Topic: Non-invasive clinical molecular imaging of immune 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.

Specific challenges to be addressed

Current pharmacodynamic (PD) assessments of immune cells are based on peripheral blood biomarkers, or from biopsy samples which are acquired by invasive procedures. Some existing medical imaging modalities provide a quantifiable, non-invasive, repeatable and localised measure of biological processes in the living body. However, current methodology and technology provides limited information on disease-relevant immune cell subtypes, or measures of direct engagement of immune targets.

Imaging tracers designed to bind specific immune cells ("immunotracers") or targets within immune pathways would enable the clinical imaging of immune cell subtypes and immune markers of disease, which in turn would provide *in vivo* insights into effects of immunomodulatory therapies at disease sites (organs/tissues) and improve knowledge about the pathophysiology of various immune-mediated diseases. The ultimate ambition of clinical imaging with immunotracers is to enable tailored immunotherapy by allowing for:

- patient stratification based on immune status (personalised medicine);
- prediction of response or long-term outcome of therapeutic interventions;
- dose selection including personalized dosing;
- target engagement within the tissue of interest both regionally and focally.

Molecular imaging agents, (hybrid) imaging modalities, and image processing algorithms to image immune cells *in vivo* are advancing within the imaging field and can provide an immediate, non-invasive read-out of target expression over time. However, further novel imaging agents and technologies will need to be developed in order to extend the applicability of immune cell imaging to additional disease areas, additional tissue sites, and/or immune cell subpopulations. Therefore there remains a need to better understand the currently available markers and validate them extensively for clinical use. Thus, a strategic consortium that can connect innovative immunology research, imaging technology, and translational development to implement transformational immunotracers in the clinic is a requirement for the successful execution of this topic.

Need and opportunity for public-private collaborative research

This topic focuses on a set of immune cells of key importance in various disease areas involving widely differing organ/tissue systems, with the ultimate goal to develop a transformational set of clinical imaging agents and non-invasive methods that are capable of monitoring immune cell phenotype and function. A large number of potential therapies acting upon these immune cells exist or are being developed, and successful methods established within this topic will be broadly applicable in many indications across many different organisations and research groups. Even though, the field of (semi-)quantitative clinical imaging of defined immune cell subsets is advancing and moving from qualitative to quantitative measures, it would still require a very broad spectrum of diverse technical and biological expertise to move forward efficiently. This combination is unlikely to be within the scope of investment and capabilities for any one company or organisation, but collaborative efforts in a public-private partnership are most likely to harness all the skills and expertise required.

The topic provides a unique platform for leading experts from industry, academia and regulators. This platform is needed not only to define and create new probes, but also for the testing/validation of imaging technologies and novel imaging algorithms, the generation of reagent packages, and ultimately for the clinical validation of the immunotracers and imaging technology in clinical trials. Generation and validation of a clinical immune-cell imaging platform that provides a non-invasive early indicator to detect mechanistic impact on immune cells of different phenotypes, correlations with efficacy, and benefit of a therapeutic intervention for various disorders will require

collaboration between a diverse set of stakeholders with expertise in immunology, imaging technologies, data management, analytics and regulatory sciences.

Scope

This topic aims to establish a consortium that can develop and validate a quantitative, non-invasive, immune cell imaging platform, which includes (novel) molecular imaging agents, (hybrid) imaging modalities, and image processing algorithms. The topic aligns with the IMI2 Strategic Research Agenda, as it aims to validate immune cell targets based on human biology and to facilitate precision medicine by stratification of patients and prediction of outcomes. In addition, it is expected that these agents will facilitate early diagnosis and/or classification of disease immune phenotype.

The following objectives are within the scope of the proposal:

- clinical validation of existing imaging agents (*e.g.* agents targeting $CD8^+$ T-cells and immune pathways);
- development and characterisation of novel molecular imaging agents to be used for imaging $CD4^+$ T-cells, CD8+ T-cells, regulatory T-cells, B-cells, macrophages, and NK-cells, reflecting the presence of these cells in tissues/organs/tumours, or denoting markers of the activation status of these immune cells;
- establishing molecular imaging platforms in disease areas for which biopsies for validation of the imaging platform can be obtained (*e.g.* Cancer, Chronic Obstructive Pulmonary Disease (COPD)/Asthma, atopic dermatitis, vasculitis, psoriasis, Sjögren's syndrome, inflammatory bowel disease (IBD), rheumatoid arthritis (RA), and transplant). The platform is initially to be validated in a small number of diseases (identified as common denominator of all participating companies), and could subsequently be used for other disease areas;
- optimisation of immunotracers to ensure appropriate specificity of binding as well as pharmacokinetic and bio-distribution profiles;
- implementing non-invasive imaging modalities that can deliver quantitative data. Whole-body imaging technologies with the capability to image deep-seated tissue/tumours are preferred (e.g. PET, SPECT, MRI, hybrid modalities, PET/SPECT-CT), but depending on the disease area other non-ionizing methods or pre-targeting approaches can be evaluated (*e.g.* optical imaging and/or photoacoustic imaging of skin lesions, salivary glands, endoscopic/bronchoscopic examinations for IBD, COPD);
- pre-clinical studies to evaluate the novel molecular imaging agents/immunotracers and the immune cell imaging platform as required to enable translation into the clinic.

Expected key deliverables

Expected primary key deliverables of the topic include:

- identification and evaluation of promising molecular imaging agents and non-invasive imaging modalities (single platform or hybrid) suitable for use with the proposed immunotracers;
- generation of immunotracers for at least two of the following key cell types of interest: CD4+, CD8+, regulatory T-cells, B-cells, NK-cells, macrophages;
- immunotracer optimisation in the context of the planned use (*e.g.* with respect to pharmacokinetic and bio-distribution profile, suitability for repeated use in longitudinal studies);
- appropriate resolution and sensitivity (at least semi-quantitative) of the immunotracer and imaging modality combination(s) to allow delineation of organs of interest and determination of relative changes in tissue immune cell involvement and/or activation status;
- clinical proof of concept utilising at least one immunotracer / imaging modality combination(s) for cells and tissues of interest;
- imaging modalities and processing tools suitable for accurate co-registration of multi-modality images.

Expected impact

Molecular imaging of immune cells could provide an early indicator of whether patients are likely to benefit from a given (immuno-) therapeutic intervention (surrogate of response). The technology to be delivered is expected to have the potential to also provide information for tissue/organ sites which are not biopsy-accessible, thus representing a significant advance in the assessment of immune cell status for the relevant indications. Patients can be stratified by marker expression, with the potential to offer the most appropriate treatment and thereby reduce the implementation of treatment regimens that are unlikely to be efficacious and would therefore have a negative benefit-risk profile for the individual patient (personalised health care, PHC). For example, the cancer–immune set point could be determined for individual patients (e.g. CD8/CD4-imaging) to determine the patient population most likely to benefit from co-stimulatory treatments.

By quantifying the impact of therapy on target cells and related pathways the planned technology is also expected to reduce ambiguity in the evaluation of efficacy during clinical trials (*e.g.* provide early indications of proof-of-concept, assessment of variability between and within individuals, facilitate Proof of Mechanism (POM) and Proof of Concept (POC) studies of new mechanisms). Spatio-temporal complexity can be studied due to longitudinal imaging capabilities.

This topic is a unique instrument to strongly support and enable research and development activities addressing diseases with a strong immunological component, for which currently no or only very limited treatment options are available. Furthermore, it will have significant impact on personalised approaches to detect and better monitor these diseases already in the early and better treatable stages. It will support and guide physicians and patients in determining the most appropriate care, leading to improved efficiency in the health care system. It is envisioned that the topic will ultimately result in the regulatory acceptance of standardised protocols with validated immune-imaging approaches. Consequently, those approaches will significantly reduce the time and cost of clinical trials.

Small- and medium-sized enterprises (SMEs) can be of great benefit to IMI2 JU projects. Their involvement in the action might offer a complementary perspective to industry and academia, and help deliver the long-term impact of the project. Therefore applicants should indicate how their proposals will impact and strengthen 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 learned where possible, thus avoiding unnecessary overlap and duplication of efforts.

In particular, the action generated by this topic should, among others consider initiatives such as the FNIH Partnership for Accelerating Cancer Therapies (PACT) https://fnih.org/what-we-do/current-research-programs/partnership-for-accelerating-cancer-therapies or the IMI projects **BTCURE** (http://btcure.eu/), **RTCURE** (http://cordis.europa.eu/project/rcn/211964_en.html), **PRECISESADS** (http://www.precisesads.eu/) and **TRISTAN** (http://www.imi.europa.eu/projects-results/project-factsheets/tristan).

Industry consortium

The industry consortium will include expertise in clinical operations, protein engineering, validation of immune cell targeting, and will contribute mainly in the form of:

- provision and detailed investigation of antibodies, antibody fragments, and/or small molecule probes;
- prospective clinical trials for selected diseases (immunotracers to be applied in these prospective on-going clinical trials with dedicated imaging activities);
- samples from prospective clinical trials;
- immuno-histochemical and other appropriate analyses of biopsy material to validate the imaging results;
- historical samples for validation;
- omics data analysis.

Indicative duration of the action

The indicative duration of the action is 60 months.

Future project extension

Potential applicants must be aware that the Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU) may, if exceptionally needed, publish at a later stage another Call for proposals restricted to the consortium already selected under this topic, in order to enhance their results and achievements by extending their duration and funding. The consortium will be entitled to open to other beneficiaries as they see fit; should appropriate imaging modalities and/or technologies are developed within the context of the consortium and require additional investigation outside the scope of the proposed sustainability plan.

Direct visualisation of immunophenotypes in target organs would advance the field by providing a mechanistic insight into the pathogenesis of disease which in turn could, with additional studies, lead to the improvement of treatment decisions for physicians and help guide therapeutics development by allowing the visualisation of response to therapy. The proposed focus is to validate existing agents that target immune cells and molecular pathways using biopsies from multiple disease areas as a starting point.

Thus, the knowledge gained from the clinical validation of existing imaging reagents should help augment the development of new tracers, and the pre-clinical studies from them will speed up patient access to innovation. However, addressing all these points is outside the scope of the current initiative as the insights uncovered by this topic will be exploratory and not definitive, and will need to be followed up by future validation studies in patients.

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 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:

- basic and clinical immunology, in particular as this relates to the proposed cell types and indications;
- expertise with appropriate non-invasive imaging technologies and optimisation of quantitative data generation and analysis;
- expertise in immunotracer development, for example in identification of (novel) selective and specific immune cell markers, generation and optimisation of targeting moiety/tracer conjugates;
- proven expertise in project administration, management and communication;

- extensive expertise in interaction and communication with Global Regulators, Patients, Practitioners and Payers, who may be members of an Advisory Board which would be established by the action. These responsibilities will be executed in collaboration with the industry consortium;
- strong Data Management expertise;
- proven experience in managing and coordinating a multi-centre multi-node clinical-research data-generation activity of comparable scope;
- essential experience in dealing with the legal and ethical challenges associated with integrating multi-centre patient-derived data, as well as physical data-processing and data management practices (privacy, security);
- proven capability to deliver analytical platforms to facilitate the above mentioned Advanced Analytical approaches for a range of scientific/medical and analytical communities.

In addition to academic groups, relevant small and medium-sized Enterprises (SMEs) with relevant proven expertise are encouraged to participate in the applicant consortium. SMEs can be of great benefit to IMI projects and, inter-alia strengthen the competitiveness and industrial leadership of Europe. Their involvement might offer a complementary perspective to industry and academia, and strengthen the long-term impact of the project. For these reasons, applicants should consider engaging SMEs throughout the proposal. Under this topic, the contribution of SMEs would be considered especially beneficial in imaging agents and technologies, advanced analytical approaches and data management practices.

The size of the consortium should be proportionate to the objectives of the topic.

Suggested architecture of the full proposal

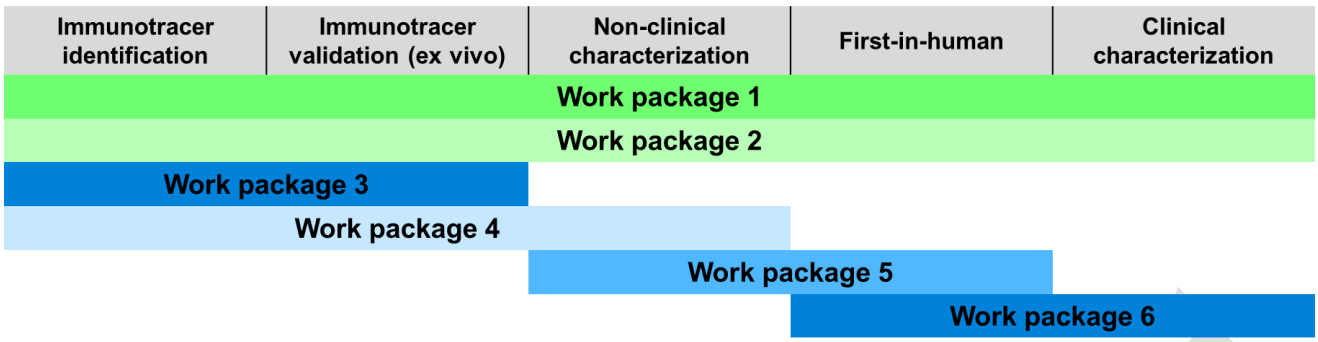
The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry participation including their contributions and expertise.

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.

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

The architecture outlined below for the full proposal is a suggestion. Different innovative project designs are welcome, if properly justified.



Work package 1 – Management, coordination, dissemination and sustainability

The goals of this work package will be as follows:

- overall coordination of the scientific and clinical work packages;
- budget administration;
- dissemination of scientific results and research data;
- development of a sustainability plan to facilitate continuation of the project beyond its anticipated duration;
- communication within the consortium and with external collaborators.

Expected applicant consortium contribution: coordination of work packages, budget administration, dissemination of scientific results and development of a sustainability plan.

EFPIA consortium contribution: communication, dissemination of results and development of sustainability plan.

Work package 2 – Data storage and analysis

The goals of this work package will be as follows:

- managing/coordinating multi-centre (clinical) research data including legal and ethical considerations;
- data sharing, data integration infrastructure, and bio-banking;
- analysis of retrospective clinical trials and design and execution of prospective clinical trials.

Expected applicant consortium contribution: coordinating a multi-centre multi-node clinical-research data-management.

EFPIA consortium contribution: prospective clinical trials for selected diseases (immunotracers to be applied in these prospective on-going clinical trials with dedicated imaging activities); provide samples from prospective clinical trials.

Work package 3 – Generation of imaging reagents to uniquely identify specific cell types

The goals of this work package will be as follows:

- specification of cell types and appropriate surface tags;
- generation of detection reagents;
- characterisation by histology and/or flow cytometry or other laboratory techniques;
- qualification of immunotracers for use in confirmatory assay types and ensures suitability in different assay types.

Expected applicant consortium contribution: identification and evaluation of promising molecular imaging agents; generation of immunotracers for at least two of the following key cell types of interest: CD4+, CD8+, and/or regulatory T-cells, B-cells, NK-cells, and macrophages; immunotracer optimisation in the context of the planned use (e.g. with respect to pharmacokinetic and bio-distribution profile, suitability for repeated use in longitudinal studies).

EFPIA consortium contribution: immuno-histochemical and other appropriate analyses of biopsy material to validate the imaging results, historical samples for validation, omics data analysis.

Work package 4 – Imaging technique development and optimisation

The goals of this work package will be as follows:

- specification of optimal imaging modality;
- development of imaging protocol for specific immunotracers (*e.g.* definition of dose, imaging time point etc.) in preclinical models and with support from data from Work Package 5, where applicable.

Expected applicant consortium contribution: biological validation of specific immunotracers in well-characterised experimental animal models; Proof of Principle preclinical imaging studies using known immuno-modulators.

EFPIA consortium contribution: biological validation of specific immunotracers in well-characterised experimental animal models; Proof of Principle preclinical imaging studies using known immuno-modulators.

The allocation and distribution of resources will be agreed during the elaboration of the full project proposal, as this is dependent on the distribution of expertise between EFPIA and successful (academic/SME) applicant consortium partners.

Work package 5 – Validation of immunotracers in animal models (non-clinical *in vivo* characterisation)

The goals of this work package will be as follows:

- validation of novel immunotracers in rodent and/or monkey models of human disease;
- in vivo pre-clinical animal models will be used to measure the utility of the immunotracers;
- characterisation of non-clinical safety.

The allocation and distribution of resources will be agreed during the elaboration of the full project proposal, as this is dependent on the distribution of expertise between EFPIA and successful (academic/SME) applicant consortium partners.

Work package 6 – Human Clinical Trials

The goal of this work package is to confirm safety or reagents and demonstrate utility in human trials.

Expected applicant consortium contribution: contribute to the preparation of regulatory documentation (Investigator Brochure, clinical protocol, Clinical Trial Application dossier etc.).

EFPIA consortium contribution: prospective clinical trials for selected diseases (immunotracers to be applied in these prospective on-going clinical trials with dedicated imaging activities); provide samples from prospective clinical trials.