Clinical and multi-omics cross-phenotyping of patients with autoimmune and autoinflammatory diseases: the observational TRANSIMMUNOM protocol

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ABSTRACT

Introduction Autoimmune and autoinflammatory diseases (AIDs) represent a socioeconomic burden as the second cause of chronic illness in Western countries. In this context, the TRANSIMMUNOM clinical protocol is designed to revisit the nosology of AIDs by combining basic, clinical and information sciences. Based on classical and systems biology analyses, it aims to uncover important phenotypes that cut across diagnostic groups so as to discover biomarkers and identity novel therapeutic targets.

Methods and analysis TRANSIMMUNOM is an observational clinical protocol that aims to cross-phenotype a set of 19 AIDs, six related control diseases and healthy volunteers. We assembled a multidisciplinary cohort management team tasked with (1) selecting informative biological (routine and omics type) and clinical parameters to be captured, (2) standardising the sample collection and shipment circuit, (3) selecting omics technologies and implementing a multidisease electronic case report form and an omics database and (5) implementing supervised and unsupervised data analyses.

Ethics and dissemination The study was approved by the institutional review board of Pitie-Salpetriere Hospital (ethics committee Ile-De-France 48–15) and done in accordance with the Declaration of Helsinki and good clinical practice. Written informed consent is obtained from all participants before enrolment in the study. TRANSIMMUNOM’s project website provides information about the protocol (https://www.transimmunom.fr/en/) including experimental set-up and tool developments. Results will be disseminated during annual scientific committees appraising the project progresses and at national and international scientific conferences.

Discussion Systems biology approaches are increasingly implemented in human pathophysiology research. The TRANSIMMUNOM study applies such approach to the pathophysiology of AIDs. We believe that this translational systems immunology approach has the potential to provide breakthrough discoveries for better understanding and treatment of AIDs.

Strengths and limitations of this study

- The study is conducted by a specialised ‘Clinical Investigation Centre in Biotherapy and Immunology’ with extensive experience in clinical immunology research, allowing standardisation of the procedure.
- A multidisciplinary cohort management team, with specialists from medical and research specialties as well as from biostatistics and bioinformatics has been gathered allowing a robust study design.
- The design integrates more than 800 clinical and biomedical information covering 19 autoimmune and autoinflammatory diseases and six related control diseases assembled in a multidisease harmonised case report form (part 11 compliant), a crucial effort for multidisease cross-analysis.
- Production of a large collection of multomics data from 1000 patient blood and faeces samples following standardised procedures that (1) are analysed through a system immunology approach together with clinical and biomedical data and (2) will benefit to the community once publicly available.
- One limitation is that TRANSIMMUNOM patients are currently sampled only once, with the goal of portraying their immune status; however, the resampling of patients at later time points is possible and could be planned according to specific scientific questions that would arise from the study or from the literature.
INTRODUCTION

Autoimmune and autoinflammatory diseases (AIDs) are the second highest cause of chronic illness in the Western world.\(^1\) Reducing their morbidity is a major public health challenge. Historically, the classification of AIDs was founded first on clinical symptoms. With the development of biomedical technologies, immune markers were then progressively included in the description of AIDs. As examples, specific autoantibodies help to define systemic lupus erythematosus (SLE), type 1 diabetes (T1D), rheumatoid arthritis (RA), mixed cryoglobulinaemia, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis and some types of myositis. Similarly, histological parameters such as inflammatory cell infiltrate help to refine the diagnosis of the different types of systemic vasculitis, such as Takayasu arteritis, giant cell arteritis and ANCA-associated vasculitis. Finally, genetic markers such as human leucocyte antigen (HLA)-B27 and \(MEFV\) gene mutations are associated with spondyloarthritis (SpA) and of familial Mediterranean fever (FMF), respectively.

Importantly, recent progress in molecular understanding of AIDs showed that there are not two distinct categories of diseases. Instead, AIDs form a continuum (the AIDC) of diseases with various proportions of inflammatory and autoimmune manifestations.\(^2\)\(^-\)\(^4\) Indeed, several cytokines are similarly modulated in different AIDs, such as interleukin (IL)-1 in FMF, uveitis and RA or IL-6 in RA and inflammatory bowel disease (IBD), IL-17 and IL-13 in SpA and tumour necrosis factor (TNF)-\(\alpha\) in RA, SpA and IBD,\(^5\) and the therapeutic inhibition of these cytokines has been successful in different AIDs.\(^6\) Shared genetic association between diseases also helps define this continuum. Many yet unknown molecular and cellular mechanisms and/or alterations may be shared as well. Embracing immune system homeostasis at a multiscale level should be heuristic. It should help characterise commonalities and differences between different AIDs and find important phenotypes that cut across diagnostic groups, likewise providing biomarkers and novel therapeutic targets for these patients.

This complex type of multiscale study can be addressed through a systems biology approach. One example of the potential of systems biology in immunology was the study of the immune response induced by the yellow fever vaccine.\(^7\) The strategy involved proteomics, transcriptomics and bioinformatics. Using this approach, the authors identified gene expression signatures that could predict the humoral immune response to the yellow fever vaccine. Similarly, several international projects, such as the Human Immunology Project consortium\(^8\) funded by National Institute of Health and the Health Human Project emanating from the Milieu Intérieur Consortium,\(^9\) have already revealed the power of multiparametric systems immunology studies.\(^10\)

We designed and launched an observational the Translational phenomics in immunopathology and inflammation: from cross phenotyping to biotherapy clinical protocol (TRANSIMMUNOM), designed to re-examine the nosology of a selection of AIDs using a multiparametric systems immunology experimental design. To that purpose, we selected 19 AIDs and six related control diseases for which multiparametric cross-analysis will be applied to clinical, biological, immunological and microbiome data between patients and in comparison with healthy volunteers (HV).

TRANSIMMUNOM was established as a multidisciplinary consortium including representatives of (1) clinical care (including medical doctors, medical technologists and nurses from the different specialties), (2) research activities (including immunologists, microbiologists, computational biologists and computer scientists) and (3) regulatory aspects of clinical trials (clinical trial
methodologists and clinical research associates). This endeavour has made possible the inclusion of patients with different diseases and followed up in different clinical departments and the completeness and standardisation of data collection and integration. TRANSIMMUNOM is funded by the French Research Agency (ANR) as a Laboratory of Excellence (LabEx).

**Study aim**
The main goal of TRANSIMMUNOM is to revisit the nosology of multiple AIDs belonging to the AIDC in order (1) to discover and validate biomarkers and novel therapeutic targets and (2) to evaluate biotherapies based on this knowledge. To this end, we propose to cross-phenotype a set of 19 AIDs through a systems immunology approach. The primary evaluation criterion is the significance of new gene expression levels, pathways and signatures involved when comparing the clinical phenotypes of different AIDs. The secondary evaluation criterion is the identification of new biomarkers and/or therapeutic targets by system biology approach. More details on primary and secondary outcome measures can be found on https://clinicaltrials.gov/ct2/show/NCT02466217.

The implementation of the study can be summarised in three steps (figure 1), from design (Step 1) to implementation (Step 2) and data analysis (Step 3).

**METHODS AND ANALYSIS**

**Study design and set-up**
The multiple AIDs selected call for multiple medical specialties and together with the systems immunology approach to be implemented; this made the endeavour necessarily multidisciplinary. Therefore, to design the study, we assembled a multidisciplinary cohort management team (CMT) (figure 2), including a clinical expert consortium (CEC) from seven specialties, nurses, biologists, clinical trial methodologists, immunologists, computer scientists and bioinformaticians. We (1) selected the list of 19 AIDs representative of the AIDC and six related control diseases and included HV, (2) established the study protocol, (3) set up a uniform and controlled sample collection and shipment circuit and (4) designed and implemented a multidisease electronic case report form (e-CRF) and a multomics database. Control diseases were selected as to contrast with the pathophysiology of the autoimmune and inflammatory diseases under study. They were chosen as having overlapping clinical manifestations but different pathophysiological mechanisms: (1) diseases with mainly an inflammatory versus an autoimmune driver (T2D vs T1D; osteoarthritis vs RA), (2) different genetic mutations (TNF-Tumor Necrosis Factor) Receptor Associated Periodic Fever - Cryopyrin-Associated Periodic Syndromes (TRAPS-CAPS) vs FMF), (3) genetic disease versus autoimmune disease of a given tissue (muscular dystrophy vs myositis) and (4) autoimmune disease that may arise as primary or secondary to other pathologies (primary antiphospholipid syndrome (APLS) vs SLE).

The study has been designed as a multidisease observational protocol of up to 1000 patients suffering from the list of selected diseases (see below). Patients are recruited and blood and faecal samples are collected once, at the time of a clinical evaluation.

![Figure 2](https://clinicaltrials.gov/ct2/show/NCT02466217)
Patients are recruited in the departments of Diabetology, Ophthalmology, Internal Medicine and Clinical Immunology at the Pitié-Salpêtrière Hospital, Rheumatology and Gastroenterology at the Saint-Antoine Hospital (Paris) and Internal Medicine at the Tenon Hospital. They are then screened and included by one of the two recruiting centres: Rheumatology at the Saint-Antoine Hospital and the Clinical Investigation Centre of Paris Est. A standard circuit for sample collection and shipment has been established and shared by the two recruiting centres. HV are selected based on internal records.

The study was done in accordance with the Declaration of Helsinki and good clinical practice. Written informed consent is obtained from all participants before enrolment in the study.

Study population

The TRANSIMMUNOM participants comprise three groups: selected AIDs, control diseases and HV. The diseases were selected based on (1) their prevalence (rare and common) and (2) the degree of autoimmune and inflammatory components of the disease so as to cover the entire spectrum of the AIDC. Selected diseases are: FMF, ulcerative colitis (UC), Crohn’s disease (CD), SpA, uveitis, myositis (in particular, polymyositis, dermatomyositis, inclusion-body myositis, necrotising and antisyntethase-related myositis), vasculitis ANCA-related (Churg-Strauss disease and granulomatosis with polyangiitis (vasculitis antineutrophil cytoplasmic antibodies (ANCA) related) and Behçet’s disease, cryoglobulinaemia and Takayasu (vasculitis non-ANCA-related) (grouped into vasculitis family); six control diseases, including TRAPS/CAPS, osteoarthritis, muscular dystrophy, type 2 diabetes and antiphospholipid antibody syndrome (APLS) (adapted from McGonagle and McDermott).
APLS for SLE, osteoarthritis for RA, muscular dystrophy for myositis and T2D for T1D. Finally, HV were also included, stratified by age in four groups (18–30, 31–40, 41–50 and over 50 years old) and matched by sex in each group (figure 3). To be in line with the human diseases, we chose to recruit patients with heterogeneous clinical profiles and with various therapies (ie, immunosuppressive therapy, biotherapy or patient with no treatment). Diverse profiles are likely to enrich the cross-evaluation potential of our analysis and allow us to identify new molecular signatures and provide new hypotheses on underlying networks.

Inclusion and exclusion criteria
Participants must be over 18 years old, either diagnosed with one selected AID in the last 8 years or with one of the control disease or a healthy subject and covered by the French healthcare system. A participant is excluded if he/she is undergoing cancer chemotherapy, presents contraindications to donating blood (according to the guidelines of WHO11), is pregnant, is affected by a chronic lifelong viral infection unrelated to the disease or had an infectious event within the previous month. Informed consent is obtained from participants at the time of the inclusion visit. The study was approved by the regulatory authorities in June 2015. We aimed to include approximately 1000 patients. As an intermediary goal, we aim to include approximately 100 healthy controls, 300 patients with T1D and T2D and 200 patients with any of the selected AIDs, control diseases or unclassified diseases.

Sample and data collection
For each participant, an anonymised subject unification (ASU) number was generated based on hospital patient number (NIP) and French healthcare registration number (INSEE). ASU is a simple four-letter code one-way encrypted to guarantee safe anonymisation.

We collect 135 mL of blood for routine lab measurements and for multiomics assays. Patients are provided with a standardised kit (Metagenopolis, INRA, France) that allows easy collection of faecal samples and maintenance of their integrity during shipment before microbiota metagenomics studies.12

In a 1-day visit (lasting about 2.5 hour), we collect all samples and all clinical and biological data, which are stored in an in-house secure e-CRF (table 1). Common clinical data include demographic data, educational level, lifestyle, personal and family medical history, current and previous treatment, ECG and quality of life questionnaires. In addition, we collect disease-specific data, such as diagnostic criteria, specific activity score and clinical status and evaluation. The diagnostic criteria CRFs are used to record international validated criteria specific to each disease and features of unclassified AIDs. Specific activity scores were selected based on international guidelines: Auto-Inflammatory Diseases Activity Index for FMF,13 simplified Mayo score for UC,14 Harvey-Bradshaw Index for Crohn’s disease,15 Bath Ankylosing Spondylitis Disease Activity Index for SpA,16 Birmingham Vasculitis Activity Score for Churg-Strauss disease, cryoglobulinaemia and GWP,17 vasculitis disease activity of National Institutes of Health for Takayasu’s disease,18 Disease Activity Score-28 for RA,19 insulin dose-adjusted HbA1c for T1D20 and the Systemic Lupus Erythematosus Disease Activity Index for SLE.19 21 Immediately after collection, samples are shipped following standardised operating procedures to (1) dedicated routine laboratories for routine biology assays at the Pitié-Salpêtrière and Saint-Antoine Hospitals, (2) the Biotherapy Department for cell immunophenotyping and sorting as well as for serum cytokine analysis, (3) the Genetics Laboratory at the Trouseau Hospital for RNA and DNA extraction prior to transcriptomic and HLA analysis, respectively, and (4) the MGP laboratory for microbiome studies. The samples are processed the same day according to specific protocols.

Data integration and storage
The CMT selected, organised and standardised 865 clinical data and routine lab data on an e-CRF and integrated them using OpenClinica, a Code of Federal Regulations (CFR)21—part 11 compliant electronic data capture tool.22

Once samples are collected and treated by the different laboratories, several million omics data are generated by using selected technologies and facilities and stored in a dedicated secure database, including deep-immunophenotyping data (circulating leucocyte subpopulations identified by flow cytometry, as an extension of our standardised

| Table 1  | TRANSIMMUNOM data description and management |
|----------|--------------------------------------------|
| **Data category** | **Data collected** | **Database** |
| Common clinical data | Demographic data | e-CRF |
| | Educational level and lifestyle | |
| | Medical personal and familial history | |
| | Current and previous treatments | |
| | ECG | |
| | Quality of life questionnaires and VAS | |
| | Physical examination | |
| Disease-specific clinical data | Diagnostic criteria | e-CRF |
| | Specific activity score | |
| | Clinical status and evaluation | |
| Biological data | Routine biology | e-CRF |
| | Serological status | |
| | Immunochemistry | |
| | HLA | |
| Omics | Deep immunophenotyping | Omics |
| | Proteome | |
| | Transcriptome | |
| | T cell receptor | |
| | Microbiome | |

e-CRF, electronic case report form; HLA, human leucocyte antigen; VAS, visual analogue scale.
method for regulatory T cell monitoring\textsuperscript{23}, proteomic, transcriptomic, T cell receptor repertoire and microbiome data. All the information is centralised on secured servers hosted by the investigator laboratory.

Data analysis strategy

Since TRANSIMMUNOM protocol is an open study, we will start analysing data progressively in order to first validate the methodologies selected (pilot study) and second to ensure sample quality and data robustness. Classical statistical analyses and modelling as well as integrative analyses will be used to identify potential biomarkers of disease as well as new therapeutic targets. As a general design, the analysis approach consist in (1) performing quality control on all the data collected using dedicated tools and solutions publicly available (including clinical data through a thorough eCRF monitoring and validation); (2) implementing supervised and classical statistical methods mastered in the team\textsuperscript{24–25} we will analyse parameter modulation (such as protein or gene expression level for cytokines and transcriptome, mean fluorescence intensity or percentage for immunophenotyping, diversity for microbiome and T cell receptor repertoire); (3) in parallel, we will implement unsupervised modelling methods publicly available or developed in the laboratory\textsuperscript{26–33} in order to identify more complex or hidden parameter modulations within each type of data sets, such as signature discovery\textsuperscript{29–32} and finally (4) once we will have complete multiparametric data sets for each subject, we will perform integrated analysis using methods relying on Regularised Generalised Canonical Correlation Analysis and variations\textsuperscript{35–39} dedicated to the analysis of structured data sets with the aim of deciphering their relationships. Lastly, biomarkers can be discovered without full knowledge of their biological meaning. This is well exemplified in cancer where resistance or sensitivity to chemotherapy can be predicted using biomarkers without understanding the underlying mechanisms. We will thus complete our pragmatic search for biomarkers by more supervised cognitive studies by collating results from our investigations with results in the literature.

These different analysis will be applied (1) between patients (regardless of the disease) and HV, (2) between patients (disease per disease) and HV and (3) between patients diagnosed with different diseases; including gender and age as a variable for stratification of the samples.

Patient and public involvement

Patients and public were not involved in the definition of the research question or the outcome measures nor the design of the study. There are no plans to disseminate the results of the research to study participants.

DISCUSSION

AIDs encompass a large panel of complex diseases with multifactorial aetiology. Recent molecular evidences suggest that some of these diseases share genetic and immune components\textsuperscript{2–6} which has been a real breakthrough in the field. Indeed, most AIDs are diagnosed based on specific criteria related to symptoms and signs, which are usually subdivided into organ specific or systemic. However, it is known that many patients suffering from one AID (organ specific or systemic) may with time develop other symptoms and signs relating to a different organ, sometimes leading to the diagnosis of a second AID. Therefore, understanding the commonalities and specificities of AIDs at a molecular and cellular level appears to be essential if we are to propose better tolerated and more effective treatments for patients with AIDs. We describe here a multidisciplinary approach applied to the design, implementation and analysis of a trans-AIDs observational protocol.

Based on translational medicine, a CMT designed an innovative protocol that allowed the inclusion of patients currently followed up in different clinical departments and ensured the completeness and standardisation of data collection and integration. The centralisation of the omics analysis and the standardisation of the techniques (flow cytometry panel, molecular biology) provided a uniformity of results. The CMT, including the CEC, recruited researchers from different fields to select, design and integrate state-of-the-art standards in clinical medicine, medical biology measurements and science. All the data collected were finally integrated in an e-CRF (database) so as to share information between all the CMT members.

Compared with other systems immunology projects focusing mainly on biological aspects, TRANSIMMUNOM (1) also collects a large list of clinical data that have been coded so as to allow a cross-analysis between clinical and biological data; (2) analyses patients with different AIDs, control diseases and in HV and (3) investigates cross-talk between the immune system and gut microbiota, as there is robust evidence that the microbiota influences the immune system and vice versa.\textsuperscript{40–44} TRANSIMMUNOM has the potential to provide fundamental knowledge about the pathophysiology of AIDs and to redefine their nosology. Indeed, we and others already showed the power of systems immunology to better understand biological processes associated with autoimmune and AIDs.\textsuperscript{24–26,28,30,45–49} Systems immunology is now seen as the future for new biomarkers and therapeutic target discovery, validated in oncimmunology.\textsuperscript{50–52} With the advance of high-throughput data modelling and integrative analyses, it has been already shown that blood can be used to follow and even predict biological process undergoing in distant tissue.\textsuperscript{34,44,53–55} We have no doubt that with the unprecedented endeavour and deep clinical and immune profiling to be achieved in TRANSIMMUNOM, we will contribute to identify new disease biomarkers and possibly new therapeutic targets.

Ethics and dissemination

The study was approved by the institutional review board of Pitié-Salpêtrière Hospital (ethics committee Ile-De-France 48–15) and done in accordance with the Declaration of Helsinki and good clinical practice. Written informed consent are obtained from all participants before enrolment in the study.
Protocol status
Step 1 is completed. We are currently at Step 2. Recruitment started in July 2015 and is expected to include 1000 patients by December 2018. A pilot study on the first 96 samples has been set up and both clinical and omics data are currently being analysed. The protocol version currently in use is V.4.0 dated 19 May 2017.

Contributors
DK initiated and obtained the funding for the TRANSIMMUNOM project as a Laboratory of Excellence from the French National Research Agency (ANR). RL, EM-F and DK wrote the manuscript with input from all the authors. SA, FB, PC, DS, AS and DK designed the TRANSIMMUNOM project. RL, FB, OB, BB, PC, GG, AH, DS, JS, PS and DK designed the study protocol. RL, CA, CR, FT, ID, SH and EM-F designed the e-CRF. EM-F, AS, MR and DK with input from FP, WC, ND and HS designed the scientific research approach. CJ provides the autoantibody assays and rationale for the selection of assays. RL, CR, OxA, JS and J-ES are in charge of patient recruitment. EV and CB were in charge of the regulatory aspects and EV led the monitoring of the study.

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Competing interests
None declared.

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REFERENCES
1. Walsh SJ, Rau LM. Autoimmune diseases: a leading cause of death among young and middle-aged women in the United States. Am J Public Health 2000;90:1463–6.
2. Mcgonagle D, McDermott MF. A proposed classification of the immunological diseases. PLoS Med 2006;3:e297.
3. Doria A, Zen M, Bettolo S, et al. Autoimmune diseases and autoimmunity: bridging the divide. Autoimmun Rev 2012;12:22–30.
4. Ciccarelli F, Martinis M, Ginaldi L. An update on autoinflammatory diseases. Curr Med Chem 2013;21:261–9.
5. Magiari L, Varszegi D, Kovess E, et al. Interleukins and interleukin receptors in rheumatoid arthritis: Research, diagnostics and clinical implications. World J Orthop 2014;5:516–36.
6. Moran EM, Mastaglia FL. Cytokines in immune-mediated inflammatory myopathies: cellular sources, multiple actions and therapeutic implications. Clin Exp Immunol 2014;178:405–15.
7. Quecoc TD, Akondy RS, Lee EK, et al. Systems biology approach predicts immunogenicity of the yellow fever vaccine in humans. Nat Immunol 2009;10:116–25.
8. Poland GA, Quil H, Togias A. Understanding the human immune system in the 21st century: the Human Immunology Project Consortium. Vaccine 2013;31:2911–2.
9. Thomas S, Rouilly V, Patin E, et al. The Milieu Intérieur study – an integrative approach for study of human immunological variance. Clin Immunol 2015;157:277–93.
10. Urrutia A, Duffy D, Rouilly V, et al. Standardized whole-blood transcriptional profiling enables the deconvolution of complex integrated immune responses. Cell Rep 2016;16:2777–91.
11. WHO. WHO | WHO guidelines on drawing blood: best practices in phlebotomy. http://www.who.int/infection-prevention/publications/drawing_blood_best/en/ (accessed 15 Sep 2017).
12. International Human Microbiome Standards (iHMS) project. http://www.microbiome-standards.org/.
13. Piram M, Koné-Paut I, Lachmann HJ, et al. Validation of the autoimmune-inflammatory diseases activity index (AIDAI) for hereditary recurrent fever syndromes. Ann Rheum Dis 2014;73:2168–73.
14. Lewis JD, Chua S, Nessel L, et al. Use of the noninvasive components of the Mayo score to assess clinical response in uclear colitis. Inflamm Bowel Dis 2008;14:1660–6.
15. Harvey RF, Bradshaw JM. A simple index of Crohn’s-disease activity. Lancet Lond Engl 1980;1:514.
16. Garrett S, Jenkinson T, Kennedy LG, et al. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 1994;21:2286–91.
17. Stone JH, Hoffman GS, Merkel PA, et al. A disease-specific activity index for Wegener’s granulomatosis: modification of the Birmingham Vasculitis Activity Score. International Network for the Study of the Systemic Vasculitides (INSSVS). Arthritis Rheum 2001;44:20:912.
18. Kerr GS, Hallahan CW, Giordano J, et al. Takayasu arteritis. Ann Intern Med 1994;120:199–29.
19. van der Heijde DM, van ‘t Hof MA, van Riel PL, et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step...
in the development of a disease activity score. *Ann Rheum Dis* 1990;49:916–20.

20. Mortensen HB, Hougaard P, Swift P, et al. New definition for the partial remission period in children and adolescents with type 1 diabetes. *Diabetes Care* 2009;32:1384–90.

21. Bombardier C, Gladman DD, Urowitz MB, et al. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. *Arthritis Rheum* 1992;35:630–40.

22. Lorenzon R, Drakos I, Ribet C, et al. Clinical data specification and coding for cross-analyses with omics data in autoimmune disease trials. bioRxiv (Epub ahead of print 5 Jul 2018).

23. Pitois E, Barbiè M, Monneret G, et al. A standardized flow cytometry procedure for the monitoring of regulatory T cells in clinical trials. *Cytometry B Clin Cytom* 2018 (Epub ahead of print 6 Jan 2018).

24. Saadoun D, Rosenzwaig M, Joly F, et al. Regulatory T-cell responses to low-dose interleukin-2 in HCV-induced vasculitis. *N Engl J Med* 2011;365:2067–77.

25. Hartemann A, Bensimon G, Payan CA, et al. Low-dose interleukin 2 in patients with type 1 diabetes: a phase 1/2 randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2013;1:295–305.

26. Allenbach Y, Chaara W, Rosenzwaig M, et al. Th1 response and systemic treg deficiency in inclusion body myositis. *PLoS One* 2014;9:e88788.

27. Terrier B, Chaara W, Dufat L, et al. Serum biomarker signature identifies patients with B-cell non-Hodgkin lymphoma associated with cryoglobulinemia vasculitis in chronic HCV infection. *Autoimmun Rev* 2014;13:319–26.

28. Terrier B, Geri G, Chaara W, et al. Interleukin-21 modules Th1 and Th17 responses in giant cell arteritis. *Arthritis Rheum* 2012;64:2001–11.

29. Pham HP, Dérian N, Chaara W, et al. A novel strategy for molecular signature discovery based on independent component analysis. *Int J Data Min Bioinform* 2014;9:277–304.

30. Rosenzwaig M, Churlaud G, Mailonne R, et al. Low-dose interleukin-2 fosters a dose-dependent regulatory T cell tuned milieu in T1D patients. *J Autoimmun* 2015;58:48–58.

31. Bergot AS, Chaara W, Ruggiero D, et al. TCR sequences and tissue distribution discriminate the subsets of naive and activated/memory Treg cells in mice. *Eur J Immunol* 2015;45:1524–34.

32. Nehar-Belaid D, Courau T, Dérian N, et al. Regulatory T cells orchestrate similar immune evasion of fetuses and tumors in mice. *J Immunol* 2016;196:678–90.

33. Plessy C, Mariotti-Ferrandiz E, Manabe R, et al. High throughput analysis of T cell antigen receptor sequences. *Biorxiv* 2015.

34. Chausabel D, Quinn C, Shen J, et al. A modular analysis framework for blood genomics studies: application to systemic lupus erythematosus. *Immunity* 2008;29:150–64.

35. Tenenhaus A, Tenenhaus M. Regularized generalized canonical correlation analysis. *Psychometrika* 2011;76:257–84.

36. K-AI C, Rohart F, Gonzalez I, et al. mixOmics: Omics Data Integration Project. 2017 https://cran.r-project.org/web/packages/mixOmics/index.html.

37. Tenenhaus A, Tenenhaus M. Regularized generalized canonical correlation analysis for multblock or multigroup data analysis. *Eur J Oper Res* (Epub ahead of print Jan 2014).

38. Tenenhaus A, Philippe C, Guillomet V, et al. Variable selection for generalized canonical correlation analysis. *Biostatistics* 2014;15:569–83.

39. Tenenhaus A, Philippe C, Frouin V. Kernel generalized canonical correlation analysis. *Comput Stat Data Anal* 2015;90:114–31.

40. Hooper LV, Littman DR, Macpherson AJ. Interactions between the microbiota and the immune system. *Science* 2012;336:1268–73.

41. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. *Cell* 2014;157:121–41.

42. Zeng H, Chi H. Metabolic control of regulatory T cell development and function. *Trends Immunol* 2015;36:3–12.

43. Atariishi K, Tanoue T, Oshima K, et al. Treg induction by a rationally selected mixture of Clostridia strains from the human microbiota. *Nature* 2013;500:232–6.

44. Kato LM, Kawamoto S, Maruya M, et al. The role of the adaptive immune system in regulation of gut microbiota. *Immunol Rev* 2014;260:67–75.

45. Tenner B, Bièche I, Maisonneuve T, et al. Interleukin-25: a cytokine linking eosinophils and adaptive immunity in Churg-Strauss syndrome. *Blood* 2010;116:4523–31.

46. Brosius FC, Ju W. The promise of systems biology for diabetic kidney disease. *Adv Chronic Kidney Dis* 2018;25:202–13.

47. Burel JG, Apte SH, Doolan DL. Systems approaches towards molecular profiling of human immunity. *Trends Immunol* 2016;37:53–67.

48. Huan T, Zhang B, Wang Z, et al. A systems biology framework identifies molecular underpinnings of coronary heart disease. *Artificial Cells, Nanomedicine, and Biotechnology* 2014;42:1207–20.

49. Cervantes-Garcia K, Husi H. Integrative analysis of multiple sclerosis using a systems biology approach. *Sci Rep* 2018;8:5633.

50. Zhao H, Li H. Network-based meta-analysis in the identification of biomarkers for papillary thyroid cancer. *Genome* 2018;6:61:160–8.

51. Irigoyen A, Jimesen C-Luna C, Benavides M, et al. Integrative multi-platform meta-analysis of gene expression profiles in pancreatic ductal adenocarcinoma patients for identifying novel diagnostic biomarkers. *PLoS One* 2018;13:e0194844.

52. Moen M, Nakai K. Integrative analysis of gene expression and DNA methylation using unsupervised feature extraction for detecting candidate cancer biomarkers. *J Bioinform Comput Biol* 2018;16:1850006.

53. Greenberg SA. Biomarkers of inclusion body myositis. *Curr Opin Rheumatol* 2013;25:753–62.

54. Chiche L, Jourde-Chiche N, Whalen E, et al. Modular repertoire analysis identifies complex coordinated type I–type. *Ann Rheum Dis* 2014;73:98–9.

55. Aghaeepour N, Gario EA, McIlwain D, et al. An immune clock of human pregnancy. *Sci Immunol* 2017;2:eaa9246.