

RESEARCH PLAN

PRESENTATION OF THE OVERALL RESEARCH IDEA

DIMENSION OF NOVELTY AND POTENTIAL FOR GROUND-BREAKING RESULTS

As background: impaired immune function has multiple causes including inherited genetic errors, infections (e.g. HIV) or iatrogenic (e.g. cancer chemotherapy, immune modifying medicine used in e.g. transplant recipients and persons with so-called autoimmune diseases) (1-7).

The infectious phenotype of interest in the project has excess risk of infection associated with impaired immune function and may present itself in three principle ways:

1. Opportunistic infection (i.e. infection linked with immunodeficiency)
2. Cancer caused by prolonged/chronic infection of pro-oncogenic viruses (e.g. EBV, HPV, HCV, HBV, etc.) or ongoing inflammation
3. Accelerated organ dysfunction, due to an extended pro-inflammatory state caused by long periods of infection and/or excess gut bacterial translocation, which can accelerate organ pathology.

An increasing number of medical specialties are involved in the care of immunocompromised patients, as immune modifying drugs are used to treat a large number of diseases (8-12). The hallmark of impaired immune function is excess risk of contracting infectious complications (i.e. the infectious phenotype – see insert (13-17)). These complications are frequently observed and leads to significant morbidity, mortality and socioeconomic costs (2,3,18,19). *Importantly, however, they do not affect all immune compromised patients and the reasons for this variation are largely unknown (12,20-24).*

Our hypothesis is that across patient populations with impaired immune function, a common pattern of un-discovered risk factors exist that explains the known variation in risk of infectious complications. To address this hypothesis, the PERSIMUNE CoE will be established. This centre will contain multidisciplinary expertise, aimed initially at understanding the mechanisms explaining the variation in risk of infectious complications among immunocompromised populations. The disease risk factors will be identified using a diverse set of methodologies, including pattern recognition from big data retrieved from routine care, studies of host and microbial genetics, imaging, and immunological characterization. This discovery process will likely identify a number of novel mechanisms of host defence. The knowledge of these mechanisms will be used to characterize large groups of immunocompromised populations and in doing so, identify clusters of factors associated with comparable types of infectious complications (3,4,25-29). From this, we will formulate a series of immunodeficiency indices (IDIs) that encapsulate this variation in risk for the various types of infectious complications. After refining and validating the IDIs, this knowledge will be used to stratify the intensity of various types of interventions aimed at reducing infectious complications, as it is hypothesized that the absolute risk reduction from use of such interventions is directly proportional to the IDIs.

The Centre will hence provide important and novel insight into this area of medicine. Existing strategies to prevent infectious complications in the immune compromised host remain blunt

and unsophisticated (20,30-32) and include provision of empirically prophylactic antimicrobial medicine, and/or screening for emerging infection using various genetic-based tests. Usually, such strategies are applied to all patients, because current knowledge is limited as to how to reliably differentiate risk of infectious complications (30-37). Additionally, strategies are designed to prevent the more severe complications, which are often costly and linked with significant adverse effects (32,38-40). This current approach underscores a shortfall in knowledge of basic mechanisms driving the risk of infection.

The key results from creating the PERSIMUNE centre will be: **(1)** discovery of novel mechanisms involved in host defence against infectious and non-infectious phenotypes of immunosuppression (including cancer and organ dysfunction); **(2)** to evaluate whether the absolute risk reduction (i.e. the number needed to be treated for one to benefit) from use of existing preventive strategies varies according to IDI; **(3)** to develop and assess novel strategies that incorporate IDIs as part of the algorithm for interventions upon which the strategy is built, and hence introduce personalized medicine as part of routine care of the immunocompromised host; and **(4)** to understand the extent to which the same novel mechanisms also contribute to disease in humans with supposedly normal immune function, and to assess whether they are also suitable targets for intervention. *As such, these results will critically enhance the understanding of basic mechanisms of host defence towards infections, cancer and organ dysfunction.*

KEY MEASURABLE OUTPUTS FROM THE PERSIMUNE CoE

As a prerequisite for the scientific projects in PERSIMUNE we will establish a classification of microbial cause of clinical syndromes seen frequently in immunocompromised host. The syndromes are 1) Fever; 2) Sepsis; and 3) Pneumonia; and the problem is that the existing microbiological technologies rarely identify bacterial or fungal cause of these syndromes in contrast to the identified sensitive markers that exist for viral pathogens. PERSIMUNE will – as part of its core activities - apply molecular technology to address this shortcoming.

After the initial studies to improve sensitivity and specificity for microbial identification in situations of infectious-related clinical syndromes; the work will continue with the main project component: identification PERSIMUNE predictive factors (PPF) allowing for personalisation of medicine. PERSIMUNE predictive factors that apply for 1+ subgroup of immune deficient hosts and for 1+ category(ies) of infectious phenotype will be identified and categorised as

- xPPFn (x=novel)
- vPPFn (v=validation of observation made by others)

The scientific priorities of investigation into the different types of PPFs will be based on the principle that excellence takes priority, which includes discovery of novel markers and the investigation into their biological mechanism over investigation of markers already identified and used as validation data, but in addition as a subject for further exploration of their biological mechanism.

The evaluation of PPFs will include:

- Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPP), and population attributable fraction (PAF)* as high as possible
 - o across subgroups and categories of infectious phenotypes

- the larger the number of subgroups and categories the better
- Independent predictive ability
 - o Differentiate between statistical prediction vs pathophysiological PPF's. PPF's that reflect varied component of the same pathophysiological process may each be novel in their discovery, and hence a key beneficial output from the CoE, despite only some of them are required to be included as part of the IDI because only some of them are independently predicting the infectious phenotype in question.
 - o confounders – understood and available – initially the centre will conduct a series of analyses based on routinely available data in order to identify such confounders, which will be required to demonstrate the degree of independency for novel identified PPF's. However, these initial steps will by themselves generate a number of PPFs, many of which of the “v” type but potentially also of the “x” type.
- The biological mechanism(s) explaining the predictive ability of the PPF. As the PERSIMUNE CoE unfolds its activities and starts to generate PPF's, it may chose to either further investigate the biological mechanisms, continue to search for other PPF's or a combination of the two.

A STRATEGY FOR ADDRESSING THE MAIN HYPOTHESIS

The strategy involves successive steps, which reflect the evolution of the IDIs as the PERSIMUNE centre develops, followed by additional research to challenge this knowledge, based on further pattern recognition of data sources from routine care, and from findings derived from the discovery phase of the centre (fig 1).

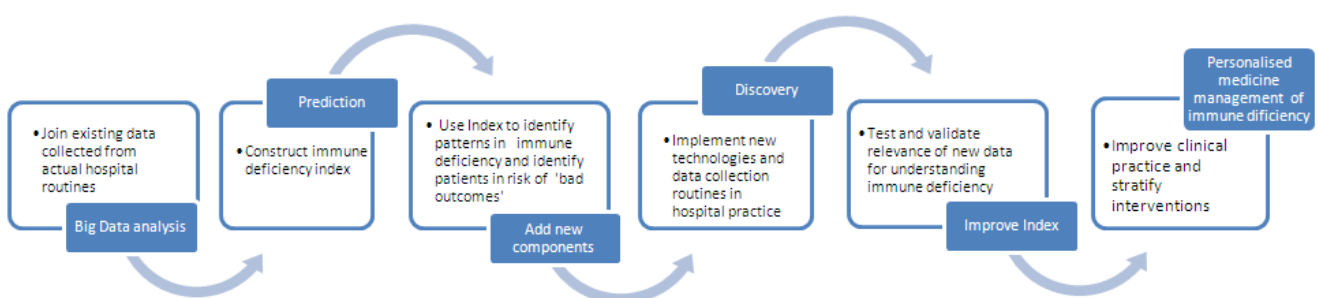


FIG. 1 TIMELINE FOR THE PERSIMUNE CENTRE CORE FUNCTION TO DEVELOP AN IMMUNE DEFICIENCY INDEX

DESCRIPTION OF THE PLANNED RESEARCH PROGRAMME

MAIN HYPOTHESES AND AIMS OF THE PROGRAMME

The programme is built on the following testable hypotheses and aims:

Main hypothesis # 1: Across populations with impaired immune function, due to a diverse set of causes, a common pattern (derived from data related to demographics, clinical history, therapeutic interventions, immune function, host genetic, composition of the microbiota, and/or imaging-identifiable subclinical processes) exists that can reliably predict the risk of developing infectious complications.

Main aim # 1: Develop and refine a series of predictive immunodeficiency indices (IDIs) that are able to reliably predict the various forms of infectious phenotype.

The Centre's workflow will be to create a continuous interaction between, on the one side, testing and validation of a contemporary version of the IDIs and their ability to predict an infectious phenotype (see fig. 1), and on the other side, use big data, including findings from biological material performed as part of the Centre's activities, in an attempt to discover new markers that contribute with predictive ability to the IDIs. Promising candidates from the discovery phase will be introduced as part of standard of care at the hospital and in doing so, will be validated prospectively. As such, there is a bidirectional interaction between the three pillars of the programme as depicted in figure 2.

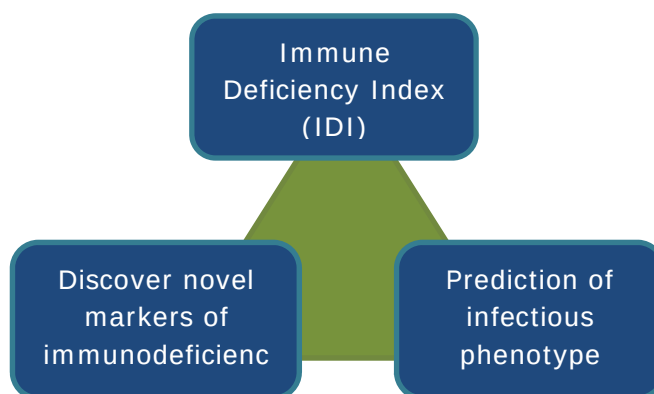


FIG. 2 THE CONCEPT OF INTERACTION

This workflow can be dissected into two main areas of work to test the following hypotheses/aims:

Hypothesis 1a: Factors already available and determined as part of routine care, when combined and appropriately analysed, will be able to predict risk of infection more reliably when combined as IDIs than what is currently possible in routine care, based on existing knowledge.

Aim 1a: Construct a new database from existing data sources currently being used for routine care, implement functions of the database as part of routine infrastructure at Rigshospitalet and as such, generate a virtual, prospective cohort of all patients followed at the hospital. A predefined set of laboratory assessments linked with immunodeficiency will be implemented as part of routine care across all clinics contributing to the new database. This information will be used to construct an initial version of the IDIs.

Hypothesis 1b: Markers of immune function (soluble or cellular), host genomic SNPs, composition of the microbiota, and/or imaging-identifiable subclinical processes will add further independent predictive ability to the IDIs being developed as part of hypothesis 1a.

Aim 1b: Perform a series of case-control studies (cases being persons with infectious complications and matched controls with comparable initial IDIs) using a panel of potential and novel factors. For factors with possible predictive ability, to then assess whether the contemporary version of the IDI's ability to predict the outcome improves when information on the factor(s) is added as an additional variable to the statistical model upon which the index is developed. If so, the marker will be included as part of routine care and from then on, be included as part of the IDIs to be prospectively validated.

A 3rd area of work in the first phase of the programme relates to testing the following hypothesis/aim:

Hypothesis 1c: The predictive ability of the IDIs improves by better ascertainment of the presence of invasive bacterial and fungal infections by use of molecular technology.

Aim 1c: The establishment of molecular technology, which is able to identify bacterial DNA in blood and other sterile body fluids. Documented invasive bacterial infections are used as positive controls and optimize the discriminatory capabilities of the assay. Clinical situations where infectious complications are probable will then be assessed. The molecular characterisation of the invading microorganisms will also be used to determine whether the microbiota is the source of such infections (see below “microbial genetics” for details).

Once the Centre has advanced its work to test these three hypotheses, it will then focus on the second main testable hypothesis:

Main hypothesis # 2: The IDIs (developed as detailed above) can reliably separate immune deficient persons by grades of risk. The absolute risk reduction by use of interventions, aimed at reducing the risk of infectious complications, will be largest for patients within the cohort at most risk, as determined by the IDIs.

Main aim # 2: Perform a series of strategic randomised controlled trials, where allocation to a given intervention, aimed to reduce a certain type of infection, is either provided as routine care to all patients or according to an algorithm, where the intensity of the intervention is graded depending on each individual patient's underlying risk of contracting an infection. Outcomes to be assessed include the infectious complications of interest, all-cause morbidity and mortality, adverse drug reactions related to the intervention, and cost.

RATIONAL AND FEASIBILITY OF THE JOINED DATABASE

The database is an essential tool to address each of the stated aims and requires multiple functionalities. All data, generated as part of routine care from multiple sources, need to be merged and/or linked into one database from where the initial IDIs can be generated (aim 1a). The database will be used to match cases and controls, as part of aims 1b and 1c, and to capture the outputs from said aims. The merger shall be done as close to real time as possible, as one of the outputs is to calculate the IDIs, which will be used to guide routine care as part of addressing aim 2.

An important component of quality control of the joined database is to ensure ascertainment of the various types of clinical phenotypes. Algorithms will be used to identify case definitions for each of these phenotypes and appropriate quality control procedures will be implemented to ensure their continued appropriate classification.



MATCH PROGRAMME

The applicant has established IT technology and an associated bio-bank that allows for prospective real-time follow-up of patients undergoing solid organ or stem-cell transplantation at the hospital, the MATCH programme (41). MATCH is an expert tool providing personalized medicine to transplant recipients, developed fully by CHIP and is implemented as a routine clinical tool with documented benefits in terms of reduced morbidity and cost of patient treatment and care.

MATCH captures routine data daily from all analytical & pathological labs, from medication systems, the national quality assurance database for rheumatology patients, and imaging data. Outputs are structured monitoring and treatment plans for all transplant patients at Rigshospitalet, and an active alerting of clinicians in case of out-of-range lab values or missed samples.

Data capture is patient-ID driven: timed requests from MATCH ensure that data from all different sources are stored in basic layer mirrored tables in MATCH, reducing pressure on source databases. The second layer is uniformed, standardised storage of data from different sources. Algorithms to issue monitoring and treatment plans, as well as alert alarms, are developed in collaboration with transplant clinicians (see fig 3).

New data from discovery labs, human and microbial genetics, and imaging data will be captured in a similar way forming the data repository for the PERSIMUNE centre.

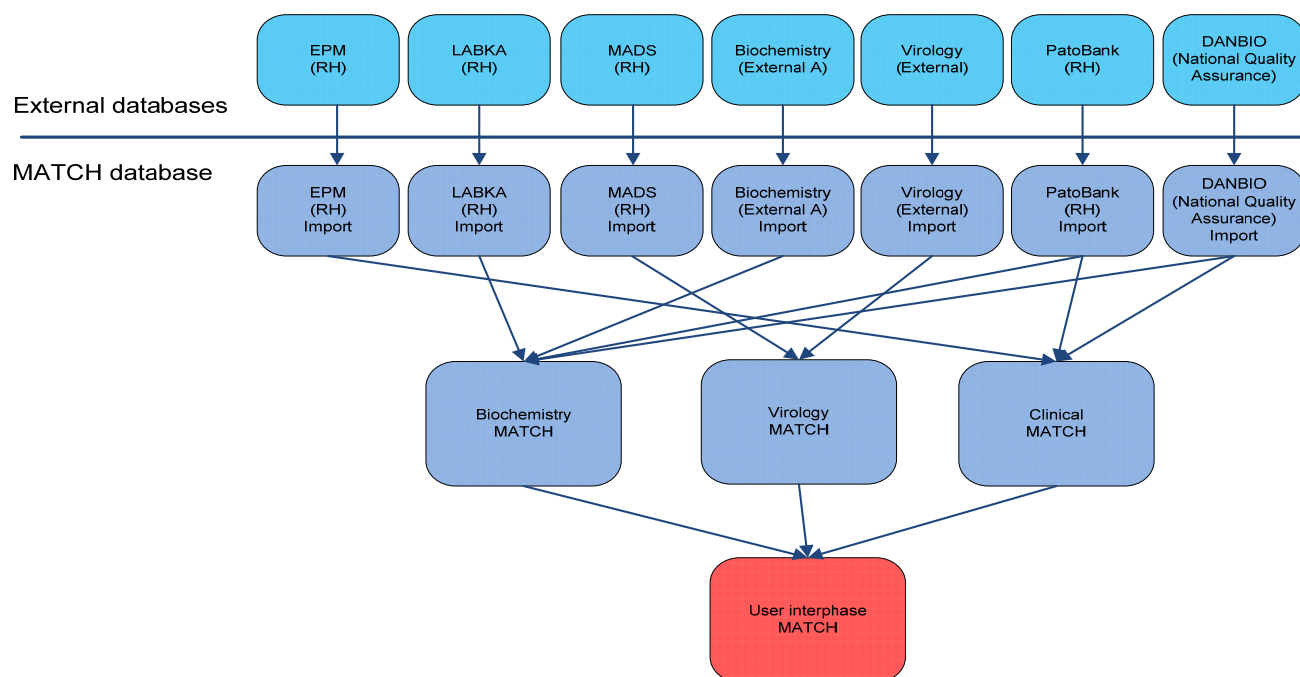


FIG. 3 THE MATCH DATABASE – A STRUCTURED APPROACH TO STANDARDIZED DATA ACCESS

Since the technology ensures real-time follow-up of patients, and the associated diagnostic and other laboratory assessments are performed as part of routine care, it can also be used to prospectively identify events suspected to fulfil case-definitions of the various types of infectious complication.

METHODS

The research method encompasses transforming the tertiary-referral hospital to a research platform for the PERSIMUNE basic science model. As described earlier multiple types of immunodeficiency patients are cared for at the hospital and we will be able to develop procedures to ensure that PERSIMUNE requirements are met:

- Include a large patient sample
- Ascertainment of the infectious phenotypes of interest
- Infrastructure to capture relevant patient information (MATCH)
- State-of-the-art diagnostic technology
- Central bio-bank facility
- Long-term and diverse scientific interest by all relevant stakeholders
- Thieve towards excellence

- o Identify novel ideas and prioritize
 - be able to also say no
- Ensure synergy from the multidisciplinary team
 - o Although the platform is Rigshospitalet – embrace international input and collaboration
 - o At Rigshospitalet
 - PERSIMUNE is part of the overall hospital immunology vision
 - Work together collegially and across departments

INSTITUTIONAL AFFILIATION OF THE PERSIMUNE CENTRE

The Centre will be an integrated part of Rigshospitalet, University of Copenhagen, which is a highly specialized hospital, located near the basic research institutes of the University. This area of Copenhagen is undergoing continuous development to further promote the vision of concentrating expertise related to health research, physics, mathematics, and biology. The creation of the Centre is hence optimally located to ensure cross-disciplinary collaboration between research groups with mutually complimentary skill-sets and backgrounds.

Rigshospitalet provides care to a large number of immunocompromised persons affiliated in particular with the following clinics: haematology (e.g. leukaemias, lymphomas – including a large human stem-cell transplant programme), oncology (all types of cancers), paediatrics (e.g. childhood leukaemias and congenital immunodeficiency syndromes), infectious diseases (HIV, adults with congenital immunodeficiency syndromes), and rheumatology (autoimmune diseases treated with immunosuppressive medication). A number of clinics (nephrology, heart, lung, abdominal surgery, paediatrics) provide care for organ transplant recipients (i.e. kidney (incl. pancreatic), heart, lung and liver) and dialysis patients. The flow of patients with immunosuppression through these clinics amounts annually to several thousand individuals. Finally, the hospital has several internationally well recognised sections that are able to provide the required technology (see below). Therefore, the hospital is extremely well suited to act as a platform for conducting the research which the Centre proposes.

ORGANISATION

The PERSIMUNE Centre will be organised as depicted (see organogram below). Lead by the centre leader, a steering committee will oversee the functions of the Centre and make decisions regarding the principle directions of research and application of various versions of IDIs in routine care. All key stakeholder sections are represented on the steering committee, which will meet monthly. The leadership group, chaired by the centre leader and with representatives from the centre main functions will obtain support from the hospital and department leadership to ensure ownership of the project and capture of eligible patients for the project at their first point of contact with the hospital.

ORGANISATION AND GOVERNANCE

Meeting structure and decision making will be further developed and described by the leadership group in Standard Operation Procedures and Charters to ensure transparency, effective communication and clarity on roles and responsibilities.

A core function comprising administrative, project management, data programming & management, statistical and bioinformatics support will be established and serve as basic support for the leadership group and steering committee.

The principles of decision-making on overall scientific direction and resource allocation will be based on whether the scientific aims of a given project are aligned with the Centre's overall scientific mission, its scientific merit and priority.

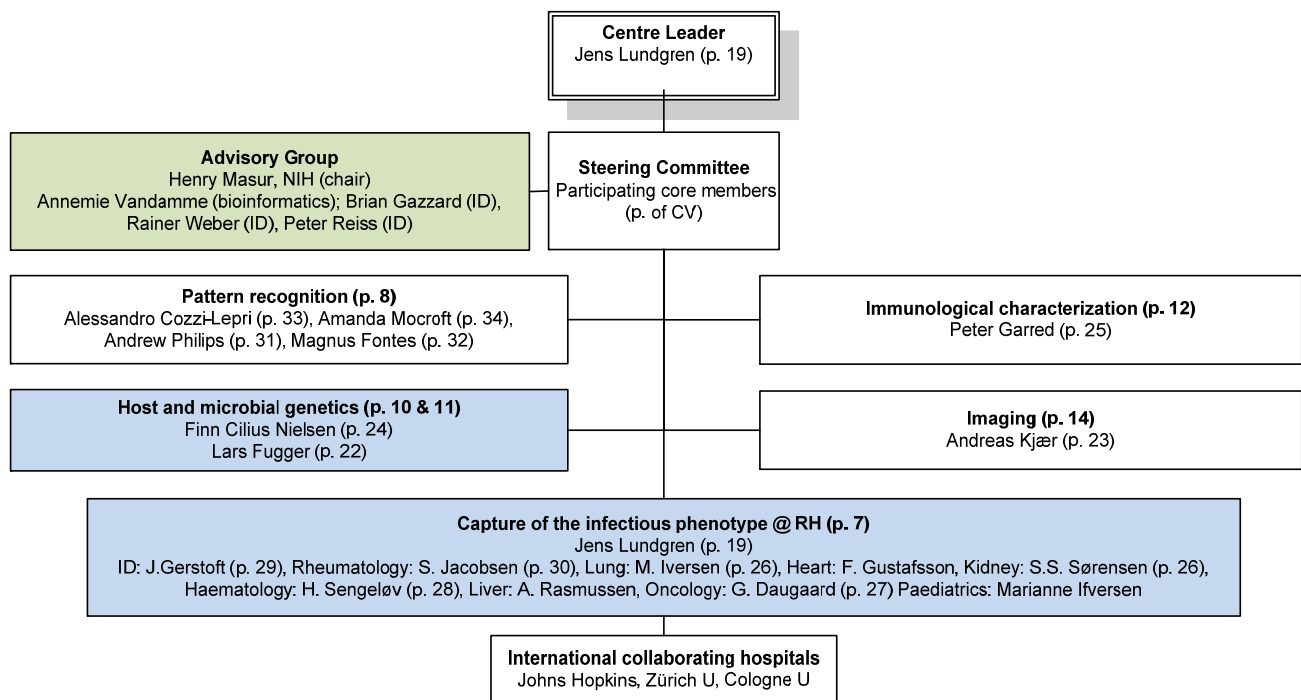


FIG. 4 ORGANOGRAM, BLUE BOXES REPRESENT CURRENT MATCH (SEE P 7) COLLABORATORS

An external advisory group will meet with the steering committee annually and provide critique of results generated so far and future research plans.

COMPETENCIES AND CAPABILITIES OF THE CENTRE

The required competences and capabilities of the Centre involve state-of-the-art international cutting-edge senior supervision, as well as the technological infrastructure of all areas of work within the Centre. This includes a collection of high quality big data from routine data sources and pattern recognition within them, genetic characterisation and analyses of host and microbial genetic information, various types of body imaging including tracer technology, and immunological characterisation.

The team of senior researchers that forms the steering committee fulfil the requested senior supervision capabilities (see organogram referring to pages showing researchers CV's). In addition to the existing expertise at the hospital, the senior researcher capabilities at the Centre are further enhanced by bringing in Prof. Lars Fugger (p. 22), Profs. Andrew Phillips, Amanda Mcroft and Alessandro Cozzi-Lepri (p. 32-34) and Prof. Magnus Fontes (p. 33; of note, Prof Fontes collaborates with Institute Pasteur's Labex project (42) – a project with direct relevance to work planned by the PERSIMUNE Centre). These experts will take an active role in all aspects of scientific work at the Centre; this would also include their physical presence at Rigshospitalet as required.

The host institution has the required infrastructures. The biochemistry clinic provides routine analyses of standard biochemistry including haematological characterisation; also, the unit on genomic medicine has documented state-of-the-art technology to characterise genetic information from host and microorganisms. The clinical immunology department has a core facility for large scale biobank storage of diverse biological materials (including full blood, cells for flow cytometry, plasma, serum, and samples from stool, respiratory tract and skin), and a section with expertise in tissue typing and immunological characterisation. Finally, the clinic of infectious diseases and rheumatology has the research group headed by the proposed leader of the Centre, which has been previously well documented for its ability to generate and analyse big data sets of the highest quality on transplant recipients (MATCH programme) and rheumatologic patients (see p. 7 & 8 for details).

The lead research team of the proposed Centre has established links with hospitals in other regions of Denmark and abroad that are involved with care of immunocompromised hosts (see organogram above). This network is envisioned to be used as part of the proposed work (networking, exchange of personnel and data, creation of collaborative project etc.). Finally, the main applicant serves in a leadership position within the global trial network INSIGHT (see below). The PI of INSIGHT, Prof. James Neaton from the University of Minnesota, endorses this application and expresses an interest to collaborate (personal communication). This is also true for the other large international consortia that the main applicant is involved with (EuroSIDA and D:A:D).

THE RESEARCH ENVIRONMENT OF THE CENTRE

The proposed Centre leader's research group, CHIP, is located at PARKEN, a new facility recently established by Rigshospitalet. The research group currently has a staff of 50 people, including a sizable international team of PhD students and post-docs, and an operational research infrastructure that interacts on a daily basis with statistical collaborators (primarily at UCL, the University of Minnesota and NIH). The facility has multiple meeting rooms, audio- and video links, and a lounge for social interaction and larger gatherings. The Centre of Excellence will use this infrastructure as well as additional adjacent office space. This will create the possibility for researchers in this programme to easily access project management tools, administrative experience, database design, bioinformatics and general IT expertise, as well as expertise in displaying complex result in user friendly interfaces for dissemination of results. The leadership philosophy of the PERSIMUNE Centre will be comparable to that applied to CHIP (see section below), namely to create a dynamic and collegial atmosphere for the researchers and support staff aimed at generating research of excellence. Critical components to achieve this are dedicated efforts to create team spirit, collective responsibility and loyalty towards the common goal. The frame for this is achieved via a continued and appropriately balanced flow of workshops, journal clubs, invited speakers, and social gatherings.

CLASSIFICATION AND ASCERTAINMENT OF INFECTIOUS PHENOTYPES IN DATABASE

The case definition is the first important step to overcome to be able to generate the basic populations of phenotypes to include in the PERSIMUNE project. By establishing and evaluating selection criteria, a list of possible events will be identified where after deeper investigation into source data will make it possible to qualify the possible events and end up with a list of confirmed events fulfilling the developed case definition criteria for each phenotype of interest.

BIO-BANK

The hospital has agreed to establish a bio-bank facility for PERSIMUNE and the leadership group will establish a Bio-bank Group to ensure linkage with existing bio-bank structures at Rigshospitalet.

The group will have responsibility for handling all ethical and legal issues related to the project and establish Standard Operative Procedures for correct collection, handling, storage and request for use of biological material.

PRINCIPLES OF FUNDING BY PROJECT ACTIVITY

The Core Function including database setup, endpoint classification and ascertainment, inventory and accessibility to biological material, as well as statistical & bioinformatics support will be centrally established and funded directly via DNRF funds.

Research projects and analyses of biological material will undergo a competitive selection process for funding via the DNRS funding and external co-funding will be expected.

THE FOLLOWING AREAS OF EXPERTISE ARE IN PLAY TO ORCHESTRATE THE PROJECT



PATTERN RECOGNITION - SUMMARY

Concept: Ensuring structured access to all important data for immune deficient patients across all routine and discovery labs, as well as all existing bio-banks, will allow the team of clinicians, lab and imaging scientists (as well as mathematical, statistical and bioinformatics scientists) to collaboratively identify elements of the IDIs, implement it in daily clinical routine, and evaluate and constantly improve it.

Experience: The MATCH programme exemplifies data collection across functions. The strong and long lasting relationship between CHIP and the statistical team at UCL, who analyse data from very large datasets, has had a positive impact on treatment and care of patients to provide the basis for guideline development.

Contribution to the project: The data managers and analytical scientists will analyse the data, produce evaluations, reports and visualisations, providing the basis for developing the IDIs in collaboration with clinicians and lab scientists.

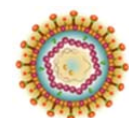


HOST GENETICS – SUMMARY

Concept: Susceptibility to infectious complications in patients with an impaired immune function may be causally associated to hereditary variants.

Experience: The laboratory provides on a routine basis genome wide analyses, ranging from high density SNP arrays to transcriptome arrays and next generation sequencing (NGS).

Contribution to the programme: Exome-sequence triads of whole blood DNA to ~100x coverage, followed by mapping in the CLC-bio workbench and up-loaded to the Ingenuity Variant Analysis for identification.



MICROBIAL GENETICS – SUMMARY

Concept: To determine whether the immunocompromised person's microbiota is the source of subsequent invading infections, and if so, what is the incubation time and

which risk factors determine this phenotype.

Experience: The main applicant has contributed to a series of studies implying that immune impairment leads to excess leakage of gut microbiota into portal circulation, which is associated with systematic inflammation and accelerated liver tissue fibrosis. The proposed work here will add to this in a more diverse cohort of immunocompromised persons.

Contribution to the programme: Genetic mapping of the microbiota by ultra deep sequencing during and follow-up, with and without evidence of ongoing infectious diseases. In latter situations, the genetic composition of the invading microorganisms will also be determined to address the concept.



IMMUNOLOGICAL CHARACTERIZATION – SUMMARY

Concept: In order to diagnose correctly and improve individualized treatment of immunocompromised patients, it is a prerequisite to understand the disturbed immunological mechanisms causing infectious problems.

Experience and examples: Highly experienced in use of most techniques to evaluate molecular, cellular and functional immune status primarily for monogenic diseases, but also routine investigations in relation to transplantation immunology, autoimmunity and leukaemia diagnostics.

Contribution to the project: Immune phenotypic analysis of leukocyte surface markers, cellular responses, T-lymphocyte neogenesis & maturation, as well as B-lymphocyte maturation. In addition, evaluation of immunoglobulins and complement, and discovery of individual susceptibilities using micro-RNA and gene methylation profiles.

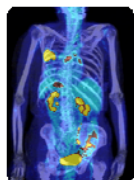
OVERVIEW OF GENETIC ANALYSIS PLANNED IN THE PERSIMUNE PROGRAM

The below genetic analyses of samples from the included immune compromised populations detailed in the three sections above (host genetic, microbial genetics and immunological characterisation) will be analysed. Source biological material is DNA or RNA extracted from host samples (blood, stool, pharynx, skin, pathological tissue, etc).

Biomarkers	Technology	Data management	Clinical End-point
Host genome	Transcriptome Array	Transcriptome analysis	Infectious phenotype
	CNV & SNP Array	Association analysis	Disease Ass. CNV & SNP
	NGS X100	Mapping & filtering	Disease Associated Mutations
	HLA-typing	Association analysis	Infectious phenotype
	microRNA profiling	Association analysis	Infectious phenotype
Microbiota	NGS X100 - X2000	Identification of Unmapped sequences	Microorganism associated with infectious phenotype

Abbreviations: CNV=Copy number variation; SNP= single nucleotide polymorphism; NGS=next generation sequencing

Source of biological material is DNA or RNA extracted from host samples (blood, stool, pharynx, skin, pathological tissue, etc.).



IMAGING – SUMMARY

Concept: Use of molecular imaging to identify and study evolution of already identified processes over time linked with IDIs. The distinct advantage hereof is to reduce error seen with other methods because of variation in sampling or dilution.

Experience & examples: Extensive experience with PET and PET/MRI; prior work focused on oncology; proven track record to develop novel tracer and develop their clinical use.

Contribution to the programme: Assess use of FDG-PET (marker of lymphocytes), and other tracers able to identify macrophages, as a screening tool for subclinical processes in patients with impaired immune function, and if so, whether these processes result in clinical disease.

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