Agenda

• PM data warehouse
• Datamanagement SIG
• How we work on standardization and QA
• What is in the data store and how do you get hold of it
  • Procedure for access to retrospective data
  • Procedure for access to prospective data
  • LabKey demonstration
• StudyManagement demonstration
Data sources for CPR-numbers in the PERSIMUNE data warehouse

**Prospective cohort**
- Filter: Consent in Labka
- Since 2015
- PM investigators
- 1,323 patients

**Oncology database**
- Filter: Referred to Dept. of Oncology
- Since 2004
- Gedse Daugaard
- 40628 patients

**Hematology**
- Filter: Referred to Dept. of Hematology
- Since 2005
- Henrik Sengeløv
- 12,309 patients

**MATCH cohort**
- Filter: Transplantation
- Since 2004
- Finn Gustafsson/Allan Rasmussen
- 2,901 patients

**Dialysis**
- Filter: Dialysis
- Since 2004
- Søren Schwartz Sørensen
- 1,567 patients

~56,000 Patients

Patients in the PERSIMUNE data warehouse

NB! Patients can come from more than one source

**Prospective patients – consent in Labka**
Current and future data sources in the data warehouse

**Demography and diagnoses**
- Sundhedsdatabanken (RegionH)

**Biochemistry**
- LabkaII (MedCom, RH)
- MedCom (Labka, national)
- Labka historic (RH)

**Imaging/Diagnostics**
- RIS (RH, HVH, BB, FRB)
- MedCom EKG (national)

**Oncology**
- Oncology (RH)

**Medications**
- EPM (RegionH)

**Microbiology**
- MedCom (MIBA, National)
- MADS (RH & MedCom)

**Pathology**
- MedCom (patobank, national)

**Vital signs**
- KISO (RegionH)

**Not yet included**
- LPR, CPR (awaiting all historic patients)
- DanSat CancerBiobank (OK’ed)
- Biobank (RegionH) (OK’ed)
- FMK / prescription database (RegionH)
- Laboratoriedatabanken (historical, exp. ultimo 2016)
- Vævstypelab & blodbanken (coll. agr. underway)
- HIV (Rigshospitalet, exp. April)
- Radiation data (under discussion)

**MEDCOM structure**
Overview of current data coverage in PM data warehouse

- **Pathology**: (N)
- **Imaging/Diagnostics** (RH, HVH, BB, FRB)
- **Oncology**: (RH)
- **Medications**: (RH)
- **Vital Signs**: (RegionH)
- **Demography and diagnoses** (RegionH)
- **Biochemistry** (N, RH)
- **Microbiology** (N, RH)

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PM data management SIG

- **Meetings once a week**
- **Agenda**
  - Data acquisition status
  - Biochemistry and Demographics
  - Microbiology
  - Medications
  - Next steps

- Michael M Madsen
- Theis Aagaard
- Boje K Ehmsen
- Marie Hellesberg
- Pernille Iversen
- Jesper Grarup
- Charlotte Matthews
- Casper M Frederiksen
- Erik V Hansen
How we work on standardization and QA

Potential problems

- Different units
- Method variation across labs
- Time/Laboratory gaps

Quality of data
- Missing values
- Duplicates
- Non-numeric values
- Normal Values change over time or lab (systematic or machine errors)
- Coding and naming

How we work on standardization and QA

Top-down
- Data structure analysis
- Data mapping
- Frequency analyses
- Result values over time by lab

Bottom-up
- Patient specific source data comparison
- Variable analyses on subset from data table

Solicit help from our friends:
- MiBa
- RH KBA
- KEA
- Sundhedsdataprogrammet

YOU
PM Date
Warehouse

DWH
Admin. Group

Data issues/corrections

Project A dataset

Corrected data

Project B dataset

Corrected data

Project C dataset

Corrected data

What is in the data store – examples

Demography and diagnoses
- Patient vital status
- Periods of contact
- Contact section
- Diagnoses

Imaging/Diagnostics
- Scan date
- Res code
- Description of findings

Medications
- Medicine, dose, time
- Dose modifications
- Route of administration
- Administrations

Pathology
- Description of findings
- Histology with SNOMED codes

Biochemistry
- Analysis identifiers
- Result values, intervals, units
- Time stamps
- Lab IDs

Oncology
- Diagnosis
- Treatment type, dose, dates
- Date of death
- Height, weight

Microbiology
- Assays for bacteria, virus, fungi, protozoa and parasites
- Antibiotics susceptibility

Vital signs
- Temperature
- Pulse
- Blood pressure
- Height, weight
When are Data available?

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<td>Datasets for subsets of the historic analysis can be requested via the PM proposal route</td>
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Procedure for access to data

- Currently data are collected and stored in the approved patient care database
  - Data protection approval: Umbrella no. 2007-58-0006, local approval no. RH-2015-04, with I-Suite no: 03605
  - Web interphase for departments to view own data under development

- Data for research purposes
  - Analysis of historic data
    - Broadly worded approval from Sundhedsstyrelsen (no. 3-3013-1060/1)
    - Broadly worded approval from the Data protection agency
    - Umbrella no. 2012-58-0004, local approval no. RH-2016-47, with I-Suite no. 04433
    - Datasets for subsets of the historic analysis can be requested via the PM proposal route
  - Analysis for specific projects outside the historic analyses
    - Already individually approved: TRIO, Liver tx, EBV, CLL projects
    - Data access for new projects via the PM proposal route
  - Feasibility request form for researchers to investigate the feasibility of planned research – form under development
  - Data request form for researchers and PM DWH group to agree on data elements, formats and required regulatory permissions
LabKey: The PERSIMUNE Collaboration and Analysis platform

StudyManagement demonstration
Study Management demonstration

Edit Flow - PERSIMUNE

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<td>2015-09-05</td>
<td>Approved</td>
<td>2015-09-11</td>
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<td>2015-10-03</td>
<td>Deadline for enrollment of the first 20 patients</td>
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Back | Add New From Step | Report | Insert all missing Revenues

SIG documents

Development of an immunology characterisation platform that provides different levels of in-depth state-of-the-art assistance tailored to prospective analyses of immune phenotype and function. To be implemented both in the clinical routine at Rigshospitalet and in JMRI projects.

The immune phenotype analysis comprises a 10 color fluorescence flow cytometry panel that in details characterises B cells, T cells, NK cells, TFH cells, Th1 cells, dendritic cells, myeloid cells, plasmablasts, functional subsets (evaluation of flowkly blasts) and neoplastic lymphocytes (identification of neoplastic E-cells). Focus will be on pathologic patterns of cell mediated: activation, exhaustion, migration potential and/or exhaustion.

The immune function analysis comprises two different analyses. Whole blood stimulation by e.g. TrueCulture™ tubes, assessing parasite function of memory cells and whole blood functional immunoassay by TOEIA and MethylBlot, assessing immune rheostatics and plated function. Focus will be on T cell, myeloid cell and platelet peripheral function and immune aggregates in vitro formation (platelets).

In addition, the immunology characterisation includes assessment of circulating biomarkers.
SIG documents

Confidential Documents

- Minutes Immunology SIG meeting 28th October 2019
- Minutes Immunology SIG TC with IFM Mira Hean 10th November 2019
- Minutes Immunology SIG meeting 11th January 2016
- PERSIMUNE Retreat February 2016, Presentation Immunology SIG

Publications of Interest

Proposal and project documents
MISPCAMP 2015
mispcamp.org

MODELING AND DATA ANALYSIS FOR THE HEALTHY HUMAN GLOBAL PROJECT
Deep phenotyping of the world’s population research camp
PUNTA DEL ESTE, URUGUAY, DECEMBER 14-17TH, 2016

MISP Research Camp
The Precision Medicine Revolution
People by Country

People by Institution

Total participants: 44
Group A – Modeling immune system

Group B – Virus evolution and adaptation

Group C – Virus and vector interactions, codon usage

Group D – Molecular components of psoriasis
The Precision Medicine Revolution

Para conocer la visión de expertos acerca del futuro de la medicina.

Viernes 18 de diciembre | De 16 a 21 horas | Sala Verdi - Soriano 914
Cupos limitados. Acceso por invitación.

Por más información: pmr@pasteur.edu.uy | www.mispcamp.org
The Precision Medicine Revolution
Feedback from workshop in Uruguay

MISP2015

Al Cozzi-Lepri
Marie Helleberg
Rasmus Lykke Marvig
Sisse Rye Ostrowski
## Agenda MISP Research Camp

### Sunday, December 13th
10:00 - 10:15  
Opening session

### Monday, December 14th
10:00 - 12:30  
Welcome/Introduction by Sisse Rasmussen and Marie & AI

<table>
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<tr>
<td>12:30 - 15:30</td>
<td>Molecular phenotyping link genetic patterns to biological processes (Group C)</td>
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<tr>
<td>15:30 - 17:30</td>
<td>Molecular phenotyping link genetic patterns to biological processes (Group C)</td>
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### Tuesday, December 15th
10:00 - 12:00  
Modelling immune response - representative models of the immune system

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<td>10:00 - 12:00</td>
<td>Modelling immune response - representative models of the immune system</td>
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<tr>
<td>12:00 - 12:15</td>
<td>Data for generating models of immune system (how do you measure?)</td>
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### Wednesday, December 16th
10:00 - 10:30  
Introduction to complex network

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<td>Introduction to complex network</td>
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<td>11:30 - 12:00</td>
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### Thursday, December 17th
10:00 - 11:00  
Network analysis I: Co-expression analysis of different systems

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<td>Network analysis I: Co-expression analysis of different systems</td>
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<tr>
<td>11:00 - 12:00</td>
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### Friday, December 18th
10:00 - 11:00  
Network analysis II: Time series analysis

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<td>Network analysis II: Time series analysis</td>
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### MISP talks

MISP talks are open to participants of the Research Camp but they are separated from the main organization of the course. Please check the official website for timezone differences.

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<td>MISP talk: The Data Challenge Teams (Group A)</td>
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<tr>
<td>14:00 - 14:30</td>
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### MISP15

MISP15 is the 54th international conference on interaction between in-house and open source software development.

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### Life Sciences

Contact us | Creative Commons license | people | 0522 is permitted | user 1234 is allowed... |
Agenda MISF Research Camp

Sunday, December 18th

19.00 - 21.00
Guides and dinner

Monday, December 19th

11.00 - 13.00
Welcome presentation
  - Agnes Harens, Cox Hithkin and new (Erlkoenig)
13.00 - 15.30
DNA data simulation in open space and times landscapes (Group 8)
  - Mauro Pygaglio
13.30 - 15.30
Molecular phenotyping link genetic patterns to biological proxies (Group C)
  - Agus Sudarono
15.45 - 17.30
Classifying molecular components at present and impact on treatment through
  personal, individual sampling and immune-phenotyping (Group 9)
  - Agus Sudarono
17.30 - 18.30
Leaves, leaves, and how to analyze leaves and apples (Group 1)
  - Abuja Mustapha and Adekunle Adewol
18.30 - 19.30
Dinner

Tuesday, December 20th

09.00 - 10.30
DNA and RNA data (Group 1) and introduction of clustering in R
10.30 - 12.00
Python
12.00 - 12.15
The best basic algorithm for selection of significant-independent variables
  - Comrade Comrade
12.30 - 13.30
Statistical genetics for the development of association models
  - Comrade Comrade
13.45 - 15.00
Statistical methods: selecting the role of genetic polymorphisms across populations with
  Simulated genome function
  - Agus Sudarono
14.30 - 15.45
Machine learning and computer vision
15.00 - 15.15
Break
15.15 - 16.45
Statistical methods: selecting the role of genetic polymorphisms across populations with
  Simulated genome function
  - Agus Sudarono
16.45 - 18.00
Presentation Group B
18.00 - 18.15
Networking
19.00 - 20.30
Dinner

Wednesday, December 21st

11.00 - 12.45
DNA and RNA data (Group 1) and introduction of clustering in R
12.45 - 14.15
Python
14.15 - 15.15
Presentation Group A
15.15 - 16.45
RNA
16.45 - 17.15
Presentation Group B
17.15 - 18.45
Networking
18.45 - 20.00
Dinner

MISP talks
The MISP talks are open to participants of the Research Camp but they are separated from the main organization of the course. Please check the official website for more information.

Friday, December 23rd

09.00 - 09.30
The Precision Medicine Revolution – MISP talks

PERSIMUNE

University of Health and Medical Sciences

17-02-2016
LabEx Milieu Intérieur
Establishing the genetic and environmental determinants of immune phenotype variation

Modeling Human Immune System

The Milieu Intérieur project is an ambitious experimental study, the objective of which is to elucidate the interactions between genetics and environment and their impact on the immune system. To enable this goal, we have developed and implemented standardized tools for studying leukocyte immune responses in whole blood against a diverse panel of stimuli, including various antigens and cytokines. This approach allows us to decipher the interactions between genetics and environment on the immune system and provides new insights into the complex biology of immunity.
Risk model for febrile neutropenia

Risk model for invasive fungal disease
Short- and long-term complications

Individualized daily routine treatment circuit
What are the implications?
Project 1: Dysbiosis of the gut microbiome before, during and after initiation of treatment

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<td>Dysbiosis</td>
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Project 1a → Project 1b → Outcomes
ALL ANIMALS ARE EQUAL
BUT SOME ANIMALS ARE
All animals are equal but some animals are more equal than others.
All immunodeficiencies are equal

but some immunodeficiencies are more equal than others

Patient related risk factors
- Age
- Sex

Treatment related risk factors
- Immunosuppressive therapy
  - CNI
  - mTOR inhibitors
  - Antimetabolites
- Induction therapy before transplantation

Transplant related risk factors
- Type of Tx
- Donor/recipient CMV serostatus
Hypothesis - Immunosuppression score (ISS)

The relative potency of immunosuppressive drugs can be estimated by assessing the risk of CMV viremia and CMV disease in HSCT and SOT recipients treated with different immunosuppressive drugs in analyses adjusting for known risk factors for CMV.
PERSIMUNE hypothesis

Common patterns exists that can reliably predict the risk of developing infectious phenotypes across populations with impaired immune function

Data to be considered
- demographics,
- clinical history,
- therapeutic interventions,
- immune function,
- host genetic,
- composition of the microbiota
- imaging-identifiable subclinical processes
PERSIMUME
Immunologic characterization panel

• A real-time state-of-the-art in-depth immunologic characterization panel for implementation both in daily clinical routine at Rigshospitalet and in PERSIMUNE projects …

Immune PHENOTYPE
Immune FUNCTION
Plasma BIOMARKERS
Immune phenotype

[10-color whole-blood real-time flow cytometry panel]

Secondary immunodeficiency

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<td>CD3</td>
<td>CD5</td>
<td>CD27*</td>
<td>PD-1L*</td>
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violet laser 405 nm excitation
blue laser 488 nm excitation
red laser 633 nm excitation

Neutrophil phagocytosis: Real-time FC detection of engulfed fluorescent E. coli (pHrodo™ BioParticles®)
Erythrocytes, functional asplenism: Real-time FC detection of Howell-Jolly bodies

Major NK, B, CD4+ and CD8+ T cell subsets
maturation-, activation-, exhaustion- and migratory potential patterns

DC and myeloid cells
subsets/subtypes and activation pattern

Custom-designed multicolor cocktail tubes/panels
Lyophilized (freeze dried) antibodies
Optimized, titrated and qualified by the manufacturer
Provides standardized and robust analysis and data readout
Flow cytometry
Status, challenges & plan

- **Status**
  - Finalized testing of flow cytometry combination tubes within weeks
  - Input from and discussions with Institute Pasteur/Milieu Intérieur
    - Currently the flow cytometry panel is in external review by European ID experts

- **Challenges**
  - Development of a data analysis platform for daily clinical and research (PM) use
  - Convince RH administration/clinicians of the clinical value of rtFC as a tool to
    - Open the “black box” and reveal immunodeficiency (in the start-up phase)
    - Risk stratify patients and guide therapy (later on)

- **Plan**
  - Validation of the new panel in Q1/2016 by
    - Comparing ~100 immunodeficient patients analyzed by old and new panel
    - Analyzing ~100 healthy blood donors and blood donor children (extended to other analyses conducted in PERSIMUNE)
  - Collaboration between RH/PM/MF to develop a data analysis platform
  - Convince RH administration/clinicians that rtFC is a must have
CMV specific T cell immunity
[Risk-stratification after solid organ TX and allogenic SCT]

- Post-transplant patients are at risk of CMV infection and/or reactivation:

<table>
<thead>
<tr>
<th>CMV status</th>
<th>CMV risk</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>D- / R-</td>
<td>Low</td>
<td>Anti-CMV short-term prophylaxis</td>
</tr>
<tr>
<td>D- / R+</td>
<td>Moderate</td>
<td>Anti-CMV prophylaxis / VL monitoring (pre-emptive) / ??</td>
</tr>
<tr>
<td>D+ / R+</td>
<td>Moderate</td>
<td>Anti-CMV prophylaxis / VL monitoring (pre-emptive) / ??</td>
</tr>
<tr>
<td>D+ / R-</td>
<td>High</td>
<td>Anti-CMV long-term prophylaxis</td>
</tr>
</tbody>
</table>

- Lack of CMV specific T cell immunity in the early (first weeks) and late (first months) post-transplant period is associated with early and late infection/reactivation of CMV
- Post-transplant CMV immunity monitoring may be a tool to risk stratify patients and hereby further optimize post-transplant care
CMV specific T cell immunity
Status, challenges & plan

• Status
  – Different methodologic platforms under review (QuantiFERON-CMV preferred)

• Challenges
  – Decide post-transplant CMV non-response cut-off values and sampling time-points for CMV immunity assessment
  • Use cut-offs recommended by manufacturer?
  • Use sampling time-points according to previous studies?

• Plan
  – (Select), setup and validate CMV immunity assay
  – Prospective investigation of (selected) post-transplant patients
    • Treatment algorithms?
  – Establishment of clinical and laboratory CMV monitoring interest group
  – Implementation in clinical daily routine
Induced immune response
[paracrine function of whole blood immune cells]

Simple, reproducible and easy-to-use
WB cultures better than PBMC reflects in vivo complexity
(T-, B- and NK cells, dendritic cells, myeloid cells, granulocytes, platelets, erythrocytes, co-aggregates, microparticles, plasma)
Provides standardized and robust analysis and data readout

TruCulture®
Status, challenges & plan

• Status
  – Some stimulants and incubation time have been suggested
    • NULL, LPS, anti-CD3/CD28 (more?)
    • 22h incubation (shorter?)

• Challenges
  – Snapshot of bulk whole blood stimulation and concurrent bystander activation
    that is highly dependent on the stimuli and incubation time

• Plan
  – Dialogue with Institute Pasteur/Milieu Intérieur about optimal stimuli and incubation times
Immune thrombosis
[WB hemostasis, platelet paracrine function & phenotype]

- Functional hemostatic whole blood tests
  - Primary hemostasis = platelet aggregation (Multiplate®, impedance aggregometry)
  - Secondary hemostasis = clot formation (TEG®, viscoelastic hemostatic assay)
- WB stimulation [TruCulture®] w/platelet derived biomarkers
- Platelet phenotype [Flow cytometry]

Thrombosis is an intravascular effector of innate immunity and platelets are specialized cells of the innate immune defense and modulators of inflammation
Immune thrombosis
Status, challenges & plan

• Status
  – TEG® and Multiplate® are real-time analyses already running 24/7 in daily clinical routine
  – TruCulture® technology – under discussion
  – Flow cytometry – under development

• Challenges
  – Convincing clinicians of the clinical value of real-time immune thrombosis and platelet function/phenotype?

• Plan
  – As for flow cytometry and TruCulture® techniques
  – Immune thrombosis and platelet function/phenotype assessed initially in research project(s)
Plasma biomarkers

• Circulating levels of biomarkers [*cytokines, chemokines, growth factors and their soluble receptors, injury/death markers and vascular adhesion molecules etc.*] reflect the *in vivo* magnitude of tissue, blood and immune cell activation and/or damage

• The selection of biomarkers in PERSIMUNE depends on a priori hypotheses and expected association(s) between these and other data collected

Implementation?
# Implementation - in PERSIMUNE projects

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generate data &amp; evidence</td>
<td>Methodology under development</td>
</tr>
<tr>
<td>Broad immunologic characterization: Phenotype, function and biomarkers</td>
<td>New approaches</td>
</tr>
<tr>
<td>Individual/project relevant analyses</td>
<td></td>
</tr>
<tr>
<td>Basic to extended immunologic characterization</td>
<td></td>
</tr>
<tr>
<td>Flexible development &amp; optimization</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Opportunities</th>
<th>Threats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improve &amp; personalize monitoring, diagnosis, risk prediction and therapy</td>
<td>Economy</td>
</tr>
<tr>
<td>Define new state-of-the-art</td>
<td></td>
</tr>
<tr>
<td>High impact research</td>
<td></td>
</tr>
</tbody>
</table>

# Implementation - in daily clinical routine

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open a black box (get info)</td>
<td>Sparse evidence for secondary</td>
</tr>
<tr>
<td>Generate data &amp; evidence</td>
<td>immunodeficiency</td>
</tr>
<tr>
<td>Clinical implementation driven by PERSIMUNE projects</td>
<td>No current guidelines</td>
</tr>
<tr>
<td></td>
<td>Initial phase ~ research</td>
</tr>
<tr>
<td></td>
<td>Later phase ~ clinically relevant</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Opportunities</th>
<th>Threats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improve &amp; personalize monitoring, diagnosis, risk prediction and therapy</td>
<td>Economy</td>
</tr>
<tr>
<td>Define new state-of-the-art</td>
<td>Lack of understanding and</td>
</tr>
<tr>
<td></td>
<td>collaboration from clinicians</td>
</tr>
</tbody>
</table>
Thx
Update from I-SIG 😊

- Flow cytometry panel development, review and upcoming validation
- Upcoming discussions on the data analysis platform
  - Magnus Fontes 😊
- Ongoing discussions on how to disseminate a basic immune phenotype flow cytometry panel in the daily clinical routine
  - Initially implemented in selected groups e.g. solid TX and SCT patients
  - Dissemination plan under development
- Recent discussions on the unmet need in assessing CMV specific T cell immunity in post-transplant patients as a risk stratification tool
  - Several CMV assays are under review and will be investigated so a real-time assay can be implemented ASAP in the daily clinical routine
- Ongoing fruitful interdisciplinary discussions
The Microbiome

Building a platform
Sampling by patient group

PERSIMUNE Retreat, Feb 2016

Empiric observation

- Across populations exposed to comparable degree of immune impairment,
- Risk of infections varies markedly
- Mechanisms explaining this variation remains unclear

Main aim of PERSIMUNE

Identify mechanisms explaining this variation
PERSIMUNE hypothesis

A common pattern exists that can reliably predict the risk of developing infectious phenotypes across populations with impaired immune function.

Data to be considered:
- demographics,
- clinical history,
- therapeutic interventions,
- immune function,
- host genetic,
- composition of the microbiota,
- imaging-identifiable subclinical processes.
Low diversity is associated with higher mortality

Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota
Gut microbiota composition in HIV-infected VU subjects differs from that of HIV-uninfected risk-matched controls

Vujkovich-Cvijin
Science, 2013
Agenda

1. Implementation of sampling from HSCT recipients
2. PM microbiome time studies
3. Building a platform, sampling by patient group

Three key steps in implementation of fecal microbiome sampling

1. Decide sampling Schedule/Policy
   - HSCT fecal sampling schedule

2. Education
   - Staff
   - Patients
   - Microbiome-sample (snap freeze + Cottingham) also done when fecal culture indicated due to diarrhoea, which in HSCT patients is typically due to:
     - Drug side-effect (prophylactic mupirocin)
     - Pseudomembranous colitis
     - GV (graft-versus-host disease)

3. Set-up and logistics
Agenda

1. Implementation of **sampling** from HSCT recipients
2. PM **microbiome** time studies
3. Building a **platform**, sampling by **patient group**

Gut microbiome **perturbed** by treatment and impacts **outcomes**

<table>
<thead>
<tr>
<th>Before treatment \ T=0</th>
<th>During treatment \ T=1</th>
<th>After treatment \ T=2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gut microbiome</strong></td>
<td><strong>High diversity</strong></td>
<td><strong>High diversity</strong></td>
</tr>
<tr>
<td>High diversity</td>
<td><strong>Dysbiosis</strong></td>
<td>High diversity</td>
</tr>
<tr>
<td>Low diversity</td>
<td></td>
<td>Low diversity</td>
</tr>
</tbody>
</table>

Outcomes
**Outcomes**, Interventions, host-related factors, and the gut microbiome

**Interventions**
- Chemotherapy
- Immunosuppression
- Transplantation
- Antibiotics

**Before treatment**
- **T=0**
  - High diversity
  - Low diversity

**During treatment**
- **T=1**
  - High diversity
  - Dysbiosis

**Host factors**
- Underlying condition, comorbidities, age, genetics, etc.

**Clinical outcomes**
- Febrile neutropenia
- Blood stream infection
- Invasive fungal infection
- Graft or organ failure
- Other: C.diff, GvHD, etc.
- Mortality

**Gut microbiome perturbation differs by patient**

Taur
CID, 2012
**T=0** gut microbiome modulates impact of interventions

- T0
- T1

**Interventions**
- Chemotherapy
- Immunosuppression
- Transplantation
- Antibiotics

Project 1: Dysbiosis of the gut microbiome before, during and after initiation of treatment

- **Before treatment** (T=0)
  - High diversity
  - Low diversity

- **During treatment** (T=1)
  - High diversity
  - Dysbiosis

- **After treatment** (T=2)
  - High diversity
  - Low diversity

Outcomes

Project 1a → Project 1b → Outcomes
Minimum two fecal microbiome samples for **time studies**

- Under forundersøgelsen
- Transplantation
- 1 uge efter
- 2 uger efter
- 3 uger efter
- 4 uger efter
- 6 måneder efter

AND/OR

- Min. one sample in this interval
- Min. one sample at 3+ months

Several **outcomes** linked to **translocation** of gut contents

**Before** treatment
- High diversity
- Low diversity

**During** treatment
- High diversity
- Dysbiosis

**Clinical outcomes**
- Febrile neutropenia
- Blood stream infection
- Invasive fungal infection
- Organ failure or GvHD
- Other: C.diff, etc.
- Mortality
**Project 2: Dysbiosis → loss of barrier function → transient translocation** of microbes or microbe products

1. Transition to dysbiosis

2. Loss of epithelial/endothelial barrier function

3. Transient translocations

---

**Agenda**

1. Implementation of **sampling** from HSCT recipients

2. **PM microbiome** time studies

3. Building a **platform**, sampling by **patient group**
What **levels of collection** within PERSIMUNE?
By **patient group**?

<table>
<thead>
<tr>
<th>Level 1</th>
<th>Faeces</th>
<th>Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level x</td>
<td>Faeces</td>
<td>Blood</td>
</tr>
<tr>
<td>Level x</td>
<td>Faeces</td>
<td>Blood</td>
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<tr>
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<td>Faeces</td>
<td>Blood</td>
</tr>
<tr>
<td>Level x</td>
<td>Faeces</td>
<td>Blood</td>
</tr>
</tbody>
</table>

**Myeloablative Allo. Transplantation**
- Level x

**Nonmyeloablative Allo. Transplantation**
- Level x

**Autologous transplantation**
- Level x

**Other hematology patients**
- Level x

**Prostate cancer**
- Level x

**Bladder cancer**
- Level x

**Testis cancer**
- Level x

**Primary unknown tumor**
- Level x

**Solid organ transplant**
- Level x

<table>
<thead>
<tr>
<th>T=0</th>
<th>T=1</th>
<th>T=x</th>
<th>T=x</th>
<th>Diarrhoea</th>
<th>Fever</th>
</tr>
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<tbody>
<tr>
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</table>

**To be decided**

**Diagnosis**
- Hemodialysis
- Peritoneal dialysis
- Pediatric cancer
- Pediatric bone marrow transplant
- Pediatric arthritis biological treatment
- Pediatric infectious phenotype
- Hiv positive
- Cystic fibrosis adult
- Viral hepatitis
- Other immune deficiency
- Autoimmune hepatitis
- Sjögren’s syndrome
- Rheumatology systemic lupus erythematosus
- Rheumatology erosive arthritis associated vasculitis
- Rheumatology biological treatment

**True potential is in adding up sequence data**

What **levels of collection** should we do for each PERSIMUNE patient group?

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**PERSIMUNE**

**Centre of Excellence for Personalised Medicine of Infections and Complications**

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**Rigshospitalet**

**Faculty of Health and Medical Sciences**

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**PERSIMUNE Project 1**

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**PERSIMUNE Project 2**

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**PERSIMUNE Project 3**

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**PERSIMUNE Project 4**

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**PERSIMUNE Project 5**

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**PERSIMUNE Project 6**

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**PERSIMUNE Project x**

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Three advantages: PERSIMUNE platform