Topic: Genome-Environment Interactions in Inflammatory Skin Disease

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 & evaluation process	2 Stages

Specific challenges to be addressed

Inflammatory skin diseases affect a significant percentage of our global population. Atopic Dermatitis (AD) affects approximately 10% of children and 3% of adults worldwide. Psoriasis (Pso) affects approximately 2% of our population. These diseases remain poorly understood with limited understanding of their mechanism, endotypes, ontology and co-morbidities, affecting the quality of effective treatments. Though there may be aspects of these diseases that overlap, their associated co-morbidities are generally quite distinct. Pso is linked with arthritis, psychiatric disorders, metabolic syndrome and cardiovascular sequelae. AD is associated with rhinitis, asthma, food allergy as well as cardiovascular complications. As a result, there is an immediate need for sophisticated, in-depth investigations of these diseases that address transformative topics; these studies include, but are not limited to, the impact of environmental factors (e.g. via the microbiome) interacting with genomic factors and longitudinal studies that elucidate molecular pathways of disease. Expanding our current knowledge will give rise to more precise, targeted treatments that can yield long-lived reductions in disease and improved patient quality of life, fulfilling unmet medical needs in patient care.

Need and opportunity for public-private collaborative research

The proposed topic addresses a complex issue related to human diseases that can only be adequately addressed by a combination of collaboration and specialised expertise, which would be impossible in the setting of a single organisation or institution. Specific contributions to a collaborative effort would likely be:

- Pharmaceutical companies possess access to clinical trial samples related to Pso and AD, and the expertise in specialised technologies that can be applied;

- Academia has the clinical expertise and patient access (both retrospective and prospective) needed, as well as unique, state-of-the-art technologies;
- Patients and caregivers, as well as advocacy groups related to these diseases, provide important inputs into the real-world issues related to inflammatory skin diseases;
- Small- and Medium-sized Enterprises (SMEs), businesses with appropriate interests and Contract Research Organisations may contribute to centralised development of key output information and deliverables.

Scope

This project is expected to be a step change in our understanding of the molecular mechanism and ontology of the two main inflammatory skin diseases: AD and Pso. Elucidating the molecular pathways of these inflammatory skin conditions over time will give rise to novel and meaningful therapeutic targets for specific patient populations and help address the complex patterns of co-morbidities. In addition, this work will identify biomarkers that will enable robust, efficient and meaningful patient management.

The overall scope encompasses both a retrospective assessment of Pso and AD patients that can aid in defining key endotypes of disease and the disease commonalities and uniqueness, as well as access to ongoing prospective studies that will embrace novel approaches and hypotheses relating to defining these.

Expected key deliverables

1) Identify shared and distinct disease mechanisms of AD and Pso:
    - Establish a BioResource that includes patient samples (blood, skin tissue) reflective of baseline status as well as longitudinal samples of patients under standard of care;
    - Investigate the genetic and epigenetic profiles of AD, Pso and healthy controls of these patient samples;
    - Investigate the transcriptome of AD, Pso and healthy controls;
    - Investigate environmental factors (e.g. microbiome) of AD, Pso and healthy controls;
    - Investigate commonalities and differences in samples (e.g. skin biopsies, PBMCs) from patients with varying levels of disease severity;
    - Apply cutting edge technical approaches to samples obtained from ongoing prospective collections/trials, including single cell profiling, high dimensional immune subset analysis and advanced bioinformatics analysis.
2) Establish a new disease ontology by defining distinct and overlapping inflammatory skin disease endotypes and co-morbidities:
    - Investigate characteristics/pathways associated with disease;
    - Investigate characteristics/pathways associated with disease progression;
    - Investigate how environment (microbiome) interacts with genomic features to drive disease;
    - Develop a molecular understanding of how these factors interact in disease;
    - Investigate the impact on co-morbidities (existing registries):
        - For Pso these would include: arthritis, cardiovascular sequelae (MI, Stroke), metabolic syndrome (insulin resistance) and psychiatric disorders (depression).
        - For AD these would include: rhinitis, food allergy, asthma and other potential comorbidities such as new cardiovascular complications.

3) Identify molecular, immunological and microbial biomarkers that inform prognosis and response to therapy of patients suffering from inflammatory skin disease. Such deliverables should be capable of improving diagnosis and directed care decisions and might include:

- Identify immunological and microbial biomarkers that inform prognosis and response to therapy of patients suffering from inflammatory skin disease;
- Identify markers that predict disease severity;
- Identify markers that predict response to treatment;
- Identify how endotypes differ in response to therapy;
- Identify how endotypes differ in prognosis.

Expected impact

Currently, Pso and AD represent diseases difficult to treat and they significantly impact quality of life and medical health care costs for patients. This topic aims to comprehensively address aspects of disease endotypes, underlying pathobiology, and factors contributing to initiation, exacerbation and severity of disease, as well as response to therapy. Consequently, there are broad impacts on key considerations of the IMI2 goals that include:

- Research and Development (R&D) Process: discovery of new pathobiological processes will help drive future therapies, as well as stimulate research into skin biology generally;
- Regulatory Pathways and Health Technology Assessment: establishment of comprehensive disease endotyping will improve directed care decisions and future clinical trial design, including biomarkers, quality of life considerations, and patient enrolment suitability;
- Clinical and healthcare practices: understanding of early life events and environmental influences over disease progression and severity will support improvement in physician recommendations and management of patients.

Potential synergies with existing Consortia

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

While there are no current consortia aimed at the scope of this topic, the proposal has potential synergies with immune-related initiatives such as IMI **U-BIOPRED** (http://www.europeanlung.org/en/projects-and-research/projects/u-biopred/home) examining asthma (potential synergy with AD outcomes), and a number of other disease specific consortia looking at microbiome regulation over disease (e.g. the Inflammatory Arthritis Microbiome Consortium as well specifically the finalised MAARS consortium: http://www.maars.eu/).

Industry Consortium

The industry consortium will contribute the following expertise and assets:

Contributions include prospective clinical study samples and/or data based on samples from atopic dermatitis and/or psoriasis trials; generating, processing and analysing RNA and other –OMICS data, precision immunology based studies incl. and as well as FACS, IHC data and methods. It also includes bioinformatics experts and data management activities as well as translational and clinical expertise. Further details are listed in the section “Suggested architecture of the project”.

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 publish at a later stage another call for proposals restricted to those projects already selected under this call in order to enhance and progress the results and achievements by extending their duration and funding to prospectively progress the findings within this consortium.
Consortia will be entitled to open to other beneficiaries as they see fit.

In the context of this topics this been specifically the translational progression and validation of key results and findings of this consortium (e.g. disease ontologies, biomarker candidates).

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.

The applicant consortium should be comprised of expertise in three key areas: clinical characterisation and patient access (incl. samples and/or data from on-going prospective collections/trials for atopic dermatitis and/or psoriasis), biological specimen-based profiling, and advanced informatics. Consequently, the consortium would likely involve partners who bring expertise in access to and use of medical record-based information; this can be from ongoing clinical care sites and from industry partners with ongoing clinical trials. For a successful applicant consortium, these samples and data need to be accessible to the whole consortium.

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 IMI IP and legal framework. Consideration should also be given to additional information that may be introduced after the start of the project but is not listed as project background at start date.

Biological profiling will encompass partners with skills in transcriptomics, genetic sequence determination (e.g. SNP variance), microbial characterisation from human samples, proteomics, lipidomics, advanced immune cell phenotyping (e.g. single cell characterization), and other specialist technologies. Advanced informatics will coordinate in-depth analysis of the input data to establish endotypes and would require expertise in big-data handling and include machine-based learning, cluster mapping and advanced algorithm development.

The applicant consortium must demonstrate significant experience, possibly through the participation of an experienced SME, in both Advanced Analytical approaches and strong Data Management practices. Advanced Analytical approaches will require the coordination of in-depth analysis of the input data to establish endotypes and would require expertise in big-data analysis and include machine-based learning, cluster mapping and advanced algorithm development. Strong Data Management experience is considered to be a critical strength of the successful applicant and therefore the applicant must be able to demonstrate previous experience of managing/coordinating a multi-centre multi-node clinical-research data-generation activity of comparable scope. Essential experience should also include the legal and ethical challenges associated with integrating multi-centre patient-derived data, as well as physical data-processing/ data-management and data management practices (privacy, security). Crucial also for a suitable applicant will be a demonstrable ability to deliver analytical platforms to facilitate the above mentioned Advanced Analytical approaches for a range of scientific/medical and analytical communities.

The applicant consortium is expected to include resources for project administration, management and communication.

In addition to industry and academic partners, 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 the academia, and help deliver 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 context of professional data management and orchestrating data collection, analysis and availability to the rest of the consortium in a centralised, scalable and sustainable manner.

Given the nature of the key deliverables it is also expected from the applicant consortium that they provide experience and interaction in communication with Global Regulators, Patients, Practitioners and Payers, who may be members of a to be established Advisory Board.

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry participation including their contributions and expertise. Further details are listed below in the outline of the contributions from the different companies as well as the outline of the applicant consortium.

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.

Industry contribution:

The EFPIA participants are companies with extensive, ongoing interests in skin diseases and have come together to address this topic in a collaborative manner aligned with the goals of the IMI programmes. The contributions are framed across the needs of the work-flow and include management support, methodological expertise and training, access to specimens and samples and data-management and data control.

Expected Applicant consortium contribution:

The Applicant consortium contributions would be expected to provide access on existing samples relevant to the skin disease topic (especially AD and/or Pso), as well as access on *de novo* samples from ongoing collection. They will provide access to thorough clinical epidemiology information related to skin diseases through comprehensive medical records. They will provide highly specialised techniques of relevance to the overall topic and science of skin and inflammation, including lipidomics, microbiome assessment, metabolomics; precision-based approaches to this is considered a strength. The applicant consortium can provide state-of-the-art approaches to studying skin biology, including 3D organotypic cultures. The applicant consortium can include members who can provide experience in advanced modelling of human diseases based on multi-parameter data streams