Topic: Emerging translational safety technologies and tools for interrogating human immuno-biology

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Topic details

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

Specific challenges to be addressed

There is an urgent need to better understand inherent risks of innovative therapeutics for Immuno-Oncology and Immuno-Inflammatory disease indications including cytokine release syndrome, infection, malignancy and autoimmunity during early (non-clinical) stages of drug development. The toxicities induced by immunomodulatory therapeutics in patients are often not detected in the young healthy animal models that are routinely used for toxicology studies either due the lack of expression of appropriate drug targets/pathways or due to differences in drug target genetics, expression and functions between animal models and the intended patient populations. Thus, innovative translational safety science tools, technologies, models and resources are needed to facilitate the development of novel immunomodulatory drugs (either immunostimulatory or immunosuppressive). Improving the predictivity of non-clinical models will help deliver safer efficacious immunomodulatory medicines to patients and contribute to the principles of the 3Rs. The topic requires a strategic consortium that will enable the sharing of experience from Regulators, Academia, and Pharma Industry, in fast evolving immune cell phenotyping technologies, complex *in vitro* model development, and characterisation of engineered and disease state animal models, as well as facilitating access to extensive immune cell and tissue biobanks (including patient-derived material). Immunomodulatory therapeutic modes of action (spanning both oncology and non-oncology therapeutic indications) for which there is existing non-clinical and clinical safety experience within the Pharma industry, Academia and Health Authorities, provide a powerful framework within which the utility of innovative non-clinical models and endpoints can be assessed for potential use in future Investigational New Drug (IND)/Clinical Trial Application (CTA)-enabling safety assessment packages.

Need and opportunity for public-private collaborative research

This topic focuses on a defined subset of immunomodulatory therapeutic modes of action (spanning both oncology and non-oncology therapeutic indications) for which there is existing non-clinical and clinical safety experience within the Pharma industry, Academia and Health Authorities. The assessment of the potential utility of integrating safety data derived from innovative non-clinical animal models and/or human *in vitro* immune cellular system into IND/CTA 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. Such non-clinical models and endpoints will need to be customised for specific immunomodulatory therapeutic modes of action, disease indications and/or anticipated toxicities. The importance of early engagement and alignment plans with a broad range of public and private stakeholders is exemplified by the themes discussed in several recent workshops and publications on the safety assessment of innovative immunomodulatory therapeutics (https://www.healio.com/cardiology/hf-transplantation/news/print/cardiology-today/%7B0387a9d3-2eb8-4ec8-a9d5-

0b32f59fe1fa%7D/fda-workshop-focuses-on-cancer-immunotherapy-associated-myocarditis-other-cv-toxicities; http://www.bionow.co.uk/events/safetyofimmunecheckpointinhibitors.aspx [1][2][3].

Scope

This proposal aims to establish a public-private consortium that will enhance translational safety assessment approaches for immunomodulatory therapeutics (spanning oncology and non-oncology indications) through development and validation of innovative non-clinical tools and technologies, supported by access to *in vitro, ex vivo* and *in vivo* model-derived immune cell and tissue resources, with an emphasis on evaluating human-relevance. Potential toxicities induced by immunomodulatory therapeutics in patients are often not evident in traditional animal models due to lack of expression of appropriate targets, pathways and/or differential expression/functions versus intended patient populations (e.g. species differences in immune cell repertoire and functions including checkpoints and MHC/peptide complex formation). Patient-derived and advanced animal models should thus enable a better understanding of the interplay between drug target and disease state-associated immune cell repertoires.

At present, *in vitro* human immune cell assays currently used to assess potential effects of immunomodulatory therapeutic agents on functional endpoints such as cytokine release or T cell activation are typically derived from healthy animals and human donors. Thus, there is a need to more accurately model the complex signaling interactions between multiple immune cells in both healthy and disease states (e.g. tumor microenvironment). Therefore the generation of comparative (cross-species) molecular, biochemical, cellular immuno-biology resources coupled to functional and phenotypic outcomes should provide better definition of limitations in the translatability of *in vivo* and *in vitro* test systems to patients and guide optimal non-clinical safety assessment strategies based on therapeutic target, modality, disease indication(s) and patient susceptibility factors (e.g. genotype; biomarkers of immune memory).

Moreover, investing in novel human relevant immune-competent microphysiological systems to assess risks associated with immunomodulatory drugs (e.g. immune-related adverse events, infection, malignancy) will contribute to the effort of reducing animal use while improving predictivity of preclinical models.

The following objectives are within the scope of this proposal:

1. Development of innovative comparative (cross-species) in situ and *ex vivo* molecular, biochemical tools and cellular profiling of immune cells (including patient-derived clinical samples) and association with functional/phenotypic endpoints to enable:
    - enhanced understanding of therapeutic target and pathway biology;
    - enhanced pharmacological and toxicological mechanistic insight and biomarker identification supporting therapeutic index determination for drug candidates and drug modalities;
    - identification of novel endpoints/biomarkers to help support safe starting dose selection for first in human studies e.g. determination of minimum pharmacologically active dose (mPAD) and minimum anticipated biological effect level (MABEL).
2. Establishment, refinement and validation of non-clinical tools and models to enable the development of novel classes of immunomodulatory medicines supporting *in vitro-in vivo* and cross-species translation:
    - comparative assessment of performance of established human *in vitro* immune cell assays (e.g. cytokine release assays; T cell activation and target cell interaction assays) based on healthy volunteer versus patient-derived cells representing specific disease states;
    - development and validation of human immune-competent organotypic and microphysiological systems for efficacy and safety profiling of immunomodulatory drugs (including back translation of clinical findings);
    - development and validation of animal models (e.g. humanized mice, genetically engineered animal models, disease models) as tools for efficacy and safety assessment of immunomodulatory drugs (including refined models to predict risk of infection / malignancy / immune-related adverse events);

- deployment of computational biology approaches for assessment and integration of large multivariate immuno-biology datasets (e.g. phenotypic-anchoring of molecular, biochemical and cellular endpoints derived from both non-clinical models and clinical trials) to reveal novel immune-biology mechanisms and translational biomarkers.

Given the significant technical and logistical challenges associated with sourcing patient-derived samples to support customised safety assessment studies, the topic will also aim to establish a network to facilitate sourcing of human-derived immune cell and tissue samples via centres of excellence for specific disease areas (patient organisations/medtech/academic partners).

Expected key deliverables

- Prioritisation of immunomodulatory therapeutic modes of action (MoA) (including Immuno-Oncology and Immuno-Inflammatory disease indications) for which there is extensive non-clinical and clinical safety experience but suboptimal prediction of human toxicities based on input from Regulators;
- Development/evaluation of innovative molecular and cellular immunophenotyping biomarkers across conventional toxicology models, "engineered" animal models, and human *in vitro models.* Provide enhanced molecular and cellular biomarkers for determination of therapeutic index (TI) and first-in-human (FIH) maximum recommended starting dose (MRSD). Benchmark biomarker performance versus patient-derived samples and assess utility for determination of minimum pharmacologically active dose (mPAD) and minimum anticipated biological effect level (MABEL);
- Development/evaluation of human *in vitro* systems (healthy donor- and/or patient-derived) and "engineered" animal models that are customised for specific therapeutic MoA and patient-relevant cell types/tissue microenvironments in order to recapitulate target engagement, pharmacodynamics and clinically-relevant toxicity phenotypes;
- Leverage consortium approach to enable sharing of experience, tools, models, biobanked samples and databases between Regulators, Academia and Pharma industry (contributing to the principles of the 3Rs);
- Establishment of a network to facilitate sourcing of human-derived immune cell and tissue samples for specific disease areas based on input from Patient Organisations, Medical Technology companies and Academic centres of excellence;
- Development of customised non-clinical safety assessment strategies (e.g. human *in vitro/ex vivo* models and/or engineered animal models) for immunomodulatory therapeutics based on therapeutic target, modality, disease indication(s), and clinical safety experience; aligned with Regulatory expectations.

Expected impact

The action generated by this topic will ultimately help deliver safer medicines to patients via:

- provision of new tools and models to enable a better understanding of the inherent safety risks of immunomodulatory therapeutics during early (non-clinical) stages of drug development;
- improvement of drug development processes and regulatory assessments for immunomodulatory therapeutics through the characterisation of innovative immune-biology models and biomarkers that complement and enhance existing non-clinical safety assessment approaches;
- better definition of limitations in the translatability of non-clinical test systems to patients, which will enable the most appropriate and efficient combinations of test systems to be used for future safety assessment of immunomodulatory therapeutics, and will also contribute to the principles of the 3Rs (i.e Replacement, Reduction, and Refinement of the use of animals for research).

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:

- Collaborative Network For Immunological Safety Research in Minipigs (CONFIRM) Inititative (https://minipigs.dk/knowledge-base/the-confirm-initiative/)
- BioSafe Expert Working Group on improving translational value of *in vitro* and animal models for assessing the pharmacology and toxicology of ImmunoOncology therapeutics https://www.bio.org/events/biosafe-meeting-agenda
- IMI2 Call 14 Topic 2 "Non-invasive molecular imaging of immune cells" https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi2/IMI2%20CALL%2014%20TOPICS%20TEXT_EN.PDF.

Industry consortium

The industry consortium will include expertise in *in vitro* and *in vivo* safety assessment models and biomarkers and will contribute mainly in the form of:

- Design and deployment of prospective *in vitro* and *in vivo* studies; provision of historical safety-related *in vivo* phenotypic data for defined therapeutic modes of action (e.g. discontinued development compounds; marketed compounds); *in silico* prediction of immunomodulatory drug-related adverse events;
- Provision of advanced technology platforms and bioinformatic support for cross-species molecular, biochemical and cellular phenotyping of immune cells e.g. spatial molecular profiling of RNA/proteins/metabolites; integrated transcriptomic and epigenomic profiling of immune cell subsets enriched by flow cytometry and/or at single cell resolution; mass cytometry characterisation of signalling pathways;
- Provision of human blood- and tissue- samples to support deployment of advanced immune cell phenotyping technologies and/or *in vitro* model development (baseline, antigen-challenged, pharmacologically-stimulated, disease states);
- Emerging human-centric *ex-vivo*/*in vitro* technologies (patient-derived and healthy volunteer-derived) will be evaluated and/or further refined for their potential to recapitulate *in vivo* human immune-biology (e.g. *in vitro* modelling of human immune responses including impact of genetic variants and immunogenicity; 3-D bioprinting and microfluidic technologies to enable derivation of complex organotypic and microphysiologic systems.

Indicative duration of the action

The indicative duration of the action is 72 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 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:

- Regulatory expertise (either as project beneficiary or member of a Regulatory Advisory Board of the project) on selection of immunomodulatory therapeutic case studies for assay/model validation and for refining criteria used to make future project decisions e.g. validation using existing examples of discontinued compounds based on clinical evidence/outcomes. Regulators from global Health Authorities will contribute to the selection of representative immunomodulatory therapeutic modes of action for which there is perceived to be an opportunity to enhance translational safety assessment;
- Expertise in customised/innovative immune cell assay/model/bioinformatics development;
- Expertise in innovative technology platforms for molecular, biochemical and cellular phenotyping of immune cells;
- Provision of human blood- and tissue- samples to support deployment of advanced immune cell phenotyping technologies and/or *in vitro* model development;
- Ability to development of *ex-vivo* / *in vitro* technologies for recapitulating *in vivo* human immune-biology;
- Given the significant technical and logistical challenges associated with sourcing patient-derived samples to support customised safety assessment studies, significant experience in the establishment of a network to facilitate sourcing of human-derived immune cell and tissue samples via academic and clinical centres of excellence for specific disease areas that may include engagement of relevant patient organisations.

In addition to academic groups, relevant 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 the provision of innovative engineered animal models and/or *in vitro* models that mimic human immuno-biology.

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 contributions and expertise provided below.

The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 rules and with a view to the achievement of the project objectives.

In the spirit of the partnership, and to reflect how IMI2 Call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, it is envisaged that IMI2 proposals and projects may allocate a leading role within the consortium to an EFPIA beneficiary/large industrial beneficiary. Within an applicant consortium discussing the full proposal to be submitted at stage 2, it is expected that one of the EFPIA beneficiaries/large industrial beneficiaries may elect to become the coordinator or the project leader. Therefore to facilitate the formation of the final consortium, all beneficiaries are encouraged to discuss the weighting of responsibilities and priorities therein. Until the roles are formally appointed through a Consortium Agreement the proposed project leader shall facilitate an efficient negotiation of project content and required agreements.

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.

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
- liase with regulatory advisors to establish framework for selection of immunomodulatory therapeutic modes of action that will be assessed using new models and biomarkers during the project
- dissemination of scientific results and research data
- development of a sustainability plan

Expected applicant consortium contribution: project management including coordination of work package deliverables, periodic reporting and budget administration, dissemination of scientific results and development of a sustainability plan.

EFPIA consortium contribution: leadership of overall project goals with respect to safety assessment applications, communication, dissemination of project results and development of sustainability plan.

Work package 2 – Innovative models for safety assessment of Immuno-Oncology therapeutics

The goals of this work package will be as follows:

- selection of clinically validated immunomodulatory therapeutic modes of action (including both small molecule and biotherapeutic Immuno-Oncology therapeutics) for which there is perceived to be an opportunity to enhance translational safety assessment;
- deployment of customised non-clinical models (with a particular emphasis on improved modelling of contributions from tumour target antigens and tumour microenvironments) to complement existing clinical and non-clinical safety profiles.

Expected applicant consortium contribution: co-lead work package, study design, provision/deployment of models and/or biomarkers, and dissemination of results.

EFPIA consortium contribution: co-lead work package, study design, provision/deployment of models and/or biomarkers, and dissemination of results.

Work package 3 – Innovative models for safety assessment of Immuno-Inflammatory disease therapeutics

The goals of this work package will be as follows:

- selection of clinically validated immunomodulatory therapeutic modes of action (including small molecule and biotherapeutic Immuno-Inflammatory disease Oncology therapeutics) for which there is a perceived opportunity to enhance translational safety assessment;
- deployment of customised non-clinical models (with a particular emphasis on improved modelling of contributions from inflammatory disease target biology and tissue microenvironments) to complement existing clinical and non-clinical safety profiles.

Expected applicant consortium contribution: co-lead work package, study design, provision/deployment of models and/or biomarkers, and dissemination of results.

EFPIA consortium contribution: co-lead work package, study design, provision/deployment of models and/or biomarkers, and dissemination of results.

Work package 4 – Innovative biomarkers for safety assessment of Immunomodulatory therapeutics

The goals of this work package will be as follows:

- develop innovative comparative (cross-species) in situ and *ex vivo* molecular, biochemical tool and cellular profiling of immune cells (including patient-derived clinical samples) and association with functional/phenotypic endpoints;
- deploy computational biology approaches for assessment and integration of large multivariate immuno-biology datasets (e.g. phenotypic-anchoring of molecular, biochemical and cellular endpoints derived from both non-clinical models and clinical trials) to reveal novel immune-biology mechanisms and translational biomarkers.

Expected applicant consortium contribution: co-lead work package, study design, provision/deployment of biomarker analytical and analysis technologies, and dissemination of results.

EFPIA consortium contribution: co-lead work package, study design, provision/deployment of biomarker analytical and analysis technologies, and dissemination of results.

Work package 5 – Clinical sample management – sourcing and logistics for assay and model development

The goals of this work package will be as follows:

- establish an IMI project-coordinated network to facilitate sourcing of human-derived immune cell and tissue samples via centres of excellence for specific disease areas;
- establish appropriate logistics for sample tracking and biobanking;
- establish framework for ensuring appropriate ethical and legal review of proposed consortium research use of human-derived cells and tissues.

Expected applicant consortium contribution: Lead work package, engage key stakeholders from academic clinical centres of excellence and patient organisations, establish an ethical review board.

EFPIA consortium contribution: Co-lead for work package, definition of specific human immune cell and tissue samples that would support model development, provision of guidance for sample tracking and biobanking.

References

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[2] Grimaldi C, Finco D, Fort MM, Gliddon D, Harper K, Helms WS, Mitchell JA, O'Lone R, Parish ST, Piche MS, Reed DM, Reichmann G, Ryan PC, Stebbings R, Walker M. Cytokine release: A workshop proceedings on the state-of-the-science, current challenges and future directions. Cytokine 2016, 85:101-108.

[3] Fernández-Ruiz M, Meije Y, Manuel O, Akan H, Carratalà J, Aguado JM, Delaloye J. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Introduction). Clin Microbiol Infect 2018.pii: S1198-743X(18)30147-2.