Topic: Supporting the development of chimeric antigen receptor T cells

All information regarding future IMI Call topics is indicative and subject to change. Final information about future IMI Calls will be communicated after approval by the IMI Governing Board.

Topic details

Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Despite recent advances in cancer treatment, the medical unmet need in oncology remains high. In the European region, cancer causes 20% of deaths and is the second cause of death after cardiovascular diseases, with 3 million new cases and 1.7 million deaths each year. Cancer is also a leading cause of death in children and adolescents around the world [1].

Engineered T cells, including Chimeric Antigen receptor (CAR) and T-Cell Receptor (TCR) engineered T cells, combine features of cell therapy, gene therapy, and immunotherapy. With two distinct autologous CD19 CAR-T-cell therapies approved by Food and Drug Administration in 2017 and European Medicines Agency in 2018, cellular immunotherapy based on autologous or allogeneic engineered T cells is emerging as a promising new treatment modality for a broad range of cancers. But although CAR-T-cell therapies have been largely successful in treating haematological malignancies, they have not been as effective in treating solid tumours [2].

These complex medicinal products have the unique ability to self-amplify and persist in treated patients. Their translation from basic and pre-clinical research to clinical trials therefore poses many challenges that slow down clinical development [3]. They have been associated with unique specific acute toxicities, with Cytokine Release Syndrome (CRS) and neurotoxicity being two most commonly observed toxicities. Animal models often fail to predict toxicities associated with the use of CAR-T cells and frequently overestimate the efficacy of the treatment, as they do not accurately reflect the tumour microenvironment (TME). Although new mouse models have recently been shown to be able to recapitulate human efficacy, CRS and neurotoxicity of anti-CD19 CAR-T cells, efforts are still needed to optimise and extend these models to other tumour antigens [2][3][4][5][6][7]. The use of alternative, non-genotoxic and non-myeloablative methods to induce lymphodepletion or better schemes for administrating existing regimens may also contribute to decreased toxicity associated with engineered T cells [3][8].

The need for Good Manufacturing Practices (GMP)-compliant manufacturing may also constitute a specific hurdle in the timely translation to the clinic. Issues may refer to consistency of clinical batches, characterisation of the final product, and definition and evaluation of specific potency criteria. Standardisation of analytical procedures would improve comparability of CAR-T-cell batches and of clinical results from patients included in different trials and/or receiving CAR-T cells from different origins [3].

Besides, there is an increasing consensus among stakeholders that patient engagement is critical to fostering patient access to innovative therapeutic solutions and delivering better patient health outcomes.

Need and opportunity for public-private collaborative research

Advancing therapeutic T-cell engineering requires progress on multiple fronts, including the development of pre-clinical models with high translational potential to predict the safety and efficacy of engineered T cells; the optimisation of lymphodepletion regimens and better understanding of its impact on the safety and efficacy of engineered T cells; better control and industrialisation of cell manufacturing sciences and regulatory compliance in the development of engineered T cells.

To address such a wide range of complex issues, there is a need for strong cooperation amongst industry, biotechs, academia, patient organisations, policymakers, public health experts and regulators, bringing their diverse expertise in the following fields:

- Development of relevant pre-clinical models of safety and efficacy;
- Standardisation of analytical methods;
- Collection of public or existing biological and clinical data related to engineered T cells and lymphodepletion;
- Modelling (Pharmacokinetics/ Pharmacodynamics (PK/PD) /lymphodepletion);
- Biostatistics;
- Quality profiles and regulatory aspects of the manufacturing of engineered T-cell therapies;
- Patient access to treatments.

This call topic also represents an opportunity to enable patients to better reflect their perspectives in CAR and TCR engineered T-cell development. Through meaningful patient engagement, all stakeholders involved in the development of medicinal products should benefit from each other's expertise and develop a better understanding of how diverse viewpoints can positively drive better medicines.

Scope

The overall objective of the call topic is to support the development of engineered T-cell therapies, including CAR and TCR engineered T cells. The call topic will address both autologous and allogeneic approaches in haematological and solid tumours.

The objectives of the call topic are:

- Optimisation of existing pre-clinical models, tools and pharmacodynamic (PD) markers to predict toxicities associated with engineered T cells, such as CRS, neurotoxicity, Graft-versus-Host Disease (GvHD), off-target toxicity of gene editing technologies and insertional mutagenesis linked to the use of viruses. Development of new models and tools if needed;
- Optimisation of existing pre-clinical models, tools and PD markers to predict efficacy of engineered T cells, including assessment of anti-tumour activity, pharmacokinetics (PK) (trafficking, homing, infiltration, persistence) and PK/PD modelling. Development of new models and tools, such as patient derived xenograft (PDXs) models relevant for heterogeneity of the tumour and potentially to study the role of TME in the case of haematological malignancies, as well as syngeneic models;
- Comparison of existing analytical methods used pre- and post-infusion of engineered T cells to define gold standard methods. New technologies may also be developed. Methods related to quantification

and characterization of engineered T cells pre-infusion (product), assessment of the clinical fate of engineered T cells (homing, persistence, expansion and efficacy), immune monitoring of patients (kinetics of reconstitution of immunity, profiling of CAR-T cells and immune response to CAR-T cells) and assessment of off-target toxicity of gene editing technologies and insertional mutagenesis linked to the use of viruses, both pre- and/or post-infusion;

- Creation of a database with historical existing clinical and biological data from patients receiving lymphodepleting regimens. Modelling of the impact of the different lymphodepleting agents on immune cells. Development of relevant *in vivo* models to evaluate new lymphodepleting regimens;
- Expert discussion on the implementation of regulatory guidance for engineered T cells, including European Pharmacopoeia and GMP for Advanced Therapy Medicinal Products (ATMPs) to define standard product profiles;
- Determination of the role(s) of patients in each R&D stage. Development of patient-friendly communication tools to improve the patient journey, and materials to facilitate the training of Health Care Providers (HCPs) on engineered T-cells to better answer patient needs;
- Expert discussion on the best path to ensure broad patient access to engineered T cells.

Expected key deliverables

The expected key deliverables will be public and should include the following:

- **Deliverable 1:** Pre-clinical models, pharmacodynamic markers or tools with high translational potential to predict safety of engineered T cells, including CRS, neurotoxicity, GvHD and off-target toxicity of gene editing technologies and insertional mutagenesis linked to the use of viruses;
- **Deliverable 2**: Pre-clinical models, pharmacodynamic markers or tools with high translational potential to predict efficacy of engineered T cells and the role of TME, including anti-tumour activity and pharmacokinetics (trafficking, homing, infiltration, persistence) and PK/PD modelling;
- **Deliverable 3**: Gold standard analytical methods used both pre- and post-infusion of engineered T cells, including quantification and characterisation of engineered T cells pre-infusion (product), assessment of clinical fate of engineered T cells (homing, persistence, expansion and efficacy/potency), immune monitoring of patients (kinetics of reconstitution of immunity, profiling and immune response to engineered T cells) and assessment of genetic modifications pre- and/or post-infusion (off-target toxicity of gene editing technologies and insertional mutagenesis linked to the use of viruses);
- **Deliverable 4:** Optimised lymphodepletion regimens for engineered T cells, based on analysis/modelling of existing lymphodepletion data and development of new *in vivo* models to evaluate impact of different lymphodepleting regimens on engineered T-cell expansion and persistence;
- **Deliverable 5**: Customised European Pharmacopoeia and GMP for ATMPs for engineered T cells to achieve standard product profiles;
- **Deliverable 6:** Communication tools for patients and healthcare providers on engineered T cells, including tools to increase the capability of patients to understand and contribute to R&D of engineered T cells, reliable and patient-friendly communication tools to improve the patient journey and to raise awareness among Health care providers (HCPs) of patient concerns;
- **Deliverable 7:** White paper on patient access to engineered T cells.

Expected impact

Applicants should describe how the outputs of the project will contribute to the following impacts and include baseline, targets and metrics to measure impact.

At the levels of R&D process, regulatory pathways and/or Health Technology Assessment (HTA), patient access processes, clinical and healthcare practices, the impact would be:

- The development of safer and more effective engineered T-cell therapies;
- The opportunity to compare data generated from standardised analytical methods;
- Increased industrial competitiveness;
- Broader patient access to engineered T-cell therapies;
- An increased awareness among HCPs of patients' concerns.

As well, the patients will benefit from the project outputs by:

- Better understanding the mode of action and procedures of their treatment;
- Having a better consideration of their perspectives by being a key actor of the whole R&D process;
- Facilitated interactions with HCPs.

For society, the impact could be:

- A better understanding of these complex therapies by the public (complexity, efficacy and safety);
- A better understanding and evidence-based development of engineered T cells might also contribute to decreasing their cost;
- Improved synergies between industry, Small and Medium-sized Enterprises and academic.

Applicants should indicate how their proposal will impact the competitiveness and industrial leadership of Europe by, for example, engaging suitable SMEs.

Potential synergies with existing consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts and funding.

In particular, potential applicants should consider any relevant work/result from other IMI2 JU projects as far as these are accessible (e.g.IMI2 call 15 topic 4: Emerging translational safety technologies and tools for interrogating human immuno-biology).

Industry consortium

The industry consortium will contribute with major assets as

- Clinical experience of engineered T-cell therapies;
- Chemistry Manufacturing and Controls (CMC);
- Regulatory.

Moreover, the industry will also contribute with the following expertise:

- Project Management;
- Communication;
- Legal/compliance;
- Modelling;
- IT support;
- Biostatistics;
- Bioinformatics;
- Molecular Biology;
- Market access;
- Patient advocacy / engagement.

Indicative duration of the action

The indicative duration of the action is 60 months.

Applicant consortium

The applicant consortium will be selected on the basis of the submitted short proposals.

The applicant consortium is expected to address all the research objectives and make key contributions to the defined deliverables in synergy with the industry consortium, which will join the selected applicant consortium in preparation of the full proposal for stage 2.

This may require mobilising, as appropriate, the following expertise and contribution with a major focus on:

- Development of pre-clinical models and tools (*in vitro* and *in vivo* models);
- Cellular and molecular biology;
- Pharmacometrics (PK-PD) / Modelling;
- Regulatory / HTA;
- Health economics.

In their short proposal, applicants should demonstrate they have access to historical data, as well as existing cohorts, of patients treated with engineered T-cells and/or receiving lymphodepletion regimens.

Patient organisations will be considered as key partners of the funded action. They will contribute to collect concerns and needs from patients and caregivers, take active part in the R&D process and ensure patient-friendly communication.

Moreover, the applicant will also contribute with the following expertise:

- Imaging;
- Immunology;
- CMC/GMP;
- Clinicians with lymphodepletion experience;
- Project Management.

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry participation including their contributions and expertise provided below.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management. The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

The architecture outlined below for the full proposal is a suggestion. The architecture of the full proposal should be designed to fulfil the objectives and key deliverables within the scope of this proposal.

In the short proposal, the consortium is expected to have a strategy on the translation of the relevant project outputs into regulatory practices, regulatory, clinical and healthcare practice. A plan for interactions with Regulatory Agencies/health technology assessment bodies with relevant milestones, resources allocated should be proposed to ensure this e.g. qualification advice on the proposed methods for novel methodologies for drug development, qualification opinion.

A plan for aspects related to sustainability, facilitating continuation beyond the duration of the project should also be proposed.

Work package 1 – Project management, coordination, communication and long-term sustainability

Description:

The goals of this work package are to support optimal project management in compliance with scientific and ethical standards and implement the strategy of the consortium and ensure appropriate dissemination of the project progress and outcomes.

Proposed objectives:

- Define work expectations of different work streams, deliverables, dates and activities and review progress regarding adherence to budget, timelines and quality (by all consortium members);
- Ensure legal and contractual management;
- Ensure the set-up of a joint governance structure (by all consortium members);
- Quality assessment of documents;
- Define project interdependencies, stakeholders and risks;
- Ensure ethics management;
- Ensure appropriate communication within the consortium;
- Ensure dissemination of the project progress and outcomes (project website, conference talks, social media presence, a project newsletter, abstracts, publications);
- Communication to wider public.

Industry contribution: will include co-leading this work package, including management of legal, contractual, ethical and quality assessment aspects, will contribute to define the dissemination and communication plan.

Expected Applicant consortium contribution: will co-lead in partnership with industry consortium and work together to define the governance structure and full work plan, will participate to communication and data dissemination

Work package 2 – Patient involvement

Description:

The goal of this work package is to guarantee that the patient perspective is taken into account.

Proposed objectives:

- Promote engagement of patients all along the R&D process;
- Ensure adequate communication on engineered T-cell therapies to patients and their family/caregivers;

- Ensure that HCPs are sensitised to patient needs;
- Guarantee broad patient access to engineered T cells.

Industry contribution: communication, collaboration with Patient Advocacy Groups, knowledge of pharmaceutical life-cycle process, market access

Expected Applicant consortium contribution: patient expertise, communication, training of HCPs, national health care authorities and societies, health economics.

Work package 3 – Models and tools to assess safety of engineered T cells

Description:

The goal of this work package is to optimise and/or develop pre-clinical models, pharmacodynamic markers and tools with high translational potential to predict the safety of engineered T-cell therapies.

Proposed objectives:

- Map existing pre-clinical models relevant to assess the safety of engineered T cells and identify gaps/needs;
- Optimise existing models and develop new models or tools to better predict safety of engineered T cells;
- Preclinical models may include models of CRS, neurotoxicity, Graft-versus-Host Disease;
- Off-target toxicity of gene editing technologies and insertional mutagenesis linked to the use of viruses could also be addressed.

Industry contribution: clinical knowledge of engineered T-cell safety concerns, preclinical models.

Expected Applicant consortium contribution: pre-clinical models including *in vivo* and *in vitro* models, technologies, immunology.

Work package 4 – Models and tools to assess efficacy of engineered T cells

Description:

The goal of this work package is to optimise or develop models, pharmacodynamic markers and tools with high translational potential to predict the efficacy of engineered T-cell therapies.

Proposed objectives:

- Map existing pre-clinical models relevant to assess the efficacy of engineered T cells and identify gaps/needs;
- Optimise existing *in vitro* and *in vivo* models and develop new models and biomarkers to better predict efficacy of engineered T cells. The development of new models relevant to study of the impact of tumour heterogeneity and the role of TME would be a plus;

- Efficacy parameters may include the assessment of anti-tumour activity (predictive *in vitro* assays and *in vivo* models) for haematological and solid tumours or any other relevant biomarkers as engineered T cell expansion and persistence;

- Development of tools and models to assess pharmacokinetics of engineered T cells, including trafficking, homing, infiltration and persistence could also be included (imaging, molecular biology);

- Immunocompetent mouse models to study the epitope spreading;

- PK/PD modelling based on the data generated in the different models (and if possible, on clinical data available).

Industry contribution: expertise in modelling, *in vivo* and *in vitro* preclinical models, PK.

Expected Applicant consortium contribution: pre-clinical models including *in vivo* and *in vitro* models, imaging, PK data, cell therapy PK/PD modelling.

Work package 5 – Gold standard analytical methods used both pre- and post-infusion of engineered T cells

Description:

The goal of this work package is to optimise/develop analytical methods and define gold standard analytical methods to be used for both pre- and post-infusion of engineered T cells.

Proposed objectives:

- Analytical methods to be standardised may include but are not limited to the assessment/quantification of engineered T cells, assessment of clinical fate of engineered T cells (homing, persistence and efficacy), immune monitoring of patients (kinetics of reconstitution of immunity, profiling of engineered T cells and immune response to engineered T cells) and assessment of off-target toxicity of gene editing technologies and insertional mutagenesis linked to the use of viruses;

- Technologies such as quantitative Polymerase Chain Reaction (qPCR), flow cytometry, Next Generation Sequencing (NGS), single cell analysis, Replication competent Lentivirus (RCL), omics may be addressed;

- Development of new tools and methods if needed;

- Technologies could be first developed using relevant *in vitro* models and could then be validated on batches/clinical samples that may be provided by clinicians treating patients with commercially available or academic engineered T cells;

Industry contribution: CMC, Translational, analytics, bioinformatics.

Expected Applicant consortium contribution: Molecular biology, imaging, immunology.

Work package 6 – Development of optimal lymphodepletion /conditioning regimen

Description:

The goal of this work package is to develop lymphodepletion models to better understand the impact of lymphodepletion on engineered T-cell safety and efficacy, and to optimise or develop new conditioning regimens.

Proposed objectives:

- Collect existing biological and clinical data from patients who received lymphodepleting regimens in the context of allograft transplantation and/or CAR-T cells and create an easy to access database by pooling collected data;
- Meta-analysis of the data;
- Modelling of the different existing lymphodepleting regimens (based on collected data);
- Development of relevant *in vivo* models (preclinical) to optimise or test new conditioning regimens and address key questions.

Industry contribution: clinical expertise, *in vivo* and *in vitro* preclinical models, PK, bioinformatics and IT.

Expected Applicant consortium contribution: historical data, literature review, bioinformatics, modelling, pre-clinical models, immunology.

Work package 7 – Data integration

Description:

The goal of this work package is to create and manage an IT platform where all data collected and generated in the context of the consortium will be stored.

Proposed objectives:

- Develop an IT platform to allow easy, compliant and secured access to all the data collected or generated during the project to all members of the consortium;
- Consider the sustainability of the platform.

Industry contribution: IT platform accessible to all members of the consortium.

Expected Applicant consortium contribution: IT and suitable data set.

Work package 8 – Customised European Pharmacopoeia and GMP for ATMPs for engineered T cells

Description:

The goal of this work package is to address some regulatory and quality aspects of manufacturing in order to achieve a standard product profile.

Proposed objectives:

- Biological and pharmaceutical characterisation of the products (i.e. potency activity, release assays, appearance);
- Critical Quality Attributes;
- Quality control, including safety tests such as RCL;
- Recommendations on the practical implementation of GMP for ATMPs and pharmaceuticals requirements;
- Some technologies developed in WP5 could also be applicable for this work package.

Industry contribution: CMC, Regulatory.

Expected Applicant consortium contribution: Academic Centers, Contract Development and Manufacturing Organisations (CDMOs) or any other organisations that are interacting with Regulatory Health Authorities, CDMOs, with access to Academic Centers.

Reference

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