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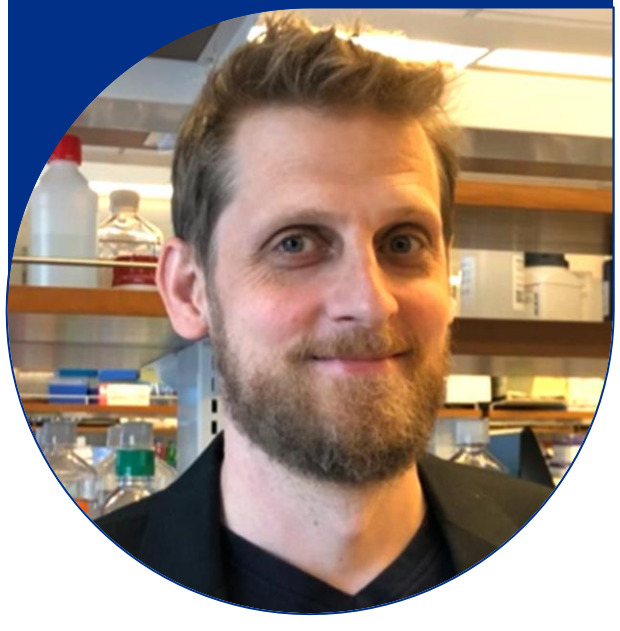
SPEAKER SERIES



Genome Institute of Singapore
A*STAR GIS

Towards a comprehensive single-cell picture of RNA isoforms in mouse and human brain and their diseases – or – Single-cell isoforms in time and space

Dr. Hagen Tilgner

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Host: Wan Yue

Thursday 30 October 2025
10.00am – 11.00am

GIS L2 – Seminar Room
60 Biopolis Street, Genome, Singapore 138672

About The Speaker

Hagen Tilgner studied computer science in Germany and France, and after a Master's thesis (for a French engineering school) at the Sanger Institute (UK), did his PhD with Roderic Guigó in Barcelona. There, he focused on RNA and the co-transcriptionality of splicing (see Tilgner et al, Genome Res, 2012 for example). His postdoctoral work at Stanford with Michael Snyder yielded the first long-read RNA publications (see Sharon*, Tilgner*, Grubert, Snyder, Nature Biotechnology'13; Tilgner*, Sharon*, Grubert*, Snyder, PNAS'14 or Tilgner*, Jahanbani* et al, Nature Biotechnology'15). His lab at Weill Cornell in New York City focuses on technologies to decipher the actions of RNA isoforms in the brain. The lab is a multi-disciplinary lab, including wet-lab technology development (e.g., single-cell isoform RNA sequencing, ScISOr-Seq, Gupta et al, Nature Biotechnology'18; SnISOr-Seq, Hardwick et al, Nature Biotechnology'22; ScISOr-ATAC; Hu et al, Nature Biotechnology'25) and dry-lab approaches (e.g., Joglekar et al, Nature Communications'21; Prjibelski et al, Nature Biotechnology'23; Foord et al, Nature Communications'21) as well as combined large-scale efforts centered on the brain (e.g.; Joglekar et al, Nature Neuroscience'24) where Maths/CS, molecular biology and neuroscience backgrounds interact to further our understanding of isoforms in healthy and diseased brain of humans and model organisms.

About The Seminar

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 in fresh (ScISOr-Seq; Gupta..Tilgner'18[1]) and frozen tissues (SnISOr-Seq; Hardwick..Tilgner'22[2]), revealing the combination-rules of TSSs, 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'21[3]), 10um (Foord..Tilgner'25[4]) and 220nm (Michielsen..Tilgner, biorxiv[5]) spots. Often, isoform switches correlate with precise boundaries of brain structures. However, fewer genes use a gradient of exon inclusion through the brain[3]. Choroid plexus epithelial cells show a dramatically distinct isoform profile, stemming most strongly from TSS[3]. During human puberty, layer4-excitatory-neuron 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. 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'24[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 in evolution (Hu..Tilgner'25[7]). Finally, we have advanced our understanding of long-read error sources (Mikheenko..Tilgner'22[8]) and implemented highly accurate long-read software (Prjibelski..Tilgner'23[9]).