BT-Cure – Personalised Medicine and Rheumatoid Arthritis

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Cartilage destruction in rheumatoid arthritis (seen from the camera of Swedish photographer Lennart Nilsson)
RA is common and prevalence increases with age

Neovius, Simard & Askling for the ARTIS Study Group, ARD 2011
Disease development in arthritis – a life-long perspective is needed

Immune response develops

Pathologic inflammatory response

Genes

Environment

Symptoms

Subclinical inflammation

RA diagnosis criteria fulfilled

Time

Joint destruction

CV complications

Lymphomas

Infections

Osteoporosis
The natural (when un-interrupted) course of Rheumatoid Arthritis (RA)

- Normal
- Autoimmunity
- Unspecific disease signs
- Established RA
- Diagnosis by patient
- Diagnosis by physician
- Chronic destruction

Time and environment

Inflammation

Genes

Time and environment
An emerging understanding of molecular pathogenesis of RA

Immune response develops

Pathologic inflammatory response

Genes

Environment

Clinical onset

Complications
Comorbidities

time
An increasing number of targeted therapies

Immune response develops
Pathologic inflammatory response

CTLA4Ig
anti-CD20
Anti-IL-1

Anti-IL6R
anti-TNF
Methotrexate

Genes
Environment
Clinical onset

Complications
Comorbidities

time
Effectiveness of treatment – here work capacity
Much better than before, but not good enough

Days off per month

First RA diagnosis

- RA (mean)
- GenPop (mean)

Early RA registry
Sick leave registry

Neovius, Simard & Askling for the ARTIS Study Group, ARD 2011
Our patients have improved and have a much better life;
But treatment is expensive, potentially risky and prevention and cure is still lacking.
Challenges for translational medicine (here RA)

• Find causes of disease – *for prevention*

• Identify disease subsets, predictors for response etc – *for more effective and more personalised use of today’s treatments*

• Find molecular mechanisms of disease – *for new curative treatments*

• *We have to study humans and their entire life and disease history to address these questions*

• *We need to combine registers, biobanks and technologies from many partners*

*Europe has by far the best structure in the world to accomplish this*
BTCure's potentials -
What BTCure has to offer to the community

European centers of excellence in RA
Patient involvement
Partnership with pharma industry

Better predictability of effects and adverse effects of existing drugs
Better infrastructure and better trial designs
Combine academic and industrial research for new innovative diagnostics and therapies

Patients
Pharmaceutical industry
Clinicians and Researchers

April 2012
UCB research, Slough, UK
Karolinska Institutet
Leiden University Medical Center
University of Zurich
University of Leeds
Charité - University Medicine Berlin
Academic Medical Center/University of Amsterdam (AMC),
Medical University Vienna
Diakonhjemmet Hospital, Oslo
Universitätsklinikum Erlangen
University of Manchester
University of Glasgow
Stichting Katholieke Universiteit, Nijmegen
Agencia Estatal Consejo Superior de Investigaciones Científicas, (CSIC)

New partners:
Uppsala University, Athrogen (SME),
Biomedcode (SME)
GSK (EFPIA)

University hospital Montpellier CHRU
University College Dublin, NUID-UCD
Institute of Rheumatology, Prague
Fondazione Humanitas per la Ricerca, Università degli Studi di Milano, FHR

Biomedical Sciences Research Center “Alexander Fleming” (Fleming)
King’s College London, UK
Deutsches Rheuma-Forschungszentrum, Berlin
TcLand Expression, Nantes, France
Institut National de la Santé et de la Recherche M, INSERM, Paris
Bristol Myers Squibb
Janssen Biologics BV, Leiden, Netherlands
AstraZeneca
Boehringer Ingelheim Pharmaceuticals research
Pfizer
Novo Nordisk, Denmark
Merck Serono
Thermo Fisher Scientific
Biomedical Research Foundation, Academy of Athens, BRFAA

University of Oxford, UK
Engagement of patient and professionals from all over Europe

PATIENTS

– Contributions from PARE (People with Arthritis/Rheumatism across Europe)
– Contributions to strategy (Annual meetings)
– Contributions to science (Patient Research Partners in several countries)
– Contributions to dissemination of results (national and European patient organisations)

PROFESSIONALS

– Contributions from professionals (physicians/scientists others) via EULAR (European League Against Rheumatism)
– Contributions to science (via Eular committee meetings)
– Contributions to research education (via exchange programs in Europe)
– Contributions to dissemination of results (via National professional organisations)
Personalised medicine in arthritis: The mouse lesson; Many ways of getting and many ways of curing arthritis

- Anti-GPI Induced arthritis
- CIA in DBA/1 mice
- TNF- transgenic mice
- Cit- XXX induced arthritis in YYY mice
- IL-1ra -/- mice

[Diagram showing various types of arthritis models in mice]
Strategy 1: European Rheumatology registers; Patient-derived information used both in daily practice and in research

Investigations of:
- Causes of disease – genes and environment
- Prediction of disease and treatment
- Monitoring effects/adverse effects of treatment
- Molecular understanding of disease for future curative treatments
- Molecular understanding of disease for future personalised prevention

Case control studies
- Healthy controls
- RA Cases
- Register for early RA
- Register for new treatments

[Graph showing DAS (Median) from 1994 to 2018]
Strategy 2: 
Alignments of arthritis in humans with arthritis in animal models

Humans
- Defined genes
- Defined triggers
- Specific immunity

Rodents
- Defined genes, triggers & causative immune reactions

Development of arthritis

Specific treatments can be developed

Treatment and cure is possible/available
Autoimmunity in RA
Antibodies to citrullinated proteins/peptides (ACPA:s) are present in 60% of RA patients
Genetic and environmental risk factors for subsets of a complex disease (here RA)

Life time risk for disease

Genes

Environment/lifestyle
RA consists of two very different disease subsets, divided by presence/absence of ACPA:s

- SE+, PTPN22
- Smoking

Environmental stimuli, immune events and interventions should be studied separately in these two subpopulations of RA

Functions of identified risk genes indicate the importance of adaptive immunity

**Phenotype**

- ACPA +
  - More destruction

- ACPA -
  - Less destruction

**Onset of disease**

**ACPA +**

- IRF-5, C-type lectins
- Infections?

**ACPA -**
Implications for public health and prevention; Impact of smoking

- **Impact of smoking on RA as a whole:** 22% of all RA cases in Sweden would not have occurred if nobody had smoked.

- **Impact of smoking on "seropositive" RA:** 33% of all ACPA + RA cases in Sweden (1996-2005) would not have occurred if nobody had smoked.

- **Impact of smoking on those with risk genes:** 55% of all cases of RA in individuals with major susceptibility genes would not have occurred if nobody had smoked.

Källberg et al Ann Rheum Dis 2011
A model for an etiology of ACPA-positive RA

Genes and environmental factors

Immune response develops

Humoral immunity

ACPA

Synovial inflammation

Bone and cartilage destruction

Complications Comorbidities

Time

Joint destruction

MHC class II

CP

TCR

Activated T cells

Activated B cells

ACPA

T

B

RF

Mφ

Activated macrophages

Imune complex formation

Lancet Feb 21, 2009; Seminars in Immunology 2011; 23: 92-98
Implications for personalised therapies
Which treatment should be chosen for which patient?
Several biomarker projects ongoing

- CTLA4lg
- anti-CD20
- Anti-IL-1
- Anti-Il6R
- Anti-TNF
- Methotrexate

Immune response develops
Pathologic inflammatory response

Genes → Environment → Clinical onset

Complications
Comorbidities
One example: Rituximab (targets B cells with anti-CD20 antibodies) works best in seropositive (ACPA and RF) positive patients (reflected in indication)

**REFLEX study**

<table>
<thead>
<tr>
<th>RF positive</th>
<th>RF negative</th>
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<tbody>
<tr>
<td>Rituximab 2 x 1000 mg (n=234)</td>
<td>Rituximab 2 x 1000 mg (n=64)</td>
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</table>

- ACR20
- ACR50
- ACR70

**DANCER study**

<table>
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<th>RF positive</th>
<th>RF negative</th>
</tr>
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<tbody>
<tr>
<td>Rituximab 2 x 1000 mg (n=122)</td>
<td>Rituximab 2 x 1000 mg (n=63)</td>
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- Placebo-adjusted ACR responses

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*Placebo-adjusted ACR responses*
Main Results (also when including "omics"): Current smoking is the most important determinant for bad response.

Use of registries and associated biobanks to analyse:
- Clinical characteristics
- Pharmacogenomics
- Biomarkers
- Environment/life style factors

Saevarsdottir S et al, Arthritis & Rheumatism, 2011
Also adverse events are “personal”
Estimated annual incidence of serious infections in RA by treatment and risk profile

A major project within BTCure
Understand and predict what may happen when patient first recognize a problem

Time and environment

Inflammation

Established RA

Unspecific disease signs

Autoimmunity

Normal

Diagnosis by patient

Diagnosis by physician

Chronic destruction

genes

30 40 50 60
Days Off Work in relation to Diagnosis per Month

RA (mean)
GenPop (mean)

Months in Relation to RA Diagnosis

Neovius, Simard & Askling for the ARTIS Study Group, ARD 2011
Detection of autoimmunity (ACPA) before clinical onset of disease
(a chip assay for ACPA:s being developed within the BTCure collaboration)

Collaboration with PhaDia within the IMI BeTheCure project
Hansson, Rönnelid et al ART Oct 2012
Presence of different ACPA:s before onset of disease

Years before diagnosis

RA diagnosis

New innovative therapies

Example 1 (ongoing investigator-initiated clinical trials)
• Treatment with anti-CD20 in ACPA-positive individuals at very high risk for future RA (Amsterdam and more)
• Treatment with anti-IgE in individuals with IgE ACPA:s (Leiden)

Example 2 (works in mice, planning ongoing for patients)
• Vaccination to re-regulate RA-specific autoimmunity (KI and more) – with ”companion diagnostics”
• siRNA- based immunotherapies (several academic partners and Arthrogen)
The challenge
Personalised early therapy and personalised prevention

Immunomodulation

Established RA

Unspecific symptoms

autoantibodies

normal

Inflammation

Time and environment

30 40 50 60

Chronic destruction
Chronic treatment
Repair
Cured