Summary KWF conference:

‘Cell and gene therapy in oncology – the development of academic innovations’

On Wednesday October 6th, the Dutch Cancer Society (KWF) hosted the conference ‘Cell and gene therapy in oncology – the development of academic innovations’ at ARTIS royal zoo. The main aim of the conference was to discuss how to bring the cell and gene therapy field forward, using a multistakeholder dialogue.

KWF report as a starting point

Academic researchers, hospital pharmacists, medical doctors, representatives of regulatory bodies, health technology assessment experts, patient associations, valorization institutes and ministries came together to discuss the findings and recommendations of the previously released report ‘Cell and gene therapy to oncological clinical practice’. This report examines opportunities and challenges for accelerating the development of academic cell and gene therapies in the Netherlands.

Highlights of the report

In the report we took a closer look at the innovation system, the system in which academic developers operate in their development efforts. A better innovation system supports and facilitates scientific and technological advances as much as possible, which allow emerging breakthrough therapies to reach patients substantially faster.

In a perfect innovation system there are two routes by which academic products can reach patients in clinical practice: the Academic route and the Commercial route. In the Academic route, innovations are developed and brought to the patient by public developers, whereas in the Commercial route, innovations are transferred to, or developed in collaboration with private entities such as spin-offs, small or medium enterprises, or larger established pharmaceutical companies (see KWF report or one-pager).

We identified three major pitfalls which need to be addressed in order to reach patients faster with new potential therapies from the academic laboratory. First, there is a gap to bridge bench-to-bedside, or, in other words, the transition from the laboratory and animal studies to treatment in clinical trials. Second, it has been shown to be difficult to scale up from early phase clinical trials to larger, late phase clinical trials within academic centers. In addition, commercial incentives hinder transfer to the private sector or access in clinical practice later on. Third, implementation of cell and gene therapies in clinical practice after successful late phase clinical trials imposes regulatory challenges for academic developers.

In three thematic sessions potential solutions to these pitfalls were discussed.

SESSION 1:

Manufacturing and quality

The first session focused on the difficulties with the bench-to-bedside transition within academia. Many experimental cell and gene therapies enter the Academic route here, because of their high risk profiles, complex production procedures, limited options for Intellectual Property (IP), heterogenous product characteristics and/or niche target populations. However, in the Academic route, bottlenecks exist that are mainly related to production under Good Manufacturing Product (GMP) regulations. Developers need to redesign products and develop procedures for quality control, under stringent regulations. These steps and the technical knowledge (also referred to as 'know-how'), is typically present in-house and at a large scale at the pharmaceutical and biotechnology companies. However, academic medical centers do not have infrastructure or capital on an industrial level. As a solution, infrastructure and financial support need to be enhanced, but to efficiently improve academic capacity it is recommended to establish a collective knowledge base for manufacturing and quality aspects to tackle translational issues in this novel field with heterogenous products.

The discussion following this session focused on the need for more knowledge sharing and collaboration not only between academics, but also between academics and other stakeholders, such as regulators, the boards of research institutes and health technology assessment bodies. Collaboration between academics to facilitate translational research would involve integrated research teams between different disciplines, such as the research team and the pharmacists of the production facilities. In this process, considerations related to regulations and health technology assessment need to be included in decision-making for shaping development trajectories.

In the UK Catapult initiative, developers are stimulated to seek scientific advice on regulatory and health technology aspects as early as possible. A dialogue on which requirements create hurdles is of equal importance. Health technology aspects include assessments of costs, the likelihood of reimbursement, and a trajectory that ensures the collection of long-term data. More interaction between academics and regulators can also be achieved and strengthened through initiatives such as STARS an EU training initiative to enhance regulatory science for academics.

KWF commits to support knowledge sharing and collaboration among academics by providing funding to enhance infrastructure for manufacturing according to GMP through the Infrastructure initiatives Call 2021-2 (See our call 'Infrastructure initiatives 2021-2'). The applicants of the DARE-NL initiative were invited to present their proposal. DARE-NL is a national initiative to support translational research of academic innovations across the Netherlands through rapid and structural knowledge exchange and collaboration (see slide deck). In the project, three platforms for cell and gene therapies are created: a knowledge framework for production related aspects, a biologics & technology hub to generate source materials and methods, and an implementation and patients outreach platform that aims to tackle regulatory and HTA related hurdles. All Dutch academic medical centers, oncological institutes and Sanquin join forces in the DARE-NL platform. Therefore, it enables to approach and interact other stakeholders through one voice and on a higher level than for individual product developments. Based on the evaluation and advice of the review board of the Infrastructure initiatives 2021-2, KWF is pleased to announce that funding for the DARE-NL initiative is granted. The planned infrastructure centrally tackles bottlenecks and will accelerate the translation of novel academic cell and gene therapies towards early and sustainable access in the Netherlands (see news release). In addition to this KWF grant, academic medical centers can support research activities to large extent through governmental funding that is intended for academic, investigational activities ('academische component').

SESSION 2:

Clinical development

The second session focused on the difficulties to move from early phase to late phase clinical trial development. Even when data from early trials show to be promising, it is difficult to scale up to larger trials by academic centers themselves. Inclusion of patients, scaling up production, and sufficient financial resources are common issues. Choosing a fitting trial design can be challenging due to small patient populations, or selection of subgroups of patients based on biomarkers in the analysis. Products could also be transferred to the private sector when de-risked by academia in early clinical trials. Yet, commercial incentives hinder transfer, and access later on. Collaboration and coordination is essential to perform late phase clinical development. If academics are supported by valorization bodies when engaging in public-private partnerships or license agreements, a partnership or transfer to industry may be less daunting. Furthermore, negotiations could be geared towards access for patients if the product reaches clinical practice, and secure research funds for academia as a sustainable model for academic product development. A central coordinating body could fulfill these roles, but it requires a large financial investment. Similar coordinating bodies have been realized in other countries, such as the UK Catapult. Catapult bodies were realized by governmental financial support. An equivalent body could be realized in the Netherland through the National Growth Fund.

In the discussion there was a focus on adaptive trial designs and regulatory aspects. Adaptive trial designs are considered important to move forward. Yet, to use such designs is not common practice yet, and concerns were expressed on the regulatory flexibility that would enable to use adaptive trial designs. The question was raised whether phase III trial designs are becoming redundant. Using real world data may be an alternative. Regulatory differences with the United States were discussed as a root cause for lagging behind in the EU when it comes to cell and gene therapy developments, but not in relation to the requirements for market entry. In particular, the national regulatory differences and various procedures among EU Member States may create a less appealing innovation system for developers compared to the US. This warrants EU harmonization of the regulatory system that precedes centralized marketing authorization. Another point of discussion was scaling up manufacturing from early clinical trials to late clinical trials, which was considered possible through collaboration among public facilities for indications with small patient populations. The Erasmus MC achieved to scale up their productions through the establishment of a spin-off company, which enabled to hire personnel required for production of a phase III trial. Different business models, collaborations, and types of agreements provide solutions for scaling up to ultimately support treatment in clinical practice.

SESSION 3:

Route to clinical practice

The third session focused on the difficulties to implement new therapies in clinical practice. Even when late phase clinical development is successful with beneficial clinical outcomes, academics struggle to bring products to clinical practice due to regulatory issues, as they do not have enough experience with, nor capacity for, valorization of research activities into medicinal products for market entry. A service for regulatory support is needed to be able to enter regulatory procedures and adhere to regulatory requirements. Support for valorization is needed to choose an appropriate business strategy that suits an individual product and its characteristics. Furthermore, there are academic products for which centralized registration is not, or not yet, feasible. These products represent a grey area in between cell and gene therapies that are commercially viable, and human cells and tissue that are not regulated as medicinal products such as allogeneic stem cell transplantation. The Hospital Exemption may be used to enable treatment in clinical practice. However, its scope and scale is rather narrow and limited to exemption situations. Consequently, for some products, neither Hospital Exemption nor centralized registration pathways may be a suitable route to clinical practice. In addition, academic medical center do not have experience with being a license holder of medicinal products.

The last discussion started with tensions to regulate cell and gene therapies as medicinal products or human cells and tissue. Questions were raised on the ownership of cell therapies when source material consists of the patients' own cells. Regulatory science could help to answer questions which products need to be regulated as medicinal product and which can be exempted through definition updates or guidelines based on previous experience or risk profiles. Furthermore, strategies for business development were discussed. Support can be provided by the Technology Transfer Offices (TTO) of institutes, Oncode, or through a centralized TTO office. It is vital to involve private parties at the right moment, which involves more than protection of IP. Oncode has experience with valorization of cell and gene therapies and collaboration with industry, and may prove a valuable partner to involve in development trajectories for new promising therapies in the field of oncology. It is being explored how support from Oncode can become more broadly accessible throughout the Netherlands. When developing your product through the Academic route it is recommended to interact with the European Medicines Agency, and to be aware of competing research activities.

Defining the most appropriate business strategies and route to clinical practice (academic or commercial) will have consequences for control over pricing and other marketing decisions. A centralized body could serve as a centralized TTO with regulatory and health technology expertise. Yet, to establish such a centralized coordinating body a large financial investment is needed. KWF commits to lobby for such a coordinating body, the development of clear, fit-for-purpose regulatory and HTA requirements, and more interaction among academics and regulatory bodies. KWF is eager to combine forces with academics and other stakeholders to bring developments in the field of cell and gene therapies within oncology further.

KWF

Dutch Cancer Society