European Innovation Council

PATHFINDER CHALLENGE
Emerging Technologies in Cell and Gene therapy
CHALLENGE GUIDE – PART I

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Challenge page: https://eic.ec.europa.eu/calls-proposals/eic-pathfinder-challenge-emerging-technologies-cell-and-gene-therapy_en

CONTENT

The Appendices that are referred to in this document are common to the different Challenges and bundled in Part II of the Challenge Guide, published on the Challenge page on the EIC Website https://eic.ec.europa.eu/calls-proposals/eic-pathfinder-challenge-emerging-technologies-cell-and-gene-therapy_en.

1. About this document

The Challenge Guide is the reference document accompanying a Pathfinder challenge along its whole life cycle, from call to achieving its objectives.

The Programme Manager in charge of this Pathfinder Challenge is the editor of the Challenge Guide. The Challenge Guide captures, at any moment, the state of play, achievements and remaining challenges, and documents the process by which the Programme Manager and Portfolio members jointly establish an evolving set of Portfolio objectives and a shared roadmap for achieving them. The most recent version can be found through the corresponding Challenge page on the EIC Website https://eic.ec.europa.eu/calls-proposals/eic-pathfinder-challenge-emerging-technologies-cell-and-gene-therapy_en.

The Challenge Guide starts out as a background document to the initial Pathfinder Challenge call. It details the intention of the call by complementing notably the scope, objectives (see Section 5 - Challenge call text) or criteria (see Appendix 3: EIC 2021 Work Programme – Evaluation criteria) set out in the EIC Work Programme. In no case does it contradict or supplant the Work Programme text. After the call evaluation, the Challenge Guide further documents the initial Challenge Portfolio that resulted from the call.

As the actions in the Portfolio unfold, the Challenge Guide further documents the evolving Portfolio Objective(s) and the progress towards achieving them, notably through the Portfolio Activities that the Programme Manager puts in place.

The Challenge Guide serves as a reference for the common understanding, rules-of-play and obligations for the EIC beneficiaries that are involved in the Challenge Portfolio. Contractual Obligations are further reference material from the EIC Work Programme are collected in Part II of the Pathfinder Challenge Guide, , published on the Challenge page on the EIC Website https://eic.ec.europa.eu/calls-proposals/eic-pathfinder-challenge-emerging-technologies-cell-and-gene-therapy_en.

2. Overall objective of the Pathfinder Challenge

This section sets out the rationale of the Challenge and it highlights some challenges and open issues that proposers may wish to address without being exhaustive. Building on the state of the art in the relevant scientific and technological domains, sets the boundaries of its scope and explains the overall objectives. This section should be read as further background to the Challenge specific part of the EIC Work Programme text (see Appendix 2).
Proposals to this Challenge are expected to explain how they relate to and intend to go beyond the state of the art, and how they interpret and contribute to the objectives of the Challenge.

The aim of this EIC Pathfinder Challenge, is to fund proposals focused on novel concept-based technologies that can contribute to the development of more effective cell and gene therapy (CGT) treatments, and on technological solutions beyond the state-of-the-art, that have the potential to overcome critical challenges currently being faced by the cell and gene therapy research community and innovation-based industry.
The Challenge as described in the Work Programme (see also section 5 in this guide) has the following objectives:

- advancing cell therapy manufacturing and products to a clinical stage,
- improving adoptive cell therapies (CAR-T, TCR, TIL),
- identifying next-generation cell therapies for cancer,
- applying cell therapy to treat cancer patients in a personalised manner,
- improving the effectiveness and lowering the risks of gene delivery systems (vectors), and
- improving gene therapy manufacturing processes and production.

In addition, with this Call, EIC aims at bringing together leading consortia and promising start-ups targeted to the above-mentioned areas creating a critical mass in these areas, which, in turn, can enhance the European technological sovereignty in the cell and gene therapy field.

State-of-the-art leading to current objectives

In recent years, cell and gene therapies are increasingly empowering modern medicine with the ability to treat and potentially cure diseases for which previously no treatment options were existing. Cell and gene therapy afford major improvements in the quality of life for patients and in some cases, such as severe neurodegenerative diseases or certain cancers they are making the difference between life and death[1][2][3].

[1] Special Issue Features State-of-the-Art in Clinical Gene Therapy. Herzog RW, Frederickson RM. https://www.sciencedirect.com/science/article/abs/pii/S1525001620304160
[2] Gene & Cell Therapy: A New Age of Medicine https://fiercepharma.tradepub.com/free/w_allj02/

In cell therapy, diseases are treated with cells grown or modified outside of the body and may originate from the patient or a donor. Once prepared, these cells are injected into a patient to reduce the effects of a disease. Stem cells, which may or may not be genetically modified, are most often used for this therapy as they can mature into specialized types of cells targeted specifically to the tissue/organ for which restoration of function is needed. Multiple scientific advancements in this field have consolidated to the point of a scientific revolution-a shift that will change how we think of medicines[4]. In contrast, gene therapy entails treating diseases at the genetic level by either deactivating, replacing or repairing the faulty DNA that is causing the disease. Functional DNA is delivered into the patient's cells by a vector, usually of viral origin. These vectors, which are either not known to cause disease or have been attenuated in a lab, carry the DNA into the host cell and insert the material into the patient's DNA. Restoring gene function, in turn, allows malfunctioning proteins to be correctly produced[5]. Finally, combined cell- and gene-based approaches in preclinical studies applying gene editing technologies are gaining the interest of cell and gene therapy scientists worldwide and have proven to be an additional strong frontier to an already accelerating domain.

The clinical success of the drugs Kymriah and Yescarta, the first ever CAR T therapy landmark approvals for the treatment of B-cell acute lymphoblastic leukemia (ALL) opened new and encouraging avenues for developers of cellular and gene therapies. As of 5 February 2021, nineteen CGT therapies have been approved by FDA and 15 by EMA [67]. Several startup companies in the field have been launched in the last years, some of which have been acquired by major pharmaceutical companies. According to the "Next generation therapeutics" feature article published in Nature journal earlier this year, only 5 of the top 20 companies in the field of cell, gene and nucleic acid therapies are large biopharma[8]. It is noteworthy, that successful gene therapy companies are currently acquired by big pharma at very high valuations underlying the importance of innovation in the field and big pharma is also investing in AAV-based gene therapy focused on rare diseases such as, Duchenne muscular dystrophy (DMD)[9]. More than 2,000 cell and gene therapy trials have been

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[3] What is cell and gene therapy? Mar 19, 2020 https://www.novartis.com/our-focus/cell-and-gene-therapy/what-cell-and-gene-therapy

[4] American Society of Gene and Cell Therapy. Different Approaches. Mar 19, 2020 https://www.asgct.org/education/ different-approaches

[5] Institute for Clinical and Economic Review. GENE THERAPY: Understanding the Science, Assessing the Evidence, and Paying for Value. Mar 19, 2020 https://icer-review.org/wp-content/uploads/2017/03/ICER-Gene-Therapy-White-Paper-030317.pdf

[6] Approved Cellular and Gene Therapy Products (FDA) https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products

[7] Why Are There Only 11 Cell and Gene Therapies in Europe? Cynober T. https://www.labiotech.eu/in-depth/atmp-cell-gene-therapy-ema/

[8] Next-generation therapeutics sustain momentum. Verdin P. Nature, June 2020 https://www.nature.com/articles/d43747-020-00914-7

[9] Seven biopharma trends to watch. Philippidis A. Jan 2021 https://www.genengnews.com/a-lists/seven-biopharma-trends-to-watch-in-2021/

conducted to date, which have led to a better understanding of treatment safety and efficacy and better protocol designs.

Rare diseases and cancers dominate the cell and gene therapy pipeline, but many other more common diseases linked to genetic disorders are all potential future targets for cell and gene therapy as well. Diseases such as Alzheimer's disease, cardiovascular disease, arthritis and others easily highlight the millions of people who could potentially benefit from these types of treatments[1011]. A recent example is the application of a dual-vector gene therapy product for congenital hearing loss[12]. Another example is the inflammation-mediated degenerative diseases[13] and diseases in which, exosomes can be used as vectors to effectively deliver the correct gene to the target tissue/organ. Infectious diseases may be the next big target for cell and gene therapy [13].

In the area of rare diseases, gene therapy advancements are transforming the lives of affected people through the development of innovative, potentially curative gene therapies. In one case, ex vivo autologous gene therapy seeks to correct the underlying cause of disease in a single administration of genetically modified blood stem cell[14].

While impressively successful in some areas, clinical cell gene therapy also faces serious obstacles that impede or complicate treatment, as is the case for other novel types of medicine. The whole process from novel concept-based research to clinical grade viral vector under GMP standard is a very demanding one, with the constant need for technological novelties to overcome challenges.

Chimeric cell therapies and release of therapeutics or recombinant biologics[15]

Off-the-shelf drugs, such as engineered recombinant checkpoint antibodies for immunotherapy that bring cancer cells and T lymphocytes in close proximity to kill them, are now in use for several types of cancers. However, the production of these antibodies is expensive, a significant percentage of patients does not respond, and they do not permeate to all sites of cancer, such as the brain. Technology now exists to engineer cells to produce these drugs in a programmed fashion and for long period. Cell and gene therapies that

[10] Gene & Cell Therapy: A New Age of Medicine https://fiercepharma.tradepub.com/free/w_allj02/

[11] Institute for Clinical and Economic Review. GENE THERAPY: Understanding the Science, Assessing the Evidence, and Paying for Value. Mar 19, 2020 https://icer-review.org/wp-content/uploads/2017/03/ICER-Gene-Therapy-White-Paper-030317.pdf

[12] Manufacturing Agreement for Dual-Vector Gene Therapy for the Treatment of Congenital Hearing Loss https://biologics.catalent.com/catalent-news/decibel-and-catalent-sign-development-and-manufacturing-agreement-for-dual-vector-gene-therapy-for-the-treatment-of-congenital-hearing-loss/

[13] Discussions at Phacilitate 2020 on Business, Manufacturing, and Future Trends. April 2020 https://bioprocessintl.com/manufacturing/cell-therapies/discussions-at-phacilitate-2020-on-cell-and-gene-therapy-products/

[14] https://www.ema.europa.eu/en/documents/product-information/libmeldy-epar-product-information_en.pdf

[15] Cell And Gene Therapy Foresight In 2020: 7 Trends To Watch. Levine B Jan 2020. https://www.cellandgene.com/doc/cell-and-gene-therapy-foresight-in-trends-to-watch-0001

combine technologies that engineer cells to enhance effectiveness and efficiency, is a trend that will continue to develop[15].

Expanding the scope of treatment to solid tumours[15, 16]

While CAR-T cells based therapies have proved efficient for treating blood cancers such as lymphoma and leukemia, solid tumours have been more difficult to fight. A successful CAR-T cell therapy in a solid tumour indication, represents currently an enormous challenge because of:

a) target antigen heterogeneity, implying a general lack in specific cell surface antigens,
b) physical barriers (like dense stroma or obscure tumour location),
c) the immunosuppressive tumour microenvironment and
d) tumour plasticity leading to loss or modulation of antigen, one of the primary tumour escape mechanisms that results in development of resistance to antineoplastic therapies.

Many of the markers used to characterize tumours can also be found in healthy tissues, consequently, CAR-T cells do not distinguish between healthy, and cancer cells causing the destruction of both. The challenge has hence shifted from "how do we kill cancer cells" to "how do we do this while ensuring healthy tissues will not be harmed". Receptors that can be molecularly turned on and off like control switches with the delivery of a small molecule are a way that some research groups have been trying in order to overcome this challenge, including using combination of machine learning and cell engineering techniques. It is expected, that such multi-targeted CAR-T cells will have better on-target/off-tumour specificity and will thus have lesser side effects than single-targeted CAR-T cells.

Tumours with immunosuppressive environment referred to as immunotherapy-cold tumours, present a particularly difficult challenge for immunotherapies. To address this challenge, CAR-T cell developers are coming up with novel mechanisms to combine CAR-T cells with pro-inflammatory cytokines for instance, with the incorporation of the cytokine gene within the CAR-T cell construct. Investigational drug, with ability to deplete immunosuppressive cell types and thus enhance the effect of administered immunotherapy, has been reported[16].

Finally, to overcome the risk of tumour plasticity and resistance development researchers are developing multi-targeted CAR-T cells that are expected to have greater specificity and lesser side effects than single-targeted CAR-T cells.

[16] CAR T-Cell Therapies: Current Limitations & Future Opportunities. Ghosh A, and Gheorghe D, Ph.D. https://www.cellandgene.com/doc/car-t-cell-therapies-current-limitations-future-opportunities-0001

Other than T cell Type R&I Developments in Cell Therapies[16]

Natural Killer (NK) cells are the new star in the domain of cellular immunotherapy, due to their tightly regulated "natural killing" of cancer cells; they play an important role in control and treatment of both solid and haematological malignancies, like acute myeloid leukemia and multiple myeloma. Baylor College of Medicine is employing NK-T cells that are known to co-localize with tumour-associated macrophages and can penetrate solid tumour tissues effectively, and Glycostem Therapeutics B.V is focusing on the development of stem cell-derived Natural Killer cells as a medicinal asset in the fight against cancer.

Development and Manufacturing of autologous CAR T cell[16, 17]

The manufacturing process of autologous CAR T cells is relatively slow, as it requires leukapheresis, followed by extraction of patient's T cells, transportation to the cell therapy manufacturing facility, genetic engineering to incorporate CARs and transportation of the finished product back to the treatment center. The period in between which is referred to as vein-to-vein time can range between three and four weeks. Being a highly personalized therapy, the complex, multistep process of generating autologous CAR T cells increases the risk of production failure, an event that delays and, in some instances, even denies access to the therapy. Therefore, new technological solutions that would help to improve and support the manufacturing step in terms of speed could have a tremendous impact[16].

Moreover, due to the fact that cell and gene therapy approaches lead to highly complex drugs, manufacturing them at high levels is a challenge. Current methods and equipment in use tend not to be sufficient in terms of robust analytical tools that are needed to guarantee quality and meet the stringent cell and gene therapy regulatory requirements. Digitalization of bioprocesses could further enable data-driven decision-making for advanced therapies. Real-time process monitoring could be possible by integrating metabolomics and transcriptomics data processed by Artificial intelligence applications. In this context, Celixir acquired Desktop Genetics for modelling CRISPR-based gene editing and Oxford Biomedical's R&D collaborates with Microsoft Research for lentiviral manufacturing.

Development and Manufacturing of allogeneic (Off-The-Shelf) CAR T cells towards generating universal CAR T cells[17]

Another way to address the above logistic challenges and waiting periods is by developing allogeneic Off-The-Shelf CAR T Cells at the crossroad of cell and gene therapy. Allogeneic CAR T cells are generated from healthy donor cells and are better in terms of quality and quantity compared with the cells derived from the patients. These CAR T cells will become available for several patients and reduce the time gap between prescribing and administering the therapy. This would be especially beneficial for patients with rapidly progressive disease. Additionally, as each batch of allogeneic CAR T cells could be used to

[17] CAR T-Cell Therapies: Current Limitations & Future Opportunities. Ghosh A, and Gheorghe D, Ph.D. https://www.cellandgene.com/doc/car-t-cell-therapies-current-limitations-future-opportunities-0001

treat multiple patients, the scalability challenges would be overcome, and the overall therapy costs would diminish. However, anticipated safety challenges, like immune rejection and graft-versus-host disease, remain to be major hurdles and cannot be disregarded. Developers of allogeneic CAR T cells are testing various gene-editing techniques to generate universal CAR T cells. As multiplex gene knockouts to generate more potent anti-cancer T cells will be reaching many more patients and indications in the coming years, the need for safety evaluation of various gene editing platforms in the clinic will increase.

Advanced technological platforms to improve cell therapy manufacturing

There is a clear need for novel technologies to advance ex vivo cell therapy manufacturing to the next level by effectively tackling current challenges like those described above, and that prevent cell therapy to reach its full potential. One such example is the cell therapy technological platform developed over a 12-year period via a multi-national research collaboration, that enables the prediction of the transcription factors and optimal culture conditions required to produce any target human cell type from any source human cell type[18].

Cell and gene therapies in a personalized manner

Autologous, allogeneic or off-the-shelf cell and gene therapies are often personalized. While in some diseases like paediatric acute lymphoid leukemia, the response rates are much higher than any other available treatment regimen, in other diseases, the clinical responses are positive only in a subset of patients. The incorporation of effective biomarker(s) and artificial intelligence could have a major impact towards enhancing the personalized feature of cell and gene therapies. On this basis, new breakthrough technological solutions in the area of lab-grown cancer organoids or organs-on-a-chip, which would allow to test the patient's response to various cell therapies and drugs alone or in combination, prior to the initiation of the treatment, are sought.

Improving gene and cell therapy delivery systems (viral and non-viral)[19]

Delivering genetic cargo to cells is another challenging area that offers opportunity for improvement. Many of the treatments rely on modified viruses to shuttle genetic instructions into the body's cells. One example, adeno-associated viruses (AAVs), can be easily administered via infusion, have proven safe in clinical testing and are commonly used in a wide range of gene therapies. Another commonly used option, lentiviruses, do integrate and can be used for many different tasks, such as engineering stem cells to correct or replace the defective DNA that drives certain blood diseases.

These "viral vectors" have enabled gene therapy to come of age after decades of stop-and-start scientific research. However, their limitations have become increasingly well

[18] https://mogrify.co.uk/science/mogrify/

[19] Gene Therapy. Review High KA, Roncarolo MG. N Engl J Med. 2019 Aug. https://pubmed.ncbi.nlm.nih.gov/31365802

understood, which is why new technological solutions, are needed. AAVs can only carry a small amount of genetic cargo and are sometimes, shut down by the body's defences. The DNA they transport also does not easily integrate into a target cell's genome, meaning the effects of AAV-based treatment may wane in cells that frequently divide. For in vivo gene therapy with AAV vectors, efforts in near future will focus on the management and elucidation of the human immune response to the vector and continued improvements in AAV vector design and development. Lentiviruses, on the other hand, have limited packaging capacity and because they can integrate into cellular DNA, there is greater risk of erroneously triggering cancer-causing mutations. Future goals for the ex vivo lentivirus-based gene therapy include better vector design, efficient largescale production and the development of less toxic conditioning regimens, in order to further improve safety.

With regards to non-viral gene delivery systems, a wide range of technologies are currently in use including, RNAi-based, electroporation-based, biocompatible hydrogel material-based which need further improvements such as, to enhance the tumor cell-specific action and increase the size of carried payload. [20, 21]

Expected outcomes and wider social and knowledge-based economic impacts

Breakthrough research and novel concept-based innovation are required to surmount the wide spectrum of challenges the cell and gene therapy community is currently facing. The purpose of this Challenge Call is exactly that, to invite proposals offering novel and beyond the–state-of the-art technological solutions targeted to these challenges.

Emerging technologies on novel cell and gene therapy can substantially contribute to advancing and accelerate the implementation of precision medicine in a wide range of areas, including:

a) to reach proof-of-concept for entirely new gene therapy treatments that have the potential to effectively treat even cure diseases,

b) to test the effectiveness of cell therapy treatments/drugs by using novel technological platforms or by improving the existing ones beyond the state-of-the-art,

c) to develop new organoids (self-organized three-dimensional tissue cultures) allowing to test treatment before their actual administration to a patient,

d) to decrease the undesirable side effect of toxicity following oncology treatments.

It is envisaged, that cell and gene therapies will revolutionise the biotech and pharmaceutical sectors by meeting challenging unmet clinical needs. The European cell and

[20] https://kodikaz.com/product-pipeline/
[21] https://likarda.com/what-we-do/technologies/

gene therapy market is estimated to increase more than 23% until 2026[22, 23, 24]. The forecasted growth of the gene therapy market in the USA is of around 27% by 2024[25].

The development of CGTs innovative treatments has the potential to cure, rather than only to treat patients in a wide spectrum of, until this time, untreatable diseases, ranging from genetic disorders to immuno-deficiencies. Therefore, the growth in CGTs will affect the researchers, clinicians and manufacturers of ex vivo and in vivo safe and cost-effective CGTs to treat diseases that have no cure at present. Clinicians applying new CGT protocols will need to receive proper training in the concepts underlying the treatment but also in the associated health care technologies, in order to treat patients effectively. Hospitals will also need to adapt to the new era by increasingly providing their patients with access to advanced therapies associated with novel disruptive technologies, such as those sought with this Call.

Moreover, the public will greatly benefit from the development of the new advanced therapies, primarily because they can potentially lead to cure. In addition, because as "single-use customised treatments", CGT can replace other therapies requiring regular visits to hospitals and thus tackling the long lasting problem of waiting lists in hospitals. Finally, CGT is expected, to decrease treatment costs, even if initially can be more expensive, because in the long run, the savings for the health care providers, will be substantial.

According to global current trends, an explosive development is foreseen for the CGT scaling up/manufacturing stage with increasing demand for new infrastructures and supply capabilities to produce CGT reagents, consumables, laboratory and medical equipment necessary to optimize, standardize and deliver the CGT treatments. Process automation for industrial production of CGTs will come hand by hand with the development of advanced manufacturing processes in the area. Additionally, new storage centres for stem cells will be created. These centres will be vital to supply the cells in demand for clinical trials, subsequent treatment and, of course, scientific research. The development of targeted and personalised CG treatment, is expected to impact on further digitising the health care system because more advanced digital tools will be required, to efficiently collect and manage data of patients both for treatment tailoring and for after treatment follow-up. The latter, will be of paramount importance to continuously ensuring, that the treatment is of

[22] Precision medicine for rapid customised treatment.
https://www.businesswire.com/news/home/20210212005462/en/Europe-Cell-and-Gene-Therapy-Market-Industry-Outlook-and-Forecast-Report-2021-2026-with-Data-driven-Insights-on-the-Impact-of-COVID-19---ResearchAndMarkets.com

[23] https://www.prnewswire.com/news-releases/europe-cell-and-gene-therapy-market-2021-2026-opportunities-in-cmo-offering-vector-manufacturing-services-robust-cell--gene-therapy-pipeline-increase-in-strategic-acquisitions-301230035.html

[24] https://www.marketresearch.com/Arizton-v4150/Europe-Cell-Gene-Therapy-Outlook-14141945/

[25] https://www.marketsandmarkets.com/Market-Reports/gene-therapy-market-122857962.html?gclid=Cj0KCQiApsiBBhCKARIsAN8o_4hLRvaM-lbYnV2_bPxKKBZHu1g8XyfGE_CBCFzSIPETKMGHBsB7WV8aAn1CEALw_wcB

the highest possible effectiveness and enhancing it, when needed, as well as allowing researchers to access such data to keep on developing and advancing in CGT.

Ultimately, the CGT portfolio is envisaged as a catalyst enhancing more and more impactful collaborations between academic researchers and companies in the field, paving the way to achieve the necessary scientific advancements in the CGT area that would enable to drive progress in patients' care.

3. Proactive portfolio management

Proactive portfolio management represents, for the EIC Pathfinder, a novel practice that underlines not only the ambition to fund high-risk projects, but also the imperative to change from a grant-giving agency (the dominant paradigm throughout Europe) to a hands-on innovation agency for all funded projects[26]. The EIC Programme Manager has a central role in this.

This section describes the EIC proactive management as applied to this Pathfinder Challenge. It starts by building the portfolios; i.e. by allocating actions into portfolios (a). Proactive management will allow to define and to update portfolio's objective and roadmap (b). Portfolio members will benefit from portfolio activities and from the access to the EIC Market Place (c).

a. Allocation of the actions into the portfolio

This section provides the Challenge specific elements of the way in which the evaluation results in a coherent Challenge Portfolio. It should be read in conjunction with the overall evaluation process as described in the EIC Work Programme text (Appendix 3).This section provides guidance to proposers on how to align their proposal with the architecture of the Challenge Portfolio as envisaged by the Programme Manager.

At the second evaluation step, the evaluation committee, chaired by the Programme Manager, builds a consistent Challenge portfolio, i.e. a set of projects supported by the EIC under Pathfinder, and contributing to the same EIC Pathfinder Challenge. In order to do so, the evaluation committee will allocate proposals into categories. These categories define the overall architecture of the targeted portfolio.

For this specific Challenge, the evaluation committee will consider in priority the following aspect to build a category of projects potentially leading to the formation of a portfolio:

- Next-generation cell therapy technologies beyond the state-of-the-art AND/OR novel concept-based gene therapy technologies and gene delivery systems, that can contribute to the development of more effective and safer cell and gene therapy treatments, respectively

The underlying rationale of this approach is to cover the element of technological novelty in the field, as broadly as possible.

If, however, further considerations need to be made to complete the portfolio, the following two considerations will be applied:

[26] 'Implementing the pro-active management of the EIC pathfinder for breakthrough technologies & innovations', Expert Group report, November 2020

1. common therapeutic indication(s) focus, in order to make the portfolio more consistent

2. Proven precision/personalised medicine approach

Finally, if, after the above approach, inadequate consistency is observed for the purpose to build a consistent portfolio, then the evaluation committee will go ahead to divide the proposals in two main categories, gene vs cell therapy approaches/technologies, generating the two respective portfolios keeping into consideration all the above.

After the selection is completed, the selected projects, once funded, will constitute the EIC Challenge Portfolio in this field.

The contractual obligations subsequent to the participation of a project into a Challenge portfolio are described in section 5.

b. Portfolio objectives and roadmap

This section documents the objectives and roadmap of the Challenge Portfolio. Portfolio Objectives are overarching objectives for the collection of projects in the portfolio, to be achieved by joint activities among the projects' participants. They are set by the Programme Manager, in close discussion with the participants. In some cases, the Programme Manager may detail, already at the time of the call, indicative Portfolio Objectives and a roadmap to reach them. In any case, they will be updated following discussion with selected beneficiaries, and revised on a regular basis, for instance based on projects' achievements, new technology trends, external inputs (other projects, new calls…), and discussions with stakeholders/communities.

For this specific Challenge, the Portfolio Objectives and Roadmap will be co-designed and agreed between the Programme Manager and the participants of the projects, once the Portfolio is established.

c. Portfolio activities and EIC Market Place

Portfolio activities are proposed and designed by the EIC Programme Manager in consultation with the beneficiaries, and where appropriate with other interested EIC Community members and other third parties. They aim at developing the cooperation within the EIC Portfolio in order to:

- achieve the Portfolio Objectives or the objectives of the actions,
- enhance research,
- prepare transition to innovation,
- stimulate business opportunities,
- and strengthen the EIC Community.

Such activities may cover - notably but not only – organization of, and participation to conferences, workshops or any EIC Portfolio or networks meetings, experience and data sharing, as well as participation in any relevant EIC Business Acceleration Services events. The responsible Programme Manager will manage the portfolio through actions, he or she sees most fitting to advise the participants in the orientations of their work, or exploring potential synergies with others, including with businesses and start-ups, for mutual benefit.

To enhance cross-fertilization activities, and to stimulate potential innovation, the EIC Programme Manager may request any beneficiary to make available - through the EIC Market Place - information on preliminary findings and results generated by the action, with the aim to probe their potential for further innovation. The EIC Market Place[27] allows the Programme Manager to have an overview of the actions, their preliminary findings and potential links between those, thanks to the underlying Artificial Intelligence tool.

The Programme Manager will accelerate the most promising portfolio projects based on work progress against previously set milestones and using the power of innovation intelligence. To accomplish that, the Programme Manager disposes of EIC tools such as, fast tracking a project to Accelerator (see Appendix 1, Active management section) and a 50K grant that can be used more than once, to the benefit of a beneficiary (See Appendix 4). Regarding the latter, the beneficiary must provide convincing and fully documented evidence that the project has arrived at a new, rather unexpected outcome that opens new opportunities and, therefore needs new or additional innovation intelligence.

At this point, the following Portfolio Activities are being scheduled:

Date	Description	Main outcomes	Reference/report
tbd	Portfolio kick-off meeting	Challenge Objectives and Roadmap	

Table 1: Portfolio Activities for Challenge Emerging Technologies in Cell and Gene therapy

[27] The AI-supported EIC Market Please is still under development, see EIC Work Programme 2021, Section 4.

4. List of projects in the Pathfinder Challenge Portfolio

(will be inserted once the Call has been evaluated and the selected proposals granted).

5. Challenge call text

(extract from
https://eic.ec.europa.eu/system/files/2021-03/EIC%20Work%20Programme%202021.pdf)

Cell and gene therapy (CGT) are widely accepted as top biomedical trends for over three years now and continue to evolve in their use for treating human diseases. CGTs are expected to increasingly shape the medical treatment and diagnosis, as we are approaching the era of precision medicine. Cell-based therapy is a promising strategy for effective treatment across a wide range of diseases though the focus so far, has primarily been on cancer, e.g. Chimeric Antigen Receptor T-cell (CAR-T) therapy made from removing T cells from individual patients, engineer them to be able to recognize and kill cancer cells before re-administer them to the same patient. CAR-T cell therapy is widely regarded as having revolutionised the treatment of some blood cancers. Recent research evidence suggests that cell therapy can effectively apply to solid cancers as well.

Gene therapy, on the other hand, is yet far from having revealed its full potential and, therefore, innovative gene therapies remain a top priority in genomic medicine. Some companies believe that, after having achieved a robust proof-of-concept, clinical development and downstream interaction with regulatory agencies will be easy. The reality, however, is that the whole process from concept to commercialisation, from research to commercial grade viral vector under GMP standards, is a very demanding one, with the constant need for technological improvements to successfully overcome challenges such as increasing accuracy/specificity and scaling up the production or the release of tests that must be completed before use in patients. Finally, combined cell- and gene-based approaches in preclinical studies, is a relatively new bio-trend that is increasingly gaining the interest of cell and gene therapy scientists worldwide.

With this Pathfinder Challenge, EIC strategically aims at reinforcing critical components of the European cell and gene therapy community, such as focused research consortia, start-ups and spinoffs, in their ability to compete and sustain in this fiercely competitive field, full of challenges and obstacles all along the way from discovery to the manufacturing step. Proposals submitted to this call should effectively address exactly that, by proposing convincing technological solutions and/or new breakthrough concepts that go far beyond the current state-of-the-art.

Proposers are invited to submit disease-specific or non-disease-specific proposals, focused on emerging technologies or technological solutions aimed to overcome the current cell and

gene therapy challenges in one or several the areas listed below, but without being restricted only to these areas.

- Advancing cell therapy manufacturing and products to a clinical stage:
    - Advanced technological solutions that can effectively support the GMP manufacturing step of cell therapy e.g. in terms of speed and cost effectiveness.
    - Novel cell therapy products, targeted to frequent diseases such as cancer and organ failure but also to less frequent diseases like immunodeficiency disorders, that can be used by clinical stage biopharmaceutical companies.
    - Cell therapy technological solutions that can improve important constraints in handling highly concentrated and complex formulations of recombinant biologics, such as controlled release of therapeutics and injectability.
- Improving adoptive cell therapies (CAR-T, TCR, TIL):
    - New technological solutions that would help to improve current adoptive cell therapy approaches:
        - i) by lowering the high cost and complexity of the procedure;
        - ii) by overcoming the long known rejection problem observed in the off-the-shelf or allogeneic CAR-T cell therapies;
        - iii) by targeting the CAR into one location, which would take away the variability problem (the CAR randomly goes into the genome of cells resulting in variable levels of potency) and
        - iv) by developing CAR-T based new immunotherapeutic approaches against solid tumours with the use of monoclonal antibodies.
- Identifying next generation cell therapies for cancer:
    - New technological platforms that can contribute to identifying next-generation cell therapies for cancer (finding new targets for the engineered immune cells to home in on, or novel source of cells for new therapeutic approaches) as well as improving existing therapies to make them more efficient and safer. The latter could include naive fully functional T-cells.
- Applying cell therapy to treat cancer patients in a personalised manner:
    - Advanced technological solutions that would enable to apply cell-based therapies to treat patients in a personalised/precision manner. Single cell-based approaches (analysing DNA, RNA, epigenetic marks, proteins, metabolites used in combination with single cell sequencing, single cell imaging and spatial profiling) in particular to allow to map the presence of individual cells in the tumour environment.
    - New technological solutions including lab-grown cancer organoids or organs on-a-chip which would allow to test the patient's response to various cell therapies and drugs, alone or in combination, prior to the initiation of the treatment, are sought.
- Improving the effectiveness and lowering the risks of gene delivery systems (vectors):

  - Novel gene therapy approaches using the power of CRISPR-Cas or other molecular machineries leading to more effective and robust gene delivery systems (vectors) and/or more precise and reliable correction of genetic mutations.
  - Technological approaches that can tackle long lasting challenges in gene therapy (e.g. the transient instead of stable expression of the transfected gene).
  - New technological solutions to reduce toxicity, as a result, of administering repetitive doses of viral vector(s) to patients in clinical trials.
  - New or improved gene delivery vehicles using next generation AAV or other recombinant vectors with the ability to target specific tissue types and persist in non-dividing cells for long periods of time.
- Improving gene therapy manufacturing processes and production:
  - With the first gene therapies on the market and dozens more in trials, the race is on to improve the production and manufacturing processes to deploy gene therapies at scale. Technological solutions are sought to effectively control challenges in the production of viral vectors at the large scales needed to reach the clinical trial step. Speed is critical, yet excessive speed can put product quality, safety, and efficiency at risk.

Specific conditions for this challenge

In order to apply, your proposal must focus on emerging technologies or breakthrough new concept-based technological solution that go far beyond the current state-of-the art, aimed to overcome cell and gene therapy challenges and obstacles companies are currently being faced with, at the preclinical or clinical level or bio-manufacturing level. Proposers can submit disease or non-disease specific proposals. Your project must aim to deliver, by its end, at least one of the specific outcomes defined for this challenge. The gender dimension in research content should be taken into account, where relevant[28].

[28] https://ec.europa.eu/info/news/gendered-innovations-2-2020-nov-24_en.