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SEMINAR ANNOUNCEMENT

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Aula Magna "C. Golgi"
Fondazione IRCCS Policlinico San Matteo

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(New York City, USA)

Completing our view of brain RNAs at single-cell and spatial resolution in health and disease

About the talk:
Complex tissue includes diverse cell types employing distinct RNA isoforms. To untangle full-length cell-type specific brain isoforms, we developed single-cell long-read technology for many thousands of cells (from previous approaches for 10-100 cells) in fresh tissues (ScISOr-Seq; Gupta..Tilgner, 2018[1]) and in frozen tissues (SnISOr-Seq; Hardwick..Tilgner, 2022[2]). These approaches revealed the rules of combination of TSSs, alternative exons and poly(A) sites and their cell-type specificity. Autism-associated exons (as previously described) but also FTD-associated exons are highly variably-used across cell types[2]. For spatial resolution, we developed spatially-barcoded isoform sequencing with 60um (Joglekar..Tilgner, 2021[3]), 10um (Foord..Tilgner, 2025[4]) and 220nm (Michielsen..Tilgner, biorxiv[5]) spots, showing that often isoform switches correlate with precise boundaries of brain structures (e.g., choroid plexus to hippocampus). However, genes including *Snap25,* use a gradient of exon inclusion through the brain[3]. Choroid plexus epithelial cells show a dramatically distinct isoform profile, which originates most strongly from TSS usage[3]. During human puberty, layer4-excitatory splicing is more regulated than in other cortical layers – probably influenced by retroviral sequences[4]. More generally, we can now detect isoform-expression variability that does not correspond to known brain structures[5].

For the NIH Brain Initiative, we have mapped single-cell isoforms across development, brain regions and species. Neurotransmitter release and reuptake as well as synapse turnover genes harbor variability in the same cell type across anatomical regions but the same cell type traced

across development shows more isoform variability than across adult anatomical regions. Moreover, most cell-type-specific exons in adult mouse hippocampus behave similarly in human hippocampi. However, human brains have evolved additional cell-type specificity in splicing (Joglekar..Tilgner, 2024[6]). Additionally, the concurrent measurement of chromatin and splicing patterns in post-mortem human brain shows broadly-speaking convergent dysregulation of both modalities in similar cell types in Alzheimer's disease but more divergence between both modalities in evolution (Hu..Tilgner, 2025[7]). Finally, we have advanced our understanding of error sources of PacBio and ONT (Mikheenko..Tilgner, 2022[8]) and implemented highly accurate long-read software (Prjibelski..Tilgner, 2023[9]).

About Prof. Tilgner:
Hagen Tilgner studied computer science in Germany and France, and after a Master's thesis (for the French ENSIMAG) at the Sanger Institute (UK), did his PhD with Roderic Guigó at the Centre for Genomic Regulation in Barcelona. There he focused on RNA and the co-transcriptionality of splicing (see Tilgner et al, Genome Res, 2012 among others). His postdoctoral work at Stanford with Michael Snyder focused on technology development, specifically for long-read transcriptomics (see for example Sharon*, Tilgner*, Grubert, Snyder, Nature Biotechnology'13, Tilgner*, Sharon*, Grubert*, Snyder, PNAS'14 or Tilgner*, Jahanbani* et al, Nature Biotechnology'15). He started his lab at Weill Cornell in New York City in 2016 focusing on technologies to decipher the actions of RNA isoforms in the brain. The lab is a multi-disciplinary lab, including wet-lab technology development (see for example single-cell isoform RNA sequencing, ScISOr-Seq, Gupta et al, Nature Biotechnology'18; Slide-isoform sequencing, Sl-ISO-Seq, Joglekar et al, Nature Communications'21; Single-nuclei-isoform-RNA sequencing, SnISOr-Seq, Hardwick et al, Nature Biotechnology'22; ScISOr-ATAC, Hu et al, Nature Biotechnology'25) and dry-lab approaches (see for example Joglekar et al, Nature Communications'21 or Prjibelski et al, Nature Biotechnology'23) meet combined large-scale efforts centered on the brain (for example, Joglekar et al, Nature Neuroscience'24). Lab members combine Maths/CS, molecular biology and neuroscience backgrounds to further our understanding of isoforms in healthy and diseased brain of humans and model organisms.

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