



PERSIMUNE

CENTRE OF EXCELLENCE FOR PERSONALISED MEDICINE
OF INFECTIOUS COMPLICATIONS IN IMMUNE DEFICIENCY

Introduction

January 2015



Danmarks
Grundforskningsfond
Danish National
Research Foundation

Rigshospitalets immunologiske vision

- 2011: immunologi valgt som central strategisk emne
- 2013: række udvalg nedsat
 - Anbefalinger færdiggjort
 - Ansøgning til grundforskningsfondet indsendt
- 2014: Ansøgning imødekommet
- 2015: PERSIMUNE åbner
 - platform for implementering af visionen
 - Defineret budget, ledelsesstruktur, og operational infrastruktur

PERSIMUNE

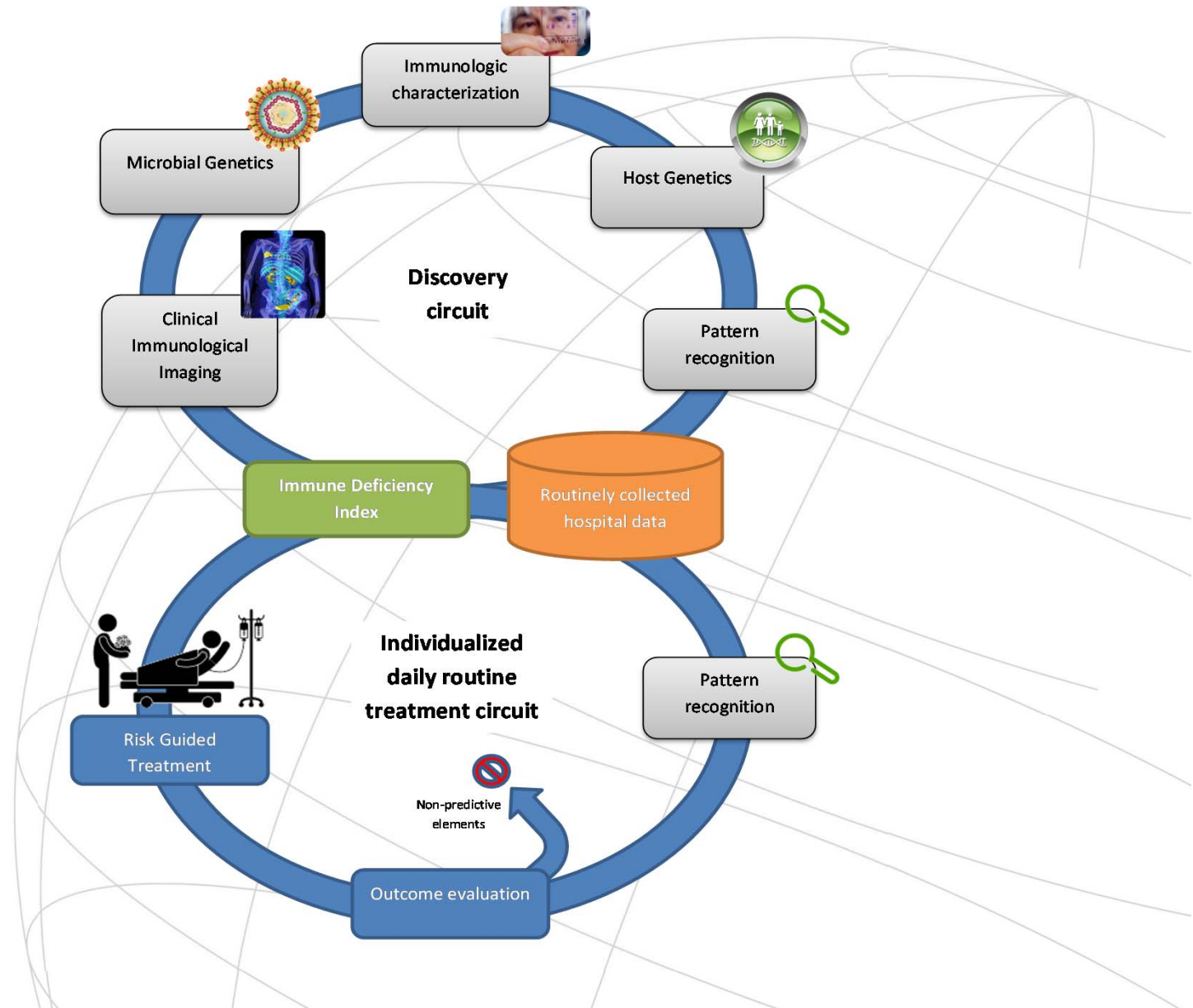
- Core-funktion for immunologiske vision = excellent forskning
- Inkludere store grupper af RH's patient klientel i fælles forskningsplatform
 - Fælles data warehouse og biobank
- "Upgrade" af bioinformatik, biostatistik, datamining, immunologi
- Budget
 - 6 årig periode - 115 millioner
 - Core-facilitet og infrastruktur, gæsteforskere, ph.d. og post.doc
 - Fysik: Øster alle 56, 5 sal

Hovedhypotese og metoder

- **Blandt patienter med nedsat immunfunktion,**
 - **mønster af ikke-identificerede risikofaktorer**
 - **forklare variationen i risikoen for at udvikle infektioner**
- **Metoder:**
 - Mønster genkendelse fra “big data” indsamlet i rutinehåndtering,
 - Værts og mikrobiel genetik,
 - Immunologisk karakterisering
 - Billeddannelse inkl tracer teknologi

Mission

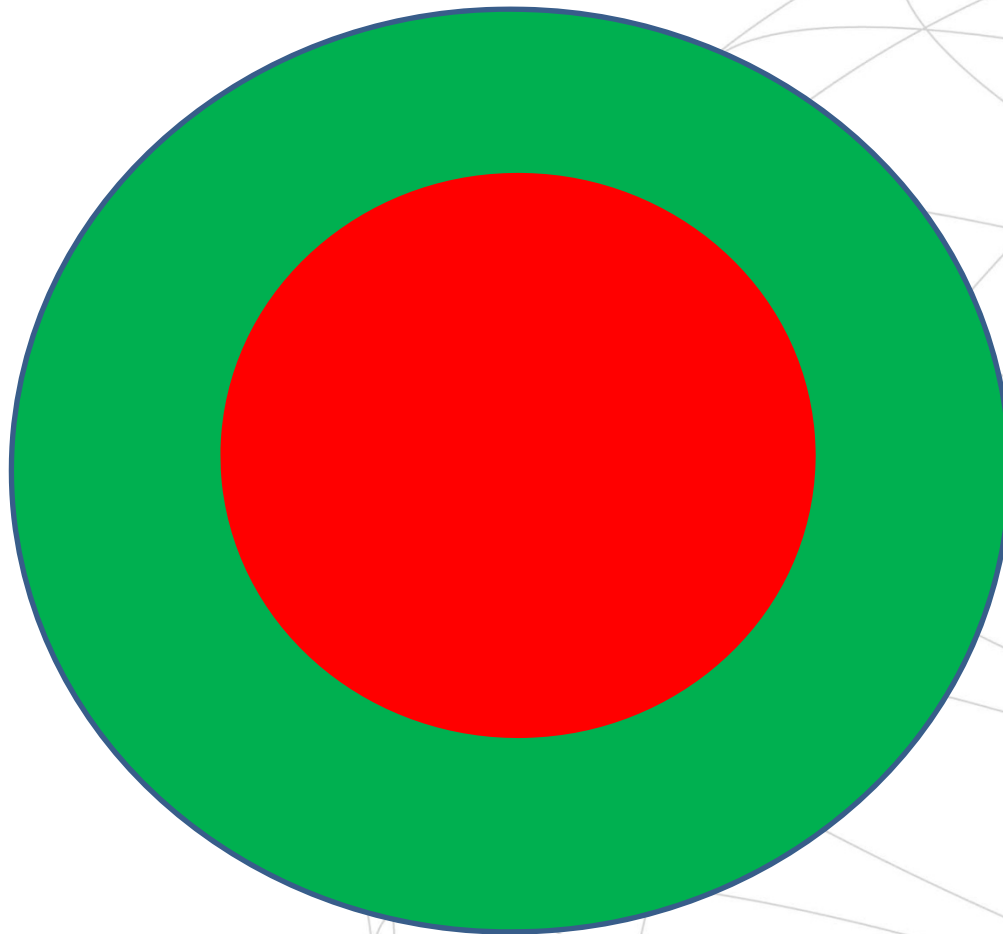
- Påvise nye mekanismer af værtens forsvarsmekanismer, og påvise de mønster af allerede kendte og nye mekanismer der bedst forklare variationen i at pådrage sig infektion(er)
- Fra dette at formulere immundefekt indices
 - indeholder viden om denne variation
 - valideres prospektivt
 - bruges til at individualisere behandling



Hvorfor fokus på patienter med nedsat immunfunktion ?

- Immundefekte tilstande
 - “Stress-test” af værtens evne til forsvar
 - Mest optimale population mhp identificere pre-eksisterende svagheder i forsvaret (signal-to-noise ratio highest)
 - Under behandling – data på allerede kendte mekanismer indsamles systematisk
 - Tillader at der kontrolleres herfor i statistiske analyser med sigte på at identificere nye mekanismer

PERSIMUNE kan mere end dets mission



Data warehouse
(rutinedata & data genereret af PERSIMUNE, eksterne data inkl nationale registre) kan bruges til andre forskningsformål

Bistå rutine behandling
(e.g. MATCH, antibiotisk stewardship)

Forbedre mikrobiologisk diagnostik

Status for implementering

- Officiel åbning: 4. februar kl 14.30 (alle velkomne)
- Workshop med international deltagelse 3-4 februar – alle velkomne
 - UCL, Institute Pasteur, Oxford University
- PERSIMUNE kohorte identificeres:
 - Relevante klinikker identificere patient grupper; uge 5/6
 - Abdominal kirurgisk, børne&unge, hepatologisk, hæmatologisk, infektionsmedicin, kardiologisk (inkl lunge), nefrologi, neurologisk, onkologisk, reumatologi
- Prospektiv inklusion starter 2. marts 2015
 - når PERSIMUNE biobank åbner

Hvordan bliver man involveret

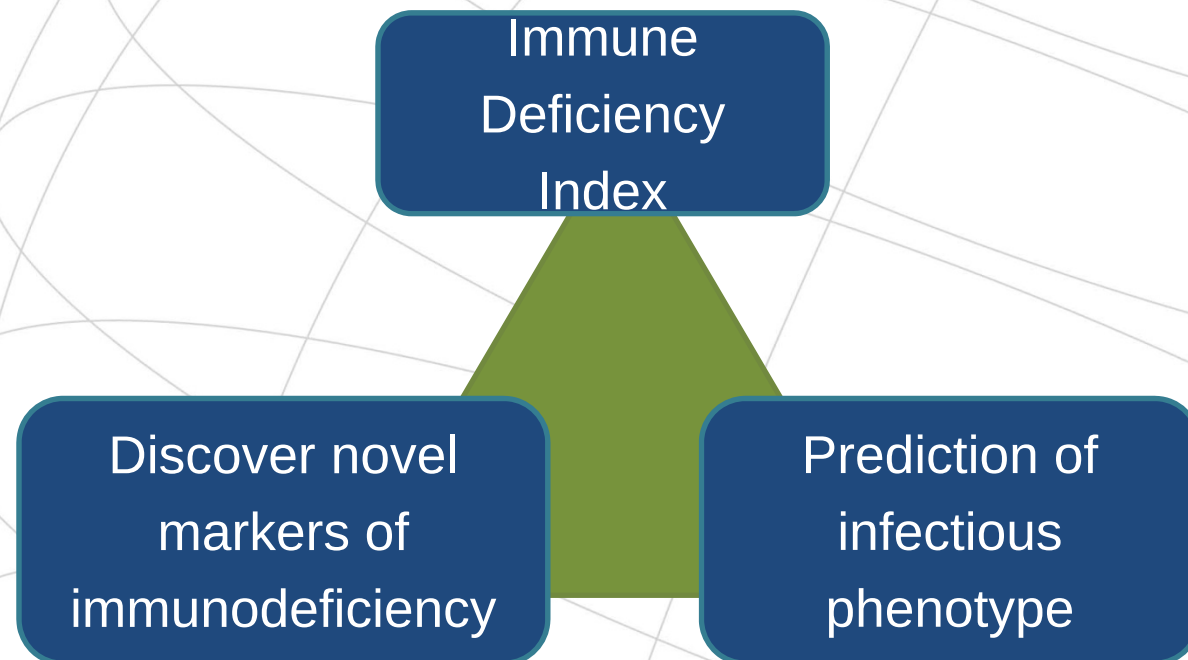
- Klinik niveau
 - Inkluder relevante patient grupper
 - Prospektivt
 - Bidrage til PERSIMUNE biobank
 - Retrospektiv re-kreation
 - Mulig bidrag fra eksisterende biobank strukturer
- Individ niveau
 - Medlem af en række “scientific interest groups”
 - Lede/bidrage til projekter
 - Hold dig informeret via
 - Website: www.PERSIMUNE.org
 - Twitter: [@PERSIMUNE](https://twitter.com/PERSIMUNE)
 - Facebook: <https://www.facebook.com/PERSIMUNE>

Back-up slides



- Immunodeficiency
 - Increases risk of contracting disease
 - ideal population for **basic science model** to better understand interaction between immune function and disease
 - Epidemic due to medicines - societal impact enlarging

The 3 pillars of PERSIMUNE



Research platform: "un-recognised invasive infections"

- Febrile syndromes with "unknown microbiological cause"
 - Frequent
 - Severe
 - Empiric antimicrobial therapy
 - Underlying cause
 - True invasive infection
 - current microbiological techniques unable to identify
 - (more likely for bacterial and fungal pathogens)
 - Non-infectious
- Initial core PERSIMUNE activity
 - Required to further categorise "cases"

What is an immunodeficient patient ?

- Two major groups:
 - Populations characterised for their increased risk of infections relative to the background population
 - E.g. HIV-infection, use of immunosuppressive therapy (e.g. transplant recipients, those receiving chemotherapy & anti-cytokine therapy etc), and known genetic defects
 - Individuals at elevated risk of infections not readable explained by excess exposure to infectious pathogens

Plans for engagement of leadership of hospital and departments

- Two page concept sheet to be circulated via directors of hospital to centre directors and department heads
 - Presentation at appropriate fora
- “Introduction tour” to heads (*et al*) of all departments engaged
- Enter formal agreement with departments in relation to:
 - Which patient categories to include in cohort – condition: always consecutive enrolment
 - Whether to include patient category retrospectively also – available biobank and data beyond routine?
 - Willingness to introduce “basic package” as part of routine care prospectively
 - Clarify additional blood work done routinely and systematically ?
 - Clarify routes of access to PERSIMUNE data warehouse ?
 - Prioritise types of desired routine feedback from data warehouse of own patient categories ?

Infectious phenotype of immunodeficiency - diseases linked with immunodeficiency

Opportunistic and/or other types of infections seen repetitively
i.e. infections linked with immunodeficiency

Cancer caused by viruses

e.g. EBV, HPV, HCV, HBV, etc

Accelerated organ dysfunction (incl. CVD, liver, kidney, cancer)
due to extended infection-related inflammatory state

Allograft rejection / Graft-versus-Host in transplant recipients
immune reaction triggered by infection

**Risk of contracting these diseases varies
across populations of immunodeficient persons**

Official opening:

Wednesday, 4th February 2015, 14.30-17.00. Rigshospitalet, Østeralle 56, 5th floor, Copenhagen

- **14.30-14.40: Liselotte Højgaard**, Chair, Board of the Danish National Research Foundation: *Opening of PERSIMUNE*
- **14.40-14.45: Jannik Hilsted**, Chief Medical Officer, Rigshospitalet, University of Copenhagen: *Welcome and introduction*
- **14.45-14.55: Karin Friis Bach**, Chair, Health Committee, Capital Region Council: *Capital region's research strategy*
- **14.55-15.05: Ulla Wewer**, Dean, Faculty of Health Sciences, University of Copenhagen (UoC): *Linking the University of Copenhagen to PERSIMUNE*
- **15.05-15.15: Jens Lundgren**, Centre Leader: *Vision, mission and aims of PERSIMUNE*
- **15.15-15.25: Magnus Fontes**, University of Lund & INSERM, France: *How to approach big data in PERSIMUNE*
- **15.25-15.35: Amanda Mocroft**, University College London, UK: *Predicting kidney disease in HIV+ patients*
- **15.35-15.45: Henrik Sengeløv**, Department of Hematology, Rigshospitalet, UoC: *Outstanding challenges in managing infections in the immunocompromised host*
- **15.45-15.50: Andreas Rostved**, ph.d. student, Department of Gastrointestinal Surgery, Rigshospitalet, UoC: *MELD scores in liver transplant recipients*
- **15.50-15.55: Isabelle Lodding**, ph.d. student, CHIP @ Department of Infectious Diseases, Rigshospitalet, UoC: *CMV kinetics predict CMV disease in transplant recipients*
- **15.55-16.00: Alvaro Borges**, ph.d. student, CHIP @ Department of Infectious Diseases: *Preventing immunodeficiency in HIV: the START study*
- **16.00-16.05: Jens-Ulrik Jensen**, post doc, CHIP @ Department of Infectious Diseases: *Liver impairment in septic shock*
- *Reception – hosted by Rigshospitalet*

Approach to study designs

- Re immunodeficient populations
 - Case:control studies
 - Case: those with infectious phenotype
 - Control: those without
 - Cohort studies
 - Variables of interest determined in larger cohort – typically as part of validation process
- Re individuals at excess risk of infections
 - Exome-sequencing of index and family members

PERSIMUNE blood work / biobank

- level 1 package:
 - Routine: B-Hæmoglobin, B-Leucocyttælling, B-Leucocyt differentialtælling, B-thrombocyttælling, P-CRP, P-Glucose, P-Karbamid, P-kreatinin, P-Kalium, P-Natrium, P-Albumin, P-LDH, P-ALAT, P-Basisk phosphatase, P-Bilirubiner, P-Koagulationsfaktorer/INR).
 - Biobank: whole blood + plasma
- Level 2 package
 - Routine: same as level 1 + quantification of B, T and NK numbers, immunoglobulins, S-ferritin
 - Biobank: whole blood + plasma
- Level 3 package
 - same as 2
 - Biobank: PBMC storage

Keys to success

- Thieve towards excellence
 - Identify novel ideas and prioritize
 - be able to also say no
 - Ensure synergy from multidisciplinary team
 - Although platform is initially RH – embrace international input and collaboration
 - At Rigshospitalet
 - PERSIMUNE = RH's immunology vision
 - Work together collegially and across departments
 - Share data and ideas
 - None of us can do this by ourselves !

Governance structure

- Leadership
 - Centre leader
 - Secretariat & administration
 - Data-management
 - Statistical resource
 - 2 vice-leaders (representing researchers and clinicians)
- Executive committee:
 - Leadership
 - 2 persons each representing
 - researchers at RH
 - clinicians from RH
 - external collaborators
- Scientific advisory committee
 - Role: review of incoming proposals
- Investigators
 - Scientific interest groups (SIG's)
 - group leaders (clinical, bioinformatics, immunology)
 - Lead department liason
 - All actively engaged (or otherwise)

Roles of governance structures

- Leadership
- Strategic direction of research within PERSIMUNE
- Provide oversight of research initiation and output
 - Decision on projects support from DNRF award
 - Grant approval for access to data and biological material collected as part of PERSIMUNE
 - Fundraising efforts (e.g. ERC)
 - Approval of release of research output
- Ensure transparent communication within network

Projects – granting approval by PERSIMUNE governance structure

- Projects using significant portion of DNRF award
 - Peer-reviewed, prioritised and approved
 - Conditional on approval also of release of research output & PERSIMUNE DNRF contract number acknowledged
- Other projects – i.e. request to access data warehouse (= use of PERSIMUNE infrastructure)
 - Approved if
 - scientific level appropriate,
 - Research aim supplementary (non-competitive) with ongoing research portfolio of PERSIMUNE,
 - clinical departments OK for use of own patients,
 - PERSIMUNE DNRF contract number is acknowledged, and
 - research output is shared with PERSIMUNE leadership secretariat prior to submission (administrative review with offer to preform scientific review)

Meeting scheduling – sections to be combined when appropriate

- Leadership
 - Weekly meetings
- Executive committee
 - Monthly meetings
- Investigator meetings
 - Quarterly
- Scientific meetings
 - Every second week (+ ad hoc)

All meetings held at PERSIMUNE HQ or 8632
(with state-of-the-art audio/video conferencing facilities)

Organisation – a scientifically strong multidisciplinary international team

