What Enhancers can tell us about Dependencies:

Influence of the Core Regulatory Circuitry on AML dependencies

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INTRO

The Core Regulatory Circuitry (CRC) is a set of genes that define cell state and identity by encoding transcription factors. In certain cancers, the CRC have been shown to be specific dependencies. We called this subset, CTRC.

We have defined MV411's CriTicalCRC, we have ChIPed and Perturbed each of its constituent.

We want to understand how the CTRC's regulation informs on dependencies

RESULTS

- We have defined the CTRC by overlapping Super Enhancer (large enhancers) marked TF genes with depmap dependency profile in AML (**J**).
- iBET drugs + RNAseq showed a transcriptional collapse of some CTRC (**K**) members. But called for better measures.
- Slamseq profiling will allow us to uncover the actual mechanism with better details (**A**)
- CRISPR + RNAseq showed patterns of regulation hinting on a set of sub circuits. Which seemed to have opposite regulation effects. Is there a transcriptional equilibrium induced by the CRCs? (**M**)
- We found some patterns of cobinding for example between MAX, MED1, MYC , LMO2, SMYND that would need to be further refined and investigated (**L**).

CONCLUSION

We are still processing our data. We envisioned a new regulatory circuit which we call CTCR. It seems to be composed of 5 sub circuits with antagonist effects. We showed how it can be targeted by drugs. We devised a model to understand how enhancer features of the CTRC can predict dependencies.

Next Steps

- We are calling differential binding algorithm on binding clusters.
- We are generating CRIPSR tilling of CTRC enhancer regions
- We are predicting TF binding sites of the CTRC members with DeepBind
- We are producing a model to predict expression/dependencies from enhancer information (**N**) (**B-D**)

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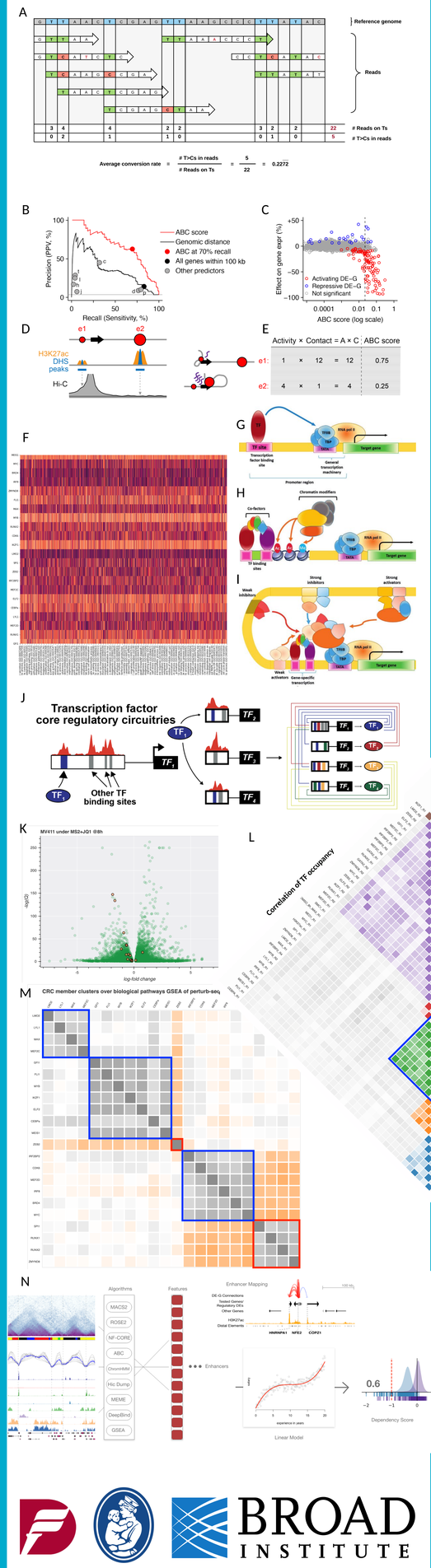

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