



Smart sensor promoters drive state-specific gene circuits to convert immunosuppressive macrophages into an anti-tumor phenotype



GENEFAB



BlueRock
THERAPEUTICS

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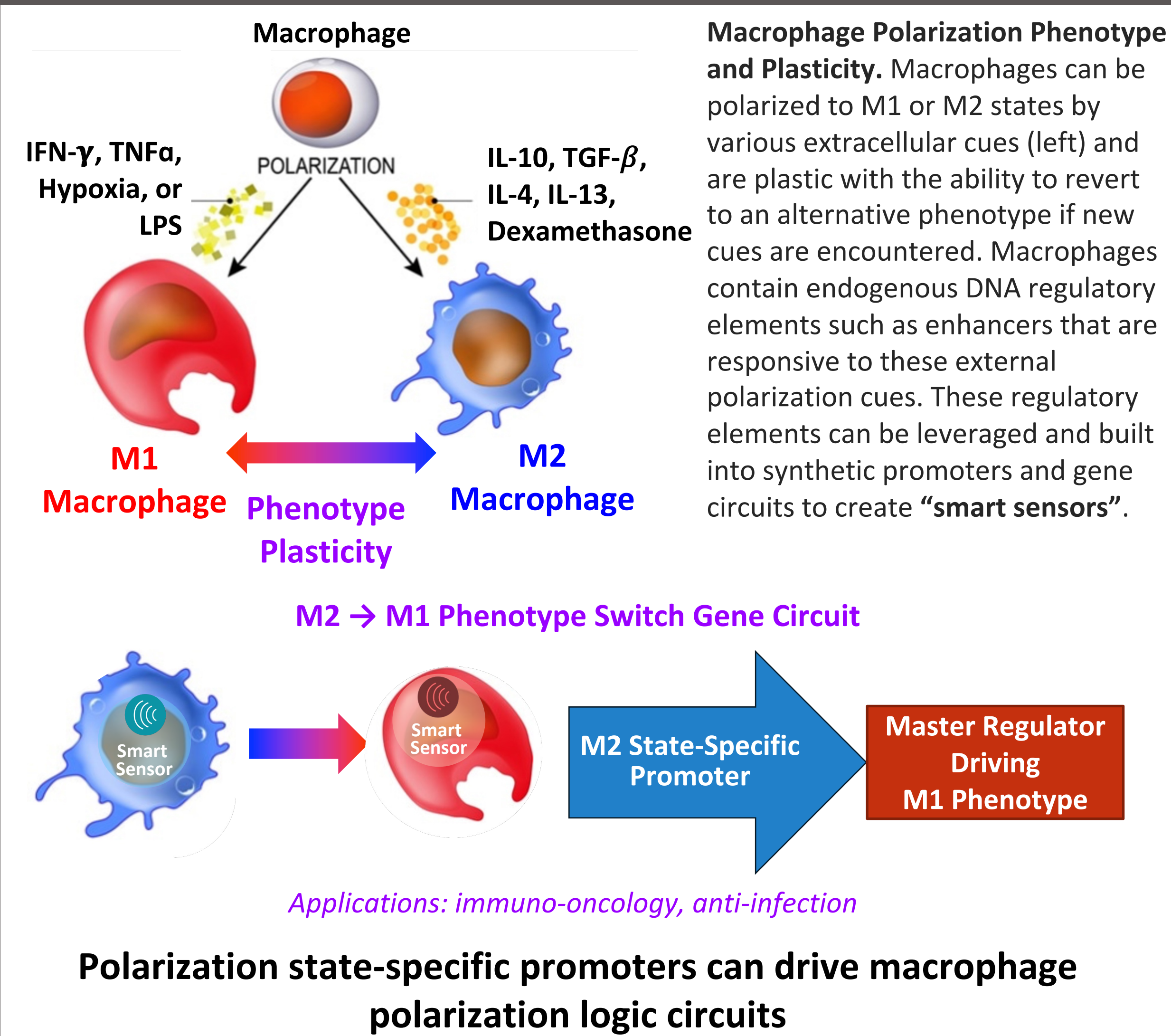
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SITC 2023

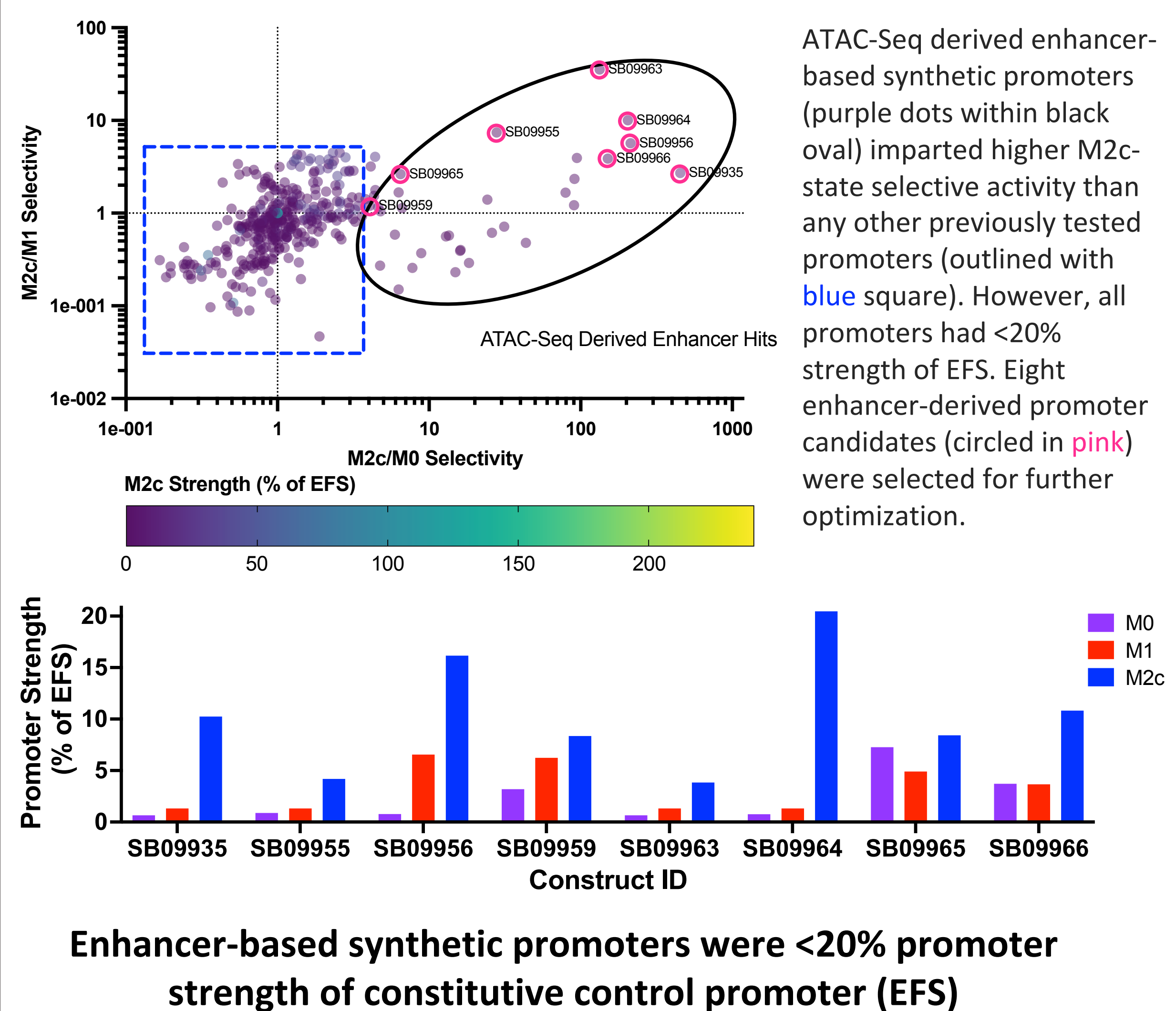
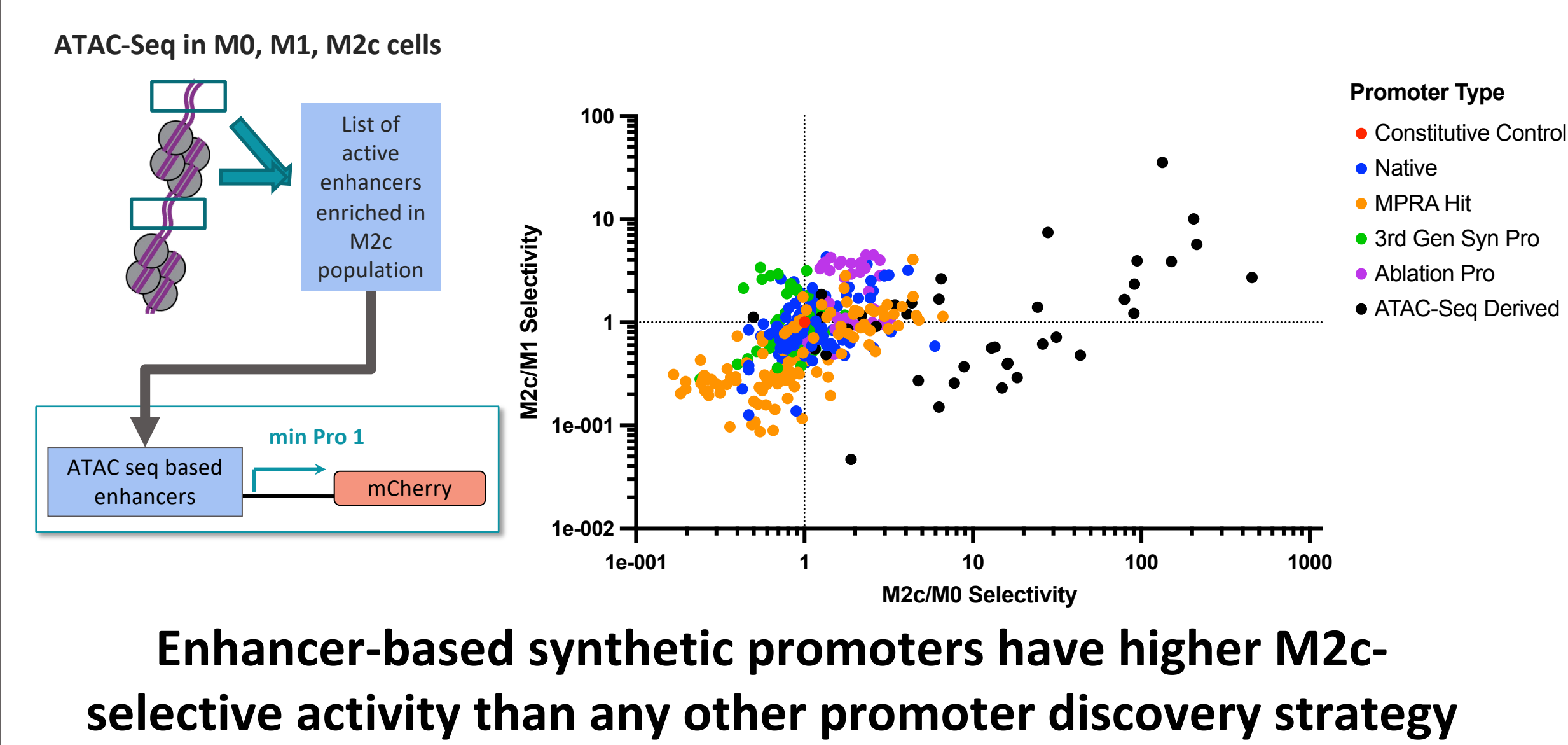
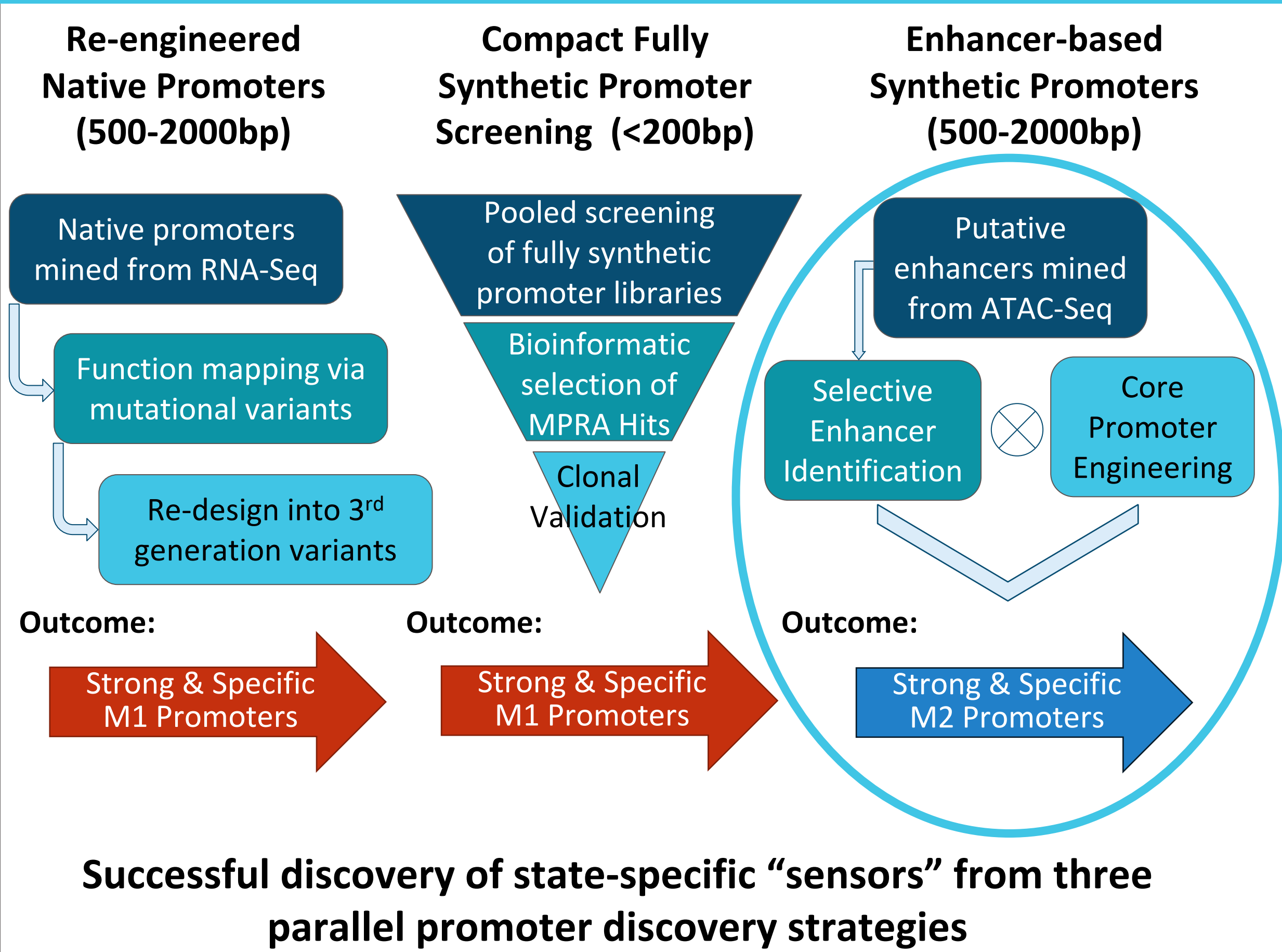
San Diego, CA

Abstract # 430

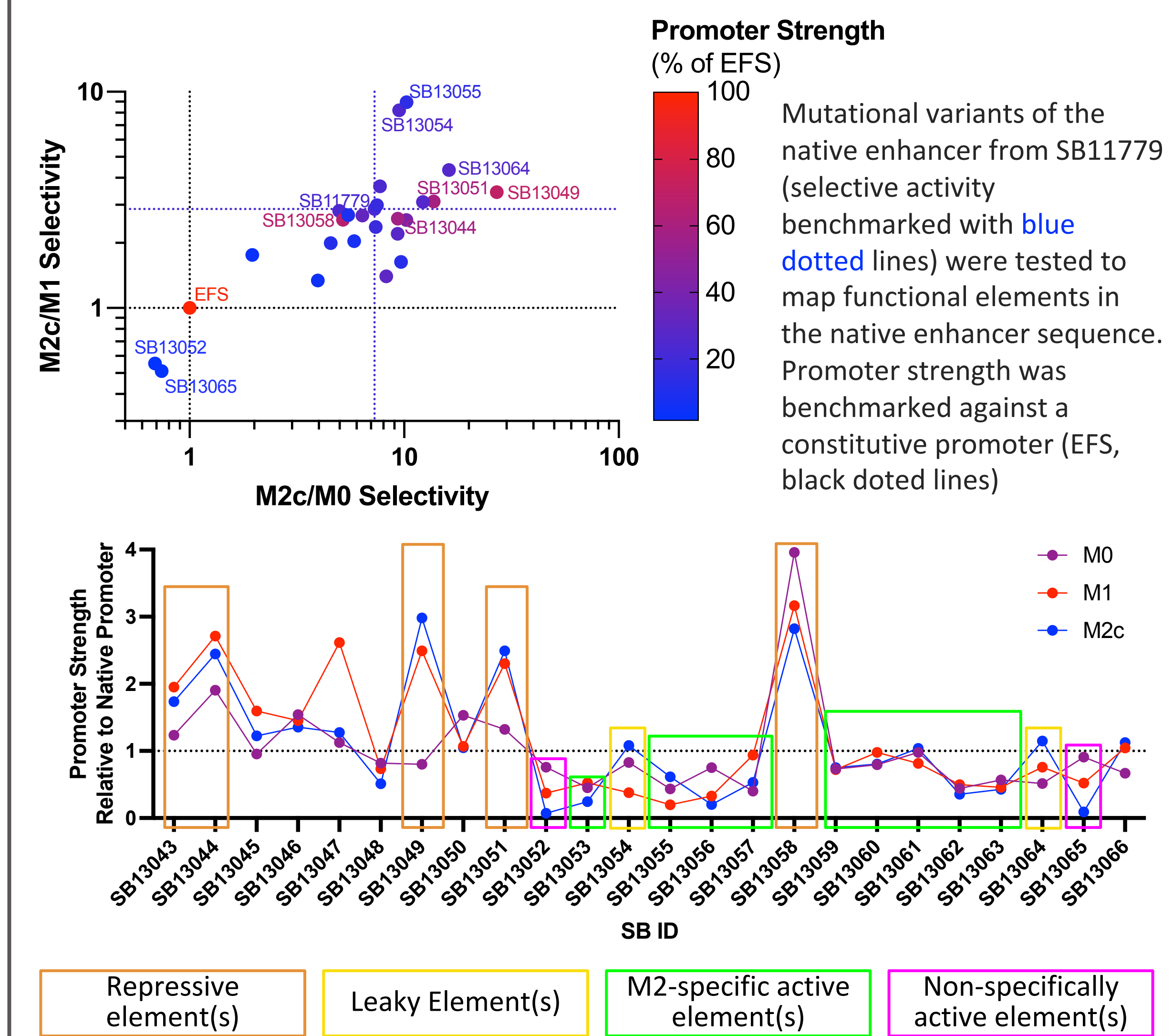
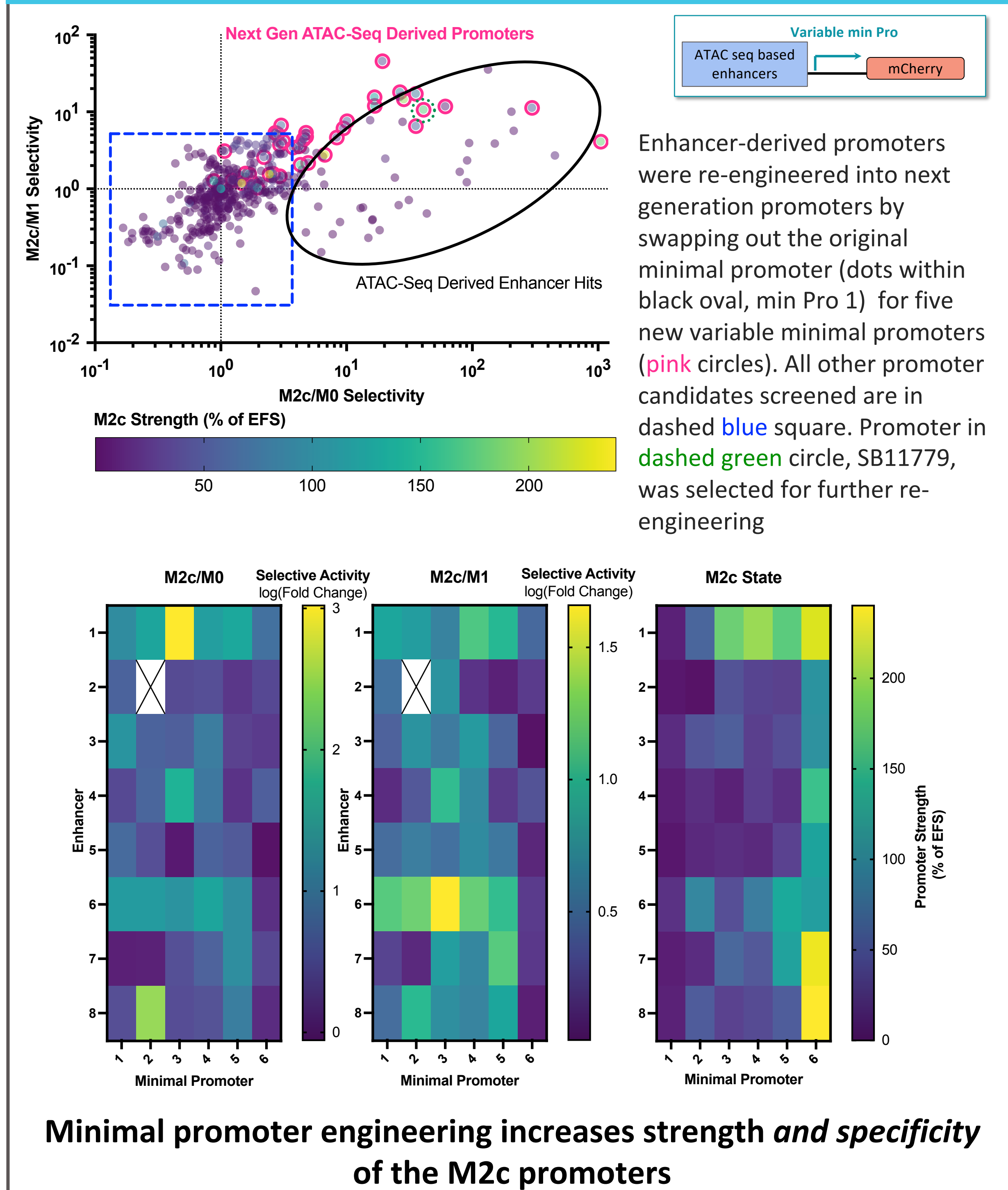
Macrophage Polarization Logic



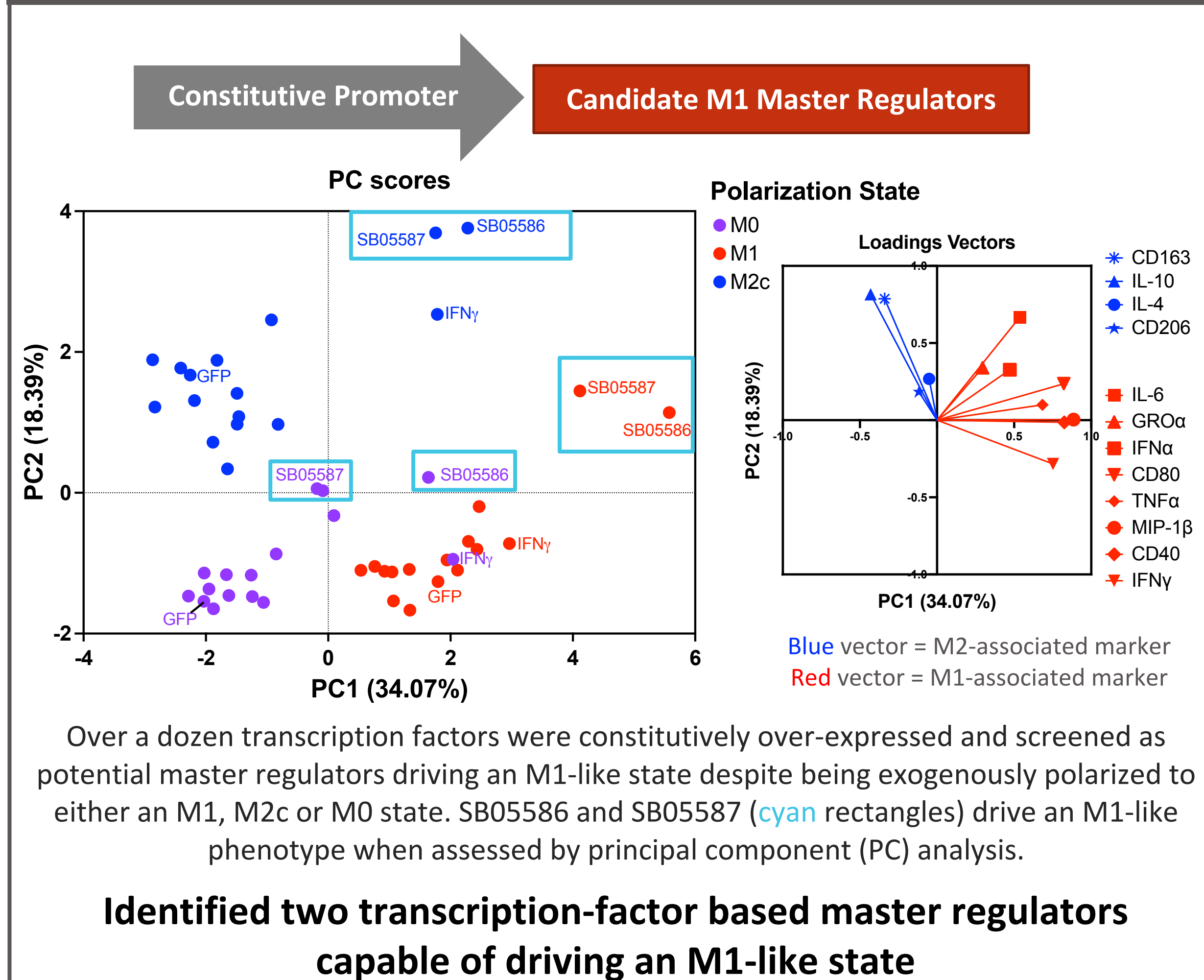
Promoter Discovery



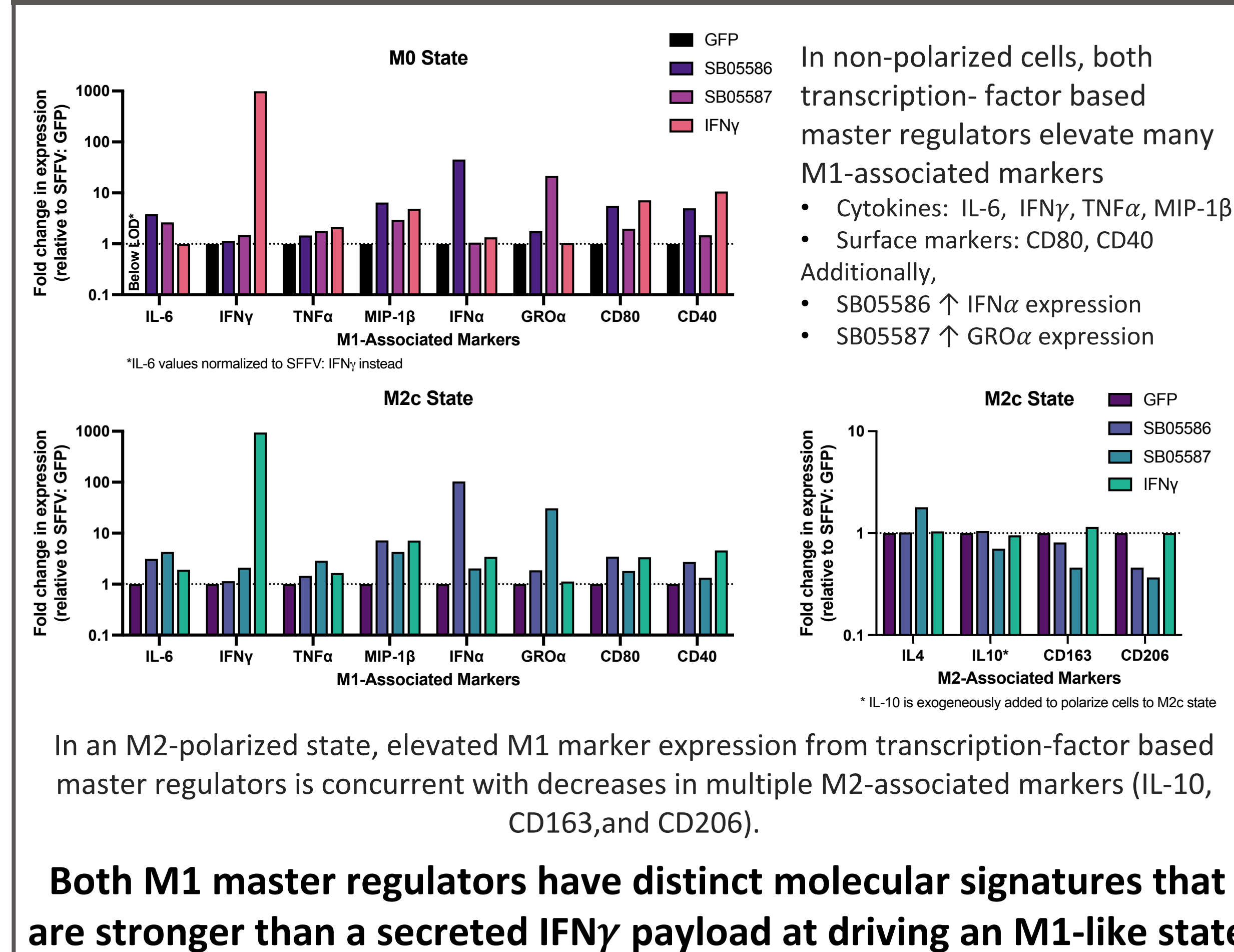
Promoter Optimization



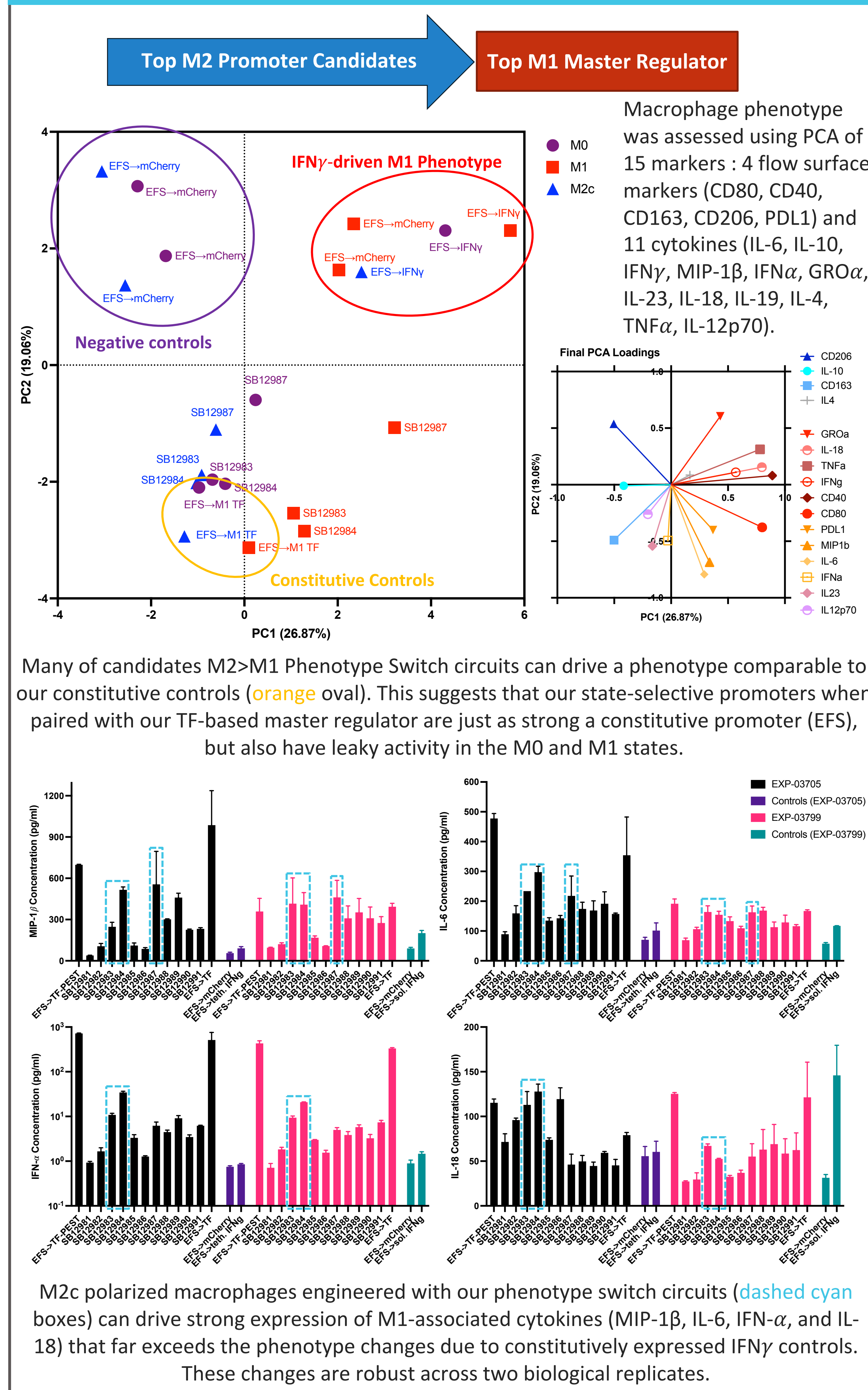
Master Regulator Screening



Master Regulator Activity



Phenotype Switch Circuit



Pairing an M2-state responsive promoter with an M1 master regulator can switch an M2-polarized cell to an M1-like phenotype

Conclusions

- Putative native enhancers mined from ATAC-Seq can be engineered into strong and M2c polarization state selective promoters when paired with certain minimal promoters
- Generation of mutational variants of native M2 enhancers enable functional identification and mapping of regulatory elements
- Overexpression of transcription factors can be used as a master regulator to drive an M1-like phenotype
- State-specific promoters can be built into smart sensor circuits to control macrophage polarization logic**
- Next Steps**
 - Optimize pairs of engineered promoters and payloads for enhanced dynamic control of macrophage cell state
 - Further testing in a therapeutically relevant model system
 - Demonstrate that an M2 → M1 phenotype switch gene circuit can turn a cold tumor hot