Innovative Medicines Initiative

BT-Cure – Personalised Medicine and Rheumatoid Arthritis

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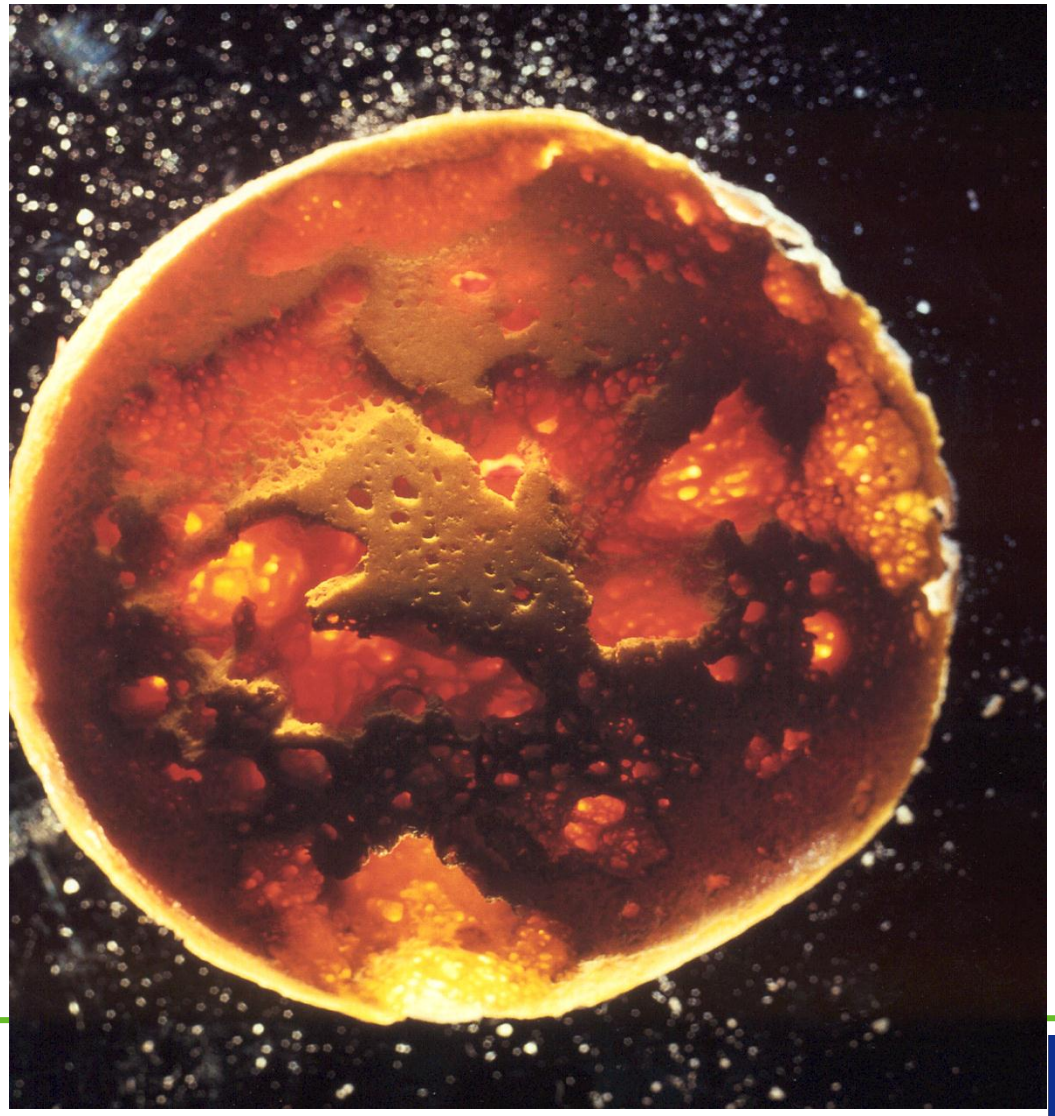
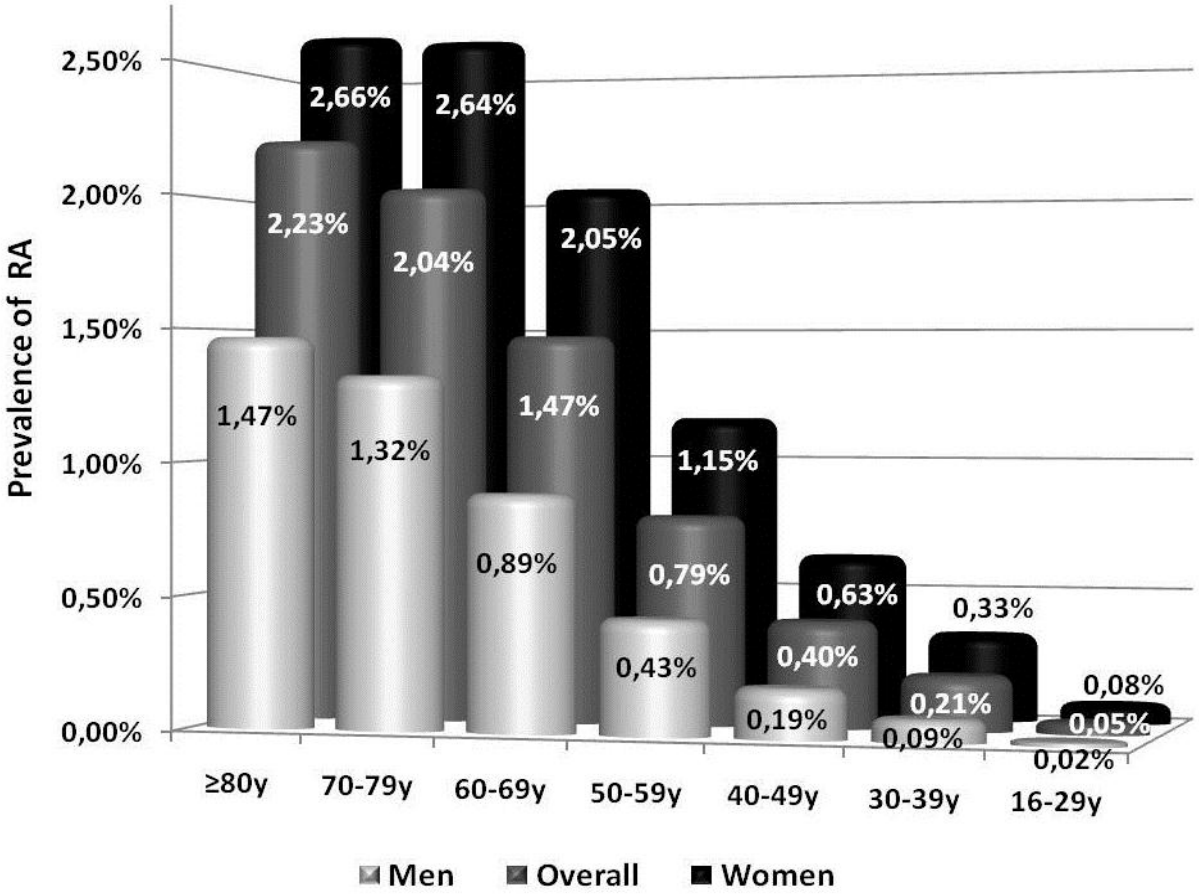
Cartilage destruction in rheumatoid arthritis
(seen from the camera of Swedish photographer Lennart Nilsson)



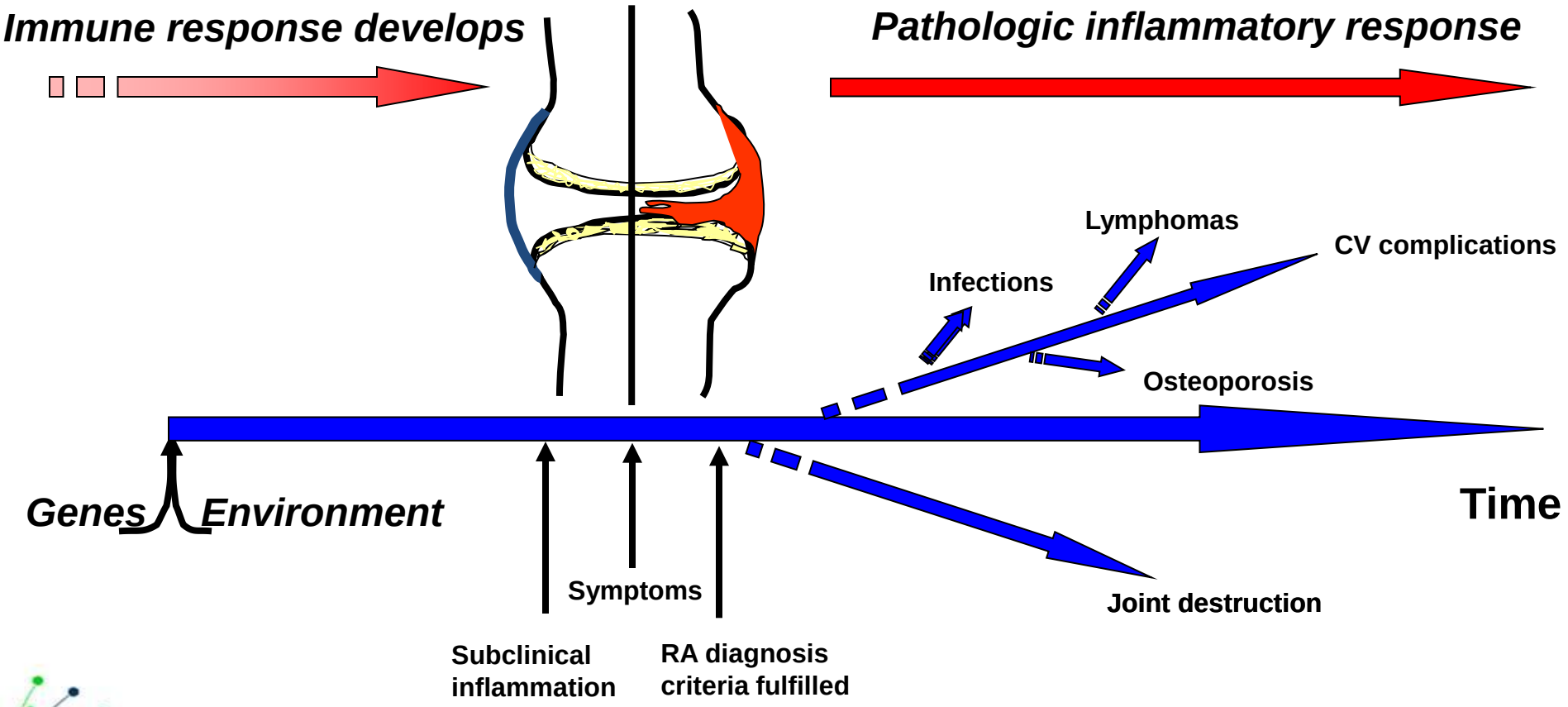
RA is common and prevalence increases with age



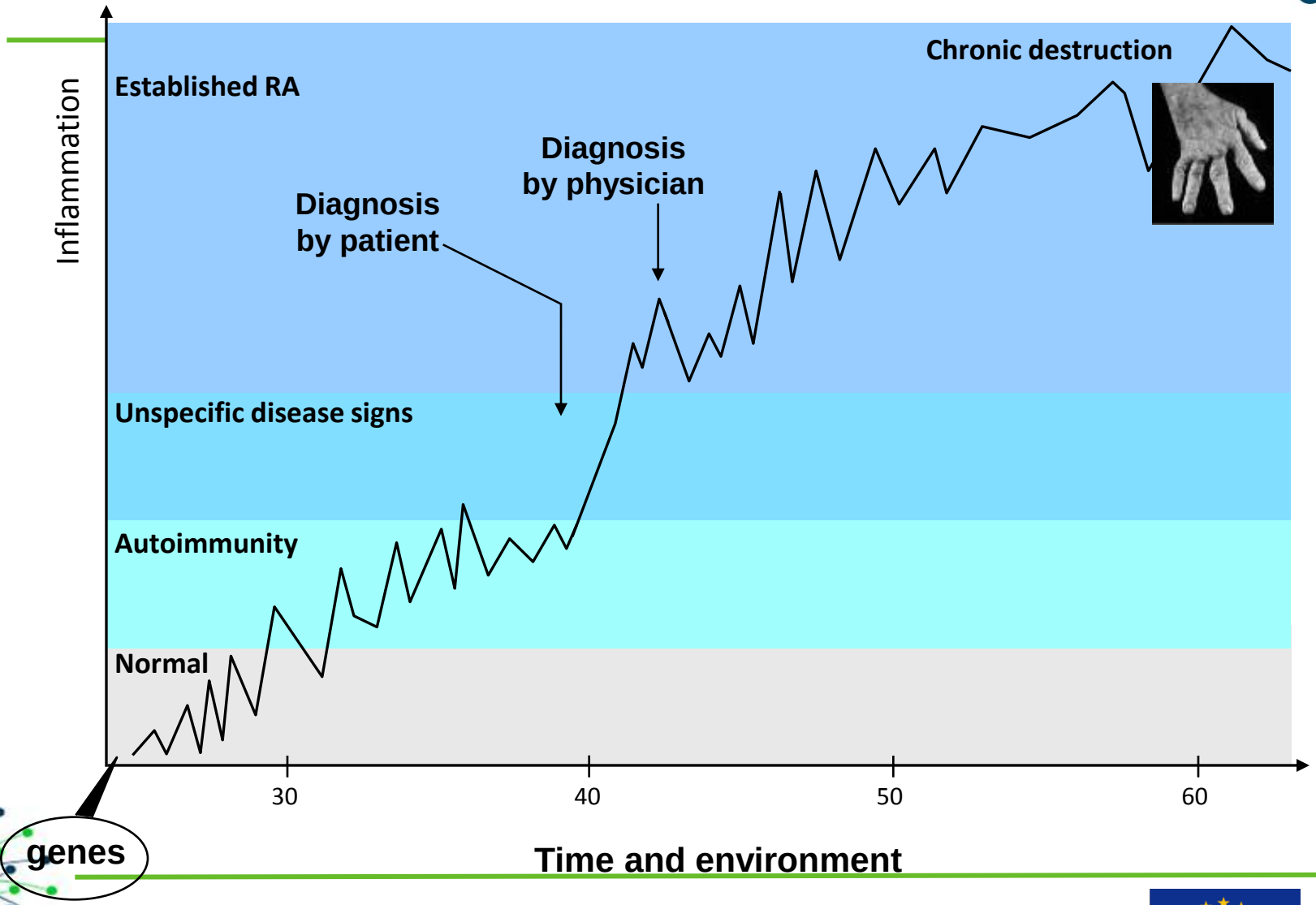
Neovius, Simard & Askling for the ARTIS Study Group, ARD 2011

Cases defined as ever having a visit in inpatient or outpatient specialist care with a diagnosis of rheumatoid arthritis, or a listing in the Swedish Rheumatology Quality Register

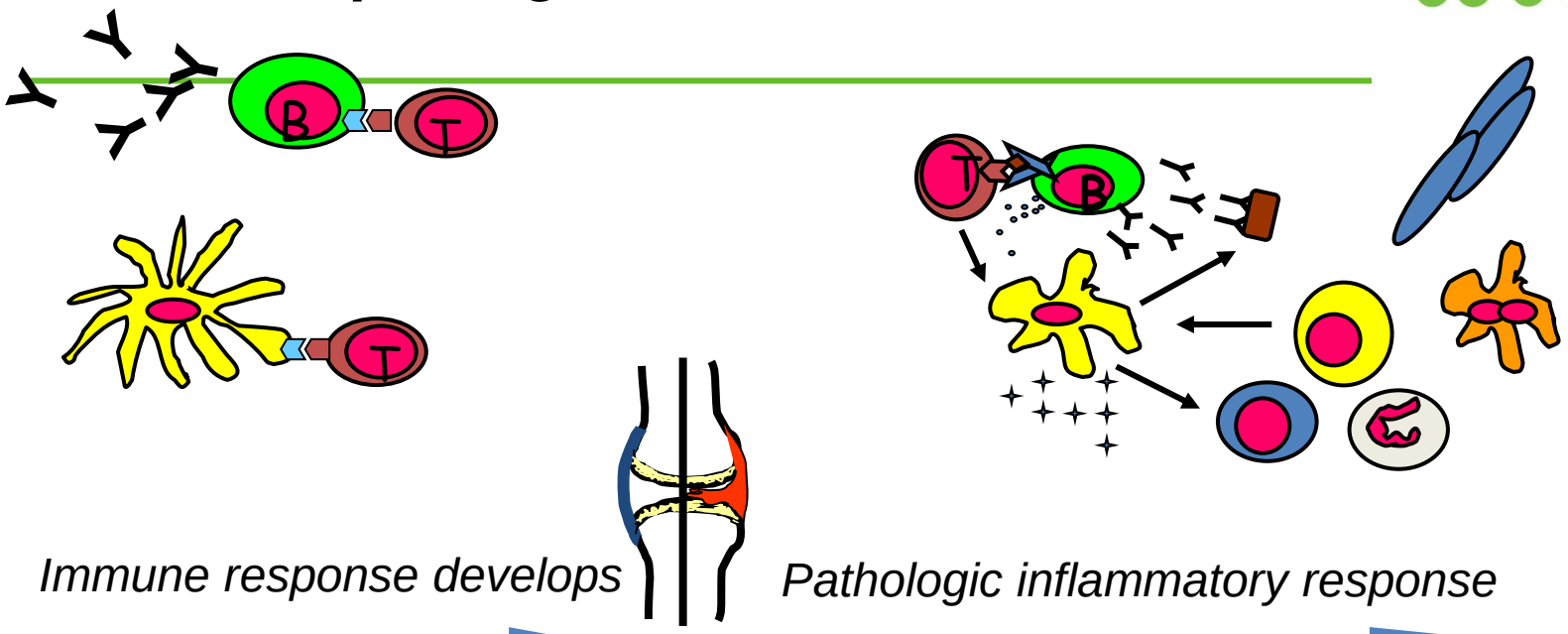
Disease development in arthritis – a life-long perspective is needed



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



An emerging understanding of molecular pathogenesis of RA



Immune response develops

Pathologic inflammatory response

time

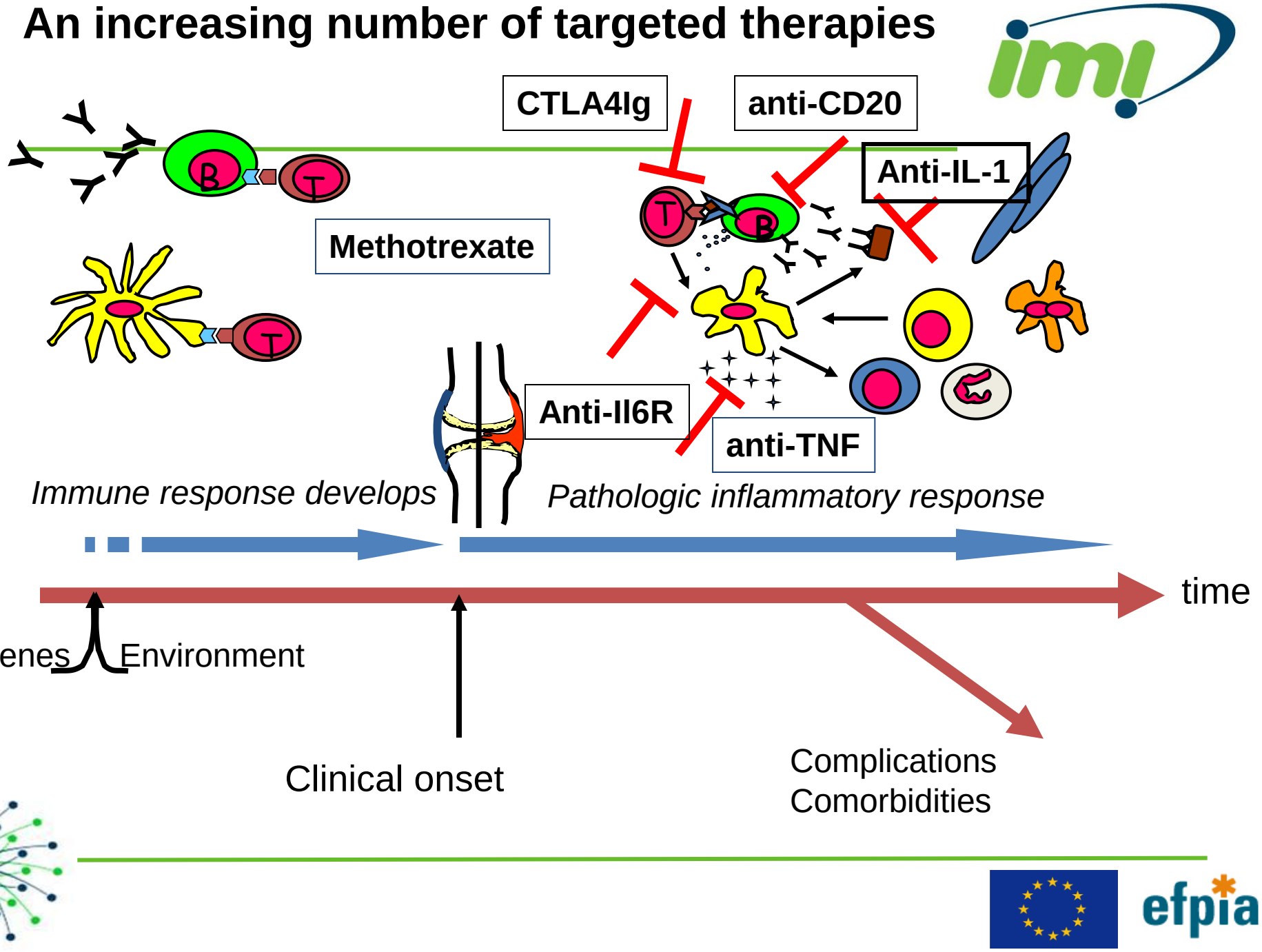
Genes

Environment

Clinical onset

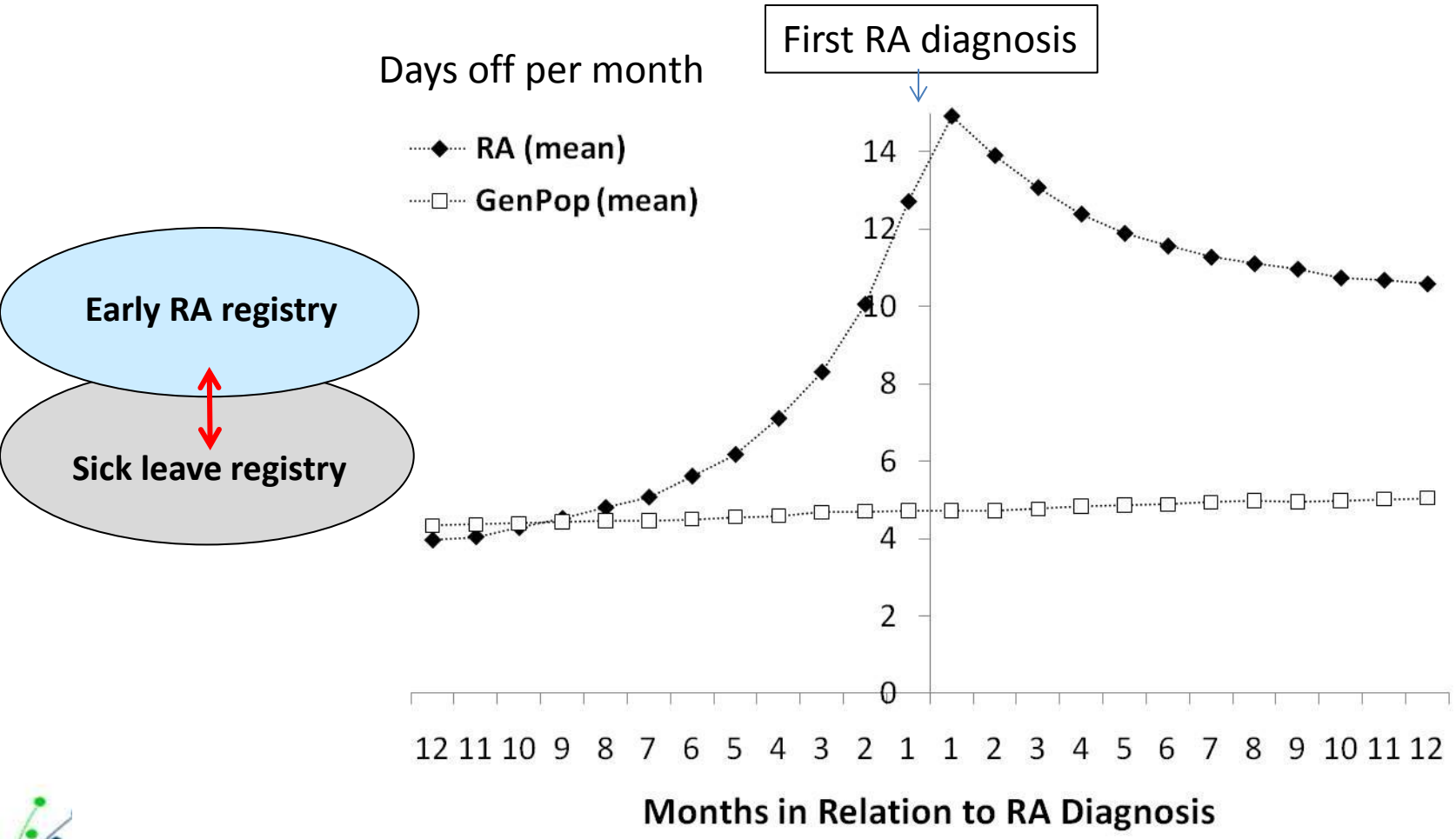
Complications
Comorbidities

An increasing number of targeted therapies



Effectiveness of treatment – here work capacity

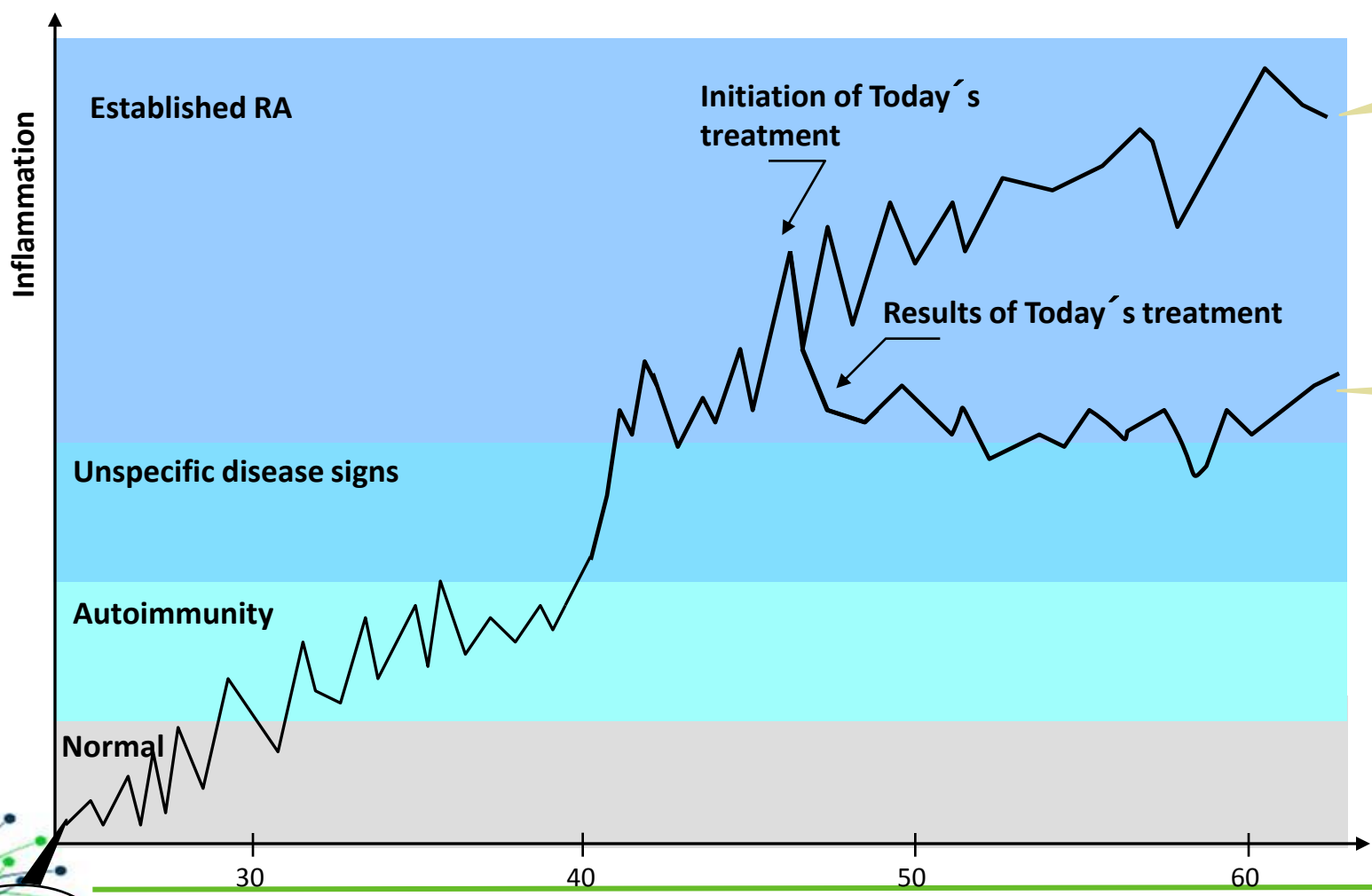
Much better than before, but not good enough



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

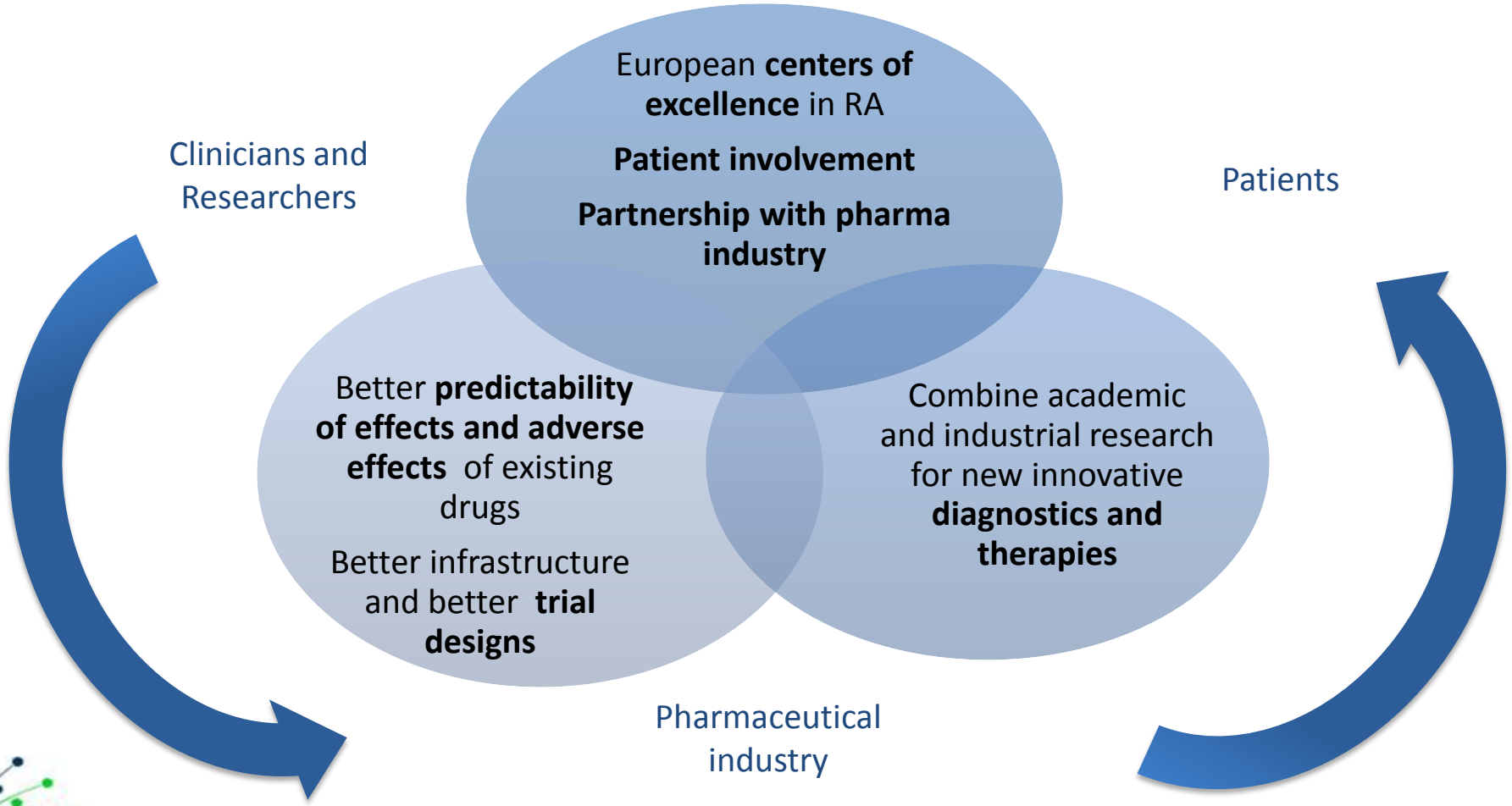


Challenges for translational medicine (here RA)

- 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

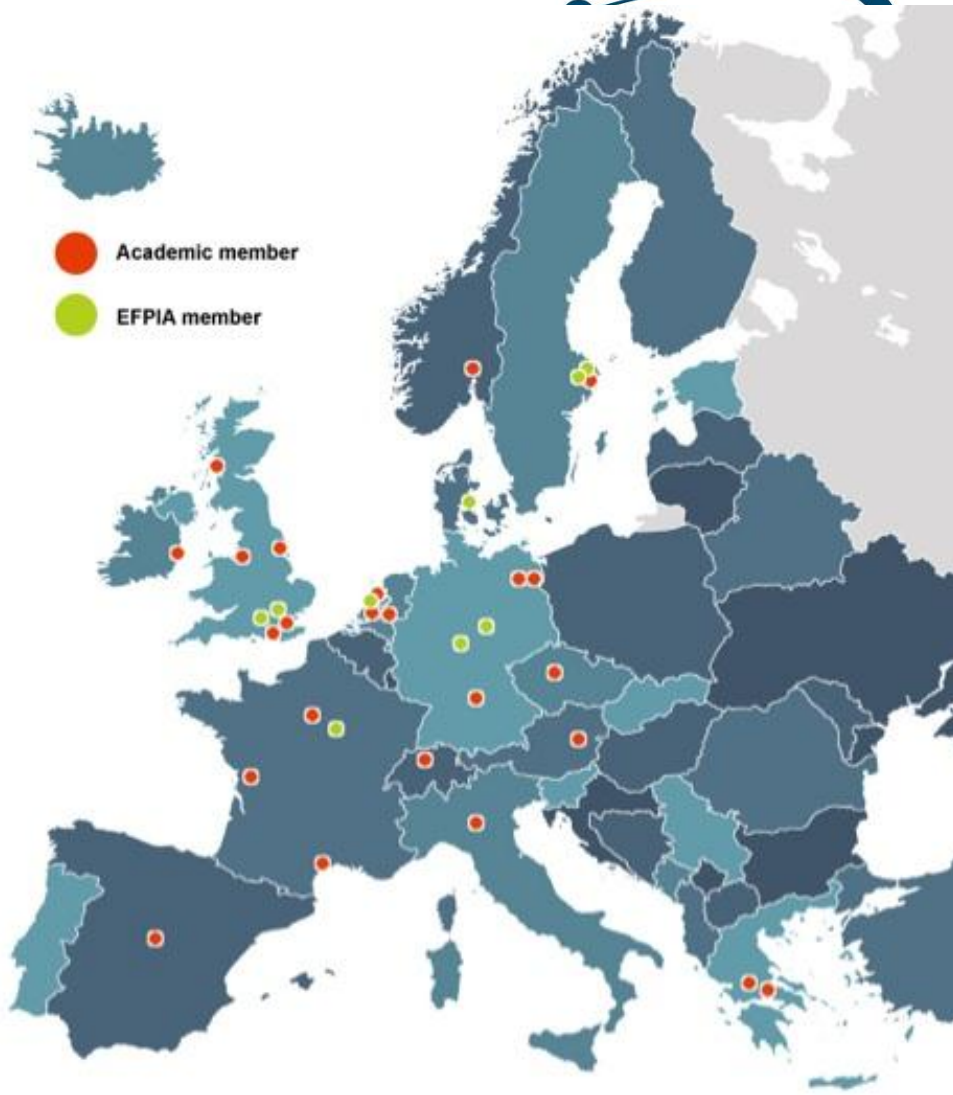
BTCure`s potentials - What BTCure has to offer to the community



Partners in BTCure

- 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)
- 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 researcl
- Pfizer
- Novo Nordisk, Denmark
- Merck Serono
- Thermo Fisher Scientific
- Biomedical Research Foundation, Academy of Athens, BRFAA
- University of Oxford, UK

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



Engagement of patient and professionals from all over Europe

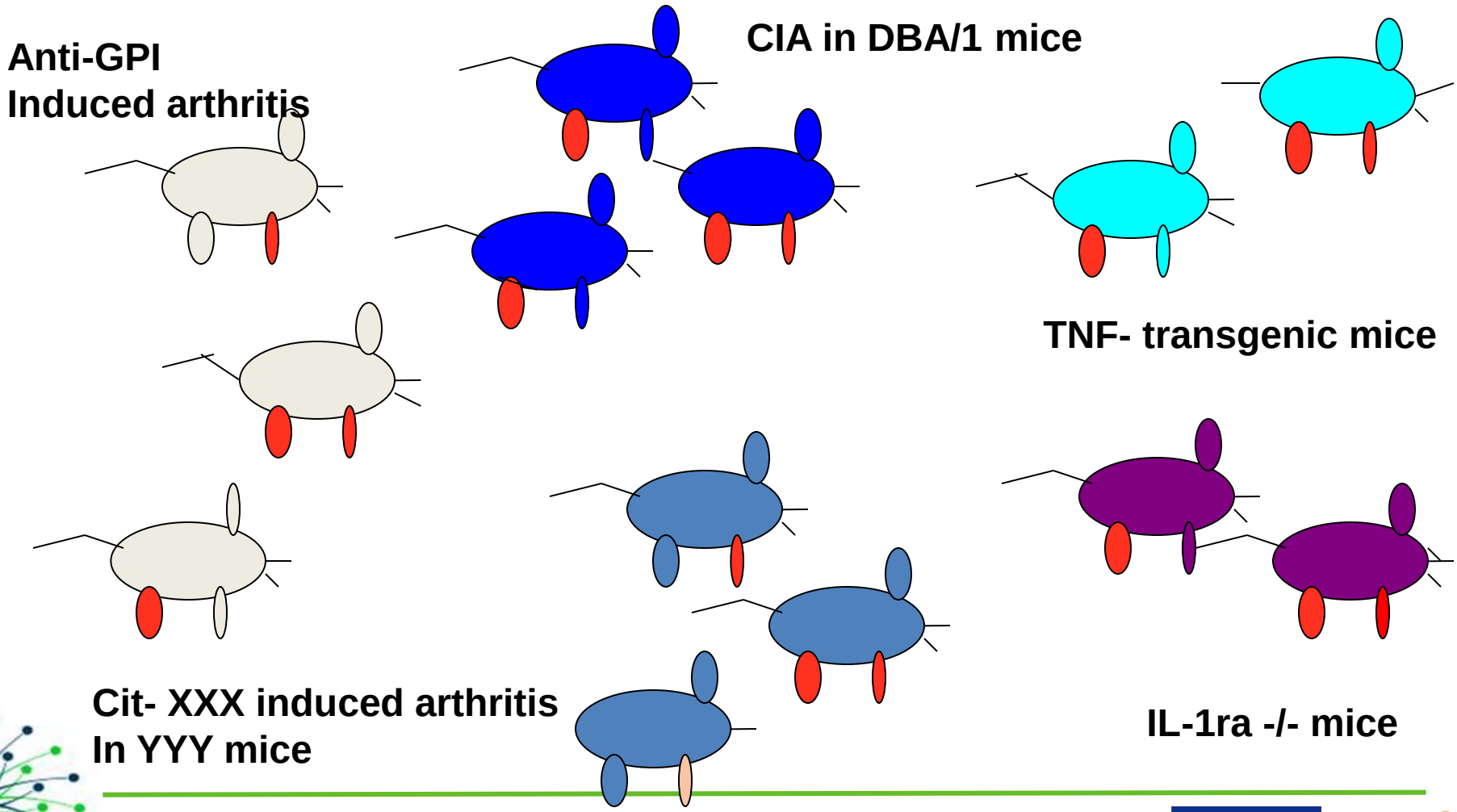
PATIENTS

- **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)

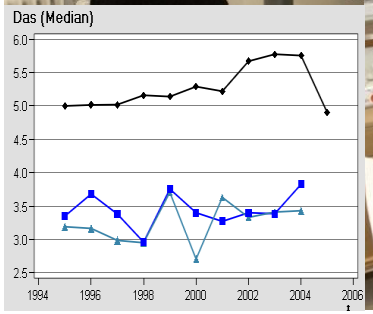
PROFESSIONALS

- **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



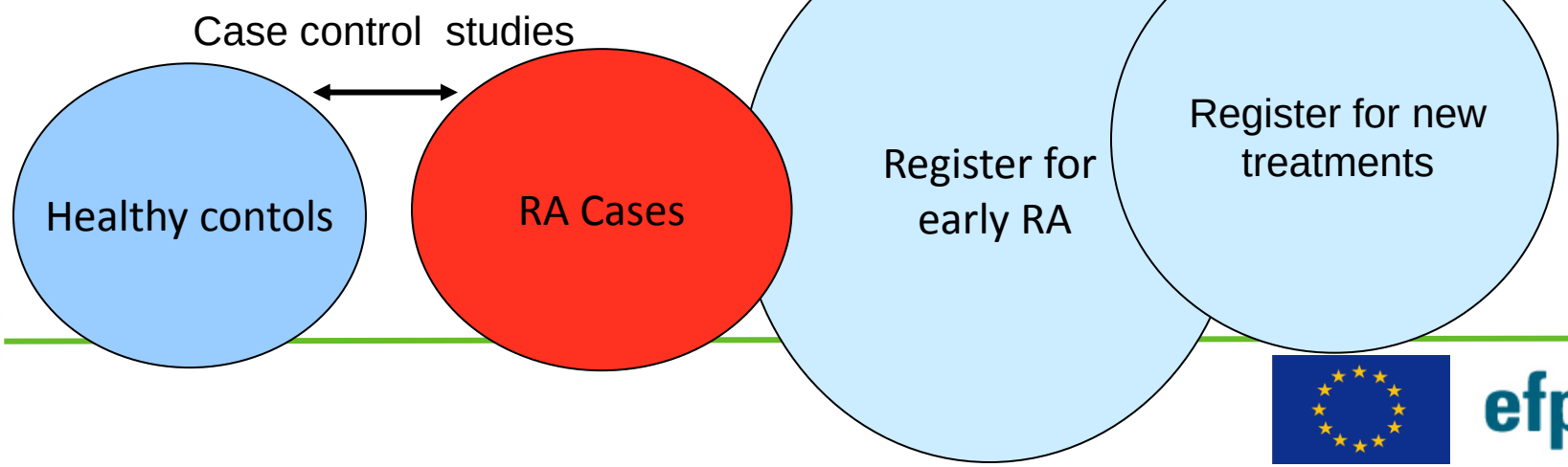
Strategy 1: European Rheumatology registers; Patient-derived information used both in daily practice and in research



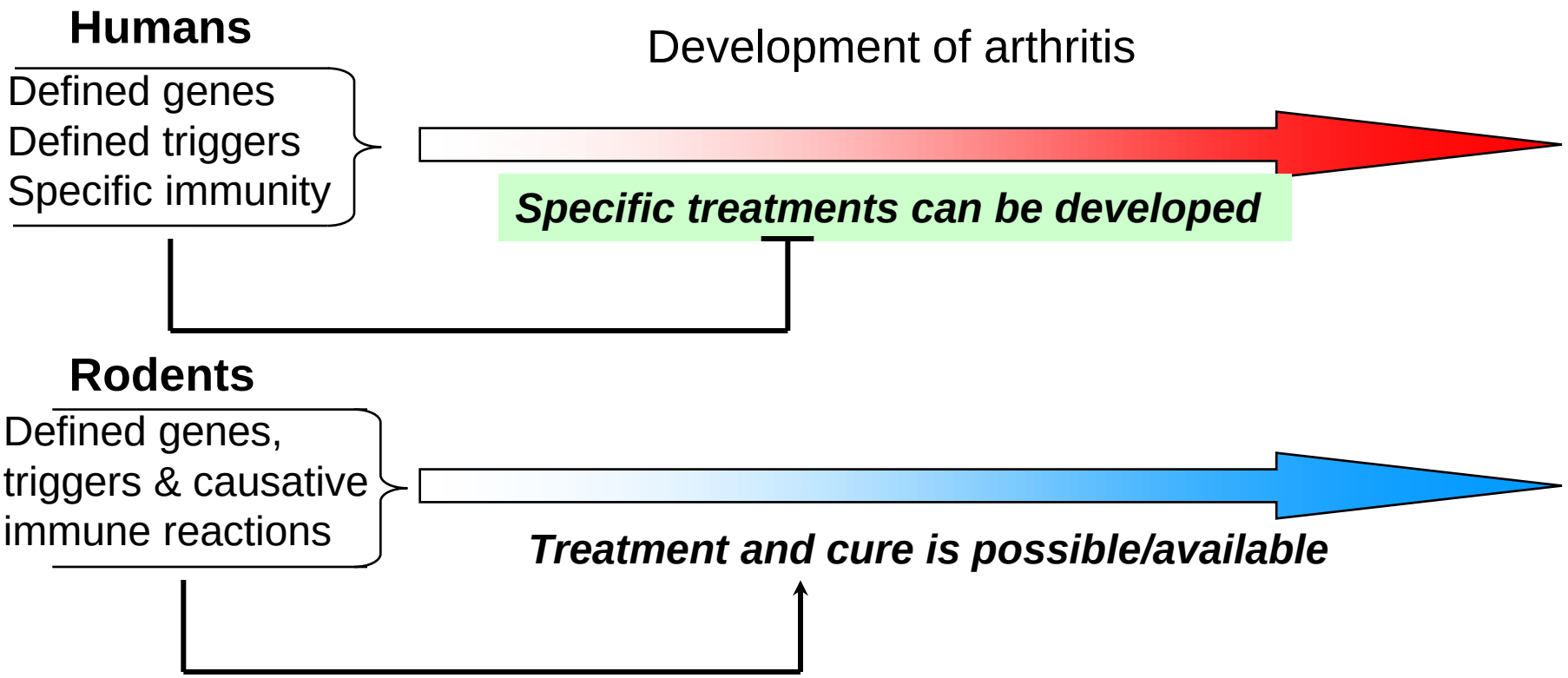
Investigations of

- **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**

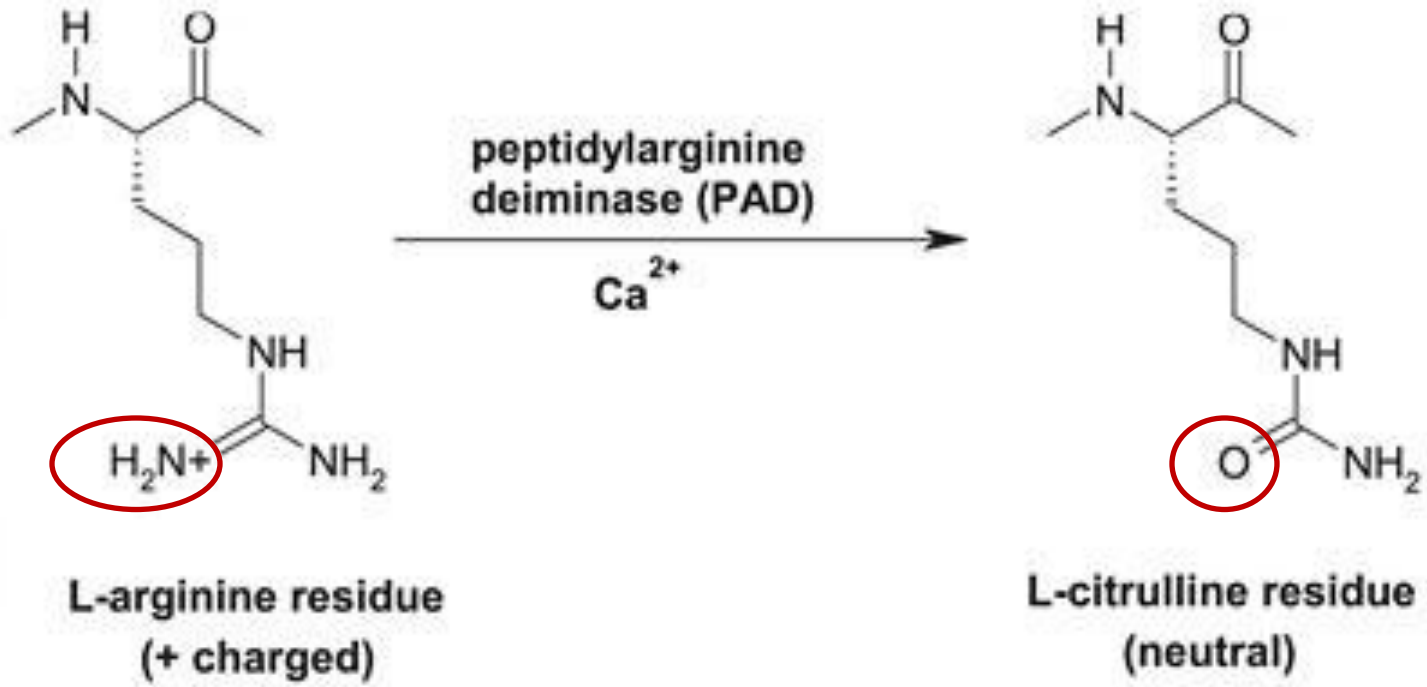


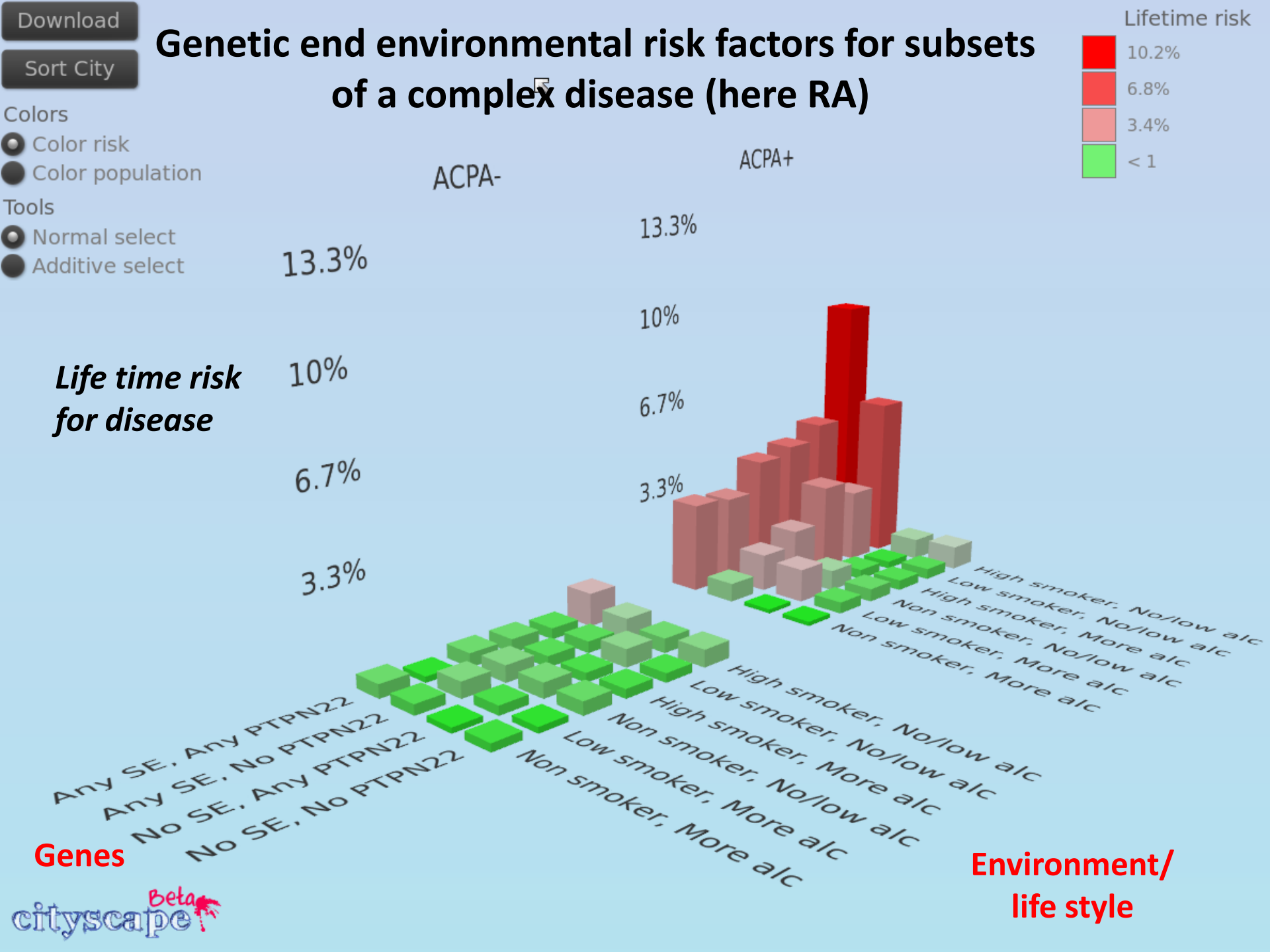
Strategy 2:
Alignments of arthritis in humans with arthritis in animal models



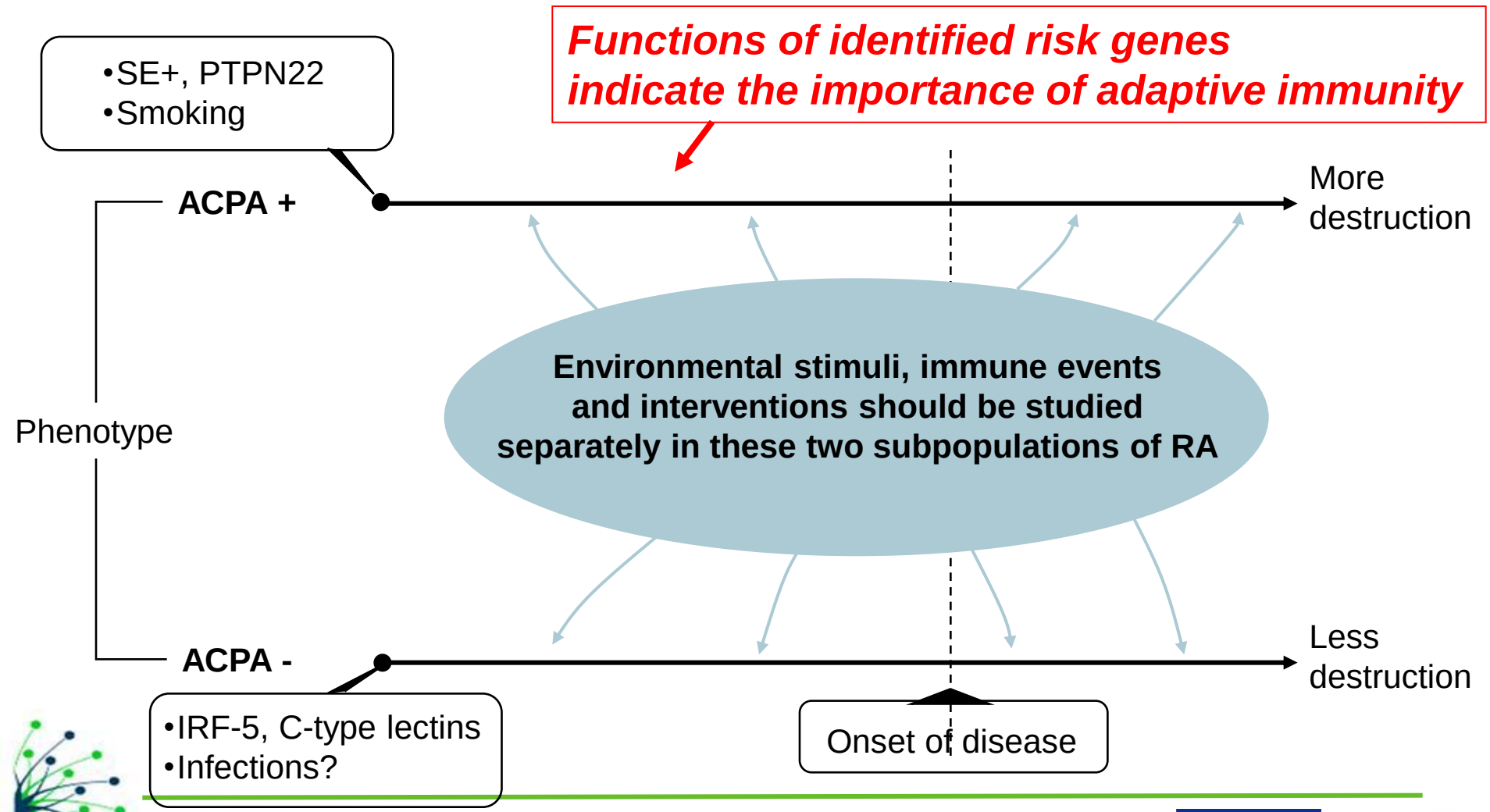
Autoimmunity in RA

Antibodies to citrullinated proteins/peptides (ACPA:s) are present in 60% of RA patients




Download
Sort City
Colors
Color risk
Color population
Tools
Normal select
Additive select
Genetic end environmental risk factors for subsets of a complex disease (here RA)
Lifetime risk
10.2%
6.8%
3.4%
< 1
ACPA-
ACPA+
13.3%
10%
6.7%
3.3%
Life time risk for disease
Any SE, Any PTPN22
Any SE, No PTPN22
No SE, Any PTPN22
No SE, No PTPN22
High smoker, No/low alc
Low smoker, No/low alc
High smoker, More alc
Non smoker, No/low alc
Low smoker, More alc
Non smoker, More alc
Genes
Environment/ life style
cityscape Beta

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

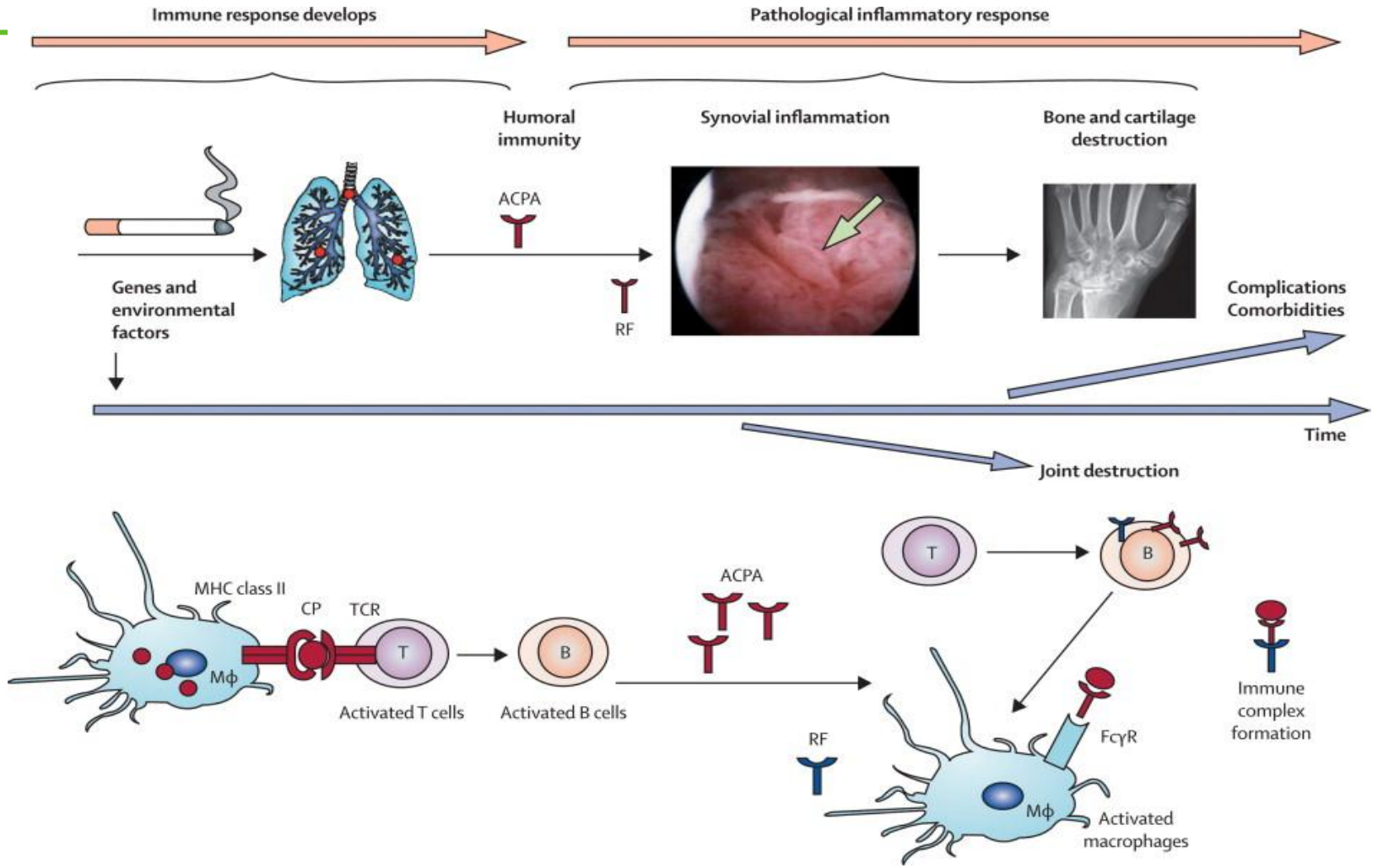


Implications for public health and prevention; Impact of smoking

- **Impact of smoking on RA as a whole:** 22 % of all RA cases in Sweden wold 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 with major susceptibility genes would not have occurred of nobody had smoked

Källberg et al Ann Rheum Dis 2011

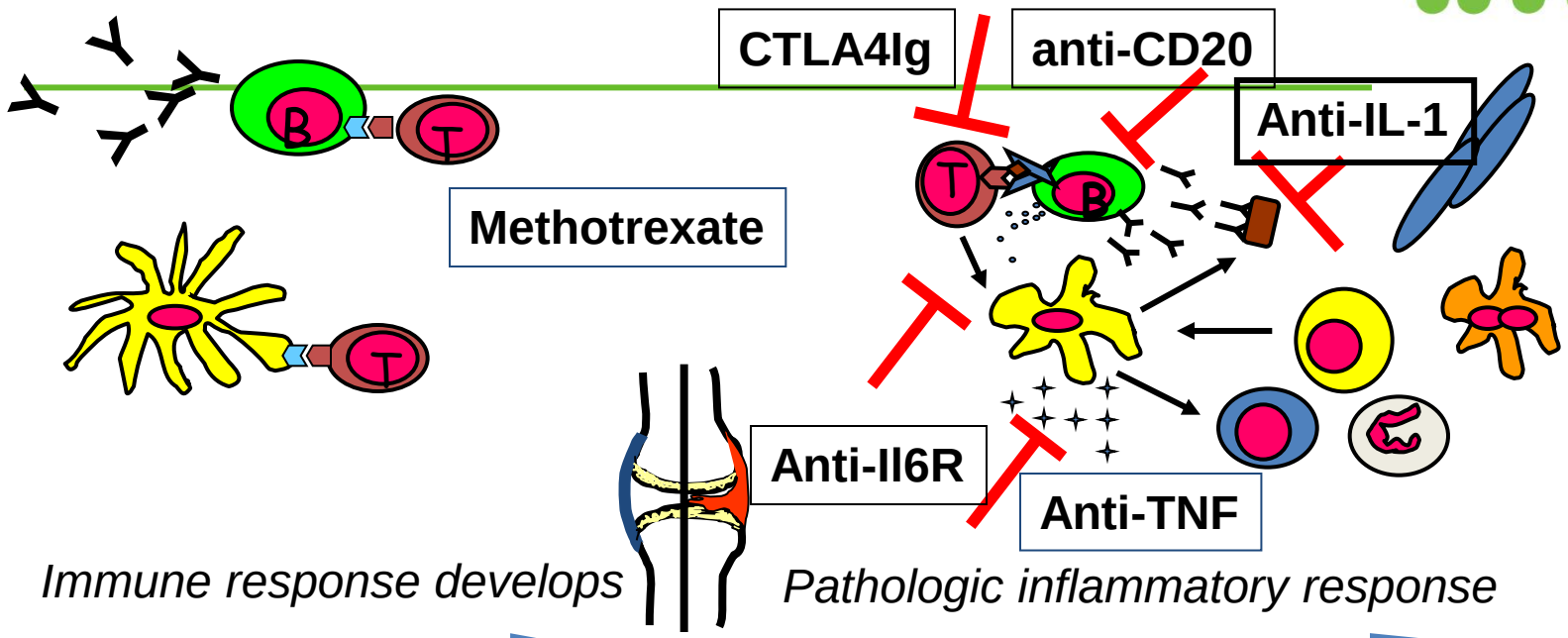
A model for an etiology of ACPA-positive RA



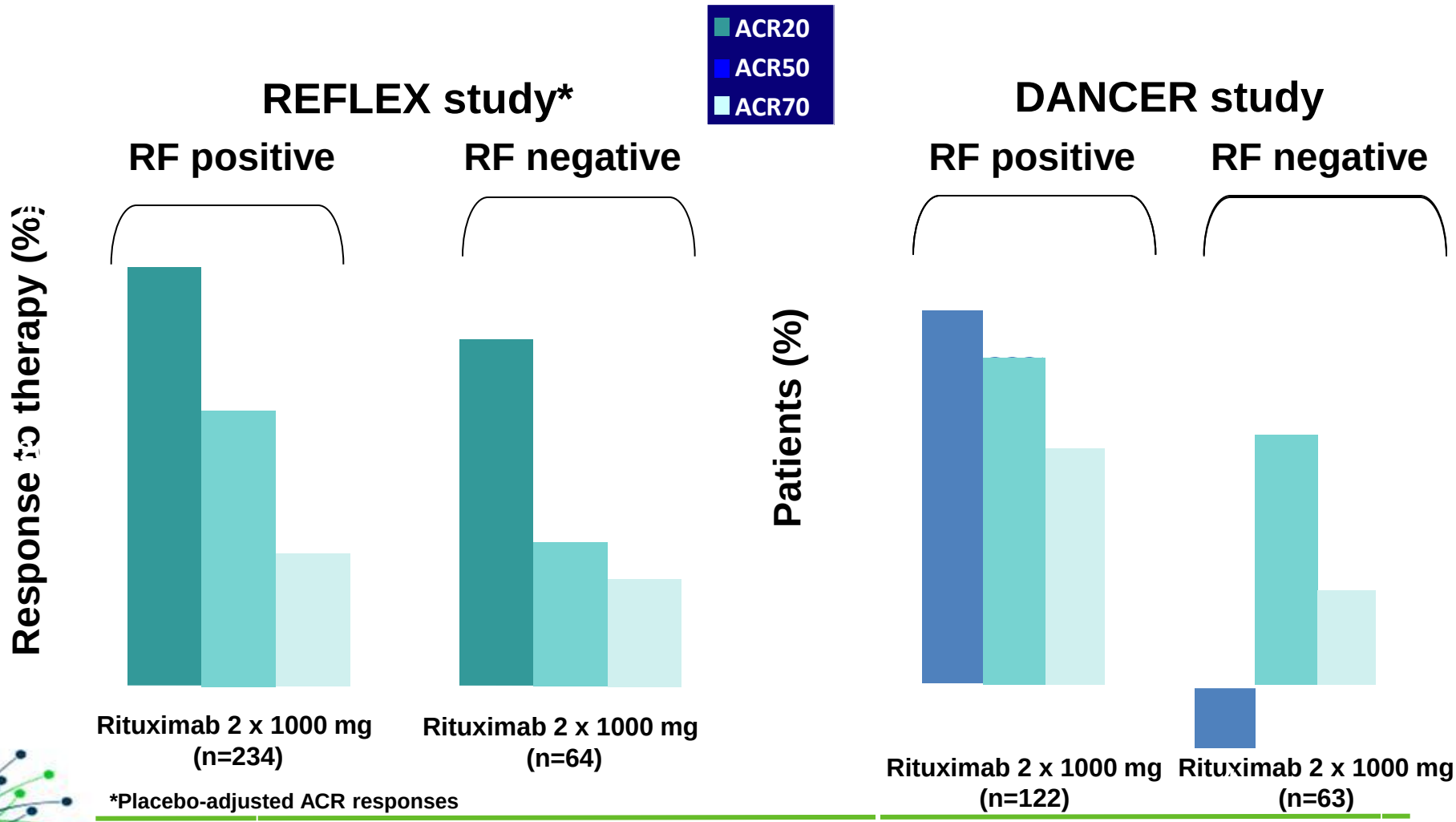
Lancet Feb 21, 2009; Seminars in Immunology 2011; 23: 92-98

Implications for personalised therapies

Which treatment should be chosen for which patient ?
Several biomarker projects ongoing



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

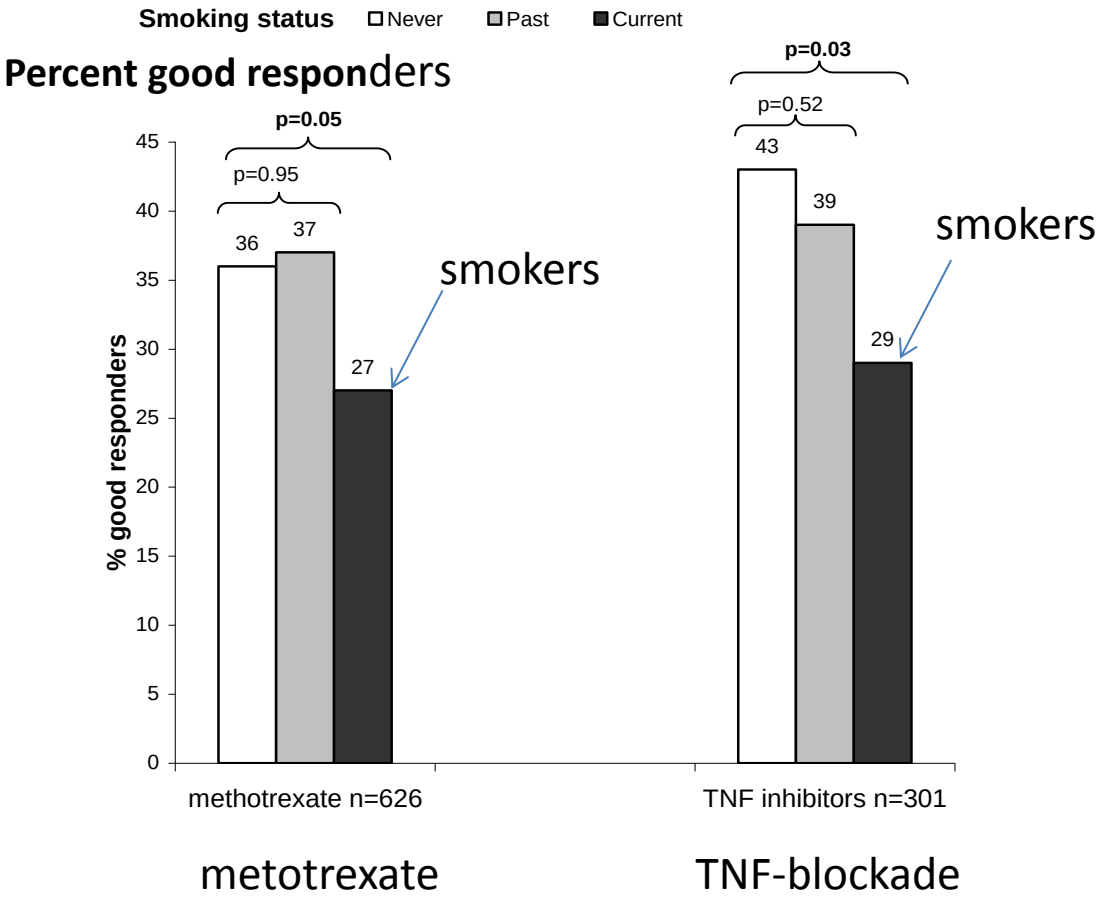


*Placebo-adjusted ACR responses

But also environment and life style affects response to therapy

Main Results (also when including ”omics”):

Current smoking is the most important determinant for bad response



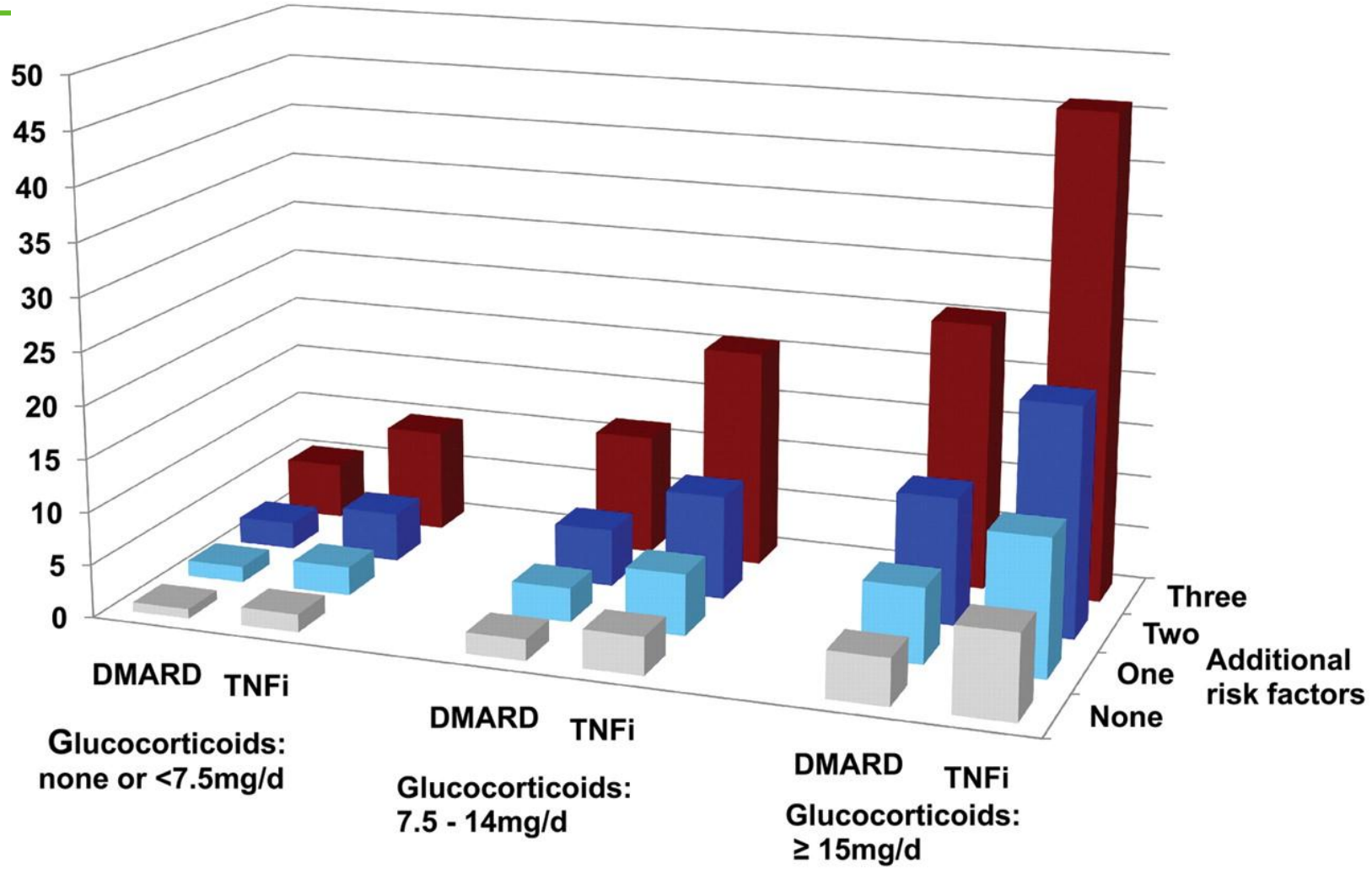
Use of registries and associated biobanks to analyse:

- Clinical characteristics
- Pharmacogenomics
- Biomarkers
- Environment/life style factors

Saevarsdottir S et al, Arthritis & Rheumatism, 2011

Also adverse events are “personal”

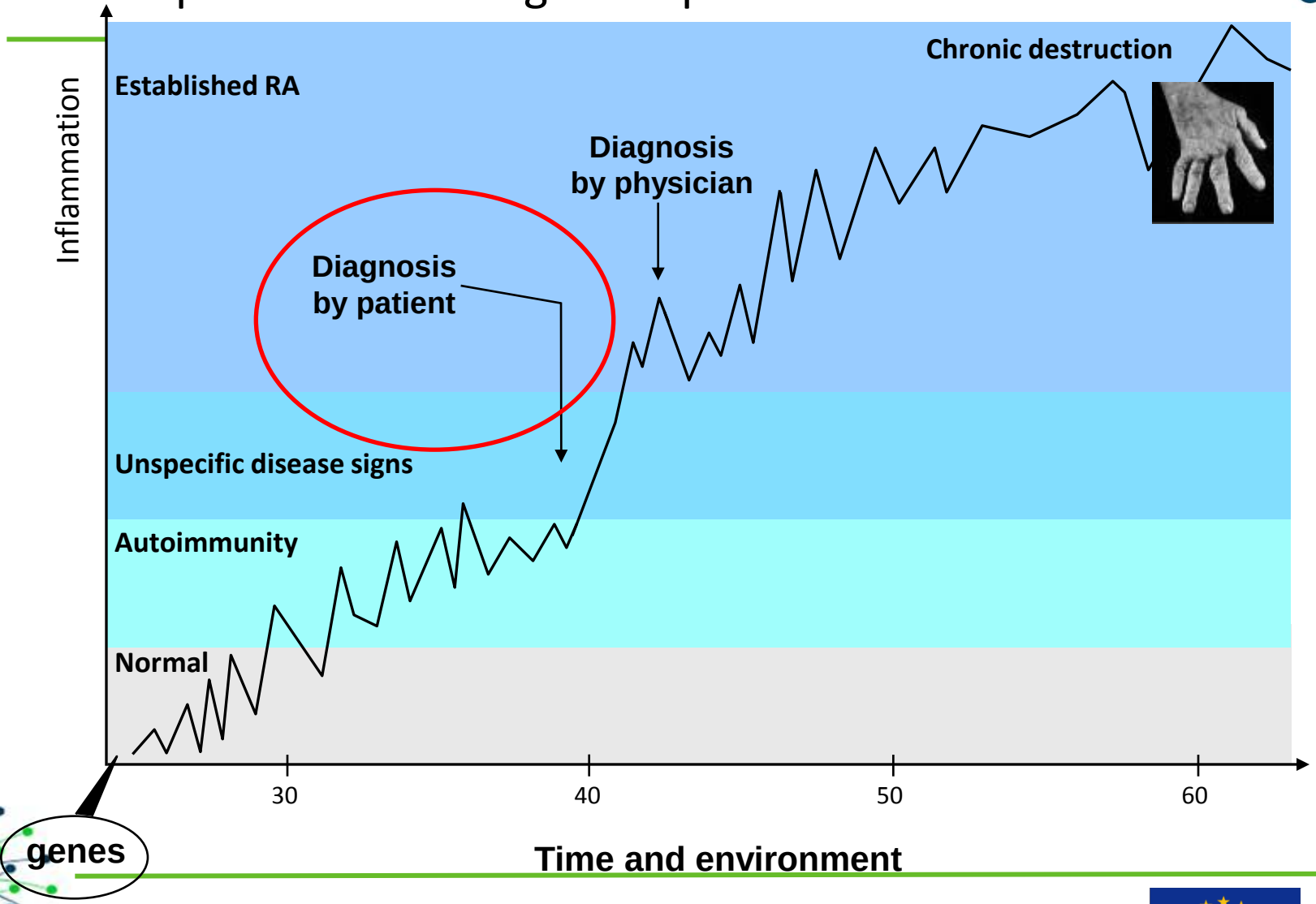
Estimated annual incidence of serious infections in RA by treatment and risk profile



Strangfeld A et al. Ann Rheum Dis 2011;70:1914-1920

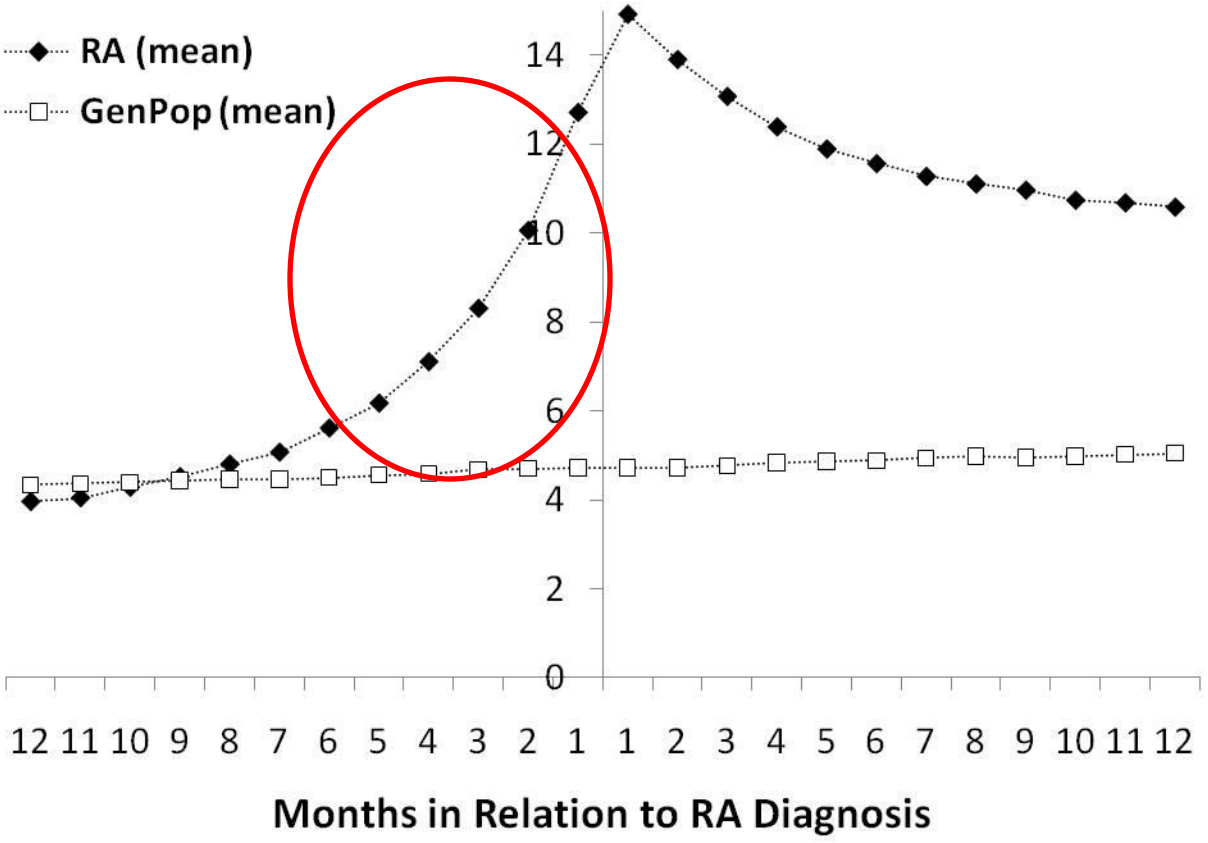
A major project within BTCure

Understand and predict what may happen when patient first recognize a problem



Days Off Work in relation to Diagnosis

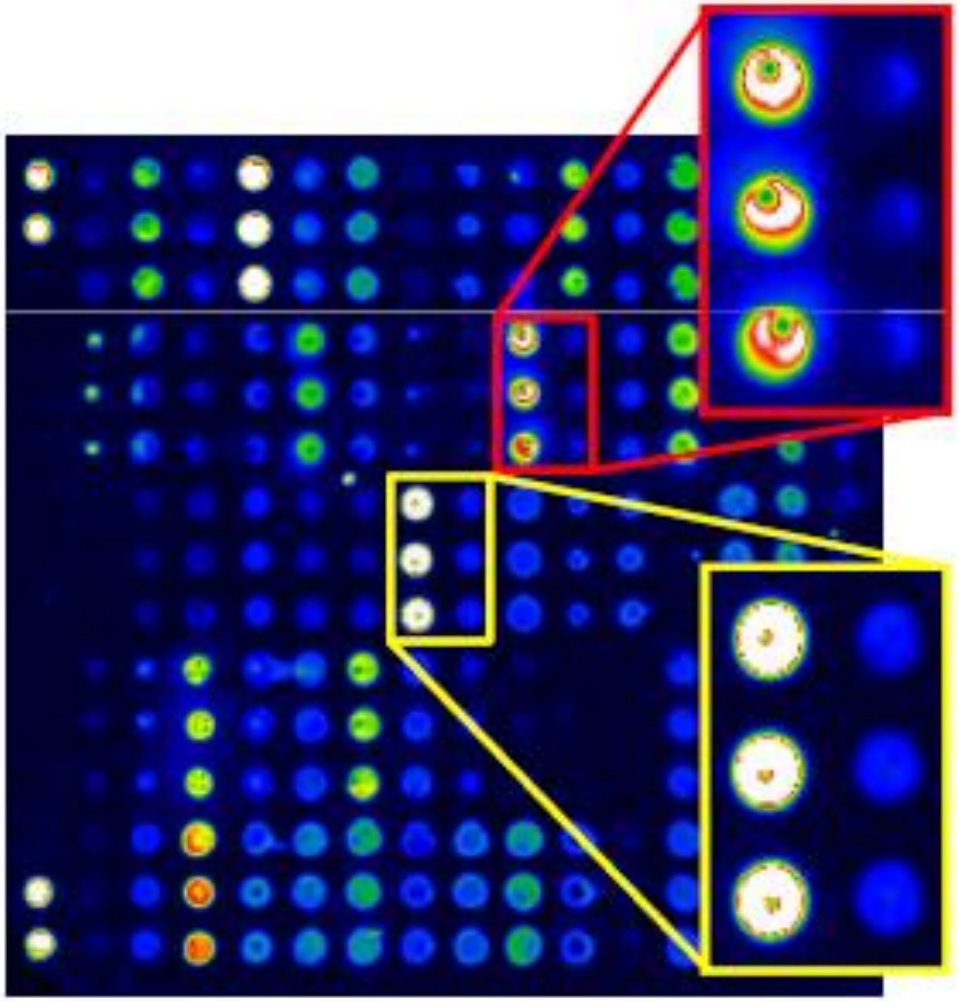
per Month



Neovius, Simard & Askling for the ARTIS Study Group, ARD 2011

Detection of utoimmunity (ACPA) before clinical onset of disease

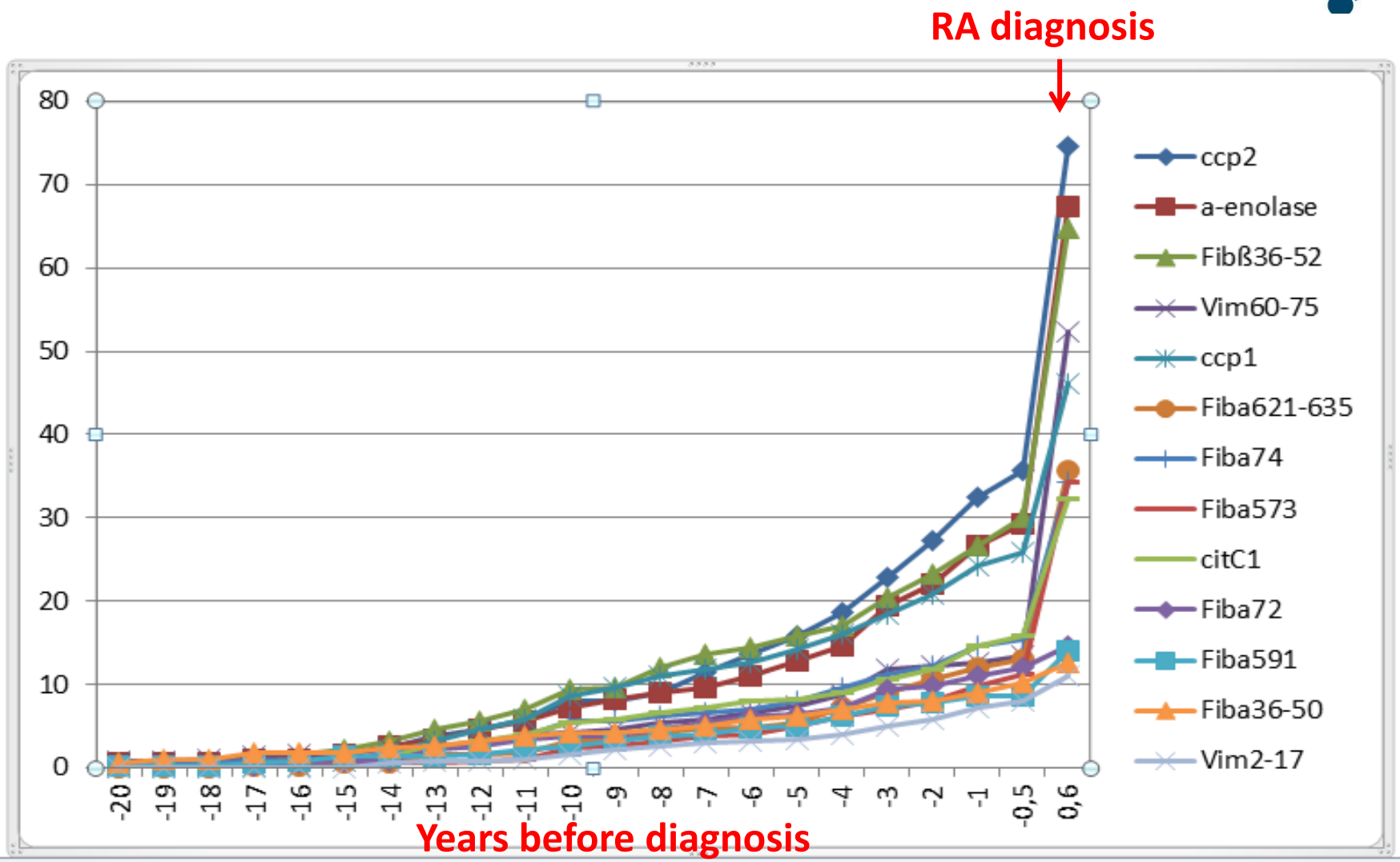
(a chip assay for ACPA:s being developed within the BTCure collaboration)



Collaboration with PhaDia within the IMI BeTheCure project

Hansson, Rönnelid et al ART Oct 2012

Presence of different ACPA:s before onset of disease



Brink M,. Rantapää-Dahlqvist et al Arthritis Rheum Jan 10, 2013

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