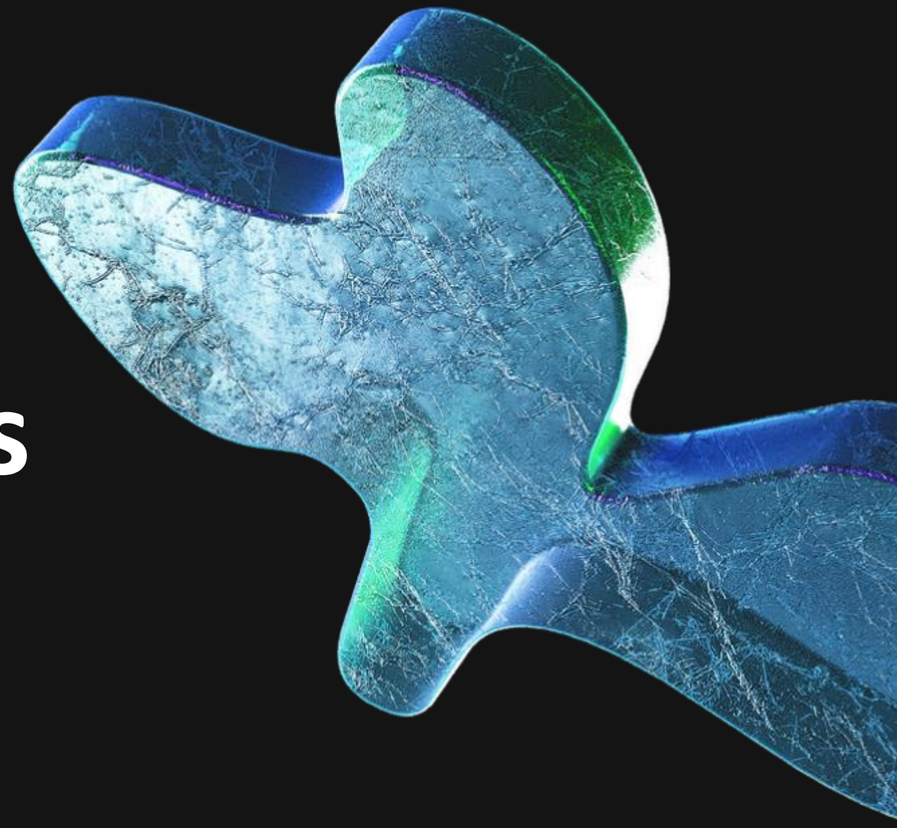
AI-powered modeling approaches to support the development of new therapies for autoimmune diseases



Philippe MOINGEON

Immuno-inflammation, Servier

September 21st, Rosa Webinar series

An independent, global pharmaceutical group governed by a non-profit foundation

31st largest pharmaceutical Group worldwide*
2nd largest pharmaceutical Group in France*

150 countries
in which the Group's medicines
are distributed

22,500 employees

Leader in cardiology
4th leading pharmaceutical group in cardiology worldwide*
3rd leading pharmaceutical group in hypertension worldwide*

€4.7 billion Group revenue in 2019/2020
- Brand-name medicines: €3.3 billion
- Generic medicines: €1.4 billion

Ambition to become
a renowned and innovative player in oncology

€626 million **EBITDA** in 2019/2020

More than 20% of Group brand-name revenue invested in R&D each year in average

*Source: IQVIA Analytics Link, MAT Q2-2021

R and D focus:
- Oncology
- Neurology
- Immunoinflammation

Outline

- **AI applications in support to drug development**
  - *A pharmaceutical industry perspective*
  - *Disease modeling applied to Sjogren syndrome (and Lupus)*
  - *Implications for drug design and development*
  - *High throughput drug discovery: the Patrimony platform*

- **In silico prediction of drug efficacy**
  - *QSP model of an anti IFNa Mab in Lupus*
  - *Causal disease representation (eg Sjogren)*

- **Conclusions and perspectives**

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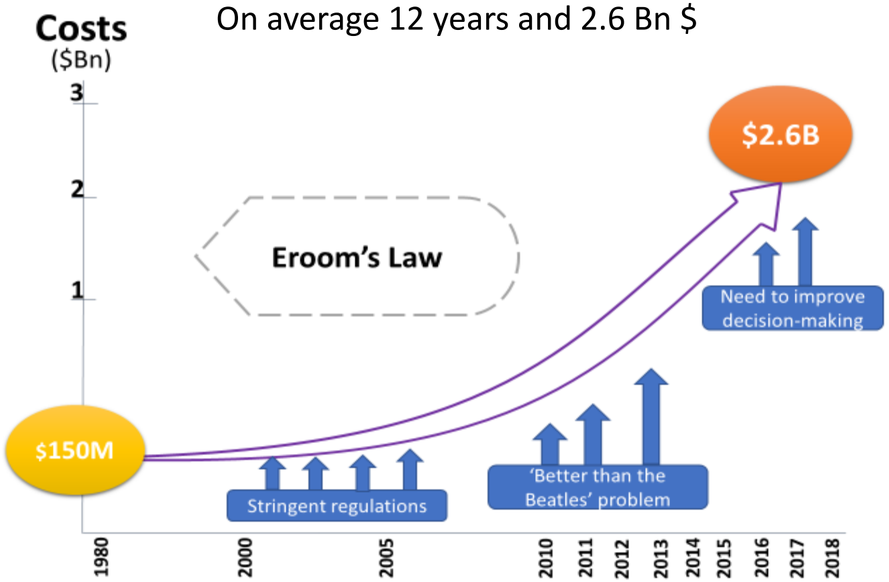
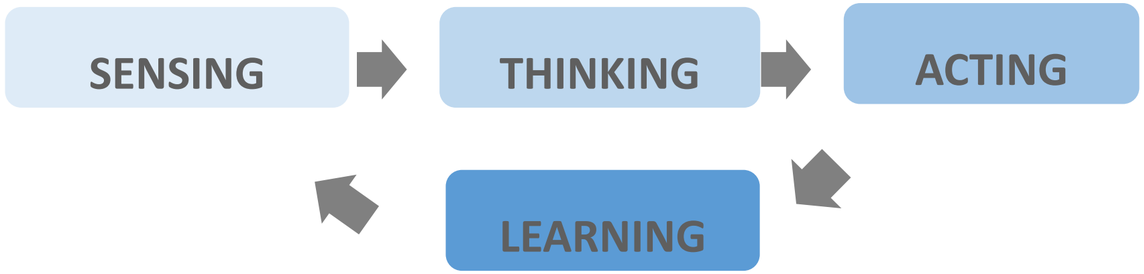
Artificial intelligence applied to challenges associated with new drug development

A

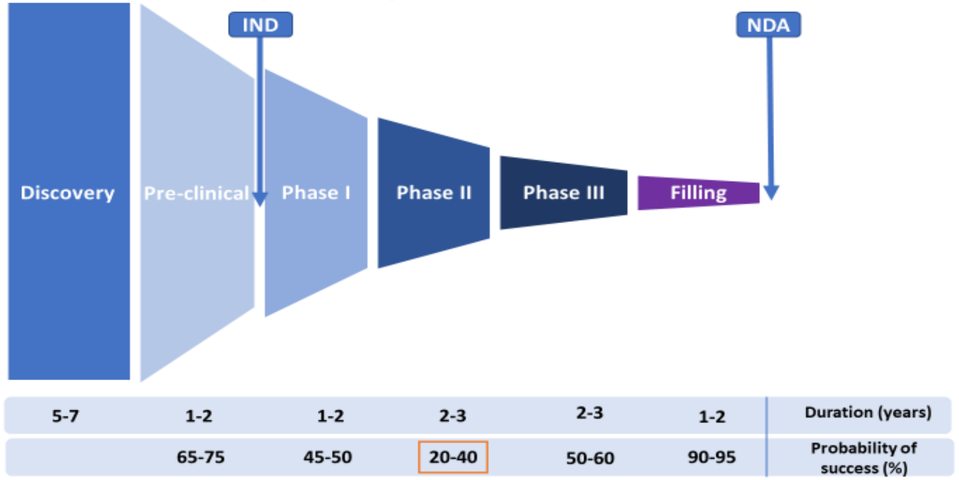
On average 12 years and 2.6 Bn $





B

Less than 7% of drugs coming from discovery eventually reach the patients

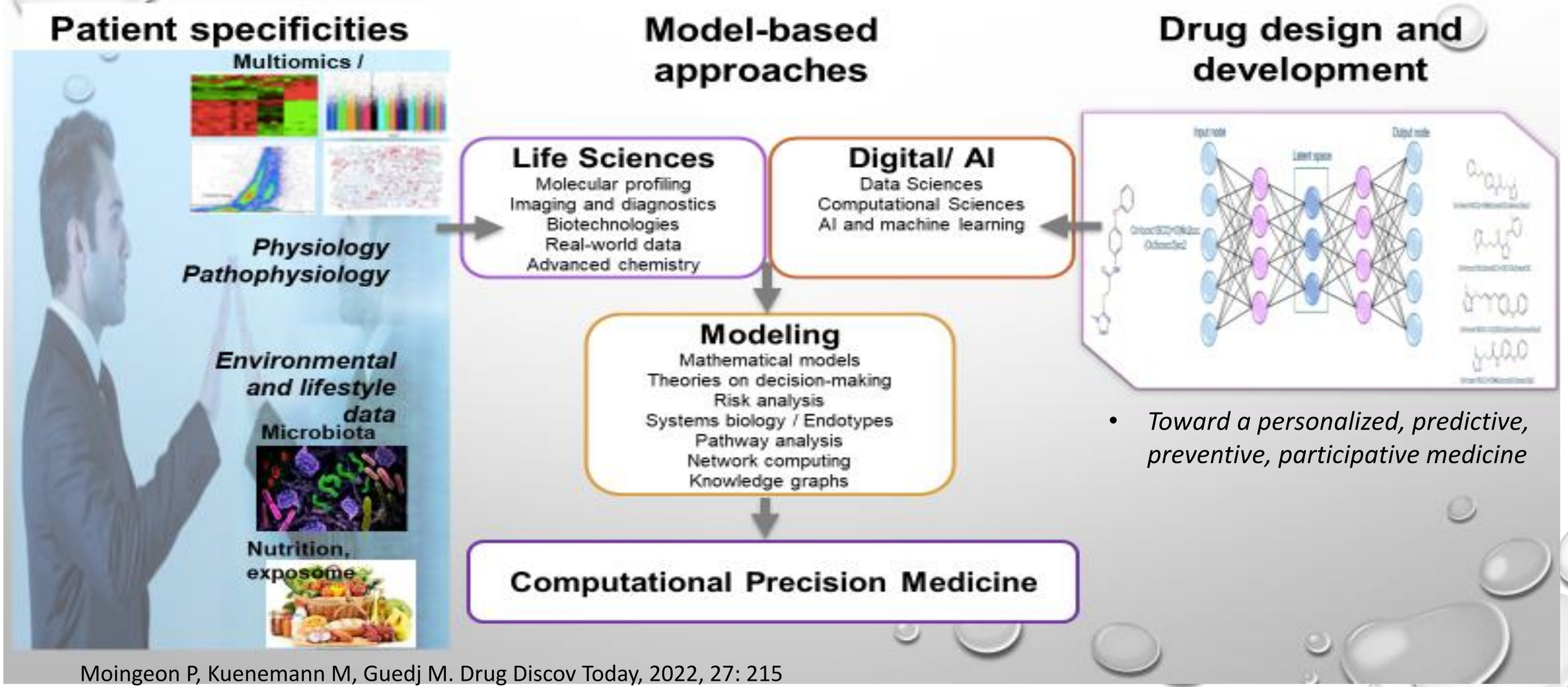


What AI can bring

- Integration of massive, multimodal, structured and unstructured data
- Creation of predictive models
- Support for decision-making

selecting the right therapeutic target, right drug-candidate and right patient

Computational precision medicine to relate patient and drug knowledge spaces



- *Toward a personalized, predictive, preventive, participative medicine*

Moingeon P, Kuenemann M, Guedj M. Drug Discov Today, 2022, 27: 215

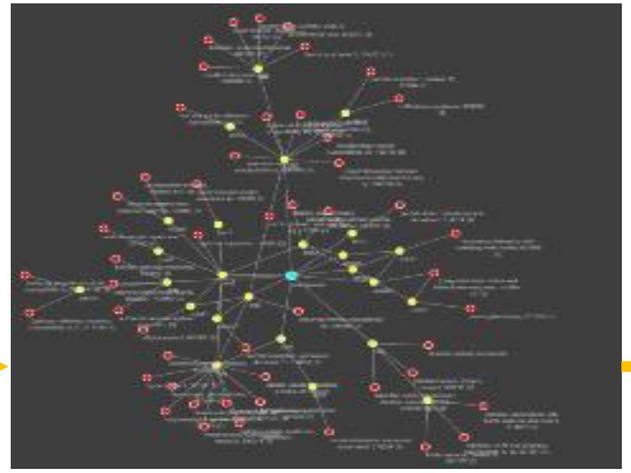
AI applications to new drug development

Disease modeling

Understanding disease complexity and heterogeneity

PATIENT STRATIFICATION

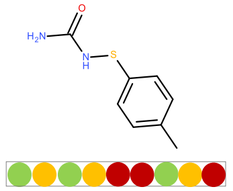
Identification of therapeutic targets

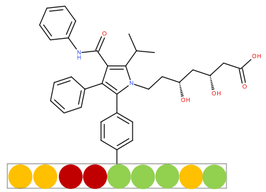


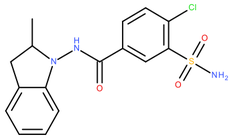
Identification of dysregulated genes/proteins/pathways involved in pathophysiology

SYSTEM BIOLOGY

Design/optimization of drug candidates



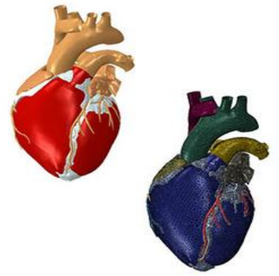




Identification of molecules interacting with target and with specific properties

MULTITASK PREDICTION OF DRUG PROPERTIES

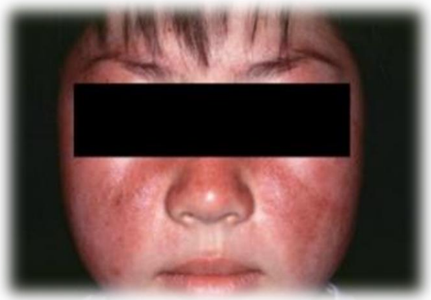
In silico evaluation of drug efficacy and safety



Digital twins, virtual patients, QSP, causal disease models

IN SILICO TRIAL SIMULATION

Systemic Lupus Erythematosus (SLE) : a complex, heterogeneous auto-immune disease



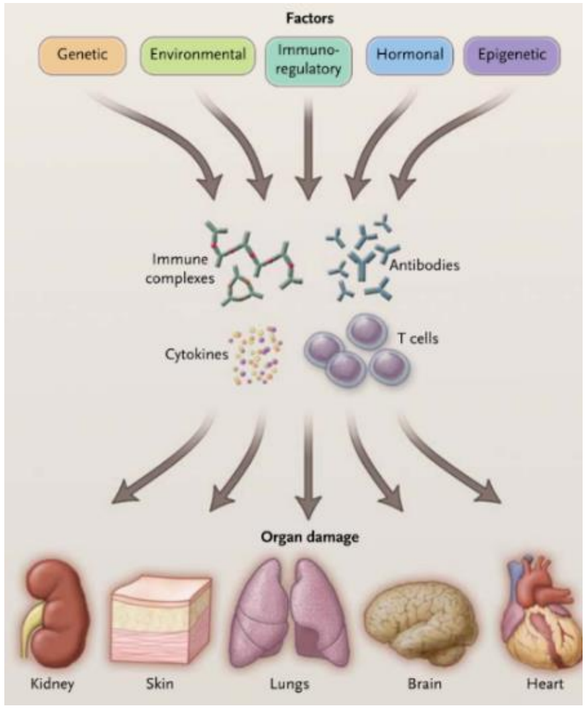
- **Diverse clinical manifestations:**
  - Skin, joints, kidney, heart, lungs, central nervous system, blood, *etc.*

  -Fatigue

- **Significant morbidity & socio economic burden**
  Survival after diagnosis ~ 95% (5yrs), 91% (10yrs), 78% (20yrs)

- **Current treatment options:**
  - Corticosteroids, antimalarials, immunosuppressors (Mycophenolate mofetil, Methothrexate, cyclophosphamide, Azathioprine), anti B cells (Belimumab), anti-IFNR MAb (Anifrolumab)

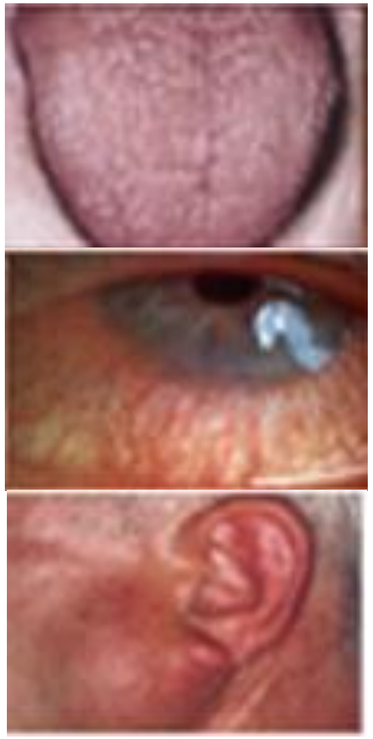
High residual unmet medical need



DRG, 2018. Tsokos, 2018.Tsokos, 2011. Durcan, 2019

Primary Sjögren Syndrome (pSS): a complex, heterogeneous auto-immune disease

- Progressive autoimmune disease characterized by dry eyes, dry mouth
- **Immune infiltrates** leading to destruction of lachrymal and salivary glands
- **Systemic manifestations** involving musculoskeletal and nervous systems, lungs, kidneys, skin and blood vessels
- **Significant quality-of-life impairment (fatigue)**
- **Increased risk** (16- to 44-fold *vs* general population) of developing **lymphoma**
- Current treatments are symptomatic



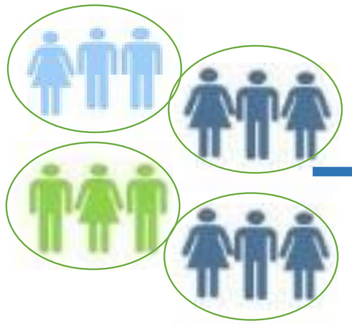
High unmet medical need

Disease modeling to understand patient heterogeneity and identify therapeutic targets: a system biology approach

Stratification of patients into homogeneous subgroups (clusters)

Cohorts of patients with Lupus or Sjogren syndrome

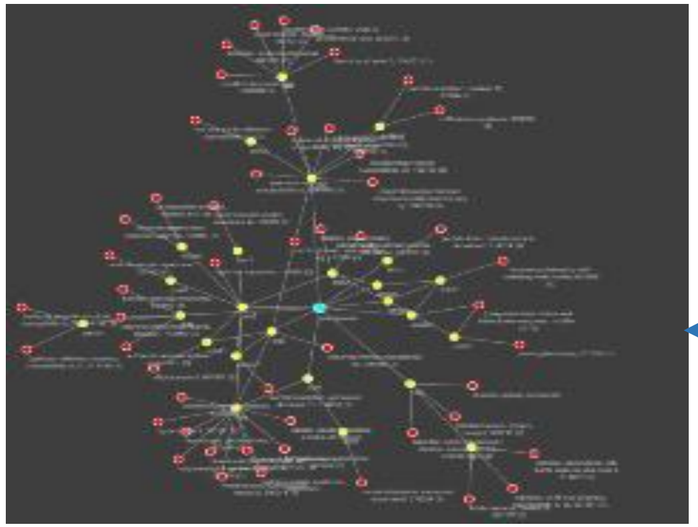
Multi-OMICs profiling



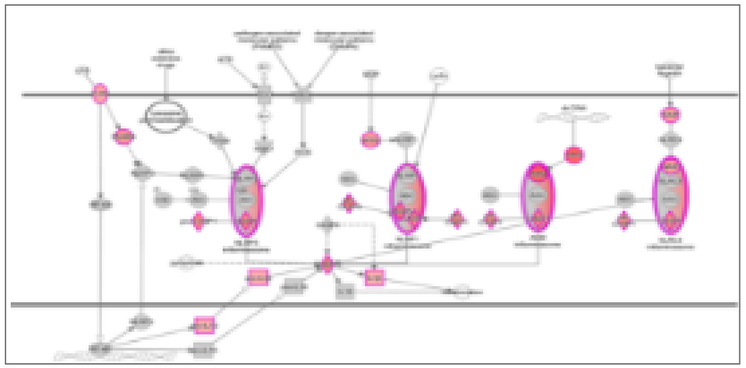
Stratification

- Clusterization of patients into endotypes reflecting pathophysiology

Analysis of dysregulated molecular pathways and target identification



Ingenuity pathway analysis (IPA)



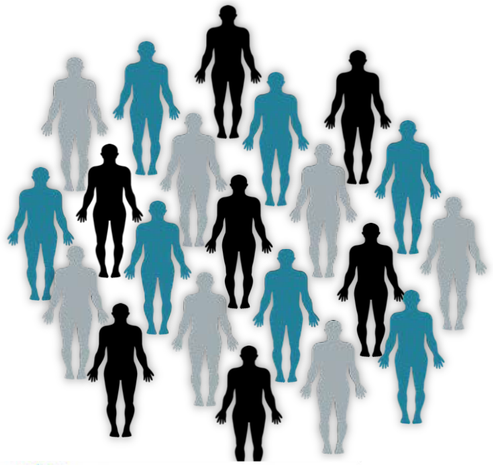
Selection of drug candidates interfering with therapeutic target(s)

- **Positioning of appropriate drug candidates in patient sub-populations (precision medicine)**
- **Design, selection, optimization of molecules interacting with the target**
- **Design of combination therapies**
- **Repurposing of existing molecules**

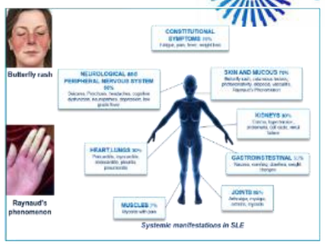
Modeling autoimmune diseases following extensive molecular profiling of patients

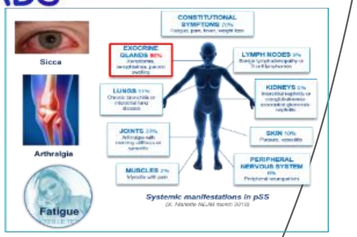
STUDY COHORT

SAMPLES & BIOBANKING



PRECISESADS

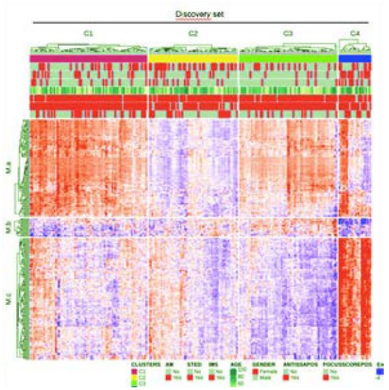




Cohort of 2000 patients with SADs including 382 pSS , 320 Lupus and 330 healthy volunteers

TRANSCRIPTOMIC DATA

Heatmap based on signature genes in pSS and Lupus PRECISESADS patients

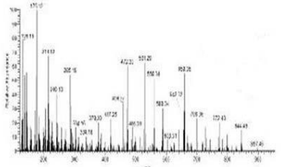


RNASeq data from whole blood

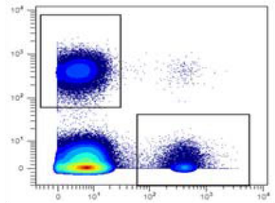
Clusters of patients

***OMICS* DATA INTEGRATION**

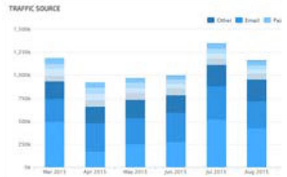
EPIGENETICS



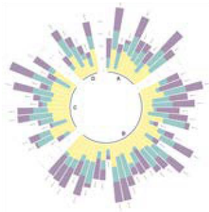
FLOW-CYTOMETRY



CYTOKINE DOSAGE

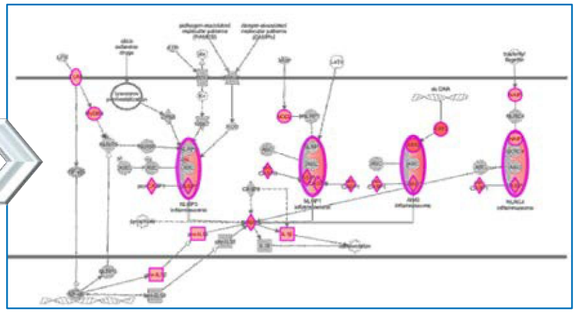


CLINICAL DATA



FUNCTIONAL ANALYSIS

PATHWAYS AND GENE SET ENRICHMENT ANALYSIS



nature COMMUNICATIONS
Nature Com, 2021, 12: 3523

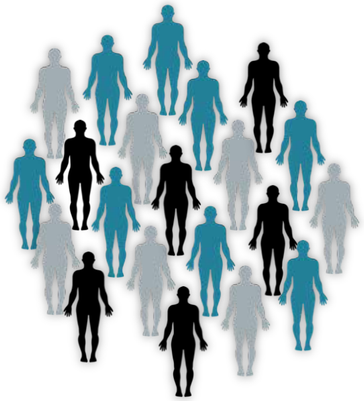
ARTICLE
https://doi.org/10.1038/s41467-021-23472-7 OPEN

A new molecular classification to drive precision treatment strategies in primary Sjögren's syndrome

Perrine Soret[1,29], Christelle Le Dantec[2,29], Emiko Desvaux[1,2], Nathan Foulquier[2], Bastien Chassagnol[1], Sandra Hubert[1], Christophe Jamin[2,3], Guillermo Barturen[4], Guillaume Desachy[1],

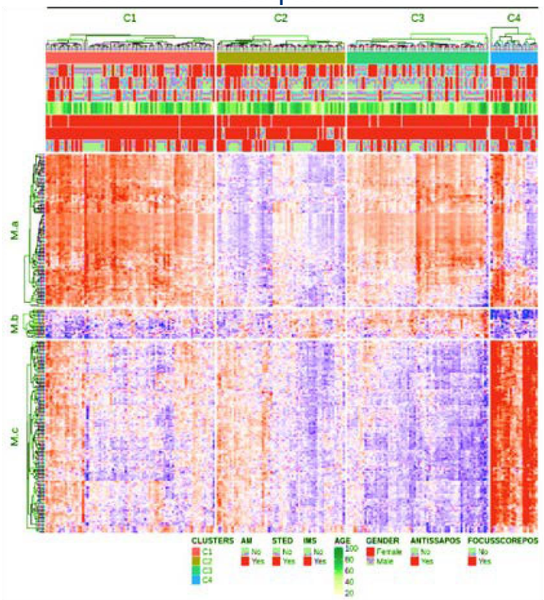
Stratification of pSS patients in 4 homogeneous molecularly defined clusters

304 pSS patients from the PRECISESADS cohort

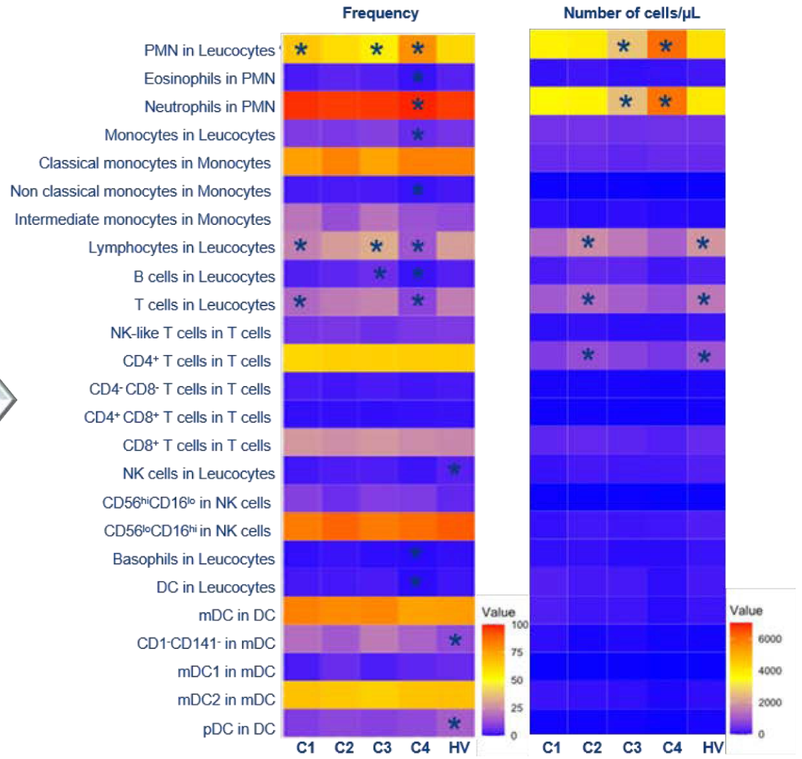


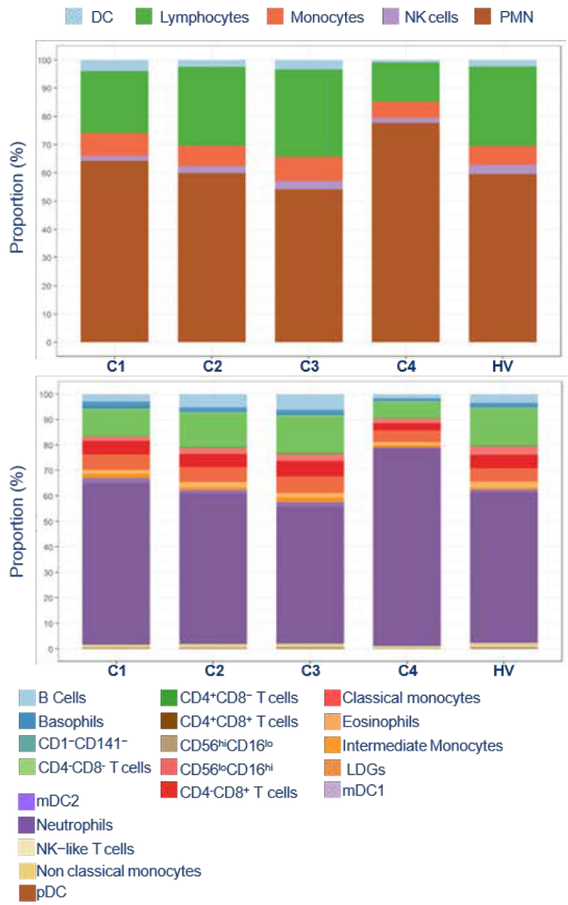
Clustering of pSS patients

Based on RNASeq data from whole blood



→4 distinct clusters of pSS patients defined by 3 gene modules (hierarchical and k-means clustering)

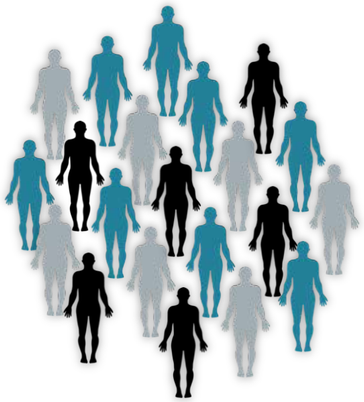




Soret *et al.* Nat Commun. 2021 Jun 10;12(1):3523.
doi: 10.1038/s41467-021-23472-7.

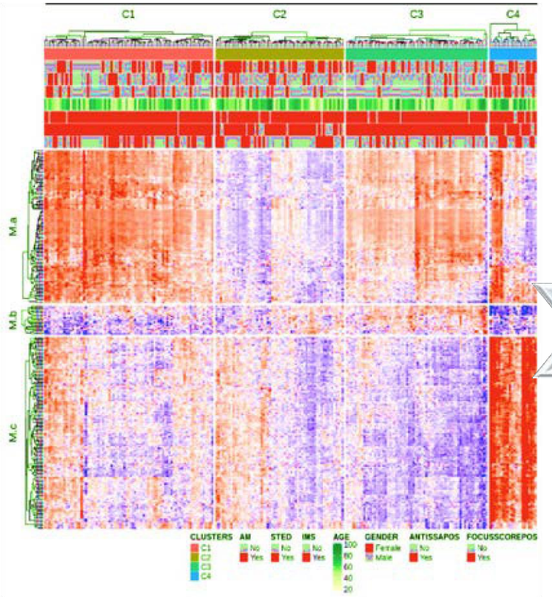
Identification of dysregulated molecular pathways in individual pSS patient clusters

304 pSS patients from the PRECISESADS cohort

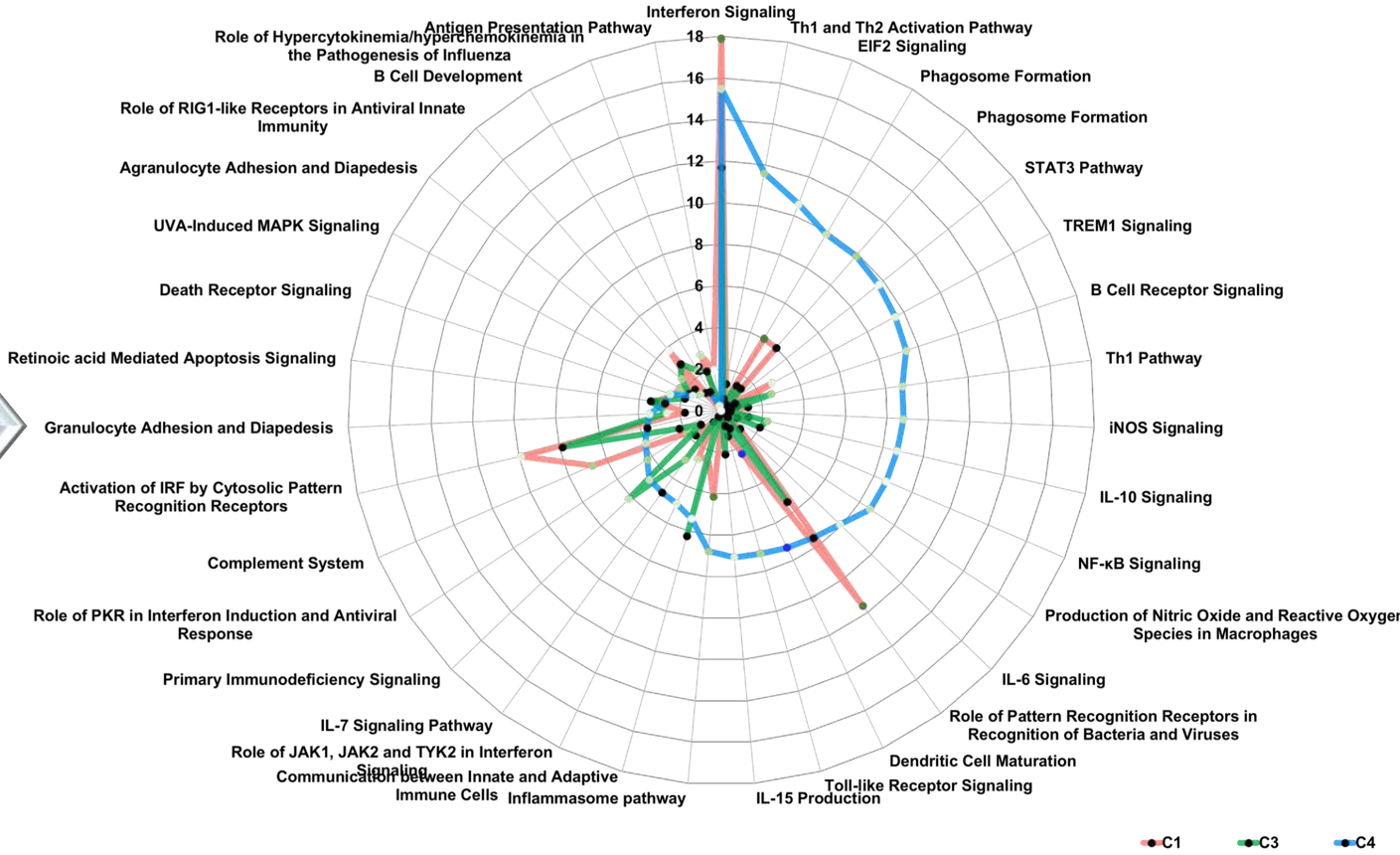


Clustering of pSS patients

Based on RNASeq data from whole blood



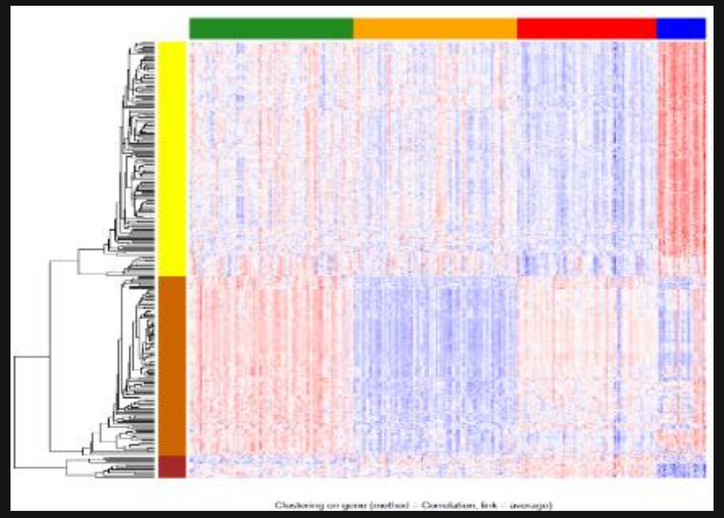
➔4 distinct clusters of pSS patients defined by 3 gene modules



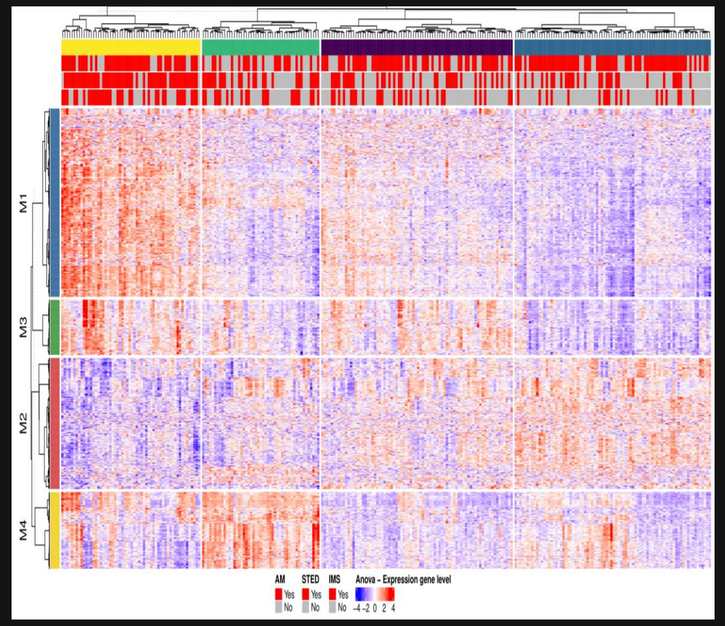
Soret *et al.* Nat Commun. 2021 Jun 10;12(1):3523.
doi: 10.1038/s41467-021-23472-7.

Functional annotation of each of 4 clusters of Lupus or Sjögren patients leads to working hypotheses regarding candidate therapeutic targets

Heat maps from transcriptomics data in the blood

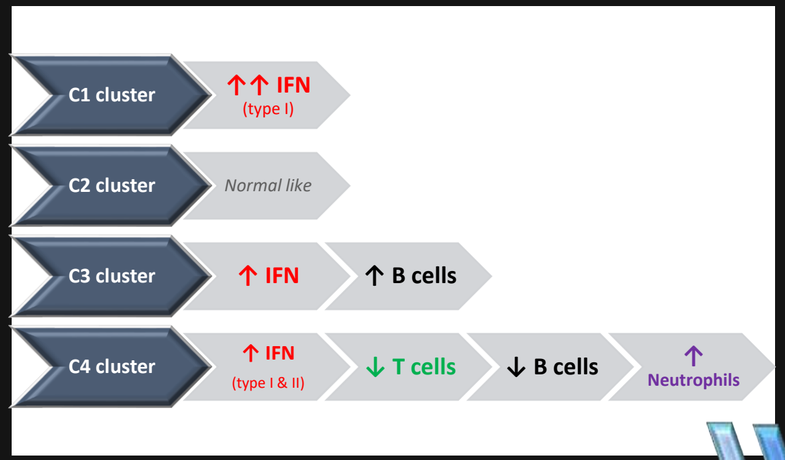


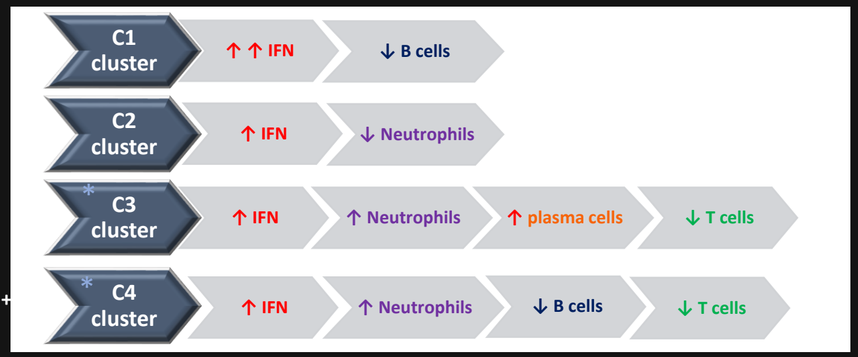
Sjogren



Lupus

Schematic representations of patient clusters

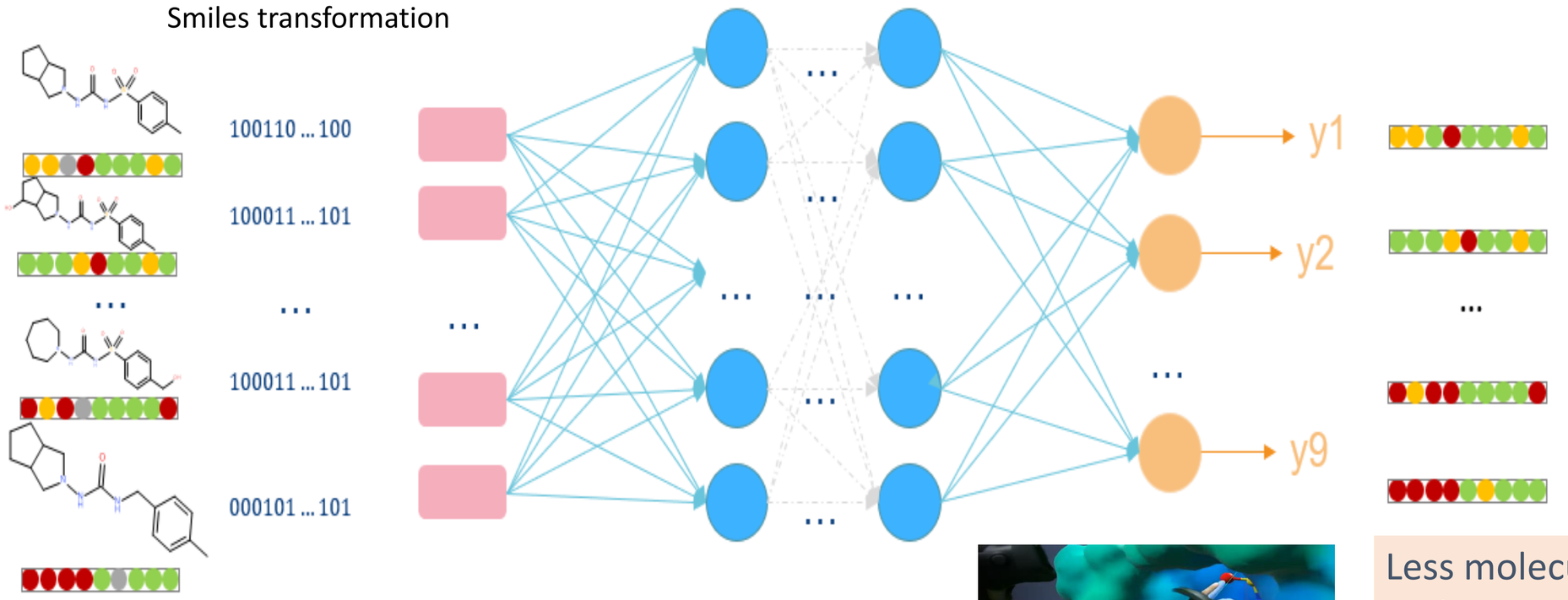




- IFNα pathway
- Combination therapies
- Pleiotropic targets

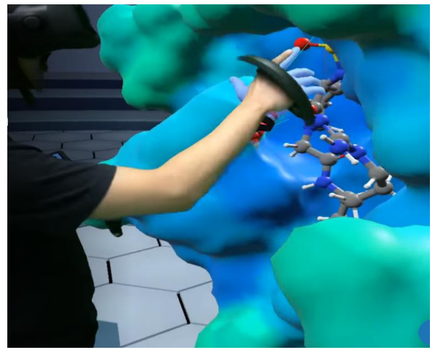
From target to drug design and optimization

- Machine learning to train neural networks for predicting properties of small chemical molecules



- Multitask parallel prediction of:
  - ✓ binding to the target (quantitative structure activity relationship, free energy prediction)
  - ✓ absorption, metabolism, distribution, excretion toxicity
  - ✓ stability…

- Generative AI to enhance the chemical space
  - *Generation of new molecules*
  - *Retrosynthesis*



Nanome

Less molecules to synthesize and test in wet labs

Industrializing AI-powered drug discovery: lessons learned from the *Patrimony* computing platform

Mickaël Guedj et al, 2022

Identify disease relevant targets
- New disease targets
- Repurposing
- Combinations
- Life cycle management

Industrialization
Web interface

Disease-agnostic → Structure

Servier

Public

Disease-specific → Modelling

Genetic | OMICs | Functional

- TTD
- GWASCatalog
- Uniprot
- NCBI Gene
- Cmap
- SIDER
- STRING
- MEDDRA
- GO
- EFO
- Drugbank
- LINCS
- GTEX
- OpenTarget
- KEGG
- RWE

sources…

Proprietary Network

neo4j

Target prioritization

Biological relevance | Causality | Safety | Innovativeness | Druggability

PATRIMONY

Selection of therapeutic modality and drug candidate(s)

Small molecule | ASO | MAb

Key achievements since 2018
- **3 diseases modeled** Sjögren & Lupus, 1 neurodegenerative disease
- **1 therapeutic project** launched for Sjögren
- **Proposal for existing drugs to be repurposed in severe COVID-19**

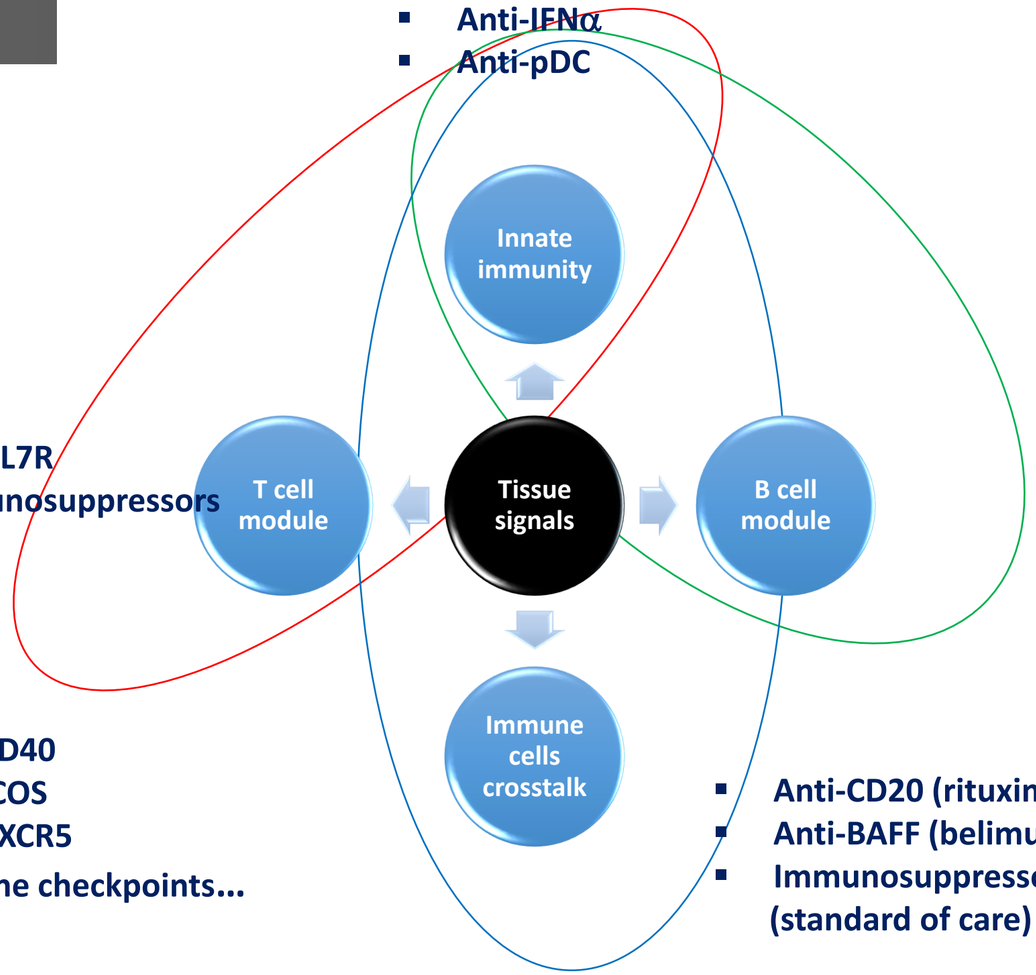
SERVIER

Model-based computational medicine to design combination therapies for autoimmune diseases

Desvaux E et al, 2021

- Anti-IFNα
- Anti-pDC

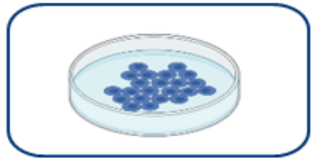
- Anti-IL7R
- Immunosuppressors



- Anti-CD40
- Anti-ICOS
- Anti-CXCR5
- Immune checkpoints…

- Anti-CD20 (rituximab)
- Anti-BAFF (belimumab)
- Immunosuppressors (standard of care)

X+Y



In vitro **validation**

- *Gene expression*
- *Immunophenotyping*
- *CRISPR-Cas9 gene editing*
- *SiRNA gene K.O*

In vivo **validation**

- *Gene editing/silencing*
- *Tool compound*

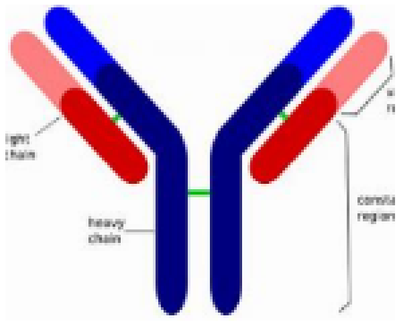
In silico **validation**

- *Gene K.O*
- *System perturbation*

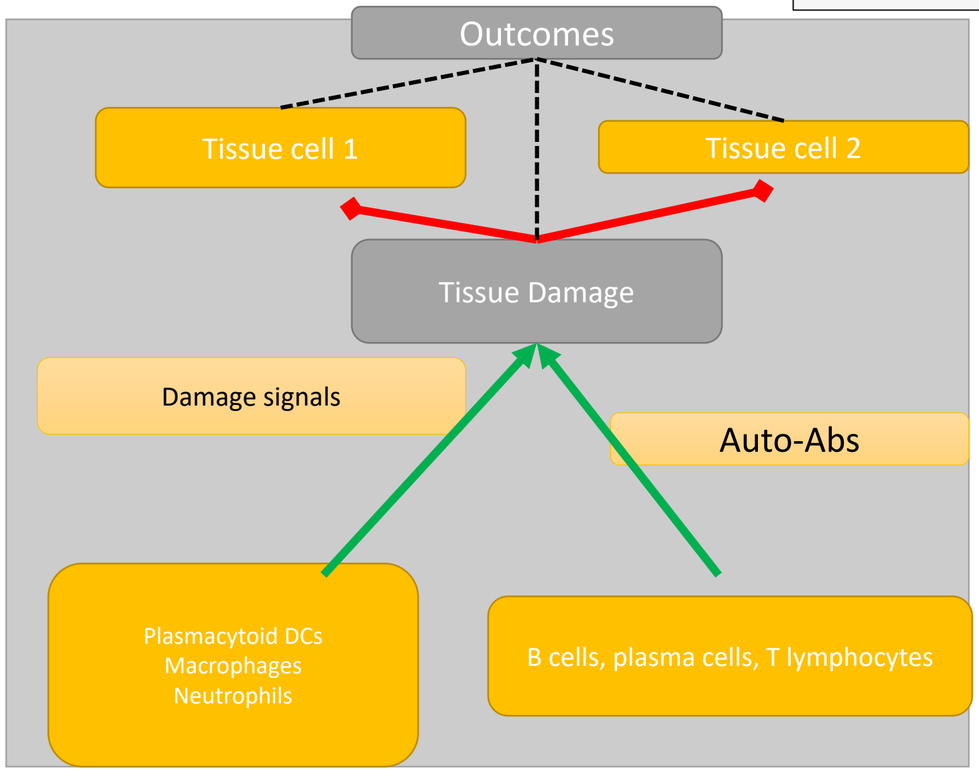
SERVIER

Quantitative system pharmacology modeling to predict the efficacy of an anti-IFNα Mab (S95021) in cutaneous Lupus

Pan neutralizing anti-IFNα monoclonal antibody



- ❑ Mechanistic, quantitative and dynamic model integrating **data on biological processes, clinical symptoms, drug characteristics (PK/PD modeling)**
- ❑ Model based on a thorough analysis of the scientific literature + proprietary data
- ❑ Representation as differential mathematical equations of **dynamic interactions between components**
- ❑ Prediction of drug efficacy, identification of candidate BMKs, dose selection, virtual patients, combination therapies



Molecular mediators

- IFNA and IFNAR
- Pro and anti inflammatory mediators
- Auto Abs, cytokines, chemokines

Cells

- Immune cells
- Keratinocytes

Physiological compartments

- Blood
- Lymph Nodes
- Target tissue

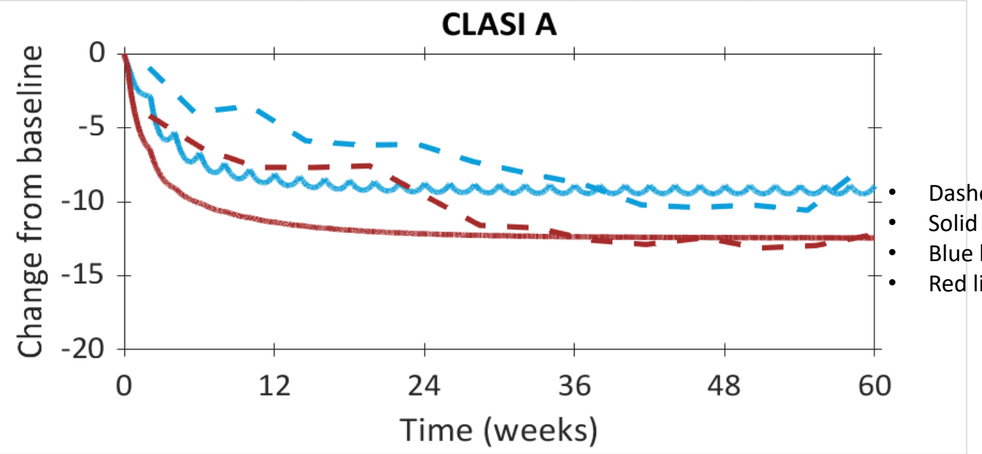
ROSA

Clinical outcomes

- Erythema, scaling, depigmentation…
  (**components of the CLASI A cutaneous scoring**)

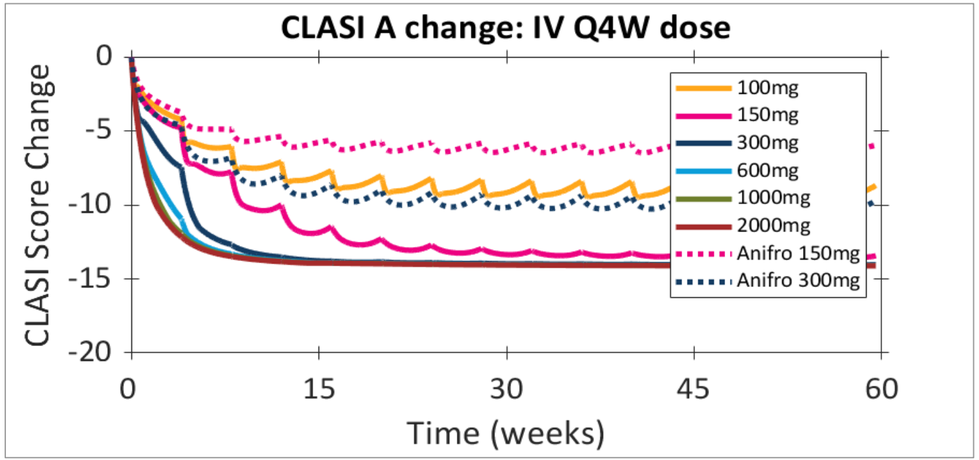
Quantitative System Pharmacology predicts the efficacy of the S95021 drug candidate to treat cutaneous Lupus

QSP confirms the efficacy of the anti IFNR MAb Anifrolumab (Astra Zeneca, registered to treat Lupus patients)



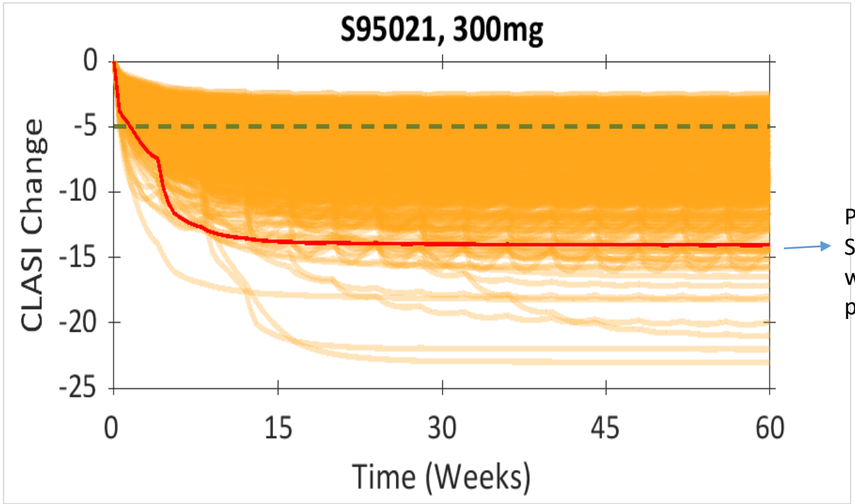
- Dashed lines: clinical data
- Solid lines: in silico modeling
- Blue lines: 150 mg
- Red lines: 300 mg

QSP predicts the efficacy of the S95021 Mab in cutaneous lupus, while suggesting the interest of high dosing regimens



Creation of virtual patients by varying parameters related to the targeted biological pathway

- *eg levels of IFN and its receptor, immune cells producing or responding to IFN*



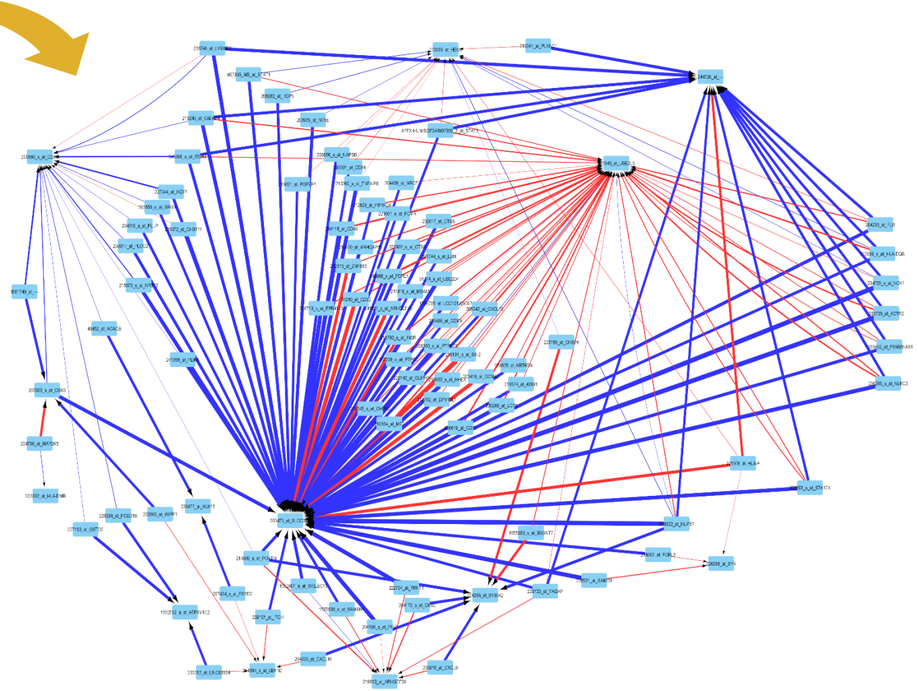
Predicted efficacy of S95021 300mg on whole Lupus patient population

Causal disease modeling of Sjogren in salivary glands by using network computing

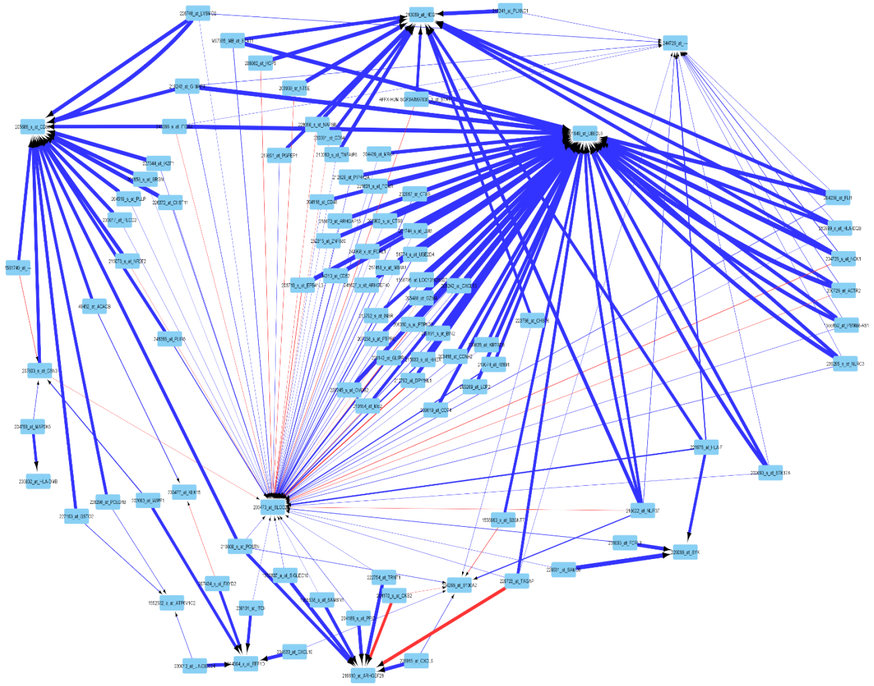
Modeling based on transcriptomics data in salivary glands of Sjogren vs Sicca patients

Interactomes of genes with inferences of influence

Down regulating
Up regulating



Sjogren in parotid glands



Control parotid

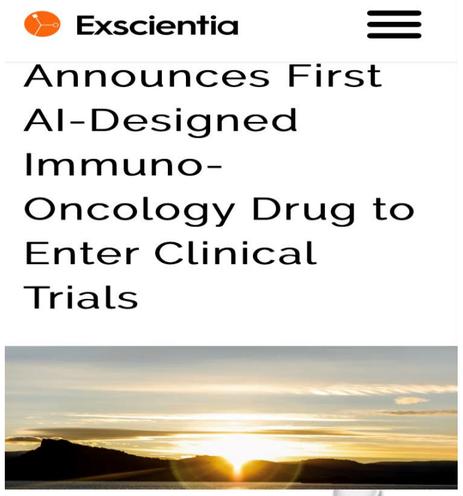
- Identification of master regulators (potential therapeutic targets)
- Computational perturbations to mimick the impact of single drug or combo therapies

Conclusions:
A revolution in new drug development

PATRIMONY

- Supporting decision-making all along drug discovery and development
- Shortening the timelines for the discovery phase
- De-risking the choice of therapeutic targets and drug candidates
- Decreasing the need for wet-lab experiments and clinical studies
- Increasing probabilities of success while reducing costs

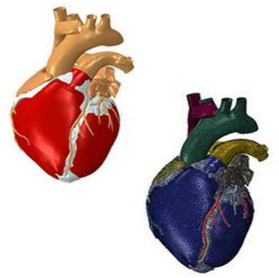
From design to preparation of phase 1 in one to two years



- Regulatory acceptance of evidence generated by predictive modeling

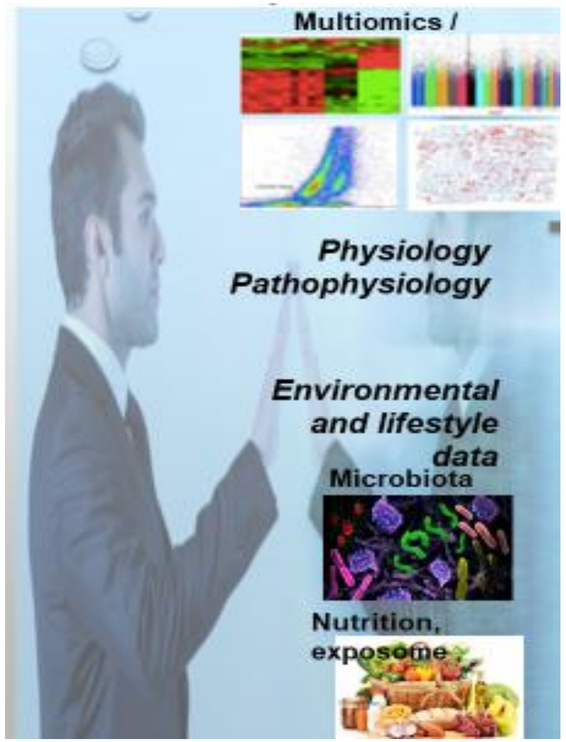
- Interest of major agencies (eg FDA and EMA) in Model-Informed Drug development to Refine, Reduce and Replace (3 R's)
- Statement from US authorities (Committee on Appropriations, 2018):

« In silico trials protect public health, advance personalized treatment, can be executed quickly and for a fraction of the cost of a full scale live trial »

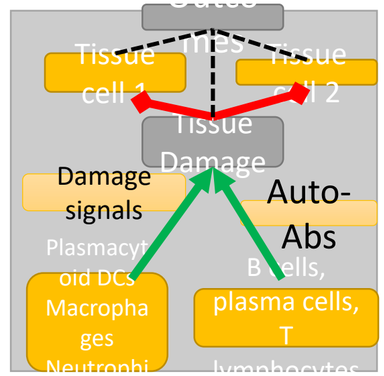


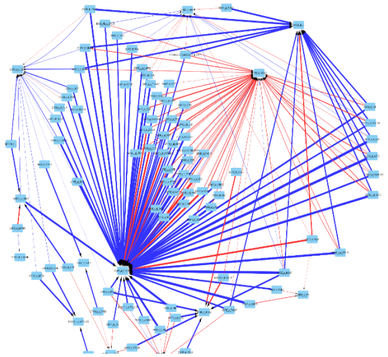
Perspectives: *in silico* prediction of drug efficacy as an important dimension of computational precision medicine

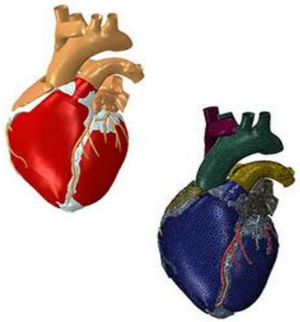
Patient specificities understood



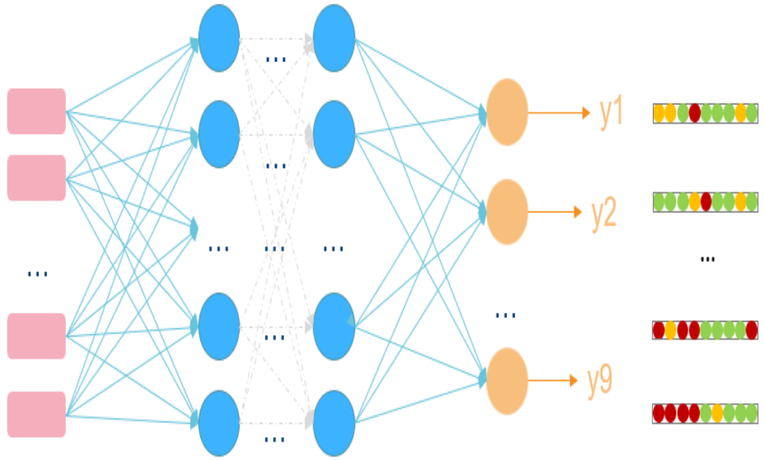
Drug efficacy and safety predicted across patient heterogeneity







Drug candidate properties predicted



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