KWF

Cell and Gene Therapy Towards Oncology Clinical Practice

Opportunities and Hurdles for Academic Innovation

Colophon
This report is a publication of KWF Kankerbestrijding (Dutch Cancer Society).

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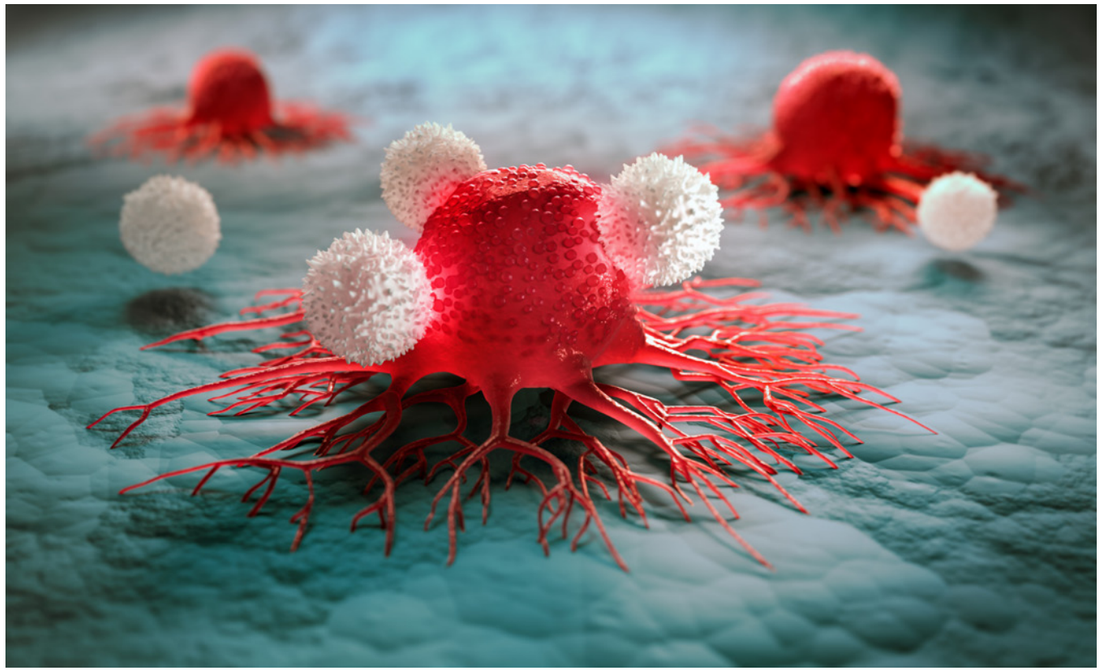


English summary

Speeding up the development of cell and gene therapies towards clinical practice by improving the innovation environment

Large patient groups need new treatment options

Despite extensive scientific efforts, major breakthroughs in traditional medicinal product development have been scarce over the last decades. The recent development of the immunotherapeutic checkpoint inhibitors has led to major improvement in treatment options for certain cancers. Yet too many patients do not respond well to new treatment options or remain condemned to medicinal products with dissatisfactory efficacy or severe side effects.

Cell and gene therapies offer new leads for improved treatment

Cell and gene therapies (CGT) is a new group of medicinal products that offer treatment for patients with lacking or dissatisfactory treatment options. Globally, the scientific community is investigating CGT as treatment for hematological and solid tumors. A few CGT are available for the treatment of hematologic tumors and show remarkable clinical efficacy over a prolonged time. New technologies are emerging, such as CRISPR-Cas for gene editing, which can speed up developments in the CGT field.

Few CGT reach clinical practice

With the exception of two CAR-T cell products, new CGTs for cancer treatment are not reaching clinical practice in the Netherlands yet. Developmental trajectories are not only hampered by scientific and technological challenges, but also by a suboptimal innovation system in both the Netherlands and Europe. Consequently, access to new CGT for cancer patients is too limited.

Scientific and technological uncertainties due to new technology

CGT is a new field of medicinal product development, leading to many scientific uncertainties related to quality, safety and efficacy. A range of challenges exist for manufacturing and quality. For example, cell-based source material originates predominantly from patients and shows interpatient variability, which leads to a high risk of batch inconsistencies. Scientific uncertainties and unknown long-term effects arise from their novel, complex mechanisms of action of viable source material, which can be genetically modified to target tumor specific characteristics. These characteristics do not match well with existing regulatory pathways for marketing authorization of medicinal products, which aim at consistent production of molecules on a large scale and robust evidence-based medicine.

Innovation system in academic medical centers is suboptimal

A large portion of GCT development currently takes places in academic medical centers, without much involvement of private companies. Medical centers typically are focused on specific CGT and cancer types, with the corresponding scientific and medical expertise. Due to this focus, scientific and technological expertise, regulatory knowledge and capacity are fragmented among medical centers. Guidelines and other regulatory standardization are lacking to a large extent due to novelty of the field and limited regulatory experience with CGT. In addition, the primary aim of academic research is to improve clinical outcomes, and less on further product development. Furthermore, the production capacity of medical centers is very limited compared to private companies, and regulatory knowledge to build a satisfactory dossier for marketing authorization is lacking. Lastly, implementation of new CGT in clinical practice is challenging.

Recommendations to facilitate further developments

Coordination and support during development trajectories by a central, coordinating body that:

- links academics, medical groups and patient representatives in the Netherlands and abroad and coordinates during and after clinical trials.
- links academic developers with private companies to continue development of commercially viable CGT.
- provides support for valorization, such as filing for Intellectual Property (IP) rights, negotiation of contracts for consortia and other public collaborations, public-private collaborations, licensing, and support to start spin-offs.

- provides support for adhering to regulatory criteria for marketing authorization and criteria for reimbursement (Health Technology Assessment – HTA).

Regulatory clarity and fit for purpose requirements for development and reimbursement by:
- more interaction among academics and regulatory bodies for dissemination of knowledge and training purposes, compliance with requirements from an early stage of development, and improvement of procedures and requirements by standardization.
- more interaction among regulatory bodies for integration and consideration of different regulatory and HTA requirements throughout dossier development.
- drafting regulatory requirements to enable implementation of non-commercially viable, academic CGT in clinical practice.

Systematic knowledge dissemination and collective production capacity by means of a platform that:
- enables a nationwide knowledge base for Good Manufacturing Practice (GMP) manufacturing, manufacturing costs and regulatory requirements.
- facilitates collaboration among manufacturing facilities to scale up manufacturing for large clinical trials or clinical practice.

Financial support for:
- CGT product development according to GMP in public manufacturing facilities, and the necessary infrastructure.
- product optimization and repurposing products in early clinical trials, possibly for new cancer types, considering added clinical value.
- academic phase II-III multicenter trials for further development of non-commercially viable CGT. Collaboration between funding bodies is needed due to high costs.
- a central, coordinating body with support for regulatory and HTA requirements, and valorization during development.

KWF commits to the acceleration and stimulation of developments in the CGT field. We aim to act now and contribute to this goal by:
- financial support to enhance infrastructure for CGT manufacturing according to GMP.
- organizing a congress to enhance public collaboration and interaction and knowledge dissemination with organization for valorization and regulatory bodies.
- lobbying for the development of clear, fit for purpose regulatory and HTA requirements, and more interaction among academics and regulatory bodies.

Nederlandse samenvatting

Een optimaal innovatieklimaat voor versnelling van cel- en gentherapie naar de klinische praktijk

Grote groepen kankerpatiënten hebben nieuwe behandelopties nodig

Ondanks intensief wetenschappelijk onderzoek zijn grote doorbraken met traditionele kankermedicijnen de afgelopen decennia beperkt geweest. Recente ontwikkelingen op het gebied van immunotherapie, in het bijzonder de zogeheten checkpointremmers, hebben de behandelopties aanzienlijk verbeterd voor bepaalde kankersoorten. Desondanks zijn er nog steeds teveel kankerpatiënten die niet goed reageren op beschikbare behandeling of aangewezen zijn op behandelingen die weinig effectief zijn en/of nadelig effecten hebben.

Cel- en gentherapieën bieden aanknopingspunten voor nieuwe behandelingen

Cel- en gentherapie (CGT) is een nieuwe groep geneesmiddelen die kansen biedt voor patiënten met weinig of ontoereikende behandelopties. Wereldwijd vindt veel onderzoek plaats naar CGT voor hematologische en solide tumoren. Er zijn al enkele CGT die hematologische tumoren effectief en langdurig bestrijden, en die ook tot de markt zijn toegelaten. Ook zijn nieuwe technologieën in opkomst die de ontwikkeling van CGT kunnen versnellen, zoals CRISPR-Cas voor gene editing.

Nieuwe therapieën bereiken de praktijk nog te weinig

Met uitzondering van twee CAR-T-therapieën bereiken weinig nieuwe CGT de klinische praktijk. Wetenschappelijke en technische knelpunten, maar ook een suboptimaal innovatieklimaat in Europa en Nederland, leiden tot stagnerende ontwikkelingstrajecten. De toegankelijkheid van CGT voor kankerpatiënten blijft hierdoor nog beperkt.

Wetenschappelijke en technische onzekerheden vanwege nieuwe technologie

CGT is een nieuw veld van geneesmiddelontwikkeling. Daardoor zijn er nog veel wetenschappelijke onzekerheden over kwaliteit, veiligheid en effectiviteit. Er zijn diverse uitdagingen voor productie en kwaliteit. Cellulair startmateriaal bijvoorbeeld, is voornamelijk van de patiënt afkomstig en verschilt van persoon tot persoon, waardoor er een grote kans is op inconsistenties tussen batches die per patiënt worden geproduceerd. Daarnaast is behandeling met levende cellen, met of zonder genetische manipulatie, gebaseerd op complexe werkingsmechanismes en tumorspecifieke kenmerken die gepaard gaan met wetenschappelijke onzekerheid en onbekende langetermijneffecten. Dit past niet goed in traditionele wet- en regelgeving voor registratie van geneesmiddelen, want die is gericht op consistente productie van moleculen op grote schaal en robuust bewijs van veiligheid en effectiviteit.

Innovatieklimaat in universitaire medische centra suboptimaal

Op dit moment vindt een groot deel van de ontwikkeling plaats in medische centra, (nog) zonder veel betrokkenheid van private partijen. Elk universitair medisch centrum heeft een focus op specifieke CGT en kankersoorten, met bijbehorende wetenschappelijke en klinische expertise. Door deze specialisatie zijn wetenschappelijke en technische expertise, maar ook regulatoire kennis en middelen te veel gefragmenteerd. Richtlijnen en andere vormen van regulatoire standaardisatie schieten nog tekort vanwege de nieuwheid en beperkte ervaring met CGT. Ook zijn universitaire medische centra vooral gericht op bewijs van effectiviteit, in mindere mate op productontwikkeling die daarop zou kunnen volgen. De academische productiecapaciteit is niet vergelijkbaar met die van de industrie, en kennis over regelgeving en het opbouwen van een dossier voor registratie is vaak ontoereikend. Daarnaast is implementatie in de klinische praktijk lastig.

Aanbevelingen voor meer doorontwikkeling

Verbinding en ondersteuning gedurende ontwikkelingstrajecten door een centrale, coördinerende partij middels:

- verbinding tussen academici, beroepsgroepen en patiëntvertegenwoordigers in binnen- en buitenland voor coördinatie tijdens en na klinische trials.
- verbinding tussen academici en private partijen voor doorontwikkeling van commercieel interessante producten.
- ondersteuning voor valorisatie, zoals het vastleggen van

Intellectual Property (IP)-rechten en contractuele afspraken voor consortia en andere publieke samenwerkingsverbanden, en ook bij het oprichten van spin-offs, publiek-private samenwerkingen en licentiëring.
- ondersteuning voor het voldoen aan regulatoire vereisten voor markttoelating en aan vereisten voor vergoeding (Health Technology Assessment - HTA).

Heldere, passende regelgeving en vergoedingsstructuren door:
- meer interactie tussen academici en overheidsinstanties voor kennisdeling en training, inachtneming van vereisten vanaf een vroeg stadium, plus verbetering van procedures en vereisten door standaardisatie.
- meer interactie tussen overheidsinstanties voor de inachtneming van verschillende regulatoire en HTA-vereisten tijdens het ontwikkelen van een productdossier.
- het opstellen van regulatoire kaders voor het beschikbaar maken van niet-commerciële, academische CGT in de klinische praktijk.

Structurele publieke kennisdeling en bundeling van productiecapaciteit middels een platform dat:
- een nationale kennisbasis vormt voor Good Manufacturing Practice (GMP)-productie, productie kosten en regulatoire vereisten.
- samenwerking tussen productiefaciliteiten vergemakkelijkt, en daarmee de voor opschaling van productie ten behoeve van grote klinische studies of de klinische praktijk.

Financiële middelen ter ondersteuning van:
- CGT-productontwikkeling conform GMP in publieke productiefaciliteiten, plus de benodigde infrastructuur.
- productoptimalisatie en doorontwikkeling in exploratief onderzoek, mogelijk voor nieuwe kankersoorten met aandacht voor de potentiële klinische meerwaarde.
- academische fase II-III-multicentertrials voor de doorontwikkeling van niet-commercieel interessante CGT. Vanwege de hoge kosten is samenwerking tussen publieke financiers nodig.
- een centrale, verbindende partij met services voor regelgeving en valorisatie tijdens ontwikkeling.

Wij als KWF committeren ons aan de verdere versnelling en versterking van de ontwikkelingen op het gebied van CGT. We dragen hier de komende tijd op drie concrete manieren aan bij:
- we ondersteunen de infrastructuur voor CGT-ontwikkeling conform GMP met financiering.
- we organiseren een congres ter bevordering van publieke samenwerking en van interactie en kennisdeling met valorisatie-organisaties en overheidsinstanties.
- we zetten ons in voor de ontwikkeling van heldere, passende regelgeving en vergoedingsstructuren door beleidsbeïnvloeding, en meer interactie tussen academici en overheidsinstanties.

Public summary

Cell and gene therapy is a promising new group of medicinal products for treating cancer. Despite their great promise, many cell and gene therapies get stuck in development and never reach the patient. In the report "Cell and Gene Therapy Towards Oncology Clinical Practice," KWF (Dutch Cancer Society) explains the underlying hurdles and the possibilities of overcoming these.

Living cells

Cell therapy is treatment with living body cells. Typically these are cells of the patient's own immune system. These immune cells are removed from the blood and undergo molecular processing so that they can better recognize and destroy cancer cells. When DNA of these cells is modified, these therapies are referred to as gene therapy.

Promising treatment

Cell and gene therapy is garnering a great amount of interest worldwide and is being extensively studied. The results are generally promising, with a perspective of effective and long-term disease control. Cell and gene therapy can make a crucial difference for cancer patients with limited treatment options in particular.

Patients should benefit more

KWF finds it unacceptable that few cell and gene therapies reach patients. In order to improve development and availability, KWF took stock of the underlying hurdles in interviews with experts in the field of cell and gene therapy and formulated concrete recommendations. The ultimate goal is to have as many cancer patients as possible benefit from cell and gene therapy.

Hurdles

- Scientific and technical uncertainties

Cell and gene therapy is a complex treatment with a patient-specific mechanism of action and a challenging production process. This gives rise to uncertainties regarding 1) research methods (few representative animal models, small patient groups) 2) safety and efficacy (results amongst patients are difficult to compare) and 3) production (consistent, large-scale production of identical medicinal products is rarely possible).

- Scale-up and further development is faltering

A large portion of the development of cell and gene therapy takes place in medical centers. This usually involves small-scale production for research amongst their own patients. Capacity and scale-up of production and large multicenter trials is insufficient. The last step to bringing a registered product on the market is rarely taken. This is associated with strict quality requirements and high costs, which academic centers are often unable or unwilling to comply with.

- Insufficient knowledge sharing and collaboration

Each academic medical center often focuses on specific cell therapies and cancer types. This leads to fragmentation and inefficient use of knowledge, expertise and financial and other resources. Especially knowledge sharing about the technical and quality aspects of product development is falling short. Commercial interests (patent rights, profit opportunities) often make collaboration with private parties difficult.

- Uncertainty about laws and regulations

Knowledge about laws and regulations as well as building a product dossier is often inadequate. This hinders the registration and approval procedures. The laws and regulations also don't mesh well with the innovative character of cell and gene therapy. Due to the rapid pace of scientific and technological developments, laws and regulations often lag behind ("regulatory lag"). Requirements for traditional medicinal products do not always translate to cell and gene therapy.

- Insufficient financing

Process and product development is very expensive due to the high costs of certified production facilities and materials. The complex and labor-intensive production process also greatly affects personnel costs. Public financing (e.g. by the government or health funds) is often insufficient.

Recommendations

- Collaboration and support by one central, coordinating party:
  - Collaboration between academics, professional associations

and patient representatives nationally and internationally during and after clinical trials.
  - Collaboration between academics and private parties for further developing commercially viable products.
  - Support with collaboration contracts, setting up spin-offs and establishing property rights such as patents and licenses.
  - Support with compliance with laws and regulations and reimbursement requirements.

- Clear, appropriate regulations and reimbursement structures:
  - More interaction and knowledge sharing between academics and government agencies to enable smoother and faster procedures, including for registration.
  - More interaction between government agencies to better align laws and regulations and reimbursement requirements.
  - New frameworks for laws and regulations to make non-commercial, academic cell and gene therapy available in clinical practice.

- One platform for public knowledge sharing and bundling of production capacity:
  - One national knowledge database for production and registration facilitates scale-up and further development.
  - Collaboration between production facilities decreases the chance of duplication or failure and facilitates scale-up of production.

- Financial support of:
  - Cell and gene therapy development in academic production facilities, including the necessary infrastructure.
  - Product optimization and further development of promising products for other cancer types.
  - Academic clinical trials for further development of non-commercially viable cell and gene therapies. Collaboration between public financiers is necessary due to the high costs.
- One central, connecting party for advice and support with laws and regulations and product development.

The role of KWF

KWF sees various opportunities for itself to accelerate and enhance development of cell and gene therapy. We contribute to this in three specific ways:

- Providing financial and knowledge-related support of infrastructure for the development of cell and gene therapy. See our Infrastructure Initiatives Call 2021-2.
- Promoting public collaboration and knowledge sharing between academics. See our Cell and Gene Therapy in Oncology conference.
- Promoting clear, appropriate regulations and reimbursement structures and more interaction between academics and relevant governmental agencies.

1. Background

Cell and gene therapy

Cell and gene therapy (CGT) is a promising new group of medicinal products for treating cancer. A large part of these therapies consists of administering cells of the patient's immune system. Dendritic cells present antigens of pathogens but also of cancer cells to T cells in order to trigger a targeted immune response. The function of T cells and Natural Killer (NK) cells is to detect and destroy abnormal or damaged cells. These can be virally infected cells but also cancer cells. T cells are activated by the detection of an antigen (adaptive immune system), while NK cells are activated, among other things, by a change of activation and inhibition signals (innate immune system). Cell and gene therapy is achieved by isolating immune cells with a specific anti-tumor function and manipulating them for treatment (cell therapy) and possibly genetically modifying them in order to bring about a specific anti-tumor function (gene therapy).

To date, two gene therapies have been marketing authorized in the European Union as medicinal products for treating B cell malignancies (B cell cancer): Kymriah® and Yescarta®. These are CAR-T cell products (CAR = Chimeric Antigen Receptor), T cells that have been genetically modified to express a synthetic CAR (receptor). The CAR constructs of Kymriah® and Yescarta® were developed so that they can detect cell membrane proteins of B cells so that the T cell kills them. The prognosis for patients with B cell malignancies in whom the cancer recurs after standard treatment (relapse) or who do not respond to standard treatment (refractory) was very poor. The CAR-T cell products have a remarkable clinical efficacy for the treatment of relapsing or refractory B cell malignancies. In the vast majority of patients, treatment with CAR-T cells leads to complete remission and an increased chance of survival after one to two years after a single treatment. There are still more CAR-T cell products in development, especially for hematologic malignancies, but research is now also being conducted with CAR-T cell products for solid tumors.[1,2] One of the big challenges is to find the correct targets so that CAR-T cell therapies do not attack healthy cells.

Other T cell-based therapies for treating cancer are still in various phases of development. In addition to genetic modification of T cells with synthetic CARs, it is also possible to genetically modify the T cell receptor (TCR). TCR-T cell products express synthetic TCR that can detect certain cancer-specific antigens. These antigens are presented as peptides on human leukocyte antigen (HLA) molecules. Detection of the HLA/antigen complex by the TCR, in combination with other signal, results in destruction of the cancer cell. HLA molecules and antigen presentation differ greatly between individuals. In contrast to CARs, which can detect certain cell types by recognizing cell membrane proteins, TCRs can very specifically detect certain cancer cells of one individual or sub-group of patients. In addition, tumor-infiltrating lymphocytes (TILs), T cells that are isolated from the patient's tumor tissue and cultivated in high quantities, are being investigated as another modality for T cell therapy.[3]

Dendritic cells that are manipulated ex vivo in order to present certain cancer-specific antigens to T cells can trigger an immune response for killing cancer cells.4 NK cells can be used as therapy by cultivating them in high quantities through the cytotoxic function for abnormal cells such as cancer cells. NK cells can also be genetically manipulated so that they express a CAR or TCR receptor and can detect antigens.[4,5]

In short, CAR-T cells, TCR-T cells, TILs, dendritic cells, NK cells and genetically modified NK cells have a lot of potential as a new treatment for both hematologic and solid tumors, in particular for patients who have few to no treatment options. New technologies for genetic modification such as CRISPR-Cas are opening doors for the next generations of gene therapies. However, there are still many scientific and technical challenges to allow further development of cell and gene therapy into safe and effective medicinal products with good product quality.

Innovation climate

Worldwide, academic medical centers play an important role in research and innovation in the area of cell and gene therapy for cancer. In the Netherlands, preclinical research and a large portion of exploratory clinical trials are conducted in the academic setting.[6,7] Lots of knowledge about complex mechanisms of action, process and product development and clinical knowledge is hence in the hands of academic medical

centers and other public institutes, such as academic research departments and blood banks. This development field for cell and gene therapy differs significantly from the development field for traditional medicinal products, in which the pharmaceutical industry plays a bigger role in multiple phases of the development trajectories.

Logically, the big role of academic medical centers is based on their clinical expertise, capacity and focus on innovative research and access to patient material that functions as starting material for cell and gene therapies.[8] Collectively, the various research groups at Dutch academic medical centers have an enormous intellectual capacity to generate knowledge and optimize innovative technologies. However, the organizational structure and involved parties in the field bring forward challenges for new cell and gene therapies to reach clinical practice. Lots of preclinical research and exploratory clinical trials are conducted within one academic medical center, causing knowledge and resources to be fragmented.[9] In addition to this fragmentation, strong representation from academia is associated with still other challenges to product development. Academic medical centers are more focused on proving efficacy than on product development. There is also often inadequate access to financial resources for larger clinical trials after exploratory clinical trials, there are few partnerships for development between academic medical centers, and knowledge about regulations and building a registration dossier is often insufficient.[10]

Problem statement

Despite the promise of improved treatments for cancer, few cell and gene therapies reach clinical practice. This further development stagnates at two moments during the development phase in particular: 1) further development from preclinical products to exploratory clinical trials (translational research), and 2) scale-up from exploratory clinical trials to later, larger clinical trials and treatment in clinical practice. In addition to scientific and technical hurdles, the innovation climate is suboptimal for further development, thereby limiting access to new cell and gene therapies for cancer patients.

Objective

It is KWF's ambition to improve cancer treatment and accelerate new developments. By facilitating the innovation climate for cell and gene therapies, KWF supports making new cell and gene therapies with clinical benefits available for cancer patients. This report offers insight into how the innovation climate for further development of academic innovations can be improved.

Basic principles

This report describes the findings based on two basic principles: 1) academic development trajectories of cell and gene therapies, and 2) the future and role of the involved stakeholders, from an academic perspective. First, the various opportunities and hurdles are explained for academic development trajectories during translational research and further clinical development of cell and gene therapies towards practice. The report explains for both phases of research how knowledge sharing and collaboration between medical centers, but also other aspects such as infrastructure, regulations and financing, have played a role in development trajectories and offer possible solutions for stagnating development trajectories of promising cell and gene therapies. Second, academic perspectives on knowledge sharing and collaboration are explained and the intended roles for academia and industry in the future. Additionally, recommendations are given for academia and other stakeholders, including KWF, for making cell and gene therapy available in clinical practice.

2. Academic development trajectories

Research on cell and gene therapy for treating cancer is being conducted at all Dutch academic medical centers (Amsterdam UMC, Erasmus MC, LUMC, Maastricht UMC, Radboudumc, UMC Groningen, UMC Utrecht), two oncology institutes (NKI-AVL, Princess Máxima Center) and the blood bank (Sanquin). Of these institutes, the Erasmus MC, LUMC, Radboudumc, UMC Groningen, UMC Utrecht, the NKI-AVL and Sanquin have a GMP-certified production facility for cell and gene therapy.

In total, 27 applications for starting a clinical trial on CGT were found in the registry of the Dutch Central Committee on Research Involving Human Subjects (CCMO) in the period from 2015 to September 2020, after applying the inclusion criteria (Annex I - Methods). Of these applications, 19 trials were approved. Of these, 14 trials are exploratory (phase I, I/II). The remaining trials concern phase II trials (n=3) and phase III randomized clinical trials (n=2).

This chapter describes opportunities and hurdles, and solutions for new cell and gene therapies to reach clinical practice. The opportunities, hurdles and solutions were formulated based on interviews with 34 Dutch academic developers (scientists, pharmacists and physicians) from the field of cell and gene therapy (hereinafter referred to as "respondents"). The research activities and related opportunities and hurdles described by respondents are divided into five categories: research (scientific aspects), production and quality (technical aspects), knowledge sharing and collaboration, regulations and financing. For each category, the described research activities and related opportunities and hurdles have been divided into two phases in the development trajectory: 1) translational research (translation from preclinical research in the laboratory to the first applications in the clinic (exploratory clinical research), and 2) continued, clinical development to large trials and clinical practice. Annex I describes the data collection and analysis methods, and Annex II contains the questionnaires for the interviews.

2.1 Opportunities and hurdles during development trajectories

Research

Translational research

In the Netherlands, preclinical research is conducted with cell and gene therapies that are at the forefront of biomedical progress and offer opportunities for improving cancer treatment. Lots of expertise has been accumulated about the cellular immunology of T cells, NK cells and dendritic cells at Dutch public institutes, aimed at both fundamental knowledge as well as innovative clinical application.

Researchers were able to take the step from preclinical research to exploratory clinical research with TCR-T cell therapy, TILs, dendritic cells and NK cell therapy. Some of these therapies (e.g. TCR-T cell and dendritic cells) are very focused on biological properties of patient subgroups or individual patients. Based on biological properties, such as certain mutations that are the origin of the cancer, suitable antigens and/or receptors are studied for a good anti-tumor response of the therapy. TIL therapy is patient-specific because it is made from the T cells of the patient's tumor, but the discussed TIL therapies are currently not being specifically modified for a certain antigen specificity. This enables to deploy this therapy broadly for a patient population with the same type of cancer, despite that the specificity of the T cells likely differs between patients. Because these therapies are made from autologous starting material (the patient's tissue or cells), they are more suitable for preparation and administration within one medical center (hereinafter referred to as point-of-care) in order to circumvent complex and expensive production and distribution systems. In addition to the first products that are tested in exploratory trials, multiple centers have a TCR, TIL or dendritic cell therapy pipeline. Translational clinical trials with autologous CAR-T cell therapy are planned in the near future in the Netherlands.

Therapies are also being developed that are bound to a lesser degree to biological properties per patient or subgroups of patients, but they can detect certain targets that are specific to the cells of a cancer type. There are T cell therapies that are not HLA-bound because they have been genetically modified to express a γδ-TCR instead of an αβ-TCR. Because of this, despite autologous starting material, γδ-TCR-T cell therapy may potentially be more widely usable than αβ-TCR-T cell therapy. CAR-T cell therapy is being studied in preclinical research, including CAR-T cell therapy that can be generated from stem cells (iPSC: induced Pluripotent Stem Cells). This can be the basis for "off-the-shelf" CAR-T cell therapy, which is made from allogeneic starting material (donor tissue and cells) instead of autologous material. NK cell therapy is inherently suited for the use of allogeneic starting material. Both γδ-TCR-T cell and NK cell therapy is being studied in exploratory clinical research.

Products that are very patient-specific and are suitable for a point-of-care model are less commercially viable and will take longer to be picked up by private parties for further development. Therefore, these developments offer opportunities for further developing niche cell and gene therapy within academia. Therapies that are less patient-specific, for example because they are made from allogeneic starting material, have no HLA restrictions or can be made "off-the-shelf", have major advantages for safety, production and employability. This offers opportunities for the further development and marketing of academic innovations as new medicinal products for a relatively large group of patients, in collaboration with private parties (see section 2.2.).

However, there are scientific hurdles for translational research. For example, it is difficult to translate cell and gene therapies that were developed in the laboratory in animal models to humans due to the high species specificity: molecular mechanisms vary greatly between mice and humans. This leads to suboptimal animal models and a low predictive value of preclinical data for clinical safety and efficacy, which leads to a high chance of failure in exploratory clinical trials. Additionally, the precision with which cells bring about an anti-tumor effect significantly impact safety and efficacy. Off-target specificity and HLA incompatibility can lead to graft-versus-host disease or rejection, for example. What's more, the efficacy must often be demonstrated in multiple, suboptimal animal models in order to amass strong evidence for the start of clinical trials. Products

have also been overtaken by other innovations, especially immune therapies such as checkpoint inhibitors, which have become available earlier in the rapidly developing immunotherapy field. This leads to premature termination of exploratory clinical trials, because patient inclusion stagnates, for example. High specificity also has negative consequences for patient inclusion due to small target populations, even for exploratory clinical trials. These scientific challenges result in long-term trajectories in order to complete validation trials from preclinical research.

Further clinical development towards practice

Various exploratory clinical trials are described whose products may be suitable for further clinical development to larger clinical trials (phase II, III), emphasized by scientific evidence for safety and indications of efficacy. The research groups developing these cell and gene therapies have a good integration between research and the clinic, and experience with cell and gene therapy. There are clinical teams with capacity for data analysis and selection for further development, plus designing and conducting a larger clinical trial under Good Clinical Practice (GCP) standards.

Despite this capacity, only two phase II clinical trials have been conducted in the past five years with a public sponsor approved by the CCMO. One study concerns a dendritic cell product and the other a TIL product. Both are aimed at treating melanoma. However, one study ended early, while the other one is still ongoing. The ongoing study has a favorable design, due to a comparator arm that consists of the second-line checkpoint inhibitor treatment. This benefited the patient inclusion. For the phase III study that ended prematurely, the patient inclusion stagnated because of the arrival of checkpoint inhibitors due to a design with a placebo arm. Choices of a clinically relevant comparator arm appear to be crucial to success, considering the speed of scientific progress and the duration of large clinical trials.

In addition to scientific progress and competition with other medicinal products, other hurdles were named for further clinical development. The mechanism of action can be aimed at a subpopulation of patients with certain genetic and/or molecular profiles. For such patient populations it is not possible to set up a national phase III study with traditional trial designs. These hurdles for small patient populations overlap with those of the further development of targeted therapies (personalized medicine) and medicinal products for rare tumors. In addition, the positioning of cell and gene therapy leads to hurdles compared to existing treatment. Cell and gene therapy as the last resort for patients with relatively late-stage cancer can be unfavorable to efficacy, while in earlier stages treatment with other medicinal products is preferred over treatment with cell and gene therapy. This has negative effects on inclusion and implementation in clinical practice. The further development of cell and gene therapy in combination with other medicinal products has resulted in toxicity in several trials. This impedes the optimization of treatment strategies for combating escape mechanisms of relapsing or refractory cancer cells.

Production and quality

Translational research

In addition to being safe and effective, a product must also be of sufficient quality for human administration. Researchers and pharmacists attempt to translate a product made in a laboratory setting in preclinical research to a product manufactured according to Good Manufacturing Practice (GMP). To this end, both the production process as well as the product itself must be developed, validated and/or optimized according to GMP standards (hereinafter referred to as "GMP-compliant process and product development").

Many Dutch public institutes have invested in GMP production facilities for cell and gene therapy. In doing so, they are able to produce cell and gene therapy for the treatment of patients at their own hospital. This small-scale production capacity is sufficient for exploratory clinical research. In addition to researchers and physicians, pharmacists from the production facilities of medical centers and other public institutes play a central role in the GMP-compliant process and product development. Respondents state that researchers with translational experience have the capacity to think in GMP terms early on and that there is good interaction with pharmacists within their own institute. This has resulted in multiple products that are manufactured according to GMP by Dutch public

institutes. Production processes are optimized in order to circumvent hurdles such as insufficient starting material. The production process of a specific cell therapy can be applied to other type of cell therapy or for another type of cancer. Equipment for automated production processes, such as bioreactors, which are also called closed systems, is used wherever possible. The use of closed systems makes quality control during production in a point-of-care setting relatively easy compared to an open, manual system for production. The risks of contamination, for example, are much lower in a closed system than in an open space. The spaces where the closed systems are located also do not need to comply with the same strict GMP requirements as the clean rooms that are suitable for production in an open system. It also makes the scale-up in a later development phase easier (see the next section). Closed systems will be used for production of CAR-T cell therapy in the point-of-care setting in the near future. This capacity provides opportunities for translational research and further development of new cell and gene therapies.

However, the transition of a product from the laboratory that was tested in animals to a product that is going to be tested in humans has greater consequences due to the required GMP standards for the materials used during the production process, the necessary facilities and the regulatory knowledge and documentation, among other things, The cellular starting material also differs (cell lines or donor material in the laboratory versus patient material in clinical trials). As a result, GMP-compliant process and product development is a comprehensive step and creates hurdles with respect to the capacity of available personnel, knowledge, infrastructure and materials. Researchers and pharmacists who work on product development according to GMP often have other primary work activities. Scientific research has more priority for researchers, while activities at the hospital pharmacy or transplant facility have priority for pharmacists. There is little personnel that primarily works in translational research and product development of cell and gene therapy. This applies to both researchers and pharmacists. Hiring permanent personnel for process and product development is not a priority for universities, making these kinds of activities dependent on project financing. As soon as employees dedicated to GMP production of cell and gene therapy decide to search of other positions in the commercial sector, personnel shortages quickly occur for continuing production. Additionally, consultation between researchers (who are not directly involved in translational research) and pharmacists for GMP production is often non-existent or occurs too late. This leads to inefficient development trajectories, because GMP and regulatory requirements for product quality are often taken into account too late, or not at all, during preclinical development. For example, it may happen that no GMP-equivalent is available for certain materials, such as excipients, that are used for the production process of the laboratory product. There are long waiting lists of up to several years for vectors used for genetic modification. These vectors are also very expensive. In addition to the lack of GMP-certified excipients, the correct equipment is not always available and the production capacity of GMP facilities is limited. These production factors lead to excessive setbacks during translational research, such as stagnation and delays, additional costs or discontinuation of development trajectories.

Further clinical development towards practice

Achieving further clinical development requires scale-up of production to be able to treat larger groups of patients in follow-up trials. Automated production processes are much easier to scale up than manual production processes. Production of cell and gene therapy in public production facilities is taking place more and more in closed systems. Large parts of production processes can be automated because of this. For production in a point-of-care setting, the production duration is short and products are made fresh. As a result, a public production facility at an academic medical center production facility has advantages over a commercial central production facility. With on-site production, the lines of distribution are shorter, faster and more affordable.

However, no Dutch public institution has sufficient capacity to scale-up the production to sufficient batches for the number of intended patients for a phase III clinical trial or for clinical practice. There are a limited number of clean rooms available per medical center. Production processes take a long time and are enormously labor-intensive, especially for cell and gene

therapies, which are largely still produced in an open system. Hence, the burden on the personnel is enormous for GMP production, quality control and batch release. One batch is often intended for treating one patient, because the therapy is made from autologous material. Scale-up is relatively difficult for autologous products compared to allogeneic products and/or options for off-the-shelf production.

Production in a point-of-care setting, distributed over several centers, is a targeted strategy for increasing production capacity and for cell and gene therapy to reach clinical practice. Scale-up by means of production by multiple centers is difficult to set up, in particular with open systems for production. Closed systems are not, or not yet, suitable for some products, or only for a small part of the production process, and pharmacists and researchers are still dependent on labor-intensive, prolonged open systems for production. Small differences in the infrastructure for production, plus vulnerability of material during distribution and variation between human starting material, yields problems for the production of consistent batches that are of comparable product quality. There is also limited expertise available for the design and development of a Target Product Profile, a product that complies with the quality requirements for registration and access to clinical practice. This can make scale-up of production impossible or cause a product not to reach clinical practice because it does not comply with quality requirements (see Regulations, section on further clinical development towards practice).

Knowledge sharing and collaboration

Translational research

Fragmentation of knowledge and resources can impede the speed of innovation and make activities costly and inefficient. Knowledge sharing and collaboration can therefore be an important way to help innovations move forward in new fields like cell and gene therapy. This applies to both within and between institutes. Traditionally, the scientific community shares information by publishing articles. This allows knowledge to be acquired at the global level. Scientists often meet at scientific conferences in order to share knowledge. Informal social relationships both nationally and internationally also play an important role in attracting the right expertise for starting development trajectories or further developments of products. Respondents have amassed knowledge internationally through these channels and set up development trajectories including GMP production for dendritic cells, NK cell therapy and TIL therapy in the Netherlands.

Within the Netherlands, partnerships have been described in interviews for various development activities, including further development of therapies for new indications (application for other types of cancer), setting up an umbilical cord blood bank and establishing CAR-T cell therapy in a point-of-care setting. Knowledge sharing and collaboration also occur within various working groups and professional associations (see section 3.1). Other researchers chose to set up spin-offs for successful lines of research. This offers opportunities for process development, financing for infrastructure, personnel and commercial further development.

However, respondents indicate that public collaboration is currently falling short. Despite the large amount of investment being made, there is especially little knowledge sharing about the technical and quality aspects of cell and gene product development, the so-called knowhow. This specific knowledge is published less frequently in the public domain due to academic or commercial interests (see section 2.3). There is room for knowledge sharing about knowhow within the ATMP Working Group for Dutch and Belgian Hospitals, but this working group is limited to a meeting of pharmacists. The Netherlands is lacking a platform for knowledge sharing about knowhow between public developers that facilitates an educational, current system or database for GMP-compliant process and product development of cell and gene therapy. Currently, most public knowledge remains too fragmented and activities remain inefficient and expensive.

Partnerships with private parties such as large and small biotechnology and pharmaceutical companies provide lots of opportunities for regulatory and financial support for GMP-compliant process and product development. For example, for setting up vector production, using closed production systems and promoting patents and valorization.

Commercial interests constitute a hurdle in the collaboration with private parties. Not all cell and gene therapies have a commercial value. That is why on the one hand it is difficult to find a private partner for the development of products with an intensive production process or with limited possibilities for intellectual property (IP), such as patents, for example. On the other hand, conflicts may occur about IP rights during public-private partnerships. Respondents mentioned such conflicts which resulted in delayed development trajectories.

Further clinical development towards practice

Respondents named several partnerships that are focused on further clinical development, such as randomized multicenter clinical trials with production at several locations. Despite difficulties in setting up production at multiple centers, several so-called technology transfers were initiated and completed. A technology transfer entails the transfer of the required knowledge, rights and possibly materials for setting up and validating production at another institute. Some institutes also produce cell and gene therapies for other public institutes. There is also national and international collaboration among clinicians for the inclusion of patients and coordination with professional associations like HOVON and international networks.

These examples illustrate opportunities for new cell and gene therapies to reach clinical practice in a point-of-care setting on a relatively small scale for small patient populations (compared to a European/global pharmaceutical scale), in a network of involved public institutes. From now on, this will be called the "academic route" to clinical practice. For one product that is currently being developed in a phase III study, the expectation is that this will be successfully completed. To be able to treat all patients who are eligible for this therapy, production at several academic centers is a necessary strategy.

Collection of starting material and treatment with cell therapy can take place in multiple academic medical centers with the necessary clinical training. However, coordination and collaboration for designing and conducting large clinical phase II and III multicenter trials are still lacking.

Hurdles are also mentioned regarding attempts to establish partnerships. A technology transfer is a loss of investment if a clinical trial is terminated early. The product quality among production facilities must be comparable, but for products with a complex and lengthy production process, the technology transfer failed due to batch inconsistencies among production facilities. Production at multiple locations also requires permits for distributing tissue and/or cellular material. Clinicians must refer patients and possibly be trained. Not all hospitals prioritize cell and gene therapy and the necessary requirements and investment.

It is also possible to clinically further develop cell and gene therapies and to reach clinical practice in collaboration with private parties, on a relatively large scale for products with a commercial value. From now on, this will be called the "commercial route" to clinical practice. The advantage of a partnership with a biotechnology or pharmaceutical company is that there is attention for IP protection, support for GMP-compliant process and product development, financing for clinical trials and support for the route to registration and clinical practice. Biotechnology companies with a point-of-care business model offer possibilities for setting up production with closed systems in academia. By setting up spin-offs, academics can establish a bridge to the commercial route and attract capital, with lots of control over IP rights and development trajectories, plus possibilities for scaling up production capacity and recruiting personnel that is dedicated to product development.

In partnerships with private parties, contractual agreements and the allocation of IP rights were causes for delayed and stagnating development trajectories. When licensing IP rights whereby all rights are sold, the innovation is in the hands of the private party, which can result in niche innovations not being further developed due to acquisitions, for example. Respondents also indicate that lengthy legal processes are needed in order to come to reasonable liability clauses.

Regulations

Translational research

In order to take the step from preclinical research to a phase I clinical trial, researchers must gain permission from the CCMO. The CCMO centrally reviews all dossiers for clinical trials with cell and gene therapy, instead of the ethics committees of hospitals. The most important parts of the research dossier are the Investigator Brochure and the Investigational Medicinal Product Dossier (IMPD). These contain all the information from the preclinical and clinical trials with the product, and information about the quality, production and control of the investigational product.[a]

The field of cell and gene therapy is relatively new and entails various products, which leads to specific requirements per product. These differences are not specified in guidelines or regulations. In addition, requirements for traditional medicinal products do not always translate well to cell and gene therapy. However, cell and gene therapies fall under the European regulation for Advanced Therapy Medicinal Products (ATMPs) and are regulated as medicinal products. The consequence is that developers run into a series of hurdles for compiling a good IMPD. For example, it is ensured that the study design and models are suitable for substantiating the safety and efficacy and that the production process and the product itself comply with GMP quality requirements. GMP production requires applying for manufacturing licenses and a solid administration.

A separate dossier is required for each experimental medicinal product, including cell and gene therapies. This also applies to cell therapies that are similar to existing, marketing authorized products, except for their specific antigen-receptor combination. For example, this applies to a dendritic cell product that has already been tested in clinical trials but presents a new antigen, or a CAR-T cell product that has already been tested in clinical trials but expresses a different CAR. Usually, this concerns product modifications in order to bring about an anti-tumor response against a different type of cancer compared to the old product. Some respondents indicated that compiling new dossiers is part of the application of a product in other types of cancer or underlying molecular mechanisms. The new antigen specificity does have consequences for safety and efficacy, after all. Other respondents view re-compiling dossiers and other regulatory requirements as a hurdle to the development of cell and gene therapy.

In addition to legislation regarding medicinal products, other legislation may be applicable to cell and gene therapy, such as the Law on Safety and Quality of Body Material (Wet veiligheid en kwaliteit lichaamsmateriaal [Wvkl]) or legislation regarding genetically modified organisms (GMO) in the case of gene therapy. Both are named as delaying factors for development trajectories due to the required applications and processes for manufacturing licenses and/or approvals. Furthermore, differences in national legislation are a hurdle to set up clinical trials in several European countries.

Respondents view the assessment of the IMPDs by the CCMO to be strict. The patient's poor prognosis is often not included in a risk/benefit assessment. The process for receiving approval to start a clinical trial is often an intensive one, requiring much interaction between the assessor and the developer in order to answer regulatory questions. This process for interaction itself is described as a hurdle for clarifying small ambiguities. Frequently mentioned, content-related hurdles are considerations for the design of the clinical trial and scientific pitfalls for demonstrating preclinical safety and efficacy, such as the uncertainty associated with the study results due to the novelty and limited availability of animal models. There may also be a so-called regulatory lag, which means that regulatory knowledge about new products and technologies lags behind due to the speed with which scientific knowledge develops. Additionally, changes have been made to GMP requirements for ATMPs over time, thereby increasing the production costs of products for new indications (other types of cancer).

Further clinical development towards practice

Traditionally, new medicinal products become available in clinical practice through market authorization and reimbursement. Cell and gene therapies are assessed as ATMPs through the central registration procedure of the European Medicines Agency (EMA) for marketing authorization that is valid in all member states. The EMA bases its decision-making for

[a] https://www.ccmo.nl/onderzoekers/standaardonderzoeksdossier/d-productinformatie

marketing authorization on a risk/benefit analysis. For reimbursement by health insurance companies, Health Technology Assessments (HTA) are conducted by the Care Institute Netherlands (Zorginstituut Nederland [ZIN]), based on a cost-effectiveness analysis as supplied by the manufacturer. In addition, a regulatory route facilitates access to experimental (i.e. non-registered) ATMPs in clinical practice in certain exceptional situations, the so-called Hospital Exemption (HE).

It is not easy to fulfill the regulatory requirements for clinical trials, registration and reimbursement, but the involved authorities offer options for scientific advice on requirements and trial design. Public developers can contact the Medicines Evaluation Board (College ter Beoordeling van Geneesmiddelen [CBG]) as well as the Care Institute Netherlands to discuss requirements and routes to clinical practice. Respondents also indicate that CCMO assessments go more smoothly the more experience has been amassed with regulatory procedures and documentation. There has also been a substantial improvement of the approval procedure for clinical research with medical GMO applications due to the adoption of the GMO Resolution (Besluit GGO). The Dutch GMO approval procedure has been significantly shortened to a maximum of 56 days, resulting in fewer delays for clinical trials with gene therapies. The HE also offers options for treating patients with cell and gene therapy outside the regulatory frameworks of clinical trials and marketing authorization. This concerns patients who are not eligible for clinical trials, for example, or for bridging the period between exploratory and clinical follow-up trials. Respondents also indicate that they use the HE to make a therapy available in clinical practice after completing clinical research. It offers an advantage because the requirements for the HE are less strict than for central marketing authorization.

However, the current regulatory frameworks do not offer sufficient space for cell and gene therapies that are not commercially viable to reach clinical practice via an academic route. The HE is intended for exemption situations and not for making an unregistered ATMP nationally available in clinical practice by hospitals. There are restrictions tied to the HE, such as the number of patients that can be treated (initially 10 per year, and at most 50 per year for subsequent licenses). HE licenses are also not granted if there is a registered alternative medicinal product for which the patient is eligible.

Registration of academic innovations would be a more sustainable alternative strategy to reaching clinical practice, but respondents indicate that it is currently not feasible for academics to aim for central marketing authorization through the EMA. The strict requirements for marketing authorization are associated with high costs. In addition, the regulatory procedures themselves are also very expensive. Furthermore, there are ambiguities regarding the obligations of a license holder and doubts about whether academic medical centers are suitable as a license holder.

Requirements for product quality in particular are a barrier for central marketing authorization through the EMA. In order to approve medicinal products for human administration, every batch must fulfill certain specifications during and after production. Because cell and gene therapies are new, however, the tests and production controls for determining the specifications of an end product often still need to be developed and validated. These tests for batch release, tests for biological potency, controls during production and differences between the investigational product and registered product give rise to many regulatory objections for marketing authorization of ATMPs.11 Respondents named tests for potency and differences between batches of various production facilities as specific hurdles to further development and scale-up under ATMP legislation, respectively. Changes in regulations cause problems with production processes and quality testing of existing products for the clinic. With protocol changes for production and quality, it is possible for the collected clinical data to no longer be linked to the new product specifications. Consequently, production changes constitute hurdles to cell and gene therapies that are in a late stage of clinical development.

In order to prevent regulatory hurdles, developers can request scientific advice from organizations such as the CBG and EMA. However, some researchers describe barriers to request scientific advice, for example fears of interference with the intended research. Additionally, inadequate expertise in compiling a Target Product Profile among researchers, a

regulatory lag at government agencies and suboptimal regulatory processes lead to hurdles and delays, just like with translational research. The Law on Safety and Quality of Body Material (Wvkl) and GMO legislation are hurdles during scale-up or expansion to multiple clinical sites.

Other than for projects that are being financed through conditional reimbursement in the basic health care insurance package or the Potentially Promising Care subsidy program (subsidieregeling Veelbelovende zorg), respondents did not describe any experience with HTA or procedures for advice on cost-effectiveness. Public developers are aware that reimbursement by health insurance companies is necessary for broad accessibility but are more focused on collecting medical data than cost-effectiveness data.

Financing

Translational research

KWF finances a significant part of preclinical research with cell and gene therapy. Financing for scientific research and exploratory clinical trials is also available from other foundations, such as ZonMw. In addition, public institutes have supported the establishment of GMP production facilities for cell and gene therapy, enabling production of these therapies on a small scale.

Yet, financing for process and product development is often seen as a hurdle. Process and product development is very expensive due to the high costs of GMP production facilities and materials, plus the necessary time commitment of highly trained personnel. These costs increase even further if the validation of GMP-compliant process and product development is inefficient, resulting in delays or stagnation, even before the clinical trial starts. Project financing and subsidies are often insufficient to fully cover the costs, and institutes are still covering these themselves, where possible. GMP-compliant process and product development is also a more technical rather than scientific step in translational research, due to which financial backers are not always open to funding this step. Respondents also indicate that when assessing financing applications there is a lot of focus on the degree of innovation of applications instead of on product development, including the redesign and application of products to other types of cancer. Product optimization requires knowledge from immune monitoring trials, but funding agencies have rejected such applications in the past.

In order to interest commercial parties to invest and engage in valorizing research activities, IP in the form of patents is essential. Respondents are more or less aware of this aspect, but the high costs of patent applications and publication pressure are hurdles to patenting innovations.

Further clinical development towards practice

There are several financial options for publicly developed cell and gene therapy to reach clinical practice. Public developers have no profit motive, making the prices of products many times lower compared to commercial products. The advantage of on-location production, in a point-of-care setting, is that the production costs are lower than those of a production chain with a complex distribution line. A number of respondents found ways to finance further development trajectories. Setting up spin-offs has been a successful strategy for financing further clinical development via a commercial route with the help of investors, with substantial control over the development trajectory and an increase in capacity. In addition, the ZIN's Potentially Promising Care subsidy program[b] offers new opportunities; this is the intended strategy for financing development trajectories for public cell and gene therapies. It is easier to start through this subsidy program than through previously granted financing by means of conditional reimbursement within the basic health insurance. Additionally, foreign financing is also available for international consortia.

However, many respondents indicate that financing for further clinical development and registration for access to clinical practice is not or hardly available for public developers. In particular, financial hurdles exist for initiating the academic route with products without a strong commercial value and earnings model. In part due to the high costs for production, for conducting large clinical trials and the difficulties to find sufficient public financing for such efforts. The production costs are high because GMP production facilities and the required materials are expensive, regulatory requirements are becoming increasingly strict and highly trained personnel has to spend

[b] https://www.zorginstituutnederland.nl/werkagenda/veelbelovende-zorg

substantial amounts of time on the production of one or several batches. Additionally, it is considerably more difficult to find investors in Europe for commercial development trajectories compared to the United States.

The high production costs and the workload of personnel are also a hurdle for making cell and gene therapies available in clinical practice, including off-label use of registered cell and gene therapies. No financing is available for a central registration procedure by the EMA, except for when working together with commercial parties that have more financial resources. The costs of an EMA procedure for marketing authorization are considerable and not feasible for a academic medical center.

2.2 Solutions for stagnating development trajectories

KWF and respondents see solutions to support experimental cell and gene therapies to reach exploratory clinical research. In order to further develop products with promising data from exploratory research, it is essential for these products to be designed so that they are suitable for scale-up, valorization, respond to the needs of clinical practice, and for trials to comply with regulatory and HTA requirements (Figure 1). This requires a multidisciplinary approach with structural knowledge sharing and collaboration, and sufficient financial resources and support for regulatory/HTA requirements and valorization.

After successful exploratory clinical research, KWF sees two routes for cell and gene therapies to reach clinical practice:

1) The academic route for non-commercially viable products whereby development and application take place within academia; and

2) The commercial route for commercially viable products, whereby study results are valorized through the establishment of spin-offs, out-licensing and/or partnerships with biotechnology and pharmaceutical companies.

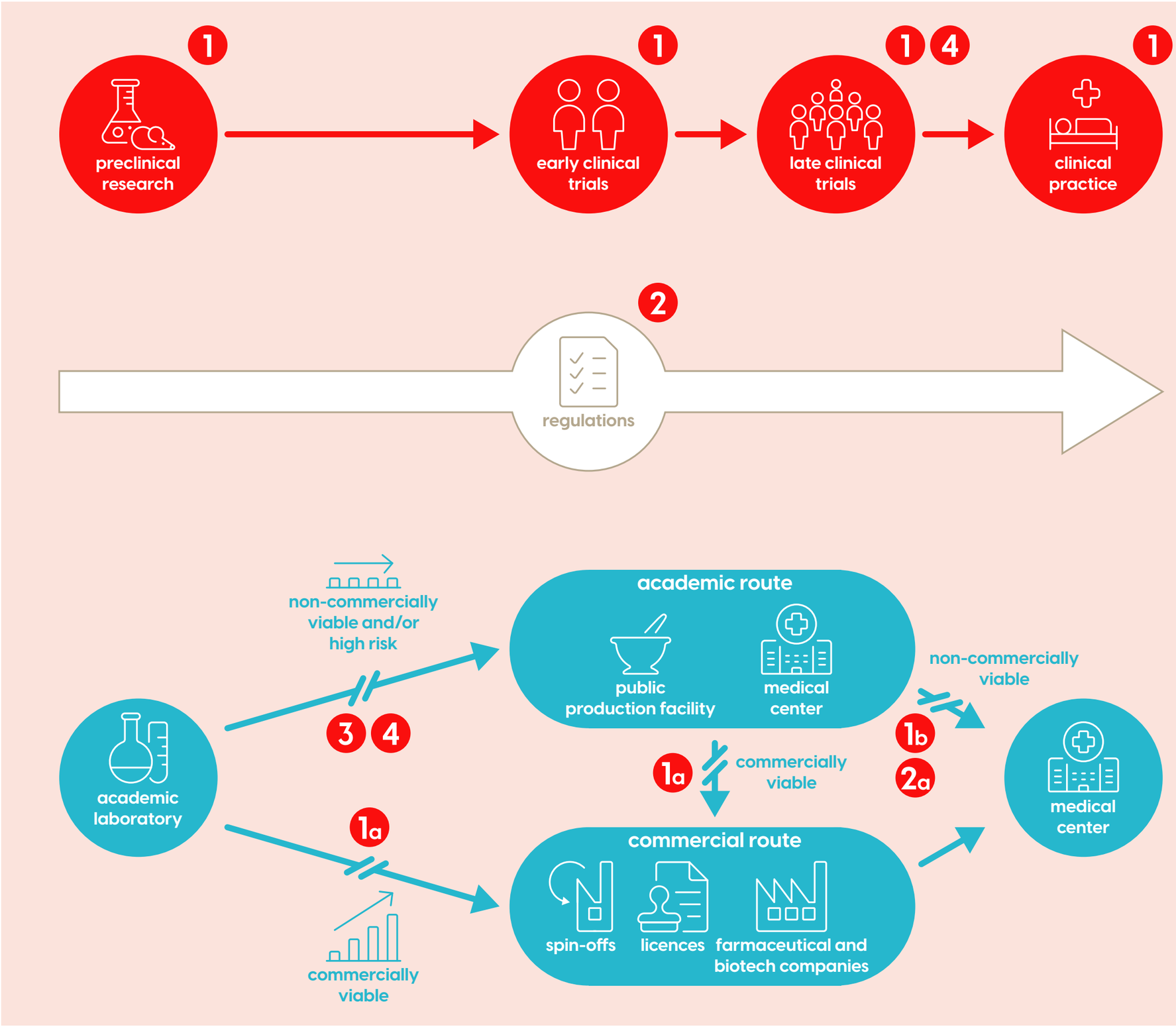
Figure 1: Hurdles and solutions for further development towards clinical practice

Red: represents the development trajectory of academic innovations from preclinical research towards clinical practice.

White: represents considerations related to the preclinical dossier, GMP production and product quality, clinical need, study design, safety and efficacy, and cost effectiveness and reimbursement, which need to be considered during the entire process in order to comply with laws and regulations and to reach clinical practice.

Blue: represents the development trajectory of academic innovations, divided between public (academic route) and private parties (commercial route).

1-4: solutions for more further development of clinically relevant cell and gene therapy.



Solution 1: Collaboration and support during development trajectories by one central, coordinating party by means of:

- Collaboration between academics, professional associations and patient representatives, nationally and internationally for coordination during and after clinical trials.
- Collaboration between academics and private parties for further development of commercially viable products.
- Support for valorization, such as establishing intellectual property (IP) rights and contractual agreements for consortia and other public partnerships, and also when setting up spin-offs, public-private partnerships and out-licensing (solution 1a).
- Support for compliance with regulatory requirements for market authorization and requirements for reimbursement (HTA) (solution 1b).

Solution 2: Clear, appropriate regulations and reimbursement structures through:

- More interaction between academics and government agencies for knowledge sharing and training, considering requirements starting at an early stage, plus improvement of processes and requirements through standardization.
- More interaction between government agencies for considering various regulatory and HTA requirements during development of a product dossier.
- Establishment of regulatory frameworks for making non-commercial, academic CGT available in clinical practice (solution 2a).

Solution 3: Collective public knowledge sharing and bundling of production capacity by means of a platform that:

- Forms a national knowledge base for GMP production, production costs and regulatory requirements. This facilitates the compilation of high-quality Investigational Medicinal Product Dossiers and Target Product Profiles. This facilitates scale-up and further development in larger clinical trials.
- Collaboration between production facilities is facilitated, and hence the preliminary scale-up of production for large clinical trials or clinical practice.

Solution 4: Financial resources for the support of:

- GMP-compliant CGT product development at academic production facilities, plus the required infrastructure.
- Product optimization and further development in exploratory research, possibly for new types of cancer with attention to the potential clinical added value.
- Academic phase II-III multicenter trials for further development of non-commercially viable CGT. Collaboration between public financiers is necessary due to the high costs.
- A central, connecting party with regulatory-related and valorization services during development.

3. Stakeholders

This chapter describes the academic perspectives on the intended future. These entail the academic ambition for the future of cell and gene therapy, academic perspectives on increased public knowledge sharing and collaboration as a possible step towards an improved innovation climate, and academic perspectives on the intended roles for academia and industry in the field of cell and gene therapy. These perspectives stem in part from interviews with respondents, but they are not necessarily linked to actual events with regard to the development trajectories that were discussed in the previous chapter. This chapter also contains recommendations for academia as well as for other stakeholders, including KWF, for making cell and gene therapies available in clinical practice. These are aligned with the solutions for stagnating development trajectories mentioned in section 2.2 and are suggestions for action for stakeholders in the cell and gene therapy field.

3.1 Academic perspectives

Academic ambition

The promise of cell and gene therapy for improving clinical practice and treatment for cancer patients is considerable. Respondents named several innovations that were developed from academic research and have the potential to improve treatment of cancer patients in the future.

This vision entails a range of cell and gene therapies, including allogeneic, off-the-shelf NK cell therapy and CAR-T cell therapy in a point-of-care setting for hematologic tumors. There are many options for TCR-T cell therapy; setting up libraries of TCR-T cell therapy including combination TCRs (mutation signature and general antigen) and TCRs without HLA restrictions. TCR-T cell therapy can be extended to solid tumors. In addition, academics have the ambition to implement first/second generation TIL therapy and dendritic cell therapies in clinical practice, or to optimize first/second generation products and expand these to several types of cancer. The development of these cell and gene therapies for cancer is among the priorities of various academic medical centers and public institutes.

There are two technological developments that can rapidly accelerate the translational research of various types of cell and gene therapies. First, the use of stem cells for various applications for regenerating tissue or cells. For treating cancer, there are also opportunities to use stem cells as starting material for making targeted cell and gene therapy. These stem cells can be differentiated to certain immune cells, with the possibility of genetic modification so that activation takes place through a certain receptor-ligand combination and/or cytotoxicity improves through the expression of certain factors. Second, new technologies for gene editing such as CRISPR-Cas. These are viewed as possible solutions for current hurdles for genetic modification with viral vectors.

In addition to cell and gene therapies, there are also other innovations that are expected to either directly or indirectly improve the treatment of cancer, such as organoids, 3D printing and bispecific antibodies. Although bispecific antibodies and other immunotherapies such as checkpoint inhibitors do

compete with cell and gene therapy, a combination treatment of biological medicinal products and cell and gene therapy offers opportunities for long-term remission and survival. Physicians also foresee more optimization of products and/or treatment regimens for appropriate use of medicinal products.

Academic perspectives on public knowledge sharing and collaboration

There is a lot of support among respondents for a network for public knowledge sharing and collaboration. Researchers, pharmacists and physicians indicate that it is not possible to further develop cell and gene therapy within an individual academic medical center or other public institute. Collaboration between centers is considered to be essential for developing new cell and gene therapies. Many public developers have an open-minded attitude towards knowledge sharing and collaboration with other public developers, provided that science is the priority and there are no commercial factors involved, such as patents.

Other networks were named that also facilitate knowledge sharing and collaboration. These are focused on the development of ATMPs (ATMP Working Group for Dutch and Belgian Academic Medical Centers),on producing human tissue and cells (JACIE network, transplantation network), or are focused on developments in relevant therapeutic areas, like HOVON in hemato-oncology. In other therapeutic areas than oncology, a consortium has been set up of public and private parties, in collaboration with technical universities, in order to encourage development of regenerative medicinal products. The listed networks can offer support for initiatives and activities regarding the development of cell and gene therapy for treating cancer.

Moreover, there are already existing organizations that offer opportunities for valorization of developments within oncology (Oncode Institute) and financing of public-private partnerships (Topsector Life Sciences & Health). Establishing initiatives with economic, ethical and regulatory support, including training, is seen as facilitating. Coordinating and supporting institutes abroad, such as the UK Catapult, are seen as an example of how the innovation climate can be improved in the Netherlands. New initiatives for cell and gene therapy are of added value when they are aligned with existing activities and networks.

However, respondents do have some concerns related to a network of public developers in the Netherlands. A network should not get in the way of current developments, for example. Respondents indicate that public developers can be skeptical of relinquishing control when joint decision-making would take place for translational research and further clinical development. This is why balancing of interests will be important for the success of a public network. In addition, respondents believe that it should also yield advantages for all those involved, even for academics who have relatively more experience than others. What must be prevented is for consultancy-type roles to arise that undermine the principle of equality within the network and create disproportional advantages and disadvantages.

Academic research is competitive because funding for research is limited. The guaranteeing of funding depends on output in the form of scientific publications to large extent. Hence, publications play an important role in the academic field. However, this hinders knowledge sharing and collaboration between groups or in a network, unless the appropriate agreements can be laid down. To a lesser degree, research is driven by patent applications which are necessary for collaboration and product development. This is why a patent application is often not prioritized over a publication in practice, except for when the institute's Technology Transfer Office (TTO) finds the costs of the patent application to be justified relative to the innovation possibilities and chances of product development. However, commercial interests can also hinder knowledge sharing and collaboration. The general perspective of IP rights is that these limit knowledge sharing and collaboration, and patents and contracts impede openness between parties. The development phase largely determines whether patents will facilitate or hinder collaboration.

Intended role for academia

Translational researchers have the ambition to discover new innovations and test these in exploratory clinical research. Further clinical development of products within academia is sometimes viewed as too risky. However, researchers,

pharmacists and physicians who are involved in clinical research strive for further clinical development of successful products via an academic or commercial route.

Many of these public developers prefer further development via the academic route given the affordability of the innovations. These academic innovations should be produced in a point-of-care setting. No distribution is needed in this case, making the production process relatively short and the products possibly more effective because they do not need to be cryopreserved. This also makes them suitable for treating patients with a short life expectancy. Academics above all want to make niche cell and gene therapies available that are adapted to the genetic mutations and antigen profiles of one single patient, by placing other antigens on a standardized cell (plug-and-play model). These include both personalized medicine and cell and gene therapies for rare tumors. Another group of cell and gene therapies that is considered suitable for a point-of-care model are products with a lengthy, complex production process without the option of IP rights. A low academic price offers opportunities for reimbursement because the products are more cost-effective than expensive commercial products. The government plays a role in deciding which products should become widely available.

However, for the academic route to reach clinical practice there is currently no platform for knowledge sharing and collaboration between public developers, there are limited financing options for products without a revenue model and there is an inadequate infrastructure for production on a scale that is sufficient for clinical practice. Even if academics can overcome these hurdles, there is a lack of the appropriate regulatory frameworks for the academic route. The HE could offer a temporary regulatory solution for production on a small scale, but registration via EMA is not feasible and is not an objective for academics. Consequently, cell and gene therapies are at risk of disappearing from clinical practice, even though they are promising for cancer patients with few treatment options and/or limited prospects.

A few public developers prefer the commercial route for further development. For cell and gene therapies with a commercial value, there are possibilities for academics to remain closely involved in further development through spin-offs. This bridge to a commercial model offers opportunities to raise capital on the road to registration and clinical practice.

Intended role for industry

For commercially viable products, especially universally applicable products that are developed for relatively large patient populations, many public developers see a role for industry to support these products reach clinical practice. This type of cell and gene therapies is more aligned with the traditional model of medicinal product development, supported by substantial infrastructure for production and regulatory capacity for registration of the biotechnology or pharmaceutical industry. Examples of universally applicable products are off-the-shelf, allogeneic cell products, such as certain CAR-T cell or NK cell products. Other commercially viable products are genetically modified cell products. The vectors for genetic modification offer more possibilities of protecting innovation with IP rights than cell products that are not genetically modified.

Some private parties have a point-of-care business model. This model has a revenue model that is based on the production process and sale of equipment and materials instead of the end product. The point-of-care business model offers opportunities to make cell and gene therapies available within public-private partnerships. A number of respondents see collaboration with private parties as an opportunity to further develop successful products by granting licenses whereby IP rights are sold or by entering into public-partnerships in which both parties fulfill a role and contractual agreements are concluded about the rights on the results, the production process, or the product and/or technology for example. The advantage of collaboration for further development with a private party is that the objectives are similar: product development for treatment in clinical practice, instead of academic interests that can occur in a partnership with other public parties. Investment risks for the private party can be mitigated by financing translational research with public funds, after which the private party can invest in the further clinical development towards practice. It is also possible for products from the academic route to be transferred to the commercial route over the course of time by

means of licenses or partnerships. If the required scale of production exceeds the academic capacity due to wider use of the product up to standard treatment, then collaboration with private parties is a possible solution for scale-up and wide availability, provided that terms and conditions to guarantee availability and affordability are agreed upon.

However, wide availability is largely dependent on decision-making about reimbursement by basic health insurance, which in turn depends largely on the price of the medicinal product compared to the patient benefit. Respondents point to a position of dominance of the pharmaceutical industry and other private parties that constitute hurdles to availability. This position of dominance is manifested in various aspects; the high prices of cell and gene therapies that are launched on the market without transparency about how these prices were decided, monopolistic situations, no availability of registered cell and gene therapies and a decisive role in setting terms and conditions for partnerships. Patents on vectors that are in the hands of industry hinder academic research, for example, on the combined use of new generations of cell and gene therapies. Acquisitions and mergers between private parties are increasingly taking place, with the risk that the developments of niche products will be terminated. Niche products may still often be of interest to smaller biotechnology companies but can be too risky for large pharmaceutical companies. Acquisitions of academic innovations or entire laboratories by private parties hinder academic freedom. Private parties focus primarily on the development of innovative products for new indications but not on making treatment available to patients who fall outside the indication for which the medicinal product is registered. Logically, there is no commercial interest in products or further development without a revenue model. Yet, these hurdles cause academics to be reluctant to work with private parties. A few respondent see no role at all for commercial parties in the development of cell and gene therapies, in particular if these are made from the patient's cells.

Public versus private role

The intended roles for academia and industry show that academic and commercial interests differ (from the academic perspective). In practice, there is a pervasive feeling among academic developers of competition and reluctance to cooperate with industry. Theoretically speaking, academic and private developments can be complementary, based on the commercial value of a product or a lack thereof. However, opinions on which cell and gene therapies are commercially viable and which ones are not can differ, both among public developers and between public developers and private parties in Europe.

In addition, private parties from non-European countries, such as the United States and China, where more research is taking place and the commercial value of cell and gene therapy is different due to other innovation climates, represent a threat to the development of cell and gene therapy in the Netherlands and Europe. If cell and gene therapy without European commercial value is made available via the academic route and under the Hospital Exemption (without obtaining or aiming for central registration), then similar American products will have a competitive advantage if these are registered by the EMA. Hospital Exemption permits are no longer granted in the Netherlands if registered products are available. It can be assumed that commercial products are much more expensive than academic products, given the prices of commercial CAR-T cell therapies. The production duration may also increase due to production at centralized factories, possibly causing treatments to become available too late after collection of starting material from patients with a short life expectancy. If the company does not market the product in the Netherlands, it will no longer be available at all. For commercially viable products that are developed for central registration, developments from other continents are also a treat, in particular for cell and gene therapies with orphan drug status due to market exclusivity.

This illustrates the necessity for public-private collaboration in the Netherlands and Europe in order to accelerate developments. Both public and private developers must compromise to take collaborative developments a step further. Academic developers could be more transparent about experimental cell and gene therapies, including those that are made available under the Hospital Exemption. The industry could be more transparent about pricing and other decision-making with regard to marketing. Legal support for negotiations for

promising, commercially viable products is essential for building a bridge for more public-private collaboration.

3.2 Recommendations per stakeholder group

KWF compiled the following recommendations for encouraging further development of cell and gene therapy. The recommendations include knowledge sharing and collaboration, infrastructure for production, improvement of regulatory frameworks and financing. They are divided per stakeholder group:

Academia - Public developers

- Integrate translational development trajectories within an interdisciplinary product team with researchers, pharmacists, physicians and patient representatives, from both within and outside of one's own institute. This increases the chance of successful development of a product with a Target Product Profile that is suitable for clinical practice.
- Share preclinical results and knowledge about production and quality as a catalyst for translational research. Public collaboration with contractual agreements can prevent hurdles for valorization.
- Share clinical results, including negative results, recommendations from scientific advice and information about the costs of production and development trajectories with other public developers, as a catalyst for further clinical development.
- Enter into collaboration with other public developers for setting up and conducting large clinical trials for further development of non-commercially viable cell and gene therapies, including the required scale-up of production.
- Enter into collaboration with private parties for further development of commercially viable cell and gene therapies, or initiate commercial development by setting up a spin-off.
- Interact with regulatory agencies at an early stage through scientific advice, including advice about clinical research (CBG) and registration obligations and requirements (EMA).
- Maintain an open, pro-active dialog with regulatory agencies in order to decrease the regulatory lag regarding innovative products and technology.
- Interact with the payer (ZIN, health insurance company) at an early stage in order to obtain clarity about

reimbursement requirements, and about determining the correct route to clinical practice (academic vs. commercial).

Academia - Institute

- Train/specialize translational researchers and pharmacists in the area of regulatory requirements and procedures needed for the development of cell and gene therapy for the clinic. These researchers and pharmacists can fulfill a "service desk" function.
- Create careers in product development of cell and gene therapy, with remuneration policies linked to product development for personnel and for the institute.
- Offer financial support for infrastructure for GMP production.

Private parties and trade associations

- Improve the coordination of partnerships with public developers, possibly through a platform for ATMP public-private partnerships.
- Increase the transparency of contractual agreements and terms and conditions during development trajectories and the post-marketing phase (including pricing, royalties, risk distribution).

Patient associations

- Tie in with evaluation committees of funding agencies.
- Tie in with committees for regulatory decision-making.
- Interact with public developers for patient advocacy in development trajectories.
- Influence policy to guarantee access to cell and gene therapies (e.g. reimbursement).

Government agencies (CCMO, IGJ, CBG, VWS, EMA, EC)

Regulation

- Offer public developers reduced regulatory rates for scientific advice and marketing authorization (CBG, EMA, EC).
- Improve regulatory knowledge sharing and interaction with public developers. Integrate academic knowledge into guidelines and standardize IMPD requirements where possible, including quality aspects, for certain product types and risk profiles (CCMO, CBG).
- Offer regulatory training for academic developers (CCMO, CBG).
- Evaluate Dutch laws and regulations, including the Medicines Act, Hospital Exemption and Wvkl, in order to establish regulations and/or guidelines for national use of academic, non-commercially viable cell and gene therapies that cannot, or not yet be registered through the EMA (IGJ, CBG, VWS).
- Evaluate European laws and regulations for a route to clinical practice for cell and gene therapies that fall under personalized medicine (CBG, EMA, EC).
- Evaluate possibilities for EU harmonization of tissue, cell and GMO legislation (CBG, EMA, EC).
- Prioritize increased interaction and collaboration between government agencies and payers (CCMO, IGJ, CBG, VWS, EMA, ZIN, EC).

Financing

- Invest in the field of cell and gene therapy for long-term growth, by means of a large financial injection for a nationally coordinating body like the UK Catapult (Nationaal Groeifonds [National Growth Fund]):
  - The coordinating body of public cell and gene therapy developers aims for more translation into exploratory clinical research and further clinical development through:
    - National knowledge sharing of translational and clinical research between researchers, pharmacists, physicians and patient associations.
    - Joint commitment to translation of new innovations to exploratory clinical trials, further development of successful products and design of phase II/III multicenter trials.

- Creation of a network of specialized production facilities.
- Connections with international consortia/networks/ commercial partners.

Payers (ZIN, health insurance companies)
- Interact with public developers early on in order to offer support for requirements for reimbursement.
- Offer training on HTA requirements for academic developers (ZIN).
- Specify guidelines for assessing the cost-effectiveness and possible reimbursement structures for new cell and gene therapies.

KWF

Connect
- Organize events such as conferences to facilitate ties among public developers and between public developers and government agencies.
- Facilitate further development in partnerships through the academic and commercial route by providing access to support for valorization and further development of both commercially viable as well as non-commercially viable products. This can be achieved in collaboration with organizations such as the Oncode Institute, for example. This can include support for the patent process, contractual agreements, socially responsible licensing, reinvestment in research (royalties) or setting up spin-offs.

Lobby
- Influence policy to enable standardization of regulatory requirements and optimization of regulatory processes for clinical trials (the Netherlands: CCMO, CBG).
- Influence policy for the benefit of a regulatory route for national use of academic, non-commercially viable cell and gene therapies (the Netherlands: IGJ, CBG, VWS).
- Influence policy for the benefit of a regulatory route for registration and/or use of personalized cell and gene therapy (the Netherlands and EU: CBG, VWS, EMA, EC).
- Influence policy for the benefit of EU harmonization of tissue, cell and GMO legislation and procedures (the Netherlands and EU: VWS, EC).

Financing
- Make financing available for promoting academic infrastructure for GMP-compliant product development (initiated by means of Infrastructure Initiatives Call 2021-2).
- When deciding on financing, give more priority to GMP product development, and product optimization and application of products for other types of cancer.

KWF and other funding agencies (Groeifonds, ZonMw, ZIN, LSH)
- Set up financing structures in collaboration with partners for further development of successful but non-commercially interesting, academic cell and gene therapies (the academic route).

4 Conclusion

There are many opportunities for improving translational research within academia in order to increase the likelihood of potential cell and gene therapies reaching exploratory clinical research. This requires a multidisciplinary approach with structural knowledge sharing and collaboration between academics, support for regulatory and HTA requirements and valorization and sufficient financial resources for the required infrastructure and product development. KWF sees two possible routes to reach clinical practice from exploratory clinical research: an academic and a commercial route. Which route is more suitable for a product depends on the individual product characteristics. Some therapies are so patient-specific that they do not lend themselves very well to a national and international marketing strategy. There is a role for academics and public institutes for making non-commercially viable therapies available to clinical practice via the academic route. However, there are hurdles that originate from a defective innovation system. The solution lies in more coordination and collaboration between academics and other stakeholders to large extent. A coordinating body can connect public developers with each other and offer the right support in order to jointly design multicenter clinical trials and production to facilitate access in clinical practice. Fit-for-purpose regulations and financial resources are needed to make non-commercial, academic cell and gene therapy available in clinical practice. More interaction between academics and regulatory agencies will prevent regulatory objections in later stages of development. In addition, solid product dossiers will make it easier to further develop promising cell and gene therapies that are commercially viable via the commercial route. A coordinating body can connect public developers with private parties and offer support for valorization and further development to the market, taking into account availability for patients and financial or other incentives for academic research. Complementary use of both routes is needed in order for all new cell and gene therapies with clinical added value to become available in clinical practice.

References

1. Mullard A. Second anticancer CAR T therapy receives FDA approval. Nat Rev Drug Discov. 2017;16(12):818. doi:10.1038/nrd.2017.249

2. Jacobson C, Emmert A, Rosenthal MB. CAR T-Cell Therapy: A Microcosm for the Challenges Ahead in Medicare. JAMA. 2019;322(10):923-924. doi:10.1001/jama.2019.10194

3. Met Ö, Jensen KM, Chamberlain CA, Donia M, Svane IM. Principles of adoptive T cell therapy in cancer. Semin Immunopathol. 2019;41(1):49-58. doi:10.1007/s00281-018-0703-z

4. Bol KF, Schreibelt G, Rabold K, et al. The clinical application of cancer immunotherapy based on naturally circulating dendritic cells. J Immunother Cancer. 2019;7(1):109. doi:10.1186/s40425-019-0580-6

5. Sivori S, Meazza R, Quintarelli C, et al. NK Cell-Based Immunotherapy for Hematological Malignancies. J Clin Med. 2019;8(10). doi:10.3390/jcm8101702

6. Boráň T, Menezes-Ferreira M, Reischl I, et al. Clinical Development and Commercialization of Advanced Therapy Medicinal Products (ATMPs) in the EU: how are the product pipeline and regulatory framework evolving? Hum Gene Ther Clin Dev. 2017;28(3):126-135. doi:10.1089/humc.2016.193

7. de Wilde S, Guchelaar H-J, Zandvliet ML, Meij P. Understanding clinical development of chimeric antigen receptor T cell therapies. Cytotherapy. 2017;19(6):703-709. doi:10.1016/j.jcyt.2017.03.070

8. de Wilde S, Guchelaar H-J, Herberts C, et al. Development of cell therapy medicinal products by academic institutes. Drug Discov Today. 2016;21(8):1206-1212. doi:10.1016/j.drudis.2016.04.016

9. Coppens DG, Gardarsdottir H, van den Bogert CA, De Bruin ML, Leufkens HG, Hoekman J. Publication rates and reported results in a cohort of gene- and cell-based therapy trials. Regen Med. 2020;15(1):1215-1227. doi:10.2217/rme-2019-0066

10. Meij P, Veltrop LA, de Wilde SP. Advanced Therapy Medicinal Products (ATMPs) naar reguliere klinische zorg. Knelpunten en Mogelijkheden. Published March 2016. Accessed April 12, 2016. https://www.lumc.nl/cen/att/80813053317221/1263833/Rapport_-_Advanced_Therapy_Medicinal_Products_naar_reguliere_klinische_zorg_2016.pdf

11. de Wilde S, Coppens DGM, Hoekman J, et al. EU decision-making for marketing authorization of advanced therapy medicinal products: a case study. Drug Discov Today. 2018;23(7):1328-1333. doi:10.1016/j.drudis.2018.03.008

12. Ten Ham RMT, Hövels AM, Hoekman J, et al. What does cell therapy manufacturing cost? A framework and methodology to facilitate academic and other small-scale cell therapy manufacturing costings. Cytotherapy. 2020;22(7):388-397. doi:10.1016/j.jcyt.2020.03.432

13. van den Bogert CA, Souverein PC, Brekelmans CTM, et al. Recruitment failure and futility were the most common reasons for discontinuation of clinical drug trials. Results of a nationwide inception cohort study in the Netherlands. J Clin Epidemiol. 2017;88:140-147. doi:10.1016/j.jclinepi.2017.05.001

14. Bekkers R, Bodas Freitas IM. Analysing knowledge transfer channels between universities and industry: To what degree do sectors also matter? Res Policy. 2008;37(10):1837-1853. doi:10.1016/j.respol.2008.07.007

15. Bogert CA van den, Souverein PC, Brekelmans CTM, et al. Non-Publication Is Common among Phase 1, Single-Center, Not Prospectively Registered, or Early Terminated Clinical Drug Trials. PLOS ONE. 2016;11(12):e0167709. doi:10.1371/journal.pone.0167709

Annex I: Methods

Scope

Cell and gene therapy

This report focuses on promising cell and gene therapies for treating cancer. All cell therapies that are made from T cells, NK cells or dendritic cells are included. Therapies that involve genetic modification of such starting material are also included, regardless of which technology is used (defined here as gene therapy).

Phases of development

Medicinal products are developed in phases, which is largely determined by laws and regulations. New innovations are first tested in animals (preclinical research) before they are tested in humans (clinical research). Prior to starting clinical research, a dossier must be compiled that offers an adequate prediction of safety and efficacy for administration to humans. The step from preclinical research to clinical research is defined as translational research in this report. In addition to evidence of safety and efficacy, it is also necessary to translate products that are suitable for a laboratory setting to a product that is produced in compliance with Good Manufacturing Practice (GMP) and is suitable for clinical administration to humans. Clinical research consists of various phases: I, II and III, or combination designs. Clinical research begins in a small group of participants and/or patients. If the results of exploratory trials (phase I/II) are positive, further development to later phases of clinical research takes place, the goal being marketing authorization as a medicinal product.

Traditionally, medicinal products are authorized to enter the market through registration based on results from phase III trials, in which large numbers of patients are included. Registration and reimbursement are traditionally the route for access to a new medicinal product in clinical practice. For cell and gene therapy, there are two regulatory paths for reaching clinical practice (outside of experimental clinical research) in the Netherlands: central registration via the European Medicines Agency and a reimbursement decision by the Care Institute Netherlands, or national authorization for production and

administration under the Hospital Exemption. In this report, reaching clinical practice concerns both regulatory routes. Chronologically, this report's analysis starts with translational research, production for clinical trials, the various phases of clinical research, up to reaching clinical practice (outside of clinical trials).

Data collection

Data about development activities and perspectives for further development of academic cell and gene therapies were collected through public sources and interviews with public developers of cell and gene therapy. Public developers are researchers and physicians who are involved in translational research and clinical trials, but also pharmacists who have a central role in the development of cell and gene therapy within academia in the production facilities of medical centers and other public institutes.

Public sources were used as a starting point to search for relevant public institutes (academic medical centers, oncology institutes and the blood bank), developers (researchers, pharmacists, physicians) and development activities (translational and clinical). First, the EudraGMDP database was used for identifying all public production facilities for cell and gene therapy with a GMP permit. Second, relevant clinical trials with cell and gene therapy were selected with the help of the register of the Central Committee on Research Involving Human Subjects (CCMO); www.toetsingonline.nl).

The information on which public institutes had a GMP production facility available was used for selecting pharmacists as a respondent. Additionally, information about clinical trials was used to select researchers and physicians as a respondent.

Clinical trials

A current overview of relevant clinical trials with cell and gene therapies that are promising for improving treatment of cancer was established, based on the following inclusion criteria: 1) experimental cell and gene therapies for which T cells, NK cells or dendritic cells are used as starting material, 2) which are or were in clinical development for the treatment of cancer in the past five years, and 3) which were developed in clinical trials sponsored by a Dutch public institute. The period of analysis was defined as approval or rejection by the CCMO in the period from January 2015 through September 2020.

The following data was extracted from the public CCMO database and tabulated per study: 1) sponsor, 2) product type (cell therapy, genetically modified cell therapy), 3) type of cell on which the mechanism of action is based (CAR-T cell, TCR-T cell, TIL, dendritic cell, NK cell), 4) technology for genetic modification (vector type, other technology, NA), 5) starting material (autologous/allogeneic), 5) indication (type of cancer), 6) clinical trial phase, and 7) single-center or multicenter study.

The information about the clinical trials was used as a starting point for the interviews (Annex II - Questionnaires) and to focus questions per interview in order to collect data about the course of the clinical trial, the historical course and the future perspective for the product. The encountered trials were all discussed with respondents.

Selected respondents

Public developers (researchers, pharmacists, physicians) were invited to participate in an interview. For each GMP production facility, one individual (head of cell and gene therapy production; pharmacist) was selected for an interview, with an invitation to other production personnel, if desired. Pharmacists and other production employees were invited first to take part in an interview (vs. researchers/physicians).

The public information about clinical trials, especially the study title and sponsor, was used to search for information about relevant research groups and the involved researchers/ physicians for both translational research and clinical research. The pharmacists also had a "gatekeeper" role for identifying other relevant respondents within their institute for an interview. Based on this method, at least one researcher and/or physician was selected as a respondent for translational research and at least one researcher and/or physician as a respondent for clinical research. A total of 36 respondents were selected for participation.

Interviews

Selected respondents (researchers, pharmacists and physicians) were invited for a 30-45 minute interview. Separate, semi-structured questionnaires were compiled for respondents based on the research activity (Annex II: 1 for manufacturers (production; pharmacists and translational researchers); 2 for translators (translational researchers and physicians) and 3 for clinicians (clinical researchers and physicians). Depending on the respondent, one or a combination of questionnaires was used.

Detailed notes were taken of each interview in transcription style, which were then validated by participants. A total of 34 respondents spread out over all relevant knowledge institutes for cell and gene therapy in the Netherlands took part in this study. Some respondents for translational and clinical research were invited for the same interview due to a joint development trajectory of one or more products. A total of 25 interview were conducted for data collection.

Data analysis

The validated notes were used to conduct a qualitative data analysis. Opportunities and hurdles, solutions and academic perspectives were encoded using Nvivo, Based on literature[11,12,13,14,15] a preliminary encoding tree was created with two branches for encoding 1) actual information about development trajectories, opportunities and hurdles, and 2) academic perspectives about science and the innovation climate.

The actual information about development trajectories (branch 1) was encoded based on 1) the development phase (preclinical research, translational research, production in facility, clinical research and clinical practice), and 2) category (skills/capacity, science/technical/medical, knowledge sharing, collaboration, regulation, financing). Codes were generated for encoding actual information for every combination of development phase and category. In addition, coding also indicated whether the actual information concerned an opportunity/positive activity, hurdle/negative activity or solution/need.

Academic perspectives (branch 2) were encoded based on categories (perspective of public and private knowledge sharing and collaboration, professional/institutional interest, role for academia, role for industry, role for KWF, future-oriented science and technological breakthrough) and codes per category. The coding also indicated whether the perspective concerned an opportunity/positive activity, hurdle/negative activity or solution/need. All codes were grouped based on this method in the Nvivo encoding tree, without coding from which institute or respondent the finding originated. Hence the analysis was anonymized. The preliminary coding tree was expanded during the encoding process. Saturation of the encoding was achieved during the analysis.

The final coding tree was extracted and served as a basis for the findings about development trajectories, solutions and perspectives that were proposed by the respondents for promoting translational research and further clinical development. The recommendations per stakeholder are based on the proposed solutions by academics, a past published report about academic development of ATMPs[c], and internal strategy sessions at KWF.

[c] https://www.leru.org/files/LR-BP-ATMP.pdf

Annex II: Questionnaires

1: Questionnaires for manufacturers of cell and gene therapy - Manufacturers

Explanation for interview: The list with clinical trials in the past five years serves as the basis for the interview (for "Production" and "Knowledge sharing and collaboration between production facilities"). For the production facility, the questions focus on production aspects and possibilities for scale-up, plus knowledge sharing and collaboration stemming from production. There are also general questions asked about perspectives for knowledge sharing and collaboration in the Netherlands, plus about the future of the field. The questions with numbers are standard questions; the questions with letters only come into play as follow-up questions to the numbered questions.

Introduction

Instructions for interviewers: explain proposals and function at KWF. Explain the project's goal (academic network for knowledge sharing and collaboration; further development).

1) Do you object to this interview being recorded? [Instructions for the interview: If needed, explain that quotes and specific information about products will not be made public and that notes will be taken about the interview that will be sent to the participant for validation.]
2) Can you please introduce yourself and tell us your position at the [institute]?

Production

Instructions for the interview: The products that are manufactured for one or more clinical trial/trials are discussed by the interviewer with the head of the production facility, based on the encountered information in the CCMO register. This concerns summarized information based on: 1) product type (cell therapy, genetically modified cell therapy, gene therapy), 2) type of cell on which the mechanism of action is based (CAR-T cell, TCR-T cell, TIL, CAR-NK cell, NK cell, DC, vector), 3) technology for genetic modification (vector type, other technology, NA), 4) starting material (autologous/allogeneic), 5) indication (type of cancer), 6) development phase, and 7) single-center or multicenter study. The questions below must be asked for these products.

3) Are these products as they are currently being manufactured suitable for further development from a production perspective? Why or why not? [Note: Can product or costs/infrastructure be related aspects"]
[Note: Ask for more details about product aspects if these are mentioned.]
   a) What makes it possible for this product to be manufactured on a relatively large scale?
   b) Could production be scaled up for these products?
   c) Would the quality have to be optimized?
   d) Are these products suitable for distribution/production at another location?
   [Note: Ask for more details about costs/infrastructure is this is mentioned.]
   e) What is needed for distribution of these products [qua infrastructure]?
   f) From which budget is the production paid [clinical department, production facility/ hospital pharmacy, preliminary reimbursement, funds/grants]?
   g) How is the distribution of fixed costs (material and facility) managed internally?
   h) Are the production costs for some products much higher than for others? Why?
   i) How could production cost be lowered?
4) [If no solution was discussed]; What is needed for further development? [e.g. increase production]
5) Is there a plan for product development? [e.g. target product profile, for registration]
6) Are there similar products that are (almost) ready for making the transition to a GMP product from preclinical development?
7) Whom can we best contact to discuss the details of translational research? [Note: the "translator"]
8) Whom can we best contact to discuss clinical development of cell and gene therapy at the [institute]? [Note: the "clinical developer" plus any PIs]

Knowledge sharing and collaboration between production facilities

Instructions for the interview: These questions are also asked based on the products that are manufactured for one or more clinical trials. The goal is to find out about the types of actions

that were or weren't taken for knowledge sharing and collaboration between production facilities and why this was or wasn't done.

9) Did the production facility share knowledge about the GMP products, in the public domain or with other institutes? This can include protocols for production, materials, methods (assays) for quality control. *[For example: (if respondent hesitates or doesn't know): publications, reports, conferences, symposia, workshops, sharing of personnel or facility, informal social relationships, financial relationship]*
   j) Why or why not? *[For example: (if respondent hesitates or doesn't know): personal attitude, strategic reasons for product development, strategic reason for funds/grants, other priorities, clinical results, production results, commercial value, possibilities]*
10) Are there partnerships for the production of these products? *[For example: (if respondent hesitates or doesn't know): consortia, technology transfers, R&D partnerships, spin-off]*
   k) Why or why not? *[For example: (if respondent hesitates or doesn't know): personal attitude, strategic reasons for product development, strategic reason for funds/grants, other priorities, clinical results, production results, commercial value, IP possibilities]*
11) Are there other cell and gene therapies manufactured in the production facility for clinical trials?
   l) [if yes, ask for more details;] What kind of product is this; where does the innovation come from; what kind of collaboration is this [R&D partnership [with UMCs/spin-offs/industry]/ participate as a site?

Perspectives

12) What do you need in order to move forward?
13) What do you think about more knowledge sharing and collaboration within academia?
   m) What is needed in order to take advantage of opportunities?
   n) Is there production capacity that is currently not being used? [scale-up for larger clinical trials, automatic/continuous production in the future]
   o) What are the biggest hurdles? *[For example: specialisms per institute, complicated sharing of knowledge and IP, no incentives/earning model.]*
   p) Under which circumstances will you stop with knowledge sharing and collaboration with other public institutes? And why? *[Note: Find out the boundary between pre-competitive research and competitive product development]*
14) Would you like to take part in a national network of public institutes in order to share more knowledge and engage in collaboration? Why or why not?
   q) Who should coordinate this?
15) Are there aspects that are important in order to get these products from academia to the patient? [For example, remuneration, distribution, collaboration with companies]
16) What is your vision for the future of this [cell and gene therapy] field?
   r) Which methods, products or technologies do you believe will be the most successful?
17) Would you like to add anything that we've not touched upon?

Conclusion

Instructions for the interview: *Explain that findings will be published in a report (aggregated level). Publication of report (website), meeting being planned (mid-2021). Thank you very much.*

2: Questionnaire for translational researchers and/or physicians - translators

Explanation for interview: The list with clinical trials serves as the basis for the interview (for "Translational research" and "Knowledge sharing and collaboration between researchers"). For translators, the questions focus on the translation of preclinical products to initial clinical trial/trials and other preclinical products in development, plus knowledge sharing and collaboration stemming from translational research. There are also general questions asked about perspectives for knowledge sharing and collaboration in the Netherlands, plus about the future of the field.

Introduction

Instructions for interviewers: explain proposals and function at KWF. Explain the project's goal (academic network for knowledge sharing and collaboration; further development).

1) Do you object to this interview being recorded? [Instructions for the interview: If needed, explain that quotes and specific information about products will not be made public and that notes will be taken about the interview that will be sent to the participant for validation.]
2) Can you please introduce yourself and tell us your position at the [institute]?

Translational research

Instructions for the interview: One or more clinical trial/trials is/ are presented to translational researchers, based on the encountered information in the CCMO register. Summarized information is first discussed by the in interviewer, based on: 1) product type (cell therapy, genetically modified cell therapy, gene therapy), 2) type of cell on which the mechanism of action is based (CAR-T cell, TCR-T cell, TIL, CAR-NK cell, NK cell, DC, vector), 3) technology for genetic modification (vector type, other technology, NA), 4) starting material (autologous/ allogeneic), 5) indication (type of cancer), 6) development phase, and 7) single-center or multicenter study.

3) Can you describe how you moved from preclinical research to clinical research for these products?
   a) What was needed in order to take the step to GMP production?
   b) What was needed to get the clinical trial/trials started?

Instructions for the interview: In addition to information about clinical trials, information about preclinical research was also sought (in general) by means of information about the researcher(s) on the institute's website and the cell and gene portfolio.

4) Are there products that are (almost) ready for making the transition to GMP production from preclinical development for clinical trials?
5) Is there a plan for product development? [e.g. target product profile, for registration]
6) Are there also products that were not further developed after successful preclinical research?
   a) Why were these products not further developed?
   b) What are the considerations when deciding whether certain products will be further developed and other won't? *[For example: (if respondent hesitates or doesn't know): regulations, clinical results (safety, efficacy), financial resources]*
7) What was needed for further developing more preclinical products in clinical trials by means of approval by the CCMO? *[For example: (if respondent hesitates or doesn't know): regulations, clinical results (safety, efficacy), financial resources]*

Knowledge sharing and collaboration for translational research

Instructions for the interview: These questions are also asked based on the products that are manufactured for one or more clinical trials. The goal is to find out about the types of actions that were or weren't taken for knowledge sharing and collaboration between production facilities and why this was or wasn't done.

8) Was knowledge shared about this translational research, in the public domain or with other institutes? This can include study protocols, materials, methods (e.g. mouse models, protocols for transduction)? *[For example: (if respondent hesitates or doesn't know): publications, reports, conferences, symposia, workshops, sharing of personnel or facility, informal social relationships, financial relationship]*
   a) Why or why not? *[For example: (if respondent hesitates or doesn't know): personal attitude, strategic reasons*

for product development, strategic reason for funds/ grants, other priorities, clinical results, production results, commercial value, IP possibilities]

9) Are there partnerships for translational research?
[For example: (if respondent hesitates or doesn't know): consortia, technology transfers, R&D partnerships, spin-off]
a) Why or why not? *[For example: (if respondent hesitates or doesn't know): personal attitude, strategic reasons for product development, strategic reason for funds/ grants, other priorities, clinical results, production results, commercial value, IP possibilities]*

Perspectives

10) What do you need in order to move forward?
11) What do you think about more knowledge sharing and collaboration within academia?
a)) What is needed in order to take advantage of opportunities?
b)) Is there production capacity that is currently not being used? [scale-up for larger clinical trials, automatic/ continuous production in the future]
c)) What are the biggest hurdles? *[For example: specialisms per institute, complicated sharing of knowledge and IP, no incentives/earning model.]*
d)) Under which circumstances will you stop with knowledge sharing and collaboration with other public institutes? And why? *[Note: Find out the boundary between pre-competitive research and competitive product development]*
12) Would you like to take part in a national network of public institutes in order to share more knowledge and engage in collaboration? Why or why not?
a) Who should coordinate this?
13) Are there aspects that are important in order to get these products from academia to the patient? [For example, remuneration, distribution, collaboration with companies]
14) What is your vision for the future of this [cell and gene therapy] field?
a) Which methods, products or technologies do you believe will be the most successful?

15) Would you like to add anything that we've not touched upon?

Conclusion

Instructions for the interview: *Explain that findings will be published in a report (aggregated level). Publication of report (website), meeting being planned (mid-2021). Thank you very much.*

3: Questionnaire for clinical researchers and/or physicians - clinicians

Explanation for interview: The list with clinical trials serves as the basis for the interview (for "Clinical trials" and "Knowledge sharing and collaboration between researchers"). For clinicians, the questions focus on the course of the study/trials and further development possibilities, plus knowledge sharing and collaboration stemming the conduction of the study/trials. There are also general questions asked about perspectives for knowledge sharing and collaboration in the Netherlands, plus about the future of the field.

Introduction

Instructions for interviewers: explain proposals and function at KWF. Explain the project's goal (academic network for knowledge sharing and collaboration; further development).

1) Do you object to this interview being recorded? [Instructions for the interview: If needed, explain that quotes and specific information about products will not be made public and that notes will be taken about the interview that will be sent to the participant for validation.]
2) Can you please introduce yourself and tell us your position at the [institute]?

Clinical trials

Instructions for the interview: One or more clinical trials is/are first discussed with the clinical researchers, based on the encountered information in the CCMO register. Summarized information is first discussed by the in interviewer, based on: 1) product type (cell therapy, genetically modified cell therapy, gene therapy), 2) type of cell on which the mechanism of action is based (CAR-T cell, TCR-T cell, TIL, CAR-NK cell, NK cell, DC, vector), 3) technology for genetic modification (vector type, other technology, NA), 4) starting material (autologous/ allogeneic), 5) indication (type of cancer), 6) development phase, and 7) single-center or multicenter study.

3) How did these trials go/how are these trials going?
   a) [In the event of inadequate explanation:] Are there trials that were discontinued/are they still ongoing/have they been completed?
4) [For unapproved trials:] Why did these trials receive a negative assessment from the CCMO?
5) [For discontinued trials:] What were the reasons for the discontinuation? *[For example: (if respondent hesitates or doesn't know): patient inclusion, production, regulations, clinical results (safety, efficacy), financial resources]*
6) [For ongoing and completed trials:] What do the results (to date) indicate?
7) [For ongoing and completed trials:] Is follow-up research planned for this product?
   b) Why or why not? *[For example: (if respondent hesitates or doesn't know): patient inclusion, production, regulations, clinical results (safety, efficacy), financial resources]*
8) Are there options to further develop one of these products as a registered drug by means of approval by the EMA?
   a. Is there sufficient capacity within [institute] to further develop these products only towards registration? Why is or isn't this necessary?
9) What is needed in order to implement this product in clinical practice?
10) Does it fit within current regulatory frameworks?

Knowledge sharing and collaboration between researchers

Instructions for the interview: These questions are also asked based on multiple clinical trials. The goal is to find out about the types of actions that were or weren't taken for knowledge sharing and collaboration between clinical researchers and why.

11) Was knowledge shared about these clinical trials, in the public domain or with other institutes? This can include clinical results. *[For example: (if respondent hesitates or doesn't know): publications, reports, conferences, symposia, workshops, sharing of personnel or facility, informal social relationships, financial relationship]*
    c) Why or why not? *[For example: (if respondent hesitates or doesn't know): personal attitude, strategic reasons for product development, strategic reason for funds/ grants, other priorities, clinical results, production results, commercial value, IP possibilities]*
12) Were there official partnerships for the development of these products? *[For example: (if respondent hesitates or doesn't know): consortia, technology transfers, R&D partnerships, spin-off]*

d) Why or why not? *[For example: (if respondent hesitates or doesn't know): personal attitude, strategic reasons for product development, strategic reason for funds/ grants, other priorities, clinical results, production results, commercial value, IP possibilities]*

13) Are there other cell and gene therapies that are tested in clinical trials in the [institute]?

e) [if yes, ask for more details;] What kind of product is this; where does the innovation come from; what kind of collaboration is this [R&D partnership [with UMCs/ spin-offs/industry]/ participate as a site?

Perspectives

14) What do you need in order to move forward?

15) What do you think about more knowledge sharing and collaboration within academia?

f) What is needed in order to take advantage of opportunities?

g) Is there production capacity that is currently not being used? [scale-up for larger clinical trials, automatic/ continuous production in the future]

h) What are the biggest hurdles? [For example: specialisms per institute, complicated sharing of knowledge and IP, no incentives/earning model.]

i) Under which circumstances will you stop with knowledge sharing and collaboration with other public institutes? And why? *[Note: Find out the boundary between pre-competitive research and competitive product development]*

16) Would you like to take part in a national network of public institutes in order to share more knowledge and engage in collaboration?

j) Who should coordinate this?

17) Are there aspects that are important in order to get these products from academia to the patient? [For example, remuneration, distribution, collaboration with companies]

18) What is your vision for the future of this [cell and gene therapy] field?

k) Which methods, products or technologies do you believe will be the most successful?

19) Would you like to add anything that we've not touched upon?

Conclusion

Instructions for the interview: *Explain that findings will be published in a report (aggregated level). Publication of report (website), meeting being planned (mid-2021). Thank you very much.*