



Modeling the regulatory network controlling dendritic cell differentiation from human monocytes

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Tutor committee:

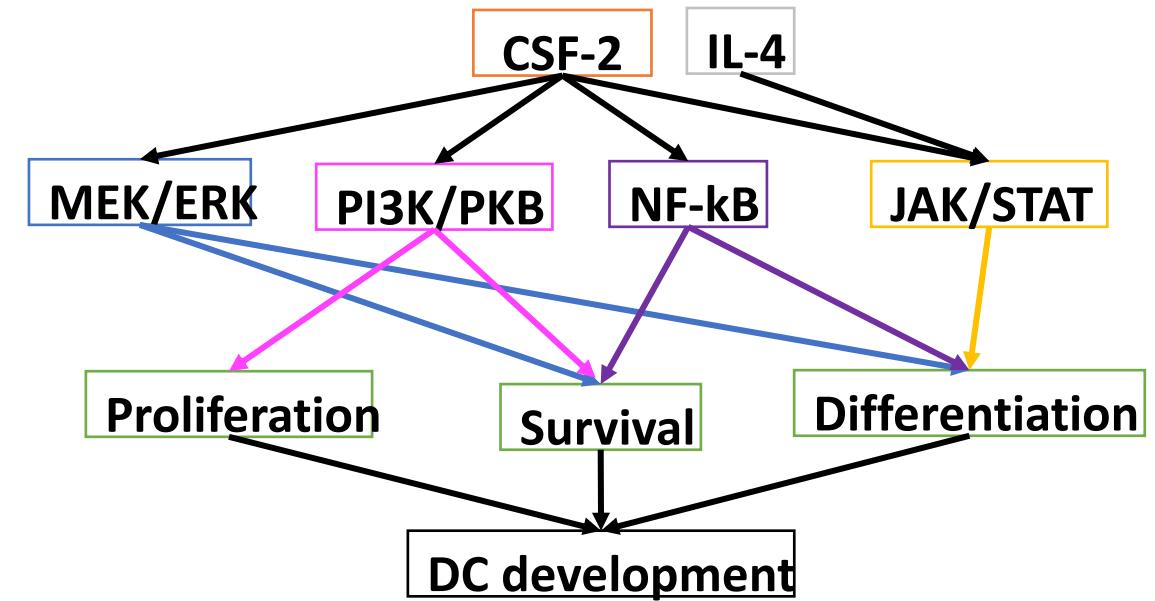
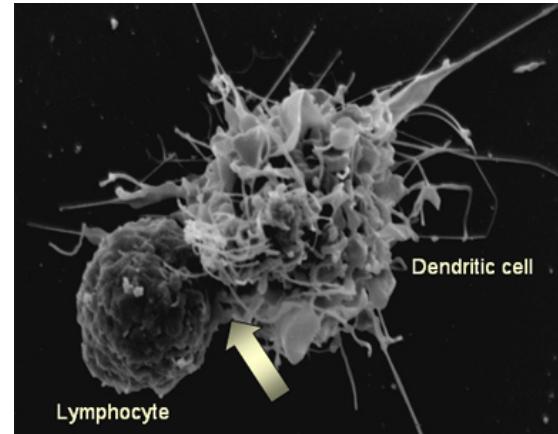
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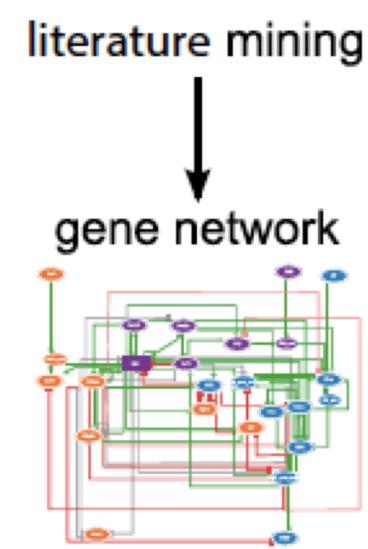
Dr. Cei Abreu-Goodger

Dendritic cells (DCs)

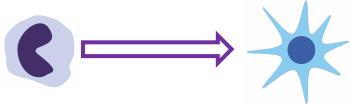
- Belong to the immune system.
- Antigen presenting cells.
- Activate naïve T lymphocytes.
- Trigger adaptive immune response.



Building a logical model



- Human data
- Same conditions of differentiation
- At least one reference for interaction



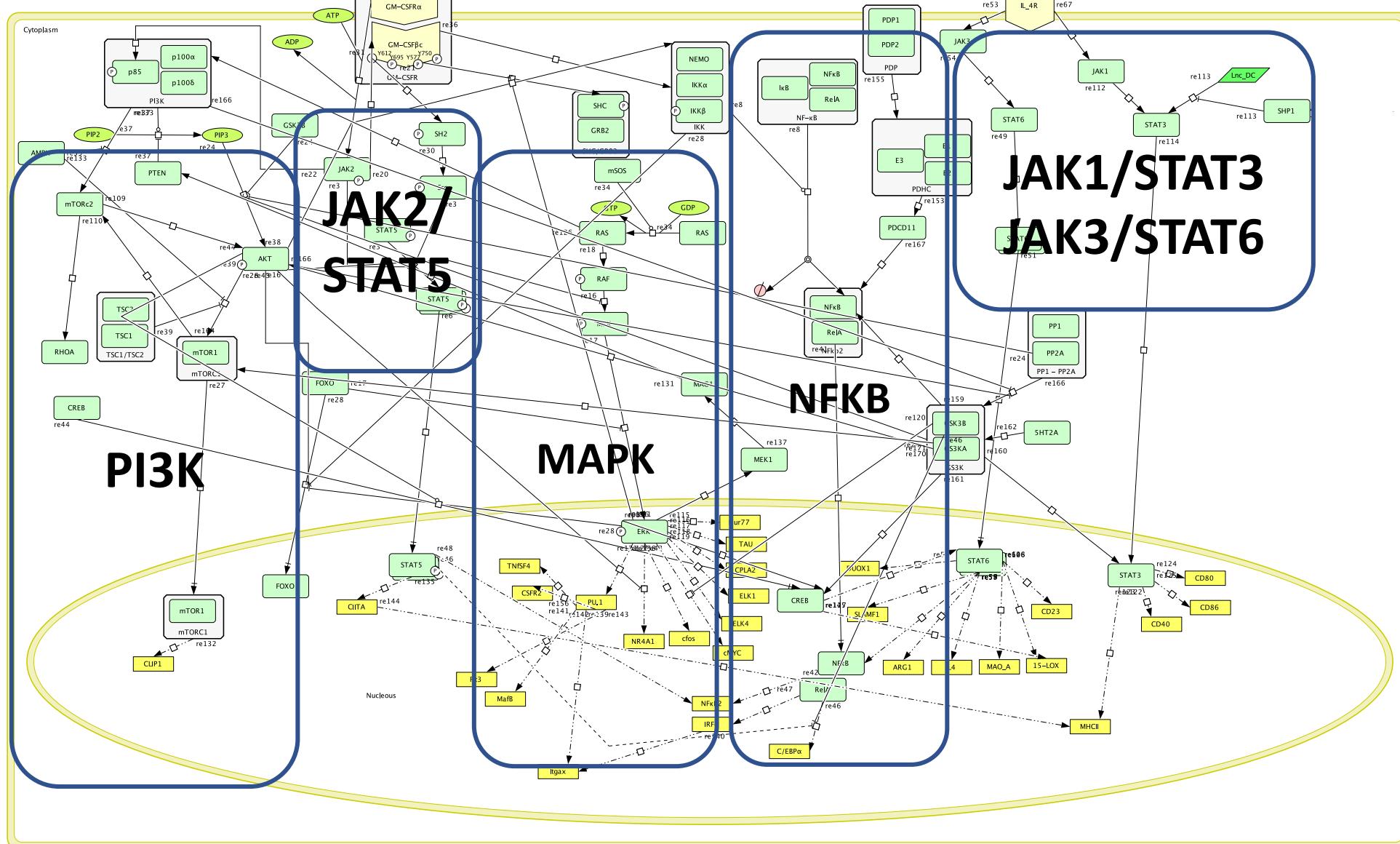
Aims

- To build a logical **model** that describes the **Monocyte** to **Dendritic cell** differentiation *in vitro*
 - Signaling pathways: CSF-2 and IL-4
- Verify the coherence between the network and transcriptional data for both cell types
- Improve the model using differential express genes and new regulation interaction

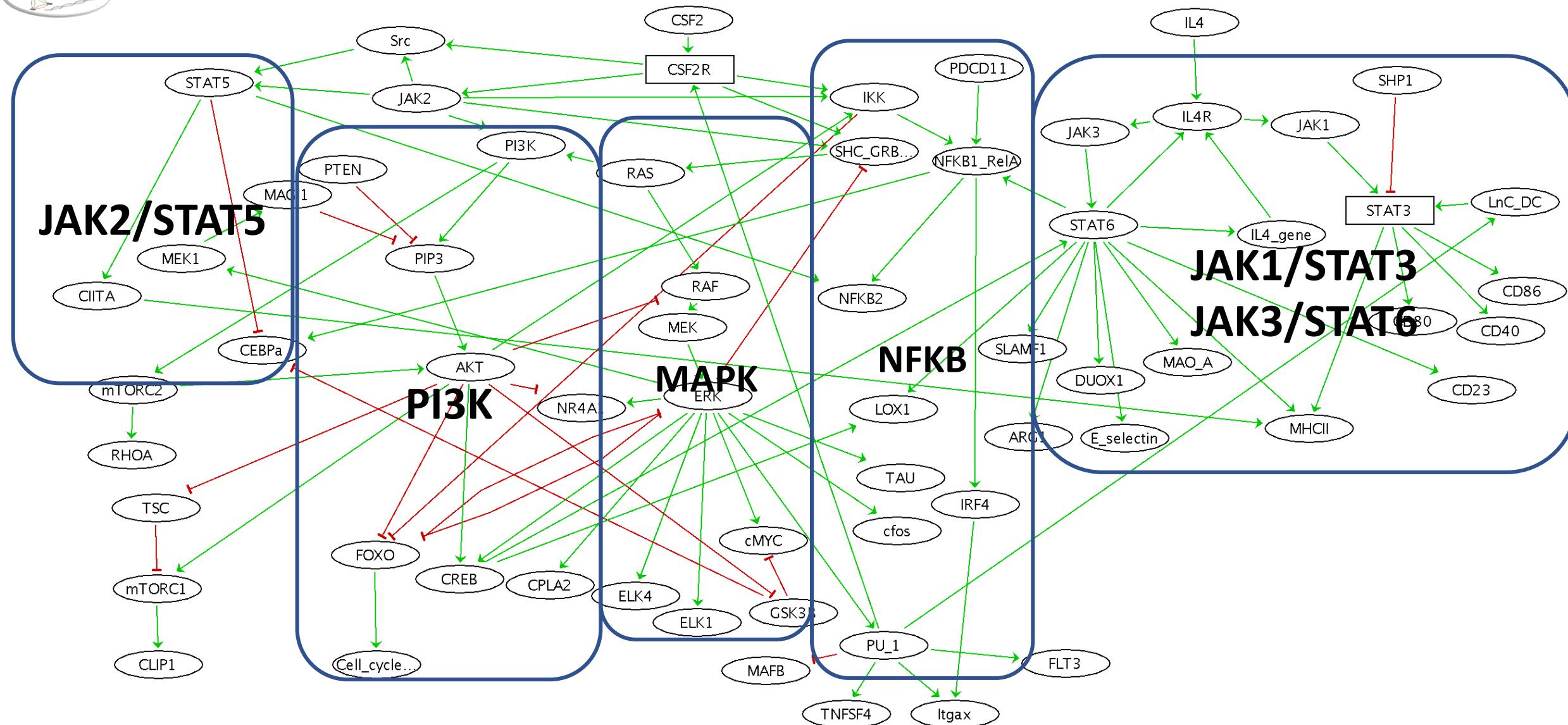


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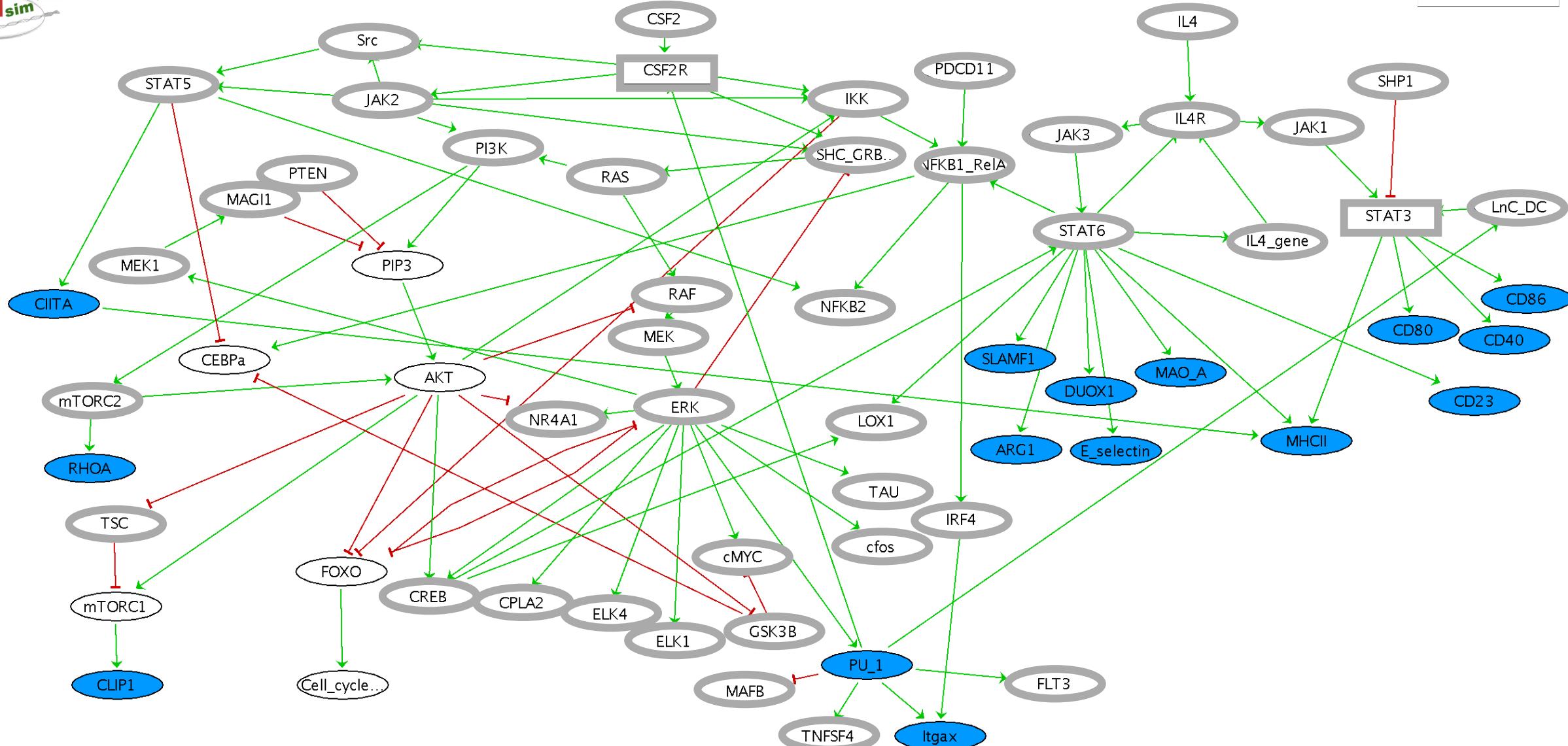
CSF-2 and IL-4 pathway mapping

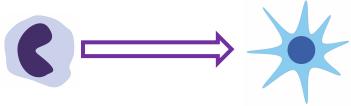


Monocyte to dendritic cell differentiation model



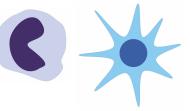
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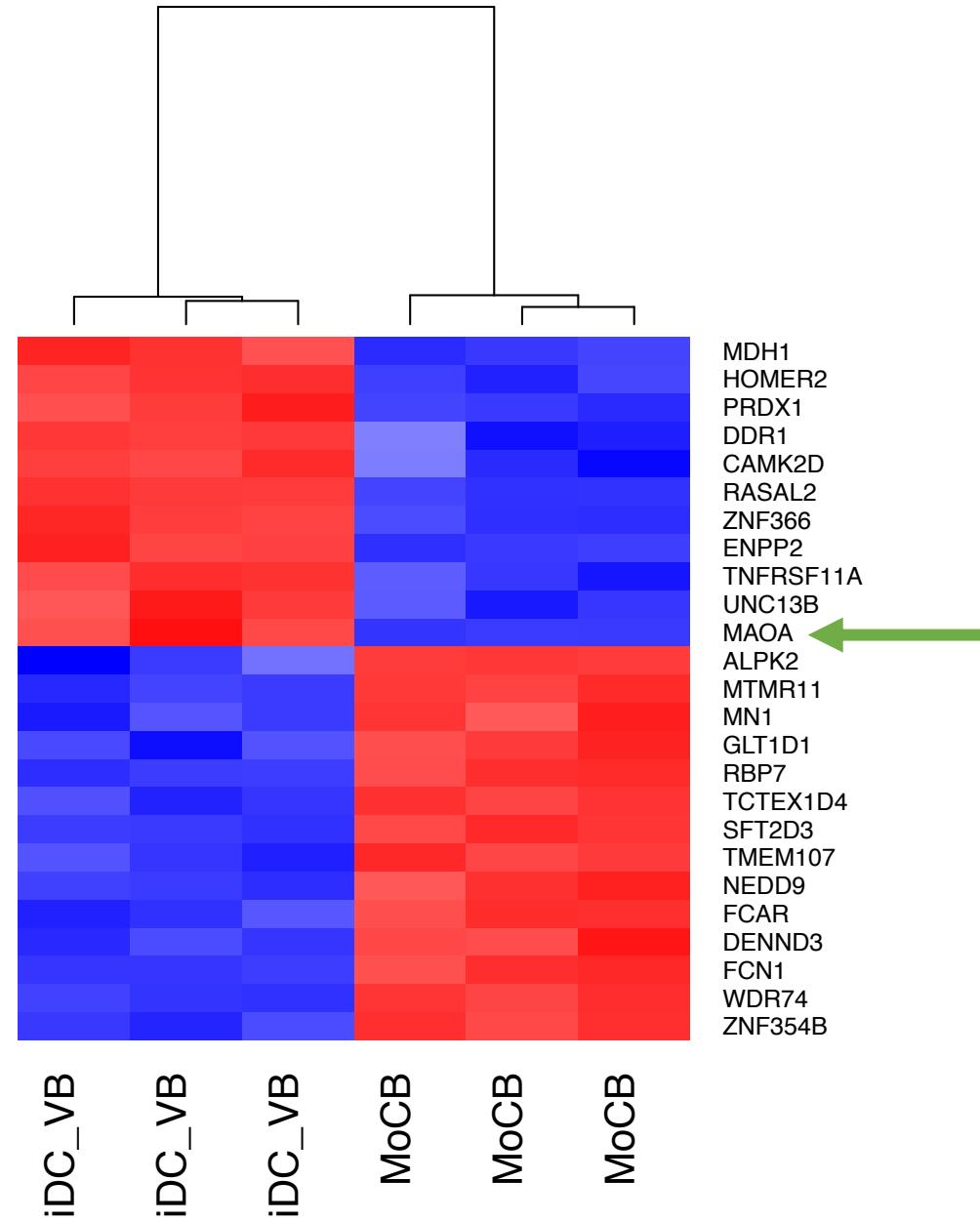
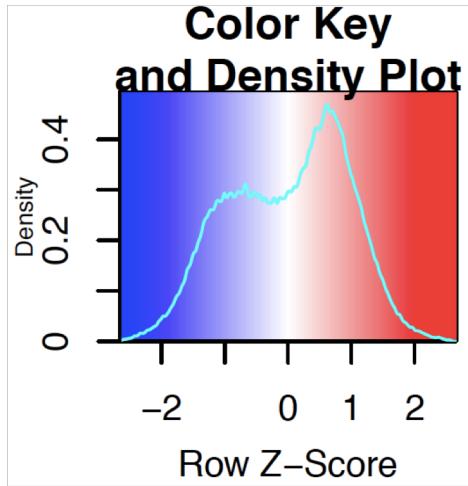


Particular aims

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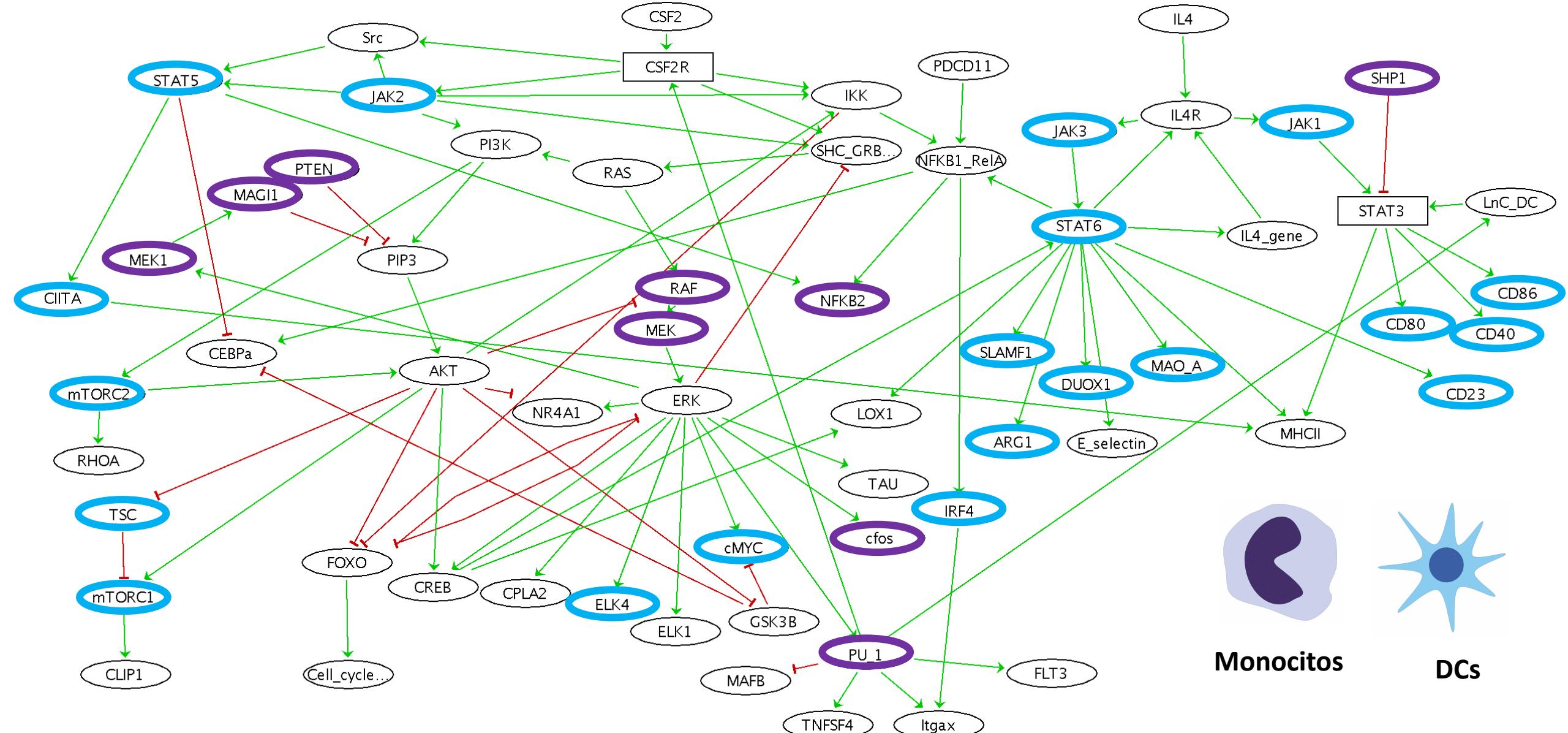


Top 25 de genes expresados diferencialmente en monocitos y DCs

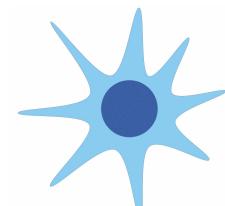


Tres replicas biológicas por tipo celular

Expresión génica diferencial dentro del modelo

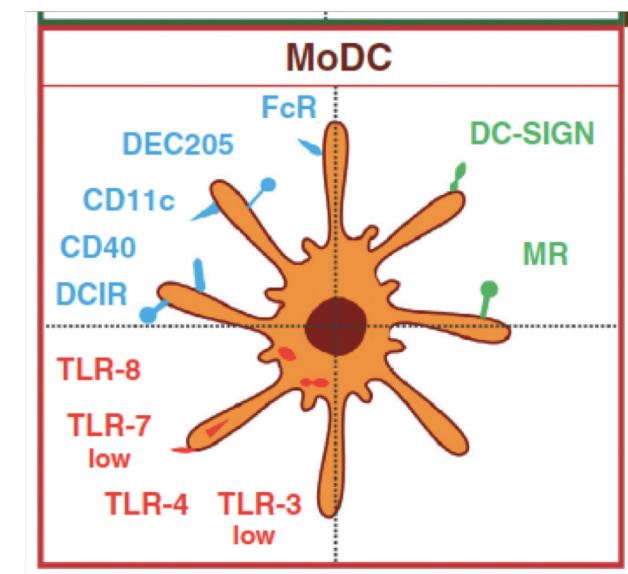
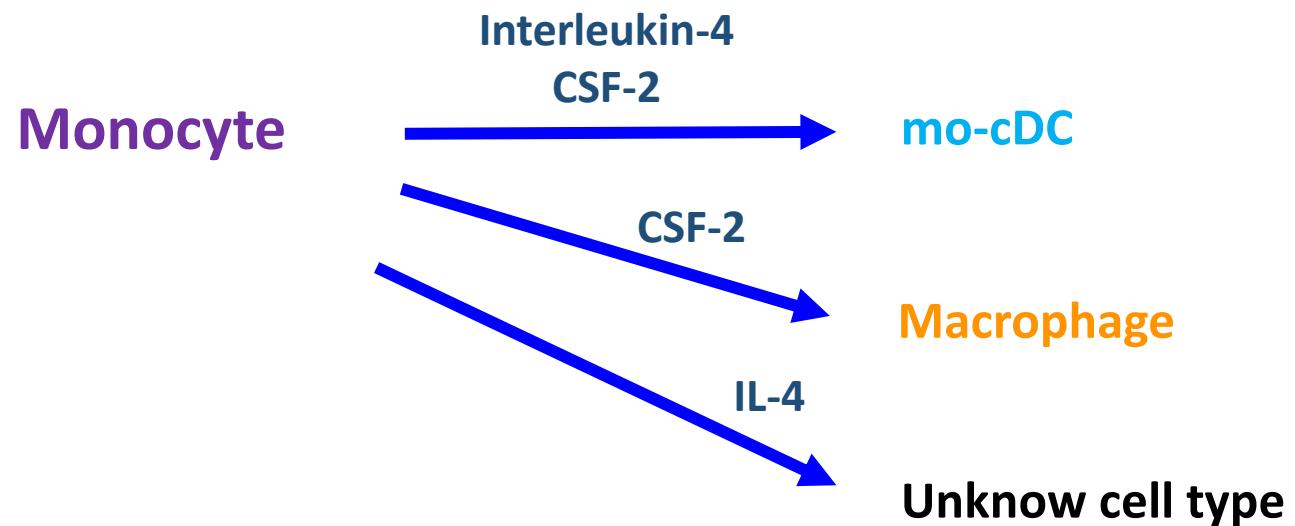


Monocitos



DCs

Stable states should reflect cellular commitment



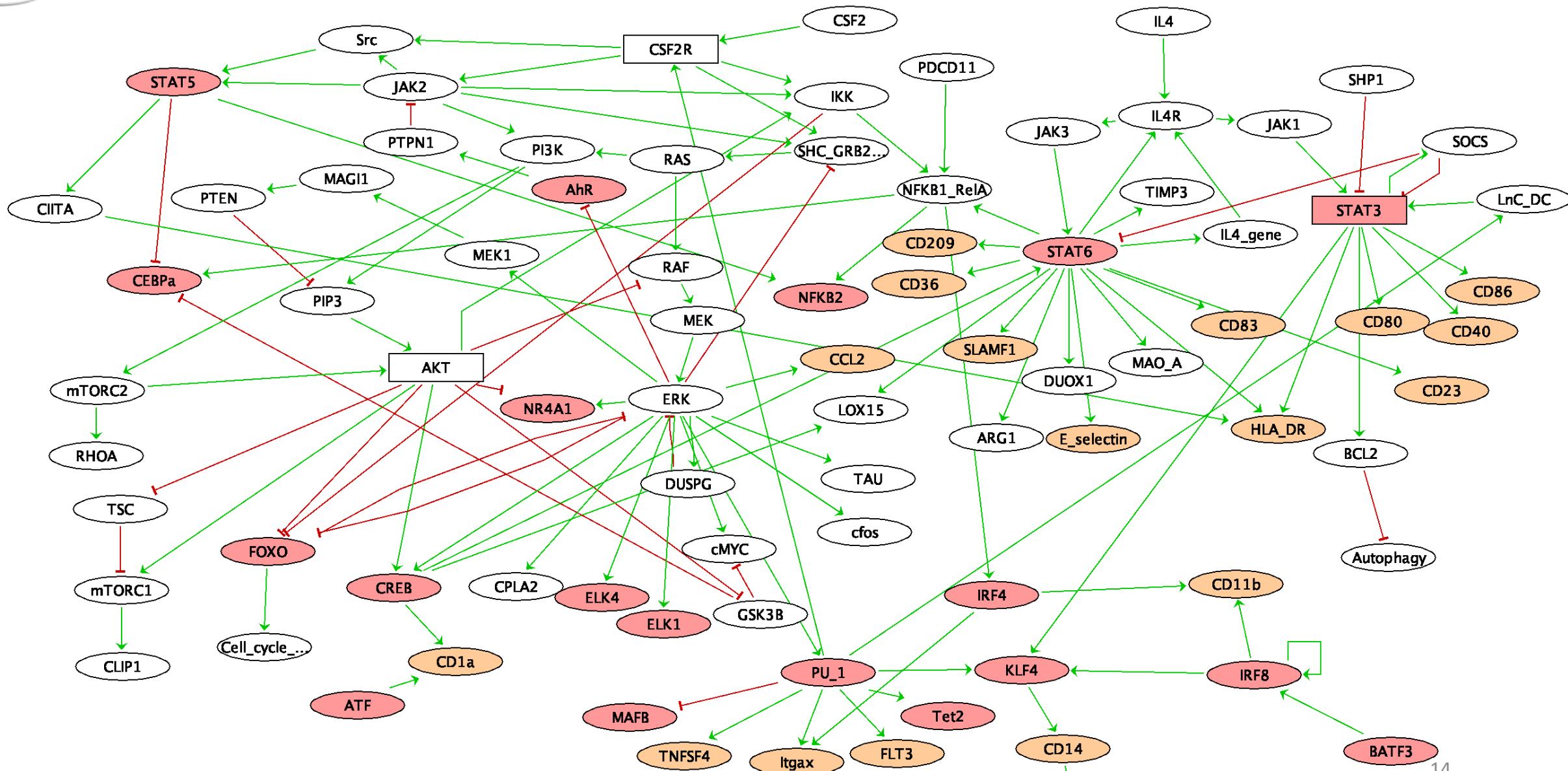
- **Blue:** antigen capture receptors.
 - **Green:** unique cell type receptors
 - **Red:** TLRs

Nodes selected to add to the model

moDCs
Monocytes
Macrophage

Nodes	Monocytes	moDCs	Mac	RNA Expression
HLA-DR	+	+	+	true
CD11c	+	+	+	true
CD1c	-	+	-	Mo y DC
CD1a	-	+	-	It is not
CD1b	+	low	-	Mo y DC
CD141	-	+	-	Mo
CD14	+	Inter	-	Mo
CD16	-	-	tissue-dependent	DCs
CD206	-	+	+	DCs
Clec9A	-	+	-	It is not
CD163	-	-	tissue-dependent	All
CD11b	+	+	+	true
MerTK	-	-	+	true
FceRI	-	+	-	true
DEc205	+			It is not
DCIR		+		It is not
TLR8		+		It is not
TLR7	-	+	+	True
TLR4	+	+	+	True
TLR3	+	+	-	True
DC-SIGN	-	+	-	
MR	-	+	-	True
KLF4	+	-	-	true

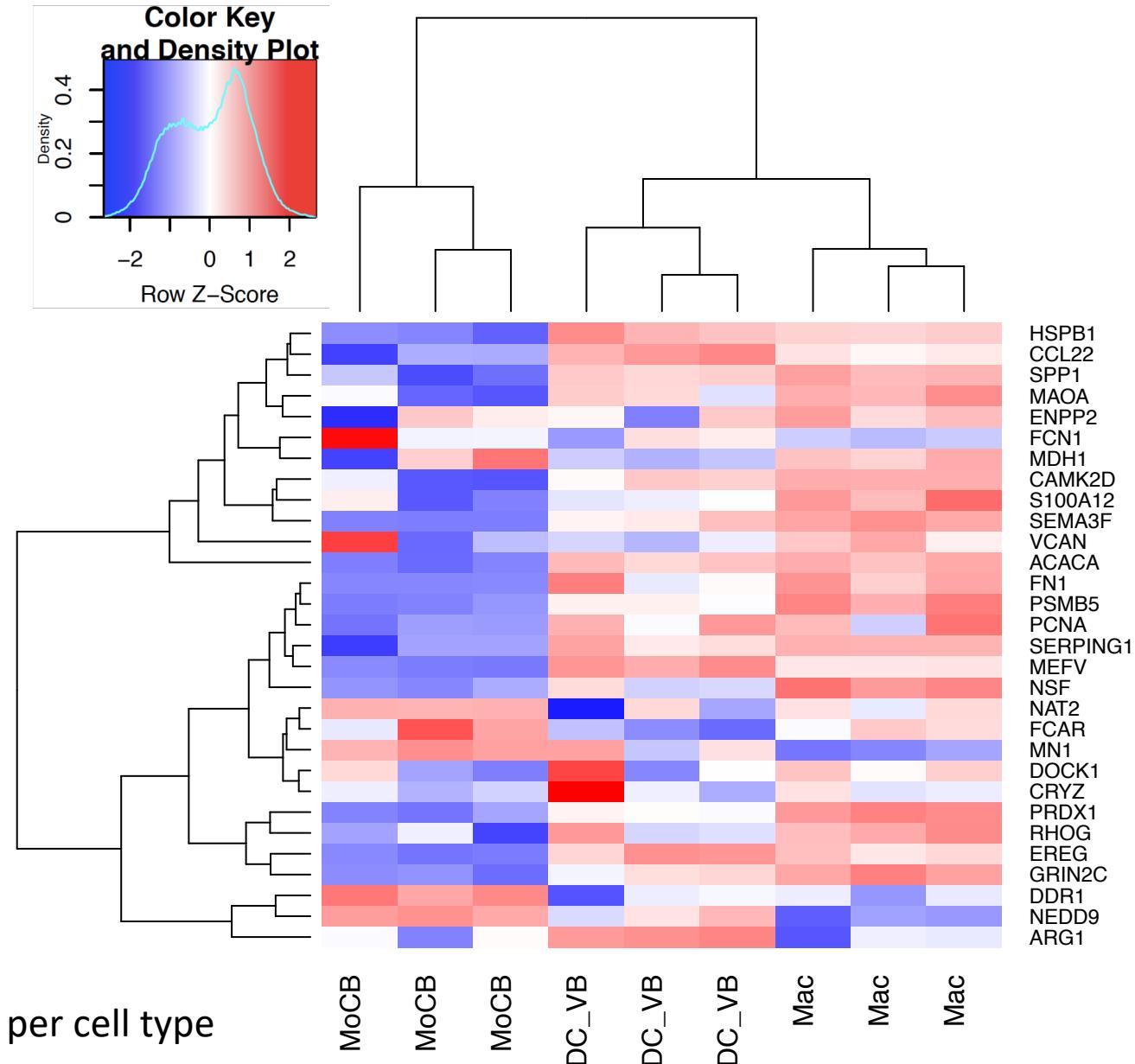
Monocyte to dendritic cell differentiation model



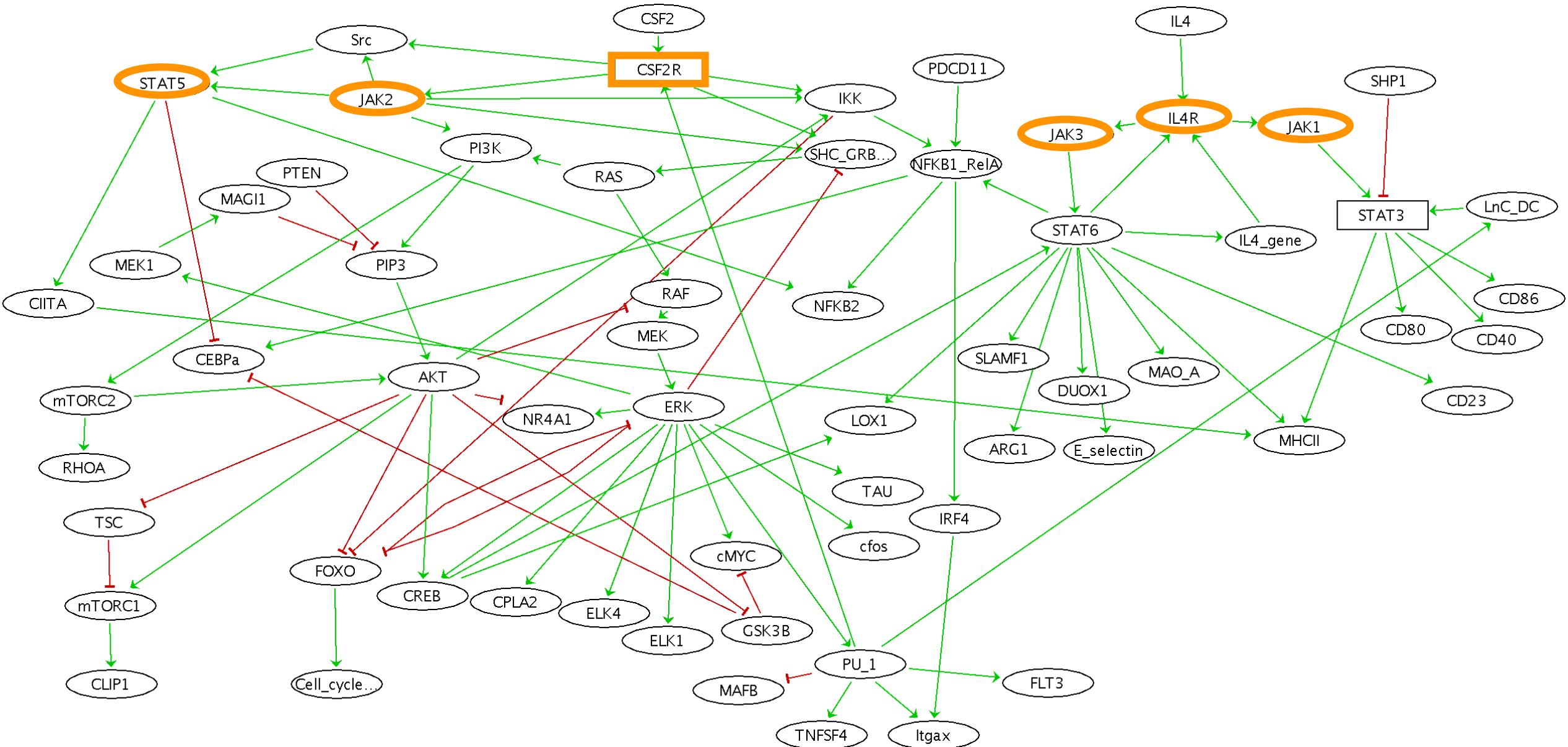


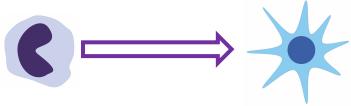
Differential expressed genes top30 of Monocytes, Dendritic cells and Macrophages

**BL
UE
PRINT**
epigenome



Genes downregulated in Macrophages inside the model

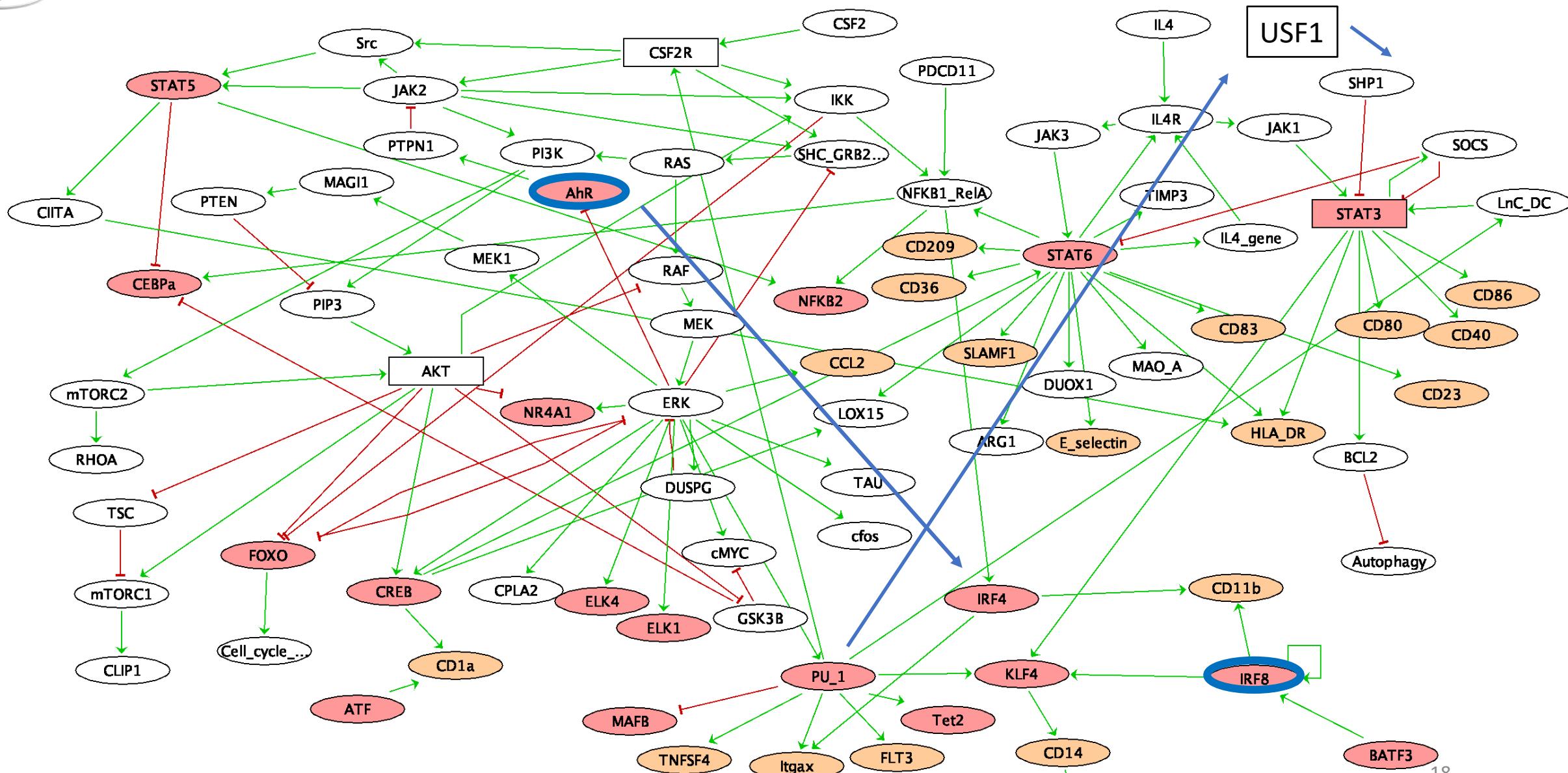




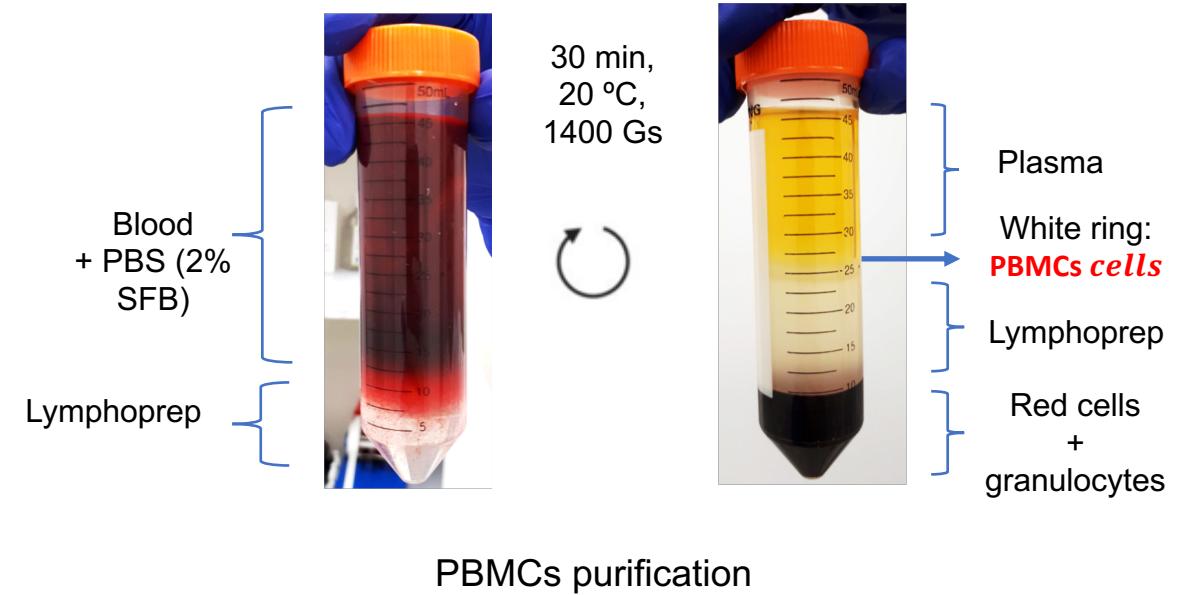
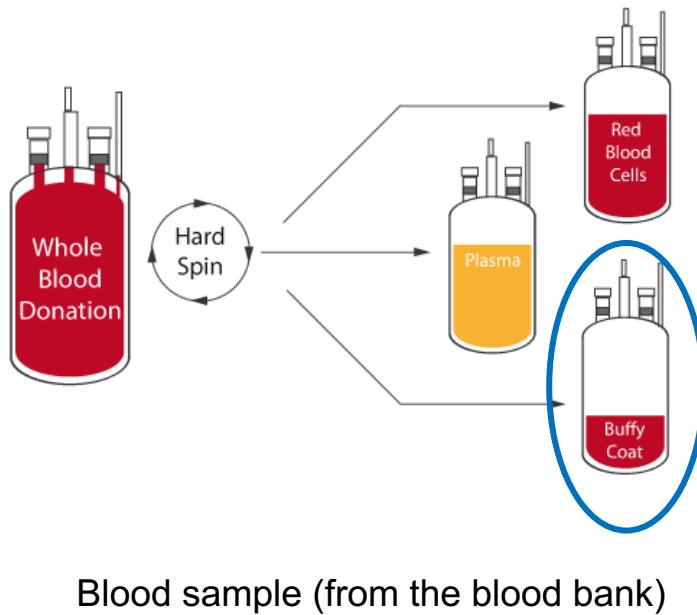
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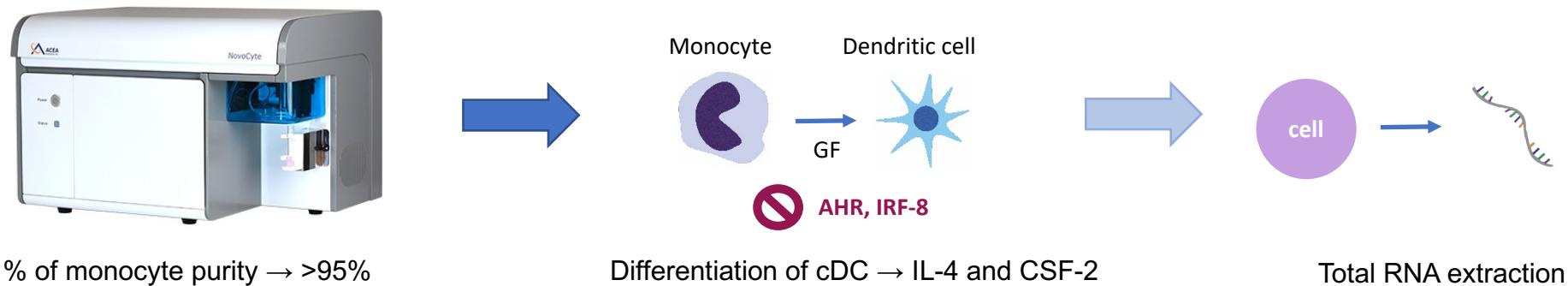
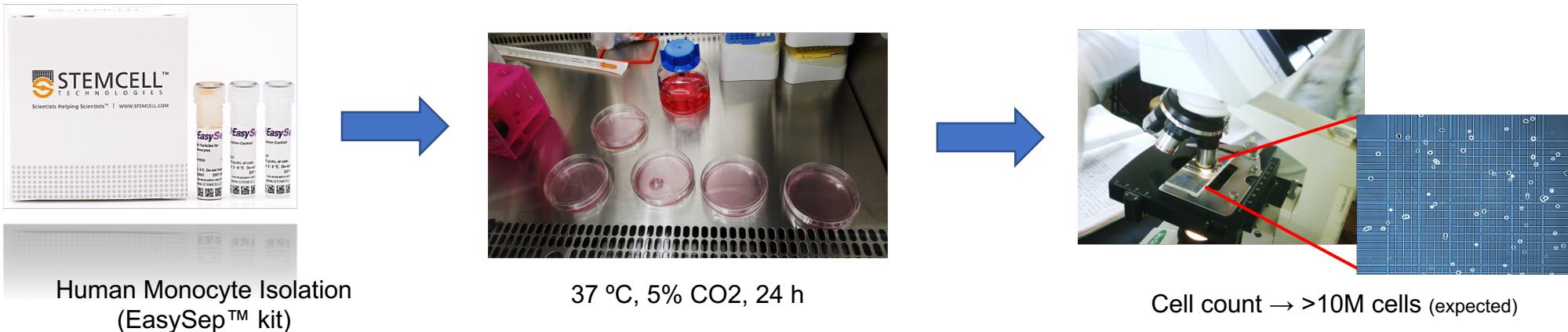
Monocyte to dendritic cell differentiation model



Experimental test of the model



Experimental test of the model



Experimental test of the model



Acknowledgements



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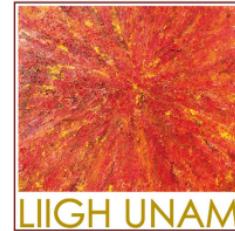
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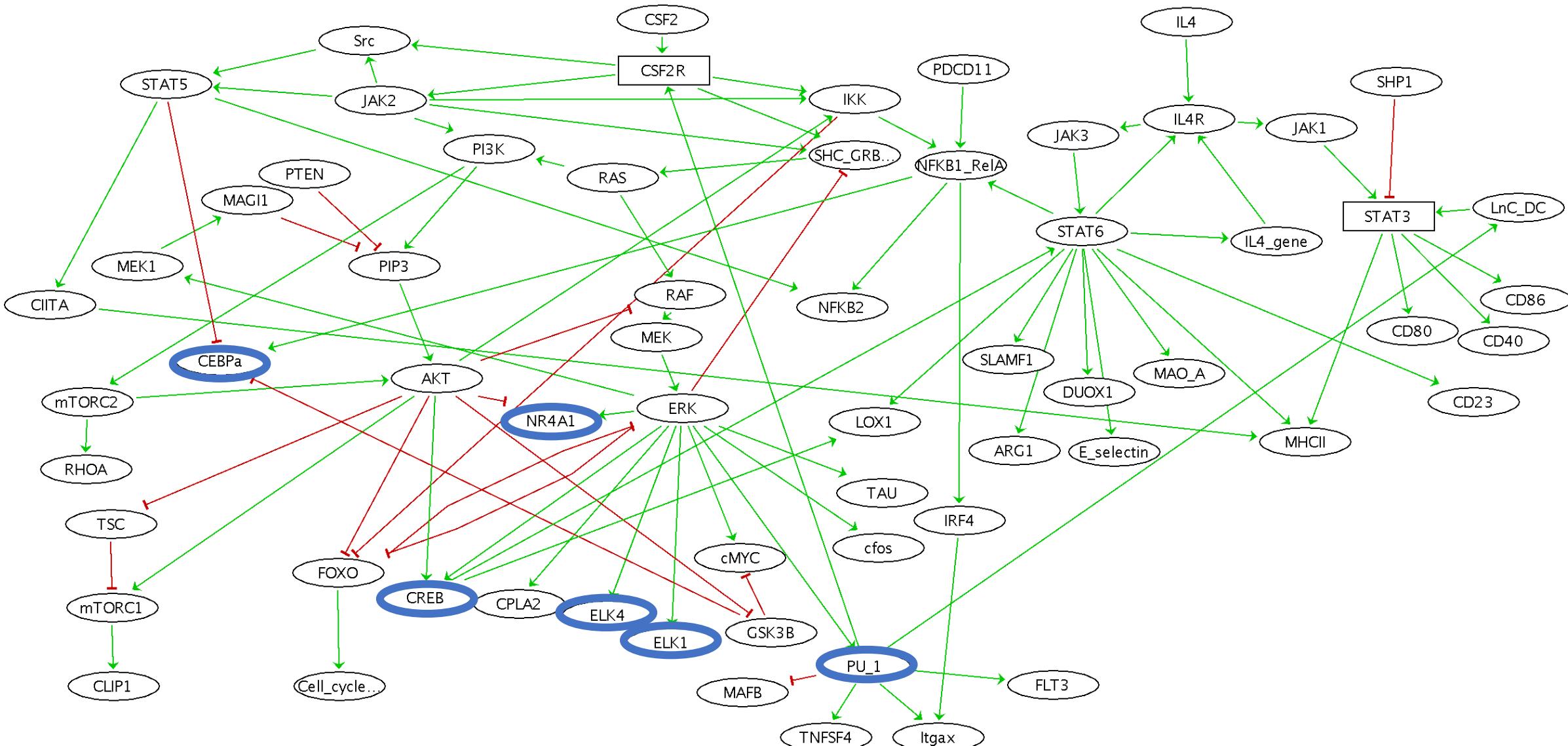
Dr Cei Abreu-Godger

Pablo González

What happened with the elements missing regulatory information?



Transcription factors to analyzed

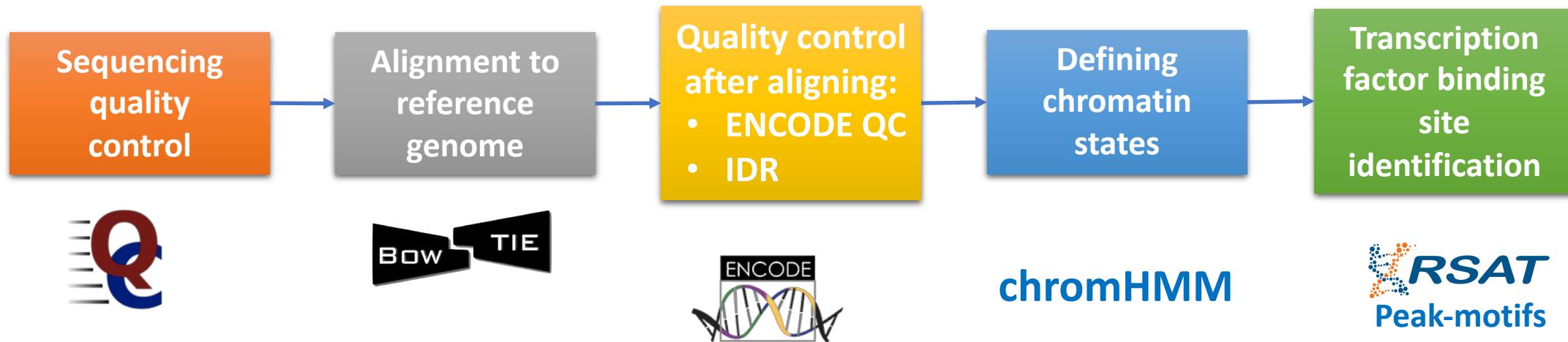




Epigenome data analysis

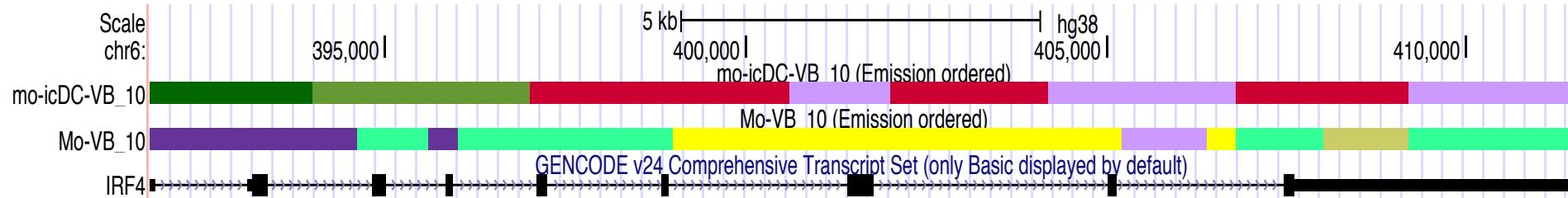
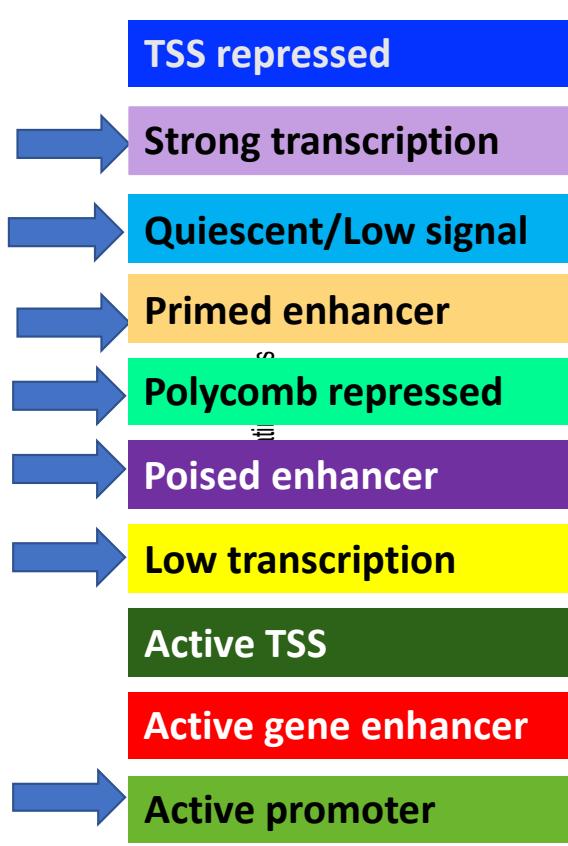


ChIP-seq data





Chromatin states definition





Identify Transcription factors from chromatin states



Chromatin state	Monocytes TFs	Dendritic cells TFs
Repression	UBIP1, ETV2, HOMEZ, POU6F1, HOXB2	NKX62, DLX3, POU6F1, LHX2, PDX1
Polycomb repressed	HOXB2, PDX1	KLF6, ZN740, EGR1, NKX62, DLX3, LHX2, EVX1, EMX1, MIXL1
Poised enhancer	SP2, MECP2	NR4A1, EGR1
Active enhancer	EGR4, ETV2	FOXM1, FOXP3, ZN148, SP2
Active TSS	MECP2	No change
Active gene/enhancer	CPEB1	HXA11, HMGA1, HXD12, HXB13, HXC13
Primed enhancer	TEAD3, NFATC1, NFATC3, BPTF, FOXM1, FOXP3	HXD3, HXA2, NKX62, DLX3, POU6F1, LHX6, NOTO, MIXL1, PDX1, NOBOX, CPEB1, ETV2, HMGA1