"Integrative Modelling and Analysis of Molecular Pathways dysregulated in Rheumatoid Arthritis"

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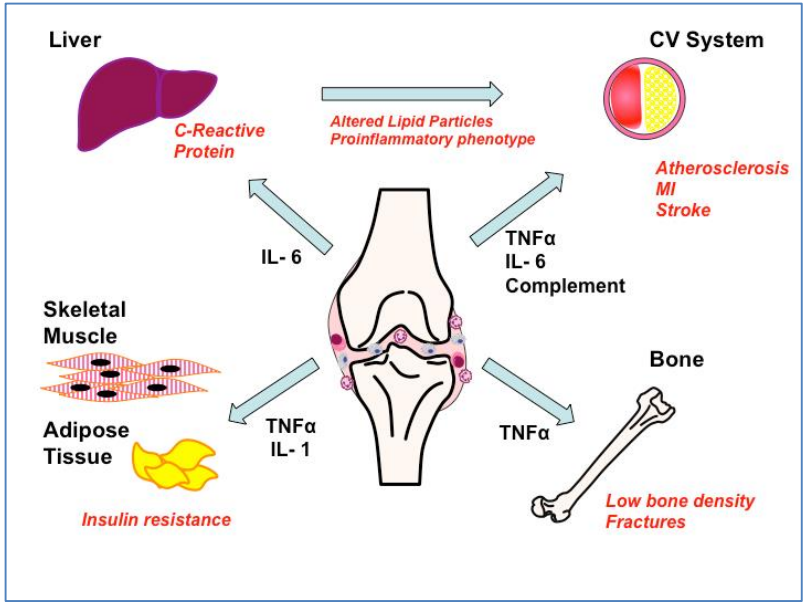
Rheumatoid Arthritis (RA):

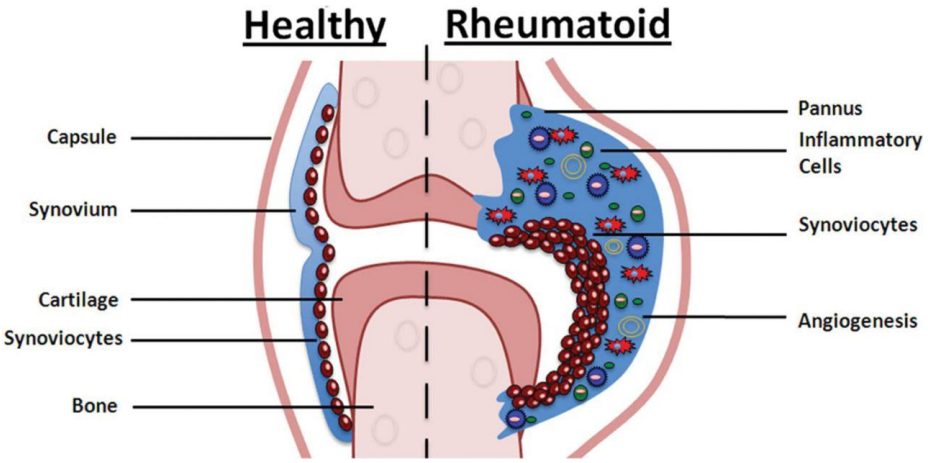
- Multifaceted autoimmune disease that causes chronic inflammation of the joints.
- **Etiology** of the disease remains **unclear**.
- Can also cause inflammation and injury in other organs in the body therefore considered as a **systemic disease**.



(Figure adapted from McInnes & Schett, 2011)

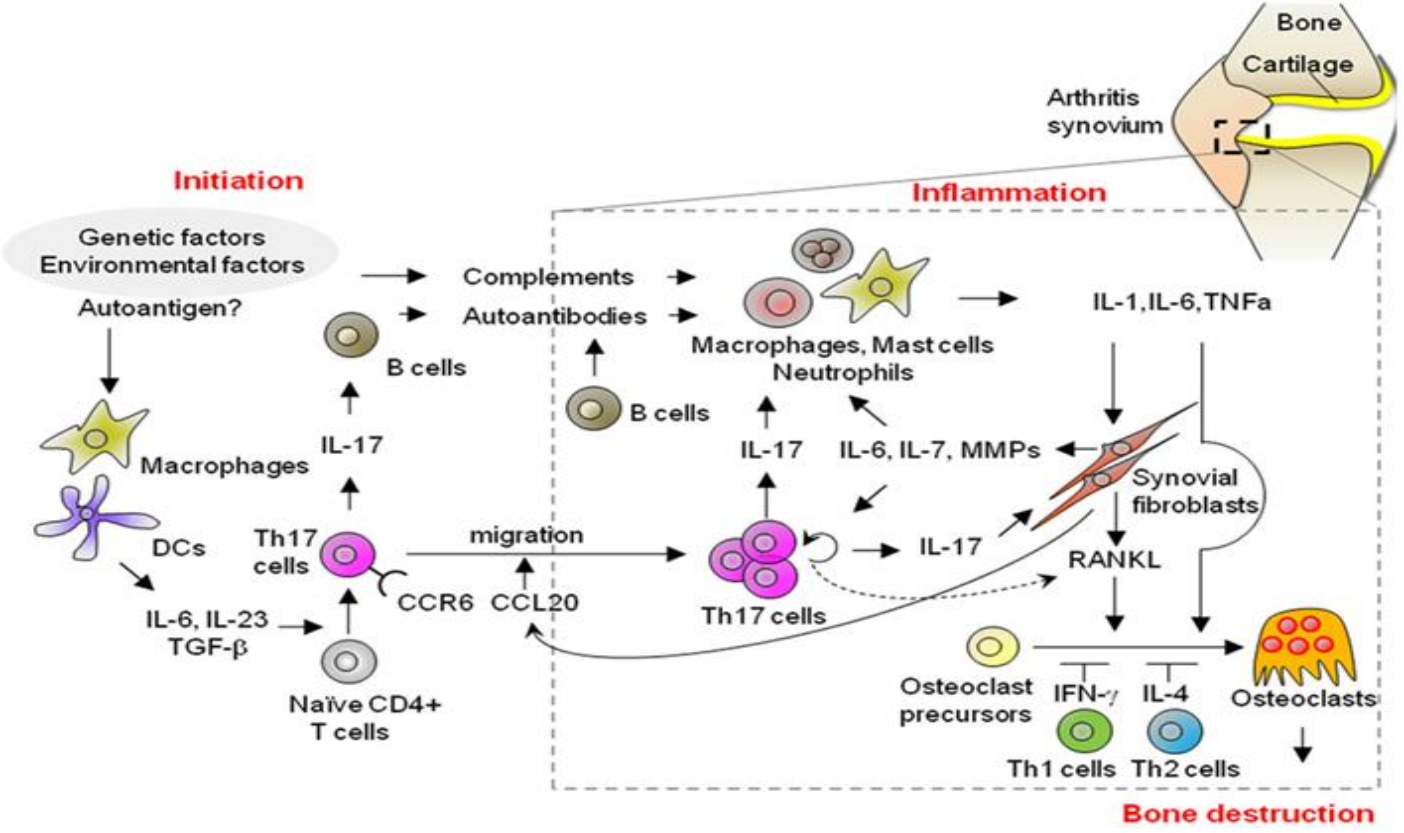
Rheumatoid Arthritis (RA):

- RA greatly affects the synovial joints in the body:
- **The immune system mistakenly attacks the synovial lining surrounding the joints leading to an inflammatory response.**
- **This response thickens the synovium by laying down fibroblasts and causes destruction of the cartilage and bone.**
- The result of this process is severe deformation.



(Figure adapted from Hawtree S, et al, 2013)

Cellular interplay in RA:

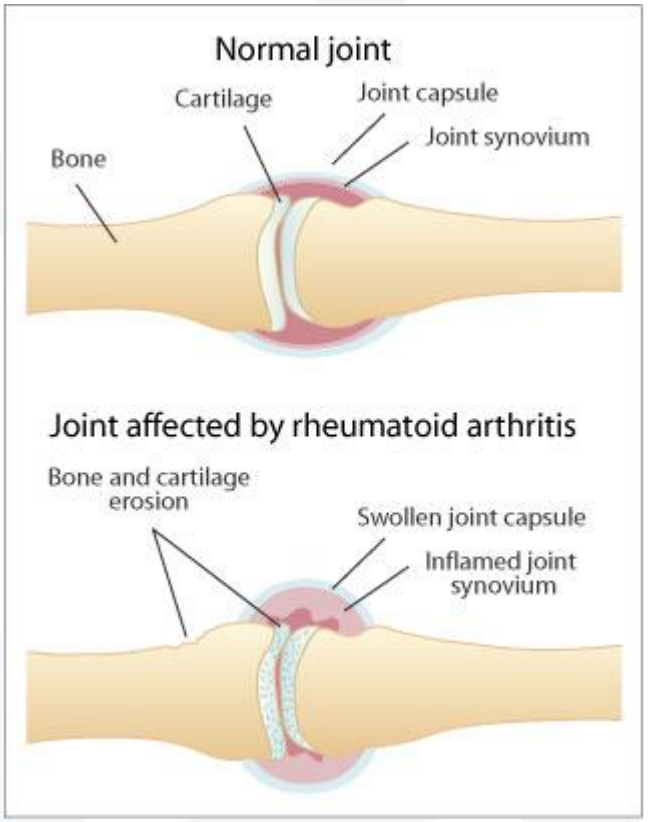


(Figure adapted from Komatsu, N. & Takayanagi, H. 2012)

Cartilage damage

- A hyperplastic synovium is the major contributor to cartilage damage in rheumatoid arthritis.
- Loss of the normally protective effects of synovium (e.g., reduced expression of lubricin) alter the protein-binding characteristics of the cartilage surface, promoting **FLS adhesion and invasion**.

- FLS synthesis of MMPs promotes disassembly of the type II collagen network.
- TIMPs, fail to reverse this destructive cascade.
- Limited regenerative potential of cartilage.



(Figure adapted from diseaseweb.org)

(Sabeh F. et al, 2010, Rhee DK et al, 2005)

Bone erosion

- Bone erosion occurs rapidly (affecting 80% of patients within 1 year after diagnosis) and is associated with prolonged, increased inflammation.

- Synovial cytokines, particularly macrophage colony- stimulating factor and receptor activator of NF-κB ligand (RANKL), promote osteoclast differentiation and invasion of the periosteal surface adjacent to articular cartilage.

- TNF-α and interleukin- 1, 6, and potentially 17 amplify osteoclast differentiation and activation.

(Shett G. et al, 2008, 2009, van der Heidje et al, 1995, Visser H. et al, 2002, Gravallesse et al, 1998,)

Objectives:

a. Creation of an updated, detailed, fully annotated, interactive **molecular map for RA** based on exhaustive curation of the existing literature and experts' validation

b. Construction of a **qualitative dynamical model**, in order to explore the dynamical properties of RA fibroblasts' activation

RA specific maps in dedicated databases:

- KEGG : 49 nodes, 18 articles used
- Qiagen : image graph, 9 articles used

- While pathways in autoimmunity can be found in other pathway databases, the disease specific maps are very few with relatively poor curation.

Molecular Interaction map of RA (Wu et al.2010):

- **Poorly annotated** CellDesigner file
- Large **heterogeneity** of source studies (PBMC, SF, PMN, cartilage)
- **False positives** possible (due to RNA expression data)
- Lack of **experts validation**
- Missing important RA players such as **HLA genes**, no **NF-κB pathway**
- No distinct **extracellular matrix compartment**
- « Phenotypes » associated with last input – sometimes irrelevant to RA (eg: metastasis)
- **Connectivity problems** (several nodes with very low degree)
- **25 studies**, including drug treatment experiments (2003-2009)

Current state of the RA map:

- We have updated the molecular map adding **35 new mediators**, derived from literature published after 2010, using public databases and exhaustive manual curation.

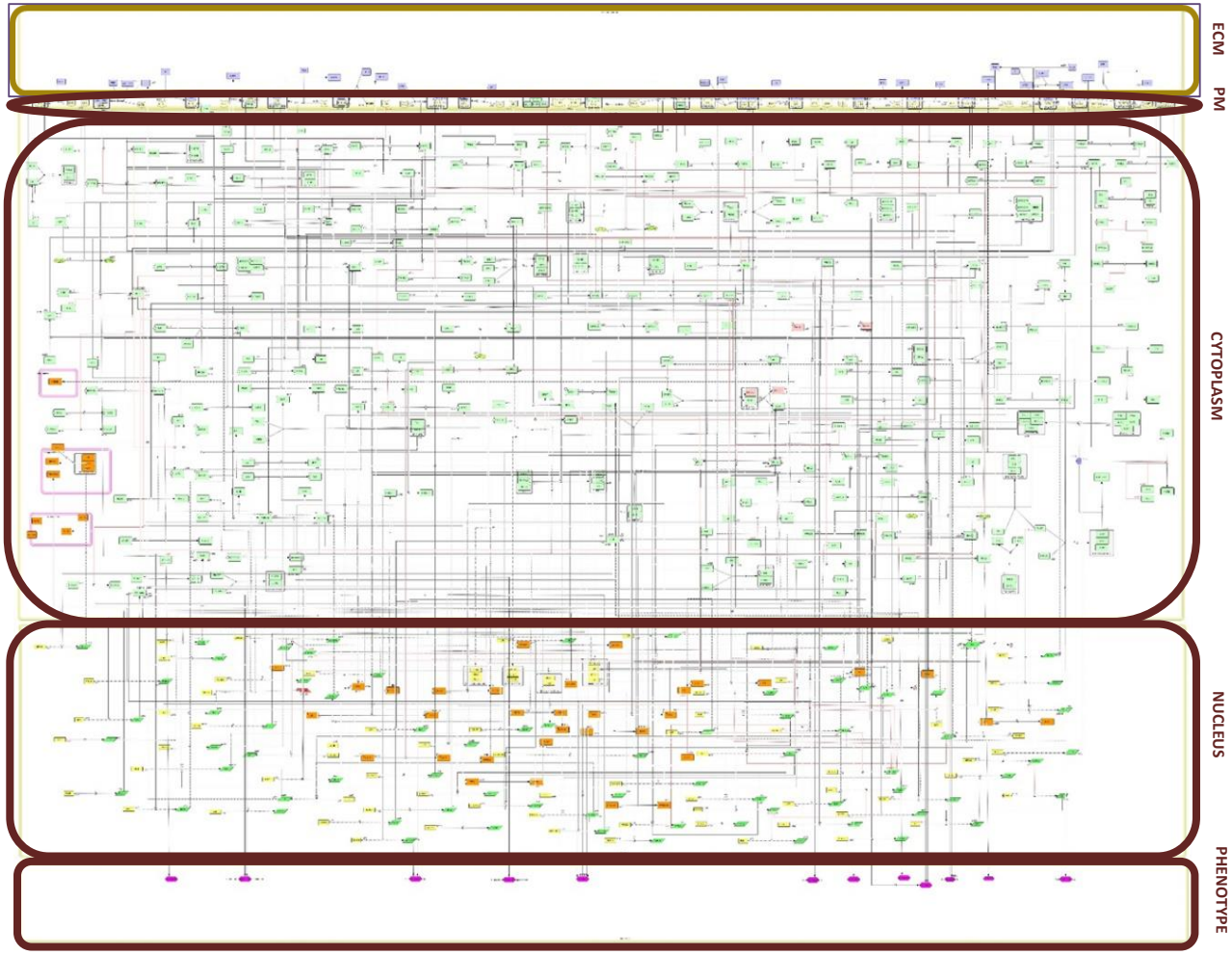
- All interactions and mediators are being reassessed using the same curation criteria.

- Detailed annotations including **PubMed identifiers, HUGO names, and Cell types** are also added to the map.

- Quality control of the integrated information and its representation is carried out by a collective effort of our collaborators (**biochemists, clinicians, immunologists), experts in RA.**

- **Ingenuity pathway analysis (IPA)** is used to check the relevance of the added molecules with RA.

Updated RA map:

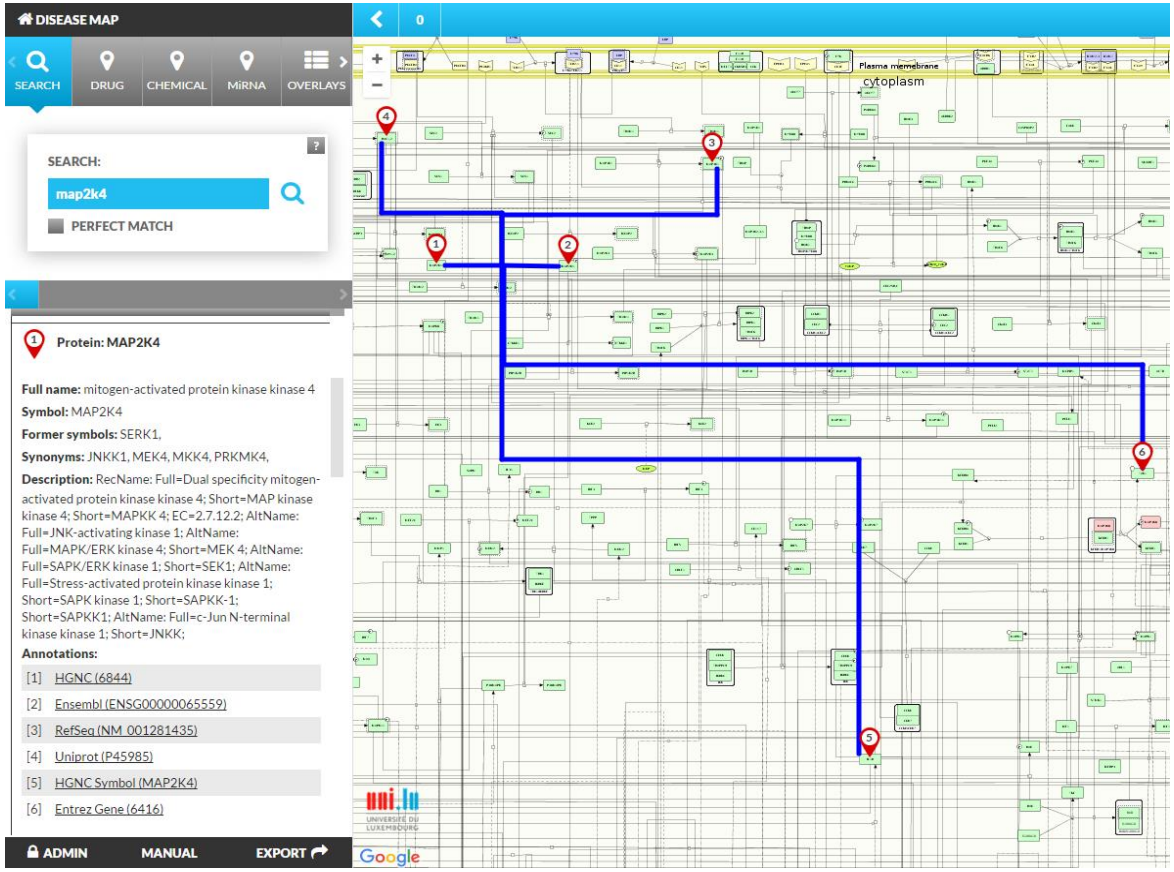


- Addition of ECM compartment
- Relocation of all extracellular and membrane proteins to ECM compartment (All in purple color)
- Addition of Plasma membrane compartment (contains receptors + membrane proteins)
- Deletion of nucleus compartment from the cytoplasm and relocation of its transcription factors to the gene regulation map now named as Nucleus
- Addition of Phenotype compartment that now includes all the phenotypes of the map
- Fully detailed MIRIAM annotation section

- Modularisation
- Testing many different algorithms avalaible and comparing results
- For the topological analyses we have used a number of Cytoscape plugins to calculate different topological parameters (centrality, shortest path, first neighbors etc.).

- Export in MINERVA format for easier access and navigation (collaboration with LCSB (easier for clinicians to use)
- **MINERVA software** is used to transform the RA map to an interactive Google map, allowing access to all information used and annotations.

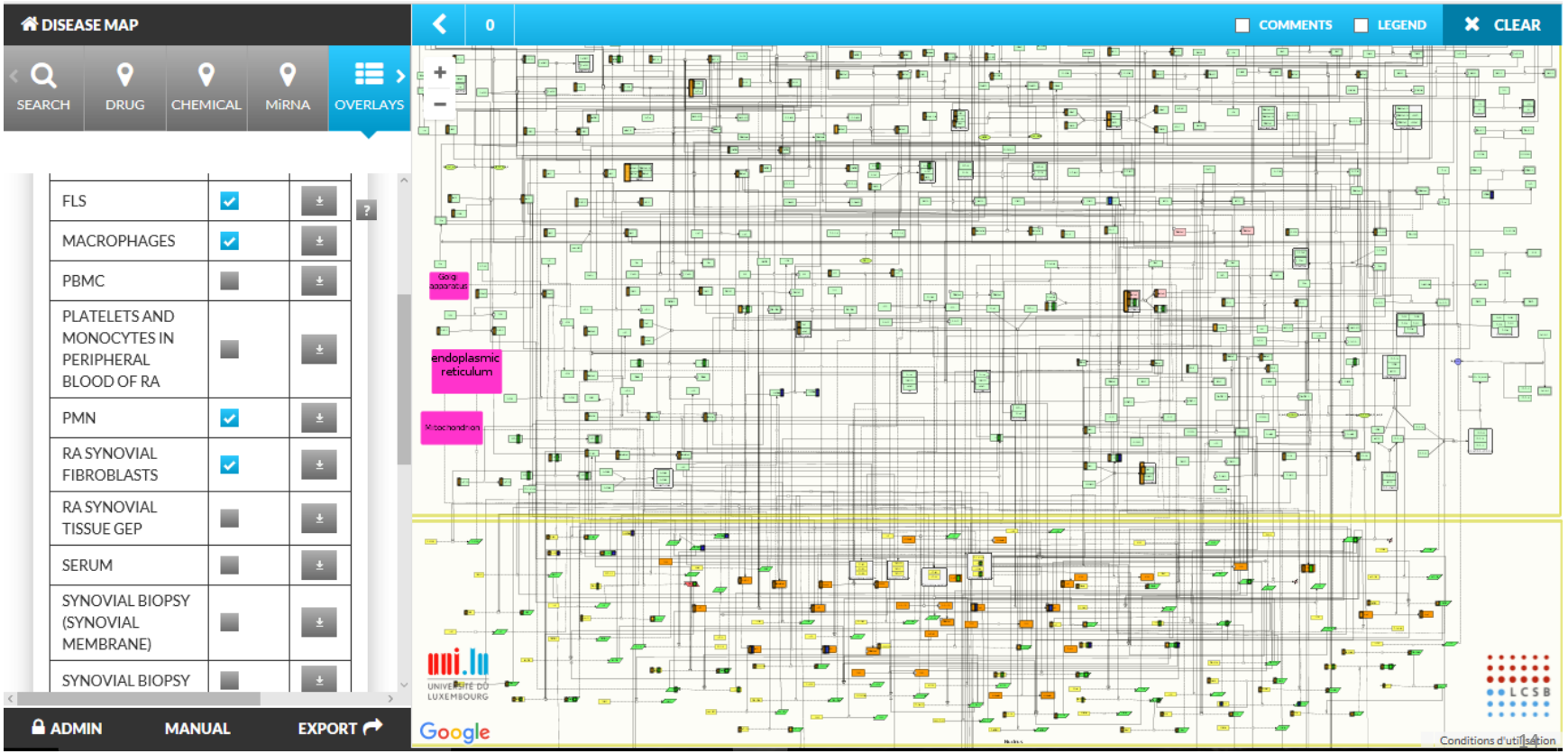
Visualization of RA map in MINERVA:



- Detailed description of all molecular species
- Automatic annotations for molecules and reactions
- Easy navigation
- Access to all data used for the map construction (PubMed IDs)

Visualization of RA map in MINERVA:

- Visualization of cell specific sub maps on the global map
- Mapping of –omic data
- Overlays of drugs and drug targets



Modelling RA fibroblasts' activation:

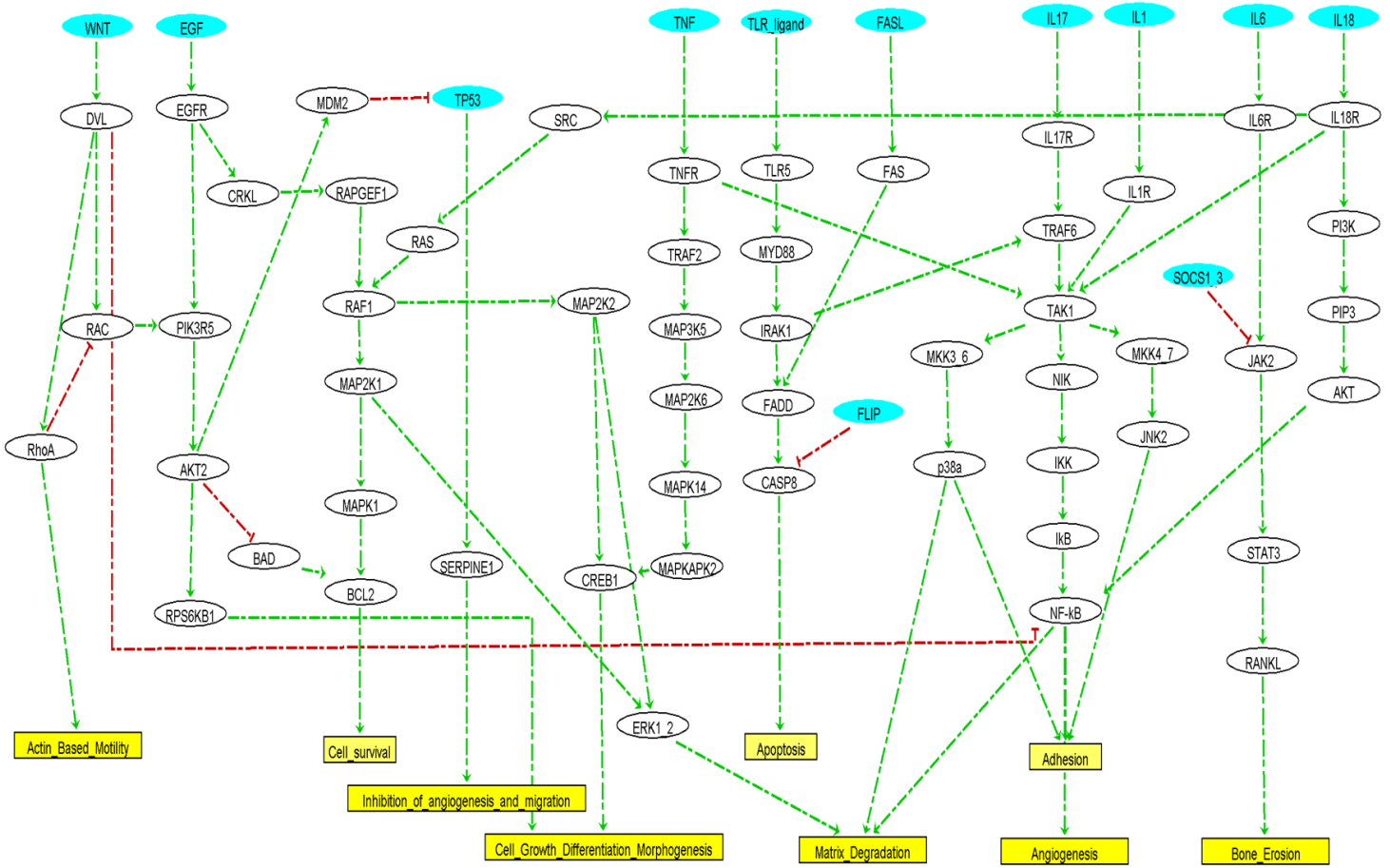
- Why RA fibroblasts?:

- Key cells in the chronic inflammation which occurs in RA.
- Express not only receptors for proinflammatory cytokines, but also TLRs .
- Exhibit high proliferative activity and produce large amounts of cytokines, chemokines, and matrix-degrading enzymes in response to proinflammatory cytokines and TLR ligands, which lead to the exacerbation of synovitis and joint destruction.
- Resistant to apoptosis
- Aggressive phenotype (highly invasive)
- Transformed aggressors of passive responders?

- With the help of the topological analysis, and Ingenuity pathway database screening we have selected a list of nodes and we are currently constructing the **regulatory graph** that will serve as a scaffold for the logical model.

- This regulatory graph of our model concerns fibroblasts' activation, consisting of 50 factors and we are further defining logical rules for each of them based on map and expert advice.

Building the regulatory graph for RA fibroblasts using GINsim:



Questions:

- Can we induce apoptosis? (either by forcing apoptosis pathway or by blocking cell survival pathways)
- Can we block structural damage by blocking intermediate components?
- Are they subjected to negative feedback control like macrophages? [*Priming in response to pro-inflammatory cytokines is a feature of adult synovial but not dermal fibroblasts*, Crowley et al, 2017]
- Do they differentiate depending on the initial stimuli? [*Rheumatoid synovial fibroblasts differentiate into distinct subsets in the presence of cytokines and cartilage*, Croft et al, 2016]
- Do we need to take into account fibroblast subset heterogeneity? [*Single Cell Transcriptomics and Flow Cytometry Reveal Disease associated Fibroblast Subsets in Rheumatoid Arthritis,* Mizoguchi et al, 2017, preprint]

Work in progress 

- To progressively improve the predictive power of the resulting model, computational results will be systematically confronted with experimental data.

- It could also serve as a basis for computing phenotype probabilities using **MaBoSS**, a software for simulating continuous/discrete time Markov processes defined on the state transition graph describing the dynamics of a Boolean network.

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