

Regulatory heterogeneity of neuroendocrine tumors

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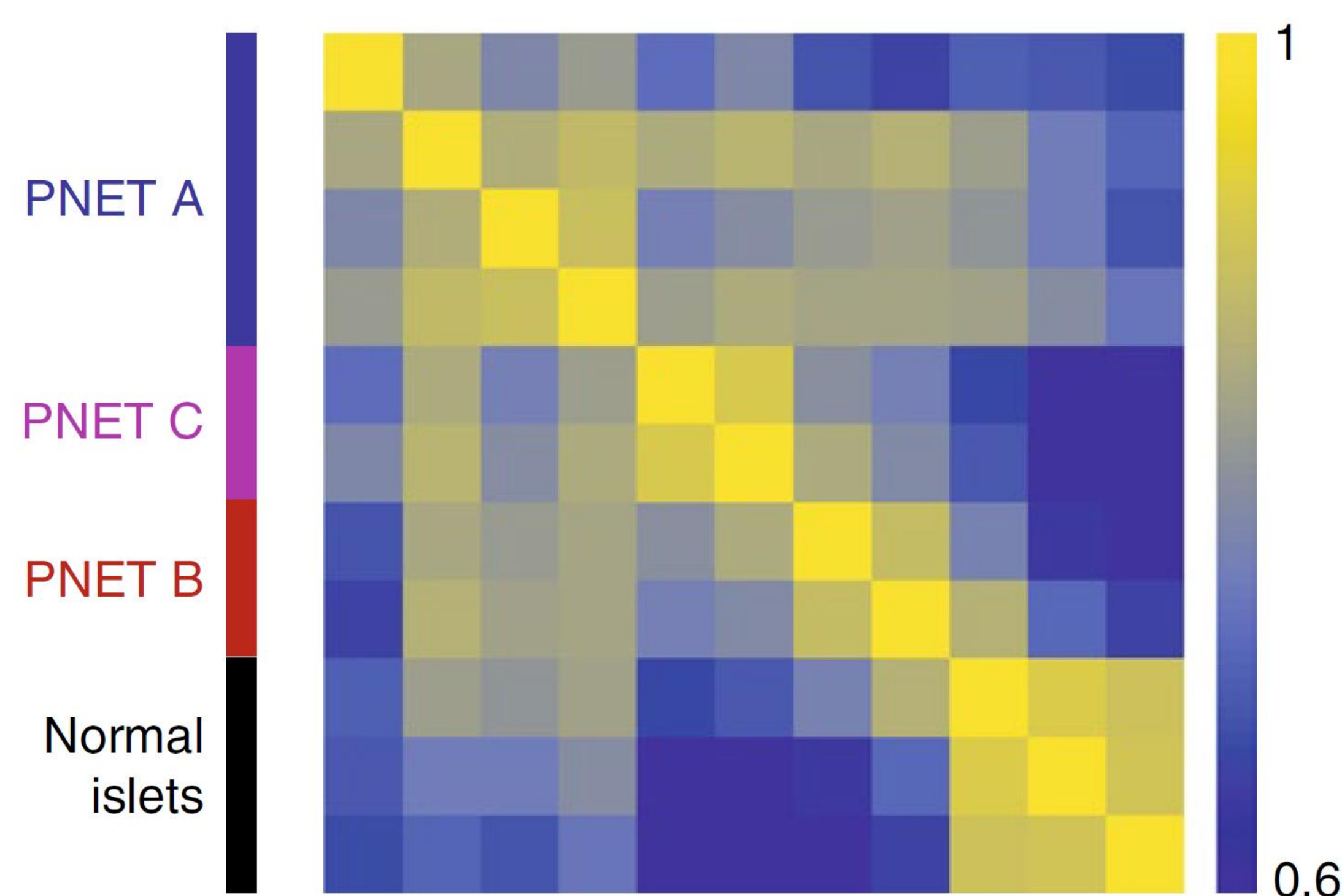
Introduction

Treating patients with neuroendocrine tumors is challenging. The two main challenges are the lack of effective drug treatments and the lack of reliable biomarkers to guide management, since patients with the same tumor grade/stage often have different clinical courses. The genetic, epigenetic and developmental programs that drive neuroendocrine tumors remain obscure, limiting our abilities to suggest new biomarkers and drug targets. We have recently successfully identified regulatory and developmental subtypes of pancreatic neuroendocrine tumors, and matching biomarkers that demonstrated clear clinical prognostic value. These discoveries were enabled by a genome-wide characterization of cis-regulatory elements (known as enhancers) and transcriptional regulatory networks. We now apply these methods to lung neuroendocrine tumors, to identify new subtypes, new biomarkers and drug targets, for this disease as well. We have characterized the transcriptomes and enhancer maps of 9 lung neuroendocrine tumors, and already begin to see potentially new sub-classifications.

Objectives

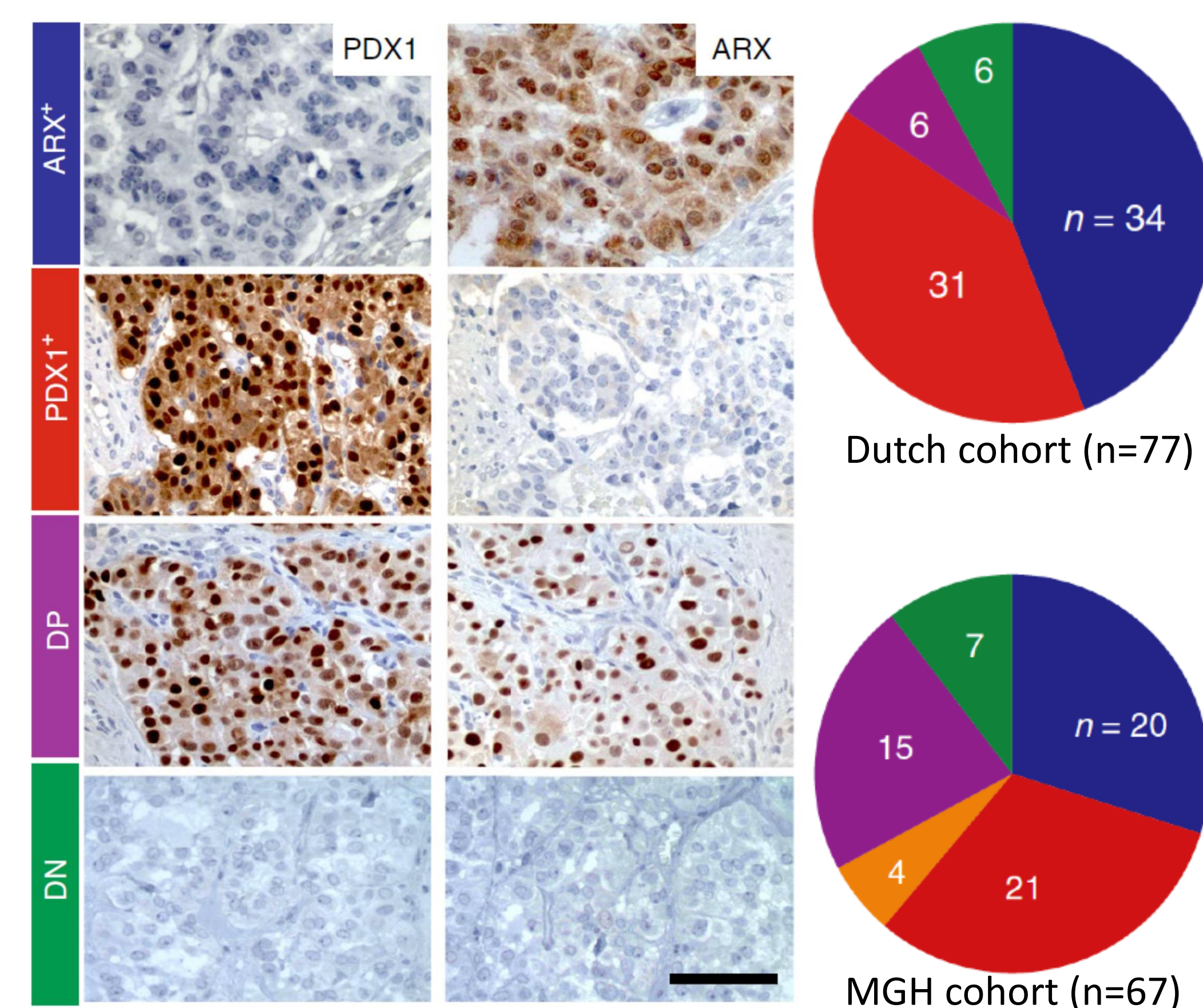
- Characterize transcriptomes (by RNA-seq) and enhancer maps (by H3K27ac) of 30 lung neuroendocrine tumors.
- Identify new, clinically relevant, sub classifications of lung neuroendocrine tumors.
- Identify new biomarkers and drug targets for lung neuroendocrine tumors.
- Compare different types of neuroendocrine tumors at different sites to identify unifying regulatory programs as well as those that are unique to each disease.

Pancreatic NETs variable enhancer landscape

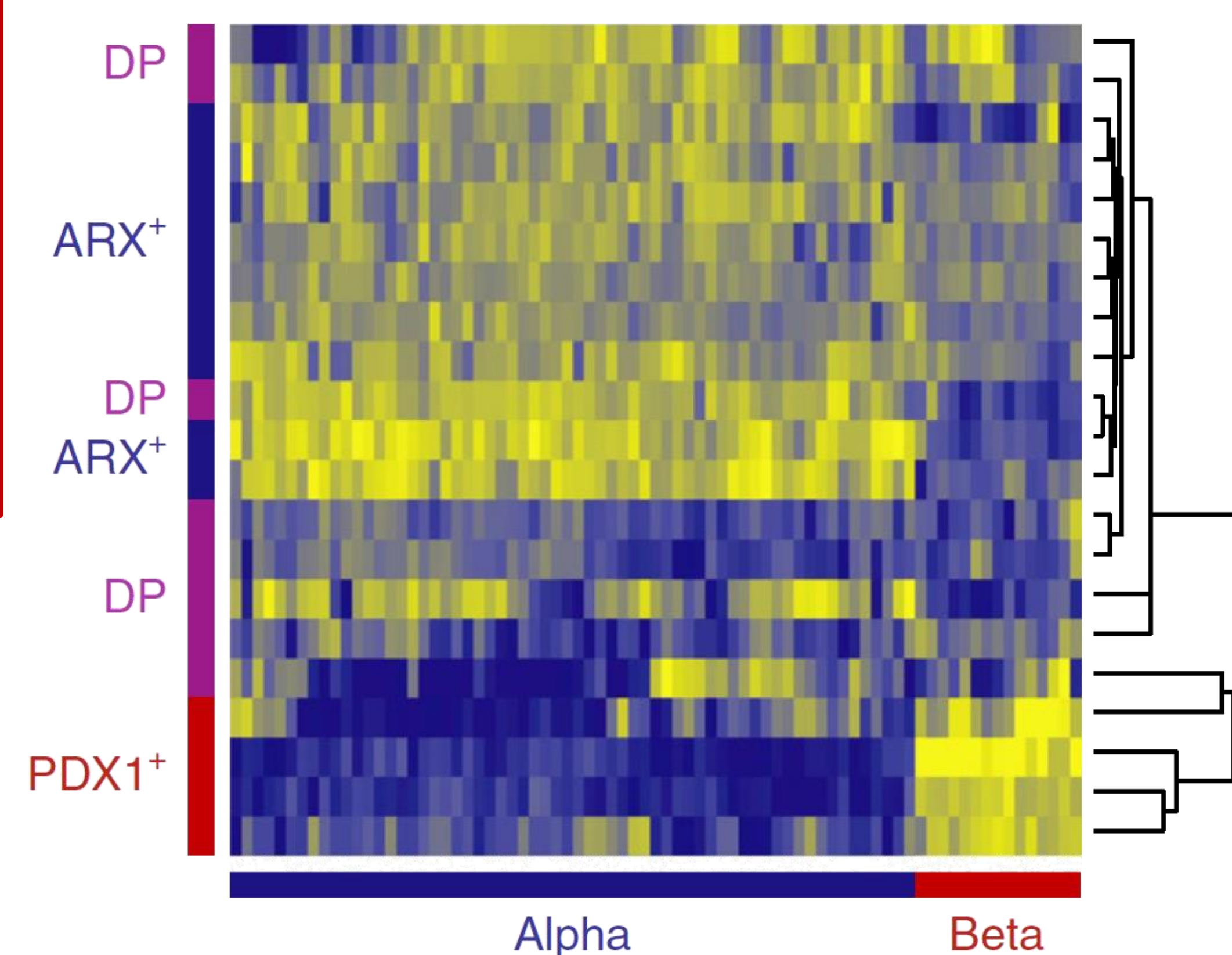


Cejas P, Drier Y, et al. Nature Medicine, 2019, doi:10.1038/s41591-019-0493-4

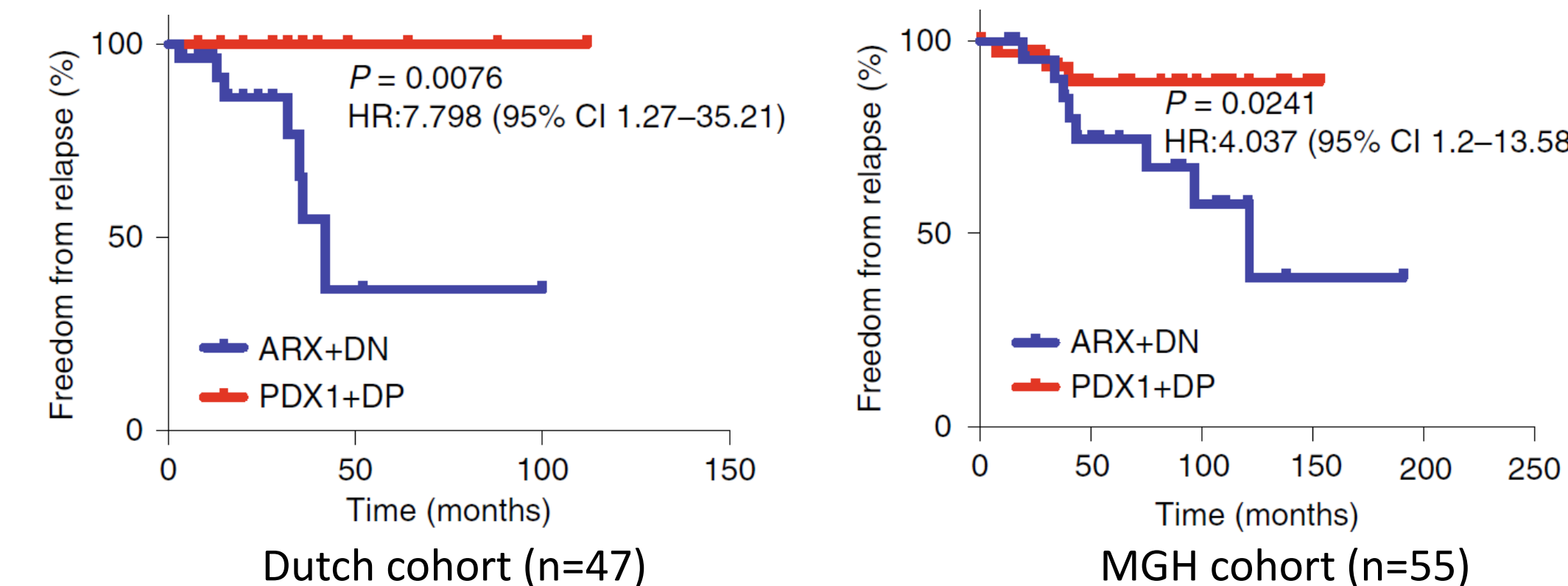
ARX and PDX1 mark novel PNET subtypes



Pancreatic NET subtypes represent distinct endocrine lineages



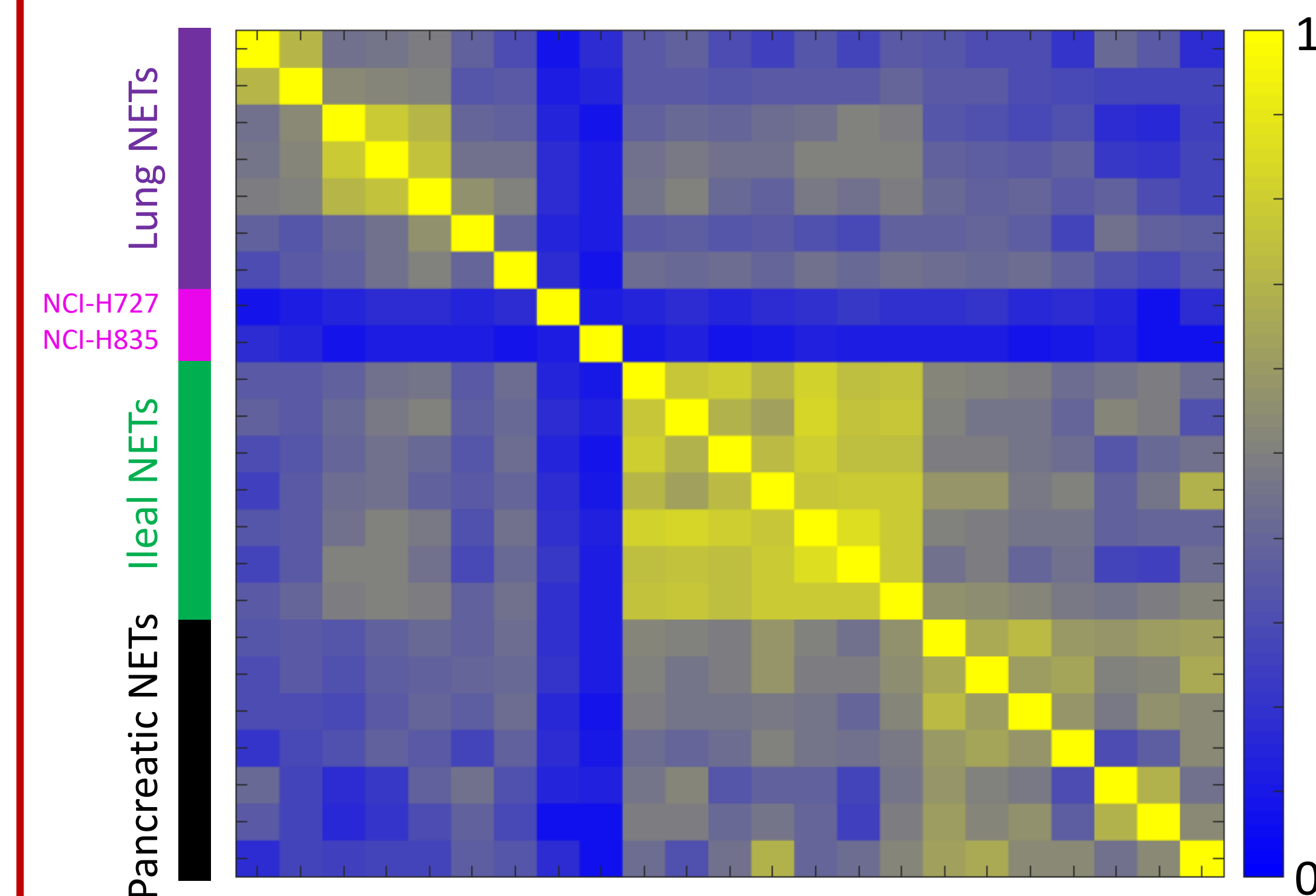
Poor survival of ARX+ PNET patients



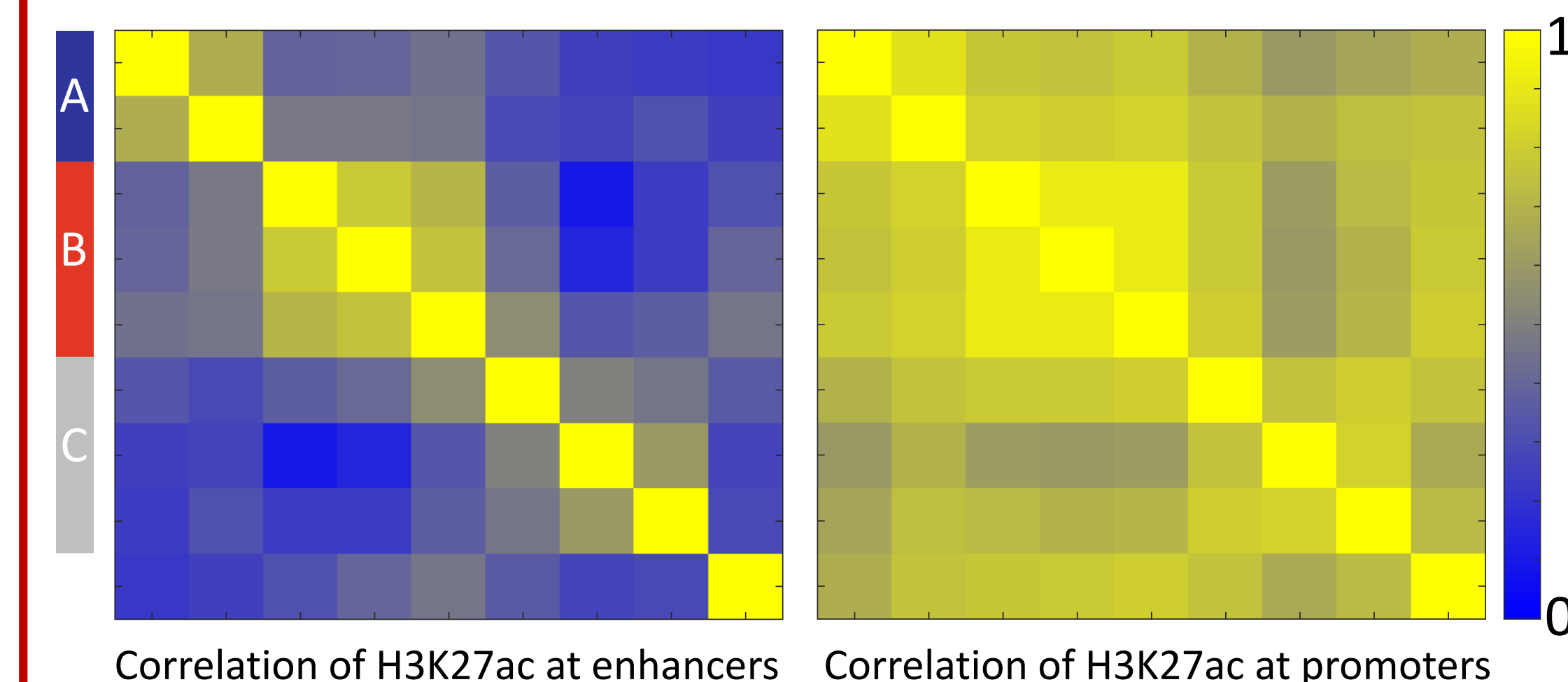
Updates on current lung NET project

- Obtained 10 primary lung typical NETs and 3 lung NET cell lines.
- Profiled enhancers of 9 lung NET tumors (H3K27ac ChIP-seq).
- Profiled transcriptomes of 5 lung NET tumors (RNA-seq).
- Profiled enhancers and transcriptomes of the NCI-H727 and NCI-H835 lines.
- Preliminary integrative analysis of data.

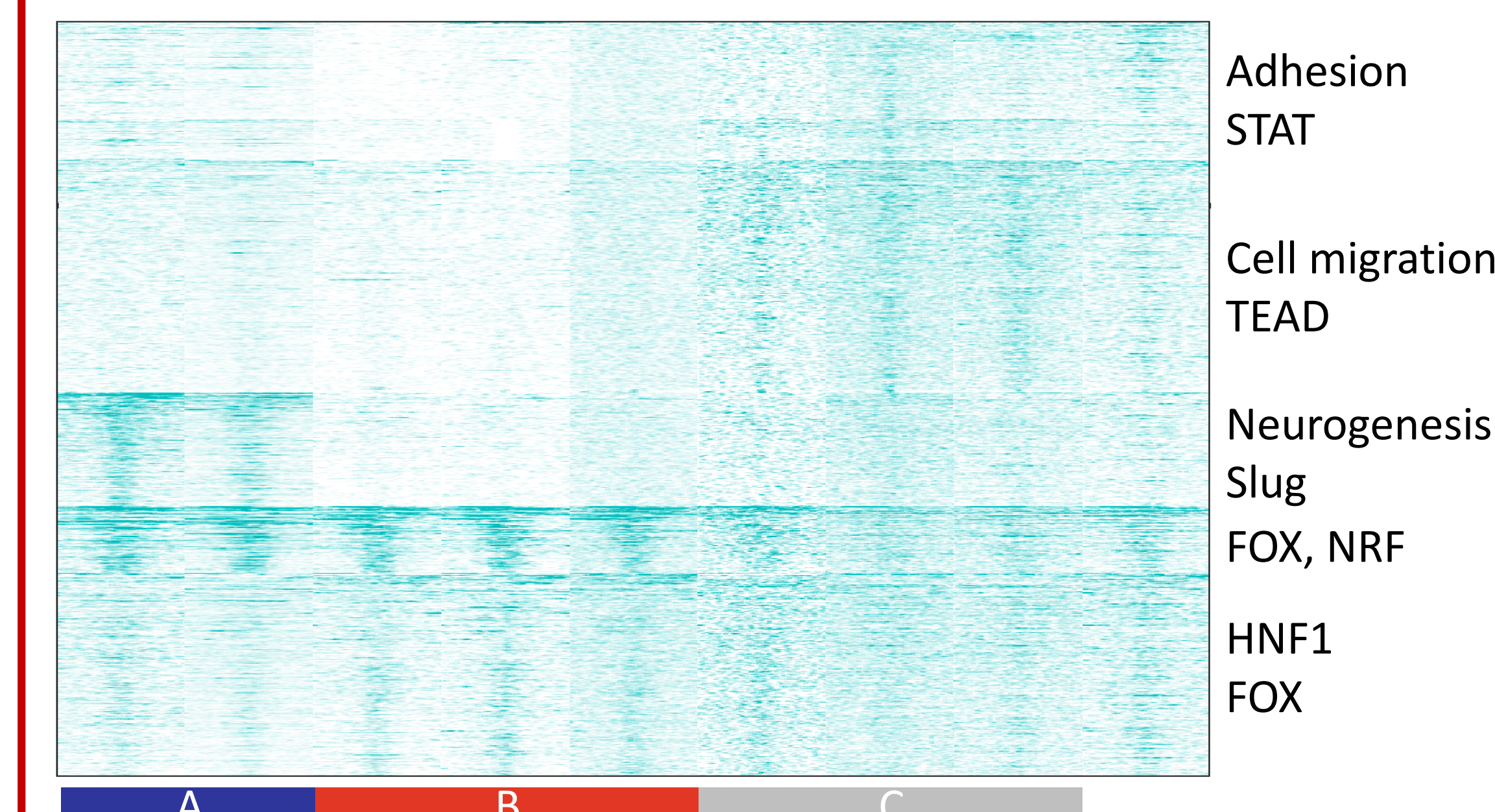
Heterogeneity of NET enhancer landscape, and lack of epigenetically faithful cell line models



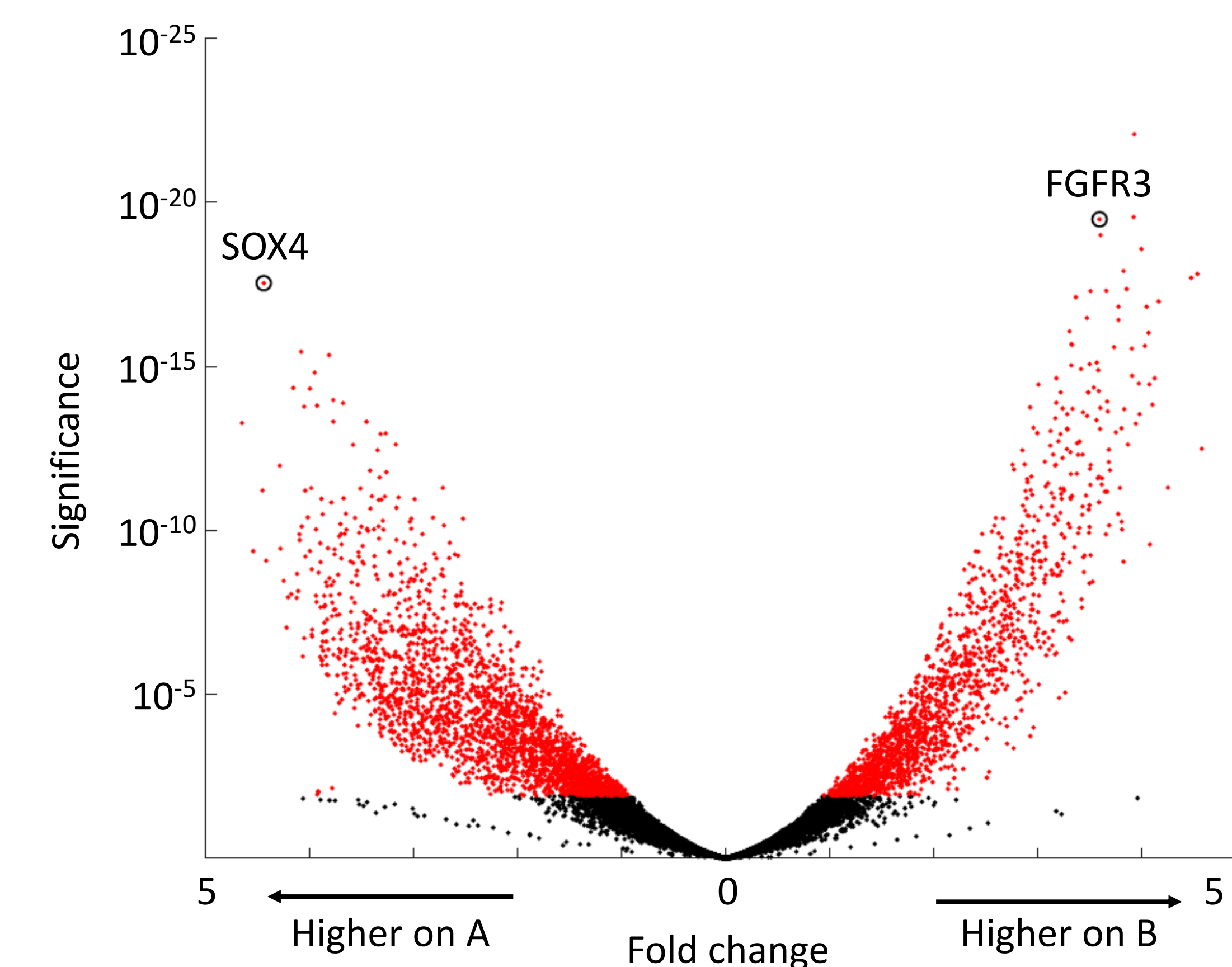
Heterogeneity of lung NET enhancer landscape



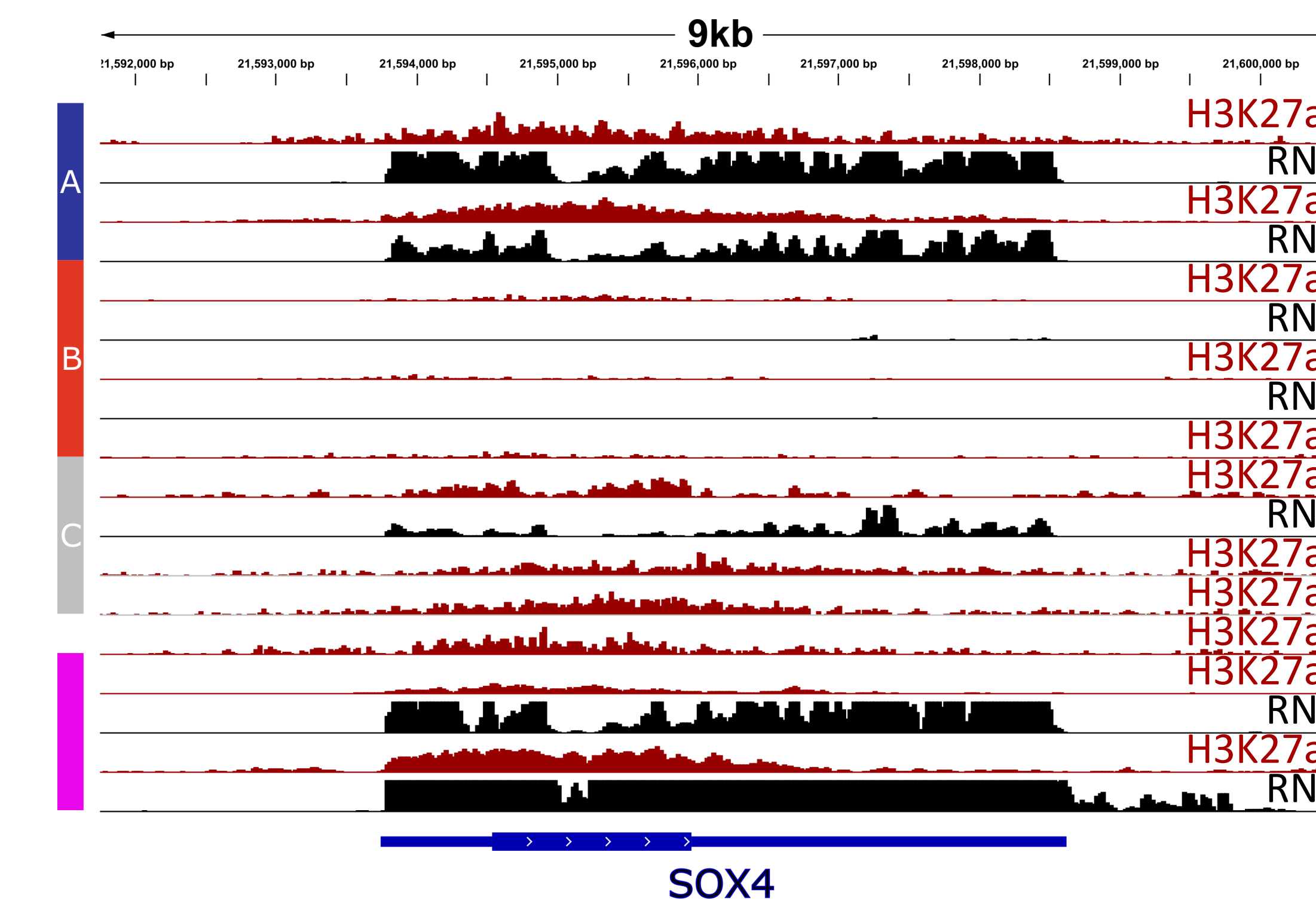
Clustering of H3K27ac reveal regulatory states



Quantitative comparison of H3K27 acetylation levels between lung NET subtypes



SOX4 differentially regulated between subtypes



Conclusions

- Enhancer mapping is a promising approach to stratify lung neuroendocrine tumors.
- Two or three regulatory subtypes of typical lung NETs are emerging.
- Need to identify or generate cell line models that better capture the regulatory landscape of neuroendocrine tumors.

Acknowledgements and contact

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- Pancreatic NET work was led by Profs. Bradley Bernstein and Ramesh Shivdasani (Cejas P, Drier Y, et al. Nature Medicine, 2019)
- Questions and suggestions: yotam.drier@mail.huji.ac.il