HOW ACADEMIC DEVELOPMENT OF CELL THERAPY CAN BENEFIT BELGIAN PATIENTS

White paper
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Anticancer Fund

Fondation contre le Cancer
Stichting tegen Kanker

Kom op tegen Kanker

CONTENT

EXECUTIVE SUMMARY

In 2020 and 2021, the *Anticancer Fund*, the *Fondation contre le Cancer/Stichting tegen Kanker* and *Kom op tegen Kanker* embarked on a major exercise concerning **academically developed autologous cell therapy in oncology**, involving all major stakeholders.

It is the desire of all three organisations that academically-developed cell therapy in oncology receiving public or charity funding in Belgium should lead to *effective* treatments, which can be brought to all patients who might benefit, in a **timely**, **safe** and affordable way. To achieve a non-commercial, academically-driven pathway, the following recommendations are being made:

- Establishment of a (national) academic cell therapy development **knowledge platform**.
- Development of sufficient **competence in academic centres** involved in point-of-care manufacture to ensure legal and regulatory compliance.
- **Collaboration on GMP manufacturing of cell therapy** (in the form of a not-for-profit manufacturing unit or collaboration between the knowledge platform and a CMO).
- **Early dialogue on clinical development** between academics and healthcare authorities (regulators and payers).
- **Greater collaboration between academic centres** in setting up **larger clinical trials** (nationally and internationally).
- Securing public **funding for large-scale clinical trials**.
- In the regulatory domain, **greater accessibility and transparency** of authorisation procedures for academics.
- A **parallel trajectory for academic development and authorisation** of cell therapy.
- Creation by the RIZIV/INAMI of a **reimbursement procedure for academically-developed cell therapy treatments** if they prove beneficial for patients.
- Intervention by the **special solidarity fund** for valuable therapies authorised under the **hospital exemption**.
- **Fair pricing** of academically-developed cell therapy.

This white paper is a starting point for discussion about our recommendations with Belgian and European policymakers. A thorough analysis of the development and valorisation of academic cell therapy **by the Belgian KCE** could lead to **a clear roadmap** for academically-developed cell therapy, from the laboratory bench to the patient, including the feasibility of a **parallel trajectory for academic development and authorisation**.

LIST OF ABBREVIATIONS

ACF	Anticancer Fund
ATMP	Advanced therapy medicinal product
BTC	Blood, tissue and cells
CAR T	Chimeric Antigen Receptor T-cell
CAT	Committee for Advanced Therapies
CMO	Contract Manufacturing Organisation
CTG/CRM	Commission for Reimbursement of Medicines
EMA	European Medicines Agency
EU	European Union
EUNETHTA	European Network for Health Technology Assessment
FAGG/AFMPS	Federal Agency for Medicines and Health Products
FCC/STK	Fondation contre le Cancer/ Stichting tegen Kanker
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HE	Hospital exemption
HTA	Health technology assessment
JACIE	Joint Accreditation Committee ISCT-Europe & EBMT
KCE	Belgian Healthcare Knowledge Centre
KOTK	Kom op tegen Kanker
MA	Marketing authorisation
MAH	Marketing authorisation holder
RIZIV/INAMI	Rijksinstituut voor ziekte- en invaliditeitsverzekering/Institut national d'assurance maladie-invalidité (National Institute for Health and Disability Insurance)
ROI	Return on investment
RUZB/CHAB	Council of Belgian University Hospitals
SMEs	Small and medium-sized enterprises
TGR/CTM	Technical Medical Council

INTRODUCTION

Autologous cell therapy (Table 1) is a promising development in the treatment of cancer. It could be a solution in situations of high unmet medical need. However, commercially-developed cell therapy is not going to solve every need. In some situations, such as small patient groups, cell therapy is not sufficiently profitable for industry. This has been illustrated by several market withdrawals of cell therapies. Because of its highly personalised nature, autologous cell therapy is suitable for manufacture at the centre where patients are treated.

Table 1. Autologous cell therapy in oncology

In oncology, autologous cell therapy is usually designed to improve the ability of the immune system to fight cancer. A specific set of cells from the patient's blood, lymph nodes or tumour are collected. In many cases the cells are modified to produce a more vigorous immune reaction against a patient's cancer cells, then reinjected into the patient, either systemically, intradermally or directly into the lymph nodes or tumour. Cell therapies include dendritic cells, tumour-infiltrating lymphocytes, chimeric antigen receptor (CAR) T-cells or T-cells with an engineered TCR, cytotoxic T lymphocytes, natural killer cells, and others.

Between 2011 and 2021, *Fondation contre le Cancer/Stichting tegen Kanker*, *Kom op tegen Kanker* and *the Anticancer Fund* invested €12.5 million in academic projects on cell therapy (see Table 2 for examples). It is essential that the results of these projects, if successful, reach patients.

Table 2. Examples of preclinical and clinical research currently supported by one of the three organisations

Indication	Type of cell therapy	Phase	Institution	Funder
Acute myeloid leukaemia	Dendritic cell	Clinical Phase II	UZA	KOTK
Mesothelioma	Dendritic cell	Clinical Phase I/II	UZA	KOTK, FCC/STK
Glioblastoma	Dendritic cell	Clinical Phase I/II	UZB	KOTK
Glioblastoma	Dendritic cell	Clinical Phase I/II	UZA	KOTK
Paediatric and adult glioblastoma and DIPG	Dendritic cell	Clinical Phase I/II	UZA	KOTK
B-cell malignancies	CAR T-cell	Clinical Phase I/II	UZA	KOTK
Colorectal cancer	Dendritic cell	Clinical Phase I/II	UZB	FCC STK
Solid tumours	Dendritic cell	Clinical Phase I	UZA	KOTK, FCC/ STK
Non-small cell lung cancer	Dendritic cell	Clinical Phase I	UZG	KOTK
Melanoma	Dendritic cell	Clinical Phase I	UZB	KOTK
Melanoma	Dendritic cell	Preclinical	VUB	KOTK
TNBC, solid tumours	Dendritic cell	Preclinical	VUB	KOTK
Non-small cell lung cancer	Dendritic cell	Preclinical	VUB	FCC/STK
B-cell malignancies	CAR T-cell	Preclinical	KUL	FCC/ STK
Various cancer types	T-cell	Preclinical	UCL	FCC/STK

Accessibility of autologous cell therapy encompasses a **robust manufacturing process, financial support** and a **realistic development plan** towards authorisation and reimbursement. So far only pharma companies have succeeded, and the prices of products are high. **Are there alternative pathways to ensure that effective academically-developed therapies, supported by public money, can be brought to patients?**

To answer this question, *Kom op tegen Kanker*, the *Fondation contre le Cancer/Stichting tegen Kanker* and the *Anticancer Fund* joined forces. KPMG was commissioned to prepare a horizon scan on the cell therapy market in oncology. This was followed by a review of the relevant literature and regulatory documents on the topic.

The three organisations then invited Belgian research teams, academic decisionmakers, payers, regulators and the Belgian HTA body to jointly address the feasibility and accessibility of academically-developed autologous cell therapy in Belgium in a series of round tables and one-on-one interviews with key stakeholders. Case studies of academic projects on cell therapy were drafted and used to inspire our round tables.

An initial round table with academic researchers and a second one with decisionmakers and tech transfer specialists from universities were organised. These led to a green paper, which gave an overview of the topic of academically-developed cell therapy and described the challenges. The green paper was discussed in one-on-one interviews with key stakeholders. Finally, public health authorities, reimbursement agencies and payers came together at a third round table to reflect on the challenges.

To conclude this process, the three organisations now present their recommendations in this white paper.

DESIRED OUTCOME

Academically-developed cell therapy in oncology receiving public or charity funding in Belgium should lead to **effective** treatments, which can be brought to all patients who might benefit, in a **timely**, **safe** and **affordable** way.

Currently, the only way to bring cell therapy to patients is via a commercial route, but pricing is extremely high. Moreover, the industry is highly unlikely to invest in therapies that will not assure a ROI, even if for some patients the therapy can potentially be very beneficial. An alternative pathway should exist.

However, patients should not receive cell therapy in a non-controlled manner, i.e. outside the bounds of a clinical trial, marketing authorisation or alternative scheme controlled by competent authorities. Cell therapy should be administered only by a competent multidisciplinary medical team. Ensuring the quality and safety of the cell product is critical.

When public or charity money is used for the initial development, a pathway to fair pricing should be guaranteed.

The three organisations are convinced that Belgian universities and university hospitals should play a central role in developing and administering cell therapy. Providing the highest-quality advanced technologies to their patients is part of their mission. This is clearly articulated by the Council of Belgian University Hospitals (RUZB/CHAB): The seven university hospitals, united in the Council of Belgian University Hospitals, have a specific role in our society in addition to offering basic care. They are the driving force behind research in our healthcare system, they are responsible for training medical specialists, and they provide state-of-the-art care to patients who have nowhere else to turn. Together they ensure continuous improvement of health care. Because the accessibility and affordability of academically-developed cell therapy may not be guaranteed in the future, the *Anticancer Fund*, the *Fondation contre le Cancer/Stichting tegen Kanker* and *Kom op tegen Kanker* are concerned that universities and university hospitals are going to be unable to play their role.

There are still many challenges **and hurdles** that need to be addressed in order to facilitate the academic development and administration of cell-based therapy in Belgium. Inspired by our round tables, in this paper we concisely describe the hurdles in four domains: manufacturing, evidence, regulatory aspects and reimbursement, and propose recommendations to tackle each challenge. Although the focus of our white paper is autologous cell therapy, several recommendations may have a wider applicability.

KEY RECOMMENDATIONS FROM THE ROUND TABLES

1

Manufacturing

Context

- Cell therapy manufacturing should comply with **current Good Manufacturing Practice (cGMP)** and be performed within the context of a solid quality management system, to guarantee the consistently high quality of cell therapy products. It requires a well-controlled bioprocess to control for the complex and variable nature of cell therapy products. The EMA has well-defined cGMP guidelines for cell therapy that describe the need for a functional quality system based on a risk-based approach.
- Manufacturing of cell therapy products, such as CAR T-cells, is currently centralised at a handful of sites in Europe and America. Centralised manufacturing of cell therapies is very costly and requires the transport of cells under very robust conditions. It also negatively impacts the vein-to-vein time (i.e. it can be a long time before a patient receives the treatment).
- An academic group in Barcelona demonstrated the feasibility of CAR T-cell manufacturing in an academic hospital, for heavily pre-treated ALL, CLL, and NHL patients, using an automated cell processing device, CliniMACS Prodigy. Several other centres have used this approach in an early clinical trial setting.

Challenges

- Academic GMP centres can be major contributors in the development of cell therapy products, but there are hurdles:
  - The adaptation of GMP rules to cell-based products in the academic hospital setting is not a trivial task. Although academic GMP facilities exist, creating a fully-compliant GMP structure inside a standard hospital environment is often prohibitively expensive or logistically challenging.
  - Acquiring GMP accreditation is only the first step. The facility must be able to continuously meet GMP standards in the long term and invest time and resources in audits and inspections.

Recommendations

- The **establishment of a national cell therapy development knowledge platform** should be considered. The Council of Belgian University Hospitals could be instrumental in creating such a platform.
- An academic centre involved in point-of-care cell therapy manufacture should develop local competence to ensure legal and regulatory compliance, supported by the knowledge platform.

- It is not desirable for every academic centre to try to set up a GMP facility on its own. Realistic alternatives include:
  - A not-for-profit manufacturing unit, with a legal structure comparable to the stem cell bank of the Red Cross.
  - **Collaboration** between the knowledge platform and a contract manufacturing organisation (CMO). A CMO provides services to other organisations, ranging from drug development to drug manufacturing. A CMO can help to ensure that an academic cell therapy facility lives up to GCP/GMP rules. If a private CMO is involved, there should be guarantees that the end user price will be fair (see below) and the cost of goods transparent.

2

Gathering of evidence in clinical trials

Context

- Before a cell therapy can be used in a clinic, developers have to provide evidence on efficacy, safety and added value. Clinical trials are necessary. The clinical development of a therapy usually begins with small studies. In later phases, clinical studies expand in size and duration. This process is often described as consisting of four phases (Phase I, II, III and IV trials). In a recent guideline, the EMA stressed that the phase concept is a description and not a requirement. The phases may overlap or be combined and can be supported by data from expanded access programmes.
- Cell therapy development may deviate from the traditional trajectory. Sometimes, trials combine Phases I and II. Large-scale, pivotal trials are not always feasible, certainly when considering rare cancers. There are examples of commercially-available cell therapies that obtained market authorisation without Phase III-trial data (Kymriah Yescarta).
- The EMA and national authorities (FAGG/AFMPS in Belgium) are responsible for protocol assistance and scientific advice about clinical trial protocols.
- FAGG/AFMPS and ethics committees are responsible for authorising clinical trials. FAGG/AFMPS organises inspections during trials to check GMP and good clinical practice (GCP, a set of standards on clinical trials that ensure the study's results are credible and accurate).

Challenges

- At a late phase of the research and development process, it is often discovered that the evidence provided by academic research does not meet the requirements of the authorities responsible for authorisation or reimbursement of cell therapy. This makes it difficult to obtain authorisation and reimbursement.
- The requirements of regulatory bodies (EMA, FAGG/AFMPS) and payers (RIZIV/INAMI) are not aligned. For example, their expectations around comparators and endpoints of clinical trials may differ.
- For a single academic centre, it is very difficult to organise the large, late-phase clinical trials required for authorisation and reimbursement. Late-phase clinical trials often need to be multicentric and international.

- In some situations, the organisation of large, late-phase clinical trials in the field of cell therapy is complex. The recruitment of a sufficient number of patients is often an obstacle. It is not clear whether regulatory and reimbursement bodies sufficiently take this into account when evaluating a therapy.
- Despite the financial support of organisations such as KotK, FCC/STK and ACF, the budgets necessary to run large-scale clinical trials in an academic context as well as to cover the costs associated with the regulatory development path are lacking.

Recommendations

- **Early dialogue** between academics and healthcare authorities (regulatory bodies, payers, HTA-agencies) should be part of the development pathway of cell therapy. This will ensure the correct decisions about clinical trial design, endpoints and comparators are made and allow the potential cost-effectiveness of the new therapy to be explored. It will also ensure the correct regulatory classification of the therapy (see Section 3 – Regulatory aspects).
  - This early dialogue should be a standard part of the protocol development for academic clinical trials.
  - Organisations such as FAGG/AFMPS, RIZIV/INAMI, KCE (on a Belgian level) and EMA (on a European level) should have clear and affordable procedures for this early dialogue. They should inform academic researchers about this possibility and assist them during the dialogue.
  - Involving EUNETHTA21 in this early dialogue may be worthwhile. This consortium of European HTA bodies should offer scientific consultations on a European level.
  - The early dialogue could provide clarity on the level of evidence required (Phase I/II or Phase III trials; single or double arm, randomised or not, etc.).
- It is often difficult for individual academic centres to deal with the requirements of the regulatory and reimbursement pathway. For example, large clinical trials cannot be organised at a single centre. **Academic centres should therefore collaborate**, both nationally and internationally.
  - The Belgian knowledge platform could be instrumental in organising multicentre trials. It could coordinate and support the organisation of academic clinical trials.
  - In some cases, clinical development of cell therapy will involve international collaboration. The EU's Beating Cancer Plan provides for the establishment of an EU Network linking nationally-recognised comprehensive cancer centres in every member state. An aim is to improve patient access to high-quality diagnostics and the latest innovative treatment. This network could also play a role in organising clinical development of cell therapy on a European scale.
  - Establishment of an EU knowledge platform for cell therapy trials.
- Academics need **public funding for large-scale clinical trial**s.
  - KCE, the Belgian healthcare knowledge centre, funds non-commercial practice-oriented trials through the KCE trials programme. The scope of the programme is currently limited to comparative effectiveness studies and repurposing RCTs. The scope should be broadened to cover registration trials of non-commercial therapies with a potentially high impact on public health. KCE has the expertise to select trials and provide trial design feedback and feasibility support.
  - Article 56 of the **Public Health Insurance Ac**t allows for reimbursement of experimental

treatments. RIZIV/INAMI can make the reimbursement dependent on conditions concerning quality and research. This article could be used to incentivise the development of academic cell therapy.

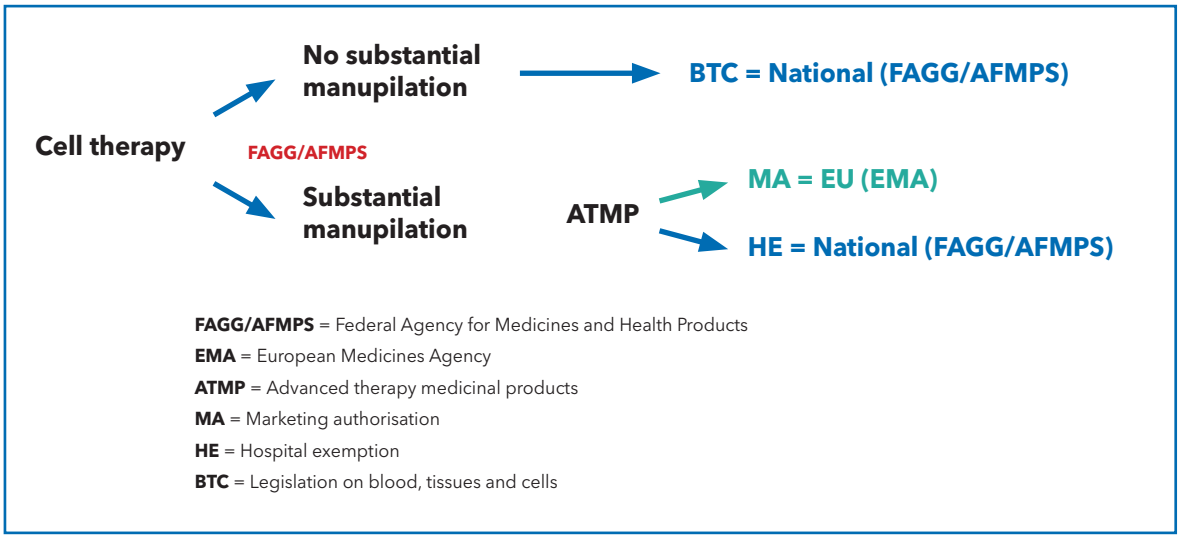
- The European Union should invest in a programme for non-profit academic clinical research. This could be part of the **European Mission on Cance**r, an important cornerstone of the European Framework programme for research and innovation 2021–2027.
- ***Regeling veelbelovende zorg*** in the Netherlands could be a source of inspiration. Through this scheme, it is possible to obtain temporary funding for treatments that appear promising but are not yet reimbursed. Research data of sufficient quality is collected on the effectiveness and cost-effectiveness of the new therapy. At the end of the project (a maximum of six years), the Dutch *Zorginstituut* assesses within six months whether the therapy can become part of their basic reimbursement package.

3 Regulatory aspects

Context

- Before a cell therapy can be used in a clinic, an authorisation stating that the therapy is safe and effective is required.
- Depending on the type of cell therapy, a different regulatory framework applies (Figure 1). If cells are used for the same essential function in the recipient as in the donor or if they are not being substantially manipulated, they fall under the EU Directives on **Blood or Tissues**. If cells are not used for the same essential function in the recipient as in the donor or if they are being substantially manipulated, they are not considered transplants and are regulated in the EU as **Advanced Therapy Medicinal Products (ATMPs)**.
- If a cell therapy is classified as an ATMP, the centralised European authorisation procedure via the EMA is applicable. If the risk/benefit balance is considered positive, it leads to a **Market Authorisation (MA)**, granted by the European Commission.
- Besides the standard MA route, the ATMP regulation allows a second, exceptional route to clinical care: the **Hospital Exemption (HE)**. This allows for the authorisation of an ATMP on a national level. There are strict conditions: the ATMP must be used on a small scale, and there must be no intention to market the ATMP. The HE can only be used for a non-routine, custom-made therapy, that is medically prescribed for an individual patient. Application of the HE differs between countries. Belgium, Germany, the Netherlands and Spain have requirements about clinical data before granting a HE. In other countries such as Austria, Finland, France and Italy, a HE can be granted without clinical evidence. Leru, a European network of research universities, is advocating for application of HEs to be harmonised throughout Europe.
- If a cell therapy falls under the blood or tissue directives, there is no European procedure. FAGG/AFMPS is responsible for quality control of the treatment.

Figure 1. Regulatory framework



Challenges

- Despite recent efforts by the EMA to reach out to academics (e.g. allowing them to use the PRIME scheme), it is still very difficult for an academic centre to become a marketing authorisation holder. Solutions proposed by regulators remain inside the current framework, which is geared to the resources and capabilities of the industry.
  - The procedure to obtain and maintain a MA is costly and complicated.
  - The holder of a marketing authorisation has several post-marketing responsibilities. For example, it must ensure the quality of the product and report on adverse events (pharmacovigilance). Within the current context, these duties are almost impossible for an academic institution to fulfil.
  - Being a MAH entails legal liability.
- In some cases, for example for ultra-rare diseases, the hospital exemption could be a way to make academically-developed cell therapy accessible. Several countries make use of HEs. France (11 authorisations), Germany (7) and the Netherlands (11) use HEs quite often. Up to now, no HEs have been issued in Belgium, and nor has FAGG/AFMPS received an application for a HE from a Belgian hospital. According to research, this can be attributed to stringent clinical data requirements and a lack of capacity to comply with conditions such as GMP in academic centres.
- A revision of several relevant European directives and regulations is ongoing (pharmaceutical legislation and legislation on blood, tissue and cells). This creates uncertainty, but also opportunities.

Recommendations

- **Greater accessibility and transparency** of authorisation procedures for academics. This entails:
  - Efforts by FAGG/AFMPS to communicate with and inform academics about the possibilities, requirements and limitations of the BTC and ATMP legislation and about hospital exemptions.
  - Collaboration between FAGG/AFMPS and academic centres to help academic centres comply with the provisions of BTC, ATMP and HE regulations.

- Efforts by academic centres to meet regulatory requirements, e.g. by establishing a national cell therapy development platform.

- The current pathway to make ATMPs available to patients is not adapted to the capabilities of academic centres. Therefore, **a parallel trajectory for academic development and authorisation of cell therapy** should be seriously considered. It is in the interests of European patients for this to be a European trajectory. We propose using the following building blocks to construct this trajectory:
  - The EMA's Committee for Advanced Therapies (CAT) is responsible for assessing the quality, safety and efficacy of ATMPs. The CAT has a certification procedure to encourage SMEs to develop ATMPs. This procedure evaluates the data required before a treatment can be used in humans. Certification confirms the data complies with the standards that apply to a marketing authorisation procedure. This is currently confined to SMEs. **The certification procedure could be opened up to academic developers**, to evaluate their quality and non-clinical data.
  - **The clinical evidence could then be evaluated by an EU-level HTA structure**, such as Eunethta21.
  - These first two steps would ensure the quality, safety, efficacy and added value of the cell therapy and could lead to the authorisation of an academically-developed cell therapy.
  - Once the therapy is used in a clinic, quality control is required. An organisation such as JACIE, Europe's accreditation body for stem cell transplantation and cell therapy, could perform this quality control, together with competent national authorities such as FAGG/AFMPS.
- A Belgian knowledge platform could help academic institutions fulfil regulatory requirements.

4

Reimbursement and pricing

Context

- Patient access to academically-developed cell therapy depends on reimbursement by the public health insurance agency (RIZIV/INAMI).
- Reimbursement of ATMPs is the remit of the Drug Reimbursement Committee (CTG/CRM) of RIZIV/INAMI. The CTG/CRM advises the government on the reimbursement of medicinal products, such as ATMPs. A drug may be reimbursed only if there is a marketing authorisation granted by the EMA. Exceptionally, a drug can be obtained before market authorisation, in cases of high unmet medical need, via an expanded access program.
- If an ATMP receives a hospital exemption authorisation, the standard procedure via the CTG/CRM is not applicable. The Special Solidarity Fund could be a solution. This fund reimburses expensive treatments for serious diseases, in exceptional circumstances.
- If a cell therapy is not classified as an ATMP, there's another path to reimbursement. The competent body is the TGR/CTM (Technical Medical Council), which will advise on whether the cell therapy is included in the list of reimbursed treatments ("Nomenclature").

- Article 56 of the Public Health Insurance Act allows for reimbursement of a novel therapy, with conditions on quality and evidence collection.

Challenges

- **Commercial cell therapy is notoriously expensive**. The two first CAR T-cell therapies, Yescarta and Kymriah, have been given price tags exceeding €300,000.
- It is **unclear how academically-developed cell therapy can obtain reimbursemen**t:
  - If an ATMP has no MA, options for reimbursement via CTG/CRM are limited. As it is difficult for academic centres to acquire and maintain a MA, it is difficult to get reimbursement for an academically-developed ATMP.
  - Our case studies show that the path to reimbursement through the nomenclature is not obvious either. In one case study, the requirements of the trajectory to reimbursement were not clear for the investigator. Another case study showed that it is difficult for an individual academic centre to comply with the evidentiary requirements of the TGR. Reimbursement was rejected because there was no large-scale study. For academic centres, it is very hard to organise such a study.
- The procedures of the Special Solidarity Fund can take a lot of time and lead to a lot of red tape; they are also opaque to applicants. This leads to financial insecurity, because the decision about reimbursement is usually made after the treatment has been administered.

Recommendations

- **Early dialogue** between researchers and payers is necessary so that the path to reimbursement and the evidentiary requirements of the existing paths are clear.
- The RIZIV/INAMI should set aside a sufficient budget and create a **reimbursement procedure for academically-developed cell therapy treatments**, provided these therapies receive certification from the CAT and EUnetHTA21, or a comparable body, has assessed the clinical evidence.
  - The CTG/CRM (Drug Reimbursement Committee) of RIZIV/INAMI can evaluate the reimbursement dossier and advise the minister of social affairs on the reimbursement of a cell therapy.
  - This procedure might be able to make use of article 56, because this allows for reimbursement while data gathering is still ongoing.
- For therapies authorised under the hospital exemption, the special solidarity fund should assess the available evidence in a transparent way and intervene if appropriate. In that case, it is important that the fund makes an effort to keep the procedure short and to communicate clearly with applicants.
- Academically-developed cell therapy should be fairly priced. A 'fair price' is justifiable, predictable and cost-effective within the aims and priorities of the healthcare system and the available budget. 'Justifiable' means a price that reflects the documented and clinically-relevant benefit of the medicine, and a reasonable relationship between the cost of bringing the product to market (including R&D, production, marketing, public/charity funding) and the price.

CONCLUSION

AKF, FCC/STK and KOTK are convinced that academically-developed cell therapy has an important role to play in cancer care. Commercial treatments are not going to solve all medical needs. Therefore, academically-developed cell therapy in oncology that meets high standards of efficacy and safety should be brought to patients in a timely, safe and affordable way.

Our round tables showed that academics encounter many hurdles in the development, authorisation, reimbursement and manufacturing of these therapies. To make progress, we believe academics should step up their collaboration, both nationally and internationally. Belgian University Hospitals should establish a cell therapy development knowledge platform.

Stronger collaboration between academics and HTA, regulatory and reimbursement bodies is another necessity. This will lead, among other things, to clinical research that is better adapted to the requirements of payers and authorising bodies.

In this specific context, clinical trials can only be performed if public funds are available.

We recommend that European and national authorities develop a parallel trajectory for academic development and authorisation of cell therapy, to guarantee quality, safety and efficacy.

Payers such as the RIZIV/INAMI have to be ready to evaluate whether treatments thus authorised should be reimbursed.

NEXT STEPS

We will encourage the authorities to implement our recommendations.

These are the next steps we will take:

- We will ask the Belgian KCE to do a thorough analysis of the development and valorisation of academic cell therapy. This should lead to a roadmap for academically-developed cell therapy, from the laboratory bench to the patient.
- We will approach Belgian and European policy makers to discuss our recommendations.
- We will explore whether our recommendations can be incorporated into European actions on research and cancer, such as the EU Beating Cancer Plan, the Cancer Mission and the revision of the general pharmaceutical legislation.

FURTHER READING

- *The global pipeline of cell therapies for cancer: Jia Xin Yu, Vanessa M. Hubbard-Lucey & Jun Tang. Nature Reviews (2019).*
- *White Paper on How to Go Forward with Cell-Based Advanced Therapies in Europe, Reinhold G. Erben et al. (2014) Tissue Engineering Part AVol. 20, No. 19-20.*
- *Discovery to Drug Development: Expanding the Role of Academic Centers: Abbie Roth (https://pediatricsnationwide.org/2017/04/24/discovery-to-drug-development-expanding-the-role-of-academic-centers/)*
- *The Third Mission of the university: A systematic literature review on potentials and constraints: Lorenzo Compagnuccia Francesca Spigarelli, Technological Forecasting and Social Change Volume 161, December 2020, 120284*
- *Cost of decentralized CAR T-cell production in an academic nonprofit setting: Tao Ran, Stefan B. Eichmüller, Patrick Schmidt, Michael Schlander, International Journal of Cancer, Early View https://doi.org/10.1002/ijc.33156*
- *Regulating gene and cell-based therapies as medicinal products: Coppens, D. G. M. (2020).*
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- *ICH guideline E8 (R1) on general considerations for clinical studies Step 5: EMA. (2021).*
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GLOSSARY

Advanced therapy medicinal product	A medicine for human use that is based on genes, cells or tissue engineering.
Autologous cellular therapy	Therapy that uses a patient's cells, which are cultured outside the body and reintroduced into the same patient.
Blood or tissue directive	The legal framework defining safety and quality standards for tissues and cells.
CAR-T cell therapy	Immunotherapy using the patient's modified T-cells (white blood cells of the immune system) to recognise cancer cells in order to target and destroy them.
Committee for Advanced Therapies (CAT)	EMA (European Medicines Agency) committee responsible for assessing the quality, safety and efficacy of advanced-therapy medicines.
Clinical trial	A study performed to investigate the safety or efficacy of a medicine. For human medicines, these studies are carried out in human volunteers.
Comparator	A medicinal product (i.e. active control) or placebo used as a reference in a clinical trial.
Competent authority	A medicines regulatory authority in the European Union.
Early dialogue	Non-binding scientific advice before the start of pivotal clinical trials (after feasibility / proof-of-concept study).
Fair price	Price of a treatment that is justifiable, predictable and cost-effective within the aims and priorities of the healthcare system and the available budget.
Good Clinical Practice (GCP)	A set of standards about clinical trials which guarantee that the study's results are credible and accurate.
Good Manufacturing Practice (GMP)	GMP (or cGMP, current GMP) are a set of standards concerning the manufacture, processing, packing, release and holding of a medicine.
Health technology assessment body	A public organisation that provides recommendations on the medicines and other healthcare interventions that can be paid for or reimbursed. These organisations look at the relative effectiveness and cost-effectiveness of medicines that have been authorised.
Marketing Authorisation (MA)	Approval to market a medicine in one, several or all European Union Member States.
Phase-I trial	A type of clinical trial in which a new medicine is given to humans for the first time. It looks at the way the medicine is dealt with by the body, its main effects and main side effects.
Phase-II trial	A type of clinical trial conducted after a Phase I trial to evaluate a medicine's effects in a particular condition and to determine its common short-term side effects.
Phase-III trial	A type of clinical trial usually conducted in a large group of patients to gather information about a medicine's efficacy and safety, to allow its benefits and risks to be evaluated.
Phase-IV trial	A trial carried out after marketing authorisation has been granted. Such trials are designed to monitor the effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.
Pivotal clinical trial	A clinical trial seeking to demonstrate the efficacy of a new drug in order to obtain marketing approval.

PRIME	Scheme launched by the European Medicines Agency (EMA) to boost support for the development of medicines that target an unmet medical need.
Preclinical study	Testing of a drug, procedure or other medical treatment (in animals or cell cultures) before trials are carried out in humans.
Randomised clinical trial	A study in which the participants are divided by chance into separate groups that compare different treatments or other interventions.
Registration trial	Clinical trial designed to support regulatory approval for a product in a country or region.
Scientific advice	The provision of advice by a competent authority on the appropriate tests and studies required in the development of a medicine or on the quality of a medicine.
Stem cell bank	Platform for the large-scale collection, preparation, storage and provision of stem cells (stem cells are special human cells that are able to develop into many different cell types).
Unmet medical need	Condition for which there exists no satisfactory method of diagnosis, prevention or treatment.

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