

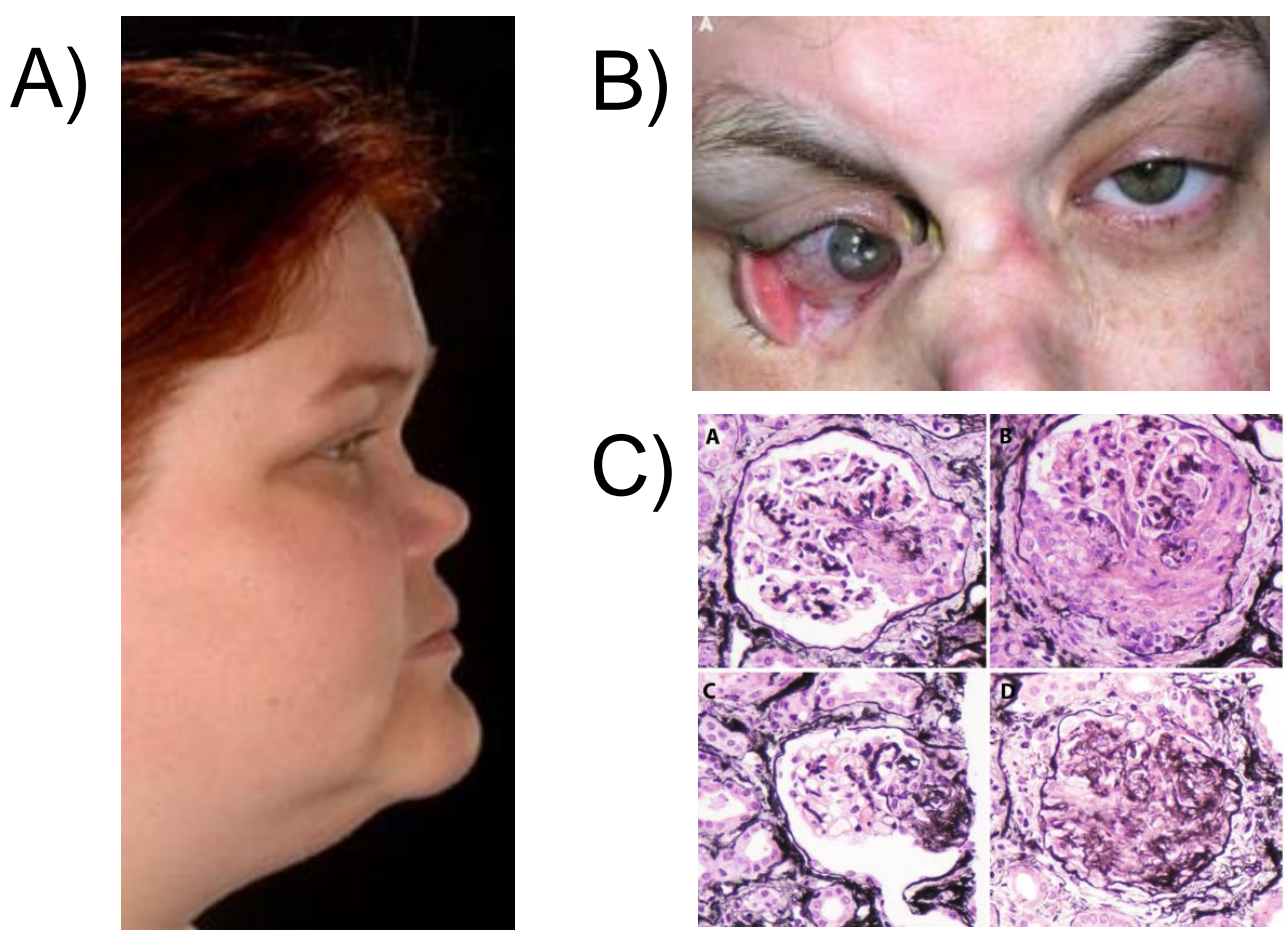


# Granulomatosis with Polyangiitis: Knowledge integration and network analysis towards mechanistic understanding of underlying pathogenesis

Granulomatosis with polyangiitis (GPA) [1] is a rare multisystem autoimmune disease targeting the upper/lower respiratory tract and the kidneys. Its characteristic features include necrotizing granulomatous inflammation and pauci-immune vasculitis in small- and medium-sized blood vessels. The mechanism underlying the pathogenesis of GPA remains unknown although a number of exogenous factors, genetic and protein biomarkers have been suggested to be of aetiological relevance. This makes the diagnosis and treatment less efficient and to date there is no cure for GPA.

Here, we have compiled and integrated heterogeneous knowledge about GPA from several resources that include meta-analysis [2,3], database resources and literature, and have generated a knowledge-network that highlights the molecular mechanisms involved in the pathogenesis of GPA. This integrated multi-layered network forms a base for identifying the regulatory clusters that may help to prioritize diagnostic markers or therapeutic candidate genes.

We envision to dive deeper into understanding the mechanism of key molecular targets of GPA from the above regulatory clusters using mathematical models. Simulating the effect of different levels of disturbance affecting the regulatory clusters may provide mechanistic insights to different aspects of the disease, for example, immunological aspects of disease relapse, and resistance mechanism to a particular drug. We believe our analysis would help designing new therapies and clinical investigations for treating GPA.



**Clinical manifestations and renal histopathology**  
A) Saddle nose deformation due to cartilage damage (PMID:25050457), B) Scleritis (eye) (PMID:15673805), C) Glomerular lesions (including crescents and sclerosis) (PMID:25056155)

## Multi-omics knowledge-network of GPA

The **phenotype** of GPA share some characteristics with other diseases. The major challenge is to establish better differential diagnosis methods and personalised treatment.

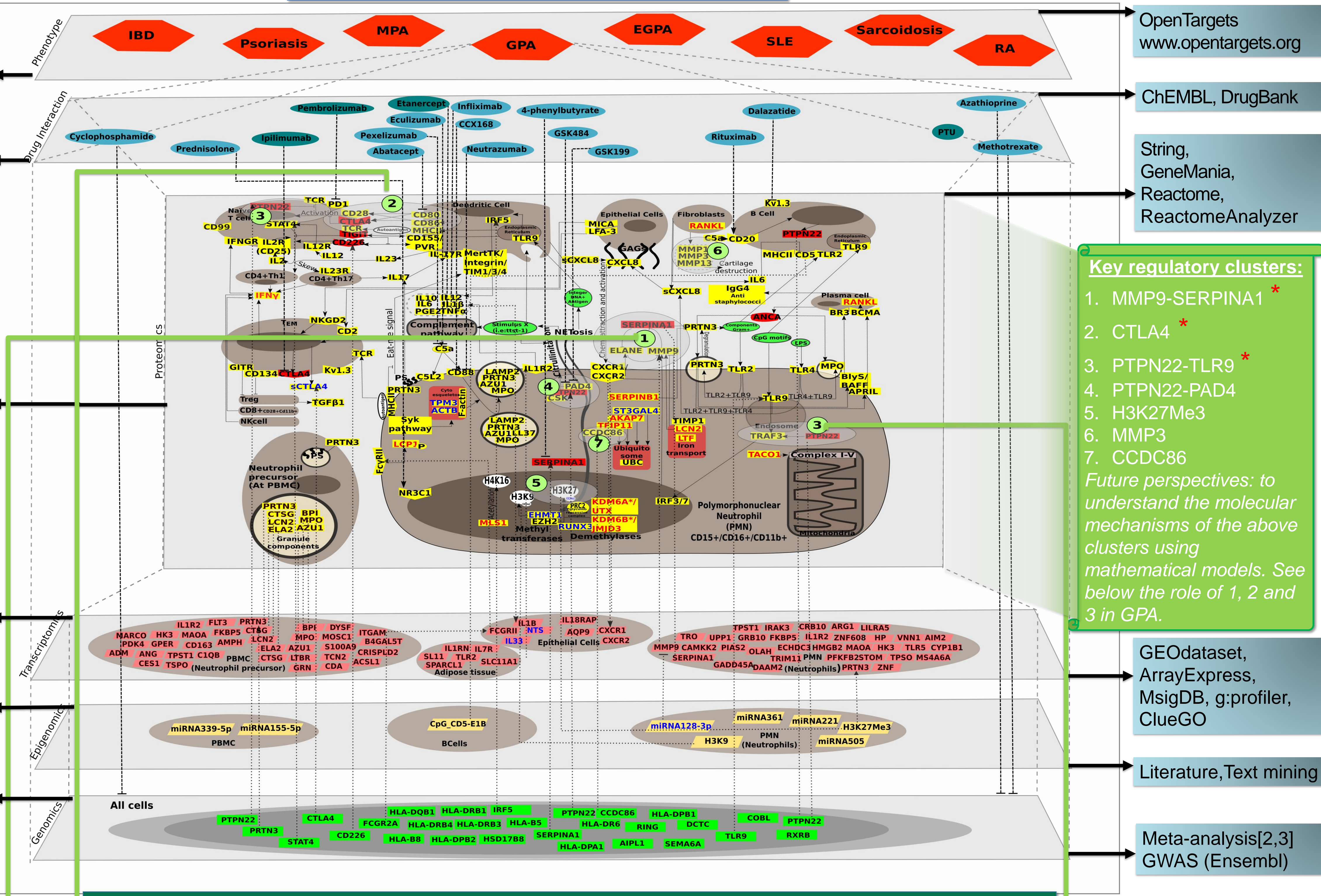
**Drug** therapy for GPA (light blue) and drugs used for other indications that trigger GPA as a side-effect (dark blue).

**Proteomics** data contains up and down regulated proteins, defective proteins and already targeted proteins. This layer form the base to identify regulatory clusters that play significant role in GPA. Regulatory clusters identified are numbered 1 to 7 and listed on the right in the green panel. The detailed mechanism of the regulatory clusters 1, 2 and 3 is illustrated below.

**Transcriptome** analysis provided genetic signatures, which seems to be a promise for more accurate diagnosis.

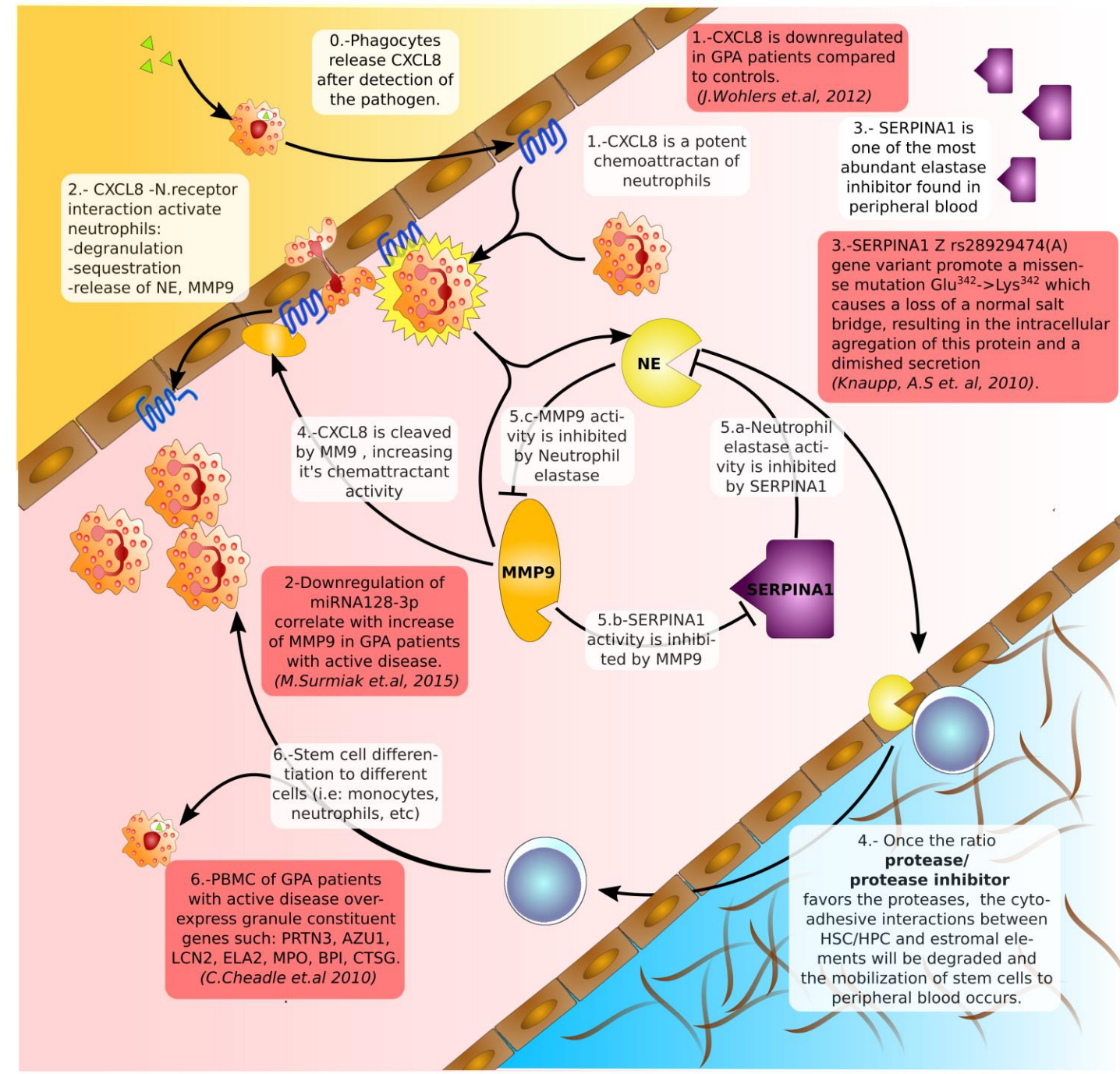
**Epigenetic** data such as CpG methylation, Histone marks and miRNA are correlated with the active disease.

GWAS and recent meta-analysis indicate a correlation between risk or protection of the disease and **gene variants** as SNPs or CNV.

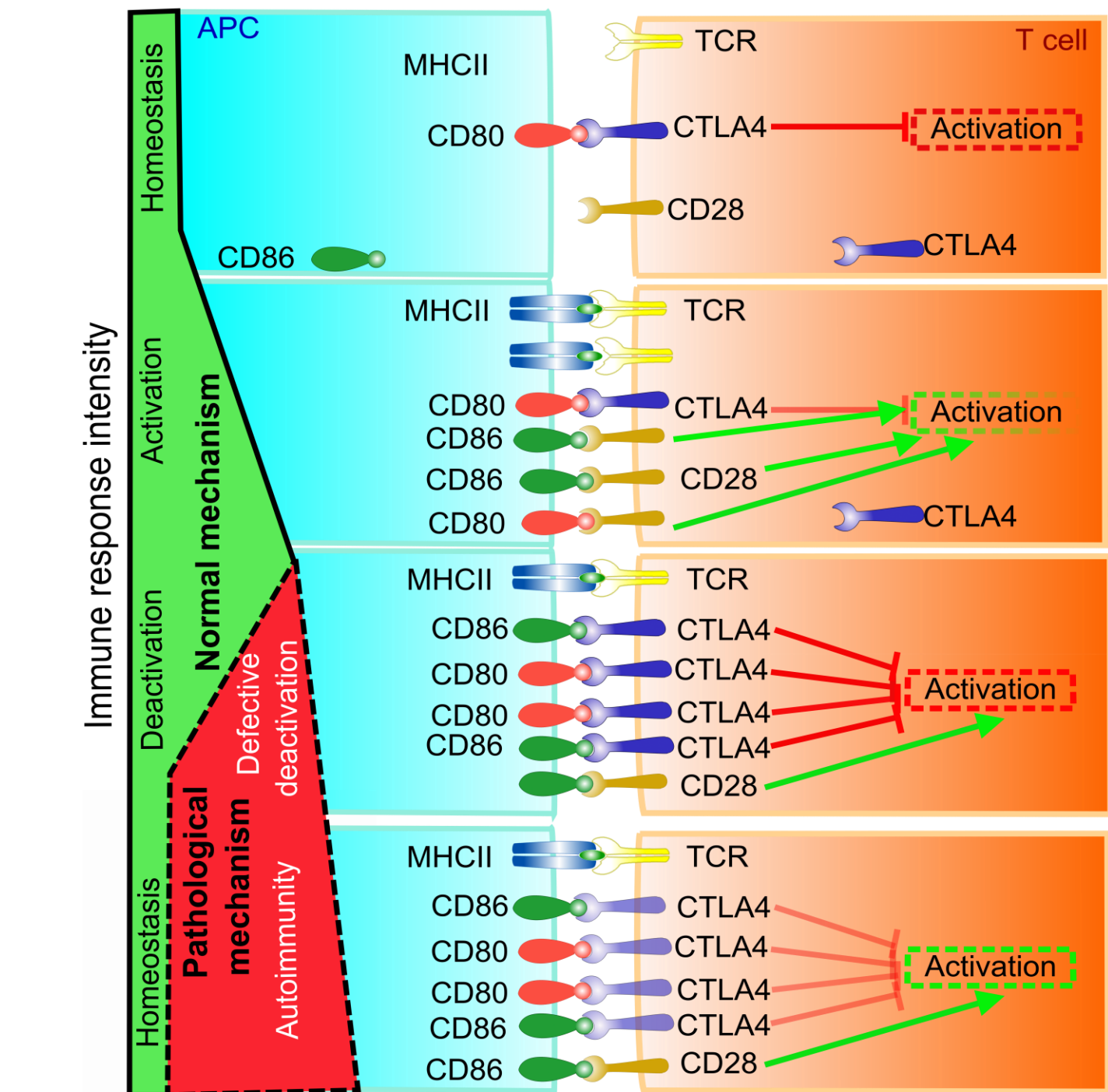


## Significant role of 1) MMP9-SERPINA1, 2) CTLA4 and 3) PTPN22 in GPA: towards developing mathematical models to understand the molecular mechanisms

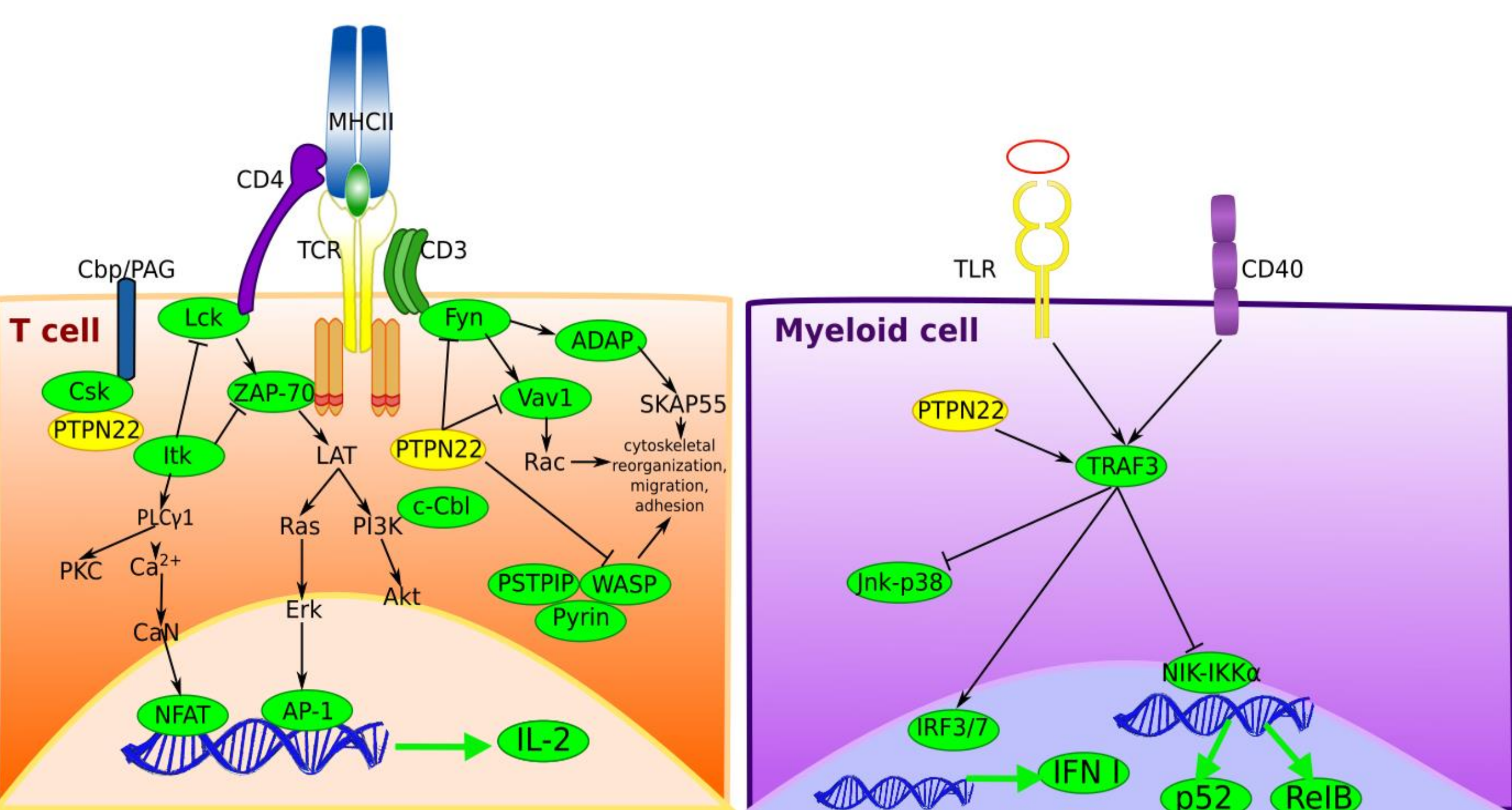
**1. MMP9-SERPINA1\* dynamics**  
SERPINA1 Z allele, dysregulated miRNA-128-3p and increase of MMP9 are well evidenced in GPA. White and red box describe the normal and pathological conditions, respectively.



**2. CTLA4\* co-inhibitory function**  
CTLA4 is essential to stop the T-cell activation and proliferation. SNP variant CTLA4 rs231775(G) is highly related with low amounts of the soluble form of CTLA4.



**3. PTPN22\* dual functionality**  
Function of PTPN22 depends on the cell. In T-cells, PTPN22 partially inhibits the pathway of T cell activation, whereas, in myeloid cells, PTPN22 participates in the stimulation of these cells after TLR stimulation. The gene variant PTPN rs2476601(A) is highly related to GPA risk.



### References:

[1] Csernok E, Gross WL. Current understanding of the pathogenesis of granulomatosis with polyangiitis (Wegener's). *Expert Rev Clin Immunol*. 2013;9(7):641-8.  
[2] Rahmattulla C, Mooyaart AL, van Hooven D, et al. Genetic variants in ANCA-associated vasculitis: a meta-analysis. *Ann Rheum Dis*. 2015;annrheumdis-2015-207601.  
[3] Kronbichler A, Kerschbaum J, Grundlinger G, Leierer J, Mayer G, Rudnicki M. Evaluation and validation of biomarkers in granulomatosis with polyangiitis and microscopic polyangiitis. *Nephrol Dial Transplant*. 2015;1-7.