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Innovation Report

CTGCT, Centre of Excellence for the Technologies of Gene and Cell Therapy: Collaborative translation of scientific discoveries into advanced treatments for neurological rare genetic diseases and cancer

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ABSTRACT

The emerging field of precision medicine relies on scientific breakthroughs to understand disease mechanisms and develop cutting-edge technologies to overcome underlying genetic and functional aberrations. The establishment of the Centre of Excellence for the Technologies of Gene and Cell Therapy (CTGCT) at the National Institute of Chemistry (NIC) in Ljubljana represents a significant step forward, as it is the first centre of its kind in Slovenia. The CTGCT is poised to spearhead advances in cancer immunotherapy and personalised therapies for neurological and other rare genetic diseases. The centre's overarching mission is to extend beyond the NIC's scientific excellence in basic research and bring new therapeutic solutions toward clinical application. The CTGCT aims to develop a broad pipeline of biomedical tools, including innovative synthetic biology tools, gene editing and splicing technologies, RNA-based technologies, immune regulation engineering and novel viral and non-viral delivery systems. The CTGCT is supported by partner institutions from the UK, the Netherlands and Germany, which already have academic good manufacturing practice (GMP) facilities for the manufacture of advanced therapy medicinal products (ATMPs) and is committed to active collaboration with clinicians and patient organizations at all stages of development to improve access to gene and cell therapies (GCTs) for patients. The Centre also seeks to collaborate with national and international academic and industrial partners, and the newly established GMP facilities will address a critical bottleneck in the translation of GCTs from research to practice. Finally, CTGCT's translational research and technology transfer units will ensure the impactful dissemination of research and innovation activities in Slovenia, throughout the Western Balkans and Eastern Europe region, and beyond. With its comprehensive approach and forward-looking vision, the CTGCT will drive transformative advances in gene and cell therapies for the benefit of patients on a global scale.

1. Introduction

Cancer and rare diseases represent a major challenge for global healthcare systems. Millions of new cases are diagnosed every year, causing great human tragedy and a significant economic burden. In 2022, there were an estimated 20 million new cases of cancer and 9.7 million cancer-related deaths worldwide [1]. The estimated number of people still alive within 5 years of a cancer diagnosis was 53.5 million. Over 35 million new cancer cases are predicted for 2050 worldwide, a 77 % increase from the estimated 20 million cases in 2022. The economic impact of cancer in Europe is expected to exceed 100 billion EUR annually [2]. In addition, an estimated 5–8 % of the European

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population lives with rare diseases [3]. There are more than 7000 different rare diseases in the EU, of which around 80 % are of genetic origin and 70 % become symptomatic in childhood.

Despite these challenges, recent advances in biomedicine offer unprecedented opportunities for the development of novel treatments. The first new gene therapy for the extremely rare hereditary disease lipoprotein lipase deficiency (LPL) was approved by the European Medicines Agency (EMA) in 2012 [4]. The first drug using CRISPR/Cas9 gene editing technology to treat transfusion-dependent beta-thalassemia and sickle-cell disease was approved in 2023, a decade after the technology was discovered [5]. In 2023, the Food and Drug Administration approved 15 new therapies in oncology in the United States, including four new T-cell activating bispecific antibodies that recruit T cells to cancer antigen-expressing cells, doubling the number of these therapies on the market [6]. A total of six chimeric antigen receptor (CAR)-cell therapies are currently on the market, all for haematological malignancies, including four targeting CD19 and two targeting BCMA antigen.

However, the translation of these scientific breakthroughs into clinical applications has been uneven, with the European Union lagging, especially in countries with lower research intensity such as Slovenia. According to the European Innovation Scoreboard, Slovenia is among the moderate innovators [7-9], which underlines the need to strengthen cooperation to bridge the gap between research and implementation.

Under the auspices of Horizon Europe, the United Kingdom Research and Innovation and the Ministry of Higher Education, Science and Innovation of the Republic of Slovenia, a teaming project aims to fill this gap by establishing the Centre of Excellence for the Technologies of Gene and Cell Therapy (CTGCT) at the National Institute of Chemistry (NIC) in Slovenia. This initiative brings together renowned institutions in gene and cell therapy research, including University College London, University Medical Center Utrecht, Charité University Hospital Berlin, and Technical University Dresden. The collaboration aims to leverage the expertise and resources of these advanced partner institutions to strengthen the CTGCT's capabilities in the areas of research, translation and innovation.

The mandate of the CTGCT goes beyond basic research and also includes the establishment of facilities for the production of clinical-grade therapeutic reagents, produced under good manufacturing practice (GMP), as well as the creation of a Translational Research Unit and Technology Transfer Office. With these initiatives, the CTGCT aims to accelerate the translation of scientific discoveries into concrete therapeutic interventions. The partner institutions will assist with the establishment of GMP facilities, innovation management, regulatory compliance, industry links, staff training and the creation of start-ups. Overall, the establishment of the CTGCT represents a significant step forward in addressing the unmet need for gene and cell therapies in Europe. By harnessing the collective expertise of its partner institutions, CTGCT aims to catalyze the development and translation of innovative therapies, ultimately improving healthcare outcomes for patients in Slovenia and beyond.

2. Project description

2.1. Project goals and objectives

The CTGCT will focus primarily on the development and translation of breakthrough technologies for cancer immunotherapy and advanced gene editing. Leveraging the expertise of NIC, the CTGCT will vertically integrate technologies from the molecular to the organismal level, including synthetic biology tools, gene editing and splicing tools, and engineering of immune system regulatory pathways (Fig. 1). A pipeline of biomedical tools will be established that includes advanced CAR T-cell technology, CRISPR/Cas mediated gene editing and RNA splicing technologies with improved safety and efficiency using lipid nanoparticles (LNPs) for delivery. Innovative therapeutic solutions will target rare genetic diseases and cancer, initially focusing on the CTNNB1 syndrome [10], Kleefstra syndrome [11], SATB2-associated syndrome [12] and hematologic cancers. Molecular design, cell culture, organoid testing, and preclinical animal studies will optimise therapeutic strategies and lead to GMP production of clinical grade reagents for use in first-in-human clinical trials at collaborating clinical centres.

To achieve these goals, the project objectives are as follows:

- Establish the CTGCT Centre of Excellence by creating a stimulating research environment, recruiting international scientists, building and managing the Centre's premises, including a GMP facility, and developing a long-term plan for financial sustainability.
- Develop a strategic research and innovation programme to increase scientific capacity, build interdisciplinary research partnerships, apply for funding programmes, and implement training programmes for researchers and staff.
- Influence GCT research and innovation in Slovenia and the region through analysis, stakeholder communication and benchmarking activities.
- Providing services and products to academic and industrial stakeholders, translating research results into therapies and disseminating

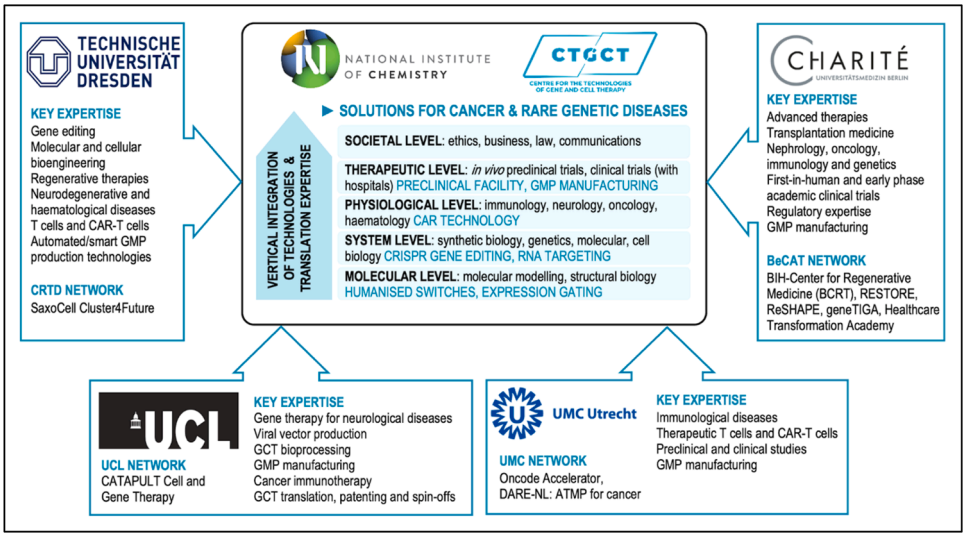

Fig. 1. Vertical integration of technologies and translational expertise of the CTGCT consortium.

scientific knowledge, products and services through the use of digitalization technologies and effective communication measures.
- Ensuring the long-term sustainability of the centre through synergies with industry partners, innovation management, technology transfer and networking with regional and international innovation players.

2.2. The consortium

The teaming project began on September 1, 2023, and will run for 72 months. The consortium partners are the NIC as coordinator, University College London (UCL), University Medical Center Utrecht (UMCU), Charité University Hospital Berlin (Charité) and Technical University Dresden (TUD) (Fig. 1).

The NIC (https://www.ki.si/en/), as coordinator, will support the development of the CTGCT through its research teams led by Professors Roman Jerala [13] and Jernej Ule [14,15], both holders of European Research Council Advanced Grants. These teams will make an important contribution together with other interdisciplinary groups at the NIC focusing on relevant areas such as bioinformatics, molecular medicine, bionanotechnology, structural biology and bioinformatics.

The advanced partner UCL (https://www.ucl.ac.uk/) brings extensive expertise in GCT through its five interdisciplinary departments. These include the Queen Square Institute of Neurology (https://www.ucl.ac.uk/ion/ucl-queen-square-institute-neurology), which will collaborate on the application of gene therapies to neurological diseases, and the GeneTxNeuro facility at the UCL School of Pharmacy (https://www.ucl.ac.uk/therapeutic-innovation-networks/about/our-networks/cell-gene-therapies/facilties/ucl-genetxneuro-vector-core-facility), which will contribute its expertise in viral vector production. In addition, the UCL Department of Biochemical Engineering (https://www.ucl.ac.uk/biochemical-engineering/ucl-biochemical-engineering) will collaborate on the development of production technologies for the bioprocessing of GCT. UCL's Institute of Immunity and Transplantation (https://www.ucl.ac.uk/immunity-transplantation/ucl-institute-immunity-and-transplantation) will assist in the development of immunotherapies. UCL's experience in implementing more than 50 GCTs will be invaluable, supported by the Translational Research Office led by Dr. Jane Kinghorn (https://www.ucl.ac.uk/translational-research/translational-research-office).

The UMCU represents a significant step forward for research and application, especially in immunological diseases. The Center for Translational Immunology (https://www.umcutrecht.nl/en/center-for-translational-immunology), in close collaboration with the Department of Hematology led by Prof. Jurgen Kuball (https://www.umcutrecht.nl/en/research/researchers/kuball-jhe), offers expertise in therapeutic T-cells and the development of CAR T-cells. UMC Utrecht's participation in the Oncode Accelerator program (https://www.oncodeaccelerator.nl/) and the DARE-NL platform (https://www.dare-nl.nl/) for cancer-specific ATMP research further strengthens its contribution.

The Charité will strengthen the CTGCT's ability to transfer research results into clinical practice. Prof. Petra Reinke is a pioneer in the field of applied cell therapies and has extensive experience in transplantation medicine, nephrology, oncology, immunology, and genetics (https://becat.charite.de/ueber_becat/team/leitung/). Under her leadership, the Berlin Center for Advanced Therapies (BeCAT) was founded (https://becat.charite.de/en/), which includes a running GMP facility with 4 clean rooms and a new GMP facility with 10 clean rooms, which is currently under construction. The manufacturing authorization of BeCAT's running GMP facility includes whole blood collection as starting material, fresh and cryopreserved regulatory and effector immune cell products as well as genetically engineered products. The focus at BeCAT is on innovative first-in-human and early phase academic clinical trials. Therefore, the team has detailed knowledge of regulatory and GMP manufacturing as well as GMP compliant construction aspects, which they share to support the CTGCT. BeCAT is also part of many large EU consortia working on advanced therapies and has many collaborations with both academic and industry partners and therefore has extensive experience in consultancy work that exactly matches the requirements of the CTGCT.

The TUD will provide expertise in the implementation of a GCT ecosystem with a focus on entrepreneurship. As translational research nucleus within the Saxonian SaxoCell "Cluster4Future" funded by the German Federal Ministry of Education and Research (BMBF), TUD provides an excellent example of implementing structures (including TUD Excellence Center for Innovation, Transfer and Entrepreneurship "TUD excite", https://tu-dresden.de/forschung-transfer/transfer and "dresden exits" start-up service, https://www.dresden-exists.de/) to turn patented inventions into marketable products, thereby strengthening the region in the emerging field of precisions medicine with "living drugs". With strong focus on automation and scalability in cell therapy manufacturing (Dr. Anke Fuchs), SaxoCell aims at lowering costs to increase accessibility of ATMPs. As university with highest number of patents within Germany (285 in 2017–2021), both TUD and SaxoCell demonstrate a strong technology transfer mindset with very successful spin-off examples in the field of adaptor CAR T (Prof. Michael Bachmann) and gene editing (Prof. Frank Buchholz). Furthermore, TUD has successfully implemented initiatives to strengthen interactions of biomedical scientists and clinicians through early career tandem programs as well as advanced clinician scientist programs to accelerate clinical translation (Prof. Martin Bornhäuser, MSNZ Early Career Center, https://tu-dresden.de/med/mf/msnz; DSCS CAMINO, https://tu-dresden.de/med/mf/forschung-internationales/nachwuchsfoerderung-dscs/weitere-foerderprogramme/advanced-clinician-scientist-programm-camino).

3. Impact

3.1. Advancements in biomedicine paving the way to novel, curative treatments for life-threatening conditions

Cancer remains one of the leading causes of mortality worldwide, responsible for nearly 10 million premature deaths annually. The progression of cancer is closely linked to immune system dysfunction, making immunotherapies — treatments that boost the body's own immune system to fight disease — a promising avenue in healthcare. Surgery, chemotherapy and radiotherapy remain the most commonly used forms of cancer treatment. However, despite considerable progress, current strategies face significant challenges [16]. These include limited efficacy in some cancers, variability in patient response and side effects. While some patients achieve a durable response, many develop resistance or relapse.

Overcoming these challenges requires innovative therapeutic approaches and a deeper understanding of tumor-immune system interactions to improve outcomes and extend the benefits of immunotherapy to a broader range of patients. As early as the late 1980s, researchers demonstrated the potential of the patient's own immune system to fight cancer. Modified T cells were used [17], paving the way for T cell-based cancer immunotherapies. Advances in the understanding of basic immunology along with the advent of bioengineering technologies have enabled the production of human T cells expressing CARs that can bind to specific antigens presented by cancer cells, become activated and exert potent anti-tumor effects [18]. CAR T-cell cancer immunotherapies are currently the most promising, with six CAR T-cell therapies for hematologic cancers currently on the market [19]. However, the major side effects, including neurotoxicity and cytokine release syndrome, and the limited potential to treat solid tumors require further investigation. Adapter CAR approaches such as the UniCAR and RevCAR system, consisting of universal CAR-T cells and antigen-specific targeting modules developed at TUD, offer enhanced safety through their switchable technology [20-22] and can increase specificity through combinatorial AND gating [20]. Both UniCAR and RevCAR are being tested in clinical trials [23]. Other components of the immune

system, such as natural killer cells [24-26], as well as less researched components, such as gamma delta T (γδT) cells, are currently being investigated. Research in the field of γδT cells is rapidly evolving, with groundbreaking technological advances paving the way for a better understanding of cancer mechanisms and unlocking the therapeutic potential of these cells [27]. A major challenge in utilizing γδT cells for therapy lies in their inherent diversity and regulation by innate co-receptors. To overcome these limitations, a next-generation CAR T cell therapy has been developed, but requires further technical improvements. One innovative approach pioneered by UMCU is to modify T cells to express a specific γδT cell receptor (TEGs). This enables the targeting of hematologic and solid tumors and overcomes the significant challenges associated with conventional CAR T- and γδT-cell therapies [28].

These developments in cancer immunotherapy may be further supported by rapid advances in synthetic biology. For example, the integration of synthetic biology techniques, such as those developed at NIC, into the design of next-generation CAR T cells should facilitate the translation of these novel immunotherapies, such as those based on γδT cells, into clinical applications. The NIC has recently developed versatile approaches to increase the efficacy and control of CAR T-cell therapies by modifying CAR receptors to regulate their activity and by introducing versatile humanised switches to modulate therapeutic T-cell activity and precise recognition of cancer markers to reduce side effects and improve safety [29-32]. By increasing the efficacy of CAR T-cells and improving persistence and penetrance, CTGCT also aims to address the limiting factors of solid tumor therapies. The tools of synthetic biology will facilitate the development of more precise and controllable cell-based therapeutics for cancer and genetic diseases. In addition to developing new modalities to control the function of CAR T-cells, the CTGCT also aims to use revolutionary genome editing tools based on the CRISPR/Cas system that allow site-specific modification and alteration of the genome [33]. Using the improved version of the CRISPR system, CCExo [34], and other internally developed CRISPR variants, universal CAR T-cells will be developed. New generation CRISPR editors, e.g. base editors [35] and prime editors [36], will be used to correct disease-causing pathogenic mutations, and catalytically inactive Cas9 or Cas13 proteins will also be used as transcriptional regulators.

In addition to novel cancer therapies, the major advances in genetics, molecular medicine and synthetic biology mentioned above (which have transformed our understanding of biological processes and led to the development of technologies for engineering biological systems) are enabling the development of new personalized therapies targeting the causes of rare diseases. The use of technologies such as next-generation sequencing has greatly expanded our ability to determine the genetic landscape of a broader patient population and facilitates the development of personalized therapies that target specific abnormalities involved in disease onset. Whole genome sequencing is being widely used to decipher the genetic basis of the disease and diagnose the disease at an earlier stage, which can be particularly useful in developmental diseases.

The NIC is at the forefront of introducing and applying synthetic biology principles to mammalian biological systems to develop new technologies for GCTs. Several technologies have been invented in the last decade, some of which have already been introduced into the clinic within a decade of their invention, e.g. the CRISPR system-based therapy Casgevy for the treatment of blood disorders [37]. The CTGCT intends to apply combinations of technologies best suited to each type of genetic disorder or disease, several of which are already approved for clinical use. For example, research at the NIC is focused on improving Cas9- and Cas13-based CRISPR technologies for more effective and safer gene therapy. Another focus of product development is the use of antisense oligonucleotides (ASOs), which are to be used as modulators for gene splicing and the correction of gene haploinsufficiency. Their in vivo efficacy is strongly related to efficient in vivo delivery. Typically, AAV vectors are used for the delivery of gene correction tools [38]. Therefore, the CTGCT will put a special emphasis on the new development of successful delivery methods, especially modified AAVs and modified lipid nanoparticles, that not only enable a highly efficient transduction rate in the target tissue, but also have a great safety advantage. Modifying the delivery tools by incorporating anti-inflammatory molecules will increase the safety of the aforementioned delivery vehicles. Lipid nanoparticles, which are currently used in several clinical trials and carry various forms of cargo [39,40], will also be anchored with specific targeting motifs that enable cell- and tissue-specific targeting of therapeutic cargo, thus allowing the direct translation of research products from the laboratory to the clinic via preclinical GLP animal studies.

3.2. Translational challenges and regulatory requirements to advance the development of novel GCTs and bring them to clinical use

The paradigm shifts from traditional small molecule pharmacological interventions (which often just treat symptoms) to living therapies offering the potential for long-term cures requires the healthcare systems to rethink their reimbursement models. GCTs that can repair select genes and introduce cells that specifically target cancer cells are already available for several diseases. However, per-patient costs of personalised therapies are currently very high, making it challenging for the health agencies to provide therapy to all patients who could benefit from it [41]. Furthermore, Southeast Europe has lagged in the translation of scientific findings into clinical practice [9]. Another challenge Europe is facing concerning GCTs is a shortage of skills in GMP manufacturing [42]. Supply chains are also complex due to the fragmented European GCT market. Thus, even though Europe has top-level GCT research, it struggles with the translation of research findings and the clinical use of GCTs.

The development and translation of GCTs requires a mix of highly skilled interdisciplinary research groups across the academic, supply chain and industry sectors, making a networked centre with GMP facilities at its core highly desirable [43]. Development of manufacturing processes in line with GMP is associated with extremely high costs (including clean room technology, reagents and consumables), and it is difficult to obtain sufficient third party funds to translate the research findings from the bench to first-in-human trials. Support of venture capital and establishment of spin-off companies are often required. The agile hi-tech centre model of the CTGCT aims to address some of the bottlenecks to drive these potential cures into widespread clinical use such as reducing the cost of manufacture, improvements to the safety profile of the therapies as well as working with the regulators on the development of specific ATMPs, using new approaches, such as n-of-1 clinical trial design for rare genetic diseases [44].

The biggest challenge in the development of ATMPs is the fact that they are highly diverse innovative products that do not fit into the established corset of traditional pharmaceutical development, production and regulation [43]. Therefore, developers and regulatory authorities have to deal with many uncertainties, which makes the process difficult for both sides. ATMP-specific legislation has been in force since 2007 (e.g. Regulation EC 1394/2007; Commission Directive 2009/120/EC). However, the ATMP sector is dynamic and constantly evolving, challenging regulators to keep up with the pace of innovation. It is therefore important to set appropriate standards and maintain a constant dialogue between developers and regulators. EMA supports ATMP developers through various mechanisms, including the ATMP pilot programme for academic and non-profit organisations [45].

Problems can already arise when classifying novel products, as these living drugs often combine different aspects and classification is not clear-cut. Here it is very helpful to establish a network of ATMP developers (such as the DARE-NL platform, https://www.dare-nl.nl/ or AMP Bespoke Gene Therapy Consortium [46]) who have already found solutions to small challenges in the development process, instead of each developer having to go their own way. Often, small adaptations of already approved processes can be applied to different disease-specific

products, supporting the idea of developing platform technologies with interchangeable elements to achieve the appropriate properties for each product, also to potentially speed up regulatory approval considering already validated process or quality control steps. As marketing authorization for ATMPs can only be granted by the EMA, network structures should be established at European level, also with the aim of overcoming the current national specificities and moving towards a more holistic approach. This is also in the interest of paving the way for transnational treatment, which is of great interest for rare diseases for which tailor-made treatment options are becoming available in specialized centres, to be able to address the entire European population already in the clinical trial phase (before market approval) and to achieve a sufficient cohort size. Here, the (long-term) follow-up of patients across borders in a different European country than where the initial treatment took place can also pose a challenge.

The long-term safety and follow-up of treated patients and the collection of real-world data after product approval are important aspects to be considered in the field of novel ATMPs. This information should be collected in appropriate registries and shared among ATMP users. Analysis of this data can provide further information on patient stratification and treatment optimization when using these novel therapeutics. An example of important real-world data also includes experience with treatment combinations such as bridging therapies that are required prior to CAR T-cell therapy [47] and impact patient outcomes in real-world scenarios outside of strictly regulated clinical trials.

In addition, cross-border reimbursement strategies for treatments provided in specialized European centers must be defined. The European Regulation 2021/2282 on health technology assessment provides the legal framework that officially supports cross-border solutions for European patients [48]. As applications for clinical trials must be entered centrally into the Clinical Trials Information System from the beginning of 2024, a first step towards harmonization has been taken, even if divergent requirements of the individual countries involved in the trial pose significant challenges for multinational European trials.

Moreover, the EU has adopted a regulation on orphan medicinal products and supports the developers of these products, which may be ATMPs, for indications affecting fewer than 5 in 10,000 people in the EU, with fee waivers, protocol support and 10 years of market exclusivity after approval. For urgent medical needs for which no other treatment is available, the EMA can grant conditional marketing authorizations, which are valid for one year and can be renewed annually. This is linked to conditions that must be fulfilled within a certain time frame. If these are fulfilled, a standard authorization can be granted, initially for 5 years, which can then be extended indefinitely if there are no contradictory data.

In addition, GMP production sites are confronted with demanding manufacturing processes that require highly qualified personnel that are not easy to find. Therefore, training programs such as the Healthcare Transformation Academy funded by the European Institute of Innovation and Technology (EIT) or the European Infrastructure for Translational Medicine (EATRIS) are of great importance, and more hands-on training opportunities for manufacturing ATMPs under GMP requirements are needed. Also, building GMP facilities suitable for manufacturing ATMPs in an academic setting is often complicated as the requirements do not fit into the standardized processes of these large institutions. Detailed knowledge is required to design these facilities in an appropriate way, optimally involving regulatory authorities, to avoid the need for significant remodeling once the facility is approved. In addition, the facilities are very sophisticated, expensive and often process-specific and are also constantly being adapted to new requirements. Here we observe a joint development of novel ATMPs and the required machinery, especially also towards process automation to reduce labor-intensive steps, but also to reduce contamination risks etc., which is welcomed by the regulatory authorities [49].

To be ultimately successful, novel ATMPs must be developed based on patient needs and accepted by the target patients, which is why the involvement of patient advocacy is essential from the early stages of development. Examples have shown how much power patients and patient organizations can have when they are convinced of a novel therapy [50]; however, the opposite effect can also be observed when patient acceptance is insufficient.

4. Discussion and conclusion

The establishment of the Centre of Excellence for Gene and Cell Therapy Technologies (CTGCT) at the NIC is an important milestone in personalised medicine. The CTGCT focuses on cancer immunotherapies and advanced gene editing techniques for rare neurological genetic diseases and aims to bridge the gap between innovative research and real-world clinical applications. The Centre's collaborative network, which includes partner institutions from the UK, the Netherlands and Germany, is an example of the critical role of international collaboration in the development of next-generation gene and cell therapies. By pooling expertise, resources and technologies across borders, these partnerships provide a dynamic scientific and translational environment that can lead to new treatment options for patients in Slovenia and worldwide. In addition, academic institutions foster multidisciplinary collaboration between researchers and clinicians, facilitating innovative approaches to overcome the limitations of existing therapies.

One of the CTGCT's key strengths is its interdisciplinary, expert approach, which utilises innovative technologies such as synthetic biology, gene editing and immunoregulation techniques to develop a wide range of biomedical tools for medical needs.

In addition, the CTGCT's Translational Research Unit and Technology Transfer Office will play an important role in disseminating research results and innovations, both within Slovenia and throughout the region. This proactive approach to knowledge sharing and capacity building will be critical to achieving breakthrough advances in gene and cell therapies and improving healthcare outcomes worldwide.

CRediT authorship contribution statement

Anke Fuchs: Writing – original draft, Writing – review & editing. **Petra Reinke:** Writing – review & editing. **Leila Amini:** Writing – original draft, Writing – review & editing. **Jurgen Kuball:** Writing – original draft. **Jane Kinghorn:** Writing – original draft, Writing – review & editing. **Duško Lainšček:** Writing – original draft, Writing – review & editing. **Zsolt Sebestyen:** Writing – original draft. **Darja Marolt Presen:** Conceptualization, Writing – original draft, Writing – review & editing. **Mojca Benčina:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing. **Roman Jerala:** Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Jurgen Kuball reports a relationship with Gadeta BV that includes: co-founder and shareholder.

Jurgen Kuball reports a relationship with Gadeta BV, Novartis and Miltenyi Biotec that includes funding grants.

Jurgen Kuball and Zsolt Sebestyen are inventors on patents with γδ TCR-related topics.

Petra Reinke reports a relationship with UK Medical Research Council that includes board membership.

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References

[1] WHO. Global cancer burden growing, amidst mounting need for services. World Health Oganisation; 2024. ⟨https://www.who.int/news/item/01–02-2024-global-cancer-burden-growing–amidst-mounting-need-for-services#:~:text=In%202022%2C%20there%20were%20an,cancer%20diagnosis%20was%2053.5%20million⟩.
[2] European Comission. Europe's beating cancer plan: Communication from the commission to the European parliament and the council. European Comission; 2022 [In:], ⟨https://health.ec.europa.eu/system/files/2022-02/eu_cancer-plan_en_0.pdf⟩.
[3] Rare diseases and European Reference Networks. Rare diseases. European Comission; 2024. ⟨https://health.ec.europa.eu/rare-diseases-and-european-reference-networks/rare-diseases_en⟩.
[4] Moran N. First gene therapy approved. Nat Biotechnol 2012;30(12). https://doi.org/10.1038/nbt1212-1153 [1153–1153].
[5] EMA. First gene editing therapy to treat beta thalassemia and severe sickle cell disease. In: European Medicines Agency; 2023. ⟨https://www.ema.europa.eu/en/news/first-gene-editing-therapy-treat-beta-thalassemia-and-severe-sickle-cell-disease⟩.
[6] Senior M. Fresh from the biotech pipeline: record-breaking FDA approvals. Nat Biotechnol 2024. https://doi.org/10.1038/s41587-024-02166-7.
[7] European Comission. European innovation scoreboard 2023 country profile Slovenia. In: European Comission; 2023. ⟨https://ec.europa.eu/assets/rtd/eis/2023/ec_rtd_eis-country-profile-si.pdf⟩.
[8] Loche A, Paolucci N, Peters N, Van der Veken L. A call to action: Opportunities and challenges for CGTs in Europe. In McKinsey & Company; 2021. ⟨https://www.mckinsey.com/industries/life-sciences/our-insights/a-call-to-action-opportunities-and-challenges-for-cgts-in-europe⟩.
[9] Zamecnik A. Access to CAR-T therapies in Central and Eastern Europe in "catch-up" mode compared to the West. Pharmaceutical Technology; 2022. ⟨https://www.pharmaceutical-technology.com/features/access-to-car-t-therapies-in-central-and-eastern-europe-in-catch-up-mode-compared-to-the-west/?cf-view⟩.
[10] Miroševič Š, Khandelwal S, Sušjan P, Žakelj N, Gosar D, Forstnerič V, et al. Correlation between phenotype and genotype in CTNNB1 syndrome: a systematic review of the literature. Int J Mol Sci 2022;23(20):12564. https://doi.org/10.3390/ijms232012564.
[11] Zdolšek Draksler T, Bouman A, Guček A, Novak E, Burger P, Colin F, et al. Exploring Kleefstra syndrome cohort phenotype characteristics: prevalence insights from caregiver-reported outcomes. Eur J Med Genet 2024;72:104974. https://doi.org/10.1016/j.ejmg.2024.104974.
[12] Zarate YA., Bosanko K, Fish J. SATB2-associated syndrome; 1993. In: GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993.
[13] NIC. Department of Synthetic Biology and Immunology. In: The National Institute of Chemistry; 2024. ⟨https://www.ki.si/en/departments/d12-department-of-synthetic-biology-and-immunology/⟩.
[14] NIC. Laboratory for RNA networks. In: The National Institute of Chemistry; 2024. ⟨https://www.ki.si/en/about-the-institute/find-employees/305/⟩.
[15] The Francis Crick Institute. RNA networks laboratory. In: The Francis Crick Institute; 2024. ⟨https://www.crick.ac.uk/research/labs/jernej-ule⟩.
[16] Arruebo M, Vilaboa N, Sáez-Gutierrez B, Lambea J, Tres A, Valladares M, et al. Assessment of the evolution of cancer treatment therapies. Cancers 2011;3(3):3279–330. https://doi.org/10.3390/cancers3033279.
[17] Gross G, Waks T, Eshhar Z. Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity. Proc Natl Acad Sci 1989;86(24):10024–8. https://doi.org/10.1073/pnas.86.24.10024.
[18] Gauthier J, Yakoub-Agha I. Chimeric antigen-receptor T-cell therapy for hematological malignancies and solid tumors: clinical data to date, current limitations and perspectives. Curr Res Transl Med 2017;65(3):93–102. https://doi.org/10.1016/j.retram.2017.08.003.
[19] EMA CAT. Committee for advanced therapies (CAT). EMA; 2024. ⟨https://www.ema.europa.eu/en/committees/committee-advanced-therapies-cat⟩.
[20] Feldmann A, Hoffmann A, Bergmann R, Koristka S, Berndt N, Arndt C, et al. Versatile chimeric antigen receptor platform for controllable and combinatorial T cell therapy. Oncoimmunology 2020;9(1):1785608. https://doi.org/10.1080/2162402X.2020.1785608.
[21] Kittel-Boselli E, Soto KEG, Loureiro LR, Hoffmann A, Bergmann R, Arndt C, et al. Targeting acute myeloid leukemia using the RevCAR platform: a programmable, switchable and combinatorial strategy. Cancers 2021;13(19). https://doi.org/10.3390/cancers13194785.
[22] Loff S, Dietrich J, Meyer J-E, Riewaldt J, Spehr J, von Bonin M, et al. Rapidly switchable universal CAR-T cells for treatment of CD123-positive leukemia. Mol Ther Oncolytics 2020;17:408–20. https://doi.org/10.1016/j.omto.2020.04.009.
[23] Wermke M, Kraus S, Ehninger A, Bargou RC, Goebeler M-E, Middeke JM, et al. Proof of concept for a rapidly switchable universal CAR-T platform with UniCAR-T-CD123 in relapsed/refractory AML. Blood 2021;137(22):3145–8. https://doi.org/10.1182/blood.2020009759.
[24] Eitler J, Rackwitz W, Wotschel N, Gudipati V, Murali Shankar N, Sidorenkova A, et al. CAR-mediated targeting of NK cells overcomes tumor immune escape caused by ICAM-1 downregulation. J Immunother Cancer 2024;12(2). https://doi.org/10.1136/jitc-2023-008155.
[25] Mitwasi N, Feldmann A, Arndt C, Koristka S, Berndt N, Jureczek J, et al. "UniCAR"-modified off-the-shelf NK-92 cells for targeting of GD2-expressing tumour cells. Sci Rep 2020;10(1):2141. https://doi.org/10.1038/s41598-020-59082-4.
[26] Moscarelli J, Zahavi D, Maynard R, Weiner LM. The next generation of cellular immunotherapy: chimeric antigen receptor-natural killer cells. Transplant Cell Ther 2022;28(10):650–6. https://doi.org/10.1016/j.jtct.2022.06.025.
[27] Sebestyen Z, Prinz I, Déchanet-Merville J, Silva-Santos B, Kuball J. Translating gammadelta (γδ) T cells and their receptors into cancer cell therapies. Nat Rev Drug Discov 2020;19(3):169–84. https://doi.org/10.1038/s41573-019-0038-z.
[28] Hernández-López P, van Diest E, Brazda P, Heijhuurs S, Meringa A, Hoorens van Heyningen L, et al. Dual targeting of cancer metabolome and stress antigens affects transcriptomic heterogeneity and efficacy of engineered T cells. Nat Immunol 2024;25(1):88–101. https://doi.org/10.1038/s41590-023-01665-0.
[29] Lainšček D, Golob-Urbanc A, Mikolič V, Pantović-Žalig J, Malenšek Š, Jerala R. Regulation of CD19 CAR-T cell activation based on an engineered downstream transcription factor. Mol Ther - Oncolytics 2023;29:77–90. https://doi.org/10.1016/j.omto.2023.04.005.
[30] Mikolič V, Pantović-Žalig J, Malenšek Š, Sever M, Lainšček D, Jerala R. Toll-like receptor 4 signaling activation domains promote CAR T cell function against solid tumors. Mol Ther: Oncol 2024;32(2):200815. https://doi.org/10.1016/j.omton.2024.200815.
[31] Plaper T, Merljak E, Fink T, Satler T, Ljubetič A, Lainšček D, et al. Designed allosteric protein logic. Cell Discov 2024;10(1):8. https://doi.org/10.1038/s41421-023-00635-y.
[32] Rihtar E, Lebar T, Lainšček D, Kores K, Lešnik S, Bren U, et al. Chemically inducible split protein regulators for mammalian cells. Nat Chem Biol 2023;19(1):64–71. https://doi.org/10.1038/s41589-022-01136-x.
[33] Jinek M, Chylinski K, Fonfara I, Hauer M, Doudna JA, Charpentier E. A programmable dual-RNA–guided DNA endonuclease in adaptive bacterial immunity. Science 2012;337(6096):816–21. https://doi.org/10.1126/science.1225829.
[34] Lainšček D, Forstnerič V, Mikolič V, Malenšek Š, Pečan P, Benčina M, et al. Coiled-coil heterodimer-based recruitment of an exonuclease to CRISPR/Cas for enhanced gene editing. Nat Commun 2022;13(1):3604. https://doi.org/10.1038/s41467-022-31386-1.
[35] Eghbalsaied S, Lawler C, Petersen B, Hajiyev RA, Bischoff SR, Frankenberg S. CRISPR/Cas9-mediated base editors and their prospects for mitochondrial genome engineering. Gene Ther 2024;31(5–6):209–23. https://doi.org/10.1038/s41434-023-00434-w.
[36] Anzalone AV, Randolph PB, Davis JR, Sousa AA, Koblan LW, Levy JM, et al. Search-and-replace genome editing without double-strand breaks or donor DNA. Nature 2019;576(7785):149–57. https://doi.org/10.1038/s41586-019-1711-4.
[37] Sharma A, Boelens J-J, Cancio M, Hankins JS, Bhad P, Azizy M, et al. CRISPR-Cas9 editing of the *HBG1* and *HBG2* promoters to treat sickle cell disease. N Engl J Med 2023;389(9):820–32. https://doi.org/10.1056/NEJMoa2215643.
[38] Davis JR, Wang X, Witte IP, Huang TP, Levy JM, Raguram A, et al. Efficient in vivo base editing via single adeno-associated viruses with size-optimized genomes encoding compact adenine base editors. Nat Biomed Eng 2022;6(11):1272–83. https://doi.org/10.1038/s41551-022-00911-4.
[39] Li S, Hu Y, Li A, Lin J, Hsieh K, Schneiderman Z, et al. Payload distribution and capacity of mRNA lipid nanoparticles. Nat Commun 2022;13(1):5561. https://doi.org/10.1038/s41467-022-33157-4.
[40] Musunuru K, Chadwick AC, Mizoguchi T, Garcia SP, DeNizio JE, Reiss CW, et al. In vivo CRISPR base editing of PCSK9 durably lowers cholesterol in primates. Nature 2021;593(7859):429–34. https://doi.org/10.1038/s41586-021-03534-y.
[41] Iglesias-López C, Agustí A, Vallano A, Obach M. Financing and reimbursement of approved advanced therapies in several European countries. Value Health 2023;26(6):841–53. https://doi.org/10.1016/j.jval.2022.12.014.
[42] Labiotech. Tackling the skilled labor shortage in biopharma manufacturing. Labiotech; 2023. ⟨https://www.labiotech.eu/opinion/skilled-labor-shortage-biopharma/⟩.
[43] Mooraj H, Kawalekar O, Gupta L, Shah S. Cell and gene therapies: Delivering scientific innovation requires operating model innovation. In Deloitte Insights. The Deloitte Center for Health Solutions; 2020. ⟨https://www2.deloitte.com/content/dam/insights/us/articles/6642-cell-and-gene-therapies/DI_Cell-and-gene-therapies.pdf⟩.
[44] Müller AR, Brands MMMG, van de Ven PM, Roes KCB, Cornel MC, van Karnebeek CDM, et al. Systematic review of N-of-1 studies in rare genetic neurodevelopmental disorders. Neurology 2021;96(11):529–40. https://doi.org/10.1212/WNL.0000000000011597.
[45] EMA ATMP Pilot. Advanced therapy medicinal products: Overview. In European Medicines Agency; 2024. ⟨https://www.ema.europa.eu/en/human-regulatory-overview/advanced-therapy-medicinal-products-overview#atmp-pilot-for-academia-and-non-profit-organisations-12380⟩.
[46] AMP BGTC. BGTC regulatory playbook version 1.0 bespoke gene therapy consortium (BGTC) regulatory playbook version 1.0 (Vol. 1). FINH AMP Bespoke Gene Therapy Consortium; 2024. ⟨https://fnih.org/wp-content/uploads/2024/04/BGTC-Regulatory-Playbook-Version-1.0.pdf⟩.
[47] Amini L, Silbert SK, Maude SL, Nastoupil LJ, Ramos CA, Brentjens RJ, et al. Preparing for CAR T cell therapy: patient selection, bridging therapies and

lymphodepletion. Nat Rev Clin Oncol 2022;19(5):342–55. https://doi.org/10.1038/s41571-022-00607-3.
[48] Angelillo L, van Steen C, Ross-Stewart K, Dehnen J, Colasante W. Viability of European cross-border access opportunities to streamline access to ATMPs. Health Policy Technol 2023;12(3):100752. https://doi.org/10.1016/j.hlpt.2023.100752.
[49] Blache U, Popp G, Dünkel A, Koehl U, Fricke S. Potential solutions for manufacture of CAR T cells in cancer immunotherapy. Nat Commun 2022;13(1):5225. https://doi.org/10.1038/s41467-022-32866-0.
[50] Braun S. Gene-based therapies of neuromuscular disorders: an update and the pivotal role of patient organizations in their discovery and implementation. J Gene Med 2013;15(11–12):397–413. https://doi.org/10.1002/jgm.2747.