12.30-14.00: PERSIMUNE structures within Rigshospitalet incl status on collaborative agreements with departments in-house, possibilities for retrospective enrolment and biobank built-up
The Rigshospitalet immunology vision

2011: immunology chosen as core strategic area
2013: committees formed
  Recommendations completed
  Application to DNRF submitted
2014: DNRF application granted
2015: PERSIMUNE opens
  Platform for implementing the vision
  Defined budget, governance structure and operational infrastructure
PERSIMUNE (PM)

- Core-function for immunological vision
  - Excellent research
- Include large groups of patients in care at Rigshospitalet as part of one research platform
  - data warehouse og biobank
- "Upgrade" of bioinformatik, biostatistik, datamining, immunology
- Budget
  - First 6 year period – 115+ mill DKr
    - Core-facility, infrastructure to run platform, guest researcher, ph.d. and post.doc
    - Head quarter: Øster alle 56, 5th floor
Main hypothesis and methods

- Among patients with compromised immune function,
  - pattern of not-yet identified risk factors exists that
  - explains variation in risk of developing infections

- Methods:
  - Pattern recognition of “big data” collected as part of routine care,
  - Host and microbial genetic analyses,
  - Immunological characterisation,
  - Imaging incl tracer technology
Mission

• Identify *novel* host defence mechanisms, and the *pattern* of novel and already known mechanisms that best *explains* the *variation* in contracting infection(s)

• From this formulate “*immunodeficiency indices*”
  – Capture knowledge of this variation
  – Validated prospectively
  – Used for further individualise care
Why focus on immunodeficiency?

• Epidemic due to medicines - societal impact enlarging
• Ideal population for basic science model
  – “Stress-test” of host defence
    • If pre-existing weakness exist earlier to identify (signal-to-noise ratio highest)
  – In care – data re known mechanisms collected systematically
    • Allows for controlling in statistical analyses when evaluating possible novel mechanism(s)
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
  due to extended infection-related inflammatory state

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

Risk of contracting these diseases varies across populations of immunodeficient persons
PERSIMUNE can do more than its mission

- Data warehouse (routine data & data generated by PERSIMUNE, external data incl national registries) for other research purposes
- Routine care (e.g. MATCH, antibiotic stewardship)
- Improved microbiological diagnostics
The 3 pillars of PERSIMUNE

- Immune Deficiency Index
- Discover novel markers of immunodeficiency
- Prediction of infectious phenotype
Main PERSIMUNE methods mission

- Transform a tertiary-referral hospital to a research platform
  - Multiple types of immunodeficiency patients cared for
  - Ensure PERSIMUNE requirements are met
    - Large patient sample
    - Able to ascertain infectious phenotype
      - Infrastructure to capture relevant patient information (MATCH)
      - Diagnostic technology state-of-the-art
    - Central biobank facility
    - Long-term and diverse scientific interest by all relevant stakeholders
PERSIMUNE cohort

• Prospective cohort
  – Consecutive persons seen for care at RH after 1st March 2015 (or later time point) that contribute to PM biobank
    • As per agreement with clinical departments
• Retrospective cohort
  – Consecutive persons seen for care at RH before 1st March 2015
    • As per agreement with clinical departments
MATCH cohort

• Consecutive transplant recipients since 2004
• Retrospectively included if transplanted before 2011
• Prospectively included from Oct 2011
• Biobank structures available
What is an immunodeficient patient?
Some more obvious than others

Patient groups w/ known for excess risk of infection(s)
• Immunosuppressive medicine (tx recipients, cancer etc)
• Anti-inflammatory medicine (autoimmune diseases)
• Defects in immune host defence (e.g. T-, B-dysfunction, HIV-infection)

• Defects in non-specific host deference (e.g. CF, dialysis)

Individuals with
• unexplained
• marked increased risk of infection
• healthy family members with accessible DNA
How do clinical departments enrol patients?

• Prospective
  – Register consecutive patients in selected groups in PM data warehouse
    • Order level 1, 2 or 3 PM LABKA package
    • Enter additional patient-group specific routine/research data

• Retrospective
  – Provide list of CPR numbers of patients to enrol to CORE (minimal requirement)
    • Provide additional patient-group specific routine/research data to PM data warehouse
    • Identify existing biobank
PERSIMUNE LABKA packages / biobank

- **Niveau 1** (cost to clinical departments: 255 kr.)
  - B-Hæmoglobin
  - B-Leukocyttet
  - B-Leukocyt differentialtælling
  - B-thrombocyttet
  - P-CRP
  - P-Glucose
  - P-Karbamid
  - P-kreatinin
  - P-Kalium
  - P-Natrium
  - P-Albumin
  - P-LDH
  - P-ALAT
  - P-Basisk phosphatase
  - P-Billirubiner
  - P-Koagulationsfaktorer/INR
  - Biobank-prøve (payed by PERSIMUNE)
  - If admitted: blood for culture (costed separately)

- **Niveau 2** (cost to clinical departments: 255 kr. + 676 kr.)
  - Niveau 1 + T, B, NK celletal + immunoglobuliner + P-ferritin

- **Niveau 3** (cost to clinical department: similar to Niveau 2)
  - Niveau 2 + living cells stored in PM biobank
PERSIMUNE biobank

- Finite budget for number of samples to collect per year
- Factors to consider when deciding on which patient groups that contribute and frequency of sampling
  - Clinical departments willingness to enrol
  - Priority of available patient groups relative to their size and PM mission
    - Overall
    - Specific projects
**PERSIMUNE patient groups (1)**

<table>
<thead>
<tr>
<th>Klinikken er indstillet på at inkludere følgende patientgrupper i PERSIMUNE (aflysting kan ske med mellemrummet)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patientgruppe 1</strong>, beskriv:</td>
</tr>
<tr>
<td>Antal patienter under aktivt opfølgning i denne patientgruppe:</td>
</tr>
<tr>
<td>Hvor ofte ses patienter rutinemæssigt i denne gruppe i Klinikken?</td>
</tr>
<tr>
<td>På hvilke tidspunkter foreskr. klinikken der tages prøver svarende til Niveau 1° på patienter i denne gruppe?</td>
</tr>
<tr>
<td>På hvilke tidspunkter (om nogen) foreskr. klinikken der tages prøver svarende til Niveau 2° på patienter i denne gruppe?</td>
</tr>
<tr>
<td>Klinikken indgår i som minimum at tage Niveau 1° analyser for disse patienter ved inklusion og derefter en gang årligt</td>
</tr>
<tr>
<td>Klinikken har som led i sin rutine, resultater fra følgende specialanalyser** ud over Niveau 1° &amp; 2° tilgængelige:</td>
</tr>
<tr>
<td>Typer af analysen:</td>
</tr>
<tr>
<td>Analyseforretningsvis:</td>
</tr>
<tr>
<td>Klinikken har selv hogedata på disse patienter samlet i en database (ud over rutinedata):</td>
</tr>
<tr>
<td>Beskriv mulighed for at overføre data elektronisk til PERSIMUNE platformen:</td>
</tr>
<tr>
<td>Ansigt antal nye patienter henvis om året i denne patientgruppe:</td>
</tr>
<tr>
<td>Ansigt antal identifikationskonsekvens patienter henvis indtil nu (fx sidste 4 år):</td>
</tr>
<tr>
<td>Klinikken har oversigt over disse patienter, og hvis ja, hvilke dataelementer ud over CPR findes lokal?</td>
</tr>
<tr>
<td>Omsætter tilgængelige data henvisnings- tidspunkt****:</td>
</tr>
<tr>
<td>Klinikken har lokal biobank, for disse patienter samt ev. kan bruges i PERSIMUNE forskningsplatformen:</td>
</tr>
<tr>
<td>Hvilke data ønsker klinikken at have adgang til for denne patientgruppe i forskningsplatformen?:</td>
</tr>
</tbody>
</table>

| Klinikken ser individuelle patienter som lidet af genetiske eller epidemiologiske infektioner uden der er en velformået underliggende årsag (inkl. at familiemedlemmer er raske): |
| Eksempler på typer af individuelle patienter: |
| Antal under aktivt opfølgning: |
| Hvor ofte ses denne type patienter i Klinikken? |
| På hvilke tidspunkter foreskr. klinikken der tages prøver svarende til Niveau 1° på denne type patienter? |
| På hvilke tidspunkter foreskr. klinikken der tages prøver svarende til Niveau 2° på denne type patienter? |
| Klinikken indgår i som minimum at tage Niveau 1° analyser for disse patienter ved inklusion og derefter en gang årligt |
| Klinikken har som led i sin rutine, resultater fra følgende specialanalyser** ud over Niveau 1° & 2° tilgængelige: |
| Typer af analysen: |
| Analyseforretningsvis: |
| Klinikken har selv hogedata på disse patienter samlet i en database (ud over rutinedata): |
| Beskriv mulighed for at overføre data elektronisk til PERSIMUNE platformen: |
| Ansigt antal nye henvisninger om året: |
| Ansigt antal identifikationskonsekvens patienter henvis indtil nu (fx sidste 4 år): |
| Klinikken har oversigt over disse patienter, og hvis ja, hvilke dataelementer ud over CPR findes lokal? |
| Omsætter tilgængelige data henvisnings- tidspunkt****: |
| Klinikken har lokal biobank, for disse patienter samt ev. kan bruges i PERSIMUNE forskningsplatformen: |
| Beskriv mulighed for at have adgang til data: |

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**Danmarks Grundforskningsfond**

**Danish National Research Foundation**

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**Rigshospitalet**

**Faculty of Health and Medical Sciences**

**PERSIMUNE**

**Centre of Excellence for Personalised Medicine of Infectious Complications in Immune Deficiency**
# PERSIMUNE patient groups (2)

<table>
<thead>
<tr>
<th>Clinic</th>
<th>Section</th>
<th>Contact</th>
<th>Pt_Group</th>
<th>Actual_Follow</th>
<th>Referred_year</th>
<th>Routine_visits_freq</th>
<th>Level_1_anal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kirurgisk afd C</td>
<td>2124</td>
<td></td>
<td>Levertransplanterede</td>
<td>370</td>
<td>50</td>
<td>Ugentligt initialt i forløbet, som minimum en gang hver sjette måned</td>
<td>1</td>
</tr>
<tr>
<td>Nefrologisk afd P</td>
<td></td>
<td></td>
<td>Nøgrettransplanterede</td>
<td>756</td>
<td>100</td>
<td>Ugentligt initialt i forløbet, som minimum en gang hver sjette måned</td>
<td>1</td>
</tr>
<tr>
<td>Hjerte</td>
<td>2153</td>
<td></td>
<td>Hjertetranplanterede</td>
<td>113</td>
<td>18</td>
<td>Ugentligt initialt i forløbet, som minimum en gang hver sjette måned</td>
<td>1</td>
</tr>
<tr>
<td>Lunge</td>
<td>2154</td>
<td></td>
<td>Lungetransplanterede</td>
<td>207</td>
<td>29</td>
<td>Ugentligt initialt i forløbet, som minimum en gang hver sjette måned</td>
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</tr>
<tr>
<td>Hæmatologisk</td>
<td>4041</td>
<td></td>
<td>Knogle marvstransplanterede</td>
<td>689</td>
<td>105</td>
<td>Ugentligt initialt i forløbet, som minimum en gang hver sjette måned</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinic</th>
<th>Section</th>
<th>Level_2_anal</th>
<th>Add_anal</th>
<th>Add_anal_freq</th>
<th>Local_DB</th>
<th>Retrosp_number</th>
<th>Retro_DB</th>
<th>Refer_date</th>
<th>Local_biob</th>
<th>Return_data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kirurgisk afd C</td>
<td>2124</td>
<td>Y/N</td>
<td>Text</td>
<td>#/month</td>
<td>Y/N</td>
<td>Number</td>
<td>Y/N</td>
<td>Y/N</td>
<td>Y/N</td>
<td>Text</td>
</tr>
<tr>
<td>Nefrologisk afd P</td>
<td></td>
<td>Y/N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hjerte</td>
<td>2153</td>
<td>Y/N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Lunge</td>
<td>2154</td>
<td>Y/N</td>
<td></td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Types of PM projects

- a) those financed directly by funding from DNRF incl all projects that uses the PM biobank;
- b) projects within the PM mission statement that are funded by PM co-funding from other sources;
- c) other projects than those mentioned under a) and b) but which uses data collected via the PM centre.
# PERSIMUNE project funding and access to data

<table>
<thead>
<tr>
<th>Funding category</th>
<th>Authorship rules</th>
</tr>
</thead>
</table>
| a) Projects, fully or partly financed by the DNRF grant  
  o Incl. all projects that uses the PM biobank | Approved by the Executive Committee after review by the Scientific Advisory Board  
  o Collaborators providing data will receive proposal for consultation  
  o Collaborators participate in project group  
  o Project groups decide authorship ranking based on the ICMJE criteria |
| b) Projects within the PM mission statement, funded by co-funding from other sources |  |
| c) Other projects than those mentioned under a) and b) using data collected via the PM Centre | The Executive Committee is informed about the project  
  o One or more collaborators use own data  
  o Extraction of data by the PM Centre based on documented, relevant approvals from authorities |
Composition of PERSIMUNE structures

• Leadership
  – Centre leader
  – Two additional representing clinics and research

• Executive committee
  – Leadership + two from each of (rotation biannually)*
    • Clinical
    • Research
    • External collaborators

• Scientific advisory committee**
  – Mixture of scientists from RH and external

• Scientific interest groups
  – Leadership**
    • Topic experts
  – Membership
    • Open to all relevant persons interested

*: based on nominations from constituency
**: mixture of junior and senior expertise
Responsibilities of structures in PERSIMUNE

• Centreleadership
  – Overall responsible for centre’s functions
    • CORE: infrastructure, budget, etc
    • Infrastructure groups: datamanagement, biobank, statistics
  • Executive committee
    – Decides on strategic direction
      • Priority of research projects using DNRF funding
      • Patient groups that contribute to PM biobank
    – Approve category a) and b) projects
      • Scientific advisory committee; recommend priority of a) and b) projects
    – Forms topics and leadership of scientific interest groups
• Scientific interest groups
  – Forums for scientific discussion
  – Topics (Feb 2015): “host genetic, microbial genetics, imaging, MATCH, neutropenia fever, microbial diagnostics, acquired immunodeficiency, non-infectious endorgan disease, cancer”
• PERSIMUNE Immunology meeting series
  – Regular scientific meetings
  – Responsible for program planning: scientific interest groups
How to make PERSIMUNE successful?

• Collaboration in collegial atmosphere aimed at scientific excellence
• Scientific activities part of one platform
  – Supplementary (but not interfering)
  – Coordinated
  – Utilise “scientific upgrades” provided by PM
• Acknowledge PM in scientific presentations and publications and inform CORE
Any project (a-c) acknowledge DNRF support by inserting:

**Study supported by grant [grant number DNRF126] from the Danish National Research Foundation**

in funding section of publications and in acknowledgement section of slides/posters
How to get involved

• Department level
  – Include relevant patient groups
    • Prospectively
      – Contribute to PERSIMUNE biobank
    • Retrospectively re-creation
      – Possible contribution from existing biobank structures

• Individual level
  – Become member of one or more “scientific interest groups”
  – Lead/contribute to scientific projects
  – Stay informed via
    • Website: www.PERSIMUNE.org
    • Twitter: @PERSIMUNE
    • Facebook: https://www.facebook.com/PERSIMUNE
Research platform: "un-recognised invasive infections"

- Febrile syndroms with “unknown microbiological explanation”
  - Frequent
  - Severe
  - Empiric antibiotic therapy
  - Underlying reason
    - Invasive infection
      - Microbiological techniques unable to identify
      - (most probable bacterial or fungal pathogens)
    - Non-infectious
- Initial core PERSIMUNE platform
  - Required to classify suspected “cases”
One-year mortality stratified according to MELD-score at day 10 post-livertransplantation

MELD score = 3.78[Ln serum bilirubin (mg/dL)] + 11.2[Ln INR] + 9.57[Ln serum creatinine (mg/dL)] + 6.43

Rostved et al, 2014
The MATCH concept

- Harmonised and systematic monitoring of transplant recipients for emerging viral infections
- Monitoring plans titrated depending on individual risk assessment
  - Donor-recipient virology, type of transplantation, viral kinetics, other risk factors
- Intense monitoring frequency during periods where a priori risk is high
- Aim: diagnose infections prior to symptom debut
- Made possible by construction of real-time updated data warehouse and “intelligent” software programming
  - + biobank and data warehouse also used for research
Severity of CMV infection at the time of diagnosis and CMV related hospital admission rates

- CMV-related admission
- Severe (≥ 30,000 cps/mL)
- Moderate (10,000-29,999 cps/mL)
- Mild (< 10,000 cps/mL)

Year of transplantation:
- 2007-2008: 46% (4% severe, 15% moderate, 34% mild)
- 2009-2010: 53% (12% severe, 29% moderate, 12% mild)
- 2011-2012: 90% (14% severe, 4% moderate, 6% mild)

MATCH program implemented

MATCH Study Group: Cunha-Bang et al,
UL97 amplicon sequencing of plasma samples during ganciclovir selection pressure

First time variants are detected by Sanger sequencing