

# The adrenergic-specific long non-coding RNA NESPR regulates neuroblastoma cell viability and survival

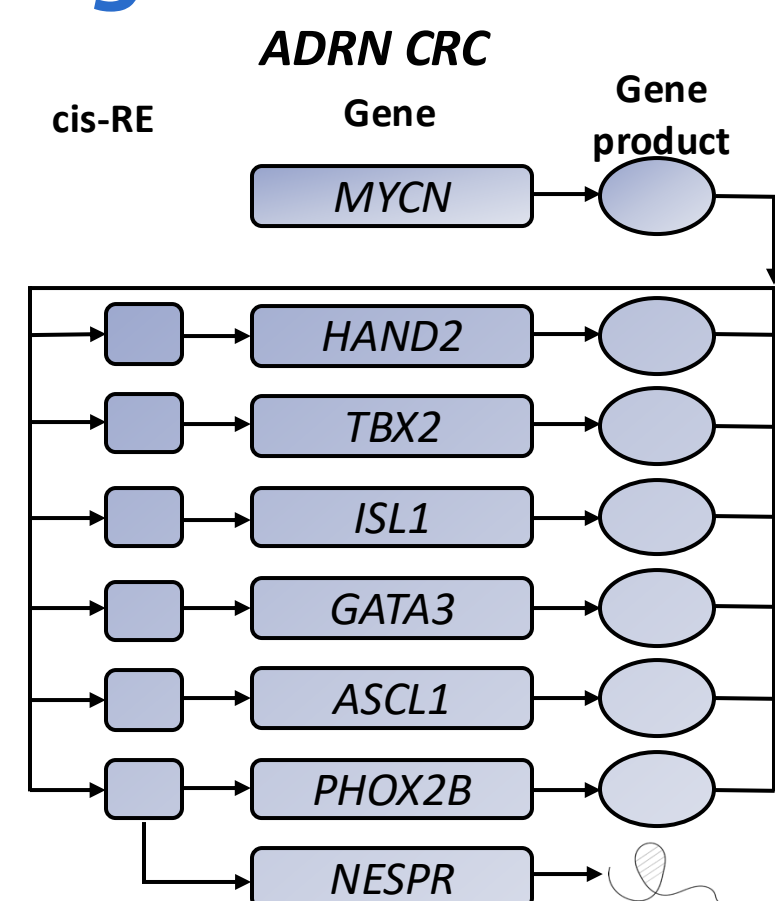
Louis Delhaye<sup>1,2,3,4</sup>, Eric de Bony<sup>1,2,4</sup>, Dries Rombaut<sup>1,2,4</sup>, Eva D'haene<sup>1,2,4</sup>, Nurten Yigit<sup>1,2,4</sup>, Delphine De Sutter<sup>1,3</sup>, Jasper Anckaert<sup>1,2,4</sup>, Bjorn Menten<sup>1,2,4</sup>, Jo Vandesompele<sup>1,2,4</sup>, Frank Speleman<sup>1,2,4</sup>, Sven Eyckerman<sup>1,3,4</sup>, Pieter Mestdagh<sup>1,2,4</sup>

<sup>1</sup> Department of Biomolecular Medicine, Ghent University, Belgium  
<sup>2</sup> Center for Medical Genetics, Ghent University, Belgium  
<sup>3</sup> VIB-Ugent Center for Medical Biotechnology, VIB, Belgium  
<sup>4</sup> Cancer Research Institute Ghent (CRIG), Ghent University, Belgium  
Presenting author: louis.delhaye@ugent.be

louis.delhaye@ugent.be  
 @ldlhaye  
 /louis-delhaye

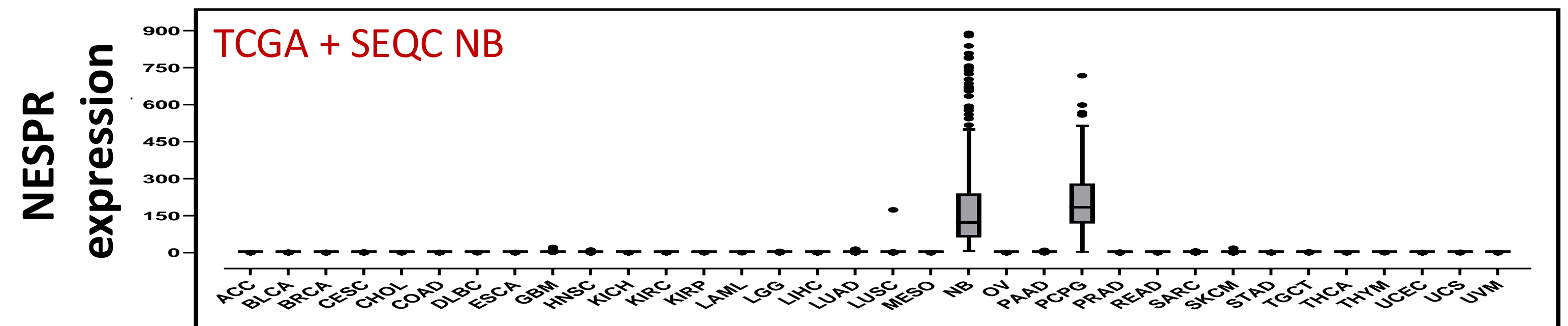
## Introduction: neuroblastoma is a heterogeneous tumor

Neuroblastoma (NB) is a childhood cancer of the sympathetic nervous system. Recent studies have shown that neuroblastoma tumors are composed of two cell identities, i.e. the **adrenergic (ADRN)** and **mesenchymal (MES)** identity. Both identities are driven by a **core regulatory transcriptional circuitry (CRC)**, which acts as an autoregulatory positive feedforward loop, to delineate the cell identity through regulation of its target genes. We identified the **long non-coding RNA NESPR** to be specifically expressed in neuroblastoma cells of the adrenergic cell identity. We show that NESPR is contained within an insulated gene neighborhood with the adrenergic core regulatory transcription factor **PHOX2B**, and that NESPR regulates **PHOX2B** expression *in cis*. Knockdown of NESPR decreased neuroblastoma cell proliferation and induced cell death, highlighting NESPR's importance in the survival of the adrenergic neuroblastoma cells

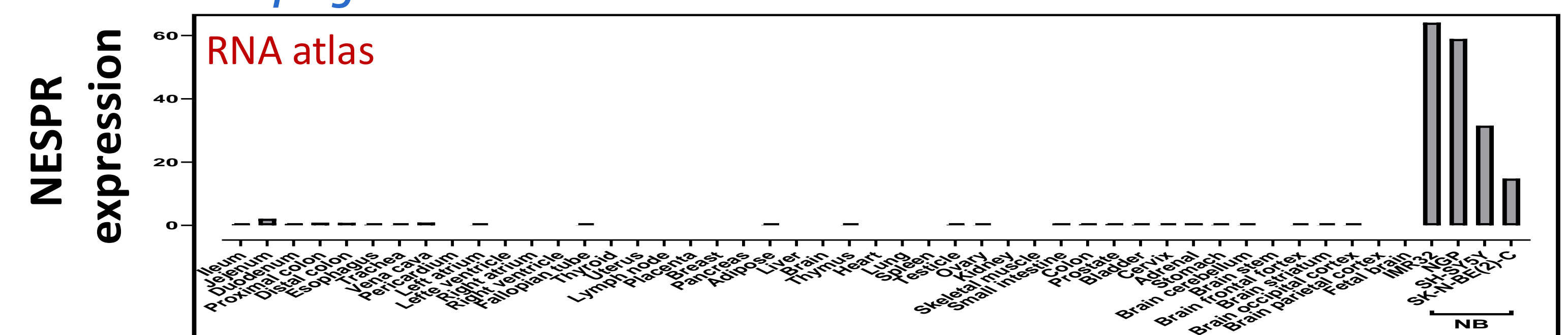


## NESPR acts as a lineage survival oncogene in NB

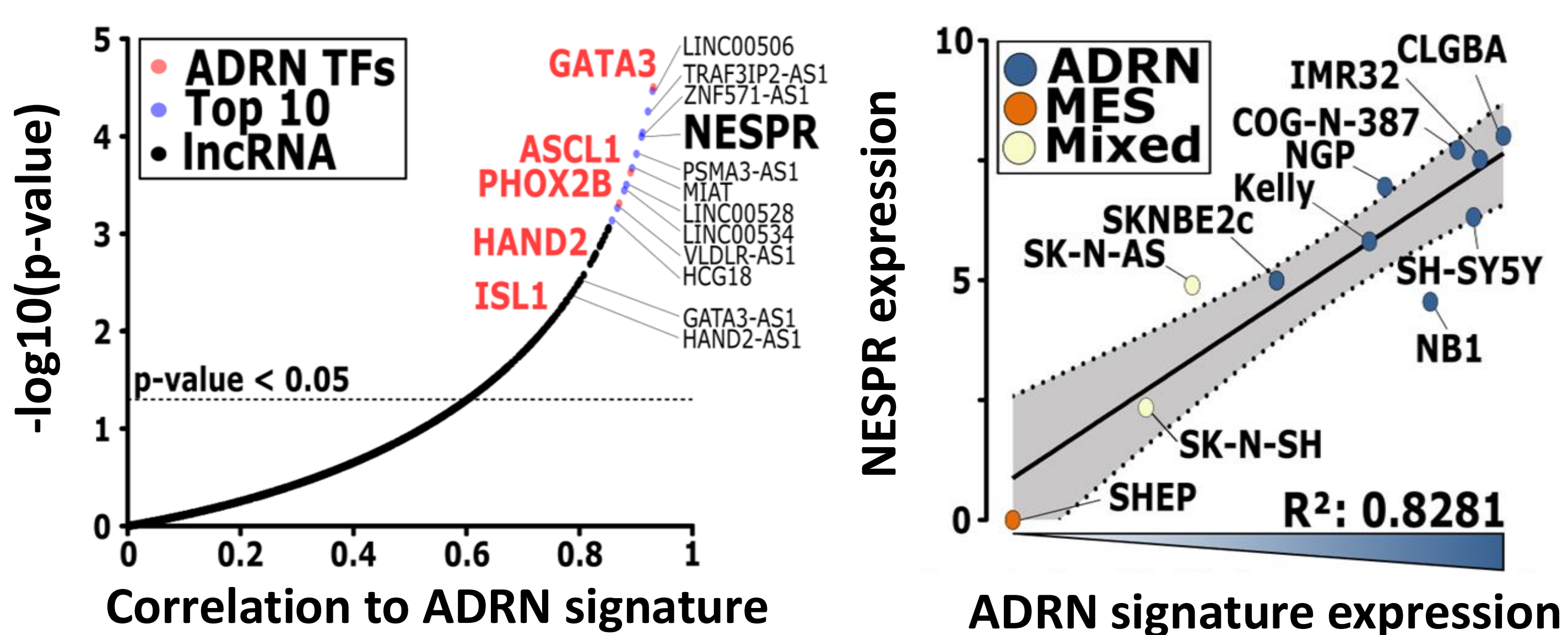
NESPR expression is restricted to cancers derived from the sympathoadrenal lineage



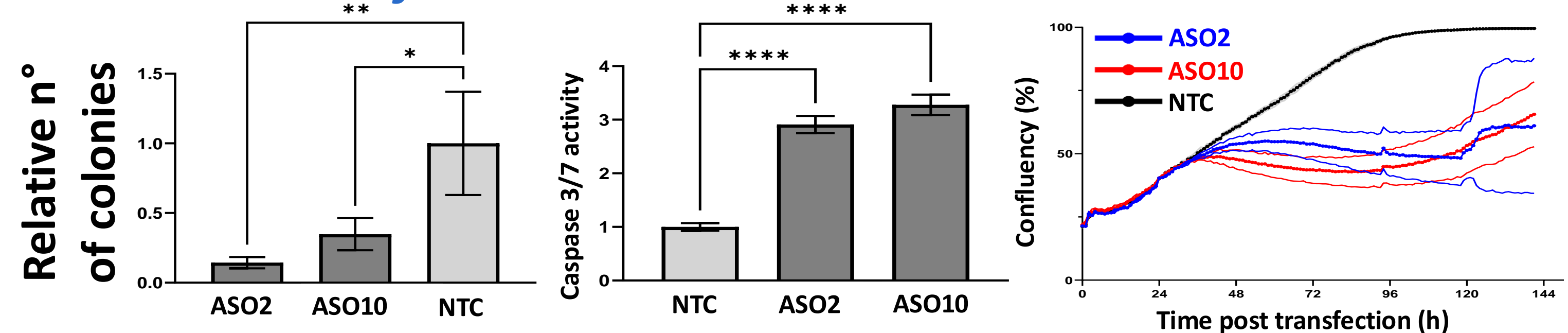
NESPR is upregulated in NB cells



## NESPR is a adrenergic-specific long non-coding RNA

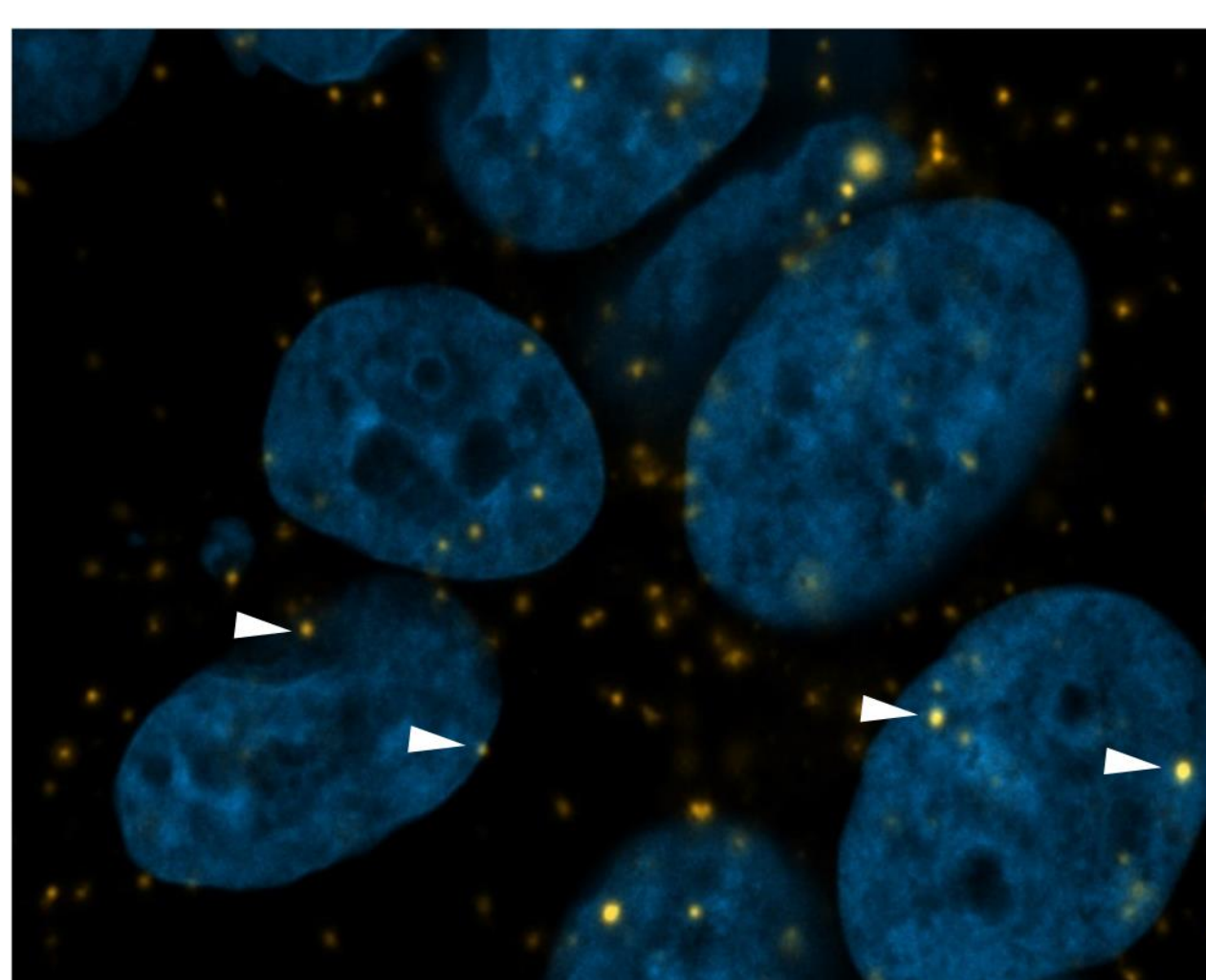


NESPR is essential for NB cell survival

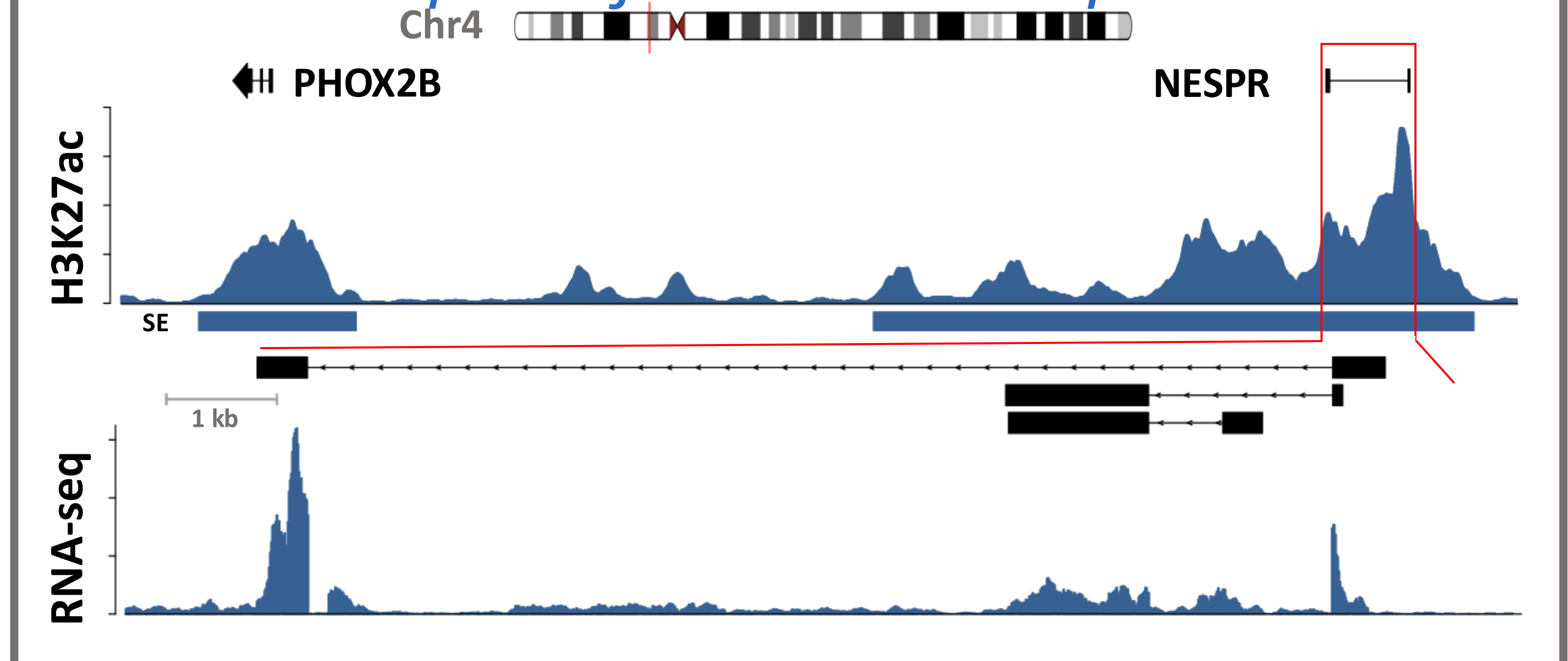


## Understanding NESPR's mode-of-action – a multi omics approach

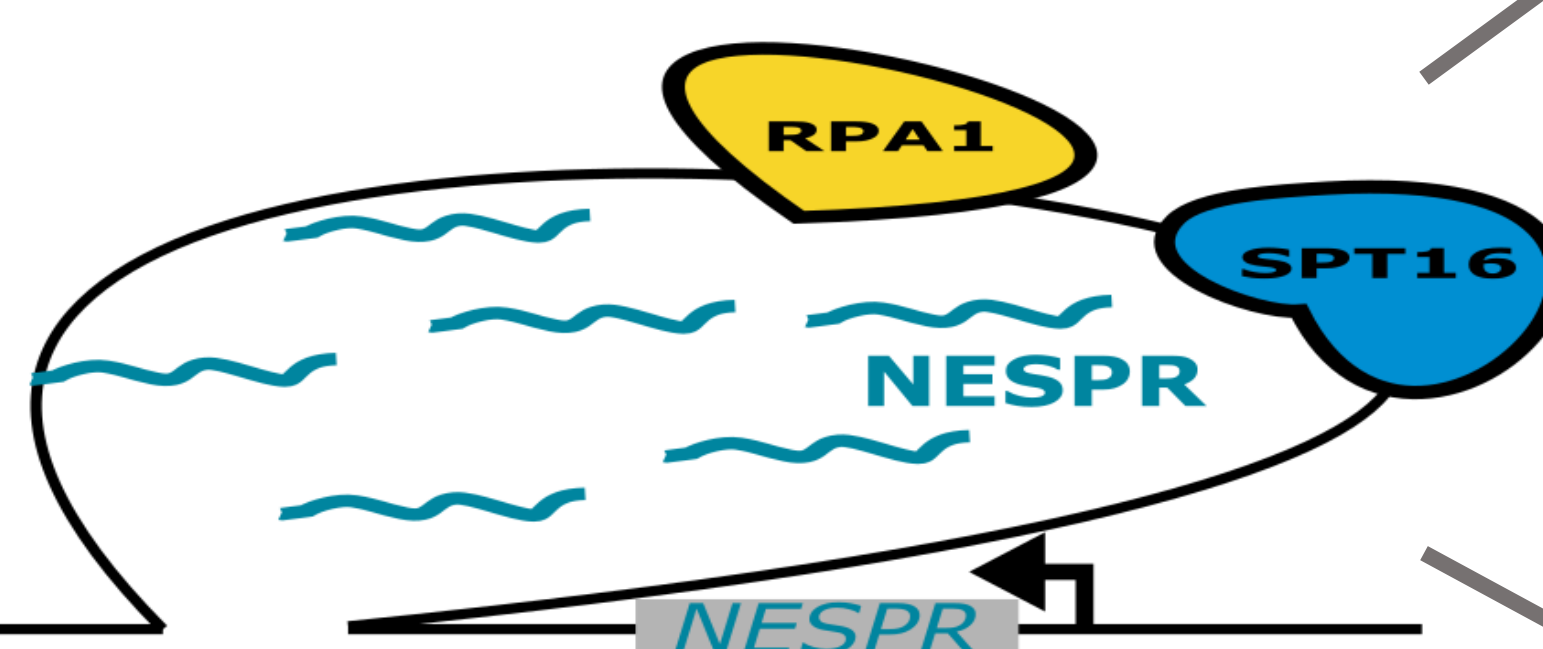
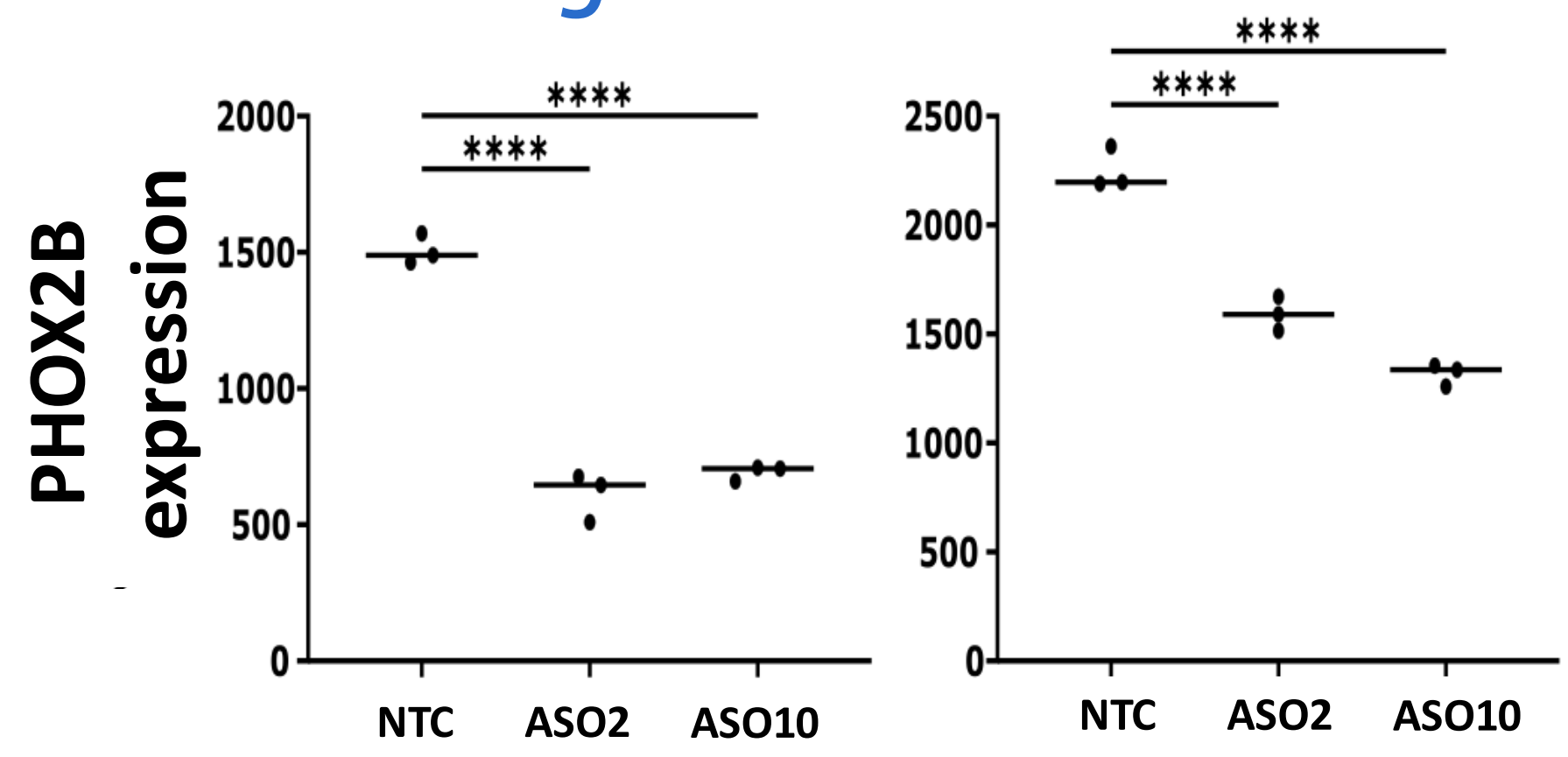
### Nuclear NESPR concentrates in distinct foci



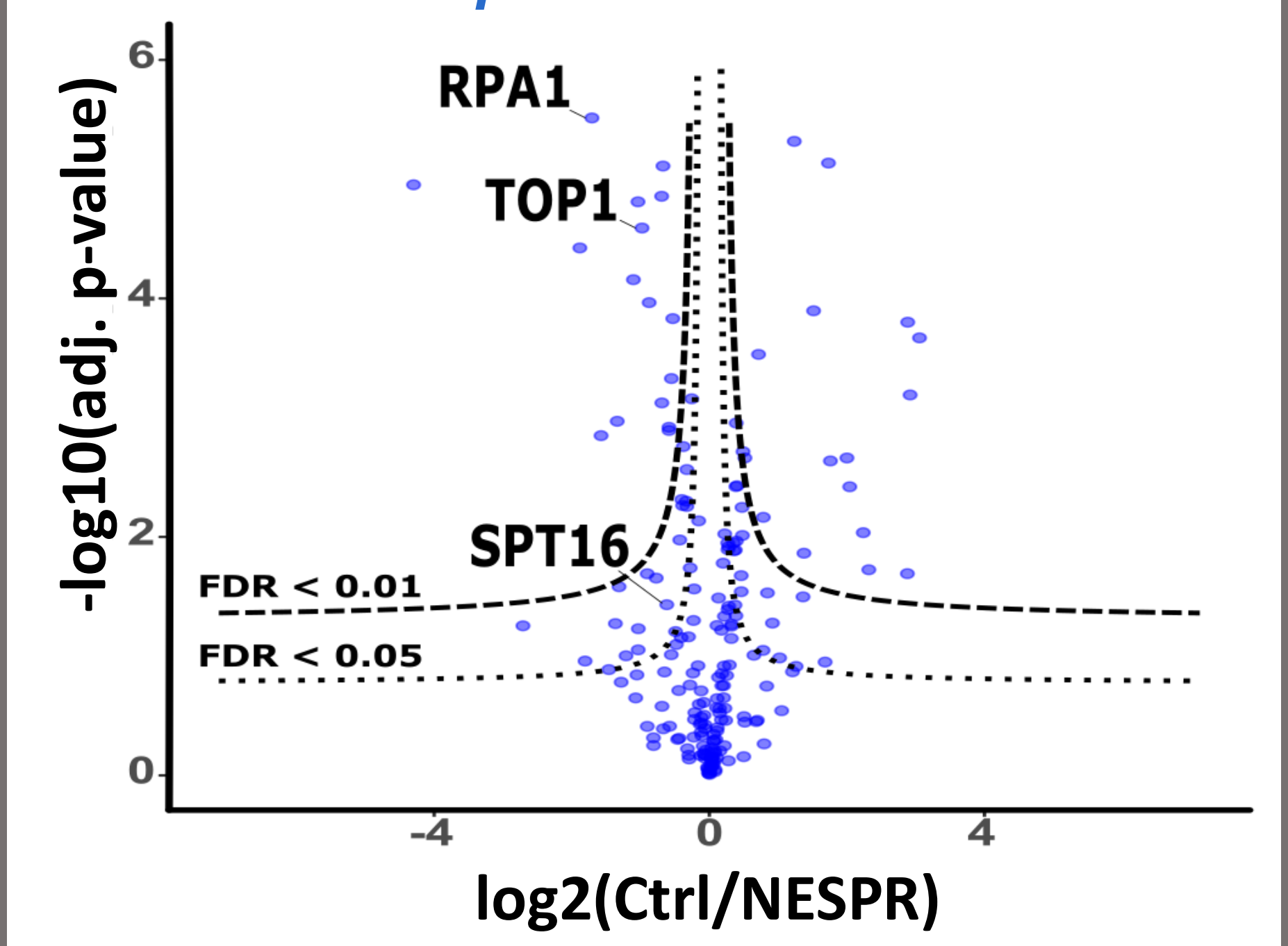
### NESPR is expressed from the PHOX2B super-enhancer



### NESPR regulates PHOX2B in cis



### NESPR interacts with transcriptional co-activators



### Chromatin looping generates a NESPR-PHOX2B insulated gene neighborhood

