Business plan

iGEM TU Eindhoven - 2021-2022

iGEM student team of Eindhoven University of Technology (TU/e)

Full Name	Function
Jolien Marcelis	Team manager
Famke Klop	Website/Wiki Captain
Wouter Langers	Lab Captain
Floor van Boxtel	Finance manager and Sponsor coordinator
Femi Hesen	Modelling Captain
Elisa Passet	Public relations and secretary
Jakob Scheele	External Affairs and Human Practices
Kim Wintraecken	Design
Rian Driedijk	Human Practices Education

Principal investigators:
Prof. dr. Maarten Merckx
Prof. dr. ir. Luc Brunsveld
Prof. dr. ir. Tom de Greef

Advisors:
Luke Rossen
Fleur Kalberg
Josephina Smits
Daniek Hoorn

IMPACT

Modular & Personalized Autoimmune Cell Therapy

Eindhoven, October 11, 2022

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1.1 | Problem statement

Currently, 3-5 % of the world population is suffering from autoimmune diseases and there are nearly 100 distinct autoimmune diseases known as of today. These types of diseases occur when the immune system attacks self-molecules and healthy cells of individuals. [1] Some autoimmune diseases are organ-specific and some consist of a variety of immunological dysfunction which leads to the involvement of multiple organs. [2] One of the most impactful autoimmune diseases in many ways is the antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) occurring equally in men and women. [3, 4, 5, 6] This chronic autoimmune disease is characterized by granulomatous and neutrophilic tissue inflammation causing necrosis of blood vessels. [7, 8] The necrosis of vessels leads to insufficient oxygen supply to the organs behind the vessels. As a consequence, a decrease in tissue functioning or tissue death occurs. AAV can be initiated in multiple organs. [9]. Three types of AAV are associated with the presence of ANCAs whereas iGEM TU Eindhoven focuses on granulomatosis with polyangiitis (GPA). The prevalence of ANCAs is the highest in patients with GPA where 90% of the patients are ANCA positive. [10] Untreated GPA is almost always lethal. [11] Patients with GPA suffer from an accumulation of inflammatory cells (granulomatous tissue) which involves predominantly the nose and sinuses, lungs, kidneys, joints, and eyes. A more elaborate explanation and visualization of the symptoms of GPA AAV is given in Figure 1.1. [7]

Table 1.

Clinical manifestations in GPA.

Organ	Clinical manifestation
Generic	General malaise, myalgia, arthralgia, anorexia, weight loss and pyrexia
Skin	Leucocytoclastic vasculitis, digital infarcts, purpura, cutaneous ulcers and gangrene
Oral cavity	Oral ulcers, oral granulomatous lesions, gingival hyperplasia with strawberry-like aspect, swallow
Eye	Episcleritis, scleritis, conjunctivitis, keratitis, uveitis, retinal vasculitis, retinal arterial or venous thrombosis, retinal exudates, retinal haemorrhages, blurred vision, blindness, proptosis and orbital granulomatous masses, epiphora
Nose and paranasal sinus	Persistent-recurrent nasal discharges, blood-stained nasal discharge, epistaxis, crusting, mucosal ulceration, nasal bridge collapse, nasal granulomatous lesions, parasinus and sinus inflammation, regional tenderness
Ear	Sensorineural hearing loss and conductive hearing loss
Upper airway	Subglottic or tracheal stenosis
Lower airway	Cough, breathlessness, stridor, wheeze, small air way obstruction, pulmonary nodules, cavitating lung lesions, pleuritis, pleural effusions, pulmonary infiltrates, pulmonary haemorrhage, alveolar capillaritis and respiratory failure
Cardiovascular	Small vessel vasculitis, occlusive vascular disease, pericarditis, pericardial effusions, cardiomyopathy, valvular heart disease, ischaemic heart disease, heart failure
Gastrointestinal	Acute abdomen secondary to peritonitis or bowel ischaemia which may be secondary to mesenteric vasculitis
Kidney	Diffuse pauci-immune crescentic necrotising glomerulonephritis, haematuria, proteinuria, cellular casts on urine cytology, renal impairment manifested as acute kidney injury, chronic kidney disease or end-stage renal failure
Central and peripheral nervous system	Headache, meningitis, seizures, cerebrovascular accidents, spinal cord lesions, cranial nerve palsies, sensory or motor peripheral neuropathy, mononeuritis multiplex, sensorineural hearing loss, cerebral mass lesions
Musculoskeletal	Inflammatory arthritis, erosive or deforming, arhtralgia, myalgia, arthralgia

Figure 1.1: Clinical manifestations in granulomatosis with polyangiitis (GPA). [7]

On average each AAV patient is hospitalized twice and the treatment costs for AAV is €6,168 ($7,296) per patient-year in the US. [12] If the symptoms of AAV include kidney failure, these costs can go up to $90,000 each year for the required dialysis. Next to the hospitalization, in the first weeks to months after hospitalization, the patient supervision is intense (weekly hospital visits). This indicates the high workload pressure on healthcare. Moreover, the prevalence of AAV is 1:8000 people and the 5-yr survival rate are estimated to be 60-97% indicating high morbidity of the disease. [8]

The main problem with many current treatments for most autoimmune diseases is that they are effective but have burdensome side effects. [8] These current treatments are often so-called immunosuppressive drugs meaning that they suppress the immune system non-specifically leading to multiple side effects and therefore detract from the patient's quality of life. Moreover, these non-specific immunosuppressive drugs make the patient more prone to other infectious diseases like for example tuberculosis. [13] This results in a limited time span in which these treatments can be used since longer use is not bearable for the patient. Another consequence of such treatments is that patients with an auto-immune disease often experience relapses because the current treatments can only be administered for a short time span. For GPA the relapse rate rises from 20% at twelve months to 60% at five years. [14] This relapse not only irreversibly decreases the patient's health further, but also increases the workload of the hospital work staff and the healthcare costs.

The problem described leads to the opportunity that iGEM TU Eindhoven discovered. The field of AAV should be heading towards treatments that are less burdensome for the patient. A potential option is via personalized therapies. A personalized tailored treatment would reduce side effects since it only gets activated when the pathogenic disease markers are present in the patient. [15] Moreover, it would be beneficial if relapse of AAV is prevented and the workload for hospitals and healthcare costs decrease. With !MPACT, iGEM TU Eindhoven is designing a Modular Personalized Autoimmune disease Cell Therapy that consists of engineered patient cells that couples presence of pathogenic biomarkers to an immunosuppressive response as tailored treatment for AAV symptoms. It needs to be administered once, prevents relapses, has less side effects for the patient and reduces the workload for hospitals. iGEM TU Eindhoven starts with designing this cell therapy for AAV and more specifically GPA, but eventually also aims to make !MPACT adjustable for other autoimmune diseases.

1.2 | Product description

iGEM TU Eindhoven has designed the cell-based therapy !MPACT for autoimmune diseases and AAV in specific. As explained in the problem statement, we focus on a subclass of AAV named GPA, but in this report we will refer to the disease in its general way as AAV. In this part the characteristics of !MPACT will be described in detail.

Many autoimmune diseases are characterized by the presence of so-called auto-antibodies. These auto antibodies are often specific per disease and can act in case of AAV as a marker for its presence and severity. For AAV these auto-antibodies are called ANCAs. The engineered cells of !MPACT recognize these auto-antibodies and, as a consequence, excrete an anti-inflammatory molecule, called interleukin-10 (IL-10) as described in Figure 1.2. IL-10 is a natural anti-inflammatory molecule and can as such decrease the inflammation in the small blood vessels of the patients. Since this cells therapy gets activated by pathogenic biomarkers of AAV, the system acts local and temporary and is therefore considered as a personalized approach for treating the disease. This way !MPACT can adjust exactly to the patient's needs, stops the progression of the disease and decreases the symptoms associated with AAV. Furthermore, at a recurrence of the disease memory cells will get reactivated so readmission of the therapy is not required. Due to this early recognition of a relapse of the disease, dreadful consequences of AAV are avoided.

The implementation of our product, as described in Figure 1.2, into a therapy that can be used by clinicians and other end-users is visualized in Figure 1.3. Here the cell therapy cycle for !MPACT is visualized that has a large resemblance with CAR-T cell therapy. CAR-T cell therapy [17] is an example of innovations in the field of ATMPs and an inspiration and proven concept for our product. The treatment that is visualised in Figure 1.3 starts by collecting immune cells from the patient by a clinician. Secondly, the cells will be transported to the manufacturing factory, where the cells will get genetically manipulated

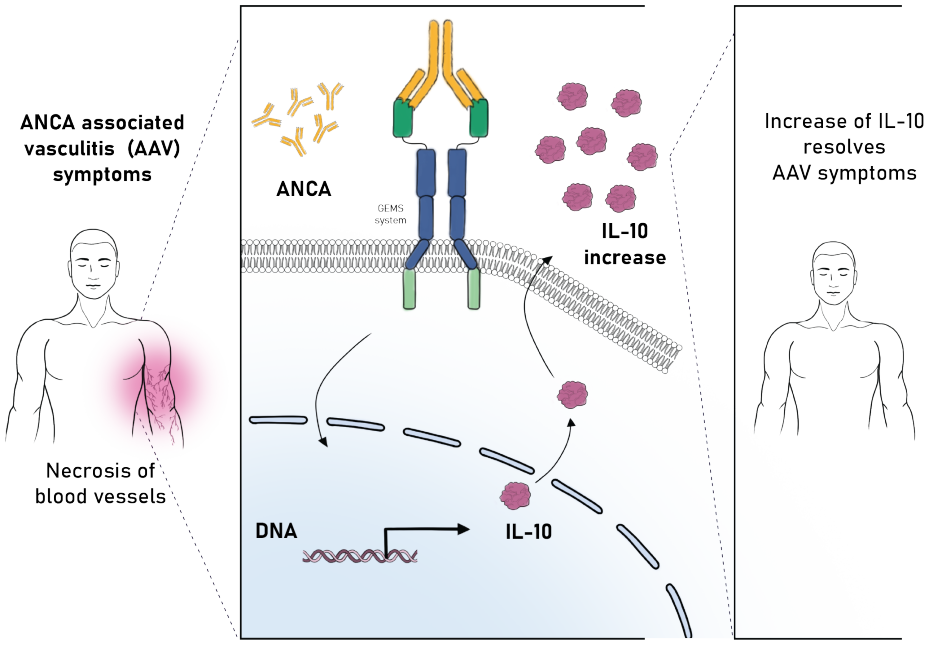

Figure 1.2: The scientific explanation of our product !MPACT specifically for AAV. First AAV is characterized by inflammation and necrosis of blood vessels. Secondly, the GEMS system [16] allows the binding of ANCA, the auto-antibodies associated with AAV. Binding ANCA enables the cell to form IL-10 and as a result, local expression of IL-10 by the cells suppresses the autoimmune response of AAV.

by integrating the genes of a synthetic receptor and the technology of !MPACT. Expansion of the amount of cells is followed by injection of the modified cells into the patient. Lastly, the cells will interact with the auto-antibodies and secrete locally and temporarily interleukin-10 to treat AAV symptoms.

1.2.1 | Main product and services

Our main product will be the patented proof of concept of !MPACT supported by preclinical and clinical phase I and IIa data, which we will be licensed to our customer who will have to further test, produce, market, distribute and sell the product.

Our therapy can be made applicable to other autoimmune diseases since the platform technology is considered modular. [16] The underlying technology of !MPACT is based on different structural parts that can be modified to bind different disease-associated molecules/antibodies. This means that the part/component that recognizes the disease-specific auto-antibodies can be interchanged to recognize another auto-antibody relatively easily. The potential of this method lies in the fact that many autoimmune diseases have a similar parthenogenesis; the body's natural defense system cannot distinguish the patient's own cells from foreign ones, causing the body to mistakenly attack healthy cells. All in all, only a very small element of the cell, namely the recognition part of the same receptor, needs to be changed for the cell-based therapy to work for another autoimmune disease. Our mission is, to develop multiple cell-based therapies to treat a variety of autoimmune diseases by adjusting !MPACT specific to other autoimmune diseases. We will start by developing !MPACT for AAV but in the future will perform R&D to discover therapies for other autoimmune diseases which we will again license to our customer.

1.3 | Value proposition canvas

The value of !MPACT can be viewed from four different perspectives. Since we aim to design a proof of concept for a cell therapy platform that could be used against other autoimmune diseases than AAV, most value is created for healthcare. At this moment there are 400 million people in the world that suffer from autoimmune diseases. The improvement of an individual's health by decreasing disease-related symptoms,

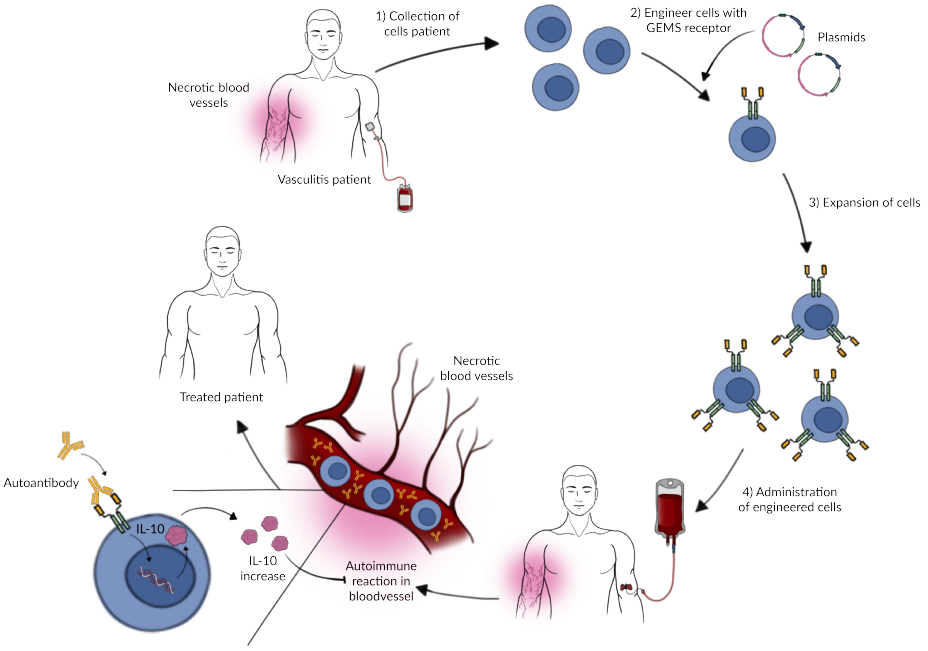

Figure 1.3: !MPACT admission cycle from a patient that follows the route of treatment implementation and manufacturing

preventing relapses, and improving the quality of life will lead to less stress, more independence, more energy, and a happier life for the patient him/herself but also family, friends and caregivers. This in turn has a secondary impact on society, as the general well-being of societies often contributes to a stronger economy due to a more sustainable and healthier workforce. [18]

Additionally, related to healthcare, is the decreased workload for healthcare workers. In the Netherlands 19% of healthcare workers in hospitals have to deal with understaffing every day. [19] Our cell-therapy decreases the number of relapses per AAV patient by 2-fold and with that the number of hospitalizations and treatments necessary. Moreover, the aftercare is less intense and demanding for the healthcare workers since our therapy has fewer side effects and does not require additional visits to the hospital. Therefore, there's a workload decrease of 50-75% for the care of patients suffering from AAV. Healthcare workers range from doctors who administer the treatment but also nurses have to perform less demanding care.

The decrease in workload for healthcare workers is correlated with less healthcare costs. When considering !MPACT specifically for AAV, it was found that on average each AAV patient is hospitalized twice and that the cost for treating AAV is €6,168 ($7,296) per patient-year. [19] If the symptoms of AAV include kidney failure, these costs can go up to $90,000 each year for the required dialysis. [20] Reducing the number of hospitalizations, the number of treatments, and the length of the treatment significantly decreases the healthcare costs for the hospitals as well as for health insurance companies. While the treatment costs for autoimmune diseases in the US are around $100 billion, the true costs are estimated much larger due to the consequences of chronic illness such as loss of wages and informal care. [21] Hence, these costs could be significantly decreased with !MPACT.

Lastly, ethical implications of !MPACT have a social impact. The often polarizing discussions on the consequences of artificially made organisms have been rising steadily over the last couple of decades. Although the discussion itself will not stop, the introduction of an effective cell-based therapy might take off some of the heat, and prove that engineered organisms can offer a safe and thus compelling solution to many of the current world problems. The responsible innovation in synthetic biology in response to COVID-19 is an example of such. [22] Besides, advanced therapy medicinal products (ATMPs) where our therapy belongs to, is a new and integrated cognitive field and product category that focuses on the incurable diseases, chronic diseases and orphan diseases that traditional drugs are not able to treat. [23]

The value proposition for !MPACT is summarized in Figure 1.4.

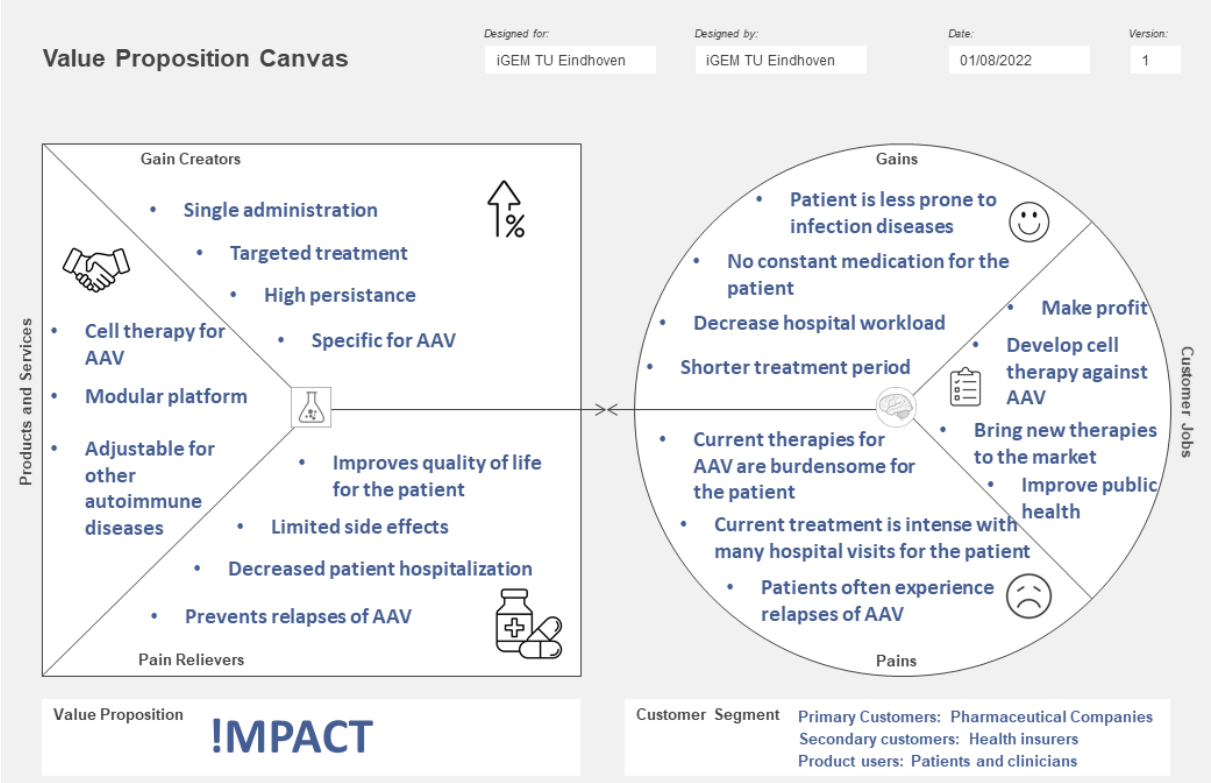

Figure 1.4: Value proposition for !MPACT

1.4 | Customer segment

The primary and secondary customers that iGEM TU Eindhoven aims to target are described in this section. Besides, the interests of other important stakeholders and product users are discussed.

1.4.1 | Primary customers

The primary customers iGEM TU Eindhoven targets are large pharmaceutical companies. The pharmaceutical industry is developing rapidly and for pharmaceutical companies, it is crucial to stay ahead of these developments. [24, 25] Therefore, pharmaceutical companies have a mission to discover new ways to improve and extend people's lives (according to Mark van Hattum, Health care relations at Novartis pharmaceutical company). !MPACT is an innovative therapy that is modular and personalized. This means our innovative therapy could help pharmaceutical companies to stay ahead of competitors and developments in the market. The pharmaceutical companies that we aim for are large enterprises that have at least 5,000 employees or an annual turnover of more than 1.5 billion euros and a balance sheet that is greater than 2 billion euros. [**?**] Furthermore, these pharmaceutical companies should have the production facilities and expertise to produce advanced therapy medicinal products (ATMPs) or be willing to invest in such facilities. Furthermore, the industry iGEM TU Eindhoven focuses on should be active in the immunotherapy sector but should not sell a cure against AAV already nor they should conduct research on a treatment for this disease. Moreover, they should have all required licenses and their facilities should be in line with all GMO laws and regulations. Lastly, our customers should hold the same standards regarding safety and ethics on genetically engineered machines as iGEM TU Eindhoven.

One of the potential pharmaceutical companies we could target and have been in contact with is Novartis. However, Novartis sells Ofatumumab, which could be used for B cell depletion as treatment for AAV. [26] Moreover, they also produce biosimilars for rituximab, also used to treat AAV. [27] Hence, we do not expect them to invest in a new therapy that potentially cuts their revenue.

A second potential primary customer we have been in contact with is Johnson & Johnson (J&J). They recently build a new production facility for the production of CAR-T cells in Belgium, which fulfills all GMO requirements and licenses. J&J does not have a therapy on the market to treat AAV yet, but they do have expertise in immunology. They even specify which partnerships they are looking for. One of these focus areas includes auto-antibody pathways in immunology and cell therapeutics. [28] This perfectly fits the design of !MPACT. J&J is also one of the largest pharmaceutical companies in the world, so also has the required infrastructure and resources we aim for. Hence, Johnson & Johnson is the first customer we will contract. Potential other primary customers can be found using a strategy that concerns three activities: [29]

1. Background research
2. Conference presentations
3. Organized one-on-one meetings

1.4.2 | Secondary customers

There is a triangle of stakeholders required to make !MPACT a successful product.These stakeholders are important members of the healthcare system in the Netherlands. The healthcare system of the Netherlands and its most important actors are described in this section.The route to get !MPACT on the market can differ per country, but often similar stakeholders of the healthcare system are involved. The values and interests of these stakeholders are important for the success of !MPACT and the connection that each of these stakeholder has with the primary customer is visualized in Figure 1.5.

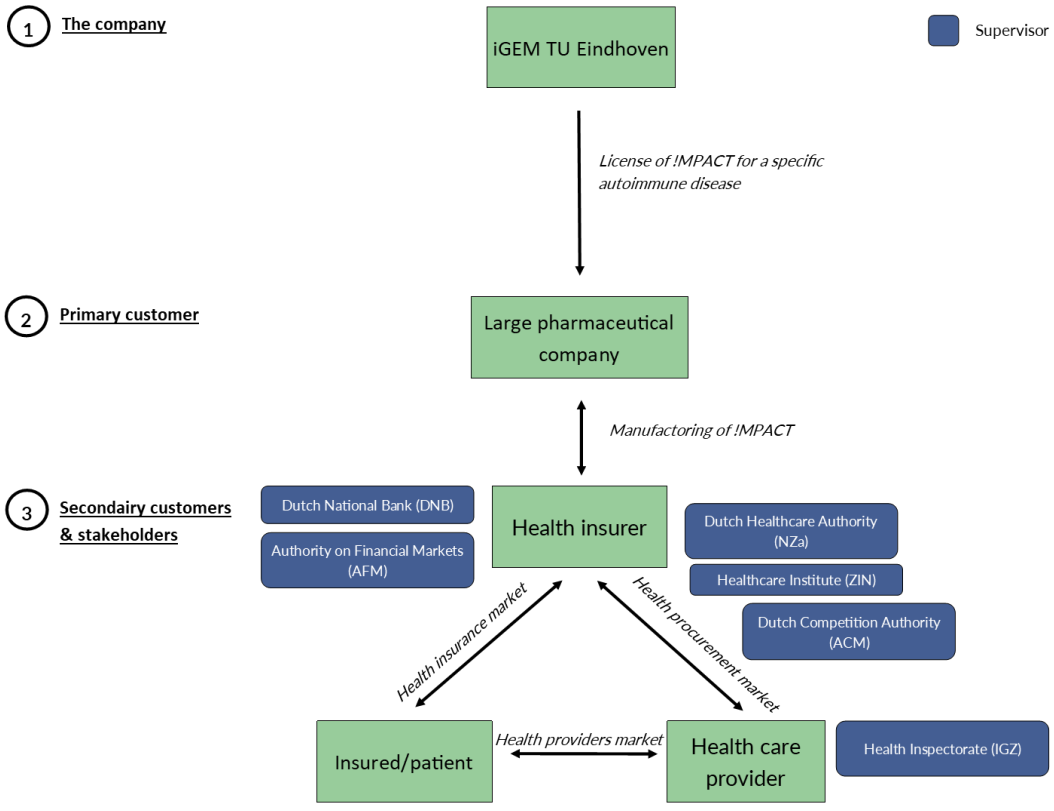

Figure 1.5: The primary and secondary customers and most important stakeholders involved in the business case of !MPACT. Figure is adjusted from slide 2 of [30]

When !MPACT is approved by the legal authorities to start its manufacturing process for clinical trials or thereafter, our primary customers will sell !MPACT to health insurance companies. Therefore, health

insurance companies are considered as the secondary customer iGEM TU Eindhoven targets. Health insurance companies have two priorities and interests. First, they focus on pharmacotherapy which means that the healthcare included in the basic care of the Dutch health insurance should be necessary and proven to be effective. Besides, there is a pharmaeconomical interest that ensures that the healthcare that is offered to society is affordable. Both interests align with those of iGEM TU Eindhoven whereas the effectiveness of !MPACT opposed to current treatments is one of our strengths which was emphasized in subsection 1.1. Besides, the mission of iGEM TU Eindhoven is "innovating healthcare and pushing the boundaries of synthetic biology" which is not possible without affordable care. Health insurance companies will decide which treatments they will (partly) reimburse, based on the advice of a board of specialists. This reimbursement is an important determinant of the success of !MPACT, whereas the therapy without reimbursement is too expensive for patients to pay.

1.4.3 | Product users

The health insurance companies will provide the treatment to the health care providers in a health procurement market. These clinicians are considered the product users and are closely involved in the development and production phases of !MPACT. Besides, they advise health insurance companies. This means that these specialists also determine which new medicine and therapies they administer to their patients. Clarifying and meeting the needs of these clinicians, to design a reliable product is of critical importance. Clinicians and hospitals in general are interested in optimizing the healthcare for AAV patients and giving the treatment that best serves the needs of the patients. This means that the effectiveness and side effects of the treatment are extremely important to these professionals. Therefore, iGEM TU Eidhoven has been involving clinicians from various hospitals and institutes, and companies, to advise us on their possible needs for !MPACT. For instance, various clinicians from University Medical Centers in the Netherlands (UMC) Utrecht, Rotterdam, Maastricht and the Catharina hospital in Eindhoven have been involved. The importance of validation and advice from clinicians during medical innovation has also been reviewed and concluded by Smith et al. [31].

1.4.4 | Hospitalization trajectory

In Figure 1.6, the hospitalization trajectory of a patient suffering from AAV in the Netherlands is shown. This clearly shows the golden standard of current treatments and the long duration and intense journey that the patient has to undergo. Besides, also the high hospital costs due to multiple readmissions are clearly demonstrated.

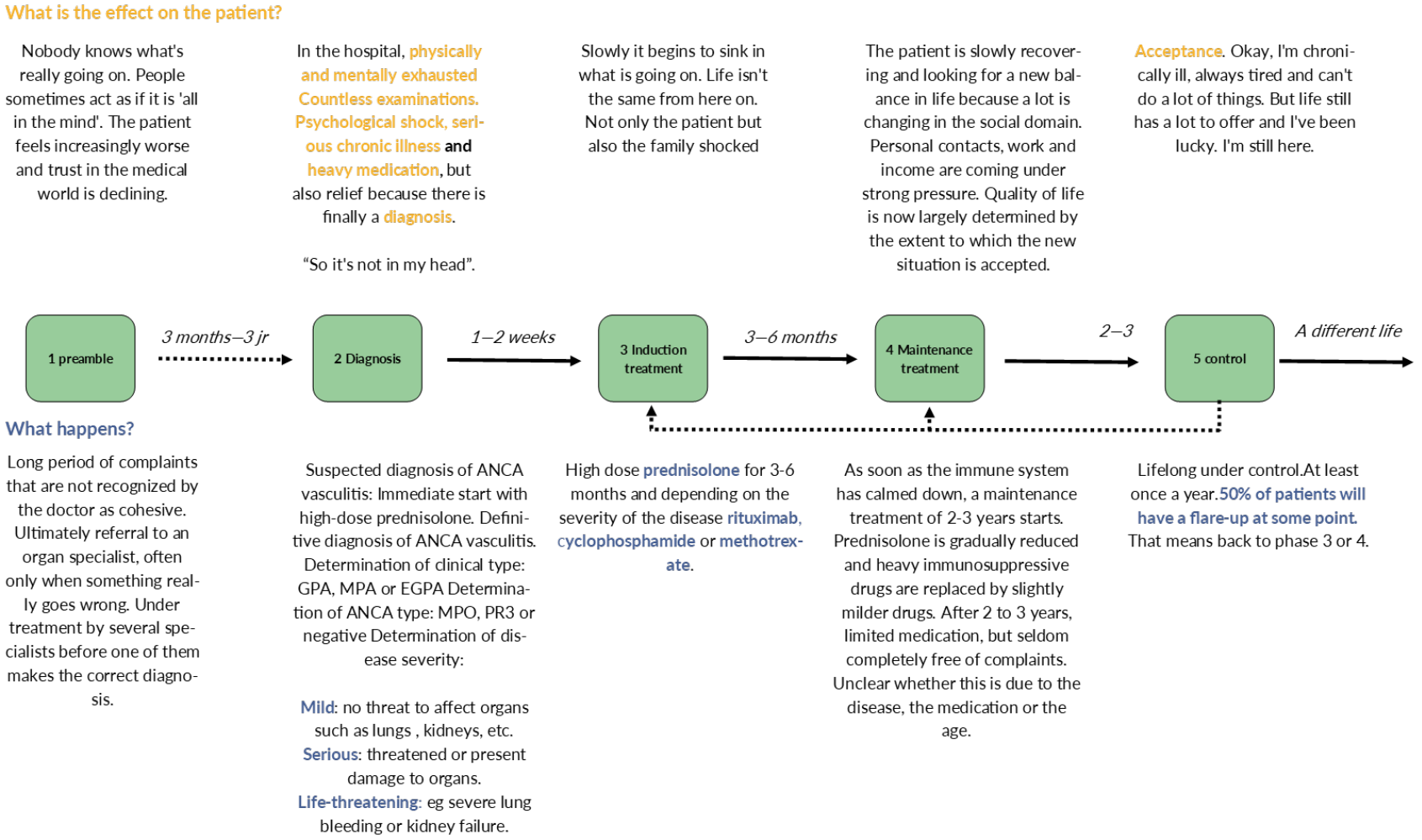

Figure 1.6: Hospitalization trajectory of a typical patient suffering from ANCA-associated vasculitis (AAV). This trajectory is based on the average patient and average duration of the 5 different hospitalization stages. It should however be kept in mind that no the disease trajectory can differ depending on the patient. The figure is translated and adjusted from [9]

1.5 | Roadmap

This year iGEM TU Eindhoven focused on the design and development of the proof of concept of !MPACT. We tested the mechanism of the simplified proof of concept in-vitro. For the next year, we aim to optimize the proof of concept and product design of !MPACT to make it potentially safer and more effective. Moreover, the goal is to translate the proof of concept to the actual therapy as described in Figure 1.3. In 2024, this therapy will be tested in-vitro and with in-silico models to obtain basic information about its safety and biological efficacy. The next step will be to not only test !MPACT by using cell lines, but also in-vivo in a variety of animal models. The pre-clinical tests have a goal to delineate the pharmacokinetic profile, general safety, and toxicity. In addition, the drug's mean residence time will be determined which depends on the metabolism, absorption, excretion, and distribution of the therapy. In 2026 we aim to start with the first phase of clinical trials and in the last year, the clinical trial IIa will be conducted after which !MPACT will be licensed to our target customer. In Figure 1.7 this roadmap for the next five years is summarized. After we successfully licensed !MPACT as therapy for AAV, we will adjust our developed platform technology to develop new therapies for auto-immune diseases such as Grave's disease or Systemic lupus erythematosus (SLE) that have similar pathogenic mechanisms. [32, 33]

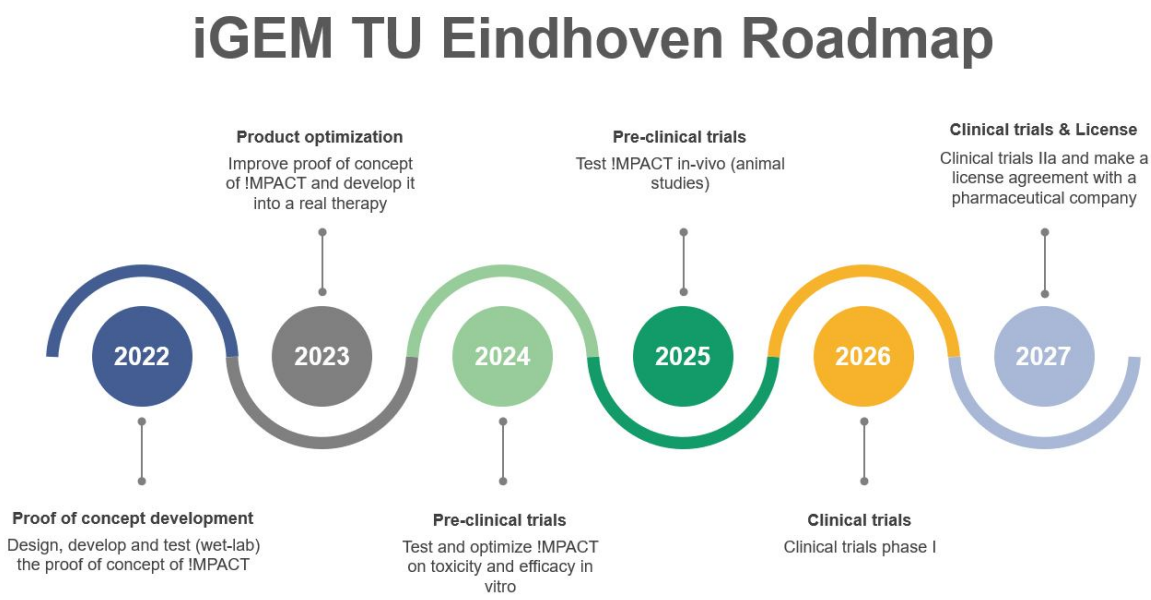

Figure 1.7: Roadmap with milestones of iGEM TU Eindhoven for the next 5 years.

2 | The entrepreneur and the winning team

2.1 | The team

The iGEM TU Eindhoven 2022 team, founded in December of 2021, developed !MPACT. The team consists of nine ambitious master's and bachelor's students with varied backgrounds ranging from expertise in biomedical engineering (modeling, programming chemical biology, synthetic biology, and organic chemistry) and experience with entrepreneurship, stakeholder co-creation and graphic design. This enables interdisciplinary, creative thinking and critically assessing deliverables from different perspectives. These qualities are required for high-quality scientific research in the development !MPACT and for new venture creation. The teammembers and their roles in the iGEM TU Eindhoven team are shown in Figure 2.1.

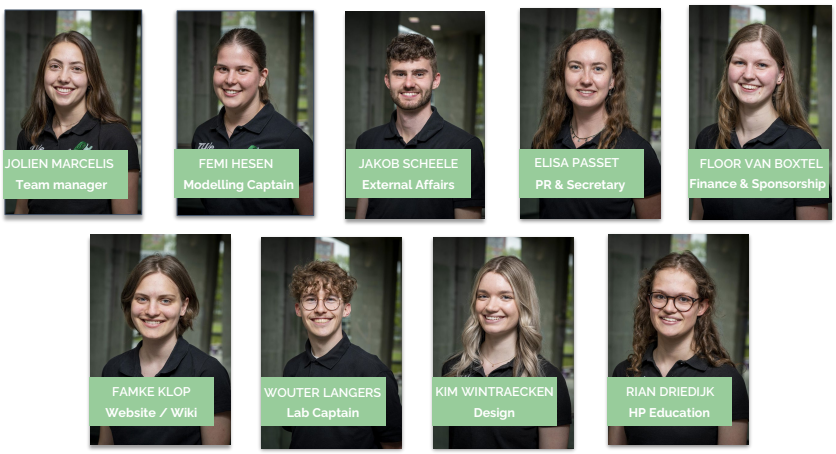

Figure 2.1: The members of the iGEM TU Eindhoven team of 2022 with their primary team roles and tasks.

Moreover, iGEM TU Eindhoven possesses general engineering hard skills such as problem-solving, analytical, and academic writing skills. Next to the hard skills, the team also has a wide variety of soft skills including, stakeholder communication, public speaking, networking, leadership, and time management skills. Particularly the soft skills are very useful to contract new partners. What is more, is that iGEM TU Eindhoven has a strong team since the team contains the complete nine Belbin roles (Table 2.1) which are crucial for effective decision-making and business processes within the team. [34, 35] These Belbin roles go together with a clear division in tasks and responsibility for every team member (Table 2.1). The wide variety in knowledge, experience, skills, character traits, and responsibilities allow for very efficient business processes such as project management, human resource management, and business development. In conclusion, the team has the required competencies and skills to start a new venture, perform research and development to optimize !MPACT, manage a long-term project and to contract new partners.

Table 2.1: All iGEM Eindhoven 2022 team members with their corresponding Belbin roles.

Belbin role	Elisa Passet	Wouter Langers	Famke Klop	Jolien Marcelis	Floor van Boxtel	Femi Hesen	Kim Wintraecken	Jakob Scheele	Rian Driedijk
#1	Implementer	Plant	Team worker	Co-ordinator	Resource investigator	Team worker	Plant	Monitor evaluator	Shaper
#2	Monitor evaluator	Specialist	Completer/ Finisher	Shaper	Shaper	Completer/ Finisher	Implementer	Shaper	Implementer

2.2 | Network

iGEM TU Eindhoven has a large network and collaborates with many different partners and stakeholders. iGEM TU Eindhoven has close ties to the Eindhoven University of Technology (TU/e) and is being supervised and advised by six principal investigators, professors, and researchers of the TU/e with expertise in synthetic biology, protein engineering, and chemical biology (Figure 2.2). Besides, our team is connected to TU/e associated organizations such as Innovation Space which offer many different training sessions to improve the skills and knowledge within the team and give access to their network. For example they offer training in presenting and acquisition, and they initiate connection with other student teams to exchange knowledge.

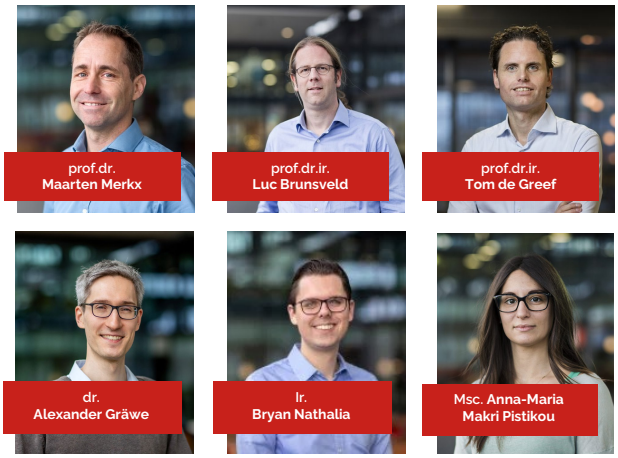

Figure 2.2: The principal investigators of the iGEM TU Eindhoven team of 2022 serve as the advisory bord of iGEM TU Eindhoven.

In addition, our team has a close relationship to the partner ICMS (Institute for Complex Molecular Systems) who offer coaching and resources applicable to wet-lab experiments and knowledge on how to translate the working of !MPACT to other stakeholders. Moreover, they include iGEM TU Eindhoven in their Highlights magazine which improves upon the reputation and brand awareness.

Next to the TU/e, iGEM TU Eindhoven also has a close relationship with pharmaceutical companies such as Novartis, who are next to partners also potential customers, who give us feedback on requirements for the next development stages in order to further develop !MPACT and our business.

In order to validate the cell therapy !MPACT, iGEM TU Eindhoven has close ties to our end-users (hospitals) such as for example Utrecht UMC, Caterina hospital, Rotterdam UMC and Maastricht UMC who gives us insights into the clear requirements of the therapeutics against AAV and user needs of our cell-based therapy.

Furthermore, the location of our team in BrainPort Eindhoven on the campus of the TU/e gives our team the required and helpful innovative environment with a large variety of expertise, resources and facilities. Many organizations that stimulate new ventures and promote high-tech developments such as the BOM and the Gate are located in this region. Lastly, iGEM TU Eindhoven is in contact with AAV patients and the Vasculitis Foundation in the Netherlands, for who the therapy is designed. They give information about their needs, pains and gains which can be used to co-create and design the best possible therapy.

Together with input from all these stakeholders iGEM designs, builds, tests, and measures the system using interchangeable biological parts and standard molecular biology techniques.

3 | Commercialization

3.1 | Protectability

An important factor in the success of !MPACT is the protectability of its technology. This protection can be classified in three different categories, namely, intellectual property rights, secrecy, and speed to market.

3.1.1 | Intellectual property rights

Existing technology !MPACT makes use of existing technology called the Generalized Extracellular Molecule Sensor (GEMS) platform. The GEMS platform is the subject of an ETH Zurich patent application published in the US and Japan. [36] However, there are now no granted patents anywhere, and our business will be located in Europe, where there is certainly freedom to operate.

Protectability and claims For reasons of protectability, our team plans to submit a patent application in the US and in Europe for the technology of !MPACT. In the application description, *antibody binding to a synthetic receptor with the efficient output of IL-10 in a human cellular system* is described in detail. More detail on the technology of !MPACT can be found in the product description, subsection 1.2. Furthermore, the platform technology that is modular, is included in the patent application product description. The claims included contain the intracellular pathway, associated linkers, antibody affinity domain sequences, and relevant mammalian cell implementation methods.

Protectability plan Through the United States patent and trademark office (USPTO), !MPACT will apply for a utility patent which generally expires 20 years after the application filing date. This will mean that our comapny has 20 years of protectability in the United States to develop and sell the !MPACT license. At the same time, we will apply for a European patent. This is an easier and cheaper alternative for obtaining individual patents in the countries that are members of the European Patent Convention (EPC). After six months, the European patent application will be published. This patent is also valid for 20 years. The simplified timeline of a European patent application is shown in Figure 3.1. After the phase IIa clinical studies (shown in **??**), a partner pharmaceutical company will receive a license for the AAV-specific technology of !MPACT.

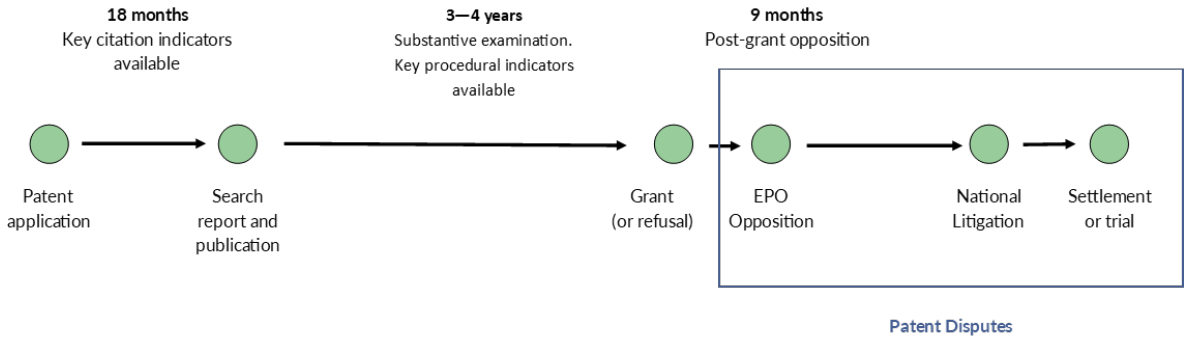

Figure 3.1: Simplified timeline of the European patent application of !MPACT for the first patent. Figure is adjusted from [37]

Our team will begin the research and development phase of a new cell therapy appropriate for a new autoimmune condition after receiving the first license. After the preliminary results are generated for this new disease, the patent application can begin.

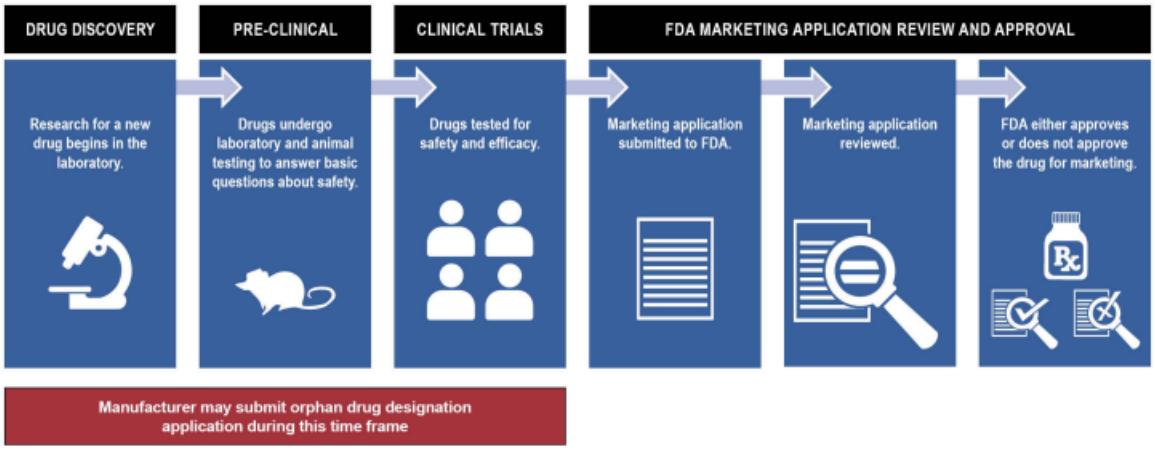

Figure 3.2: Drug development and the marketing and approval steps by the FDA (source [40])

Orphan drug designation Rare diseases are a global issue, therefore, the EMA and FDA work closely together on the designation and assessment of such medicine. [38, 39] For instance the FDA and EMA have common procedures for applying for orphan designation and submitting annual reports. This is advantageous because it saves us time and effort when we apply for these jobs. applications. According to the definitions of the EMA and FDA, AAV qualifies as an orphan disease. [40, 38] !MPACT meets the requirements for orphan designation because it is therapeutic for a chronic, debilitating disease, that has a prevalence in the EU of no more than 5 in 10,000 and because !MPACT will significantly help AAV patients.

In the drug discovery phase, we will file an application for orphan drug classification, which provides patenting benefits after the clinical trial phases. Once the drug is on the market, benefits include 10-year market exclusivity and protocol support. Figure 3.2 shows this procedure in a graphical way. For pediatric orphan drugs, the market exclusivity can be extended for an additional 12 years. Additionally, pharmaceutical firms that manufacture orphan drugs may apply for specific EU-funded grants. The pharmaceutical businesses that will be granted a license by our company will benefit from all of these advantages.

3.1.2 | Secrecy

Secrecy on the technology of !MPACT is extremely important to ensure that the patent gets approved. This is why every founder of iGEM TU Eindhoven, partners and investors should sign a non-disclosure agreement. This intensive process is needed to ensure that no insightful knowledge leakes to competing companies.

3.1.3 | Speed to market

The patent rights of !MPACT are valid for 20 years at the European and United States markets. Because of this limited timeframe, the iGEM TU Eindhoven team should focus on an appropriate speed towards the market. This is enabled by prioritizing research and development and substantially participating in clinical trials for the development of the therapy. The team should also invest early on in relations with pharmaceutical companies such that they get interested in !MPACT. Selling the license of !MPACT as soon as possible to a potential company is in the interest of both parties. Our team generates profit as soon as possible, whereas the pharmaceutical company gets the license as soon as attainable and has patent rights for as long as possible.

3.1.4 | Disclaimer

Although we have reached out to experts for legal protection of the technology of !MPACT, we did not manage to achieve a patent for !MPACT before the Grand Jamboree. We have decided to disclose the technology of !MPACT during the Grand Jamboree and with relevant stakeholders such that we can present our project in the best way possible. Moreover, we wanted to get the most relevant feedback on how to improve our design to make it more feasible, desirable, and responsible. On contrary, as discussed in the Proposed Implementation we aim to expand and optimize the mechanism underlying !MPACT after the Grand Jamboree even further. Through non-disclosure agreements, we will discuss with relevant stakeholders on the technical details of these optimizations and file a utility patent for the improved design through the process described in the previous section Intellectual Property. Our experience has taught us the value of intellectual property, and we would advise future iGEM teams to consider legal protection as early as possible in the project.

3.2 | Analysis of the value chain

To reach the end consumer, the value chain of the pharmaceutical and clinical research industry should be considered. It is of critical importance to determine the position of !MPACT in the value chain. We have to determine which assets we own as a start-up and which assets are in hands of other stakeholders to handle the right commercialization strategy. All stakeholders have to be identified and for each step along the value chain it should be determined whether a collaboration with a third party is necessary. The structure of the complementary assets (concentration) determines whether they are freely available (fragmented) or strongly concentrated.

First, it has to be determined which steps are necessary to reach the end consumer. In the traditional pharmaceutical industry we consider five operations, including drug discovery, drug development, production/manufacturing, distribution, and marketing & sales, which go parallel to the the drug development process Figure 3.3 [**?**, 41]. In addition, secondary assets are added to the value chain. At this moment !MPACT is positioned in the ”drug development phase”.

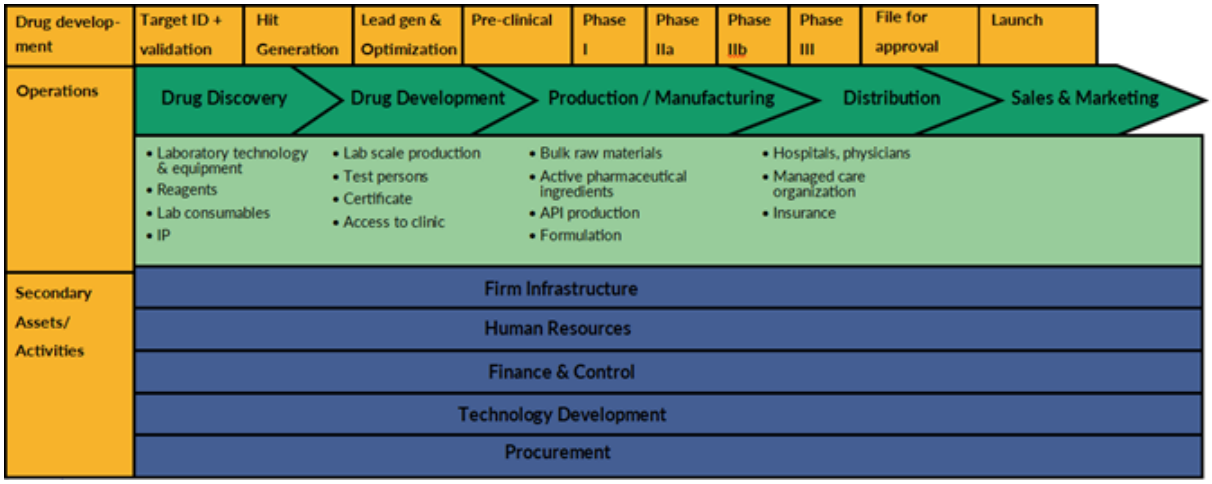

Figure 3.3: The value chain in clinical research industry

The second step is to identify all third parties along the value chain. In Table 3.1, a summary overview is given of all relevant third parties in each step of the value chain with corresponding examples. The structure of the complementary assets are given and the assets that are readily available in-house are allocated.

Table 3.1: Summary overview of the assets and corresponding third parties that possess the assets along the value chain.

Value chain	Third parties	Structure	Bargaining power of complementary assets
Drug discovery	Research institutes and academia such as UMC's and Universities who own laboratories and lab equipment. Eppendorf and ThermoFisher sell consumables and lab equipment. NEB, Qiagen, Promega, Sigma-Aldrich, Bio-Rad who sell chemicals and lab consumables.	Dense concentration	In house: laboratories, lab equipment, licenses for doing drug research. Freely available: lab consumables, chemicals, kits
Drug development	Research institutes (UMC's) who are capable of lab scale production and doing pre-clinical trials. Hospitals, UMC's and companies for drug research such as CHDR and Novartis who conduct clinical research and can allocate healthy volunteers.	Resources for lab scale production have an average dense concentration. Resources for clinical trials have a fragmented concentration	In house: Lab scale production is partly in-house available although upscaling and quality improvement is necessary. Additional lab facilities for lab-scale production are limited available. Resources for clinical trials are scarcely available and difficult to acquire.
Production/ manufacturing	Pharmaceutical companies such as Novartis, Lonza, Janssen Pharmaceuticals who can safely and effectively produce medical products in large amounts.	Resources for production have a fragmented concentration	In house: N/A Equipment, raw materials, large-scale production facilities are scarcely available and difficult to acquire.
Distribution	Health insurances (Zilveren Kruis, VGZ, CZ, Menzis), Hospitals (doctors, physicians), Pharmaceutical companies (Novartis, Lonza, Janssen Pharmaceuticals) who can take care of the distribution of medical products effectively.	Resources for product logistics and storage have an average dense concentration. Resources for market licenses, and insurance licenses have a fragmented concentration	In house: N/A Logistical resources are available. Resources for market and insurance licenses are scarcely available and difficult to acquire.
Sales & Marketing	Pharmaceutical companies (such as Novartis, MSD, Janssen Pharmaceuticals)	Resources for marketing and sales have an average dense concentration	In house: N/A Resources for marketing and sales are available. A good brand is scarcely available.

3.3 | Commercialization strategy

From the analysis of the value chain it can be concluded that iGEM TU Eindhoven possesses or has easy access to the assets necessary in the drug discovery phase. In all other phases, however, not all assets are in-house or freely available which means that large investments or collaborations with third parties are needed to acquire them. [42] It is therefore decided that iGEM TU Eindhoven only performs the first stage and part of the second stage of the value chain. This means that iGEM TU Eindhoven focuses on the drug discovery part of the drug development until the phase IIa clinical trials, since a successful clinical IIa clinical trial serves as a golden standard for a proof of concept in clinical research. [43] This strategy goes hand in hand with the recent trend in the pharmaceutical industry. Since 2004, the pharmaceutical industry dramatically outsources a large amount of R&D activities which is due to the high risks and costs involved in the R&D stage. In the new business models, the traditional large pharmaceutical companies start to focus on specific (latter) stages of the drug development process to reduce overall costs. As a consequence, strategic partnerships that include outsourcing of services get encouraged. [**?**]

3.3.1 | Commercialization strategy environment

To commercialize the technology, it will be legally protected in order to license it on the technology market which include the large pharmaceutical companies. As is explained in the "Protectability" section, subsection 3.1, the proof of concept and the technology that underlies the engineered cell can be very well protected. On the other hand, the complementary assets to bring the cell therapy to the market are not freely available and are mainly in hands of large pharmaceutical companies. Based on the commercialization environments described by Gans and Stern's(Table 3.2), this means we are dealing with the "Ideas Factories" situation. [44] In this situation you have to collaborate with external parties because complementary assets are tightly held by them. However, since there is high bargaining power as a result of the well protected technology, it is possible to make contract agreements. [42] The incumbents have high bargaining power because of the complementary assets they own and iGEM TU Eindhoven has high bargaining power because of the strongly protected technology. The goal is thus to search for the incumbents that are most in need for the technology, since this optimizes the bargaining power of iGEM TU Eindhoven to make an attractive deal for licensing the proof of concept to these external parties.

3.3.2 | Partners & Resources

As explained in the section "3.2 Analysis of the value chain", not all assets are available or are inherent to large investment barriers. Therefore, partnerships are inevitable for a successful commercialization strategy. The commercialization strategy for the next five years is visualized in a Gantt chart Figure 3.4.

Proof of concept development
The first phase of RD to design, develop, test, and optimize the proof of concept of !MPACT will be carried out in partnership with Maastricht and Erasmus University Medical Center (UMC). To be specific the Vasculitis Expertise Centrum (VEC) of Maastricht UMC and the laboratory of immunology of Erasmus UMC. [45], [46] These partners have respectively expertise in the pathogenic mechanism of AAV and in the development of T-cell therapies to tune the immune system. Moreover, they bring in more resources to do high-quality research, have a strong relationship with the clinic, and have access to patients. They benefit since they are part of state-of-the-art research in their field and because they will obtain a share of our new venture. Resources are shared in the partnership and include expertise, clinical data, laboratories, lab equipment, lab consumables, biological agents, and human tissue. As explained in Table 3.1, most resources required in this phase such as laboratories, low-end lab equipment, lab consumables, and biological agents are freely available on the market at relatively low costs and therefore available within iGEM TU Eindhoven. Other resources such as high-end laboratory equipment that we do not own ourselves are available at the Technical University Campus advantageous. The partnership, therefore, focuses on sharing information (such as patient data and expertise) and offering human tissue and some high-end lab facilities.

Pre-clinical trials
Resources for pre-clinical trials are only partly in-house but relatively easy to access. Since not all

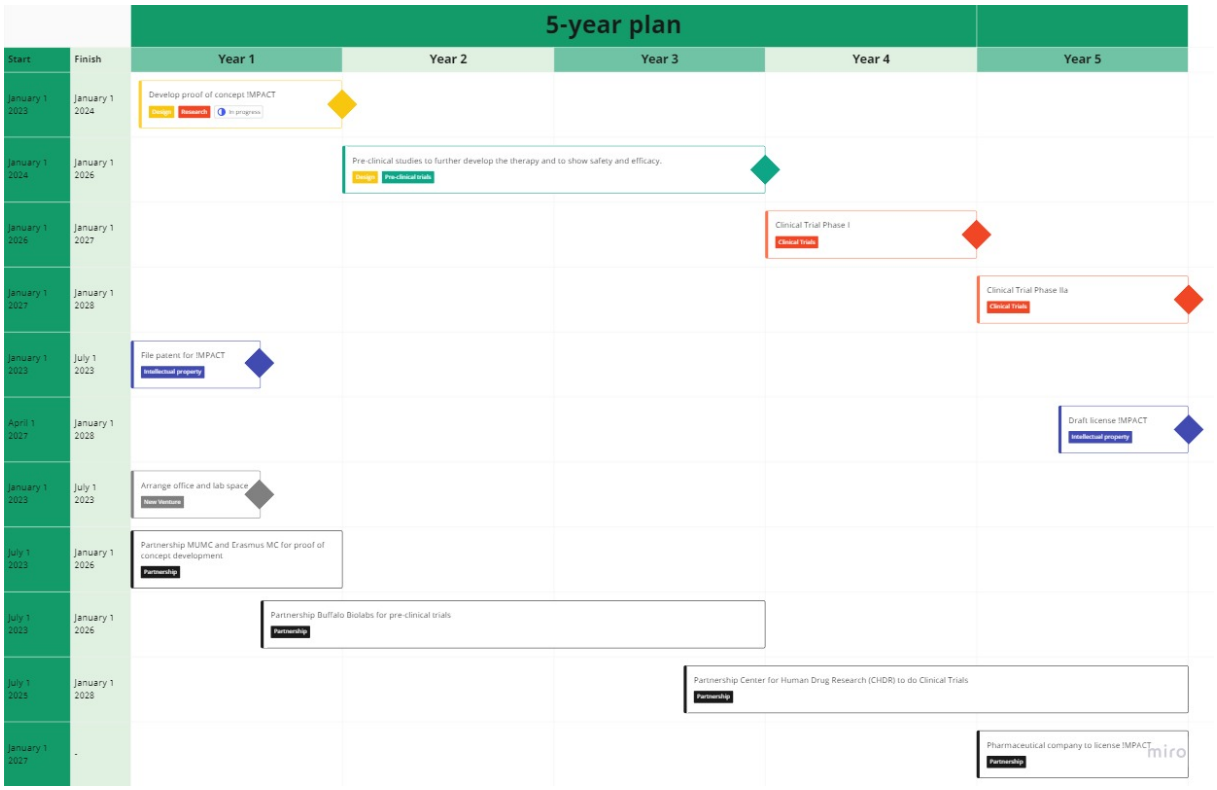

Figure 3.4: 5-year plan to successfully license !MPACT to a target customer

resources are in-house and since large investment costs are required to obtain them (e.g. advanced lab equipment, animal care, appropriate lab environments, in-silico models) we will outsource most of these activities to a company specialized in preclinical research services such as Buffalo Biolabs. They are specialized in immunotherapy, offer in-vivo research, offer support services, and have all the required resources. They own in-vitro laboratory spaces including tissue/cell culture labs. In addition, they offer histology hematology services, and bioanalytical services. They have the required imaging techniques and licenses to perform animal studies in multiple species from monkeys to pigs to mice. [47] Therefore, they are considered to the perfect candidate for a partnership to perform pre-clinical trials.

Clinical trials
Clinical trials require a huge amount of expertise, licenses, large facilities, tons of equipment, trained work staff, analysis tools, etc. The required resources are, therefore, very hard to acquire yourself and have a large barrier to entry so a partnership is essential. We outsource the clinical trials together with the Centre for Human Drug Research (CHDR) which is an independent institute that specializes in cutting-edge early-stage clinical drug research. (Our Building — CHDR, n.d.) Since we only perform clinical trials phases I and IIa, the CHDR is the ideal candidate. The CHDR offers state-of-the-art facilities to accommodate early-phase clinical trials. They own a First-in-Man unit and top-notch volunteer accommodation, dedicated research rooms, and efficient sample management. [48]

Clinical trial phase IIb – Market entrance
Large pharmaceutical companies to which we license the proof of concept !MPACT have the required resources to do large clinical studies (phase IIb and III), they own large business units and have a well-known brand name to market the new therapy. They have production facilities or enough financial resources to invest in them and they own the required distribution channels and infrastructure. They have regulatory units to file for market authorization and they know the laws and regulations for market entrance in different countries as they have multiple branches (geographical reach). They have close relationships with hospitals and doctors. Moreover, they have experience in bargaining with governments for the price of a new therapy to ensure successful market access (reimbursement). For iGEM TU Eindhoven, it is impossible to acquire all these resources in the limited amount of time (patent period). Hence, we mustn't perform this part of the value chain ourselves and instead license our product to large pharmaceutical

Table 3.2: Commercialization strategies environments

Excludable Technology	Incumbent Complementary Assets Add Value: **No**	**Yes**
No	The Attacker's Advantage	Reputation-Based Ideas Trading
Yes	Greenfield Competition	Ideas Factories

companies who perform the drug development process from a clinical phase IIb until the market entrance.

Greg Wiederrecht, P.h.D, Managing Director in the Global Healthcare Investment Banking Group at RBC Capital Markets, also explains the benefits for the large pharma companies; they simply cannot work in every single sub-therapeutic area. Specialization by biotech companies is much more effective. [49] A study has found that therapies produced by pharma-biotech alliances are 30% more like to reach market authorization. [50] The question however is, how do we as a biotech company raise the interests of large pharma? Greg Wiederdrecht believes that large pharma prefer innovative, first-in-class assets in areas of unmet medical needs, which perfectly fits the situation of !MPACT as therapy for AAV. In addition, large pharma need some clinical evidence, which is why we decided to develop !MPACT until phase IIa. Moreover, large pharma requires backup designs, which means we will develop multiple (around ten) potential series of !MPACT to fall back upon. Lastly, large pharma insists on worldwide rights, which means we will only license !MPACT to one target customer. [49]

The second important question is what steps are required to reach a successful license partnership and what does this process look like? After the initial meeting between a large pharmaceutical company and a biotech company, the pharmaceutical company receives a non-confidential written dossier. This dossier is first pre-screened by the evaluation team of the pharma company. If it is reviewed as credible, it is passed on to a scientist or clinician within the company with expertise on the topic, who looks into it in more detail. They often require a confidential dossier, for which first a non-disclosure agreement is signed. After they successfully reviewed the confidential dossier, a face-to-face meeting is arranged in which subject matter experts discuss their findings. If the proposal is still interesting to the pharmaceutical company, they first require to test the therapy. This means we have to execute a material transfer agreement so that !MPACT can be tested by the pharmaceutical company in internal assays. The pharma will have an internal meeting with key executives to come to the final decision for a strategic partnership. [49] After this phase, the negotiation about the partnership contract starts. Depending on the quality of the intellectual property, the clinical results obtained, and the market interest for !MPACT, iGEM TU Eindhoven will have a certain bargaining power to make the best agreement possible.

To increase our chances of interest from pharmaceutical companies we use three spearheads to put !MPACT on a pedestal. [29]

1. Differentiation; Make clear what makes !MPACT is different compared to other products in the same sector and other solutions to fulfill the same needs (competition).
2. Real-world efficacy and safety; show convincing results of !MPACT in representative physiological conditions (clinical data).
3. Route to market; The current market we aim to target and the regulatory pathways we take.

4 | Marketing strategy

4.1 | Market analysis

iGEM TU Eindhoven aims to target a small niche of the 400 million patients in the world that suffer from autoimmune diseases. [51] The team focuses on patients suffering from AAV, which comes down to around 2-3 million patients in the world and a potential addressable market of around 550-825 billion euros assuming an annual contract value per patient of 275.000 euros. [7] Since laws and regulations for market entry with a cell therapy differs between countries and because intake of the therapy in the health insurance is of critical importance, first two major, well developed, and well known market niches are targeted that include the USA and Europe. The number of patients with AAV in the USA and Europe add up to 215.000 – 430.000 patients and a total addressable market of 60-118 billion euros. [7] Additionally, !MPACT is designed for PR3-ANCA positive patients and patients with renal involvement, since it is proven that ANCA rises correlated with relapses in patients with renal evolvement. [52] It is found that 36% of all AAV patient are PR3-ANCA positive and from those PR3-ANCA positive patients, 59% have renal involvement. [53, 54] Moreover, only around 90% of the citizens of the USA have health insurance. [**?**] Taking those additional factors into account, the serviceable addressable market is expected to consist of around 46.000 – 91.000 patients and has a value of 13-25 billion euros given that all health insurance organizations in the USA and Europe incorporate the cell therapy against AAV in the insurance. The size of the market iGEM TU Eindhoven is hoping to obtain with the cell therapy within 12 years (return on investment time as consequence of IP expiring) is eventually 35% of the serviceable addressable market. A total of 35% of the patients with renal involvement progressed to end-stage renal disease (ESRD) associated with lifelong dialysis and intensive care. [55] It expected that all patients who have lifelong dialysis are willing to undergo the cell therapy and get prescribed the new therapy that is significantly more effective and cheaper than current treatments. This eventually leads to a market share (SOM) of around 4.4-8.8 billion euros within 12 years. The PAM, TAM, SAM and SOM are summarized in Figure 4.1.

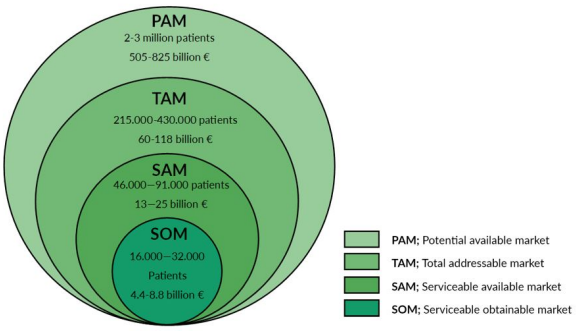

Figure 4.1: The expected PAM, TAM, SAM and SOM for !MPACT

In the future the cell-based therapy could potentially be used as a system for other autoimmune diseases since it is a modular platform. Although iGEM TU Eindhoven will start with developing the cell therapy for AAV, there are currently more than 80 different autoimmune diseases with a possibility to apply our therapy. If we look at the growth of the market iGEM TU Eindhoven is active in, we find that the total global market for autoimmune diseases shows an annual growth rate (CAGR) of 11.2% for the period of 2019-2024. [56] The vasculitis treatment market is to grow with a CAGR of 5.7% compared to 2018. [57] Furthermore, the field of synthetic biology is rapidly growing. The global market for synthetic biology is expected to register a CAGR of 19.23% during the forecast period of 2022-2027. Besides that, governments of various countries have been providing research support for synthetic biology. [58] US FDA-approved modified cellular treatments are already available which makes patenting our treatment and entering the market easier.

4.2 | Competition

When benchmarking !MPACT against the competition, three indirect competitive therapies to go into AAV remission can be identified. These include glucocorticoids such as prednisolone that acts as an anti-inflammatory drug, Cytoxan (cyclophosphamide) which kills immune cells that cause damaging inflammation, and Rituxan (rituximab) which is an antibody that inhibits the protein called CD20 and therefore reduces the number of B cells. [59] B cells are the immune cells responsible for the production of ANCA who trigger the immune system to start attacking blood vessels in AAV. [7] Glucocorticoids are often used in combination with one of the two other therapies to induce and maintain remission. [7] Since there are no other a cell therapies, ATMPs or patient tailored treatments specific for AAV available no direct competitors can be identified yet.

Among many manufactures that produce prednisolone, some include Pharmacia and Upjohn Co, Akorn Inc, Sandoz Inc, Watson Laboratories Inc, Private Formulations Inc, Roxane Laboratories Inc, Sperti Drug Products Inc, Merck and Co Inc, Novartis Pharmaceuticals Corp, and many others. [60] Cyclophosphamide is manufactured by Baxter Healthcare corporation and distributed under the brandname Cytoxan. However, also other companies such as Roxane Laboraties, produce and sell it as the generic drug cyclophosphamide. [61] Ritxumab was developed by Biogen Idec and is co-promoted by Genentech, a subsidiary of Roche. Currently, also biosimilars of rituximab are present on the market. [62]

The current treatments for AAV of the above mentioned manufactures are compared with !MPACT Table 4.1 based on the costs,persistance (how long the drugs remains in the body), effectiveness, side effects, workload for hospitals, and usage duration (how long the treatment takes). In addition, the possibility of a relapse of AAV is indicated for each therapy.

Based on Table 4.1, we can identify several selling points of the designed cell therapy of !MPACT compared to the competitive treatments. The two most significant advantages of the cell therapy are visualized in the USP Table 4.1.

Table 4.1: Benchmarking !MPACT to indirect competitors

	Prednisolone	**Cyclophosmphamide**	**Ritxuximab**	**!MPACT**
Manufacturers	Pharmacia and Upjohn Co, Akron Inc, Sandoz Inc, Watson Laboratories Inc, Merk and Co Inc, Novartis Pharmaceuticals Corp etc.	Baxter Healthcare corporation, Roxane Laboratories etc.	Roche (Biogen Idec, Genentech)	Licensed to clients of iGEM TU Eindhoven
Costs	Low	Low- Medium	Medium - High	High
Persistance	hours	hours	6 months (2 injections)	Expected at least 5 years
Efficacy	Low	Medium	Medium	High
Side effects	Infections, increased BMI, reduced bone density, steroid induced Diabetis Melitus, raised BP, GI side effects, increase in statin dose, fraqility fracture and skin changes. [63]	Myelosuppressions, hair loss, nausea, vomiting, fatal cardiomyopathy, pneumonitis, long fibrosis, chest deformity, gonadal damage, teratogenic effects, bladder toxicity, carcinogenic effects, hepatoxicity. (Ahmed & Hombal, 1984)	Infections, hypogammaglobulinemia, progressive multifocal leukoencephalopathy, fulminant liver failure, late-onset neutropenia. [64]	Not yet investigated
Usage duration	3- 6 months	3-6 months	3-6 months	One injection
Possible relapse of AAV	Yes	Yes	Yes	No

It can be concluded that the current treatment possibilities for AAV still have many disadvantages. First of all, they do not cure the disease, hence long term treatment is necessary and relapses of the disease are frequent. Multiple hospitalizations significantly reduces the quality of life of the patient. Due to intensive treatment procedures and because of the additional hospitalizations, high healthcare costs are perceived and a hospitals experience a high workload. Thirdly, the current treatments have many side effects and adverse events that can also bring risks to the health of patients and decrease their quality of life. Lastly, the overall survival rate for AAV is around 75% which could be higher with a therapy that would be more specific and more effective for AAV. Based on Figure 4.2, we can identify several selling points of !MPACT compared to the competitive treatments. !MPACT is more specific for AAV (as !MPACT gets only activated by disease specific biomarkers) , which is expected to result in less side effects. Our cell therapy responds to a relapse of the disease and therefore prevents reoccuring clinical manifestations of AAV. As a consequence, relapses of the disease will not occur anymore which prevents multiple hospitalizations, reduces healthcare costs, and lowers the workload of the hospital staff. Hence, it is expected that !MPACT would increase the survival rate for AAV. The two most significant advantages of the cell therapy are visualized in Figure 4.2

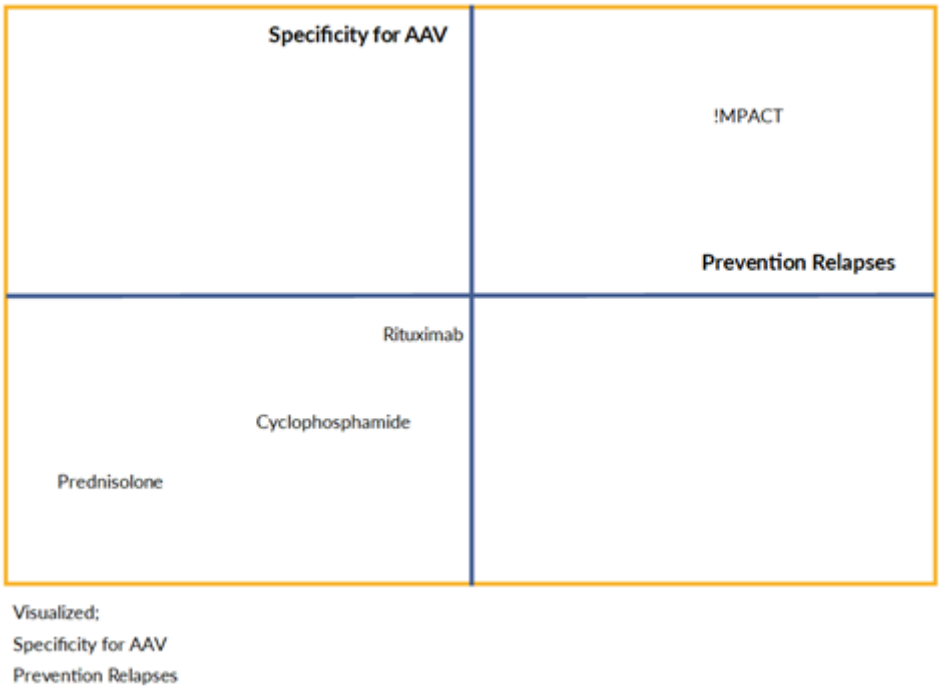

Figure 4.2: Unique Selling Point (USP) of !MPACT compared to the main competitive treatments for AAV.

4.3 | SWOT analysis

A SWOT analysis is is a strategic management technique used to help our new venture identify Strengths, Weaknesses, Opportunities, and Threats related to business competition.The SWOT analysis we performed is summarized in Figure 4.3

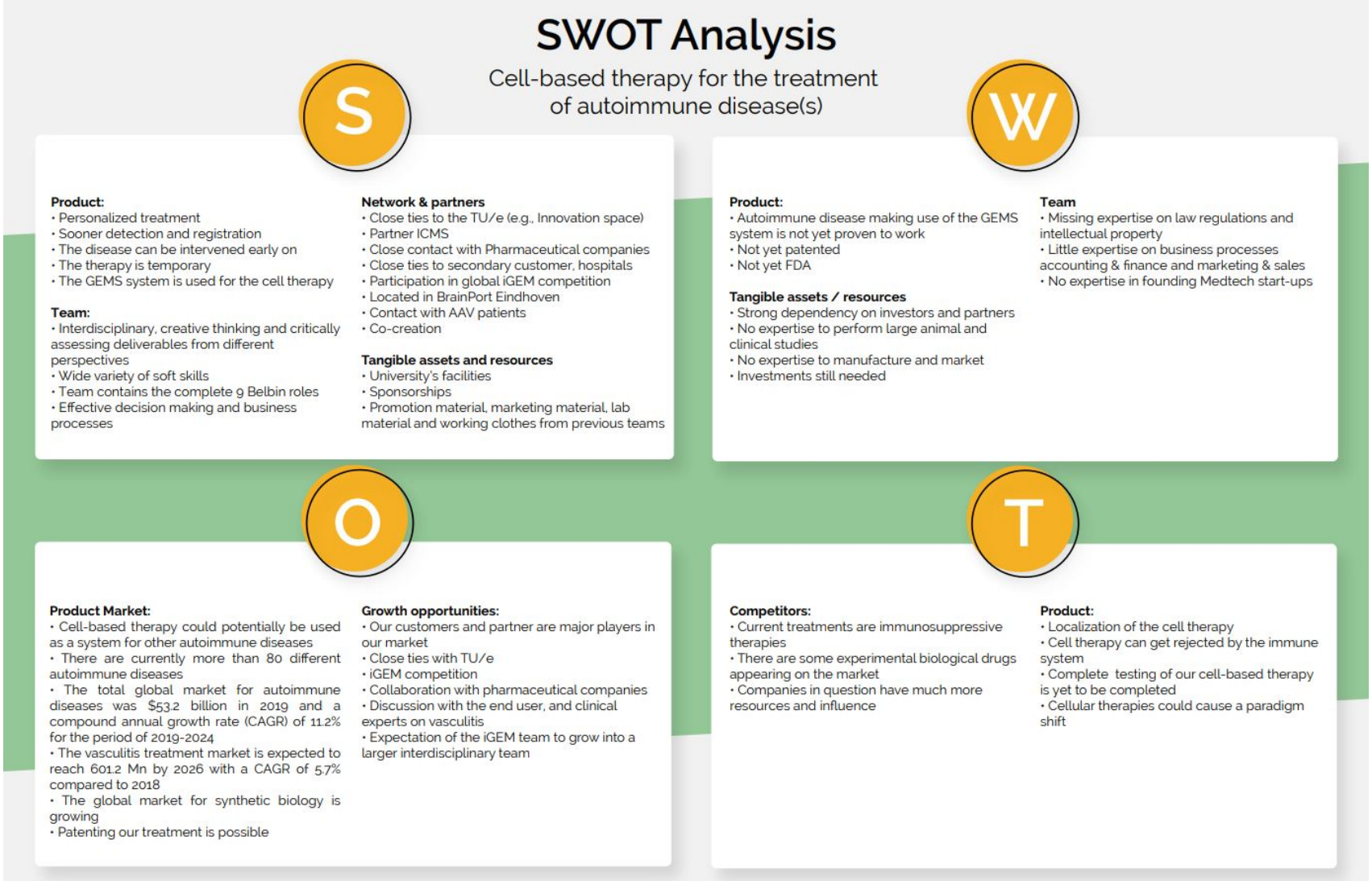

Figure 4.3: SWOT analysis iGEM TU Eindhoven

4.4 | Marketing

iGEM TU Eindhoven has limited resources for marketing and not yet a strong brand to perform effective marketing of !MPACT. Therefore, iGEM TU Eindhoven strives for a marketing license agreement with a large pharmaceutical company that has a strong brand, such as Novartis or Janssen Pharmaceuticals, since they get the authority to use, market, sell, and distribute !MPACT. [65] As explained in subsection 3.1, we license our utility patent to the pharmaceutical company based on royalties. [66] However, several suggestions to assure effective marketing by the licensee are made.

4.4.1 | Marketing goals

The goal of pharmaceutical marketing is to first of all, to create brand awareness for !MPACT, the licensee, and iGEM TU Eindhoven to establish ourselves as a trusted entity in the community. Secondly, the goal is to educate healthcare professionals (HCP) on !MPACT and the associated disease AAV. Next to HCP, the aim is also to educate patient communities like for example the Vasculitis Stichting on the innovative cell therapy. Fourthly, it is important to disseminate critical information about !MPACT, side effects and effectiveness after launch. The goal is to improve website visibility, to specify the key actions required to return on marketing investment, and lastly the main goal is to increase the sales of !MPACT by the pharmaceutical companies to maximize the return on investment. [67]

4.4.2 | Marketing strategies

An effective pharmaceutical marketing strategy of !MPACT includes a mixed approach of both directing and indirect marketing strategies. [68]

Direct marketing strategies include detailing, samples, educational & promotional meetings, promotional mailings, journal & web advertisements and direct-to-customer advertising. [68] Detailing consists of face-to-face promotional activities specifically focused on doctors, physicians and hospital directors. This includes activities such as doctors' visits to pitch !MPACT. Providing physicians with free samples of !MPACT is also found to significantly improve the sales of new drugs. Educational and promotional meetings are conferences where leaders in the field (often physicians) discuss the use of !MPACT. Promotional mails are typically unsolicited and consist of brochures that describe positive results of recent clinical trials. Journal advertisements and publications increase the trustworthy of the drugs and publicity of the new drugs among experts in the field. Direct-to-customer advertising is directed towards the general public and patients which has proven effective in motivating patients to ask for the brand product and causes the patients to talk to doctors about the product.This type of advertising is only allowed in the US. This type of advertising can be performed by means of social media campaigns, PCC advertising, print advertising, TV commercials and general conferences. [68]

Indirect marketing consist of two main activities: Continuing Medical Education (CME) such as medical education courses and Grants to Health Advocacy Organizations (HAO). HAO's are very influential organizations who aim to expanding support for medical research and the availability of healthcare services. Grants to HAO's have proven to endorse the position of the respective pharmaceutical companies. [68]

5 | Risk and uncertainty

5.1 | Risk identification assessment

In order to identify the main risks, the business model will be evaluated with a focus on potential risks. Specifically, each risk is evaluated among a five-point Likert scale for impact, probability, and non-controllability, varying from 1 (low) to 5 (high). Based on these 3 factors, the risk index is calculated by multiplying the three factors. A high index number means it is a key risk and should be monitored and managed well, while a low risk index means that it should only be monitored. The risk evaluation is presented in Table 5.1.

5.2 | Managing risks

In order to manage risks, four strategies could be considered that could either reduce or prevent risks: partnering, networking, strategic options, and compartmentalizing risks. In regard to legislative and product risks, partnering would be the most effective strategy to reduce these risks. Especially a collaboration with a pharmaceutical company or research institute can decrease risks associated with the therapy, as they can add expertise to the R&D, clinical trials, and production of !MPACT. Partnering with legislative organizations, such as law firms specialized in life sciences and health care, but also partnering with patent offices can reduce legislative and policy risks. In this way legislative activities can be outsourced to specialists. Therefore, they might provide us with relevant insights and tools for our venture to reduce these legislative risks.

In regard to security risks, networking would seem the most effective strategy. Having an IT expert or IT connection with a company that could provide the relevant security information (e.g. advisory report) for our (medical) data, might be very helpful to reduce security risks, such as data theft or privacy infringement. Especially since no members in our venture have great IT experience/knowledge, having someone that has actual experience with common IT threats and knows how to solve/control them most effectively, is very valuable. This mainly explains the low controllability for security risks in Table 5.1.

In regard to economic and networking risks, strategic options can be effective. Especially for competition, it can be useful to analyze multiple scenarios in which competition might become a threat and how our venture could react to these threats. Based on the multiple scenarios, we could develop various business models that respond to each specific scenario. By having these various business models, we could respond quicker on specific changes within the market, such as pricing. For instance, if competitors have cheaper drugs with more or less the same effect, we should have a plan B (e.g. a business model based on pricing) ready to modify our business model quickly and become competitive immediately. In this way, we could reduce the economic risks (e.g. loss of financial gains). For funding, it would also be sensible to have various scenarios in mind how we want to be funded and by whom. Especially analyzing the effects of being funded by a specific company/partner and how this would affect our future reputation and venture building are cases that should be looked at in a broader perspective. This also applies for selecting collaboration partners (pharmaceutical companies). By using this broader perspective, we could get a better idea who we should collaborate with/be funded by and therefore reduce either the economic as the network risks.

Lastly, for management risks, it might be useful to consider the compartmentalizing risk strategy. Since experts, administrators, and lab staff are three different departments within our venture, it might be useful to assign each department with a specific responsibility that brings certain risks. For instance, experts might be assigned to tasks that involve product and legislative, while administrators might be assigned to tasks that involve economics which they have to manage. For lab staff, two departments could be created: one department for the practical lab work and one department for working out the results and setting up new experiments. In this way, one could reduce the work pressure and, therefore, reduce the management risks.

Table 5.1: Risk evaluation of the business model based on impact, probability, and non-controllability .

Risk	Impact	Probability	Non-controllability	Risk index
Product risks				
No safe therapy	4	4	3	48 (High)
No effective therapy	5	3	3	45 (High)
No specific therapy	4	4	3	48 (High)
No sufficient clinical trials possible	4	3	4	48 (High)
Too many side effects	4	2	3	24 (Medium)
Too expensive to produce	3	2	3	18 (Low)
Not incorporated in health insurance	5	3	3	45 (High)
No sufficient persistence	4	4	3	48
Security risks				
(medical) data safety	4	3	2	24 (Medium)
Legislative and policy risks				
Lack of licenses	5	2	2	20 (Medium)
Negative change in laws & regulation	4	2	5	40 (High)
Lack of IP	4	2	2	16 (Low)
Economic risk				
Lack of funding	4	3	2	24 (Medium)
No viable business plan	4	3	3	36 (Medium)
Pricing	4	3	2	24 (Medium)
Competition	3	2	4	24 (Medium)
Network risks				
No customer	4	2	3	24 (Medium)
No partner	3	3	3	27 (Medium)
(Covid-19) pandemic	2	2	5	20 (Medium)
Lack of promotion	3	1	2	8 (Low)
Management risks				
Limited experts	4	2	2	16 (Low)
Limited lab staff	3	2	2	12 (Low)
Limited administrative staff	2	1	2	4 (Low)

6 | Financial planning

6.1 | Revenue-cost analysis

To execute the business plan of the firm, a financial plan needs to be developed. Therefore, assumptions have to made on the expected cost structure and revenue streams.

The fixed costs include human resources expenditures, training expenses, services rendered by third parties, infrastructure operational costs, and marketing costs.In addition, costs to legally protect !MPACT, costs to draw up a license for the IP of !MPACT and the R&D expenses to develop !MPACT are also considered fixed costs since iGEM TU Eindhoven will not be a production company. Therefore, we have excluded direct variable costs. The revenue hypothesis is based on the expected license fee that pharmaceutical companies have to pay to exclusively further develop and market !MPACT.

iGEM TU Eindhoven worked out the financial plan together with Ambagon Therapeutics and new venture from the Technical University of Eindhoven. Ambagon therapeutics started as a spin-off company of the TU/e in 2020 and aims to develop a new class of medicines that can modulate previously undruggable targets and influence currently accessible ones in new ways. [69] Ambagon Therapeutics has experience in starting a new life science venture as spin-off from the TU/e. Hence, they form the perfect partner to discuss revenue and cost assumptions.

6.1.1 | Costs assumptions - Fixed Costs

Human resources

iGEM TU Eindhoven 2022 currently consists of nine team members. For the next five years, each team member will be assigned a job title depending on their current team role. Job titles crucial for a MedTech start-up include CEO, CSO, CFO, CDO, CMO, Legal Assistant & Office Administrator, Medical Laboratory Technician (MLT), and Clinical Study Manager. [70] The salaries of all job functions will remain the same in the first five years. The first year's salary is based on the minimum gross salary as stated in the CAO of Ph.D. students in the Netherlands (ranging from 2395€ to 3061€ per month). [71] The salary costs for the employer are actually higher than the gross salaries of the employees due to holiday allowance, employee insurance, and healthcare contributions. The holiday allowance is legally 8% of the gross salary. The costs for employee insurance and healthcare premiums are jointly between 19% and 24% of the gross salary including holiday allowance. [72] The index and accumulated salary increase percentage is based upon the growth target for nominal wages (3.5%).[73] An overview of the total costs for the employer per employee per month is given by Table 6.1.

Table 6.1: Overview of the total costs for the employer per employee per month.

Year	Gross salary employee	Holiday allowance (8%)	Employee insurance & Healthcare premiums	Total costs for the employer per employee
1	€ 2.395	€ 192	€ 517	€ 3.104
2	€ 2.479	€ 199	€ 535	€ 3.213
3	€ 2.565	€ 206	€ 554	€ 3.325
4	€ 2.655	€ 223	€ 573	€ 3.441
5	€ 2.748	€ 220	€ 593	€ 3.561

Training expenses

The total training expenses are on average expected to be 1678 euros per year per employee based on literature. [74] Since iGEM TU Eindhoven is associated with the TU/e and InnovationSpace, expertise and many training facilities are freely accessible. Therefore, the expected training expenses are minimized and expected to be around 1000 euros per employee per year.

Services rendered by third parties

The services that iGEM TU Eindhoven aims to outsource include five major expenses: legal & regulatory costs, clinical study expenditures, costs for pre-clinical trials (such as animal testing), consultancy fees, and accountancy.

For R&D, clinical trials, and marketing of medical products, especially for ATMPs, there are many rules and regulations and several licenses required. The legal and regulatory services will be outsourced to third parties since our team lacks expertise on legal and regulatory compliance. Based on conversations with multiple MedTech start-up companies (Ambagon Therapeutics, CiMaas) costs for outsourcing these services are expected to be roughly 150 euros per hour. The total legal and regulatory costs are estimated at 6000 euros per month (40 hours a month).

Since we start as a student team from the Technical University of Eindhoven, we do not have the facilities nor the expertise to conduct high quality (pre-)clinical trials. As is explained in Chapter 3, the goal is to license our proof of concept !MPACT to a large pharmaceutical company. (pre-)Clinical evidence is necessary to convince our primary customer to license our product. The golden standard for clinical evidence is phase IIa data. iGEM TU Eindhoven aims to outsource clinical trials phase I, phase IIa and pre-clinical trials, because resources are not available within the team and require huge investments. Pre-clinical trials include in-vitro and also in-vivo animal testing. The total costs for pre-clinical testing are estimated at 62 million euros and is expected to take 2 years. This comes down to 7.75 million euros per quarter. [klotz, 2014]

Clinical phase I and IIa studies are relatively small compared to phase IIb and phase III and, therefore, require significantly less expenditures than phase IIb and phase III require. The costs for phase I clinical studies are expected to be 1.4-6.6 million euros and for phase II clinical studies 7.0-19.6 million euros. Since AAV is a relatively rare disease and because ATMPs are complex, finding enough participants for clinical studies can be found very difficult. Therefore, we expect the costs for the clinical trials to be above the average. Going with the worst case scenarios clinical trial I costs 6.6 million euros and clinical phase II costs 19.6 million euros. [75] Since we only aim to perform until phase IIa we expect that this is half of 19.6 million euros and therefore 9.8 million euros. The total costs for phase I and IIa clinical trials, therefore, come at 16.4 million euros. We have learned from the CHDR (Centre for Human Drug Research) that 1/10 drugs do not pass clinical studies and that you have to take into account the costs for the failures. Therefore, we estimate the total costs for clinical trial I and IIa at 16.4 million x 10 = 164 million euros. Based onl literature clinical phase I is expected to take half a year to a year and clinical phase IIa one year. [76] The average costs for clinical trial phase I thus come down to 16.5 million euros per quarter and phase IIa come down to 24.5 million euros per quarter.

Since we aim to design a new cell therapy that is based on complex technology and combines interdisciplinary fields of research, different types of expertise are required. Our team does not have expertise in all these fields and we do not have experience in creating new ventures. Therefore, we aim to compensate for the lack of expertise and experience by hiring consultants. It is found that most MedTech consultant firms charge an average of 150 – 200 euros per hour. [77] Since we expect to hire two consultants (technology and business consultancy) of around 20 hours a week, we forecast 32.000 euros a month for consultancy.

Lastly, accountancy is a service that we wish to outsource partially. The typical accounting fees for small businesses fall between 1000-5000 euros annually. [78] For accountancy we have however some expertise within the team and we are supported by the iGEM TU Eindhoven Stichting that fulfills most of the accountancy tasks and ensures continuity. On the other hand, if we grow as a start-up, most of the accounting tasks will have to be outsourced. We thus expect average accountancy costs of around 3000 euros a year.

Infrastructure and operational costs

The infrastructure & operational expenses consist of IT costs, office rent, travelling, equipment maintenance, insurance and office supplies. Other infrastructure & operational expenses are expenditures to obtain and maintain the IP rights for !MPACT, the costs to settle a license agreement with our primary customer, and the R&D costs to develop and test the concept of !MPACT.

Based on literature, on average the costs of IT support for small businesses hover around 58.000 euros annually. [79] These costs include expenses for equipment, software services, internet, website, and data storage.

Taken the analogy with Ambagon, a life science start-up company with a staff of nine people requires a laboratory space of around 100 m2 and 40 m2 of office space. At the TU/e Eindhoven Campus in the current market, the rent of a laboratory of 50 m2 is around 2500 euros and an office of 20 m2 around 1000 euros. This adds up to a total rent of 7000 euros a month. Insurances of the laboratories and offices spaces are part of the rent.

In the Netherlands it is legally established that the employer can reimburse a maximum of 0.19 euro per kilometer for the employee, without paying taxes. The tax-free fixed travel allowance is then a maximum of 82 euros per month. [80] The average home-work distance in the Netherlands is 19 kilometers. [81] This concerns a net fee of 65.74 euros per month per employee. [82] For nine employees this adds up to around 600 euros each month in total. In addition, business related travelling costs are expected to be around 400 euros each month (congresses, business meetings etc.). In total this adds up to travelling expenses of 1000 euros each month.

Lab equipment maintenance expenses of high-end equipment (e.g. mass spectrometer) are around 20% of their total costs of ownership. Discussions with Ambagon Therapeutics, however, learned us that it is not profitable for a small company to buy high-end equipment yourself. You could better outsource these activities because high-end lab equipment is abundantly present at the TU/e campus. Meanwhile, the maintenance costs for low-end equipment (e.g. cell based research) are estimated at 10%. Expecting an investment for lab equipment of 100.000 per lab (see investments section) this translates to 20.000 euros

maintenance costs over a period of 5 years and thus 4000 euros per year for two laboratories.

Licenses for working with GMOs in the laboratory, the use of GMO's outside the laboratory and licenses to do animal and human studies etc., are budgeted at 1200 euros a year.

Businesses with around ten employees are estimated to spend around 75 euros each month on office supplies such as paper, pens staples, ink for the printer, furniture, equipment, etc. [83] This adds up to 675 euros per month.

Literature shows that the costs to file most utility patent applications are between 8.000 and 15.000 euros. Complex patent applications, however, can cost 20.000 euros or more. [84] Due to the complexity of the technology in the cell therapy !MPACT and the complexity in its use, we expect that filing a patent will cost around 20.000 euros. Also after filing for a patent, there are more expenditures ahead. First of all, the majority of the patent applications get rejected by the Patent Office. It is expected that a response to this rejecting costs between 3.500 and 4000 euros. Typically a patent application is rejected 1 to 3 times. [84] Adding this all up, 32.000 euros is budgeted for obtaining IP rights on !MPACT. After you get approval you have the legal right to prevent others making, using, selling or importing your invention. The patent will expire typically 20 years after you received the IP. However, if you want to keep the patent enforceable during this period, you will have to pay maintenance fees which are 6.300 euros for small companies such as iGEM TU Eindhoven 2022 (315 euros per year). [84] This means that in the 20 years, it is estimated we need 38.300 euros to obtain and maintain the patent on !MPACT.

Drafting a patent licensing agreement can be a very complicated task and usually requires knowledge in the field of IP. Since team members of iGEM TU Eindhoven do not possess these skills, this task is will be outsourced to intellectual property attorneys who are specialized in license agreements. An intellectual property attorney knows what terms and clauses must be included in the agreement to protect the interests of both parties and to follow all laws. According to ContractsCounsel's marketplace data, the average licensing agreement drafting costs around are 680 euros. [85] After the agreement is settled, you need a lawyer to review the document for renewing it to ensure that it is legal and fair for both parties. The licensing agreement review costs are 733 euros according to ContractsCounsel's. [85] In total this means around 1500 euros is needed to settle a licensing agreement.

Together with start-up company Ambagon Therapeutics, the R&D costs to develop and test the concept of !MPACT are estimated. The monthly costs for biological agents, chemicals, and lab consumables to conduct research are estimated at 10.000 euros per scientist. Considering that 4 staff members will be full-time in the laboratory, this adds up to 40.000 euros per month for 5 years of research. In total this results in R&D expenses of 2 million euros to develop !MPACT.

Marketing

Research has shown that a marketing budget for life science companies is somewhere around 8-13% of the revenue. Small businesses in life science typically spend 7-8% of revenue in marketing. [86] On the contrary, as a result of discussions with Ambagon Therapeutics, it became clear that a new venture like iGEM TU Eindhoven does not have to include marketing activities in an early business stage. This is due to the fact that in the beginning no revenues are made and no product has entered the market yet. Only minimal brand marketing activities need to be carried out and are estimated at 1000 euros a month.

6.1.2 | Revenue assumptions

The license for !MPACT is provided to only one licensee such that they exclusively have the right to use, produce, market, sell and distribute !MPACT. To determine the license fee of !MPACT, multiple factors are taken into account. The first step is to determine the type of payments that are going to be required as part of the licensing deal. Secondly, a combination of two methods are used to determine the total license fee. The cost approach is used to determine the minimal license fee since method is suitable for complex patents that have not been proven in the market yet. Here the value of the intellectual property is based

on the costs of developing it.[87] Lastly, the calculated license fee is validated by the income approach. This controls the value of the IP based on the income that is expected to generate in the future.[87]

The intellectual property royalties are charged by a combination of royalty percentages and a minimum royalty payment. Since clinical phase IIa evidence of !MPACT is already published at that point in time, the risks are significantly less for the licensee, which increases the negotiating power of iGEM TU Eindhoven. iGEM TU Eindhoven aims for a royalty rate of 9.6% for a period of 15 years, which means that the licensee must pay 9.6% of the net gross revenue they generate by the intellectual property during this period. Literature namely shows that an average royalty rate of 9.6% is paid by pharmaceutical companies.[88] [89] A minimum royalty rate is implemented by means of the cost approach to at least earn back the investments necessary to develop !MPACT. The total development costs for iGEM TU Eindhoven to develop !MPACT in the first 5 years add up to almost 230 million euros. To earn this back in 15 years, the minimum royalty payment per year is 15.3 million euros.

The income approach is used to determine the royalty fee that the licensee (pharmaceutical companies) are expected to pay iGEM TU Eindhoven. The price a pharmaceutical company (the licensee) can asks for a treatment with !MPACT when it is completely developed, depends upon the value for the patient (which is often calculated as healthy years of life gained). It is expected that the value for the patient is much more than the currently available immunosuppressive drugs used to treat AAV, but it is not expected to completely cure the disease as is the case with CAR-T cell therapy. It is found that the costs for current treatment for AAV with Rituximab (an often used immunosuppression) is almost 20.000 dollar per treatment and given that a patient diagnosed with AAV on average gets two treatments because of relapses this would add up to 40.000 euros.[90] If AAV leads to kidney failure, dialysis becomes necessary and the therapy costs increase by around 90.000 euros each year. It is expected that !MPACT only requires one single treatment and therefore also significantly decreases hospital care and workload of healthcare staff every year. However, since the CAR-T cells for cancer showed exceptionally good results and often cure the disease, it is also expected that the price for !MPACT to treat AAV should be lower than the price for CAR-T cell therapy (on average 373.000 euros). Therefore, we expect the price a pharmaceutical company could ask for !MPACT should be less than 373.000 euros but significantly more than the current 40.000 euros for treatment and is therefore estimated at 275.000 euros.

By means of the price a pharmaceutical could charge when !MPACT is developed, the revenue can be calculated for the pharmaceutical company (licensee). Together with the expected costs for the licensee, the profit for the pharmaceutical company could be estimated. The revenue is calculated as:

$$Revenue = Timespan \cdot patients \cdot revenue_{patient}$$

It is found that on average cell therapy development takes 12 years and that intellectual property is viable for 20 years which means profit has to be made in 8 years. As explained the section 4.4 Market analysis the SOM consists of maximal 32.000 patients with AAV in the US and Europe, which comes down to 4000 treatments each year (for 8 years long). Given the price of 275.000 euros for the cell-therapy this gives a revenue as follows for the licensee:

$$Revenue = years \cdot cases \cdot euros$$

$$Revenue = 8 \cdot 4000 \cdot 275.000 = 8.8 \; billion \; euros \; in \; 8 \; years.$$

The costs for the licensee to further develop, produce and market !MPACT are calculated by the following formula given that the R&D phase until phase IIa is already successfully completed by iGEM TU Eindhoven:

$$Costs = costs \; of \; clinical \; studies \; phase \; IIb \; and \; phase \; III + production \; costs + EMA \; approval \; costs + marketing \; costs.$$

It is found that clinical studies cost for IIb and III are respectively around 98 million and 529 million euros on average, assuming again that only 1 out of the 10 clinical studies succeed.

[91] This adds up to 627 million euros that pharmaceutical companies have to spend to further develop !MPACT. Based on conversations with CiMaas and Johnson & Johnson the production costs for a cell therapy are on average 80.000 euros per treatment which adds up to a total amount of 1.28 – 2.56 billion euros for treating all possible patients in Europe and the US by the licensee. Approval costs and marketing costs are together around 25 million euros and also 50 million euros unforeseen costs are taken into account. This gives a total cost structure for the licensee of:

$$Costs = 627\ million + 2.56\ billion + 25\ million + 50\ million = 3.19\ billion\ euros$$

This would give a profit for the licensee of 8.8 billion euros – 3.19 billion euros = 5.61 billion euros spread over 8 years.

Therefore the maximal royalty payment iGEM TU Eindhoven receives over the 15 year license contract period is 9.6% of 5.61 billion euros which comes down to 539 million euros in total and 39.5 million euros a year calculated based on the income approach.

6.2 | Investments

Three investments are required to validate and test the proof of concept for !MPACT.

First, two new labs are necessary to continue the R&D for !MPACT. Based on discussions with Ambagon Therapeutics, we expect we need a ML-1 laboratory of 50 m^2 and a 50 m^2 ML-2 laboratory, taking into account we have a team that consists of 9 members of which 4-5 members will be full-time working in the lab. In the Netherlands, the costs of building these lab that fulfill all safety criteria and meet the GMO regulations, are expected around 15.000 euros per laboratory based on expertise of Ambagon. In this estimation, ventilation, infrastructure, lab benches and safety measures are taken into account. The depreciation time is estimated at 10 years minimally.

Secondly, basic lab equipment is required. For a laboratory with a size of 50 m^2 , an investment of 100.000 euros is expected to buy all necessary lab equipment. In this calculation, equipment taken into account include two biosafety cabinets, centrifuges, pipette sets, glassware, refrigerators, freezers, oven, incubator, sondicator, gel electrophoresis equipment, bunsen burners, weighing machine, nanodrop, microscope, fluorescence spectrophotometer, rotators, etc. As explained, high-end laboratory equipment will not be purchased and the associated services will be outsourced.

Lastly, the furnishing the office is expected to cost 1500 euros per office based on discussions with Ambagon Therapeutics. In total for two offices, this adds up to 3000 euros.

6.3 | Finance

In order to finance the investments mentioned above and to survive the so-called “valley of death”, a significant investment is required.

Equity is the best approach to finance the venture because of three main reasons. In the first place, we do not have the collateral, nor credit ratings to qualify for a significant loan. Secondly, we already have some liquidity problems, due to the 5 year period in which we do not make any revenue. The interest that would have to be paid in return for the loan will make the liquidity problems even worse . Lastly, through using equity instead of debt, we can involve a venture capitalist in our start-up, who has a lot of entrepreneurial knowledge and a large network, which can enhance the growth of our venture.

A second option for finance are business angels. Business angels are private individuals usually with business experience, who directly invests assets in a new and growing venture. Typically a business angel gets a leading role in the company and thus interferes with the daily decision-making of the firm. Next to the assets a business angel brings in, he/she also brings in knowledge, skills, experience and a large network which could benefit the growth of the firm.

The expected flow of financial income in the first year is through a research grand. We learned from experts at our university that research grands are often around 1 million euros to stimulate fundamental research. A research grand is therefore ideal to cover the expenses of the first year in which iGEM TU Eindhoven tests and further develops the proof of concept of !MPACT. Secondly, we also aim to include a business angel half-way of the first year, who typically also bring in a maximum of 1 million euros. A business angel could share his experience and network to attract the interest of venture capitalists. To start with pre-clinical trials in year 2, a huge investment of 70 million euros by venture capitalists is required to do 2-years of pre-clinical trials. In year 4 an additional 155 million euros by venture capitalists is required to perform 2 years of clinical trials (phase I and phase IIa).

6.4 | Cash flow

Based on the previous topics of the financial statement the cash flow can be calculated. This cash flow demonstrates that there is always sufficient liquidity to not go bankrupt, since available liquidity (treasury position) is always larger than 0. Additionally, there are signals that we will most likely not face liquidity problems in the future. For example, the Current Liabilities Coverage Ratio is almost always above 1, which demonstrates that we can easily pay off our current liabilities in a certain period with the inflowing cash during that period (Carlson, 2021).

This healthy liquidity status is validated by two observations:

1. The fact that we choose equity over debt, which leads to no current interest debt.
2. The large equity cash inflow early in the venture's life cycle, which assures sufficient cash to overcome the period in which there is no positive cash flow arising from net profit.

The only period in which we could potentially face any liquidity problem is quarter 12, in which the Current Liabilities Coverage Ratio is at the lowest point throughout the venture's life cycle, with a value of 0.99. Yet, this number is almost at the standard of 1, meaning we do not see any immediate threats.

The cash flow and treasury position throughout the coming 5 years are visualized by a cash flow chart Figure 6.1

6.5 | Feasibility

Based on all of the aforementioned statistics and ratios, it can be concluded that iGEM TU Eindhoven will have a bright financial future. There will be a near-five-year period in which there will be losses, but this is common for life science start-ups. Additionally, there are no significant liquidity issues, and the firm will eventually make a net profit of in 5 years. These facts, combined with the fact that investors can decide to make a performance-based deal with lower investment risks, makes it very attractive for venture capitalists to aid this new venture as well.

Figure 6.1: Cash flow plan with treasury position for the next 5 years

7 | Growth and exit

The growth potential of !MPACT is described in this section. This includes building the growth potential, considering new or different markets and possibly new product and service development. This all because Burns et al. showed that growth comes from market penetration, product/service development, market development and/or unrelated diversification. [92] The goal of this analysis is eventually to increase sales by penetrating the healthcare market.

7.1 | Growth potential

Growth can be enabled through different strategies. These are extensively described by Burns et al and visualized in Figure 7.1.

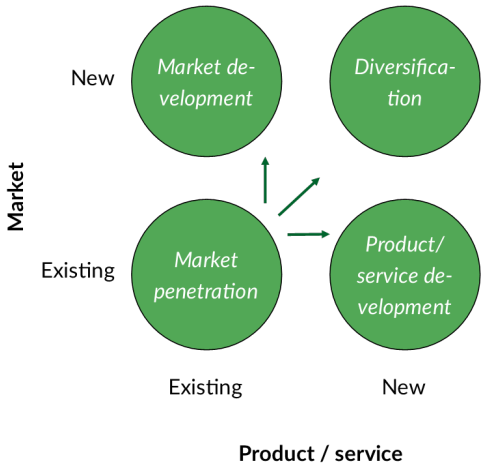

Figure 7.1: Growth potential based on the market and product/service potential. Adjusted from Burns et al. [92]

Here the first and foremost growth potential of iGEM TU Eindhoven is by our entering and thus existing product/service and the existing market development (left top corner in Figure 7.1). Our potential customers (pharmaceutical companies) and partner manufacturing companies (Thermo fisher Scientific Inc) are major players in the market. At this moment, Thermo Fisher Scientific Inc is part of the five major players in the synthetic biology market. [58] When intensifying this partnership and exchanging knowledge and expertise increases the credibility and reputation of iGEM TU Eindhoven. This enables a stronger position in the market. Moreover, the iGEM competition to which the iGEM TU Eindhoven team already participates is internationally well known and strengthens our reputation within the synthetic biology market.

Besides, the close ties our team has to the Eindhoven University of Technology gives us opportunities to participate in several networking events such as for example career development days, open days, attending congresses, attending lectures, and the TU/e contest. This would lead to more brand awareness, credibility, and possibly new customers and investors. Collaboration with pharmaceutical companies such as Novartis, Organon, UMC Maastricht, and Thermofisher helps with the credibility of our project and allows access to more resources (clinical and animal trials and manufacturing equipment/capacity). Other events include discussions with the end users of the therapy (foundation for vasculitis patients) and clinical experts on vasculitis. When incorporating the input of these crucial stakeholders in the project and therapy design the tendency of pharmaceutical companies to become a customer of iGEM will increase.

Besides, the adjustment and expansion of the therapy to other markets is another growth potential. New market segments such as vasculitis patients that are positive for other antibodies, for instance, myeloperoxidase (MPSO) are a mere example [7]. These growth opportunities that lie within the product are key competencies for our team. Furthermore, the treatment can be adjusted to even other autoimmune diseases by adjusting the modular parts of the system. This enables our adjusted product to enter other

autoimmune disease markets. There are more than 80 different autoimmune diseases currently known where the global autoimmune disease therapeutic market.

Lastly, the current focus is on the market in America and Europe but expansion to other geographical areas is part of the growth potential of our team. Especially in companies based and active in Japan could be of interest due to the large market size of pharmaceuticals there.

7.2 | Exit strategy

The definition of entrepreneurial exit is extensively defined by DeTienne et al. through "Entrepreneurial exit is a process, by which the founders of privately held firms leave the firm they helped to create thereby removing themselves, in varying degrees, from the primary ownership and decision-making structure of the firm." [DeTienne, 2010??] The varying degrees and outcomes can either be due to failures or successes. The possible successful outcomes of the founders of !MPACT is discussed in this section.

The phase of the company (1 conception gestation, 2 infancy, 3 adolescence, 4 maturities) upon the exit depends highly on the exit strategy. The exit has as goal to ensure the growth of the business whereas the founders of the company are most essential in establishing the basic structure for !MPACT. This is why the founders will likely exit the company starting from the adolescence phase. The motives for the exit are described in Table 7.1.

The entrepreneurial exit can have positive and negative changes for the company. Besides, the exit may change the competitive balance of the industry and enhance regional economic development. Due to the given reasons, a valid and well-considered exit strategy is needed.

The exit options of the founders of !MPACT are considered a sell-out or initial public offering (IPO). Both options have a basis exit strategy that focuses on increasing the role of stakeholders and pressure to develop the exit strategy, see Table 7.1. These stakeholders are considered clinicians and pharmaceutical partners with a license of !MPACT. Also, pharmaceutical partners that are considered advisors or investors of the company are considered here. Besides, the influence and control of the advisory board that consists of professionals concerning the science should be increased. This board ensures the quality of the product and the company after the founders have exited the company.

Also, this strategy focuses on psychological ownership which should be transferred to the new management team. For this, the physiological ownership should to some extent already be there. This ensures that there is a structure in place in which the health of the company matters to a number of individuals. Besides, these should also be the individuals that can take action when the company is expected to take an unhealthy tour.

Table 7.1: Exit strategy of the founders of !MPACT in the adolescence phase of the company

Exit motives	Pressure of stakeholders Professional management team
Exit strategy	Increasing role of stakeholders and pressure to develop exit strategy Psychological ownership
Exit options	Sell-out IPO (initial public offering)

8 | Business model

The business model is ”the heuristic logic that connects technical potential with the realization of economic value”, as described by Chesbrough et al. [93] In this section the business model of !MPACT is explained. All components of the business model are summarized in Figure 8.1.

8.1 | Key partners

Our customers and key partners are large pharmaceutical companies. These companies have the means to produce and launch new medicine and therapies on the market. Their customers are amongst others, hospitals that treat autoimmune diseases. The clinicians in the hospitals are the users of !MPACT. Finally the last key partners are patients with an autoimmune disease for which the treatment is designed. We looked at the value of !MPACT for these patients and hospitals, because this is relevant for pharmaceutical companies when they buy therapies (according to Mark van Hattum, Health care relations at Novartis pharmaceutical company).

8.2 | Key activities

Our key activity is Research & development, because labwork is most important for the development and quality control of !MPACT. When looking at the entire timeline of developing a new treatment Figure 3.3 in section 3, we are completing the clinical research industry of !MPACT untill phase IIa of the drug development timeline. Thus, the entire ‘Research & Discovery’ step and a big part of the Non-Clinical Development step. From this moment, we have patented our proof of concept and will license the patent out to large pharmaceutical companies who will carry out the following steps in the value chain.

Research & Development consists of ‘Pre-discovery’ and determining if there is an ‘unmet need’. ‘Unmet need’ refers to a disease for which either no suitable medicine is available, or medicine exists, but this causes unacceptable side effects in some patients that prevent them from taking it. This is the case for many autoimmune diseases and also for the one we are starting with, AAV. The goal of this first part is to gain insights into the autoimmune disease AAV. Non-Clinical Development consists of (1) target selection, (2) lead generation, (3) lead optimization, and (4) non-clinical safety tests. When we arrive at step 4, which includes animal tests, pharmaceutical companies will take over the development.

The first part of Non-Clinical Development, target selection, includes selecting the best molecule to target. Diseases occur when normal body processes are altered or do not function properly. When developing a treatment, it is important to understand in great detail (at the level of the cells) what went wrong. This means that the abnormal processes can then be targeted and corrected. Selecting the best molecule to target is thus essential. In our case, the targets are autoantibodies (ANCA) that are found at elevated levels and attack healthy cells.

Lead generation consists of finding a molecule that will interact with the target. In our case, a large molecule (protein) is found that interacts with the target: the GEMS system. Once the leads have been generated or found (in our case the GEMS system), the next step in the process can be taken.

Lead optimization. This includes modification of the molecule to improve its effectiveness. The key activity here is to adjust the GEM system in such a way that it can couple with ANCA. These modified molecules are tested to determine which structure has the best efficacy and is better tolerated (safety). The key activity here is to test whether this modification enables a response within the cell which results in local expression of IL-10, and to test whether the local expression of IL-10 suppresses the autoimmune response of AAV. The molecules with better efficacy and safety can then go on to be further tested. Including creating a mathematical model to simulate our mechanism. In addition, with this model, we can select variables and constants to calculate the quantities needed to for example produce IL-10. Besides that, we can use our model to validate lab results.

Around this stage, the scientific and technical information about the candidate substance (e.g., its

molecular structure and effects) is usually patented, to protect the substances as intellectual property. Another key activity is thus to complete a patent application for the structure/function of our new therapy. This prevents another person or business from copying our formula and selling it without consent. This patent process for medical treatments can be very complex and will require us to hire an attorney to handle it properly.

In the entire process of developing a new treatment, the costs are enormous. Therefore activities concerning sponsorships and funding are needed. To get these sponsorships and funding, activities such as networking, presenting and organizing events are needed. It is important to establish grants (public money) from the Dutch government at an early stage. By showing the value our therapy can have for society (faster treatment - lower workload - cost reduction due to less hospitalization) and by showing supporting research that demonstrates the therapy's efficacy. It is also a plus for pharmaceutical companies if the formula is in at least the initial phases of an FDA approval track. A key activity here is getting the government to cooperate with legislation and regulations. Starting with the Netherlands, but also already looking at Europe. Both the supporting research and the start of the FDA approval track add to our credibility as well as increase the overall value of our therapy. When a therapy has shown promise as a potential medical treatment and is moving forward toward regulatory approval, that's generally when a pharmaceutical company will choose to move in with an offer to buy out the program.

8.3 | Key resources

The most important assets needed for our proof of concept consist of lab materials needed to fully test our proof of concept. iGEM is allowed to make use of the university's facilities like the Biolab. Here other key resources will be used and tested such as the auto-antibodies, cells and other material needed for our wet-lab experiments.

Besides that, essential is the office spaces, furniture, hardware software, analysis tools and meeting rooms iGEM has access to. Furthermore, the TU/e as well as ICMS sponsors us with cash to carry out the project and wet-lab experiments. Previous iGEM teams have preserved a certain amount of cash next to promotion material, marketing material, lab material and working clothes.

Knowledge and advice from our advisors, Tom de Greef, Maarten Merkx, and Luc Brusnveld, (professors at the TU/e department of biomedical engineering) are essential and unique where they give feedback and advice related to the science used in our project. Lastly, experts/advisors on patents, such as intellectual properties are essential to our team where we require their knowledge to be able to patent our innovative idea where the skills on patents is currently limited within the team.

8.4 | Key proposition

!MPACT a Modular & Personalized Autoimmune Cell Therapy.

We aim to develop a personalized therapeutic for the treatment of autoimmune diseases, starting with the autoimmune disease ANCA-associated vasculitis (AAV). AAV is characterized by inflammatory cell infiltration causing necrosis of blood vessels. When necrosis of vessels occurs the organs behind them start functioning less or even die. AAV affects about one in 8000 people and has a 5-year survival rate of 60-97% (depending on the type of AAV). Currently, there is no treatment but the condition can be treated with medicines to lengthen the lives of patients. However, these treatments fully downregulate the immune system.

Our cell-based therapy improves upon that, as it is a more personalized treatment. In our therapeutic, the production of IL-10 (an anti-inflammatory molecule that suppresses the autoimmune response of AAV) stops when no disease-associated molecules (called ANCA) are present anymore. Meaning that our therapy is only active when needed and thus temporary.

This also works the other way around. In the current treatment that exists for AAV, there is a chance of 50% of the disease flaring up, meaning the treatment has to start over and the patient has to be

hospitalized again. In our therapy, the cells already injected [1] into the patient's body immediately start producing IL-10 when the ANCA's are present again. Meaning the patient does not have to be hospitalized ánd the disease is treated at a much earlier stage because our therapeutic immediately starts treating the disease before the patient even starts noticing symptoms. Moreover, our therapy is able to treat the disease locally. The produced IL-10 will namely be directed towards the site of inflammation. This enables direct targeting and removal of the antibodies. For example, you direct the cell to go to the lymph nodes and very specific target and remove the ANCA's there.

Concluding, our therapy enables sooner detection and registration of the disease and as a result, the disease can be intervened early on. Our therapeutic thus functions on demand to treat the disease. Besides, eventual relapses of the disease can be intervened immediately and the treatment is local.

8.5 | Customer segment

The global autoimmune disease therapeutic market is estimated to grow from $53.2 billion in 2019 to $90.7 billion by 2024 and has a compound annual growth rate (CAGR) of 11.2 over this period. We aim at a single-sided market. For a part of the discovery phase (animal and clinical trials) and the entire development phase, large pharmaceutical companies are needed. And large pharmaceutical companies need proof of concepts like ours to stay ahead of the market.

Our primary customers are thus large pharmaceutical companies. We patent our proof of concept therapy and license the patent out to pharmaceutical companies that can and want to develop it further and who also want to do this in collaboration with us.

Buyers of our product are thus large pharmaceutical companies. They are needed to go from the discovery phase, in which we will be active, to the development phase. When the therapy is fully and successfully developed, pharmaceutical companies will sell it to hospitals that treat autoimmune diseases. Health professionals will then once a year inject the cell-based therapy into patients with an autoimmune disease. The users of our product are thus in the end the hospitals that treat patients with autoimmune diseases and the patients themselves.

The pharmaceutical industry is developing rapidly and for pharmaceutical companies, it is crucial to stay ahead of these developments. Therefore, pharmaceutical companies have a mission to discover new ways to improve and extend people's lives (according to Mark van Hattum, Health care relations at Novartis pharmaceutical company). Our cell-based therapy is based on the Generalized Extracellular Molecule Sensor (GEMS) system. This system is recently discovered and our therapy builds further on this. Meaning our innovative therapy could help pharmaceutical companies to stay ahead of competitors and developments in the market.

8.6 | Customer relationship

The interaction with the pharmaceutical companies will be through dedicated personal assistance; the pharmacist will have one-on-one contact with a contact person from within our company. Important here is to establish a long-term relationship, as we aim to collaborate on the further development of the treatment.

8.7 | Channels

The channels that could be used to reach out to possible pharmaceutical customers would be by directly approaching pharmaceutical companies that are specialized in the development and scale-up of cell-based treatments.

We create awareness of our therapy at pharmaceutical companies through paper publications of our therapy, and exposure through TU/e and the iGEM contest. We create interest in our therapy through

symposia and events. One of such event is the Mini-Jamboree which we will be organizing ourselves in October. And desire is created by involvement in research trials.

8.8 | Cost structure

With this therapy, we aim for a value-driven cost structure. The focus is thus on creating more value for the therapy rather than producing it at the lowest feasible cost. Similar therapies such as Car-T cell therapy follow a similar strategy.

Fixed costs that are included in the development of our proof of concept therapy applicated to AAV are the costs of product materials, research and development, rental of laboratory facilities, taxes and laboratory technicians. The total research and development costs are expected to be $17.500,00. Relatively low, whereas materials and machinery that can be used from the TU/e are sponsored and therefore not included. Costs will also be made for patent applications which are estimated at $11.500,00. Furthermore, marketing such as advertisement and promotional costs are budgeted at $13.025,00. All general and variable costs such as events and conferences are estimated to be $17.000,00. All team members are voluntarily working on iGEM TU Eindhoven therefore no employee or labour costs are included in our cost structure. Besides that, the office space is sponsored by the TU/e.

8.8.1 | Cost structure pharmaceutical companies

Because this therapy has yet to be approved for use in a clinical environment, there are several expenditures associated with the improvement and optimization before it is placed on the market. The therapy has to be approved by the Food and Drug Administration (FDA) and/or European Medicines Agency (EMA). This includes a range of expenditures since the therapy must go through four clinical trial phases before being considered by either the FDA or the EMA. However, because our proof of concept therapy will be sold to pharmaceutical companies before the clinical trials, such costs are not applicable to our business plan. However, to our investors, such costs are of interest and therefore a rough estimation is given. Expectations are that the clinical studies will take approximately 6-7 years and cost between $50 and $100 million. Different phases of these clinical studies are roughly, phase 1 (a few months), phase 2 (months till 2 years), phase 3 (1 till 4 years), FDA approval followed by phase 4. The cost structure is attached.

8.9 | Revenue streams

Our main revenue stream will be by patenting the proof of concept therapy, and licensing the patent out to pharmaceutical companies, so they can further develop and produce the cell-based therapy and eventually help distribute them to more health care practitioners. Our company will thus focus on creating proof of concepts, starting with the application on AAV, but later on other autoimmune diseases. For each autoimmune disease that we make our innovative idea applicable to, we will patent the system and license it. This will increase the value of our company, and is our main revenue stream.

Looking at similar therapies, like the CAR-T therapy, we expect the pharmaceutical company using our therapy to eventually get immense profit. They have large costs for the clinical trials, however, the pricing of the product can, and will be very high. Just like for CAR-T therapies, we expect the pharmaceuticals to get a total profit of 0.7 billion 5 years after entering the market. We ask about 0.5% of this price. Therefore the pricing of our proof of concept therapy will come down to 3 million euros. The revenue stream is visualized and attached.

Business Model Canvas

!MPACT a Cell-based therapy for the treatment of autoimmune disease(s)

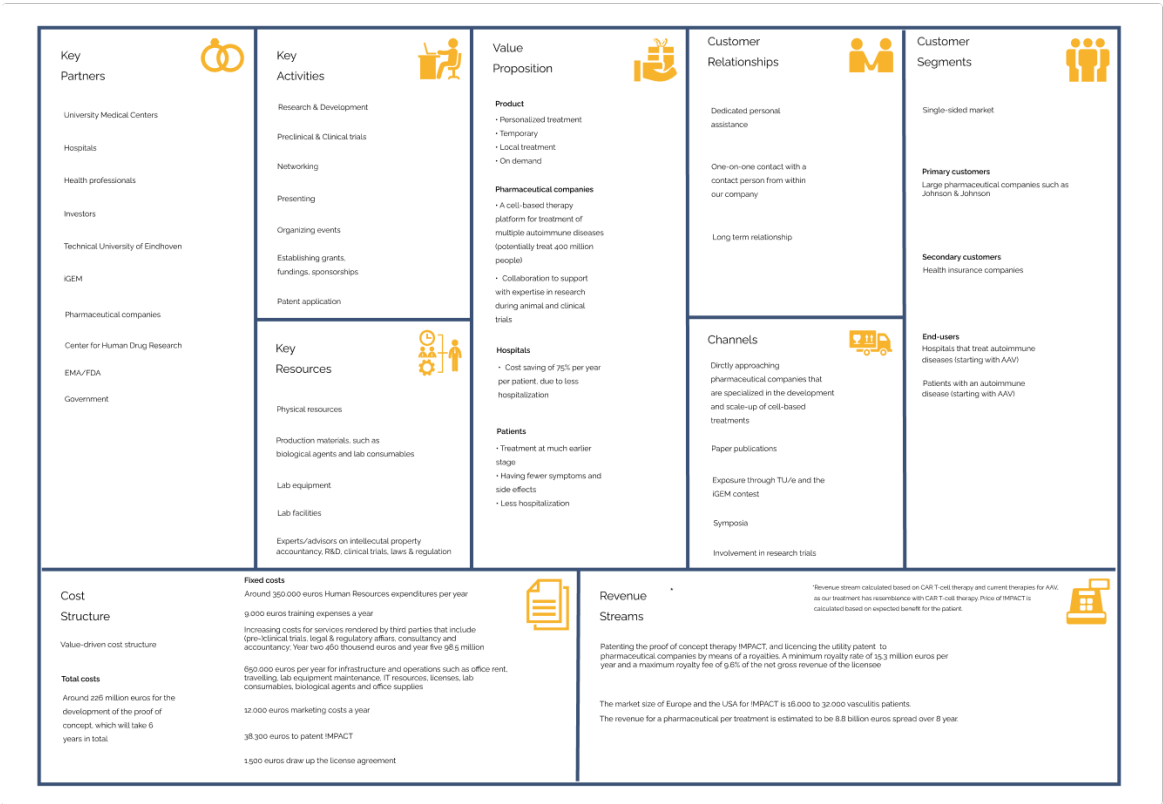

Figure 8.1: Business model canvas of !MPACT

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