Topic: Targeted immune intervention for treatment of non-response and remission

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.

Subtopics and the Call Process

A large number of patients suffering from immune-mediated diseases fail to respond to current standard of care treatments or quickly relapse on, or following, treatment. Currently, one of the most challenging questions in human immunology is to understand whether it is possible to accurately predict which patients will fail to respond to treatment, sustain a longer term treatment response, or suddenly flare up during periods of disease control. The topic focuses on the application of state of the art molecular and immune technologies and sophisticated informatics approaches on highly annotated pre- and post-therapy bio-samples obtained from patients with Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA), Multiple Sclerosis (MS), Ulcerative Colitis (UC), Crohn's Disease (CD), Asthma, and Chronic Obstructive Pulmonary Disease (COPD) in order to identify novel biomarkers that are predictive of clinical disease behaviour and response. A major aim, beyond studying an individual disease, is the discovery of cross-disease biomarkers with relevance to a group of immune-mediated inflammatory diseases. Biomarkers of treatment or therapeutic response to a given therapy across multiple diseases may provide key insights. To ensure that the topic attracts high-level clinical and scientific expertise for these selected indications, and to provide in-depth technical knowledge for the profiling and informatics of bio-samples, the topic is divided into the following four subtopics:

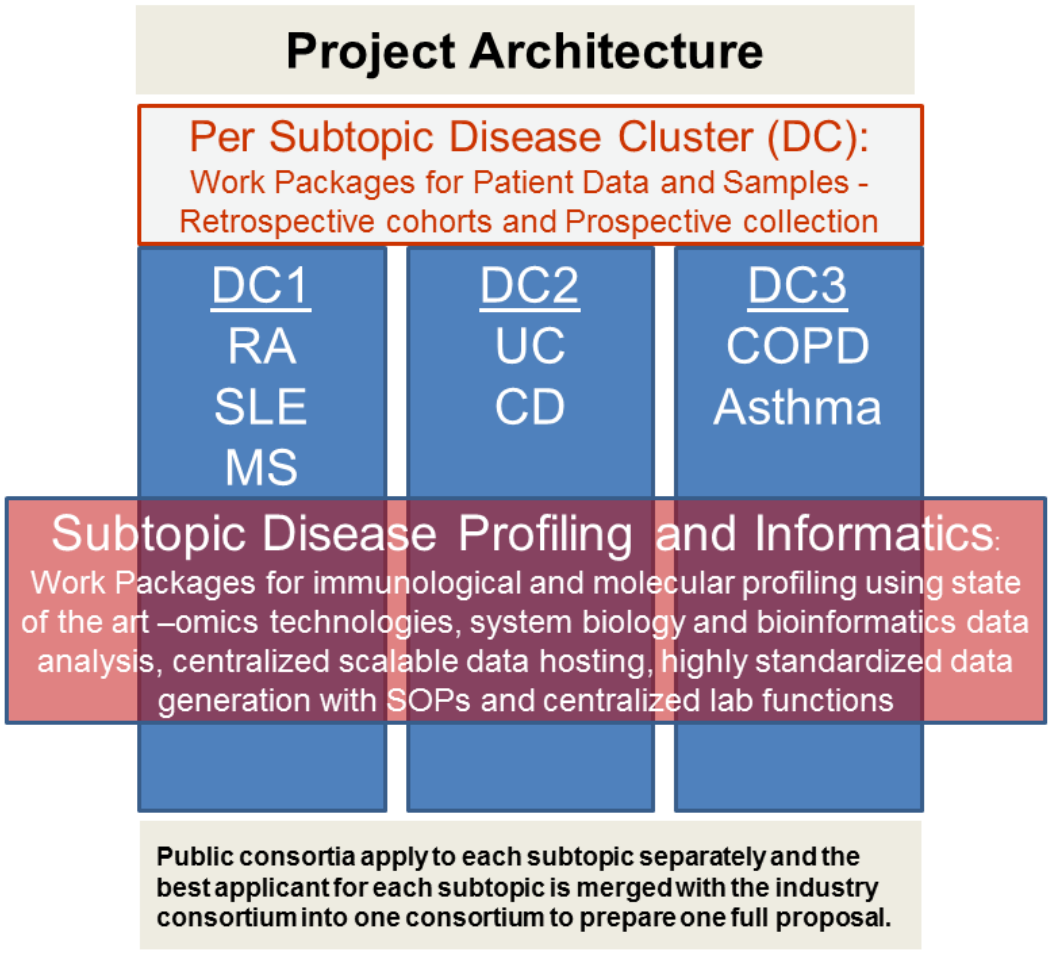
Subtopic 1, Disease Profiling and Informatics: state of the art molecular and immune technologies in combination with cutting edge systems biology approaches to identify biomarkers predictive of treatment non-response, relapse and flare-up;

Subtopic 2, Disease Cluster 1 (DC1): SLE, RA, and MS;

Subtopic 3, Disease Cluster 2 (DC2): UC and CD;

Subtopic 4, Disease Cluster 3 (DC3): Asthma and COPD.

Subtopics 2-4 focus on specific disease clusters. Applicant consortia will comprise disease-specific experts in clinical, scientific, biostatistics and regulatory affairs who have access to retrospective and prospective patient cohorts, bio-samples and data. These disease cluster teams will collaborate among each other and with the "Disease Profiling and Informatics" Subtopic 1 team in order to establish novel biomarkers and algorithms predictive of clinical disease behaviour and response.



Two-stage Call process: at stage 1, sub-consortia will be formed for each subtopic 1-4 and, at stage 2, the selected sub-consortia will be combined with the Industry consortium into a single consortium.

At Stage 1, applicant consortia should submit short proposals to only one of the subtopics 1-4.

Applicants can submit short proposals to any of the subtopics and to more than one, provided a separate short proposal is submitted for each subtopic.

A key objective of this topic is to create a research and technology platform for all the Disease Clusters to discover and validate novel biomarkers predictive of treatment response or non-response. To maximise cross-learning and to enable data sharing, it is envisioned that a single full proposal should be submitted at stage 2. This full proposal will include activities covering all four subtopics and their specific work packages.

Thus, at stage 2 the full proposal will be submitted by the consortium composed of the winning applicant sub-consortia of all four subtopics and the industry consortium.

An overall coordinator (selected from the winning consortium of the subtopic 1 Disease Profiling and Informatics) and an overall project leader (from the industry consortium) will be nominated by the consortium at the start of the full proposal preparation.

In the event of no short proposal being over the threshold for one/two disease cluster subtopic/s, the second stage of the Call will still be initiated by the merger of the remaining consortia and the industry consortium, but the net IMI2 funding and the EFPIA in-kind contributions will be adapted appropriately.

Considering the essential role of subtopic 1 for the preparation of the full proposal and implementation of the funded action, potential applicants must be aware that the whole topic may be discontinued and the stage 2 evaluation may not take place if no short proposal is selected under this subtopic.

Specific challenges to be addressed

A high percentage of patients suffering from immune-mediated disease do not respond well or at all to currently available treatments, and relapse on treatment. Currently, there is a lack of mechanistic understanding of non-response combined with an absence of biomarkers to predict clinical responses. Detailed analysis of clinical samples before and during treatment would enable breakthrough discoveries into the mechanisms, the clinical management of non-response, and identification of patients prone to relapse.

We have a poor understanding of the immune factors driving chronic progressive diseases, triggers of immune-mediated exacerbations and relapses and their underlying molecular signals. These episodes are highly clinically relevant, yet often poorly controlled. The topic, through the study of patients that respond or do not respond to treatment, as well as placebo patients, aims to identify molecular mechanisms that can be targeted to control immune-mediated exacerbation and relapse. The topic represents a great opportunity for the use of patient-centric monitoring/sampling devices in order to obtain correlated data from patient reported outcomes/symptoms and associated bio-samples (e.g. tissue biopsies from skin, kidney, mucosal and lung, sputum, stool, blood and urine). Patient bio-resources should be ideally matched with high dimensional profiling of patients' signs and symptoms including patient reported outcomes, and use of digital tools to capture patient outcomes and environment.

The topic addresses the challenge of translating insights from treatment non-response and disease exacerbation into new treatment paradigms at the individual patient level.

Need and opportunity for public-private collaborative research

In a field of medicine where the diseases and underlying science are so complex, no critical mass exists to make significant progress. In order to develop a better understanding of human immune-mediated diseases, only a large international scientific collaborative project that includes excellence in academia, the pharmaceutical industry, SMEs and regulatory authorities, coupled with a critical amount of high quality data, can be successful. Hence, translating basic science into the clinic cannot be achieved by a single entity but requires the definition of common strategies, setting new standards and the necessary critical mass created by all key stakeholders both from the private and public sectors. The proposed work will focus on seven prominent immune-mediated diseases where a public-private partnership will advance our understanding and help accelerate the development of personalised drug treatments for patients.

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

Scope

The action generated by this topic aims to provide better control of immune-mediated diseases.

In particular, the topic aims to identify new approaches to:

- characterise human immune-mediated diseases;
- profile and analyse immune cells obtained from non-blood tissues;
- discover individual disease and cross-disease biomarkers predictive of treatment response, non-response, relapse and flare-up;
- perform early clinical trials (e.g. in patient populations pre-enriched for certain molecular pathways; adaptive and basket trial designs etc.) and identify potential new novel patient-centric treatment approaches. The

focus will be on patients from well-characterised immune-mediated diseases (SLE, RA, MS, UC, CD, Asthma and COPD).

The ultimate goal is to develop a translational research platform that will improve patient management and personalised treatment by identification/validation of predictive biomarkers for non-response, rapid progression and remission. This would lead to an increased likelihood of treatment success with decreased costs for:

- patients and society, due to fewer side effects and a reduction in treatment of patients unlikely to respond;
- pharmaceutical companies, due to decreased development costs as a function of being able to demonstrate efficacy in smaller, more targeted patient populations that are likely to show greater or earlier response rates.

Expected key deliverables

Subtopic: Disease Profiling and Informatics

- Molecular profiling of non-responders that will lead to a better understanding of the pathways regulating the response to treatment in seven different diseases (RA, SLE, MS, UC, CD, COPD and asthma), and reveal drug targets for therapeutic intervention.
- Discovery of biomarkers predictive of clinical responses (e.g. non-response, depth of remission).
- Establishment of technology platforms, including transcriptomics (e.g. single cell-, BCR-, TCR-, RNA-Seq), genomics (e.g. SNP, Immunochip, exome sequencing), microbiomics, metabolomics, epigenetics (e.g. DNA methylation, ATAC-Seq, ChIP-Seq), immunophenotyping (flow cytometry/CyTOF), proteomics and exosome profiling.
- Utilise a core set (scRNA-Seq, genetics, microbiomics (stool)) of state of the art and emerging molecular and immune technologies and cutting edge systems biology approaches to profile and analyse non-blood affected disease tissue samples to identify biomarkers predictive of treatment non-response, relapse and flare-up.
- Single cell RNA-Seq of non-blood tissue samples to determine the role of different cell types and identify distinct cell sub-populations that contribute to clinical response and disease progression and correlate with peripheral markers/signatures.
- Analysis of -omics datasets leading to the generation of novel methods and models to predictively identify and stratify non-responder and relapse-prone patients aligned with specific therapies.
- Generation and hosting of an integrated large-scale data storage and computing platform to collect, store, analyse and integrate data to allow data mining for new targets and pathways.
- Establishment of a bio-samples repository to allow for the identification, tracking, storage and retrieval for subsequent profiling and analysis.

Subtopics DC1, DC2 and DC3

- Analysis of retrospective and prospective clinical and biomarker cohorts with access to patient data and bio-samples.
- Patient bio-resources that should be ideally matched with high dimensional profiling of patients' signs and symptoms including patient reported outcomes and use of digital tools to capture patient outcomes and environment.
- Establishment of an interface with the Disease Profiling and Informatics subtopic 1 to efficiently receive, send, track and store data and bio-samples, and establish necessary processes for high dimensional data analysis.
- Functional and clinical validation of biomarkers using human-based disease models (e.g. organoids/ organ on a chip).

Development of future guidance for emerging biomarker validation and clinical application in immune-mediated diseases allowed by early engagement with European Medicines Agency (EMA) / Food and Drug Administration (FDA).

Expected impact

Currently patients are treated as a "statistical mean" due to our limited molecular insight into individual patients' disease biology and treatment response. This approach fails to appreciate the underlying heterogeneity in disease mechanisms that leads to indistinguishable clinical phenotypes. Better understanding of the link between the molecular characteristics of disease and non-response to targeted drug treatments will increase the likelihood of treatment success and thus decrease costs to patients (side effects) and society.

Similarly, establishment of early markers of response will allow the identification of disease endotypes that may be responsive to different therapies.

The proposed precision-immunology approach is expected to achieve a reduction in failure rates in early clinical trials and to provide access for novel therapeutics to the optimal patient populations. Insights gained from this study will inform the design of platform trials for single indications with multiple mechanisms, further supporting precision-medicine approaches. In addition, a more accurate definition of subcategories of auto-immune disorders and their responses to particular therapies on an individual patient level will fuel novel target discovery, decrease Phase 2 proof of concept (POC) attrition, and decrease the costs of development to achieve regulatory approval and appropriate reimbursement.

To this end, the action generated by this topic would be a powerful and unique instrument, with the capability to significantly move forward the development of a consensus on the best treatment options for defined subgroups of patients with high unmet medical needs, such as patients suffering from immune-mediated diseases. Such an instrument currently does not exist within Europe or elsewhere. Furthermore, beyond advancing our understanding of the disease, informing personalized approaches to patient care, and delivering potential novel treatments, the topic has the potential to establish Europe in a leadership position in this field of biology and medicine.

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 from this topic should, among others, consider:

- IMI projects:

  BTCURE (http://btcure.eu/)

  RTCURE (http://cordis.europa.eu/project/rcn/211964_en.html)

  PRECISESADS (http://www.precisesads.eu/)

  U-Biopred (http://www.europeanlung.org/projects-and-research/projects/u-biopred/home)

  INNODIA (https://innodia.eu/)

  European Lead Factory (https://www.europeanleadfactory.eu/)
- Human Immunology Project Consortium (**HIPC)** (https://www.immuneprofiling.org/hipc/page/show)
- CD and UC: Inflammatory Bowel Disease Biomarkers Programme (**IBDBIOM**) (http://www.ibdbiom.eu/)
- MS: **MultipleMS** (http://www.multiplems.eu/) and **EUReMS** (http://www.emsp.org/projects/eurems/)
- RA and SLE: Accelerating Medicines Partnership (**AMP**) (https://www.nih.gov/research-training/accelerating-medicines-partnership-amp)

- SLE: **SYSCID** (http://syscid.eu/) and **Lupus Europe** (http://www.lupus-europe.org/)
- Asthma and COPD: **Ga2Len** (http://www.ga2len.net/), **synergy-COPD** (http://www.synergy-copd.eu/)
- MS, RA, SLE: Immune Tolerance Network (**ITN**) (https://www.immunetolerance.org/)

Industry consortium

The industry consortium will provide bio-samples (e.g. blood, stool, sputum, urine, tissue biopsies, DNA, RNA) and patient characterised datasets (deep-clinical phenotyping) from various prospective clinical trials (baseline, active comparator and/or placebo) for SLE, RA, MS, UC, CD, Asthma, and COPD. Note that there will be a difference in design of these clinical trials, and specificities of the available bio-samples will be confirmed during the full proposal preparation. 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 industry consortium will contribute with technology platforms for bio-sample analysis to complement technologies provided by the public participants.

The industry consortium will include bioinformatics and systems biology experts and clinical statisticians. Immunology expertise to contribute to functional validation of pathways and targets will be made available, as well as biomarker expertise to support validation activities and assay development.

Indicative duration of the action

The indicative duration of the action is 84 months.

Future Project Expansion

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.

A consensus is emerging that common immune-mediated diseases share common pathways, with molecular support provided by analysis of transcriptomics, HLA haplotypes and GWAS studies. One of the primary goals of this topic is to identify a multi-parameter, cross-disease “profile” of responder versus non-responder patients. However, this profile will be derived from a limited number of patients, so it cannot be assumed that the profile defining these categories is exclusive in determining response. For example, there may be some patients with a non-responder profile who actually may benefit from the treatment. Thus, the candidate responder versus non-responder profile uncovered by this topic will be exploratory and not definitive, and will need to be followed up by future validation studies that include large numbers of patients. Also, it is critical to maintain long-term follow up of the patients in these studies to validate which candidate biomarkers can accurately predict the depth of remission.

Future follow up studies will also be necessary as some patients may be non-responsive to therapy by virtue of having generated anti-drug antibody responses with initial or subsequent loss of efficacy. Thus, anti-drug responses may need to be assessed in patients on clinical trials of therapeutic proteins for incidence, titer, neutralizing activity, and duration, as well as to generation of hypersensitivity responses. The generation of such anti-drug antibody responses and clinical responses may identify a distinct population of patients and provide a profile of those most prone to generate anti-drug antibody responses. This may lead to the development of tolerance induction protocols for such patients.

Applicant consortium

One applicant consortium per each subtopic will be selected on the basis of the submitted short proposals.

The first-ranked applicant consortium of each subtopic is expected to address all the research objectives of a particular subtopic and to make key contributions to the defined deliverables in synergy with the proposed industry consortium contributions (stage 1).

Applicants should summarise their know-how and expertise to demonstrate their ability to make critical contributions to the expected key deliverables within the duration of the action.

All first ranked applicant consortia of each subtopic are expected to work collaboratively with the industry consortium to develop a full proposal combining the key objectives of each individual subtopic (stage 2).

This may require mobilising, as appropriate, the following expertise and resources.

Expertise and resources required for Subtopic Disease Profiling and Informatics

- experience in the establishment of a bio-sample repository to allow for the identification, tracking, and storage for subsequent profiling and analysis;
- expertise in standardised isolation, storage, processing and –omics analysis;
- expertise in generation and hosting of an integrated large scale data platform and bioinformatics pipeline to collect, store and analyse these data;
- expertise in data integration and/or harmonisation techniques and cutting-edge systems biology approaches to model multiple –omics datasets from multiple diseases to identify biomarkers that predict treatment non-responders or relapse-prone patient populations;
- expertise in informatics analysis and modelling to support patient stratification, future clinical trial design and precision medicine approaches;
- experience in collaborative functional validation of novel pathways, drug targets and biomarker candidates;
- expertise in the development of human-based disease models based on novel insights from the –omics studies (e.g. organoids). Note mouse models are not applicable;
- proven expertise in efficiently managing and maintaining time lines for large, multi-institutional scientific projects and proven expertise in project management;
- the full consortium is expected to have a strategy for the translation of the relevant project outputs into regulatory, clinical and healthcare practice. A plan for interactions with regulatory agencies and patient advocacy groups with relevant milestones and resources allocated should be proposed by consortia applying to subtopic 1.

Expertise and resources required for Subtopics DC1, DC2 and DC3

- access to pre-existing bio-samples (non-blood tissues required and matching blood samples desired) and patient data from retrospective biomarker and clinical trials suitable (e.g. tissue frozen, not fixed) for profiling using state of the art and/or emerging technologies;
- ability to conduct interventional prospective biomarker trials to obtain clinical data and bio-samples;
- centralised lab functions for state of the art and emerging technologies for –omics analysis (e.g. single cell transcriptome analysis, spatial transcriptomics, genomics, epigenetics, microbiome, metabolomics, flow cytometry/CyTOF, proteomics, and exosome profiling) in clinical sample types (e.g. tissue biopsies, sputum, stool, blood, plasma, urine) across the selected diseases;
- inclusion of patients and patient organisations in the consortia applying to the disease cluster subtopics (DC1, DC2, DC3) is actively encouraged.

Partners providing medical record-based information (e.g. data from registries, bio-samples) 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 intellectual property (IP) and legal framework. Consideration should also be given to any additional information that may be introduced after the start of the project but is not listed as project background at the start date. The applicants need also to take into consideration that the sharing of data and samples within the consortium should be allowed and be in conformity with the applicable data privacy laws and laws regarding ethical matters.

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, among other things strengthen the competitiveness and industrial leadership of Europe. Their involvement might offer a complementary perspective to industry and the 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 for the establishment of a bio-sample repository, the generation and hosting of an integrated large scale data platform, and the specialty profiling of bio-samples, using state of the art and/or emerging technologies. In addition, SMEs would be considered beneficial for the project management and administration capabilities required of the applicant consortium, which is expected to include resources for project administration, management and communication.

The size of the applicant consortia should reflect the expertise needed to achieve the proposed objectives of the subtopic and to be in line with the proposed budget, while ensuring the manageability of the final consortium to allow efficient and effective team work. Therefore, the size of the applicant consortium needs to be justified in the proposal.

Suggested architecture of the full proposal

Each applicant consortium should include its suggestions for creating the full proposal architecture in its short proposal, taking into consideration the industry contribution, existing technology platforms, and the clinical and scientific expertise needed for the immune-mediated diseases being studied. The final architecture of the full proposal will be defined by the participants in observance of IMI2 rules and in contemplation of achieving 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.

Governance of the overall project will be assured by the project coordinator and the scientific project lead.

The coordinator will be agreed upon by the full consortium created by the merger of the winning subtopic consortia at the start of the preparation of the full proposal and it will be nominated from the winning Disease Profiling and Informatics subtopic 1.

This may require slight adjustment of the Disease Profiling and Informatics subtopic work package 1 to accommodate any new structure changes. This topic consists of four subtopics, each with several distinct and common work packages, which in combination will deliver the objectives of the project. In the full proposal, the subtopic-specific governance structures will be maintained and guaranteed for each sub-topic by a partnership among the leading members of the respective applicant consortium together with one leading member designated by the industry consortium (see above, industry consortium section).

Particular attention will be given to implement the scientific exchange of the specialist experts within and across the four subtopics, ensuring the integration of learnings, synergies and cross-fertilisation, and thereby maximising the outcome of this action.

Sustainability

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 and for the short proposals submitted to each subtopic is a suggestion; different innovative project designs are welcome, if properly justified.

All Subtopics

Common Work package: Project Management, communication, dissemination and sustainability

This work package should be described by each submitting applicant consortium, and should include the elements necessary to ensure the proper functioning of each subtopic, bearing in mind that some modifications will be necessary at the stage 2 full proposal to adapt for an overall governance and integration, and that several activities will be shared among all participants of the full consortium to insure integration and avoid redundancy.

The goals of this work package will be as follows:

- overall coordination of the scientific 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, development of a sustainability plan.

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

Subtopic Disease Profiling and Informatics

Work package 1 – Profiling

The goals of this work package will be as follows:

- coordinate the receipt, curation, storage and retrieval of bio-samples;
- reduce technical variability introduced during sample processing;
- minimise batch effects via centralized profiling on the same platforms\instruments.

Expected applicant consortium contribution:

- molecular profiling of non-blood tissue samples from DC1, DC2 and DC3 patients using RNA-Seq, single cell RNA-Seq, genetics (all three required), and flow cytometry/CyTOF (desired);
- profiling of DC1, DC2 and DC3 patient stool samples using microbiome and metabolome (required for DC2 and desired for DC1 and DC3);
- epigenetic, metabolomics, microbiomic (lung, skin), proteomic and exosome profiling on patient bio-samples from DC1, DC2 and DC3 (desired);
- to limit batch effects and to ensure comparable results across these diverse sets of bio-samples the profiling of DC1, DC2 and DC3 bio-samples should be performed at the fewest sites possible, on the same instruments and utilize a common core set of standard operating procedures for sample isolation, preparation and labelling. In addition, development of a quality control plan that includes control steps, control samples, blinding operators and randomisation of samples is desired;
- develop a bio-repository platform for the receipt, curation, tracking, storage and retrieval of bio-samples received from DC1, DC2 and DC3;
- transfer of profiling datasets to a centralised scalable data hosting and computing platform.

EFPIA consortium contribution:

- EFPIA partners may, if relevant, provide molecular profiling of bio-samples from DC1, DC2 and DC3 patients using RNA-Seq, single cell RNA-Seq, genetics (all required), and flow cytometry/CyTOF (desired);
- profiling of DC1, DC2 and DC3 patient stool samples using microbiomics and metabolome (required for DC2 and desired for DC1 and DC3);
- epigenetic, metabolomic, microbiomic (lung, skin), proteomic and exosome profiling of non-stool bio-samples obtained from DC1, DC2 and DC3 patients (desired);
- transfer of profiling datasets to a centralized scalable data hosting and computing platform generated and maintained by the Disease Profiling and Informatics Subtopic;
- provide informatics support to the Disease Profiling and Informatics Subtopic.

Work package 2 – Informatics

The goals of this work package will be as follows:

- characterise variations in–omics datasets generated at high resolution;
- establish a centralised, scalable data hosting and computing platform;
- identify novel biomarkers predictive of clinical disease behaviour and response;
- develop disease and clinical response-specific data that can be used to identify biological targets for drug development and biomarkers for patient stratification.

Expected applicant consortium contribution:

- analysis of –omics datasets of treatment non-responders to discover novel biomarkers predictive of clinical responses;
- use sophisticated data integration and harmonisation techniques and apply cutting-edge system biology approaches to model multiple –omics datasets from multiple diseases to identify biomarkers or clusters of biomarkers that predict non-response. Inclusion in project plan of data sets from other consortia (such as those mentioned in the Synergies section) via proposed collaborations could be considered;
- molecular profiling of non-responders that will lead to a better understanding of the pathways regulating the response to treatment in the seven different immune-mediated diseases and reveal drug targets for therapeutic intervention;
- analysis of –omics and clinical datasets to provide a better understanding of human immune-mediated diseases;
- integration of historic and prospective data for the identification of biomarkers and generation of models that predict treatment non-responders and/or relapse-prone patient populations in the seven indicated diseases. Determine whether commonalities exist (e.g. biomarkers) across the seven different diseases for identifying treatment non-responder and relapse-prone patients. Opportunities to integrate biomarker data of disease non-response from other disease could be considered if relevant;
- provide analysis and models to support patient stratification, future clinical trial design and precision medicine approaches;
- establishment of a centralised scalable data hosting and computing platform to enable data storing, sharing and data mining.

EFPIA consortium contribution:

- EFPIA partners will, where applicable, transfer prospective –omics and clinical datasets to the Disease Profiling and Informatics subtopic for data hosting, mining and analysis;
- provision of scientific, clinical, profiling and informatics expertise for patient data and -omics datasets;
- provision of informatics expertise for discovery and confirmation of potential biomarkers predictive of clinical responses.

Subtopic DC1 - SLE, RA, and MS

Work package 1 – DC1 diseases, patients, cohorts, validation

The goals of this work package will be as follows:

- provide longitudinal bio-samples, including non-blood tissue samples from DC1 patients suitable for profiling by multiple –omics and emerging technologies;
- interface with the Disease Profiling and Informatics teams to integrate the required clinical and scientific DC1 expertise and ensure appropriate design and interpretation of the data analysis;
- develop confirmation and validation assays using human models and primary cells.

Expected applicant consortium contribution:

- access to pre-existing DC1 patient cohorts, clinical data and a minimum of three longitudinal bio-samples for each patient, obtained pre-treatment, early post-treatment (2-4 weeks), and at the time of peak clinical response for the specific treatment and disease being studied from retrospective studies. For at least one of these time points, a non-blood affected disease tissue sample, such as RA synovium, lupus skin and/or kidney, or MS cerebrospinal fluid is required; and other matching tissue samples, such as joint fluid, blood, plasma, stool and urine samples are desired. Additional bio-samples are highly desired including follow-up samples taken during the remission and/or relapse phase or after treatment is withdrawn;
- interventional (approved standard of care therapies only) prospective biomarker trials to obtain clinical data and at least three longitudinal bio-samples for each patient, obtained pre-treatment, early post-treatment (2-4 weeks), and at the time of peak clinical response for the specific treatment and disease being studied. For at least one of these time points, a non-blood affected disease tissue sample, such as RA synovium, lupus skin and/or kidney, or MS cerebrospinal fluid is required; and other matching tissue samples, such as joint fluid, blood, plasma, stool and urine samples are desired. Additional bio-samples are highly desired including follow-up samples taken during the remission and/or relapse phase or after treatment is withdrawn;
- retrospective and prospective DC1 patient cohort immune interventions should ideally be an EMA/FDA approved targeted immune-therapy (biologic or small molecule therapeutic) which includes anti-TNFs: infliximab, adalimumab, certolizumab, golimumab, etanercept and biosimilars; BAFF inhibitor, benlysta (belimumab); hydroxychloroquine. Broad immunosuppresants such as azathioprine and non-immune therapy such as antibiotics are to be excluded from the study. Non-approved and off-label used drugs are not recommended;
- provide non-blood tissue samples suitable (e.g. frozen, not fixed) for single cell RNA-Seq and genetics (required) and other –omics, such as epigenetics, metabolomics, flow cytometry/CyTOF, proteomics and exosome profiling (desired). Note, for samples in which single cell RNA-Seq is performed it is desired that bulk RNA-Seq also be performed in parallel or duplicate sample aliquots be stored for future sequencing; however, bulk RNA-Seq should not be performed in lieu of single cell RNA-Seq;
- provide longitudinal stool samples from DC1 patient cohorts suitable for microbiome and metabolome are desired;
- breath analysis for volatile organic compounds (VOCs) on DC1 patients is desired;
- provide bio-samples, clinical data and any relevant datasets to the Disease Profiling and Informatics Subtopic for profiling and data analysis;
- interface with the Disease Profiling and Informatics subtopic to ensure that clinical and scientific expertise in DC1 diseases is fully integrated into the design and interpretation of the data analysis being performed by the informatics teams;
- develop confirmation and validation assays using human models such as organoids and “skin and/or kidney on a chip” type assays that focus on primary cells are desired.

EFPIA consortium contribution:

- provide highly annotated clinical data and three or more longitudinal bio-samples for each patient with SLE, RA, or MS obtained pre-treatment, early post-treatment (2-4 weeks) and at the time of peak clinical response from the standard of care/active comparator arm of prospective clinical trials;
- provide samples and/or profiled –omics datasets to the Disease Profiling and Informatics subtopic for profiling, storage, data hosting and data analysis;
- provide scientific, clinical and developmental expertise to the DC1 and Disease Profiling and Informatics teams;
- interface with the Disease Profiling and Informatics subtopic to ensure that clinical and scientific expertise in DC1 diseases is fully integrated into the design and interpretation of the data analysis being performed by the informatics teams;
- provide scientific expertise necessary to develop human based models for confirmation and validation studies.

Subtopic DC2 - UC and CD

Work package 1 – DC2 diseases, patients, cohorts, validation

The goals of this work package will be as follows:

- provide longitudinal bio-samples, including non-blood tissue samples from DC2 patients suitable for profiling by multiple –omics and emerging technologies;
- interface with the Disease Profiling and Informatics teams to integrate the required clinical and scientific DC2 expertise and ensure appropriate design and interpretation of the data analysis;
- develop confirmation and validation assays using human models and primary cells.

Expected applicant consortium contribution:

- access to Crohn's Disease (CD) cohorts including inflammatory disease, fibrostenosis and fistulising sub-groups, with and without active peri-anal disease. Other considerations would be early onset disease vs. late onset disease, post-operative Crohn's Disease, and patients with extra intestinal manifestations. Overlap with autoimmune disease would be of special interest;
- access to ulcerative colitis cohorts (UC) based on disease distribution, extent of ulcerative colitis (E1-E3); special interest would be to study hospitalized acute, severe UC responsive vs. non-responsive to anti-TNF. UC with extra-intestinal manifestations, risk of deep venous thrombosis and overlap with psoriasis would be special populations of interest. Early onset disease vs. late onset disease analysis is desired;
- access to pre-existing DC2 patient cohorts, clinical data and a minimum of three longitudinal bio-samples for each patient, obtained pre-treatment, early post-treatment (2-4 weeks), and at the time of peak clinical response for the specific treatment and disease being studied from retrospective studies. For at least one of these time points an affected disease mucosal tissue sample is required and other matching tissue samples, such as blood, plasma and urine samples are desired. Additional bio-samples are highly desired including follow-up samples taken during the remission and/or relapse phase or after treatment is withdrawn;
- interventional (approved standard of care therapies only) prospective biomarker trials to obtain clinical data and at least three longitudinal bio-samples for each patient, obtained pre-treatment, early post-treatment (2-4 weeks), and at the time of peak clinical response for the specific treatment and disease being studied. For at least one of these time points an affected disease mucosal tissue sample is required and other matching tissue samples, such as blood, plasma and urine samples are desired. Additional bio-samples are highly desired including follow-up samples taken during the remission and/or relapse phase or after treatment is withdrawn;
- provide a minimum of three longitudinal stool samples per patient suitable for microbiome and metabolome (both required). Samples where 16S data is available is desired. Metabolomic platforms that assay microbial and host bio-actives and IgA sequencing is desired;

- retrospective and prospective DC2 patient cohort immune interventions should ideally be an EMA/FDA approved targeted immune-therapy (biologic or small molecule therapeutic) which includes anti-TNFs: Infliximab, adalimumab, certolizumab, golimumab, and biosimilars; anti-integrin: vedolizumab and natalizumab, and anti-p40: ustekinumab. Broad immunosuppressants such as azathioprine and non-immune therapy such as antibiotics are to be excluded from the study. Non-approved and off-label use is not recommended; however, Fecal Microbiota Transplantation (FMT) intervention(s) may be considered;
- for DC2 immune intervention endpoints the clinical phenotype of primary non-response should be distinguished from secondary loss of response. In the later subgroup, inclusion of secondary loss of response in patients without anti-drug antibody is desired. Responders should have a clear 6-12 month response to the drug. Other notable sub-groups include treatment long term responders (>5 years ideally on mono-therapy). While it is understood that clinical studies in patients with IBD use a variety of endpoints to define response and remission (including PRO and endoscopy/histology as per draft guidance from EMA and FDA), the present IMI2 collaboration uses for consistency the classical clinical endpoints;
- Crohn's Disease Activity Index (CDAI): response defined as ∆baseline ≥100, remission absolute CDAI < 150;
- Mayo Clinic Score (MCS): response defined as ∆baseline ≥ 3, remission absolute MCS < 2 with bleeding subscore 0 or 1; partial MCS, i.e., without endoscopy, is also acceptable;
- provide non-blood tissue samples (required) and matching blood samples (desired) suitable (e.g. frozen not fixed) for single cell RNA-Seq and genetics (required) and other –omics, such as epigenetics, metabolomics, flow cytometry/CyTOF, proteomics and exosome profiling (desired). Note, for samples in which single cell RNA-Seq is performed it is desired that bulk RNA-Seq also be performed in parallel or duplicate sample aliquots be stored for future sequencing; however, bulk RNA-Seq should not be performed in lieu of single cell RNA-Seq;
- breath analysis for volatile organic compounds (VOCs) on DC2 patients is desired;
- provide bio-samples, clinical data and any relevant datasets to the Disease Profiling and Informatics Subtopic for profiling and data analysis;
- interface with the Disease Profiling and Informatics subtopic to ensure that clinical and scientific expertise in DC2 diseases is fully integrated into the design and interpretation of the data analysis being performed by the informatics teams;
- develop validation assays using host epithelial cell – immune cell, host immune cell and microbe, host epithelial cell and microbe are examples of host microbial interactions. Organoid and “gut on a chip” type assays that focus on primary cells is desired.

EFPIA consortium contribution:

- provide highly annotated clinical data and three or more longitudinal bio-samples for each patient with UC or CD obtained pre-treatment, early post-treatment (2-4 weeks) and at the time of peak clinical response from the standard of care/active comparator arm of prospective clinical trials;
- provide samples and/or profiled –omics datasets to the Disease Profiling and Informatics subtopic for profiling, storage, data hosting and data analysis;
- provide scientific, clinical and developmental expertise to the DC2 and Disease Profiling and Informatics teams;
- interface with the Disease Profiling and Informatics subtopic to ensure that clinical and scientific expertise in DC2 diseases is fully integrated into the design and interpretation of the data analysis being performed by the informatics teams;
- provide scientific expertise necessary to develop human based models for confirmation and validation studies.

Subtopic DC3 – Asthma and COPD

Work package 1 – DC3 diseases, patients, cohorts, validation

The goals of this work package will be as follows:

- provide longitudinal bio-samples, including non-blood tissue samples from DC3 patients suitable for profiling by multiple –omics and emerging technologies;
- interface with the Disease Profiling and Informatics teams to integrate the required clinical and scientific DC3 expertise and ensure appropriate design and interpretation of the data analysis;
- develop confirmation and validation assays using human models and primary cells.

Expected applicant consortium contribution:

- retrospective and prospective DC3 patient cohort immune interventions should ideally be approved drugs such as Xolair, Mepolizumab, Bronchodilators (LABA, SABA, LAMA), anti-inflammatory agents (ICS, oral steroid, Roflumilast), antibiotics and placebo arm (with or without standard of care treatment);
- DC3 patient immune intervention trial endpoints should include FEV1, EXACT for Respiratory Symptoms and St George's Respiratory Questionnaire for quality of life assessment for COPD patients, Asthma Control Questionnaire, Asthma Symptom Score, rate of exacerbations, time to next exacerbations;
- access to pre-existing DC3 patient cohorts, clinical data and a minimum of three longitudinal bio-samples obtained pre-treatment, early post-treatment (2-4 weeks), and at the time of peak clinical response for the specific treatment and disease being studied from retrospective studies. For at least one of these time points a non-blood affected disease tissue, such as sputum, lung biopsy, or bronchoalveolar lavage (BAL) fluid is required; and other matching tissue samples, such as blood, plasma, stool and urine are desired. Additional bio-samples are highly desired including follow-up samples taken during the remission and/or relapse phase (exacerbation) or after treatment is withdrawn;
- interventional (approved standard of care therapies only) prospective biomarker trials on DC3 patient cohorts to obtain clinical data and at least three longitudinal bio-samples obtained pre-treatment, early post-treatment (2-4 weeks), and at the time of peak clinical response for the specific treatment and disease being studied. For at least one of these time points a non-blood affected disease tissue, such as sputum, lung biopsy, or bronchoalveolar lavage (BAL) fluid is required; and other matching tissue samples, such as blood, plasma, stool and urine are desired. Additional bio-samples are highly desired including follow-up samples taken during the remission and/or relapse phase (exacerbation) or after treatment is withdrawn;
- provide non-blood tissue samples suitable (e.g. frozen not fixed) for single cell RNA-Seq and genetics (required) and other –omics, such as epigenetics, metabolomics, flow cytometry/CyTOF, proteomics and exosome profiling (desired). Note, for samples in which single cell RNA-Seq is performed it is desired that bulk RNA-Seq also be performed in parallel or duplicate sample aliquots be stored for future sequencing; however, bulk RNA-Seq should not be performed in lieu of single cell RNA-Seq;
- provide sputum or BAL fluid suitable for lung microbiome (required) and stool samples suitable for microbiome and metabolomics (desired);
- analysis of exhaled breath volatile organic compounds (VOC) for patient stratification and as an endpoint is desired for retrospective studies and required for prospective studies;
- transfer bio-samples, clinical data and any relevant datasets to the Disease Profiling and Informatics Subtopic Teams for profiling and data analysis;
- interface with the Disease Profiling and Informatics subtopic to ensure that clinical, developmental and scientific expertise in DC3 diseases is fully integrated into the design and interpretation of the data analysis being performed by the informatics teams;
- develop validation assays using host epithelial cell – immune cell, host immune cell and microbe. Organoid and "lung on a chip" type assays that focus on primary cells and originating from stratified patients are desired.

EFPIA consortium contribution:

- provide highly annotated clinical data and three or more longitudinal bio-samples for each patient with asthma or COPD obtained pre-treatment, early post-treatment (2-4 weeks) and at the time of peak clinical response from the standard of care/active comparator arm of prospective clinical trials;

- provide samples and/or profiled –omics datasets to the Disease Profiling and Informatics subtopic for profiling, storage, data hosting and data analysis;
- provide scientific, clinical and developmental expertise to the DC3 and Disease Profiling and Informatics teams;
- provide informatics, scientific, clinical, and developmental expertise to identify respiratory phenotypes that steer away from asthma and COPD and are more aligned to “treatable traits” and their response to standard of care;
- interface with the Disease Profiling and Informatics subtopic to ensure that clinical and scientific expertise in DC3 diseases is fully integrated into the design and interpretation of the data analysis being performed by the informatics teams;
- provide scientific expertise necessary to develop human based models for confirmation and validation studies.