetically modified organisms (GMO) regulation. For smaller biotech firms and academic organisations these barriers are hard to overcome.

Despite the shortage of lentiviral vectors which hampered the manufacturing process of CAR-T, large pharmaceutical firms do have the resources to adopt the vein-to-vein process and build their own manufacturing plants. However the knowledge that is needed for CAR-T development is often created in academic settings, making the diffusion of knowledge between academic institutes and pharmaceutical firms an important part of the innovation system of CAR-T. Future knowledge development and treatments in hospitals, *sustainability* (C8), may be under pressure if the number of different CAR-T treatments grows. Hospitals may need more funding and human resources to keep up with the growing number. Experts believe that, if sufficient research on allogenic cell therapies is done it will in the future replace autologous cell therapies, which neglects the vein-to-vein process and the associated barriers.

Another important barrier is described by the flawed relation between *knowledge development*, *strategic focus, evaluation processes* and *market formation*. The lack of results from research for CAR-T when compared to small molecule treatments impairs the ability of regulatory and reimbursement agencies to assess the efficacy and safety of CAR-T to their standards. Due to MM being an orphan disease, not much data can be gathered about safety and efficacy. Negotiations about the price between

pharmaceutical firms and reimbursement agencies for a treatment slow down or even break down because there is no consensus about how much data constitutes sufficient evidence for the safety and efficacy of disease. CAR-T developers and reimbursement agencies need to align their data requirements in order to increase the availability of the technology for patients. An underlying problem of this lack of consensus is the lack of knowledge development on CAR-T. Not sufficient data is available in the case of multiple myeloma, because 1) it is an orphan disease and there are simply not many cases to derive data from. And 2) the innovation system is still at the end of the development stage and more time and resources are needed for organisations that perform research to develop sufficient knowledge on the efficacy and safety of CAR-T.

A barrier regarding the creation of legitimacy was the lack of a sense of urgency to develop CAR-Ts for MM. If there is no sense of urgency to create CAR-T or infrastructure and regulations surrounding the technology, organisations are not incentivised to develop the technology and other aspects needed to make it available.

Finally, the lack of harmonisation of regulations or procedures forms a barrier for organisations developing CAR-T treatments. When regulations or procedures differ from country to country, it takes more effort for CAR-T developers to comply with the regulations or procedures in all countries. This effort can be time consuming and thereby delaying the development and by extension the availability of treatments. Harmonisation efforts were present in the EU and the Benelux but are not sufficient or have not yet come into effect.

6.2. Practical relevance and policy recommendations

To overcome the barriers identified in the previous section, some policy recommendations to different actors involved in CAR-T development are given. Until allogenic cell therapies become the safe and effective standard for CAR-T treatments, it is important to increase the availability of autologous treatment as much as possible. Availability can be increased in several ways. First, to improve *resource mobilisation* and *receptivity*, more manufacturing facilities for CAR-T products can be built in Europe by firms which have the resources to do so. In addition, the lentiviral shortage problem could also be solved by establishing more facilities to manufacture the viruses or resources should be invested in technologies that can create CAR-T products without viral particles. These facilities require enormous investments and can therefore only be built by organisations with access to large pool of resources, the pharmaceutical companies.

Recommendations for the Dutch and Belgian governments are; first: invest more in academic hospitals so they can perform research and development and are able to hire more educated employees in the future when the number of CAR-T treatments starts to increase rapidly. The latter will increase *knowledge development* and the institutional readiness of hospitals. And second, a recommendation which is also aimed at pharmaceutical companies, start cooperating in developing guidelines for wat

constitutes evidence about the safety and cost-effectiveness of CAR-T treatments. Reaching consensus could possibly speed up several stages in CAR-T development. In addition to this, it is valuable for the Belgian and Dutch government to adept a market access/reimbursement system like that in Germany. Make sure the treatments are already available during negotiations about the costs of the treatment. This is not only a benefit for the patients but is also an opportunity to collect more data on the effectiveness of CAR-T treatments. This thus increases *knowledge development* and *evaluations processes*.

On a European level harmonisation of regulations and procedures regarding CAR-T development and market access should have priority. Organisations like the EMA, CAT and EC should actively harmonise regulations. In addition, regulators should start to investigate the regulations that will be necessary for allogenic CAR-Ts at an early stage. Starting early with investigations into the future technology will increase the involvement and influence of regulators. Regulators can learn from the involvement through cooperation with other organisations, such as hospitals and CAR-T developers. Next to the benefits for regulators, CAR-T developers become familiar with the regulations which they have to comply to at an early stage, giving them time to adapt. This will cause less slowing down of the development of allogenic CAR-T therapies.

Another recommendation concerning the development of allogenic CAR-T treatments is supporting the biotech- and pharmaceutical companies and the academic institutions to generate more knowledge on allogenic cell therapies. Autologous CAR-T treatments are, at the moment, further developed than allogenic CAR-T treatments. Several experts think that allogenic cell therapies eventually will be a more common form of treatment. Switching for autologous to allogenic would neglect many barriers that currently arise for autologous cell therapies, the entire vein-to-vein process for example. However, an extensive amount of research needs to be performed regarding the efficacy and safety of these kinds of therapies before allogenic cell therapies can enter the market. First, fundamental research in academia needs to be funded by the government to answer the basic questions about the safety and efficacy of allogenic CAR-T therapies. Should the results about efficacy and safety be positive, then pharmaceutical companies should invest resources in clinical trials to advance the treatment. To achieve availability of allogenic treatments as soon as possible it is important that the knowledge created within academia spills over to developers quickly.

To ensure these knowledge spill overs, the *demand for new technology* and *evaluations processes* categories and the *knowledge diffusion* function must be performed well. This leads to the next recommendation; conferences, meetings and symposia organised by advocacy groups should be held frequently and be as accessible for all different actors involved in CAR-T development, such as governmental agencies and researchers. International conferences are seen as most useful. Organisations in CAR-T development can incentivise employees to attend conferences and share the newly acquired knowledge within the organisations to achieve even more knowledge diffusion.

7. Discussion

This research mapped the emerging innovation system and the institutional readiness of organisations and institutions involved in the development of CAR-T treatments for multiple myeloma in the Benelux countries between 2011 and 2020, using the TIS framework (Hekkert et al., 2007) and IR framework (Webster & Gardner, 2019). Chapter 7.1. discusses the theoretical relevance of this research, 7.2. reflects on the research methods that were used and improvements of those theoretical frameworks, methods and results and 7.3. suggests areas for further research.

7.1. Theoretical relevance of the research

This research derives its theoretical relevance from three important contributions to literature. First, technological innovations systems literature was previously used for radical innovative medical technologies. For example, Kukk et al. (2016) used TIS to describe the case of Herceptin and Tarceva, two personalised cancer treatments used in oncology treatment. However, a TIS analysis was until now not used for technologies involving the vein-to-vein process that is necessary for CAR-T treatments. This research presented the important interactions in a TIS framework for the development and early take-off phases of an autologous cell therapy. The development of autologous cell therapies was not explored using the TIS framework before.

Second, this thesis adds to institutional readiness literature by exploring the IR framework in two new ways. 1) Webster and Gardner's (2019) framework was initially developed for regenerative medicine, whereas this thesis explores the institutional readiness for a specific upcoming technology which is becoming more relevant by the day. 2) This thesis explored the IR of CAR-T beyond advanced therapy treatment centres. As Webster and Gardner (2019) suggested, the IR framework is applicable in other organisations, such as pharmaceutical firms, drug approval agencies and treatment reimbursement agencies.

Finally, this thesis relates Webster and Gardner's (2019) institutional readiness framework, including its IR categories to a Technological innovation system approach, showing interactions between innovation on a systemic and organisational level for an ATMP like CAR-T. Because of the explorative nature of this research, this model of the interactions between functions and categories is by no means complete. For example, other research by Binz et al. (2015) also research institutional connections to TIS for the case of potable water use. Binz et al. (2015) conclude the institutional creation of legitimacy of a technology is not solely impacted by the number of actors, such as advocacy groups. However, this research shows that aspects of institutional readiness are important in the developments of an innovation system regarding a technology like CAR-T. Several links between the TIS functions and IR categories are shown in this thesis (figure 8), but research like Binz et al. (2015) suggests that further research is needed to fully develop a framework for interactions between TIS and IR. A useable framework will allow for better assessments of the development of TIS and IR of technologies like CAR-T in the future.

7.2. Reflections on the research

This chapter discusses shortcomings on the theoretical framework, methods (internal and external validity, then the geographical scope) and results.

The theoretical frameworks that were chosen because they were expected to complement each other, which according to the tentative framework they do. The IR framework is relatively new, and it therefore invites some criticism. As was noted in chapter 5.4., some of the functions show much similarities. When measuring IR in the future it is important that the categories measure all aspects of IR but measure those aspects only once. It is therefore important to clearly demarcate the categories and combine categories that measure similar aspects of IR.

A shortcoming of the methods used in this thesis is the fact that the data is only interpreted by one researcher. This may have caused biases from the researcher and affects the descriptive validity. However, all aspects of the research also were discussed with an external supervisor during the whole research process. In addition, one interviewee, an external supervisor and the external expert provided feedback on the results which increased the descriptive validity. Reliability is ensured by providing the interview guide (appendix I) and a list of interviewees in order to achieve transparency about the data collection.

The geographical scope of the research included Belgium, the Netherlands and Luxembourg. However, very little data about Luxembourg was acquired in the desk research and the interviews. This means that conclusions derived from the data are not applicable for Luxembourg. Furthermore, research on a European level would suit this kind of research better because many regulations are determined on a European level.

An aspect of the research which impacted the results is the composition of the pool of experts and stakeholders. Table 3 in chapter 3.3. shows that 16 interviewees contributed to this research. Two aspects of the pool of interviewees are not entirely representative of the field and therefore may have affected the outcome of the research.

First, many of the interviewees are employed by a pharmaceutical firm, which affects the interpretive validity. Due to most data being gathered from actors from the pharmaceutical industry, their viewpoint is overly represented. Although statements and citations in the data are retraceable to the interviewee from whom the data is retrieved, readers should be aware that most interview statements and citations are retrieved from people in the pharmaceutical industry. Having many interviewees from the pharmaceutical industry did provide an opportunity for a more comprehensive view of that part of the innovation system. The interviewees from the pharmaceutical industry were from different parts of the organisation and the CAR-T development process, such as market access, regulatory, vein-to-vein

managers and clinical trial managers, which yielded exhaustive insights in the CAR-T adoption process in pharmaceutical firms.

Second, the pool of interviewees should contain as much different viewpoints as possible in order to present a complete picture of the development of the CAR-T innovation system. Attempts were made to reach out to as much different organisations as possible, but the following are still missing in the results; 1) a patient advocacy group, which could yield insights about patient perspective and effects of lobby activities from the advocacy group. 2) A private insurance company would have been insightful for what happens to a CAR-T treatment if governmental reimbursement organisations reject the treatment. 3) Several governmental agencies in all the different countries, because many different agencies are responsible for the development of CAR-T and may have different perspectives on CAR-T development. 4) Finally, next to the initiator of the PRIME initiative, EMA is the approval agency in Europe and an could provide valuable data about *market formation* and *guidance of the search*. These organisations and more interviewees from hospitals were contacted, but no response was received, or the interview request was declined due to time constraints or the current Covid-19 situation.

7.3. Suggestions for future research

There are several directions for future research that would help the further development of CAR-T and our insights concerning gene and cell therapy innovations.

First, this research focussed on CAR-T for MM in the Benelux. Regulations and institutions are different in other countries, therefore research in other countries could be interesting. Especially comparative studies between well performing and bad performing countries in CAR-T development could yield important information about especially regulatory challenges. Several interviewees suggested that CAR-T development in the US and China is further than in Europe. Researching the influence of the Food and Drug Administration (FDA) versus the influence of the EMA on the development of CAR-T therapies can identify the differences in CAR-T policy. Further research can focus on finding the impact of different policies implemented by the EMA and the FDA.

Second, given that autologous CAR-T cell therapies are, according to the interviewees most likely a precursor of allogenic cell therapies, research into the innovation system and institutional readiness of allogenic technologies is necessary in order to make it more available. Not only will this help the adoption of allogenic cell therapies in countries like Belgium and the Netherlands. It will also increase the availability of CAR-T therapies in 3rd world countries. Which is not contained in the scope of this research but nonetheless is relevant for the availability of CAR-T when viewed from the perspective of UNSDGs. IV13 stated that in 3rd world countries the institutions will not be ready to form the proper infrastructure for the vein-to-vein process, which would immediately rule out the possibility of autologous CAR-T treatments becoming available in 3rd world countries in the near future. The developments of allogenic cell therapies could solve this problem.

Third, the framework presented in figure 8 provides relations between categories of IR and functions of TIS based on desk research and various exploratory interviews. Effects of institutional readiness categories on the development of new advanced medical technologies should be measured. Meaning that an analysis could be performed to determine what interactions have the most effect on the readiness of organisations and the availability of CAR-T. This could highlight which categories are more important and should provide an operational framework for measuring IR. The tentative framework in figure 8 should be expanded if possible, several influences of TIS on IR were found, but not many the other way around. Future research could focus in more depth on the specific impacts of institutional readiness on the TIS functions and the diffusion of CAR-T to fully understand its impact of the interactions between IR and TIS. Merging IR categories that are very similar, like *receptivity* (C6) and *adoptive capacity* (C7), is also a topic for further research that might yield a more useable framework.

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Appendix I – Interview Guide

Introductions

My name is Gijs Lunenborg and I'm studying sustainable business and innovation at Utrecht University. From now until September I'm writing my master's thesis. The subject of my thesis is to better understand the challenges related to the development of advanced therapy medicinal products, especially CAR-T technology. More specifically my thesis will exploratively assess the institutional readiness and performance of the CAR-T innovation system that surrounds CAR-T for Multiple Myeloma in the Benelux. For this research I will analyze the development by interviewing experts and other involved stakeholders currently active in CAR-T's innovation system.

Confidentiality

I want to record this interview to use it in as data for my research. You will remain anonymous in the research. All your data is handled with care and won't be used outside this research. Is it ok with you if I record this interview?

If you want to you can provide comments on the interview report.

Questions

1. What is your role in the development of CAR-T/ATMPs? Or How are you involved in this development? Could you briefly describe your role and responsibilities?
2. Historically, where have new ATMP/CAR-T developments originated from?
3. Which (internal/external) stakeholders are involved in these developments and how?
4. What are the main drivers for developing ATMPs/CAR-T technologies? Are these internal drivers or external?
5. In your opinion what do you think will be the main barriers (factors which have a negative influence) to develop ATMPs/CAR-T technologies? Are these internal drivers or external?
6. What is the main difference between the development of traditional medicine and cellular based technologies like CAR-T?
7. In the framework that is used in this research there are several themes that are important in innovation processes. I want to ask, per theme, how important do you think it is for CAR-T development.

- Entrepreneurial activities:
    - There are 5 clinical trials for CAR-T in the Benelux active for MM. Will this number grow rapidly the coming years?
    - Kite, Janssen & Novartis are developing CAR-T Treatments for MM in the Benelux, are you aware of any other companies?
- Knowledge development:
    - The number of scientific articles published within the Benelux has been rising from almost none 2010 to more than 10 every year over the last 3 years. Why did this rise in scientific papers start in 2017?
    - For MM specifically still only about 3 articles every year are published. Is the amount of research in the Benelux adequate for the development of CAR-T for MM within the Benelux?

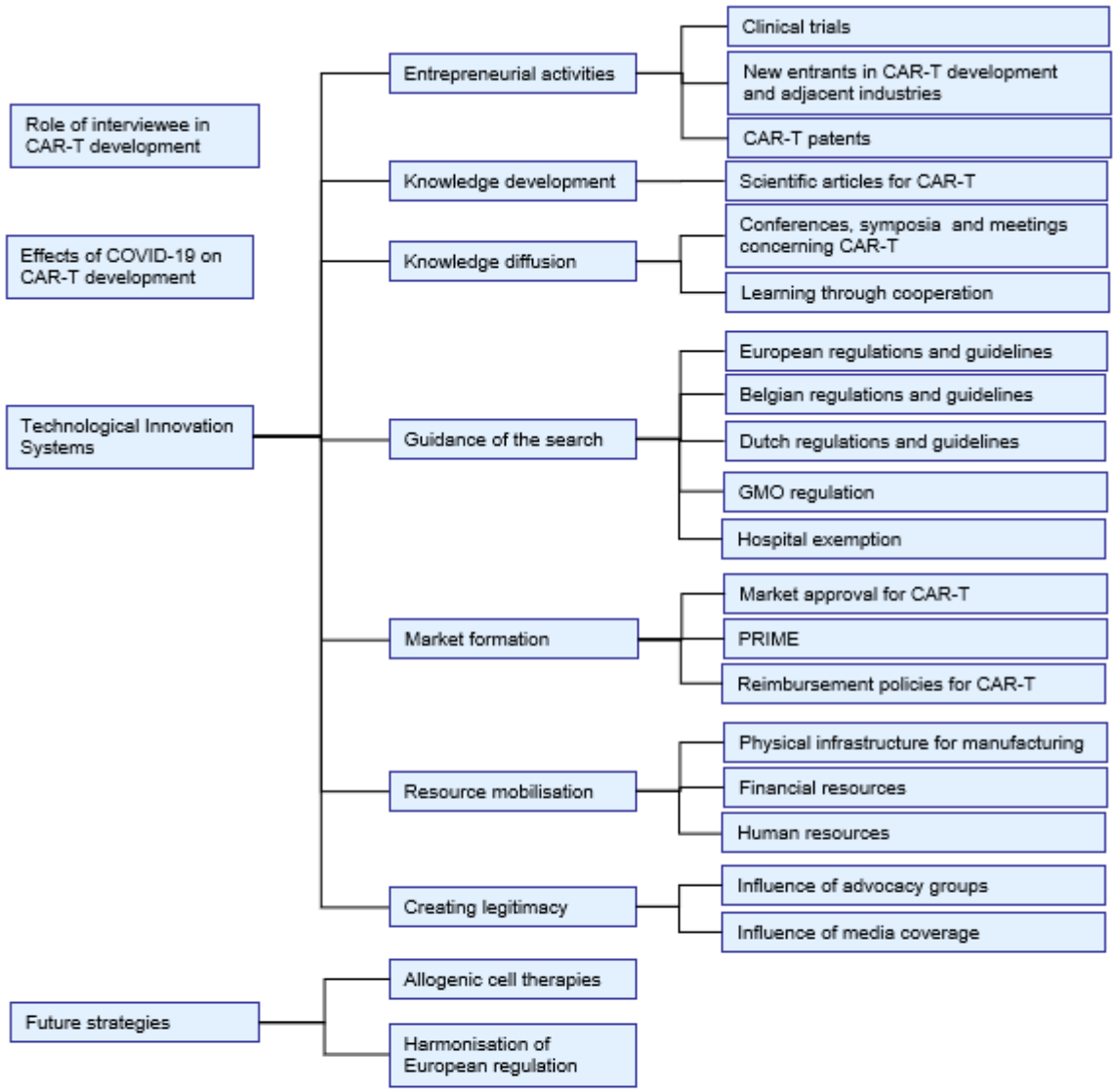
- Knowledge diffusion:
    - There are no CAR-T conventions in the Benelux itself, however there are four yearly conferences in Europe, do these conventions have an impact on the development of CAR-T? What is this impact?
    - Are you aware of other workshops, symposia and conferences with CAR-T as topic?
- Guidance of the search:
    - The regulation for harmonisation of CAR-T application for approval is drafted by the European Commission but not yet active because of implementation problems. What sort of barrier does the lack of harmonisation cause?
    - Does the PRIME initiative from the ema impact the development of CAR-T? If yes, how?
    - Does Hospital Exemption influence the development of CAR-T? If yes, how?
- Market Formation:
    - There are European and national guidelines for Good manufacturing practices and good distribution practices (like the COGEM CGM/200123-01 advice from last January or IGJ), how do influence the development of CAR-T?
- Resource mobilisation:
    - Are enough people adequately trained to work with CAR-T in hospitals and manufacturing plants? If not, which measures need to be taken
    - Is in the Benelux the infrastructure in place that follows the guidelines set by the EU and national governments and is able to produce and distribute CAR-T sufficiently and constantly? What kind of infrastructure is needed and why?
    - The input financial resource for R&D for CAR-T was for the most part provided by public organisation like the EU and national governments, this is now shifting to funding by larger biotech firms. How does this impact CAR-T development?
- Creating legitimacy:
    - How does BENELUXA create a favourable development climate for CAR-T products?
    - KWF, CARAMBA and Myeloma Patients Europe are several advocacy groups active in the Benelux how do efforts of these advocacy groups impact the development of CAR-T?
    - About 60 news articles about CAR-T where published in the Netherlands and Belgium respectively of the last 10 years, how does this amount of media coverage have an impact on the decision making in CAR-T development? Why is the media coverage so low?

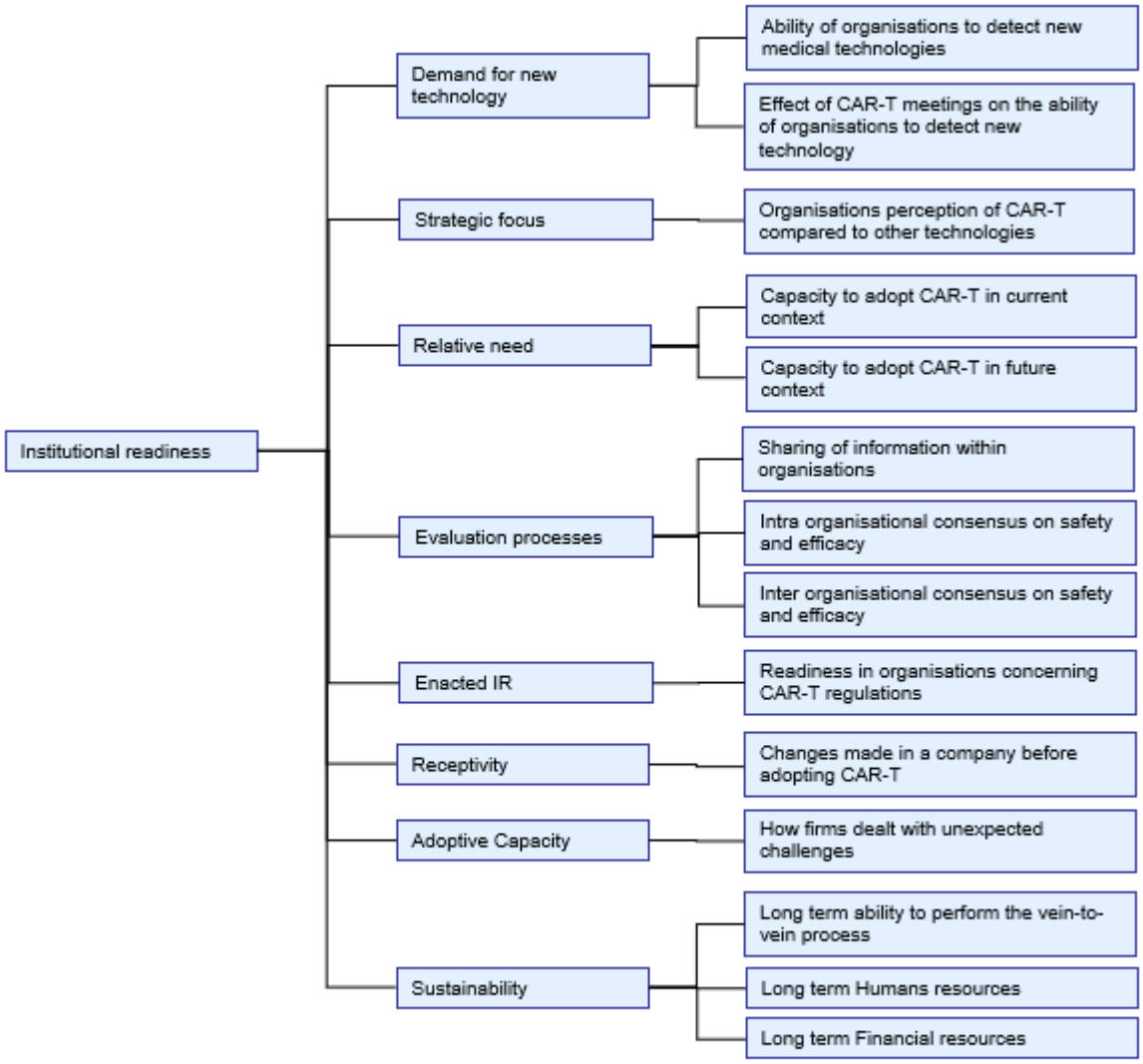
8. Within organisations there are factors that influence whether that specific organisation is ready to be a part of the CAR-T development. The following questions are about the readiness of your organisation.
    - How does your organisation make sure it has the adequate people, knowledge and resources to be able to recognize an unmet medical need?
    - How does the organisation compare new CAR-T technology to other technologies for that unmet medical need? Does the organisation have the adequate people knowledge and resources to compare the technologies?
    - How does the organisation make sure they have the adequate people, knowledge and resources to develop CAR-T? Are there any barriers for the acquisitions of all these aspects?
    - How does the organisation evaluate the value of CAR-T and how is this information shared within the organisation?
    - How does the organisation prepare for the adoption of CAR-T within the organisation?
    - What parts of the organisation must make changes in order to work with CAR-T? Are these parts of the organisations prepared to change?
    - Was there any challenge you did not know before the adoption of CAR-T that arose during the adoption of CAR-T within your company? How did you company respond to this? And how is this for other organisations?
    - How is your company able to work with (produce, evaluate or make policies for) CAR-T in the long term? And how is this for other companies?

    - Are smaller biotech firms and hospitals ready for the adoption of CAR-T?
9. Does the latter aspect of CAR-T development within firms that we discussed earlier have an influence on the development of CAR-T as a whole?
10. How should (previously mentioned) barriers be tackled? Which actors should be a part of this process?
11. What are the most significant differences between the development of CAR-T in Belgium compared to the Netherlands? Why do these differences exist?
12. Are there specific strategies that should be considered when developing CAR-T?
13. Are there specific actors, institutions or other part of the developments of CAR-T that you think are relevant for this research that we haven't discussed yet?
14. Could I contact you again if I have further questions?
15. Do you have any comments or questions about my research?

Thank you for your time!

Appendix II – Codes




Institutional readiness
Demand for new technology
Ability of organisations to detect new medical technologies
Effect of CAR-T meetings on the ability of organisations to detect new technology
Strategic focus
Organisations perception of CAR-T compared to other technologies
Relative need
Capacity to adopt CAR-T in current context
Capacity to adopt CAR-T in future context
Evaluation processes
Sharing of information within organisations
Intra organisational consensus on safety and efficacy
Inter organisational consensus on safety and efficacy
Enacted IR
Readiness in organisations concerning CAR-T regulations
Receptivity
Changes made in a company before adopting CAR-T
Adoptive Capacity
How firms dealt with unexpected challenges
Sustainability
Long term ability to perform the vein-to-vein process
Long term Humans resources
Long term Financial resources