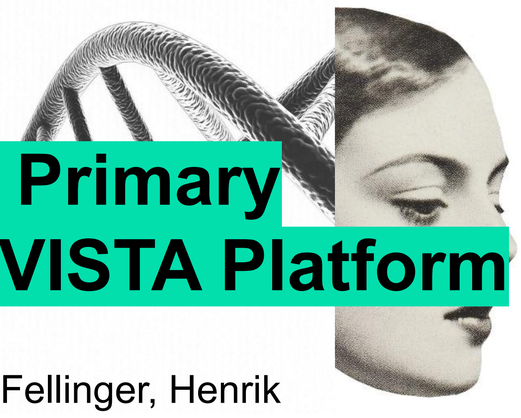
CRISPR Screening for Target Discovery in Primary Human Monocyte-derived Cells Using the VISTA Platform



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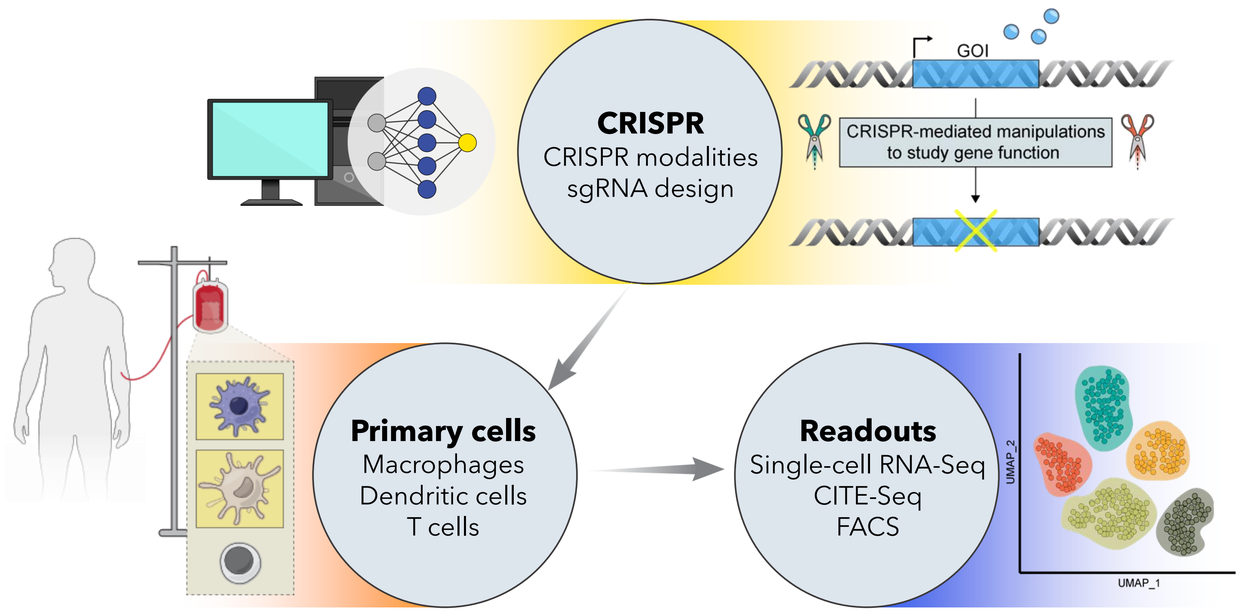
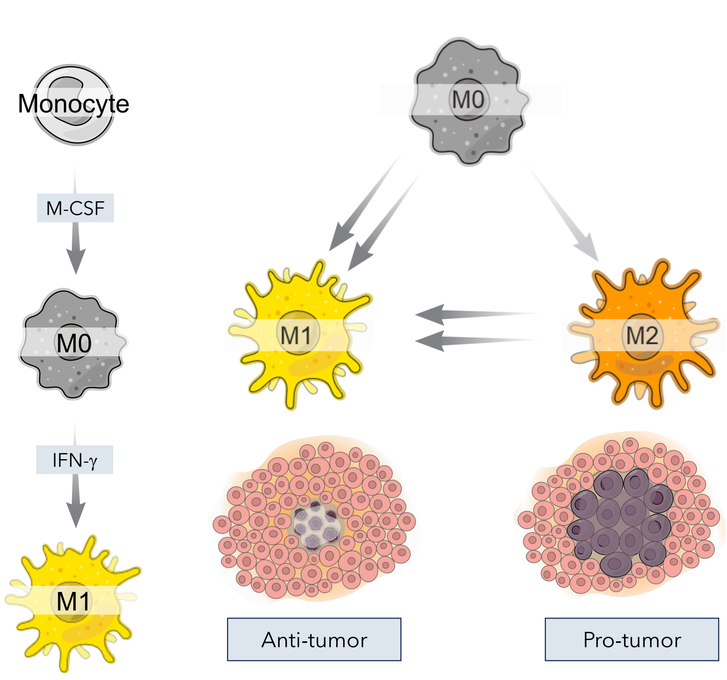
About Myllia's VISTA™ platform

Macrophages and dendritic cells are central players in the innate immune system. Their dysregulation is implicated in a wide range of diseases, including autoimmunity, inflammation, cancer, and infectious diseases. However, novel drug target identification in these cells has been difficult because these cells were - until now - refractory to high-content CRISPR screening approaches. At Myllia, we have solved this problem and have developed the **V**ersatile **I**ntegrated **S**creening for **T**arget **A**nalysis - **VISTA™** platform, enabling CRISPR screens in primary human myeloid cells. The platform links CRISPR perturbation to transcriptomic responses, thus providing high-content functional readouts of novel gene targets involved in regulating many processes, including the tumor-immune interface relevant for immuno-oncology. **Here, we present a pooled CRISPR screen to dissect IFN-γ signaling in monocyte-derived macrophages (MDMs) and dendritic cells (MDCs).** Our platform thus enables large-scale CRISPR screens with complex readouts to support drug discovery campaigns.

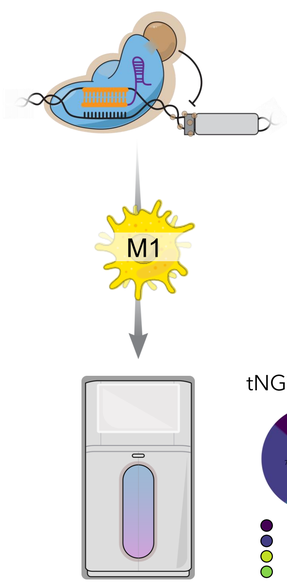
1 The VISTA™ platform



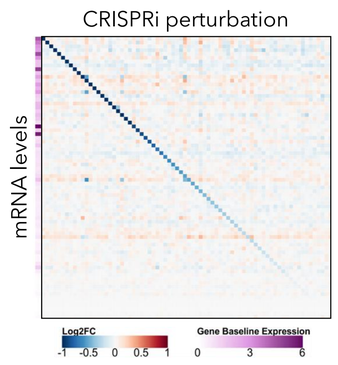
2 Macrophage polarization mechanisms



3 CRISPRi screens in macrophages

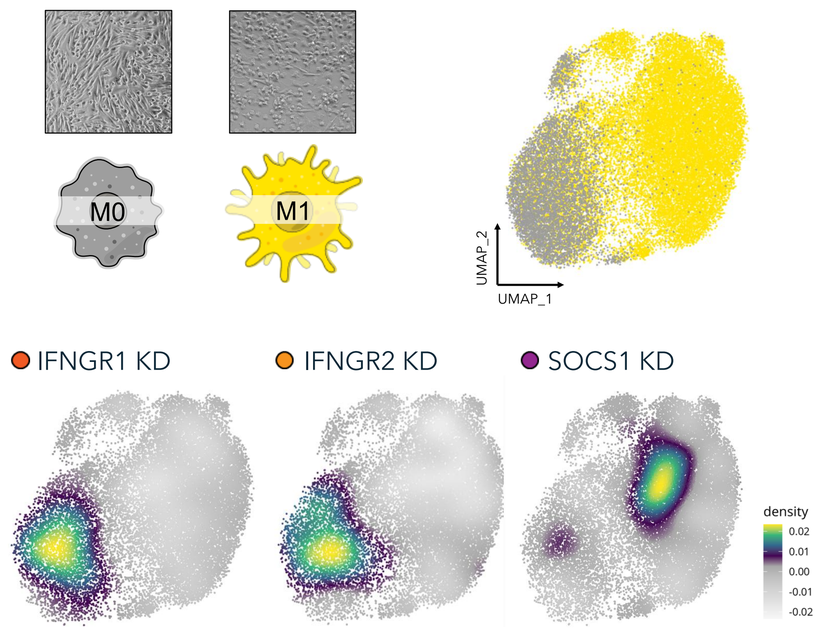


A pooled CRISPR interference (CRISPRi) screen in primary human macrophages targeting 78 genes.

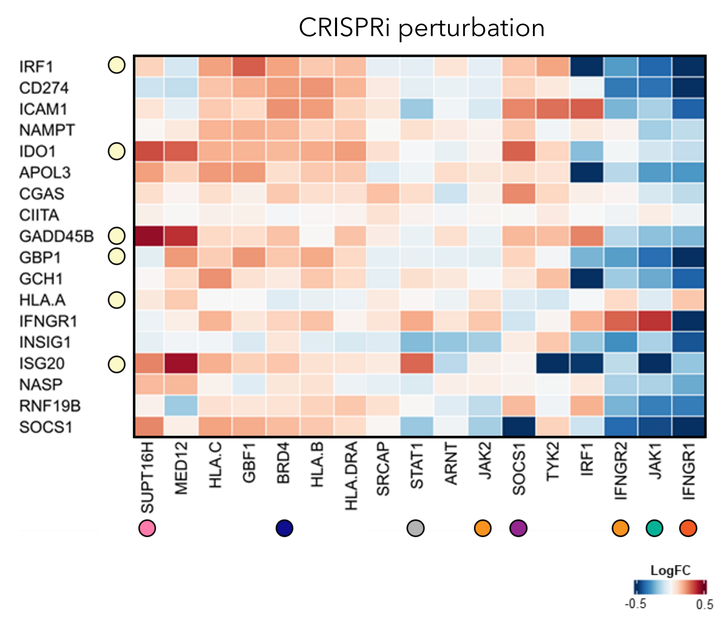


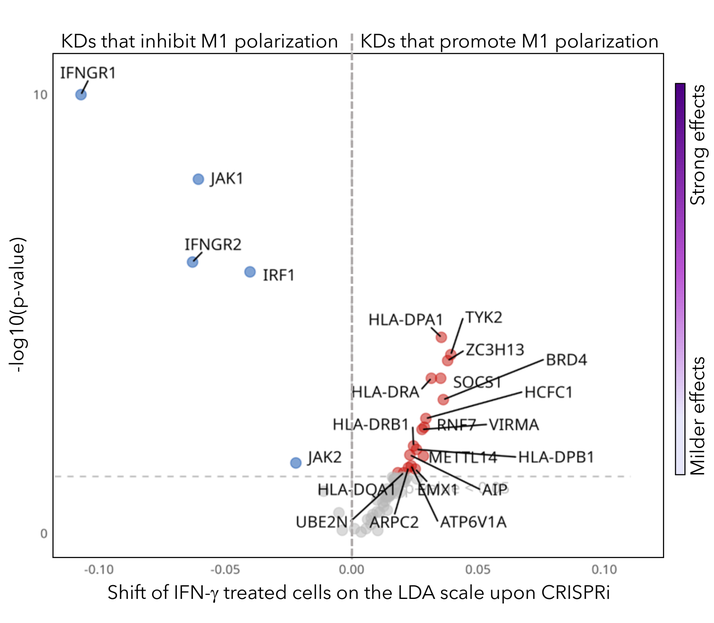
A significant knockdown was achieved for 68 out of 78 genes (p-value < 0.05).

4 Polarization states resolved by scRNA-Seq

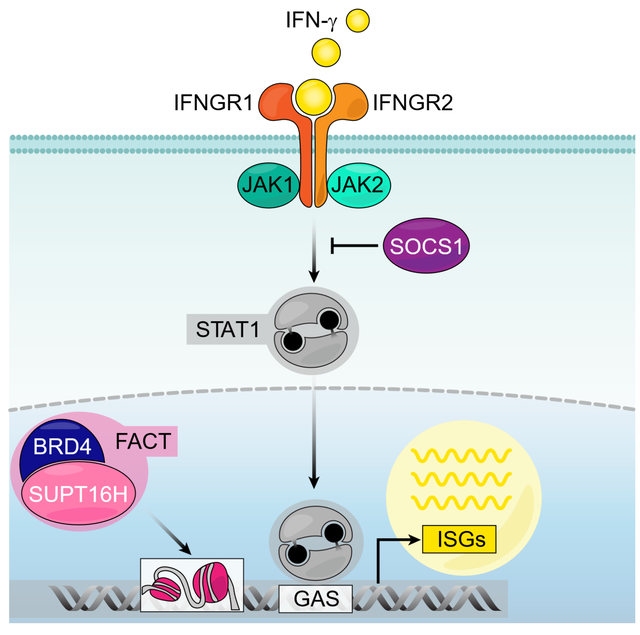


5 VISTA™ identifies key macrophage regulators and signatures





6 Perturbations affecting IFN-γ signaling



Conclusions and Outlook

- 5 positive and 20 negative regulators were identified that modulate M1 polarization via IFN-γ signaling
- The VISTA™ platform enables pooled CRISPR screens combined with single-cell RNA-Seq in various primary human cell types, including macrophages, dendritic cells (and T cells)
- Key features of Myllia´s VISTA™ platform include:
  - Unbiased drug target discovery
  - Target identification in blood-derived primary human cells
  - Targets with higher chance of translating *in vivo*

We are looking for a strategic partner to initiate drug target discovery programs across several disease areas in primary human macrophages and dendritic cells, incl. autoimmune disease, inflammation and oncology.

Contact us

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