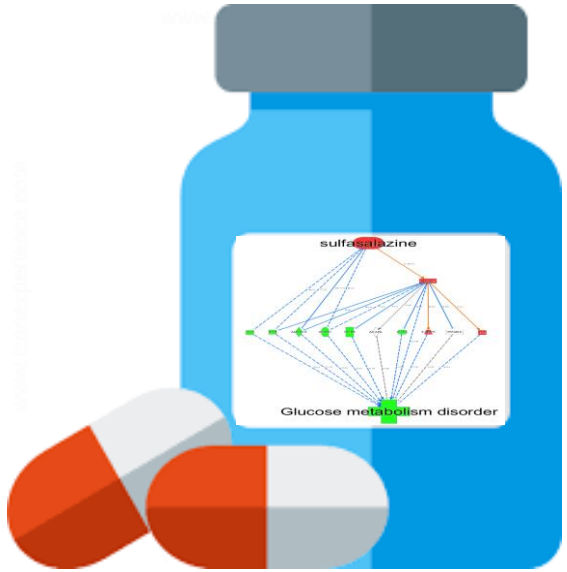
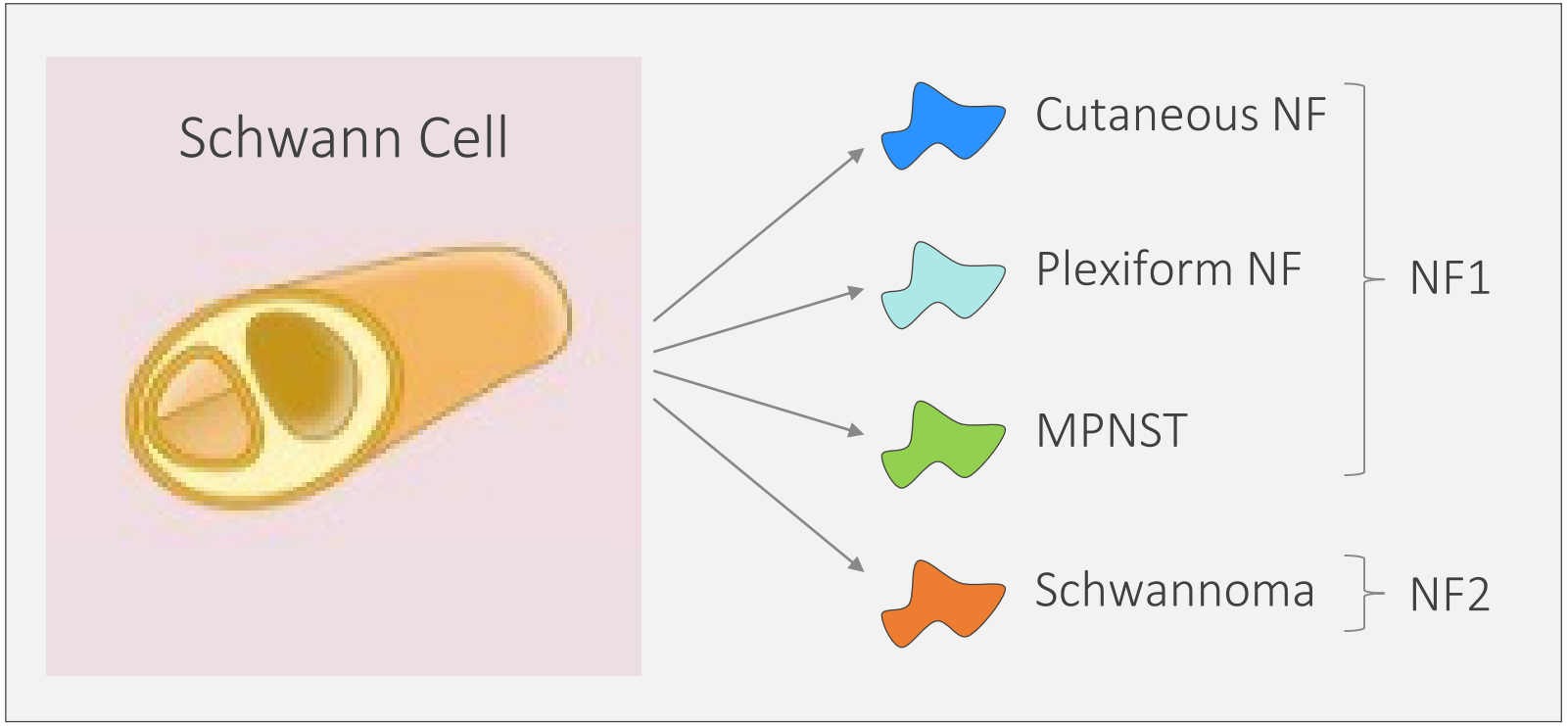
Inferring regulators and pathways involved in NF1 and NF2 tumors originating from Schwann cells using gene expression data



Team QIAGEN

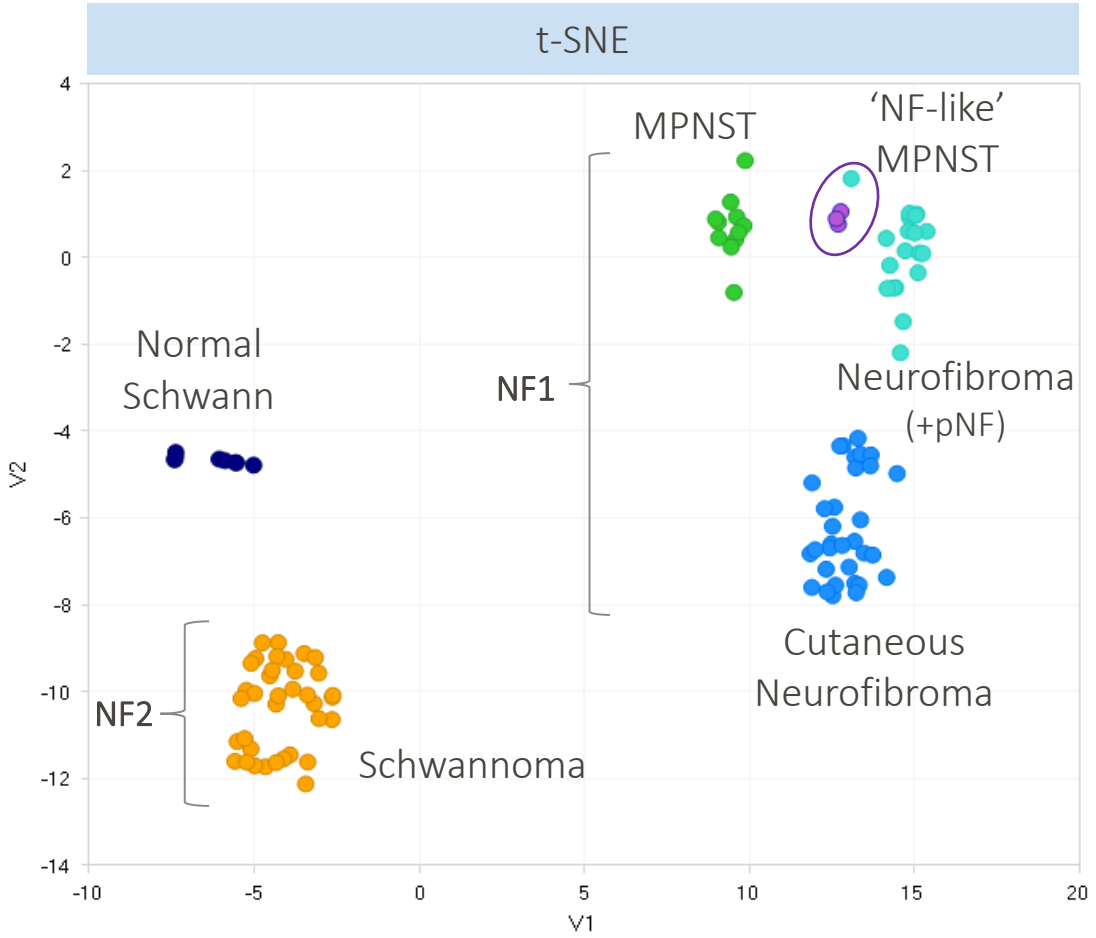
Goal

Using RNA-Seq data, differentiate NF tumor types and determine key regulators and potential drug targets



Data Analysis

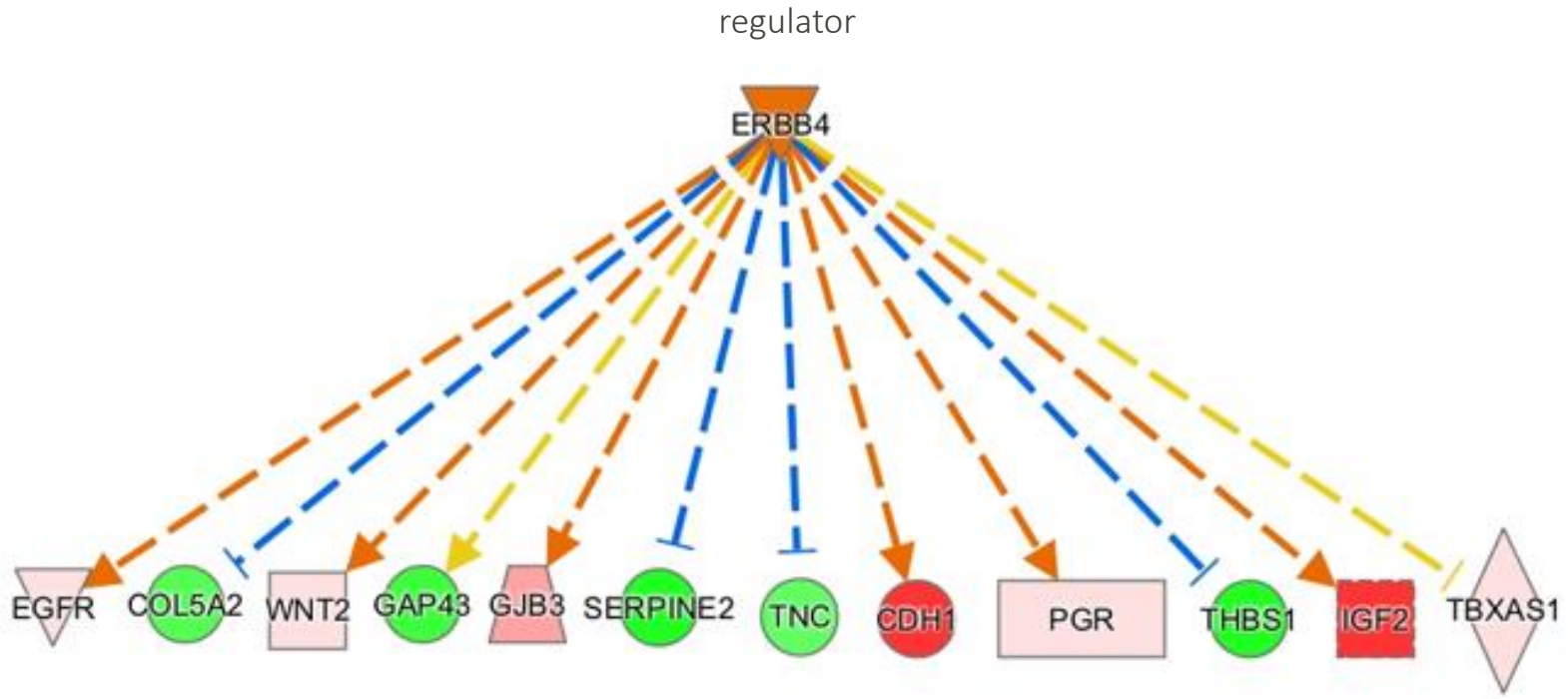
- Data processing and dimensionality reduction lead to clear separation between NF tumor type clusters
- Normal Schwann cell data was added from external public sources



- Differential gene expression between clusters (DESeq2)

- Tumor vs. normal

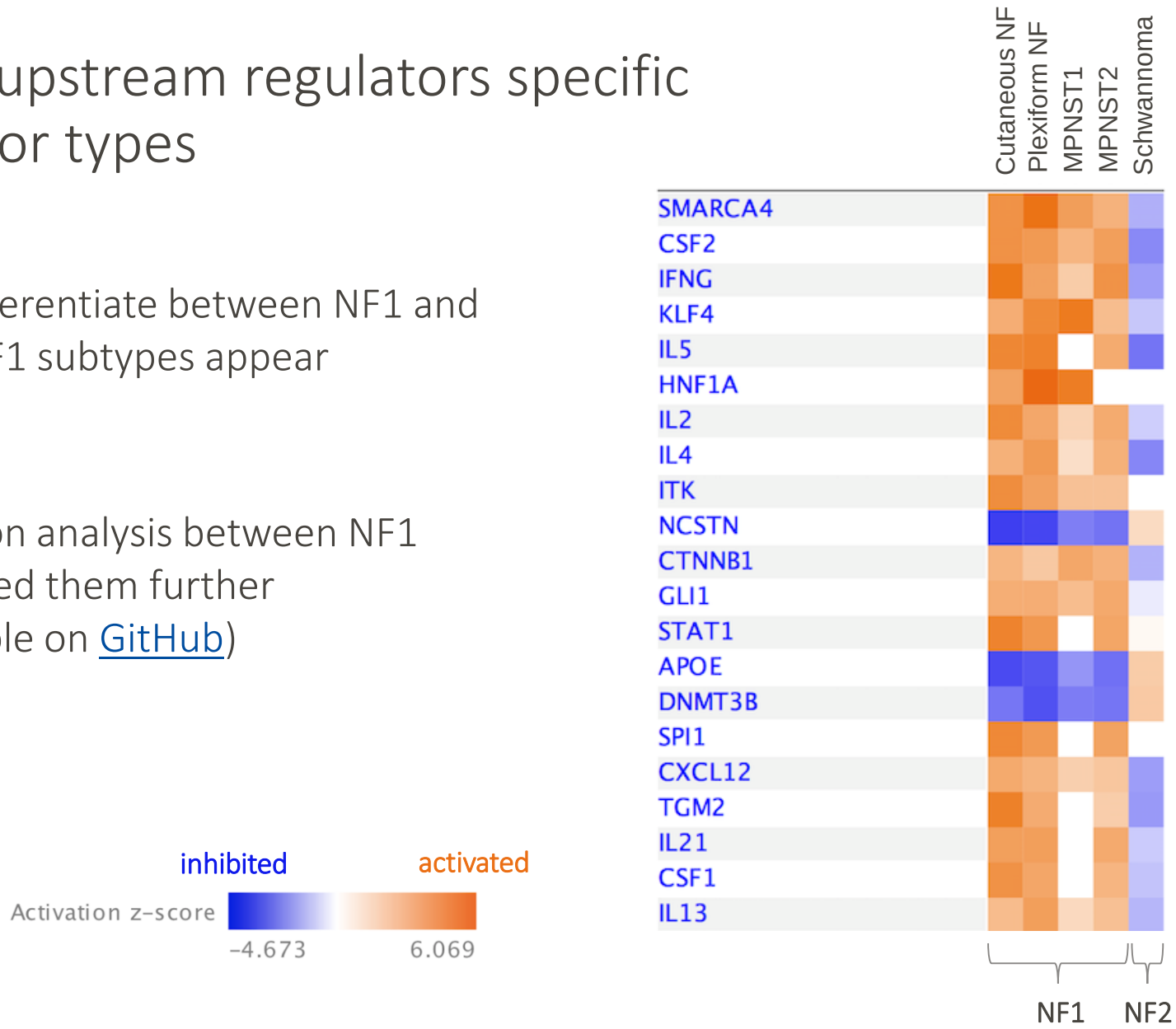
Upstream Regulator Analysis



- Uses prior knowledge from the literature (curated content)
- Infer molecules ("regulators") that have potentially **caused** the observed gene expression changes
- Krämer et al. Bioinformatics 2014 (PMID:24336805)

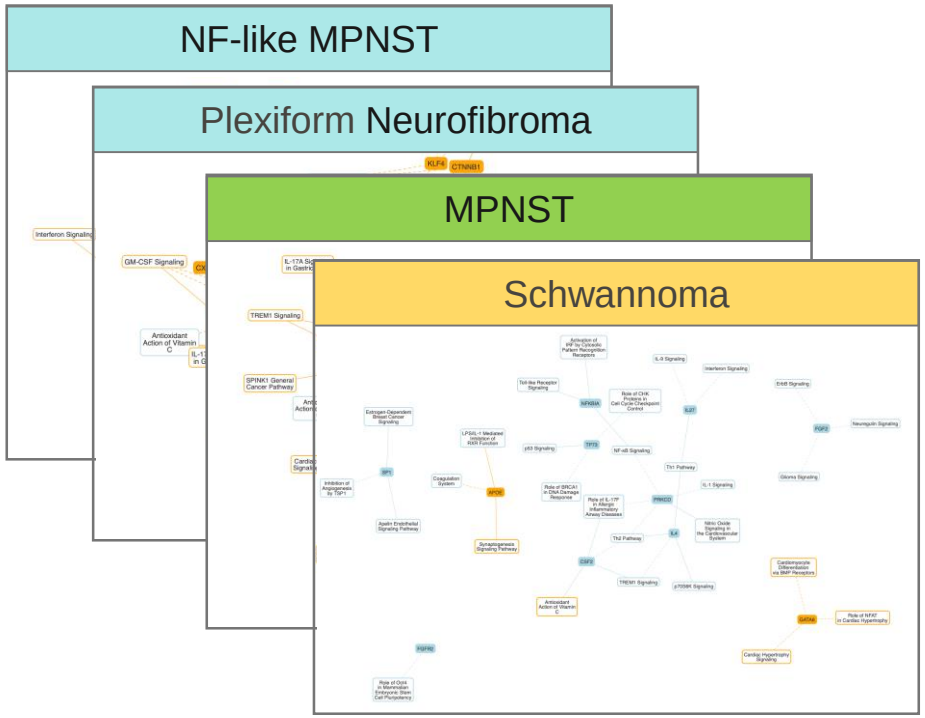
Identified potential upstream regulators specific to the different tumor types

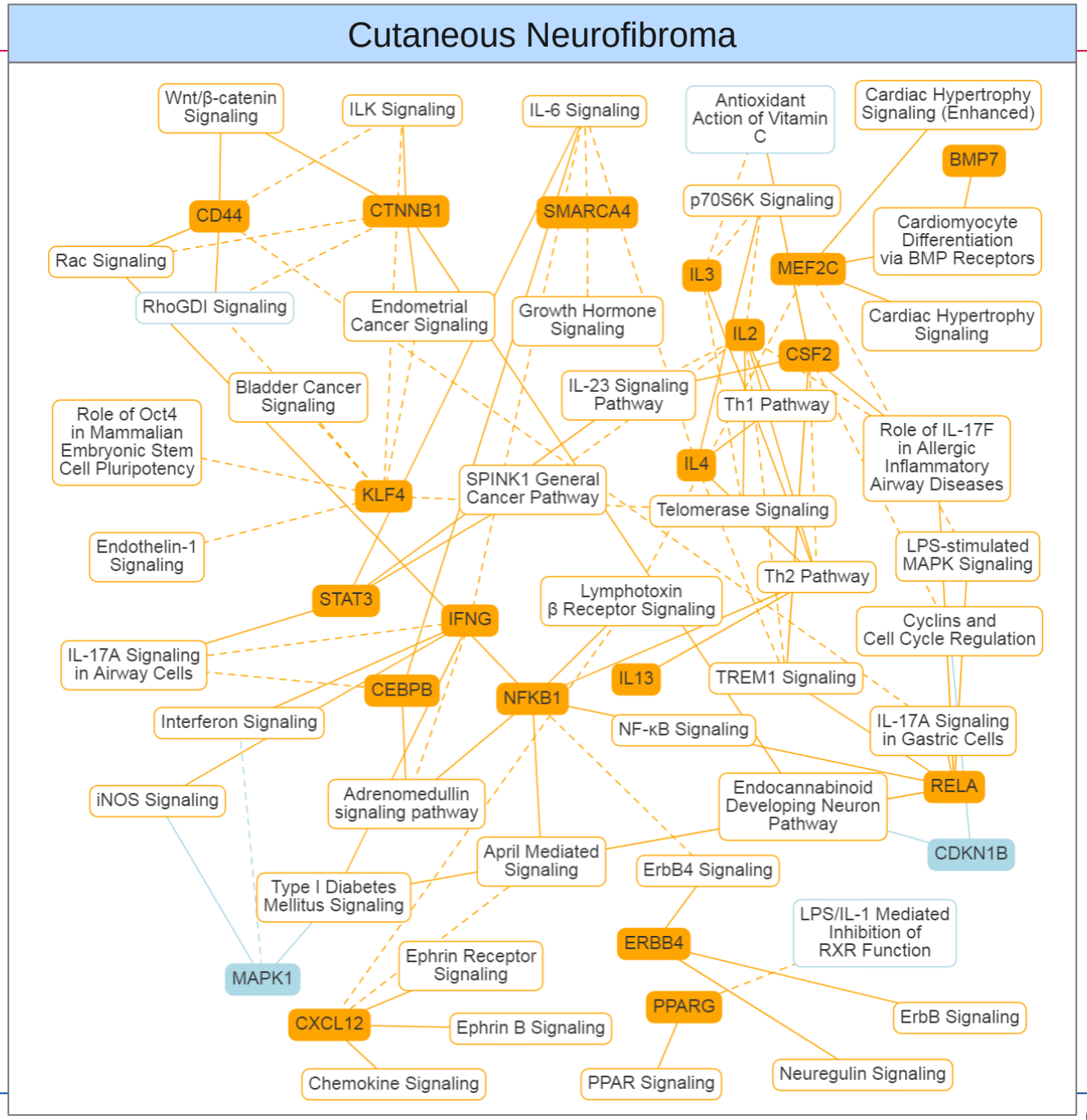
- Upstream regulators differentiate between NF1 and NF2 tumor types, but NF1 subtypes appear relatively similar
- A subsequent comparison analysis between NF1 tumor types differentiated them further (not shown here; available on GitHub)



Machine-learning augmented pathway analysis

- Connects upstream regulators to signaling pathways to provide biological context
- Driven by curated content
- Prioritizes and infers relationships

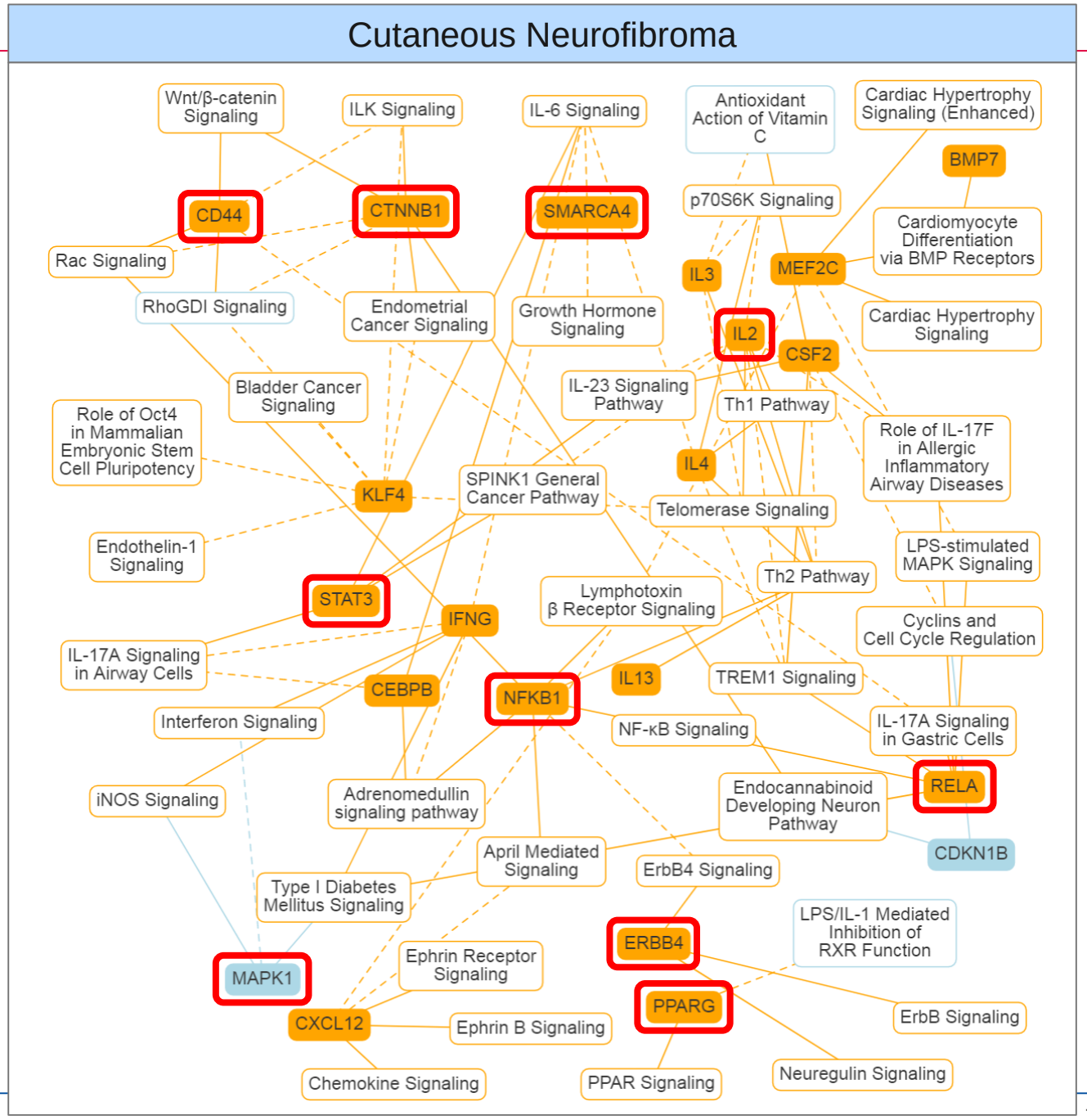




Potential drug targets in the network can be identified and evaluated

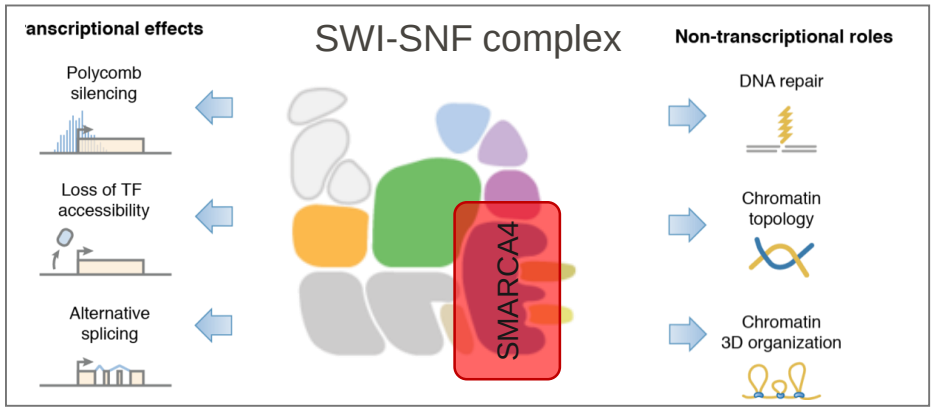
- Networks depict potential therapeutic hypotheses in the context of tumor-specific drug targets
- Both direct targets (upstream regulators) and indirect targets (biological pathways) can be considered

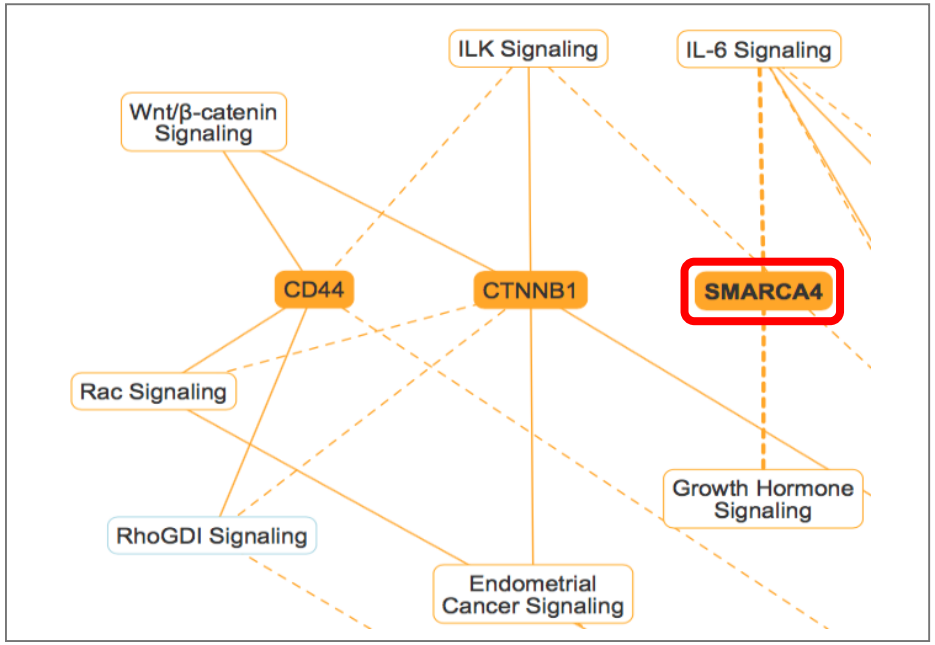
DRUG TARGET EXPLORER hits: TARGET



Hypothesis: SMARCA4 is a potential target for NF1-driven tumors

- SMARCA4 is top-scoring upstream regulator
- Chromatin regulator (SWI-SNF complex)
- Binds β-catenin (Wnt pathway)
- Wnt/β-catenin Signaling in network (CTNNB1, CD44)
- Wnt Signaling is a known pathway in Neurofibromatosis
- SMARCA4 is commonly thought of as a tumor suppressor but its upregulation is also potential mechanism of tumorigenesis:





SCIENTIFIC REPORTS

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High expression of *SMARCA4* or *SMARCA2* is frequently associated with an opposite prognosis in cancer

Received: 21 July 2017
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Published online: 01 February 2018

Jose A. Guerrero-Martínez & Jose C. Reyes

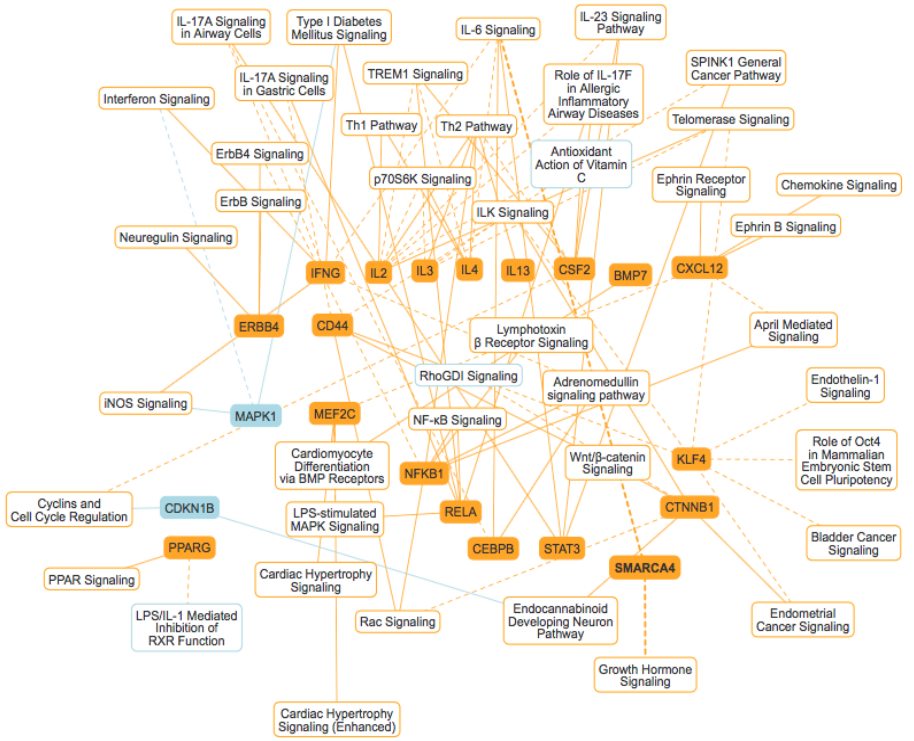
Conclusions

- RNA-Seq data + prior knowledge (curated content) can differentiate NF1 and NF2 tumor types
- This can be used for target discovery

Future directions

- Connect with NF researchers to evaluate this approach and initial findings
- Cross reference hypothetical drug targets with data from tumor type specific drug screening assays
- Expand this approach to other tumor types where suitable data is available

Hypothetical key regulators of NF1-driven tumorigenesis in Schwann Cells



More detail and resources available at:
https://github.com/SVAI/nf-qiagen

TEAM QIAGEN

Recently formed cross-functional data science team at QIAGEN Bioinformatics

Our goal: Use QIAGEN's content and tools to discover new biological insights

If you have a research question that could benefit from this approach, contact us at:

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