Positioning of the research program in regards to scientific, medical and socio-economic stakes at the national and European levels (mapping)

Chronic inflammatory diseases, including autoimmune diseases (CID), such as inflammatory bowel diseases, rheumatoid arthritis, psoriasis, multiple sclerosis and systemic lupus erythematosus, constitute a special group of disorders that can lead to irreversible destruction of the affected organs causing severe disability and severely altering patients' quality of life[1–7]. In recent decades, the prevalence of these diseases has increased dramatically and by 2030, CID will affect more than 10% of French and European people[4,5,8,9]. The costs of these chronic diseases are rapidly increasing and are becoming a major concern for the healthcare system and, globally, for society as a whole. In France, the direct and indirect costs of CID could reach more than 200 billion per year. Importantly, the indirect costs of this group of diseases are particularly high, as they mainly affect young people and have a strong negative impact on work productivity and the need for long-term care by the health system and French society[7,10]. Aware of this worrying situation, French research groups with strong expertise in basic, translational and clinical research have tackled these issues and demonstrated strong leadership with world-renowned key opinion leaders. Although progress has been made, there is no curative therapy and therapeutic success remains difficult to predict in individual patients, increasing the risk of disease progression and organ damage. To break the glass ceiling in better understanding the underlying mechanisms of CID and radically transforming the therapeutic management of patients, we propose to create a unique nationwide consortium bringing together and coordinate transdisciplinary expertise in distinct CID including competencies in basic, translational and clinical research. Within the 5-years period of the program, this unprecedented initiative will put France in the spotlight, reinforce its leadership, be highly attractive for emerging talents, accelerate the development of innovative therapeutic strategies, and lead to innovative concepts of public-private partnership based on new classifications and therapeutic approach in CID.

France's position (strengths/weaknesses) with regard to the program's research

France has a strong leadership and legitimacy owing to its world-renowned key opinion leaders and high standard publications. Strengths include well-organized and world-renowned clinical research groups with strong French and European networks and existing large nationwide cohorts of patients with CID. Thanks to French rare disease network, cohorts of patients with rare CID could also represent highly relevant models. In addition, a strong international expertise has been developed by several French basic science teams with a wide panel of skills. Thus, CID currently represent a privileged field particularly conducive to public-private partnerships leading to the development of new devices or innovative treatments. Furthermore, French patient associations on CID are particularly involved in research initiatives. One important weakness in the field is however the lack of collaborative studies that can benefit from recent transformative approaches to compare pathogenesis and concepts across common and rare CID and delineate: i) the earliest events to target for optimizing rapid and durable resolution of inflammation and for future disease prevention; ii) the mechanisms leading to refractoriness to treatment that need to be tackled to prevent or reverse progression to irreversible tissue damage. However, such a comparative study, which could ultimately allow the rethinking of classification and therapeutic approaches in CID, necessitate: i) the accelerated dissemination of bioinformatics and AI skills that are still insufficiently shared in the field of CID, ii) the shortening of administrative processes for comparing cohorts and implement new sample collections. The program trajectory will move from revisiting classification of CID through molecular signatures to individualized care and prevention.

RESEARCH PROPOSAL:

Strategic vision: **Chronic inflammatory diseases, including auto-immune diseases (CID),** are a group of common disorders that are clinically heterogeneous and share numerous features at the genetic, molecular and cellular levels. **The research proposal is therefore based on the view that many of the mechanisms that drive and maintain inflammation are overlapping across different CID**. Accordingly, we intend to bring together knowledge from a panel of cohorts or experimental models of frequent and rare CID to address key questions, share and, where necessary, develop innovative state-of-the-art approaches to build common concepts, and hierarchize the most prominent mechanisms according to the disease stage and targeted tissue. Although the proposal is dedicated to the analysis of common polyfactorial forms of CID, the analysis of rare forms of CID may provide valuable additional information to identify or validate key signaling pathways or cellular players. By establishing this collaborative effort across expert teams in CID, we aim to overcome barriers of knowledge, revisit CID classification and pathogenesis, generate new concepts that can be translated into substantial breakthrough in CID management and create a national ecosystem conducive to drug development through public-private partnerships.

Description of the program and its objectives: **The program will be structured according to a patients-centered bidirectional translational, transversal and transdisciplinary approach** with four different axes.

Axis 1: Using different interoperable epidemiologic approaches based on health system database (SNDS…) or other national databases (geographic, pollution, ecological…), incident population-based cohorts or cohorts of patients at an early stage, we will attempt **to identify shared common lifestyle or environmental predisposing factors across diseases including potential infectious or non-infectious triggers that could be targeted to prevent or treat CID at an early stage**.

Axis 2: Taking advantage of pre-existing cohorts selected for the high quality of patient phenotyping (classification criteria, disease form, activity score) or the development of new cohorts of patients at different stages of the disease including early stage without any treatment and refractory state, we intend to develop and share **state-of-the-art approaches** (including proteomic, metabolomic, metagenomic, genomic, single cell approaches in blood and affected tissues and spatial transcriptomics in order to address three complementary objectives: 1) **To redefine classification of CID** moving from phenotypical to biological/molecular definitions, 2) **To identify key cellular players and signaling pathways mobilized first at the early phase of inflammation grounded on cooperative studies between groups working in different CID** in order to assess the respective initiating role of innate and adaptive immune cells but also of non-hematopoietic cells, including stromal cells, epithelial cells and neurons that may drive or participate in the recruitment and activation of immune cells and thereby instruct a deleterious cross-talk between these cells within tissues. The analysis of the emerging role of clonal hematopoiesis[11,12] in the initiation of inflammation will be encouraged, as well as that of gender-related factors[13]; 3) To elucidate the **cellular and molecular mechanisms that perpetuate inflammation and/or link chronic inflammation to tissue remodelling and fibrosis,** particular attention will be paid to the epigenetic changes and somatic events[14] affecting the different tissue components and to the role of the pro-inflammatory microenvironment and epithelial/endothelial mesenchymal transition leading to fibrosis or to malignant transformation[14–16]. Where relevant, we will explore how mechanisms shared between common and rare diseases caused by high-penetrance genetic variants can

help validate signalling pathways, explore cellular plasticity and fibrosis reversal. To validate the pathogenic role of candidate pathways and cell types, we will share relevant mouse models or develop non-animal pre-clinical models based on organoid-based approaches including precision cut tissue slices, air-liquid interface organoid cultures, and organ-on-chip.

Axis 3: Based on existing or new cohorts, including ancillary studies from clinical trials (especially those with a placebo arm), our objectives will be **to identify and/or validate biomarkers to tailor therapeutic management of CID.** Particular attention will be paid to the identification of prognostic biomarkers to distinguish patients with poor prognosis or refractory to standard treatment who require early and/or more aggressive therapeutic strategies from those with low risk of disease progression, to identify predictors of therapeutic efficacy and to stratify treatments according to disease severity subgroups or involved pathways. As in axes 1 and 2, we will use a transversal and collaborative approach across different CID to identify serum, tissue or imaging biomarkers, taking advantage of the use/development of innovative methodologies as described in the section describing the future actions (see below).

Axis 4: Aware of the timeline for conducting clinical research, **we will take advantage of existing or proof-of-concept clinical trials,** including innovative designs such as basket trials and digital twins, comparative studies between CID, connected devices, AI and mathematical modelling, to **test or validate personalized therapeutic strategies** in groups of patients stratified according to new biological classification of CID and/or specific biomarkers, to identify the best window of therapeutic opportunity, and optimal short-term endpoints to improve natural history of CID, and the potential additional or synergistic effect of combined or sequential therapies. Innovative strategies including drug repositioning, cell therapy, mRNA-based therapy, synthetic antibodies, T-cell therapy protocols and design of non-viral vectors for nucleic acid delivery will be encouraged.

Description of the actions that will be undertaken: We will 1- build a consortium of expert teams on CID, 2- inventory the technological, computational, modeling approaches and therapeutic expertise available within the consortium to assess the need and funding for platforms accessible to consortium members to support patient immunophenotyping, facilitate single cell and spatial transcriptomic approaches, promote preclinical animal and non-animal validation studies of therapeutic targets, enable the seamless translation of non-invasive magnetic resonance or ultrasound based imaging biomarkers from the preclinical to the clinical level; 3- collaborate with Inria to support and accelerate data integration and the use of AI for biomarker identification and patient stratification; 4- identify experts in regulatory agencies to optimize timeline for study approval; 5- organize scientific calls to support projects across CID, involving several teams and/or multidisciplinary approaches and implementing complementary competencies from other fields; 6- organize a call for 4 junior chairs to encourage innovative approaches and commitment of high potential young scientists or physicians; 7- organize regular communication between members of the consortium to foster discussions, identify needs, monitor progress, 8- plan additional communication events including a summer school with all CID-related stakeholders, to promote training of young physicians and scientists.

Identification of the program leader and partners: **(please see Appendix)** A scientific committee in charge of the scientific guidance will coordinate the operational and scientific aspects of the program, supported by an advisory board providing advice and complementary competencies and an administrative staff (see appendix). A large network of partners will be involved and selected based on their scientific excellence and the needs of the program, and will regularly interact with the scientific comittee through the actions described above.

Complementarity with existing actions, within the framework of the agency or more extensively

Potential links with actions in Horizon Europe or in other countries

According to the recent creation of the French Agency for health research programs driven by the French National Institute of Health & Medical Research (Inserm), our program will involve partners from the six collegiums (Research organisms, Universities and schools, Hospitals, institutes, agencies and representative from the socioeconomic ecosystem). A particular attention will be paid to avoid overlap with existing health priority research programs and infrastructures (PEPR) projects such as PEPR SAMS (Alimentary systems, microbiome and health), BBTI (biological therapies and bioproduction of innovative therapies) and MED-OOC (Organs and Organoids on chip) but synergistic and complementary collaborations will be encouraged where relevant. Our program, which is in line with pillar II of Horizon Europe funding program for research and innovation ("Global Challenges and European Industrial Competitiveness"), especially cluster 1 on health dedicated to "Tackling diseases and reducing disease burden", and the objectives of the EU4Health program aiming at preventing and detecting chronic diseases, will not be redundant with the IMI-3TR European program which included only a very limited number of French teams, was mainly focused on respiratory diseases most of which are outside our scope, and systemic lupus erythematosus, with a limited number of transversal studies across CID, and will end in 2026. Our research program will be unique as, there is no similar nationwide initiative in Europe or other continents combining the skills of all the national best basic, translational and clinical research teams. Some French research groups working on CID are not limited to French borders and include European centers. As some French key opinion leaders on CID are head or involved in steering committees of European or international societies, networks and/or cohorts, our program will take benefit from it to develop collaborations in Europe and beyond.

Appendix

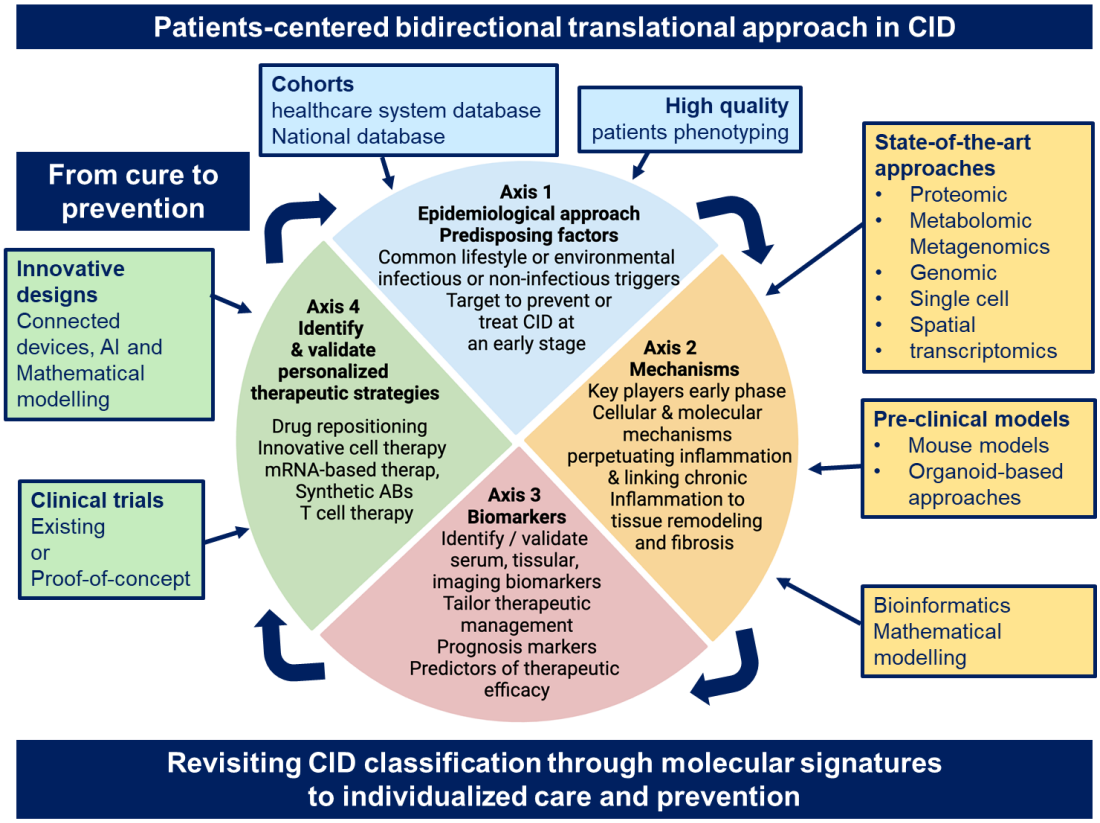

Figure 1: Graphical abstract summarizing the objectives of the TRANSCEND-ID project

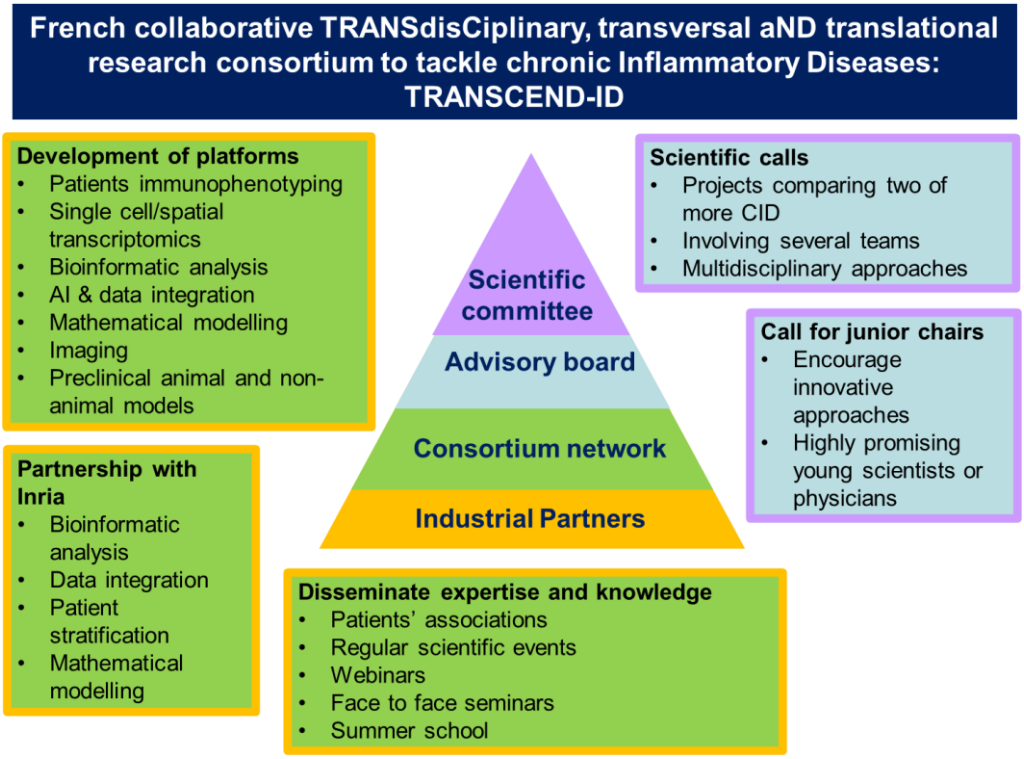

Figure 2: Operational organization of the TRANSCEND-ID project

French collaborative **TRANS**dis**C**iplinary, transversal a**ND** translational research consortium to tackle chronic **I**nflammatory **D**iseases: **TRANSCEND-ID**

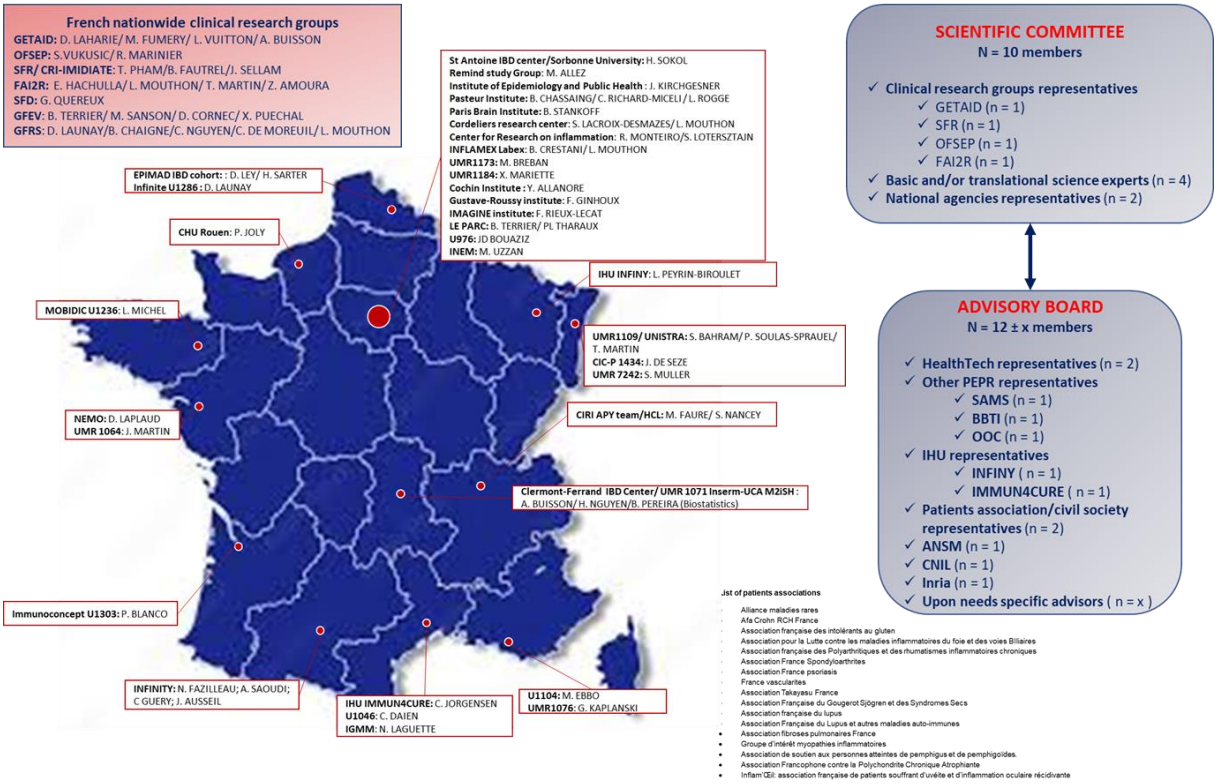

Figure 3: Description of the scientific committee, the advisory board and the consortium network of the TRANSCEND-ID project

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