

# Topic: Early diagnosis, prediction of radiographic outcomes and development of rational, personalised treatment strategies to improve long-term outcomes in Psoriatic Arthritis

All information regarding future IMI Call topics is indicative and subject to change. Final information about future IMI Calls will be communicated after approval by the IMI Governing Board.

## Topic details

Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages
IMI2 Strategic Research Agenda - Axis of Research	Innovative medicines
IMI2 Strategic Research Agenda - Health Priority	Immune-mediated diseases

## Specific challenges to be addressed by public-private collaborative research

Psoriatic arthritis (PsA) is a chronic immune-mediated disease involving axial and peripheral joints, nails, skin and entheses. Cutaneous manifestations often precede articular symptoms and it has been estimated that about 20-30% of psoriatic patients develop arthritis or enthesitis over the time [1]. In fact, this precedence of cutaneous symptoms may give as much as about 7 years to predict, detect and potentially treat PsA [2].

Although still a matter of debate, the pathogenesis of PsA is multifactorial and includes genetic and environmental triggers, like dysbiosis, infections or a mechanical stress, which could induce and maintain the aberrant activation of the innate and adaptive immune system.

Current therapeutic approaches aim to cover the entire clinical spectrum of PsA, from nail and skin involvement to joint, tendon and entheses damage and inflammation. The newest discoveries in PsA pathogenesis have promoted the development of several drugs with different mechanisms of actions targeting molecules involved in both musculoskeletal and cutaneous manifestations. The choice of the best treatment for PsA patients should rely on a global evaluation, including the predominant clinical manifestations, comorbidities or contraindications to the therapy [3].

There are still a large number of patients suffering from PsA that are diagnosed after several years of signs and symptoms (late diagnosis) and fail to respond to current standard of care treatments or quickly relapse on, or following treatment. Currently, it is felt that the earlier PsA can be diagnosed, the better the treatment could influence the disease. It also seems that the pathophysiology of PsA evolves with the "age" of the disease which may give opportunities to discover new targets in early PsA patients.

The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) identified the following major unmet medical needs:

- early diagnosis of PsA either in psoriasis (PsO) patients or in patients without initial psoriasis skin manifestations. Significant delay in diagnosis contributes to poor clinical and radiographic outcome;

- identification of patients at risk of progression to PsA early. Defining the predictors of progression to PsA in patients with skin PsO will enable earlier intervention and possibly even prevent development of PsA;
- definition of the clinical, genetic, immune factors or protein biomarkers that predict disease progression in PsA patients at time of diagnosis;
- better prediction, at diagnosis, for prognosis and stratification by therapeutic needs.
- The focus of this topic on such a multifactorial disease represented by its different forms through a wide patient population, which goes beyond the more homogeneous ones enrolled in clinical trials for registrations of new drugs, would require a broad spectrum of expertise to be adequately addressed. In this context, collaborative efforts among pharmaceutical industries, academia, small and medium-sized enterprises (SMEs) and patient organisations in a public-private partnership are most likely to harness all the skills and expertise required. Lastly, the involvement of representatives of health and regulatory authorities will ensure the necessary regulatory guidance paving the way towards the regulatory acceptance of “early PsA” diagnostic methods and personalised treatments. A synergy is expected from industry and other stakeholders joining forces, in this particular area of medicines innovation.

## Scope

The overall scope of this topic is to provide patients and physicians with new tools including clinical data patterns, biomarker profile patterns and imaging analysis for a better control of PsA. The aim of this topic is to characterise the natural history of PsA from psoriasis to “early” PsA to “full-fledged” PsA, as diagnosed by the Classification Criteria for Psoriatic Arthritis (CASPAR). This characterisation will be based on discovering new biomarkers and endotypes, constructed on genetic, transcriptomic, proteomic and/or clinical markers. To identify those endotypes, Artificial Intelligence (AI) and Machine Learning (ML) processes will be needed.

In particular, the topic aims at the following specific objectives:

- To enable rheumatologists, dermatologists and general practitioners to make early diagnosis of PsA in patients with PsO and other rheumatic disorders;
- To early identify patients at risk of progression to PsA in order to enable earlier interventions and possibly prevent PsA development;
- To define the factors that predict disease progression in PsA patients, including early prediction of bone/joint damages, leading to the development of more adapted treatment strategies;
- To develop rational and personalised treatment strategies (e.g. select the optimal first line or second line treatment based on patient characteristics) with optimised outcomes in PsA patients and reduce the disease burden.

## Expected key deliverables

- Early diagnosis of PsA in PsO patients:
  - Identification of predictors of disease progression e.g. genetic, transcriptomic, proteomic and/or clinical biomarkers assessed through longitudinal follow-up until evidence of CASPAR;
  - Identification and characterisation of biomarkers to predict, diagnose and monitor PsA in patients with PsO and to assess treatment response;
  - Biomarkers of tissue damage, predicting disease progression among PsA patients;
  - ML/AI tools to identify novel biomarker signatures;
  - Digital tool(s) developed for use by physicians and/or patients.
- Early prediction of bone/joint damages in PsA patients:
  - Identification of poor radiographic outcomes;
  - Biomarker assay(s) to identify patients that may rapidly develop bone or joint damages, indicating that these patients need strict control of PsA.
- Prediction of best treatment for patients at diagnosis:

- Biomarker assay(s) to assess response/non-response for various treatments of PsA;
- Development of a PsA specific algorithm to estimate the expected response to treatments.
- Creation of a tissue library, accessible by all involved parties, comprising skin, synovial tissue, synovial fluid and/or peripheral blood cells (including CD4+ and/or CD8+ T cells and/or other lymphocytes, monocytes) for analysis;
- Development and implementation of new techniques for diagnostic use e.g. Peptide Immunoaffinity Enrichment with Targeted Mass Spectrometry (Immuno-Multiple Reaction Monitoring, iMRM), Mass Cytometry (CyTOF and/or Fluidigm) and other techniques for single cell analysis to support detailed investigation of signalling cross-talk within and between relevant cell populations;
- Novel methods for data mining and AI-driven information extraction;
- Letter of support from regulatory bodies (e.g. the European Medicines Agency, EMA and/or Food and Drug Administration FDA) on the potential for qualification/validation of the biomarker(s) and their clinical applications (context of use) in PsA.

## Expected impact

In their proposals, applicants should describe how the outputs of the project will contribute to the following impacts and include wherever possible baseline, targets and metrics to measure impact:

- “Early PsA” diagnosis and earlier personalised treatments to patients would impact the disease progression and ultimately prevent PsA development. AI would help identifying endotypes which could take into account the clinical and biological heterogeneities of PsA;
- Development of objective and sensitive functional measures would enable the early diagnosis of PsA in PsO patients and the early prediction of bone/joint damages in PsA patients, yielding long-lived reduction in disease and improvement of patients’ quality of life;
- Improved rates of treatment successes through better understanding of the relation between molecular characteristics of PsA and treatment responses would reduce costs to patients (side effects) and society (economics).

In their proposals, applicants should outline how the project plans to leverage the public private partnership model to maximise impact on innovation, research & development; regulatory, clinical and healthcare practices, as relevant. This could include a strategy for the engagement with patients, healthcare professional associations, healthcare providers, regulators, HTA agencies, payers etc, where relevant.

In addition, applicants should describe how the project will impact on competitiveness and growth of companies including SMEs;

In their proposals, applicants should outline how the project will:

- Manage research data including use of data standards.<sup>1</sup>
- Disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences Research Infrastructures.<sup>2</sup>
- Communicate the project activities to relevant target audiences

## Potential synergies with existing consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures<sup>Error! Bookmark not defined.</sup>) in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, and duplication of efforts and funding.

## Industry consortium

<sup>1</sup> Guidance on data management is available at [http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management\\_en.htm](http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm)

<sup>2</sup> <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

The industry consortium plans to contribute the following expertise and assets:

- Translational Medicine Expert: leading role from a strategic, scientific, organisational and project management perspective;
- Data Manager: support to organise and control database systems within the project generated from this topic and other IMI funded projects;
- Biomarker Expert: scientific adviser to make sure that the selected biomarkers are relevant or sufficiently innovative;
- Bioinformatics Expert: analysis of large datasets (Big Data) to find predictive signatures of disease and response to therapy;
- Statistical Expert: scientific adviser to make sure that the statistical approaches are relevant or sufficiently innovative;
- Pharmacometric Expert: scientific adviser to make sure that the pharmacometric approaches are relevant or sufficiently innovative.

During the funded action, members of the industry consortium plan to contribute scientifically relevant activities for generating data / collecting samples in prospective activities that are part of broader clinical studies independent from, but carried out in connection with the action and necessary for achieving its objectives. The introduction of the data constitutes an in kind contribution which entails access rights to these project results in line with IMI2 JU IP rules. The estimated in kind contribution for the prospective activities to generate these data and samples is EUR 9 880 000.

The data and samples collected are planned to come from the prospective studies described below, and consist of the following data/samples types & volume:

<b>Study description</b>	<b>Data/sample description</b>	<b>Number of involved patients</b>
Phase 3, 2 arm study in PsA	Placebo arm only, 16 week treatment duration	190
Phase 3 PsA study	Placebo arm only, 16 week treatment duration	200
Phase 3 b PsO study	Placebo arm only	50

These data and samples are essential for achieving the objectives of the project.

## **Indicative duration of the action**

The indicative duration of the action is 60 months.

This duration is indicative only. At stage 2, the consortium selected at stage 1 and the predefined industry consortium may jointly agree on a different duration when submitting the stage 2 proposal.

## **Expertise and resources expected from applicants at stage 1**

The stage 1 applicant consortium is expected, in the submitted short proposal, to address all the objectives and key deliverables of the topic, taking into account the expected contribution from the industry consortium which will join at stage 2 to form the full consortium.

The stage 1 submitted short proposals should include suggestions for creating a full proposal architecture.

**This may require mobilising, as appropriate the following expertise:**

- SMEs with past and present experience on genetic, transcriptomic, proteomic, biomarkers, AI/ML techniques and “big data” management techniques;
- Patient associations and/or patient advocacy groups in PsO/PsA to ensure access to data and information;
- Regulatory agencies and/or HTA agencies and/or health authorities interested in innovative PsO/PsA assessments and new diagnostic tools to build a strategy for regulatory qualification/acceptance of project outputs;
- Academics and/or clinical trial centres experienced in PsO/PsA clinical, biological and imaging assessments;
- Strong Data Management experience in managing and coordinating a multi-centre multi-node clinical-research data-generation activity of comparable scope. Essential experience should also cover 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);
- Demonstrated ability to deliver analytical platforms for a range of scientific/medical and analytical communities;
- Expertise in a) clinical characterisation and patient access (incl. samples and/or data from on-going prospective collections/trials for PsO and/or PsA), b) biological specimen-based profiling, and c) advanced informatics;
- Expertise in access to and use of medical record-based information;
- Skills in molecular epidemiology, clinical science, and integration of biological profiling with relevant datasets;
- Proven expertise in rigorous programme management of large and complex multi-stakeholder projects, including expertise in risk management and sustainability of results.

**It may also require mobilising, as appropriate, the following resources:**

- Access to clinical cohorts and corresponding datasets of PsO and PsA patients, particularly longitudinal timed assessments. For a successful project, samples and data will need to be accessible to the whole consortium. Since access to clinical information and specimens is critical to the overall success of defining endotypes and the project goals, applicants should demonstrate their capacity (e.g. patient consent or waiver to consent) and the process by which they can provide access to these. Applicants may involve academics, medical centres with existing materials, biobanks, or organisations planning or actively participating in clinical trials and able to obtain consent. Access to large number of patients is essential to ensuring the statistical power for definition of endotypes. Value is seen in both cross-sectional and longitudinal approaches but longitudinal data (e.g. patients before and after therapy) is of higher value.

Partners providing medical record-based information as project background must be mindful that they, as background contributor, should have sufficient title to said background to authorise its use within the project pursuant to the IMI2 JU IP and legal framework.

**Considerations for the outline of project work plan**

In their stage 1 proposals applicants should:

- Give due visibility on data management; dissemination, exploitation and sustainability; and communication activities. This should include the allocation of sufficient resources for these tasks which will be further developed in stage 2 proposal.
- Consider including a strategy for ensuring the translation of the projects results to drug development, regulatory/ Health Technology Assessment (HTA) settings (e.g. through

scientific advice/ qualification advice /opinion, etc.), clinical and healthcare practices and/or decision making processes.

## **Additional considerations to be taken into account at the stage 2 full proposal**

At stage 2, the consortium selected at stage 1 and the predefined industry consortium jointly submit the full proposal developed in partnership. The full proposal is based upon the selected short proposal at stage 1.

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.

### **Data Management**

In their stage 2 proposal, applicants should give due visibility to data management including use of data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first 6 months of the project. The DMP needs to be kept up to date with the needs of the project and as such be updated as necessary during its lifetime.<sup>3</sup>

### **Dissemination, exploitation and sustainability of results**

In their stage 2 proposal, applicants must provide a draft plan for dissemination and the exploitation, including sustainability of results. A full plan as a distinct deliverable must be delivered within the first 6 months of the project<sup>4</sup>, and updated during the project lifetime and could include identification of:

- Different types of exploitable results;
- Potential end-users of the results;
- Results that may need sustainability and proposed sustainability roadmap solutions.

Sufficient resources should be foreseen for activities related to dissemination and exploitation, including the plan for the sustainability of the project results. This may involve engaging with suitable biological and medical sciences Research Infrastructures (RIs).<sup>5</sup>

### **Communication**

The proposed communication measures for promoting the project and its findings during the period of the grant should also be described and could include a possible public event to showcase the results of the project.

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<sup>3</sup> Guidance on data management is available at [http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management\\_en.htm](http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm)

<sup>4</sup> As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply

<sup>5</sup> <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

## References

- [1] Mease PJ. Psoriatic arthritis assessment and treatment update. *Curr Opin Rheumatol.* 2009;21(4):348-55.
- [2] Scher, JU, Ogdie A, Merola JF and Ritchlin C. Preventing psoriatic arthritis: focusing on patients with psoriasis at increased risk of transition. *Nat Rev Rheum,* 2019, 15;153-166
- [3] Talotta R, Atzeni F, Sarzi-Puttini P. Psoriatic arthritis: from pathogenesis to pharmacologic management. *Pharmacol Res.* 2019 Sep 7:104394. doi: 10.1016/j.phrs.2019.104394.

Indicative text