Topic: Microenvironment imposed signatures in tissue and liquid biopsies in immune-mediated diseases

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

Unmet medical need:

Biological therapies have provided significant therapeutic benefit to patients with immuno-inflammatory diseases, but many patients fail to respond completely and efficacy is lost in many patients over time. The tissue microenvironment interacts with and influences immune cells to form functional cellular niches that play a role not only in the onset and progression of disease but also in the response to therapy. Inaccessible tissue and invasive biopsy procedures have prevented in-depth interrogation of these microenvironments, resulting in a major gap in our basic understanding of immune cell action mechanisms. Therefore, how they interact with each other and their environment, and how they can be monitored and pharmacologically manipulated to better control disease, remain elusive.

This topic aims to profile tissue-specific microenvironments to improve knowledge of pathophysiology of various immune-mediated diseases (such as inflammatory bowel disease: Crohn's disease and ulcerative colitis; and skin related diseases e.g. atopic dermatitis, cutaneous lupus, psoriasis) and identify signatures that can be correlated in body fluids (i.e. blood), 'circulating signatures', to inform on disease progression and to monitor treatment.

Challenges for medicines development:

Medicine development strategies that are based on reliable organ and tissue specific signatures that reflect the disease-specific tissue microenvironment have the potential to tailor treatment to patient-specific needs and have the potential to be transformative. Such strategies are currently unavailable and therefore reliable and validated signatures have to be established.

Scientific opportunities:

Understanding the role of the crosstalk of tissue and immune system for progression/remission of immune diseases will uncover disease-relevant, actionable parameters in tissue. Correlating these signatures with 'circulating signatures' in blood ('liquid biopsies') will improve and enable human target validation and patient stratification, as well as develop more effective and safer therapies.

Need and opportunity for public-private collaborative research

The proposed work with a focus on inflammatory bowel disease and skin diseases, will advance our understanding and help accelerate the development of personalised drug treatments for patients. However, in immune mediated diseases where the underlying science is so complex, no critical mass exists to make significant progress. The magnitude of the challenges to be addressed by the successful consortium requires a large international scientific collaborative project that includes: i) the clinical and technological excellence in academia; ii) the clinical development expertise of pharmaceutical industry; iii) technological expertise of small and medium-sized enterprises (SMEs) and; iv) advice on signatures validation and adoption for clinical trials from regulatory authorities, coupled with a critical amount of high quality data. Such collaboration of a consortium of

pharmaceutical companies and public institutions will enable evaluation of both existing and novel technologies to identify and validate tissue-specific signatures. The cross-industry nature of the collaboration will allow consorted validation of such signatures to enable regulatory suitability and adoption into future trials. Advice from regulatory authorities, such as the U.S. Food and Drug Administration (FDA) and/or European Medicines Agency (EMA), will be sought to facilitate regulatory suitability of identified signature(s) for future clinical trials and medicine development.

To achieve significant impact and drive a timely change in the field, it is necessary to kick-start the process by building on all available assets and learnings via a combination of key resources globally and mobilising stakeholders in EU Member States and H2020 Associated Countries and potentially beyond.

Scope

Overall objective of the project

The ultimate goal to be achieved by the consortium is to identify key organ and disease-specific signatures with correlates in body fluids that may predict disease, track progression and/or therapeutic response. These signatures will enable tailored treatment pathways to the disease mechanism and ultimately provide superior therapeutic benefit to patients.

Scope for the project

In order to achieve the ambitious overall objective, a set of specific objectives should be addressed by the applicants.

1. Identify and evolve the state-of-the-art novel technologies to interrogate both immune and non-immune cells in target tissues at single cell level to better understand pathways regulating disease and to define tissue/disease-specific signatures, which can be correlated in peripheral blood. The technologies for the identified signature need to be adaptable and of sufficient robustness for use in clinical trial.
2. Evaluate above technologies in existing clinical retrospective cohorts as well as samples from ongoing clinical trials made accessible by both academic and industry partners.
3. Perform a bespoke, enabling clinical study to verify signatures. This will be a non-interventional prospective study, run as a collaborative effort between industry and academic partners.

Expected key deliverables

With the aim of profiling tissue-specific microenvironments and identifying circulating signatures necessary to inform disease progression and monitor treatment, the following key deliverables are expected:

- identification and optimisation of promising technologies and/or platforms suitable to profile cells in a disease-specific tissue microenvironment. A non-exhaustive list of examples of such technologies can include but is not limited to: single cell sequencing, multiplex immunohistochemistry, immunophenotyping, immune repertoire and ‘omic’ approaches, such as metabolomics, autoantibody profiling, miRNA profiling, epigenomics, microbiomics, transcriptomics, etc.;
- generation of both tissue and body fluid (e.g. blood) profiles using above outlined technologies using existing clinical material, including longitudinal samples, available from biobanks, academic partners and/or industry partners. In addition to existing clinical samples (if applicable), industry partners are expected to provide clinical material and clinical parameters from prospective studies;
- evaluation of comparability of tissue profiles between fresh and stored (e.g. fresh frozen, formalin-fixed paraffin-embedded (FFPE)) samples;
- mapping of tissue profiles against profiles from body fluids (e.g. blood) and clinical parameters to identify specific and robust liquid signatures representative of disease tissue microenvironment;

- validation of identified signature(s) in both tissue and body fluid in longitudinal patient cohorts made available from prospective clinical trials performed by industry partners. These include, but are not limited to, samples from placebo cohort and baseline samples;
- correlation of clinical profiles and parameters to determine the stability of the signature and/or the ability of the signature to track clinically relevant changes of disease progression and/or response to treatment;
- generation of raw data repositories with access for all consortium partners;
- development of software and bioinformatics packages for full data integration and analysis;
- design and development of a database/IT infrastructure allowing for query of data sets and long-term housing of data within the consortium. Design and execution of a high-quality, multi-centre, non-interventional, longitudinal study to verify the identified tissue and blood signature(s) in at least one disease (gut or skin related) involving both academic and industry partners;
- further confirmation of signatures by analysing samples from independent prospective clinical trials in complementary indications, performed by the EFPIA industry partners.

Expected impact

In-depth characterisation of the tissue microenvironment will provide better disease understanding, which represents a significant advance in the assessment of both immune and non-immune markers in relevant diseases. The signatures, but potentially also the relevant (novel) underlying technology, will advance clinical monitoring in both clinical trials and standard patient care. These tools will allow earlier detection of disease progression or identify patients at risk and therefore will allow earlier or more tailored treatment. In clinical trials, these less invasive tools will allow better or earlier detection of treatment response, but may also allow better patient stratification and prediction of treatment response. The proposed non-interventional clinical study will allow verification of signatures and facilitate the implementation of these signatures as decision-making tools for other clinical studies. The less invasive nature of the detection of these signatures is highly attractive, as it will significantly reduce the burden to patients in clinical trials and can complement diagnosis.

The multi-partner, multi-stakeholder and cross-sector approach of this consortium will also allow for a more standardised future adoption of these signatures across industry and pave the way for regulatory approval of improved, clinically relevant tools to monitor disease progression.

Applicants should indicate how their proposal will impact the competitiveness and industrial leadership of Europe by, for example engaging suitable SMEs. In particular, the inclusion of SMEs into the consortium will maximise the opportunity for suitable technology for the identification of disease-specific signatures of the tissue microenvironment to be identified and, more importantly, ultimately implemented in multi-centre clinical trial settings under good laboratory practice (GLP) conditions.

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.

The following completed, ongoing or forthcoming initiatives (the list is not exhaustive) have been identified and could be considered by the applicants.

IMI projects:

- **BTCURE** (http://btcure.eu/)
- **RTCURE** (http://cordis.europa.eu/project/rcn/211964_en.html)
- **PRECISESADS** (http://www.precisesads.eu/)

Please note that during the project implementation phase the applicants could also consider other potential knowledge generated by the forthcoming projects under IMI2 JU in the area of genome-environment interactions in inflammatory skin disease (https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/open-calls/1.%20IMI2_C13_TOPICS%20TEXT_EN.pdf) and targeted immune intervention for the management of non-response and relapse (https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi2/IMI2%20CALL%2014%20TOPICS%20TEXT_EN.PDF).

Other European and international initiatives:

- Human Immunology Project Consortium (HIPC) (https://www.immuneprofiling.org/hipc/page/show),
- Inflammatory Bowel Disease Biomarkers Programme (IBD-BIOM) (http://www.ibdbiom.eu/),
- Inflammatory Bowel Disease Characterisation by a multimodal integrated biomarker study (IBD-CHARACTER) (https://cordis.europa.eu/project/rcn/106191_en.html),
- A System Medicine Approach to Chronic Inflammatory Disease (SYSCID) (http://syscid.eu/),
- Biological Therapy Cycles Towards Tailored, Needs-driven, Safer and Cost-effective Management of Crohn's Disease (BIOCYCLE) (https://biocycle-project.eu/),
- SLE: Accelerating Medicines Partnership (AMP) (https://www.nih.gov/research-training/accelerating-medicines-partnership-amp),
- Relapses prevention in chronic autoimmune disease: common mechanisms and co-morbidities (RELENT) (https://www.relent.eu/),
- Lupus Europe (http://www.lupus-europe.org/),
- Systems medicine of chronic Inflammatory Bowel Disease (Sysmed IBD) (https://www.sysmedibd.eu/),
- A comprehensive transdermal therapy concept for non-healing wounds and other skin disorders (DERMADROP) (https://cordis.europa.eu/project/rcn/197053_en.html),
- Integral cell-biology platform for the development of the first effective treatment of radiodermatitis (SkinXCare) (https://cordis.europa.eu/project/rcn/206799_en.html),
- Neuron/mast cell interactions in skin diseases (NEMESIS) (https://cordis.europa.eu/project/rcn/211014_en.html).

Industry consortium

The industry consortium is composed of the following EFPIA companies:

GSK (lead)

Sanofi (co-lead)

Eli Lilly

Novartis

Pfizer

The industry consortium will provide bio-samples (e.g. blood, urine, tissue biopsies) and patient-characterised data sets (deep-clinical phenotyping) from various prospective clinical trials (baseline, active comparator and/or placebo) for IBD including ulcerative colitis and Crohn's disease and skin disease, including atopic dermatitis, cutaneous lupus and psoriasis. Furthermore, industry partners will contribute activities related to these samples as in-kind contribution. Note that there will be a difference in design of these clinical trials, and the specificities of the available bio-samples will be confirmed during the full proposal preparation. It is also expected that longitudinal analysis of these bio-samples may be limited in comparison to bio-samples from cohort available to public partners due to the relatively short duration of most clinical trials. In addition, the availability and disease type of the bio-samples

obtained from future prospective clinical trials performed by the industry consortium carries some attrition risk due to discontinuation of development activities, incompatibility of informed consent for certain profiling and analyses and/or legal considerations.

The activities related to samples or data generated in the context of the aforementioned prospective clinical studies sponsored by the respective company will only be reported as in-kind provided that i) the cost to generate and provide relevant samples or data is incurred during the term of such Action (project), ii) the relevant activities are described in the Full Proposal and Grant Agreement's Description of Action, iii) and that these samples and data are necessary to achieve the objectives of the Action.

As a non-exhaustive list of examples such in-kind costs incurred may include full time equivalent (FTEs), clinical research organisation (CRO) costs, lab/assay costs, investigator fees, per each company's usual cost accounting practice.

The industry consortium may contribute with technology platforms for bio-sample analysis to complement technologies provided by the public participants.

The industry consortium will include informatics and systems biology experts and clinical statisticians. Immunology expertise to contribute to the validation of liquid signatures will be made available, as well as biomarker expertise to support validation activities and assay development implementation into regulated environment e.g. GLP.

Clinical expertise will be provided to design and follow the verification trial.

Indicative duration of the action

The indicative duration of the action is 60 months.

Future project expansion

Potential applicants must be aware that the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking 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 the results and achievements by extending the duration and funding. The consortium will be entitled to open to other beneficiaries as it sees fit.

In the context of this topic, it is envisaged that data generated by the consortium in the early stages will provide key information that may warrant applying for a project expansion to allow inclusion of additional clinical trials that will enable verification of signature in diseases that are outside the current scope. Such extension could also include cross-disease comparison and/or even interventional clinical studies with existing or new therapeutics.

Indicative budget

The indicative EFPIA in-kind contribution is EUR 15 500 000.

Due to the global nature of the participating industry partners, it is anticipated that some elements of the contributions will be non-EU/H2020 Associated Countries in-kind contributions.

The financial contribution from IMI2 is a maximum of EUR 15 500 000.

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 resources:

basic and clinical immunology, which relates to the following indications: inflammatory bowel disease (Crohn's disease and ulcerative colitis) and skin related disease e.g. atopic dermatitis, cutaneous lupus and psoriasis;

expertise in clinical care of patients with inflammatory bowel disease or skin diseases;

demonstrated access (e.g. patient consent, waiver consent, etc.) to resources of existing longitudinal, clinical bio-specimens and/or samples from biobanks as well as from the ongoing clinical studies related to the above conditions, to enable evaluation of existing and novel technologies as outlined in the key deliverables section. Strong expertise and proven delivery of technologies, as outlined in the key deliverables section, that are suitable to characterise the tissue microenvironment. Such technologies should allow for an identified signature to be readily and feasibly implemented in clinical trial settings i.e. GLP conditions. In particular, single cell profiling technologies are of interest;

consequently, partners providing medical record-based information as project background must be mindful that they, as background contributor, should have sufficient title to said background to authorise its use within the project pursuant to the IMI2 JU IP and legal framework. A similar approach should also be applied in case of additional information that may be introduced after the start of the project but which is not listed as project background at start date;

proven capability to deliver analytical platforms to facilitate the above-mentioned advanced analytical approaches for a range of scientific/medical and analytical communities;

proven experience in managing and coordinating a multi-centre, multi-node, clinical-research, data-generation activity of comparable scope;

expertise in clinical study design;

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);

essential experience in operationalising large multi-centre clinical trials.

In addition to academic groups, SMEs with relevant proven expertise, relevant technology and proven record of delivery of peer-reviewed data sets are encouraged to participate in the applicant consortium. SMEs can be of great benefit to IMI projects and 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 technologies to characterise the tissue microenvironment or body fluids, advanced analytical approaches and data management practices.

In addition, the applicant consortium is expected to include resources for project administration, management and communication.

At the full proposal stage, the pharmaceutical companies with other industry partners are expected to bring expertise in novel or existing technologies to characterise tissue, blood and other matrices. They will provide clinical samples, including clinical profiles and parameters, from prospective clinical trials that will be used for identification and validation of signatures of the tissue microenvironment. In addition, they can also provide support by provision of specific technology, bioinformatics analysis and/or clinical trial expertise.

The consortium will engage with regulatory authorities, such as the FDA and EMA to seek advice on utilisation and validation of identified signature(s) for the clinical trial, as described in work package 6, and for adoption by other future clinical studies outside this proposal.

The topic is focused on technology evaluation followed by validation of signatures in a non-interventional trial. The nature of the trial (non-interventional) is expected to have limited long-term benefit to patients and likely beyond the duration of the project when signatures can be implemented in interventional clinical trials. Therefore, engagement with and input from patient groups will be sought later in the process when validated technologies and signatures have been established.

The size of the consortium and expertise provided within it should be proportionate to achieve all 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 contributions and expertise provided below.

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.

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.

All beneficiaries are encouraged to discuss the project architecture and 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 – Project management

This work package will contain details of the proposed structure for project management to track progress of deliverables and individual work packages. The goal of this work package is the overall project coordination and communication, including:

define work expectations of different work streams, deliverables, dates and activities and review progress regarding adherence to budget, timelines and quality;

ensure legal and contractual management;

ensure the set-up of joint governance structure;

ensure appropriate communication/dissemination within the consortium and with the external scientific community and the public;

ensure interaction with regulatory bodies, as necessary (e.g. for qualification process/advice of identified signatures);

develop and manage communication via a web portal and other social media tools with a repository of key documents;

quality assessment of documents;

ensure that key cross-functional partners are engaged;

define project interdependencies, stakeholders and risks;

ensure ethics issues management.

development of a sustainability plan including a strategy for access to data beyond the duration of the consortium.

Work Package 2 – Identification and characterisation of tissue specific signatures using new and existing technologies

The goals of this work package are to characterise the tissue microenvironment and accessible matrices, such as blood, using multiple technologies, both novel and existing. Selected technologies will be evaluated in a non-interventional clinical study (work package 6) and will need to be GLP compliant. Signatures found in blood or other matrices will be correlated with signatures found in the

tissue (not necessarily identified by the same technology). Technologies to be considered, but not limited to, are:

single cell sequencing or profiling of isolated cell types in blood and tissue;

multiplex analysis FFPE tissue;

'omics' analysis.

Work Package 3 – Utilisation and validation of disruptive liquid biopsy methodology

The goal of this work package is to evaluate disruptive liquid biopsy technologies, such as ultrasound-induced liquid biopsies, in a translational setting to establish specific diseases signatures in blood. These technologies and subsequent qualification of pre-analytical procedures will evaluate whether the tissue microenvironment can release soluble mediators into the blood stream that can be measured and used as a signature of the tissue microenvironment.

Work Package 4 – Bioinformatics approaches

This work package will describe the bioinformatics platforms and analyses strategies that will be built and used to analyse and correlate the data from work packages 2 and 3. These platforms and strategies will be defined at stage 2 of the proposal, but will include: the generation of data repositories for raw data with access for all consortium partners; development of software and bioinformatics packages for full data integration and analysis; and the design and implementation of a database and IT infrastructure to allow for query of data sets and long-term housing of data within the consortium.

Work Package 5 – Validation of identified signatures

The goal of this work package is to validate signatures that are identified in work packages 2 and 3 using longitudinal biopsy and blood (or other matrices) patient samples that are made available from consortium partners as part of ongoing prospective clinical trials or ongoing clinical monitoring.

Work Package 6 – Verification of identified signatures in a clinical multi-partner study

The goal of this work package is an extension of work package 5 by designing and delivering a non-interventional, enabling clinical trial to validate the identified signatures to better understand disease progression.

It is expected that the pharmaceutical partners will provide key input in the regulatory framework, trial design and clinical protocol etc., while the academic partners will operationalise the study. The final design of the study and selection of patient populations is to be decided by the consortium and will commensurate with the available budget, but aims to recruit in excess of 500 participants (for a single disease). The trial will include multiple centres and include patients with different degrees of disease severity. Patients will receive standard of care requiring a sufficient number of patients to be recruited across different treatment regimens and will require follow up on disease progression of at least one year, with liquid samples taken at multiple time points and biopsies at both baseline and one year follow up. Although this will be a non-interventional study, patient reported outcomes and clinically relevant disease measurements will need to be included. This will enable any identified signatures to be rapidly adopted into future, interventional, clinical trials and help with better monitoring of disease progression and/or treatment response.

Industry contribution:

Key contributions from industry partners will include:

bio-informatics expertise (work package 4);

provision of clinical trial bio-specimens and/or corresponding analytical data, including clinical parameters. These include bio-specimens from new, prospective clinical trials (work package 5), but can also include existing samples (work package 2);

clinical trial development expertise (work package 6).

Expected applicant consortium contribution:

Key contributions from applicants are expected to be:

technologies to characterise tissue and easily accessible matrices, such as blood (work package 2 and 3);

provision of bio-specimens to aid in technology evaluation (work packages 2, 3 and 5);

bioinformatics expertise (work package 4), including input into and implementation of software and bioinformatics packages for deep profiling, full data integration and analysis;

provision of technologies to allow implementation of identified signatures for measurement in GLP environments and allow validation of identified signatures (work package 5 and 6);

operationalisation of the multi-centre, non-interventional clinical study to include recruitment of in excess of 500 participants for a single disease (work package 6).