

Integrative proteogenomics for the discovery of diagnostic biomarkers and therapeutic targets

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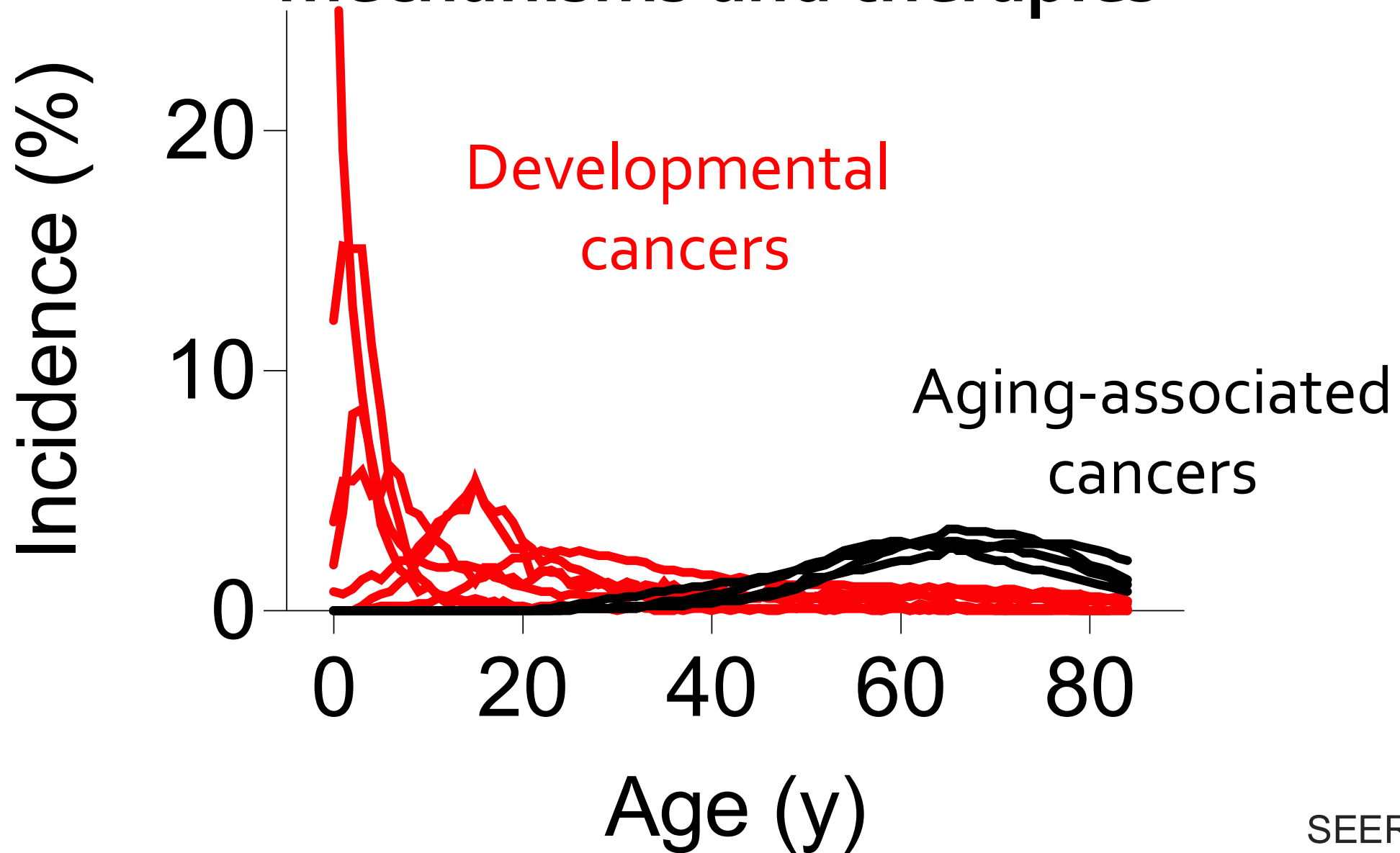
Sloan Kettering Institute & Department of Pediatrics

Memorial Sloan Kettering Cancer Center

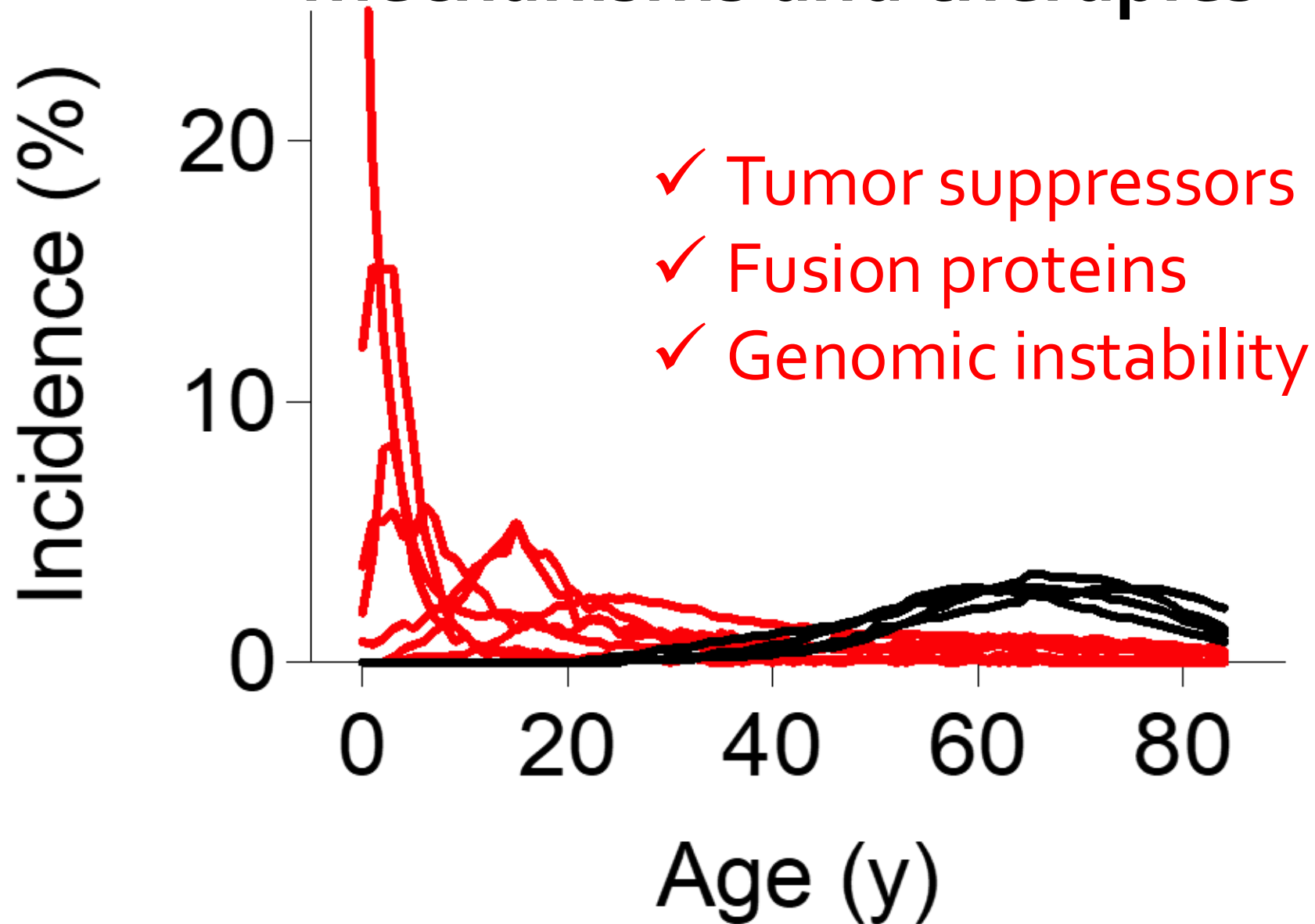
<https://alexkentsis.net>

@KentsisResearch

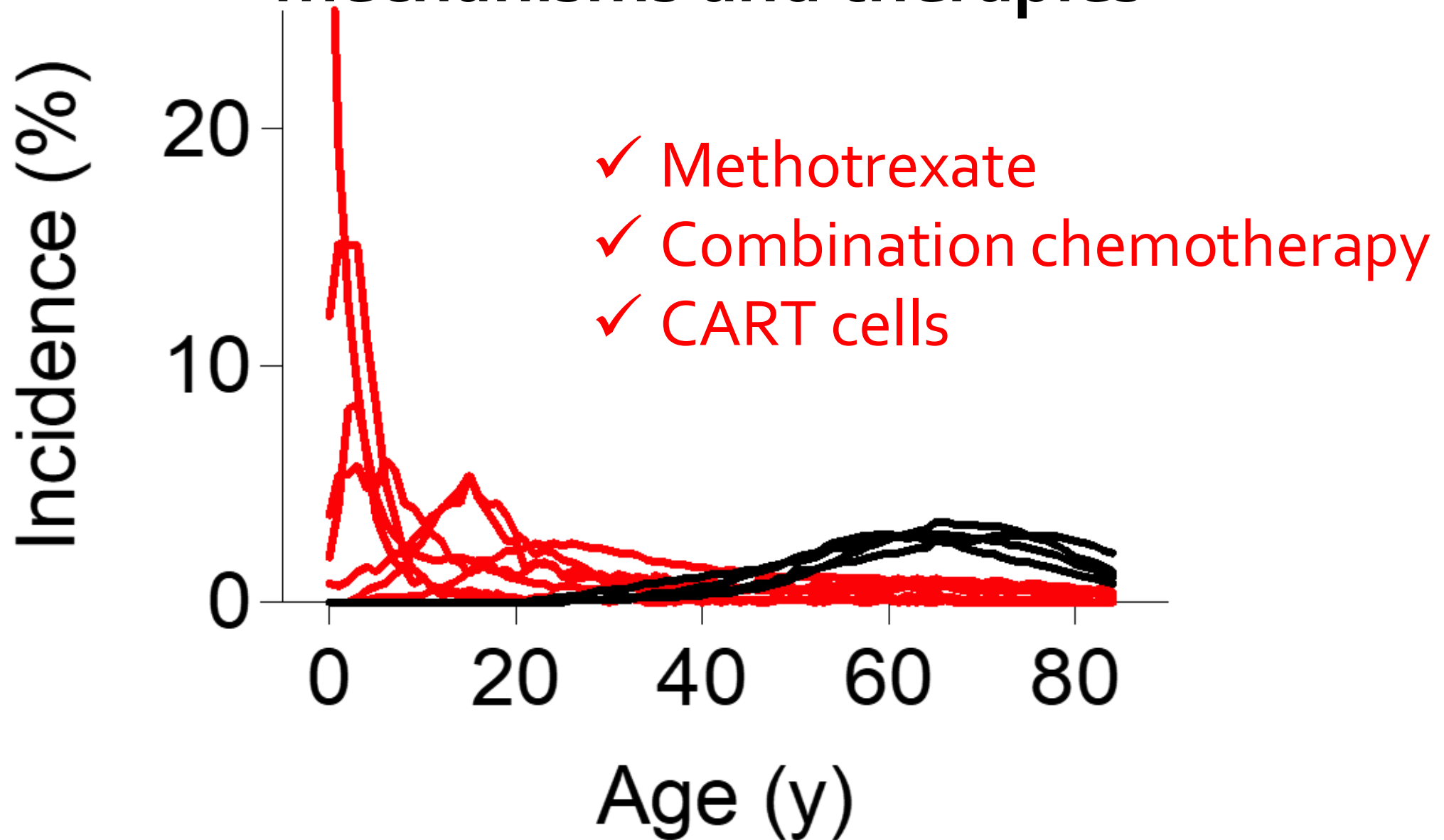
Rare childhood cancers have revealed universal mechanisms and therapies



Rare childhood cancers have revealed universal mechanisms and therapies

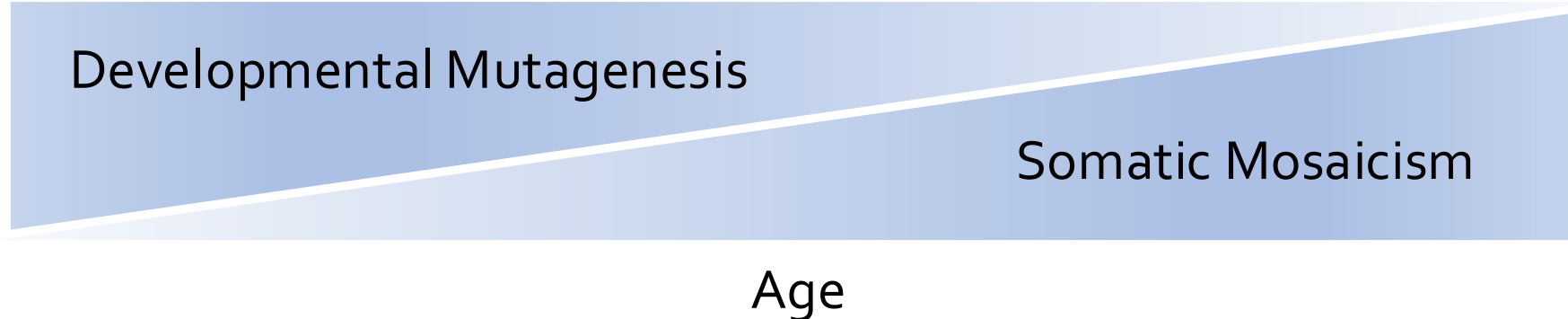


Rare childhood cancers have revealed universal mechanisms and therapies

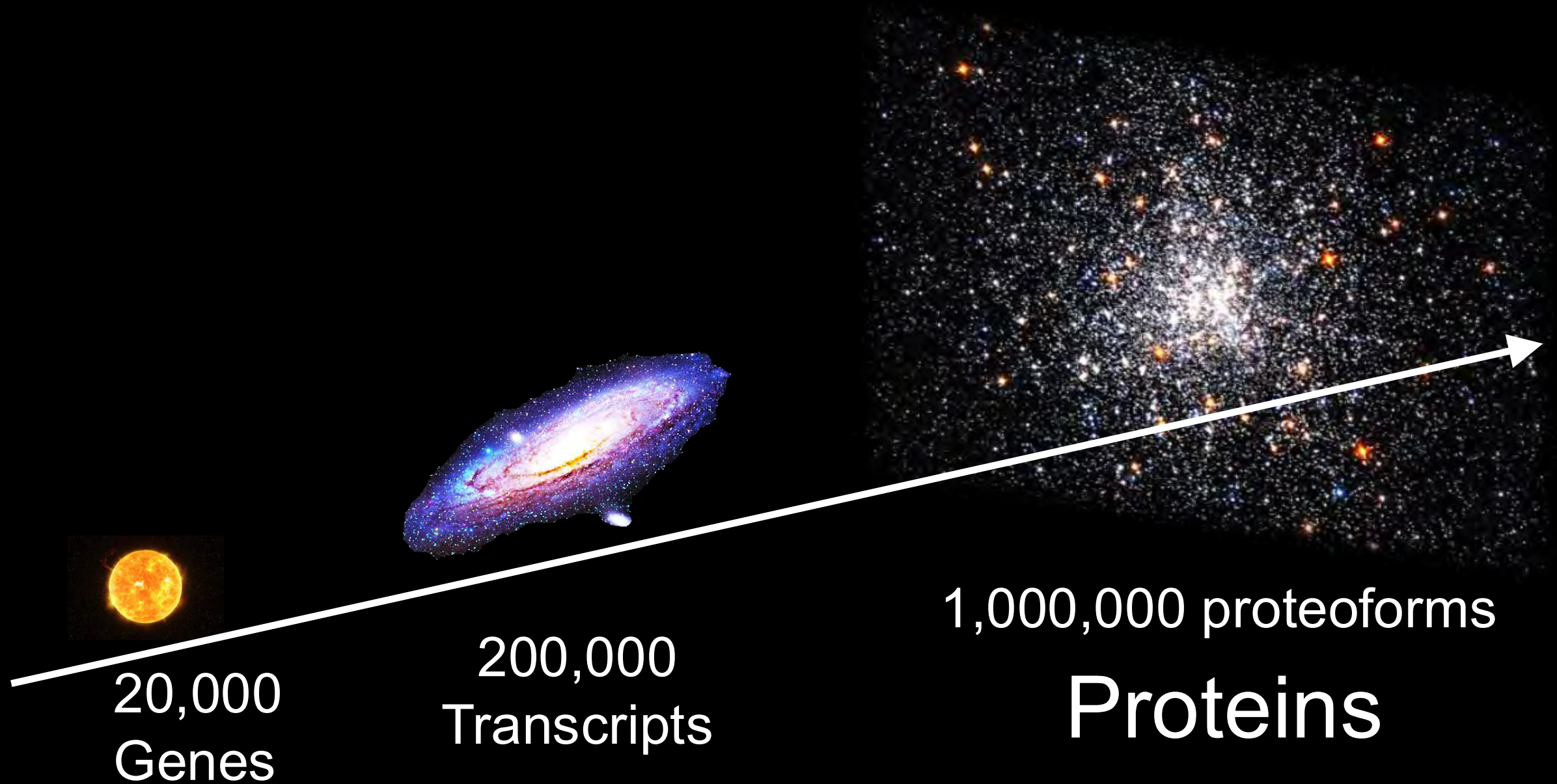


Why do young people get cancer?

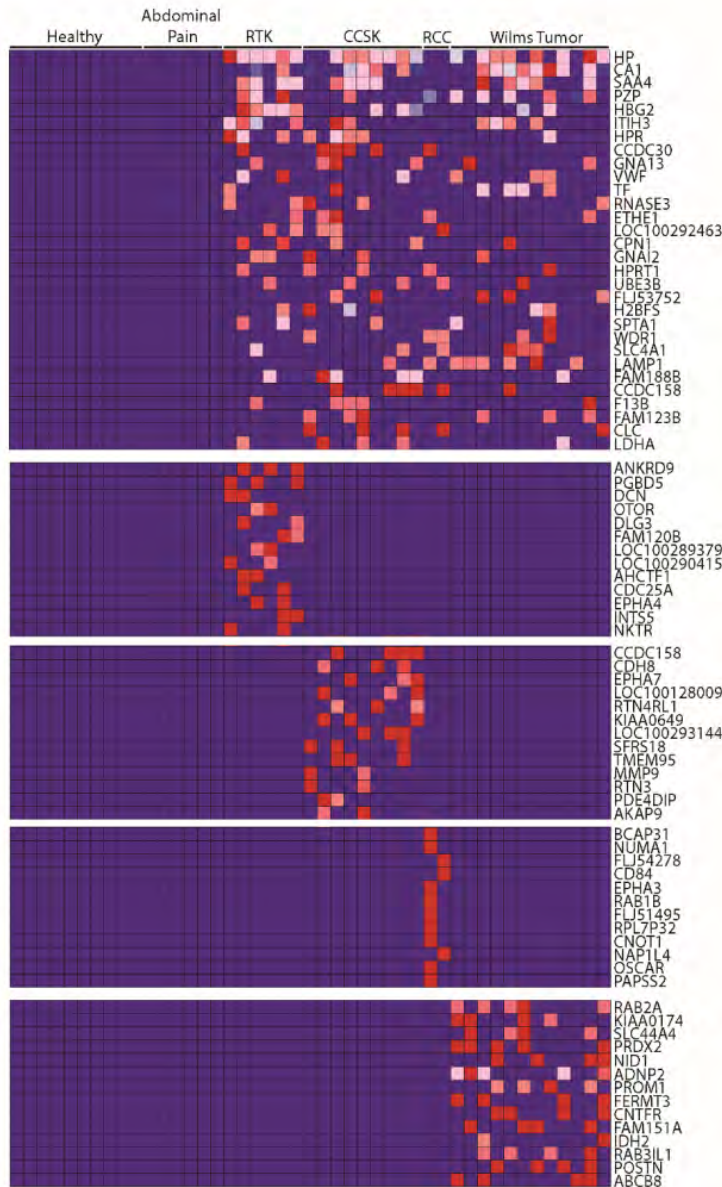
**Cancer is a disease of
somatic mutagenesis**



How do we find disease mechanisms and therapies?



Proteomics for discovery of cancer mechanisms

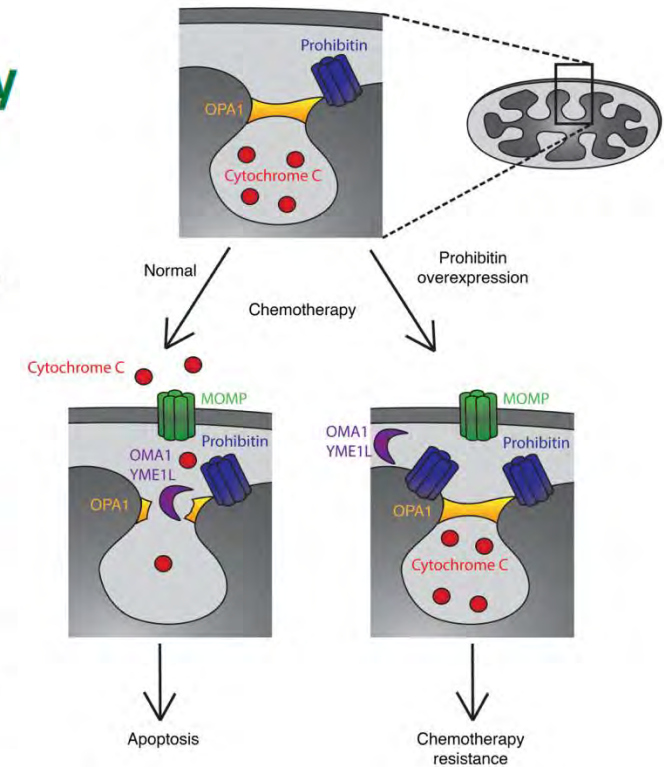


Prohibitin is a prognostic marker and therapeutic target to block chemotherapy resistance in Wilms' tumor

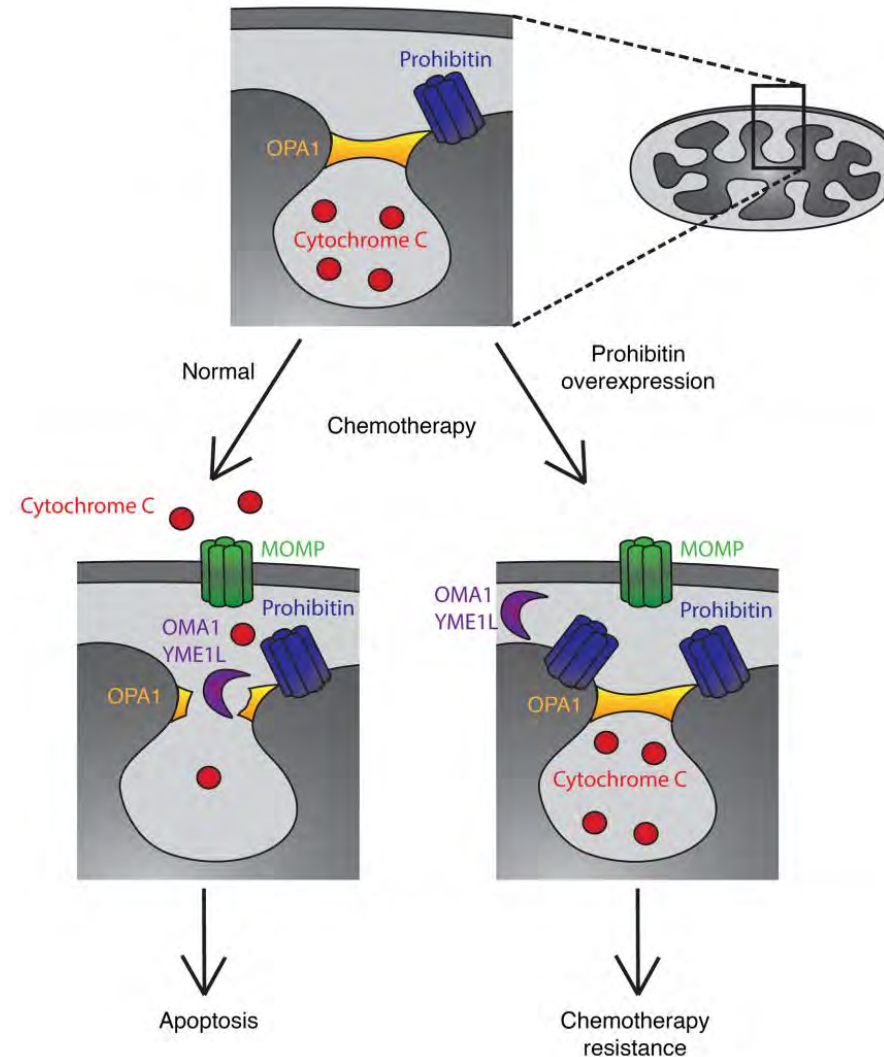
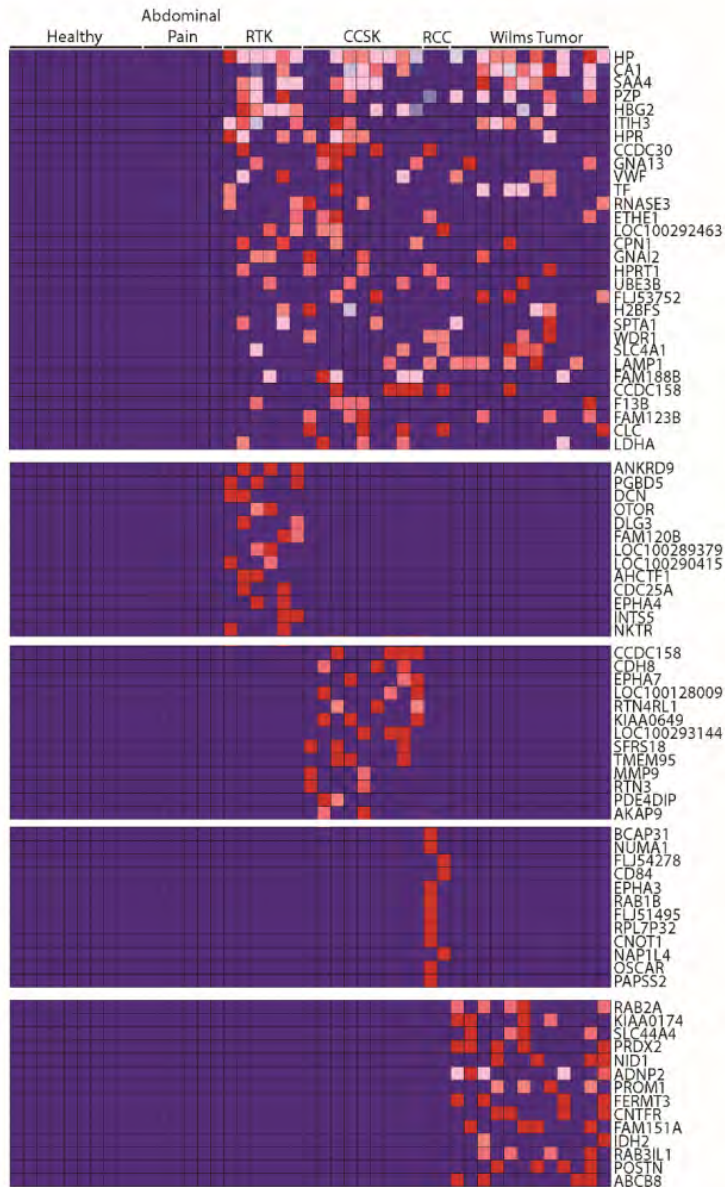
Michael V. Ortiz,¹ Saima Ahmed,² Melissa Burns,³ Anton G. Henssen,¹ Travis J. Hollmann,⁴ Ian MacArthur,¹ Shehana Gunasekera,¹ Lyvia Gaewsky,⁵ Gary Bradwin,⁵ Jeremy Ryan,³ Anthony Letai,³ Ying He,⁶ Arlene Naranjo,⁶ Yueh-Yun Chi,⁶ Michael LaQuaglia,^{1,7} Todd Heaton,^{1,7} Paolo Cifani,⁸ Jeffrey S. Dome,⁹ Samantha Gadd,¹⁰ Elizabeth Perlman,¹⁰ Elizabeth Mullen,³ Hanno Steen,² and Alex Kentsis^{1,8,11}

Prohibitin promotes dedifferentiation and is a potential therapeutic target in neuroblastoma

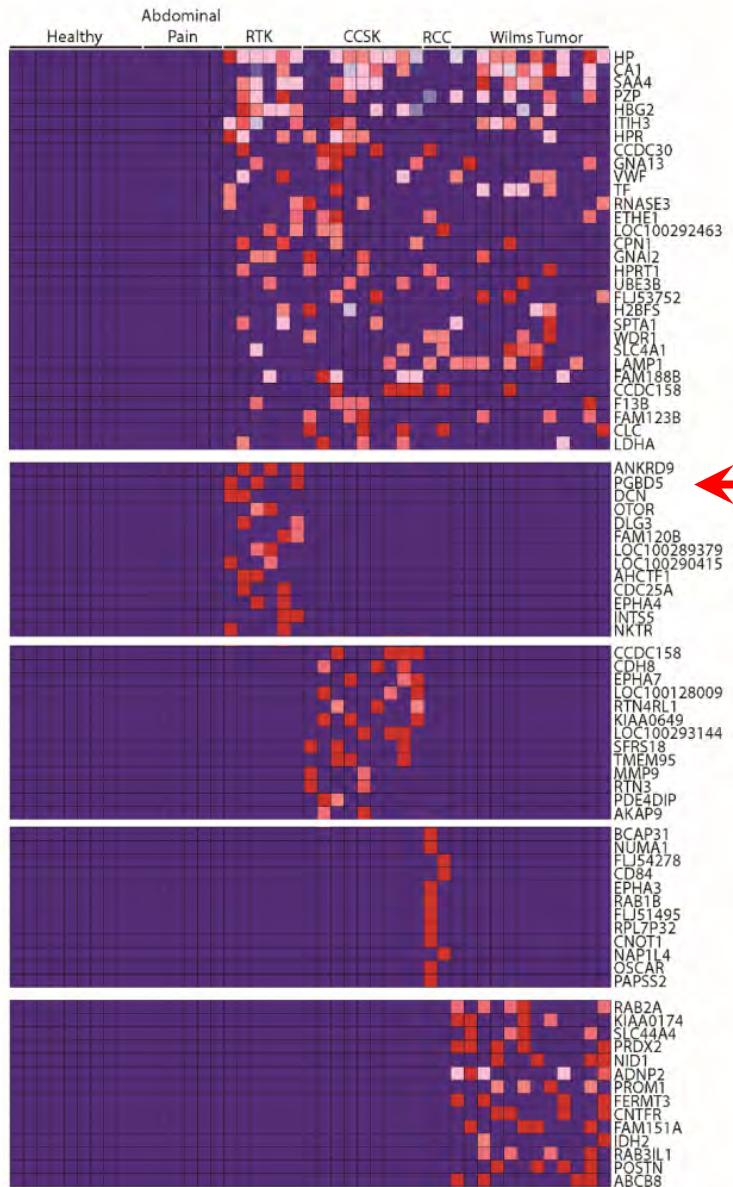
Ian C. MacArthur,^{1,2} Yi Bei,¹ Heathcliff Dorado Garcia,¹ Michael V. Ortiz,³ Joern Toedling,¹ Filippos Klironomos,¹ Jana Rolff,⁴ Angelika Eggert,^{1,5,6} Johannes H. Schulte,^{1,5,6} Alex Kentsis,^{3,7} and Anton G. Henssen^{1,5,6,8}



Proteomics for discovery of cancer mechanisms



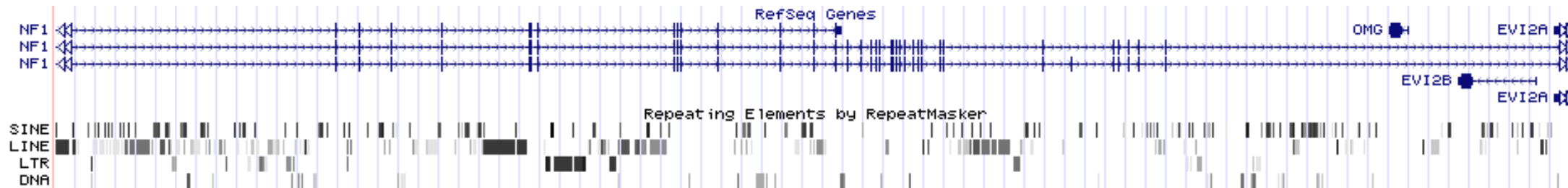
Proteomics for discovery of cancer mechanisms



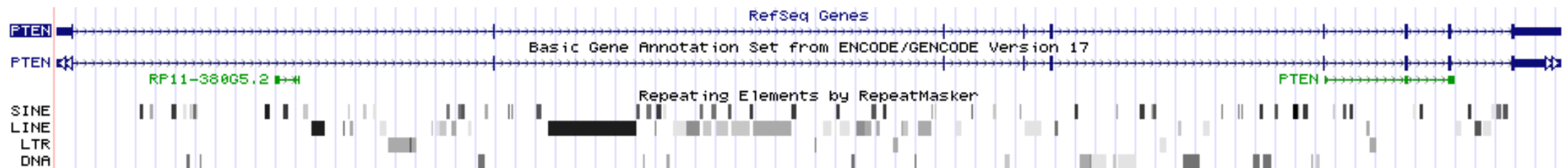
← PiggyBac Transposable Element Derived 5 (PGBD5)

Human genome is derived from transposons

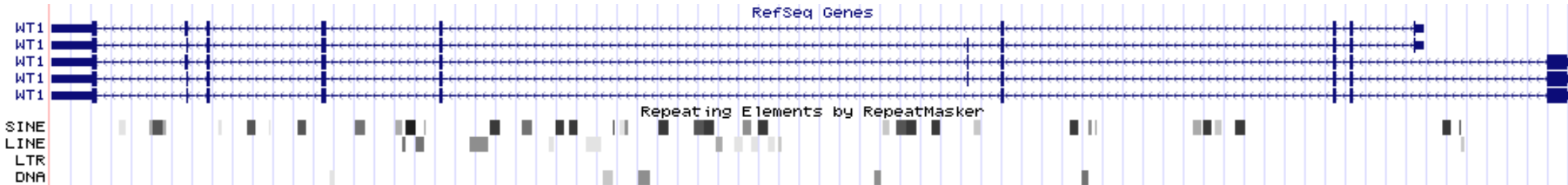
NF1



PTEN



WT1



Transposons drive evolution

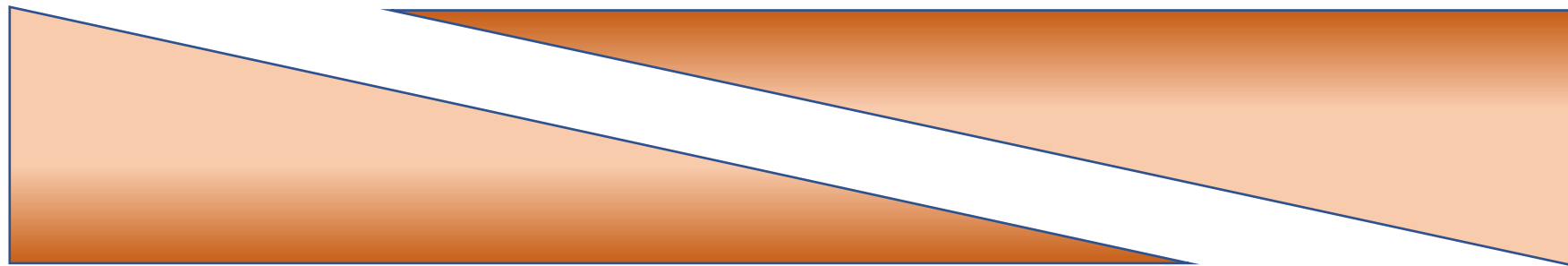
Selfish evolution

Co-option

Domestication

Transposon

Host



Introns

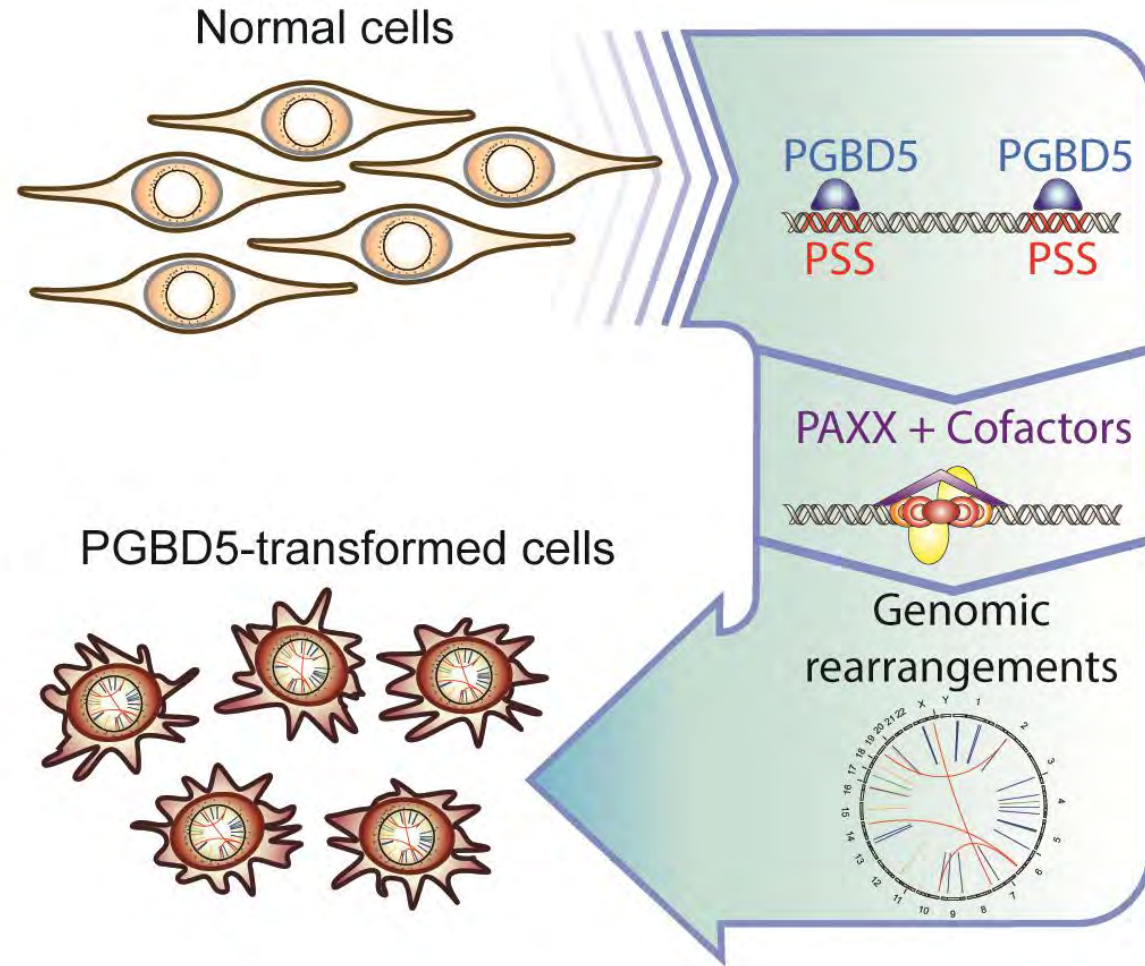
Telomeres (TERT)

Centromeres (CENPB)

Developmental enhancers (LTR)

Transposase-derived genes (RAG1/2, PGBD5)

PGBD5 is a developmental mutator in young-onset solid tumors

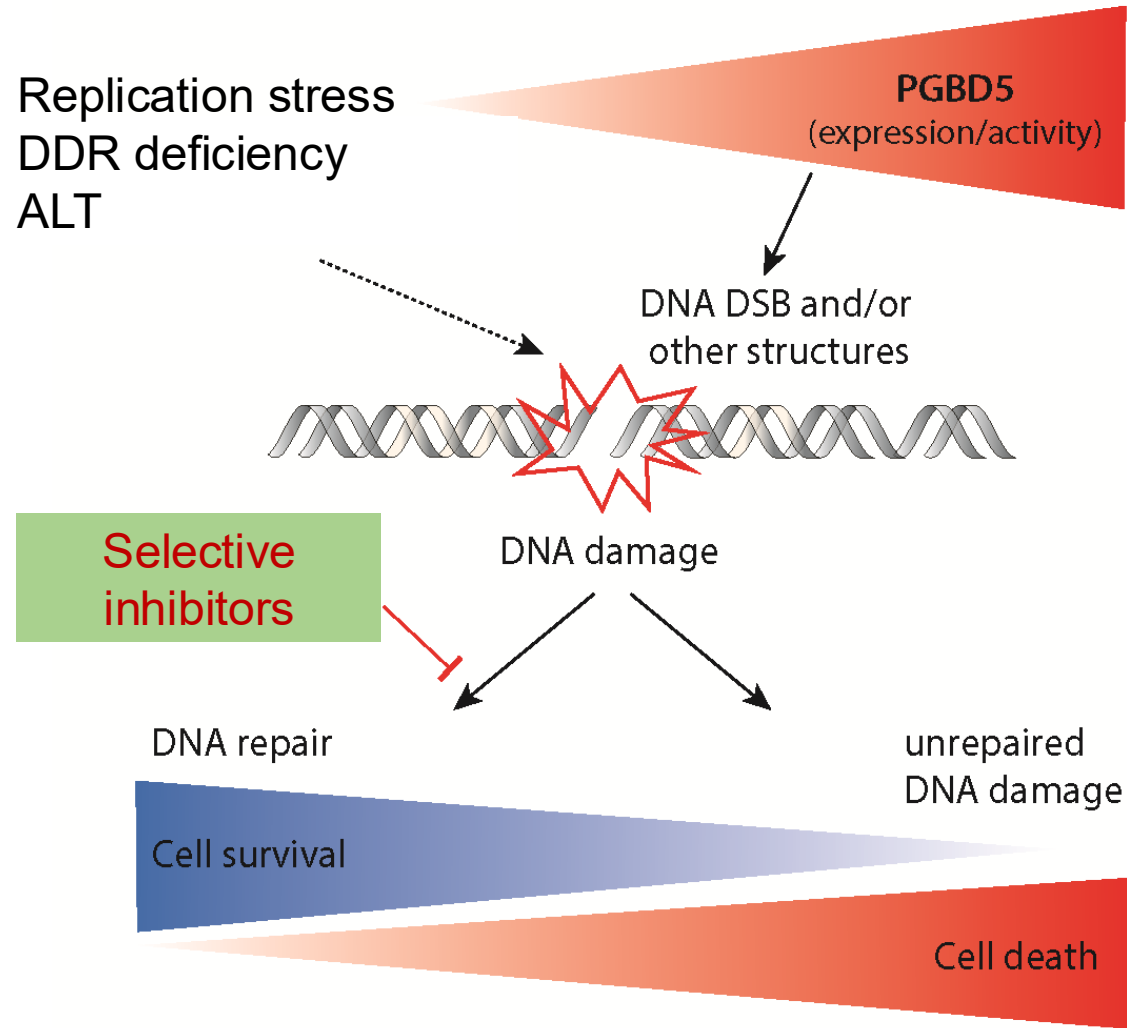


Henssen et al, Kentsis 2015
Henssen et al, Kentsis 2016

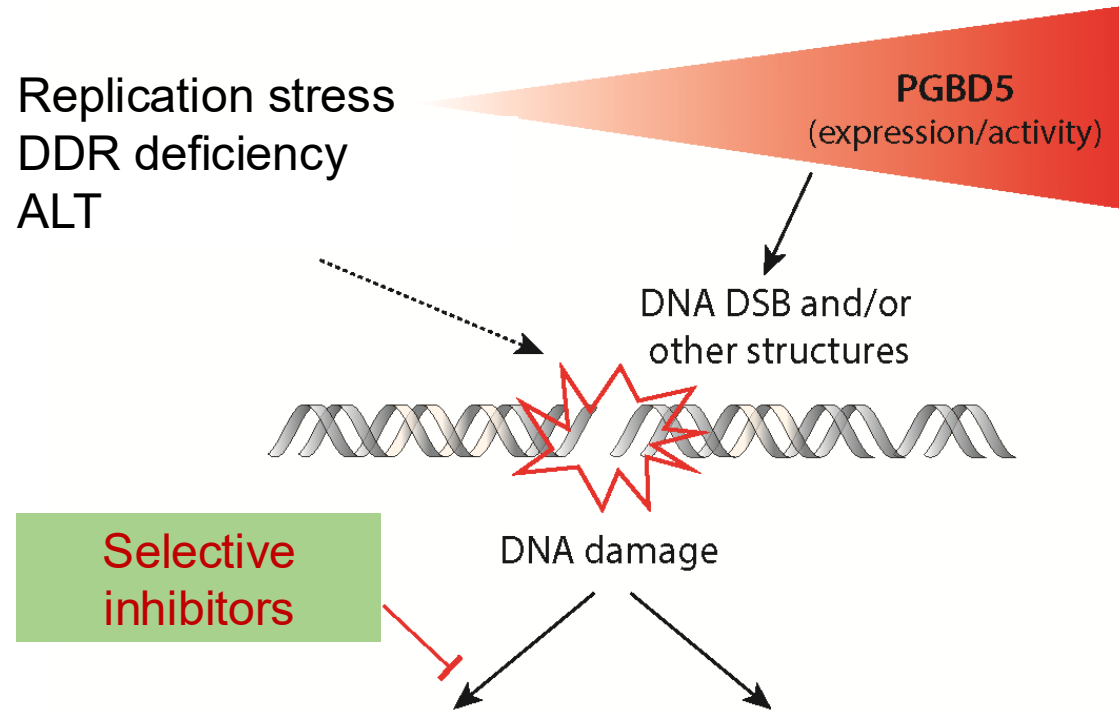
Henssen et al 2017a, 2017b
Yamada et al, Kentsis 2024

Kazansky et al, Kentsis 2025
Jubierre et al, Kentsis 2026

Therapeutic targeting of PGBD5-induced DNA repair dependency in young-onset solid tumors



Therapeutic targeting of PGBD5-induced DNA repair dependency in young-onset solid tumors



Synthetic lethal targeted therapies of oncogenic mutators

Proteomics for discovery of disease mechanisms

Integrative proteogenomics

Cifani et al 2018, Kwok et al 2023, Kulej et al 2025
<https://github.com/kentsislab/ProteomeGenerator3>

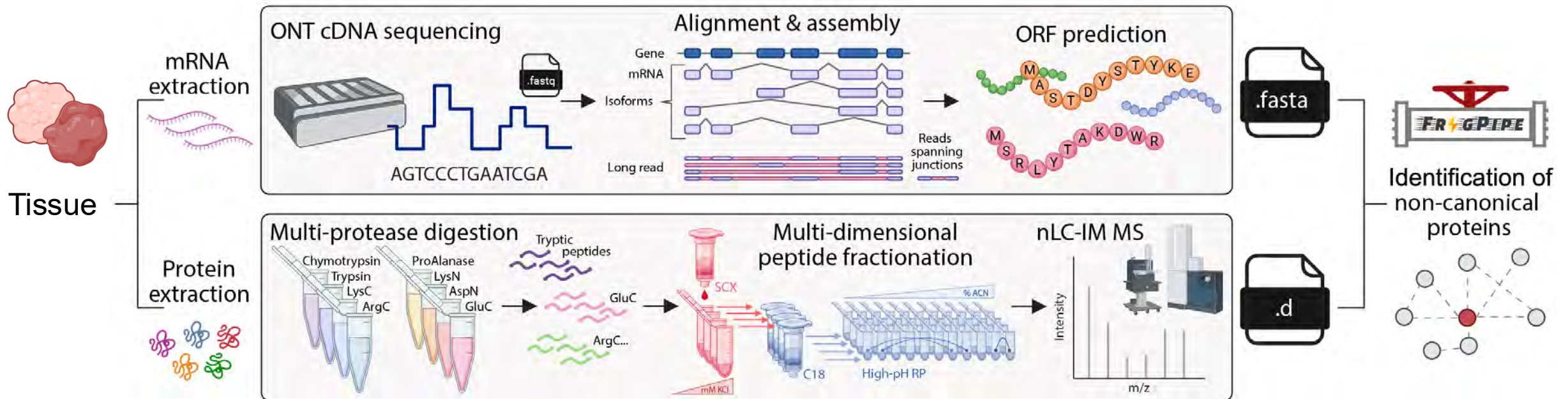
Protein modifications and interactions

Ser et al 2019 (XL-MS), Cifani et al 2021 (AIM)

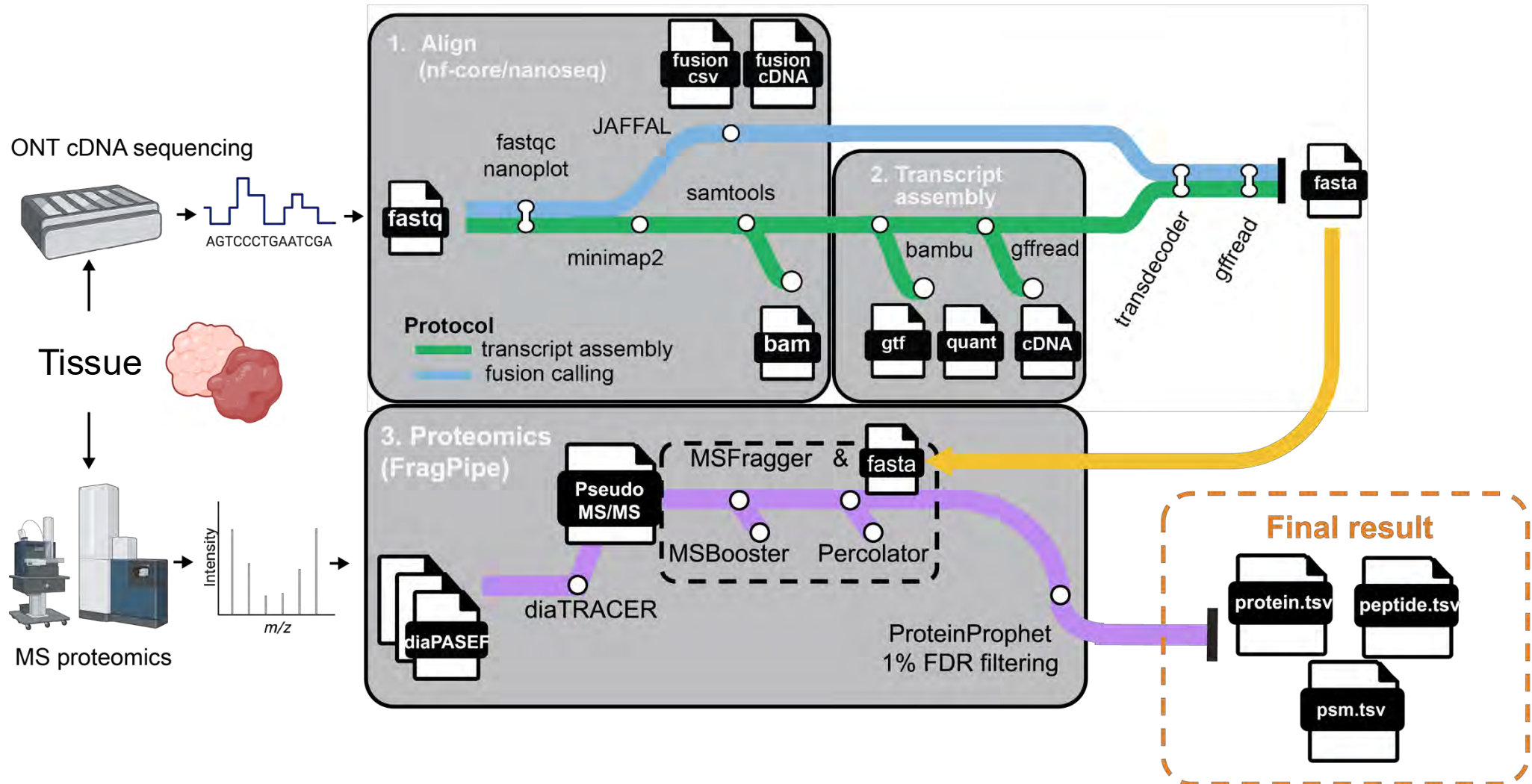
Quantitative Cell Proteomics Atlas

Cifani et al 2017, Cifani & Kentsis 2022
<https://QCPA.mskcc.org>

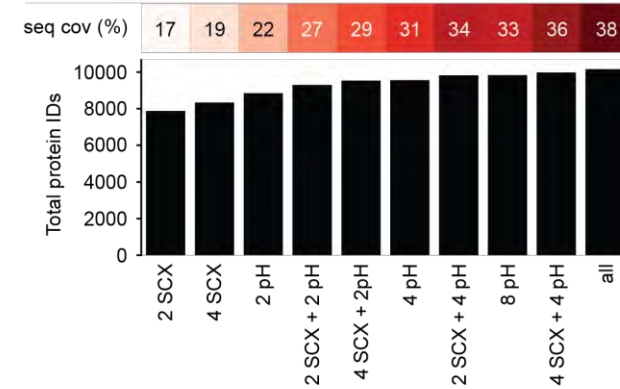
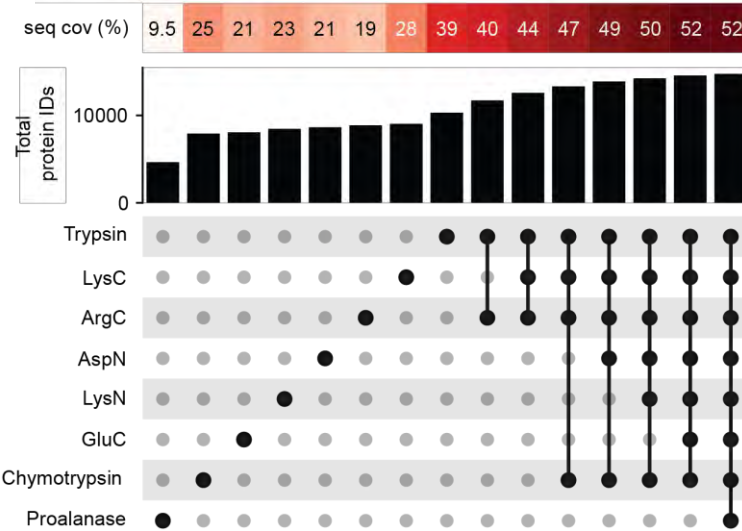
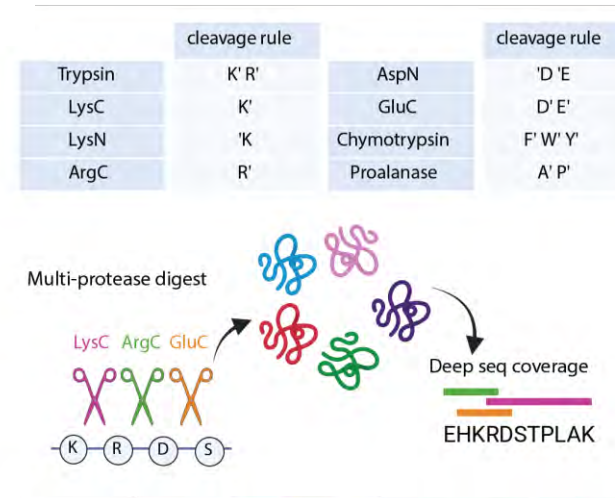
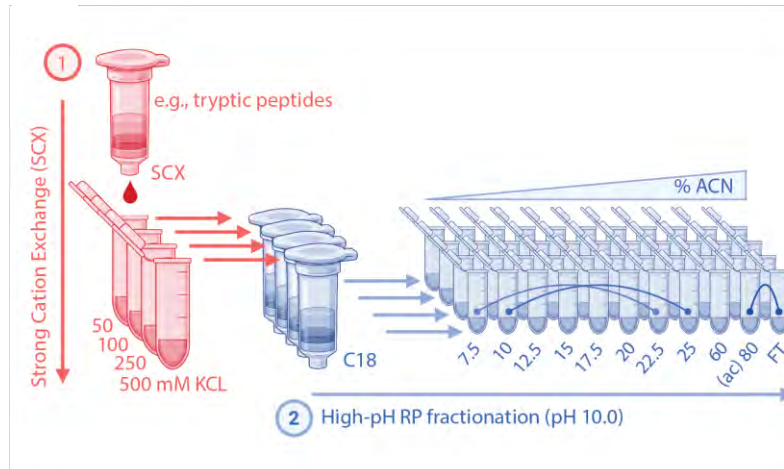
End-to-end proteogenomics using long-read transcriptomics and multi-dimensional proteomics



End-to-end proteogenomics using long-read transcriptomics and multi-dimensional proteomics



Proteogenomics maximizes proteome coverage

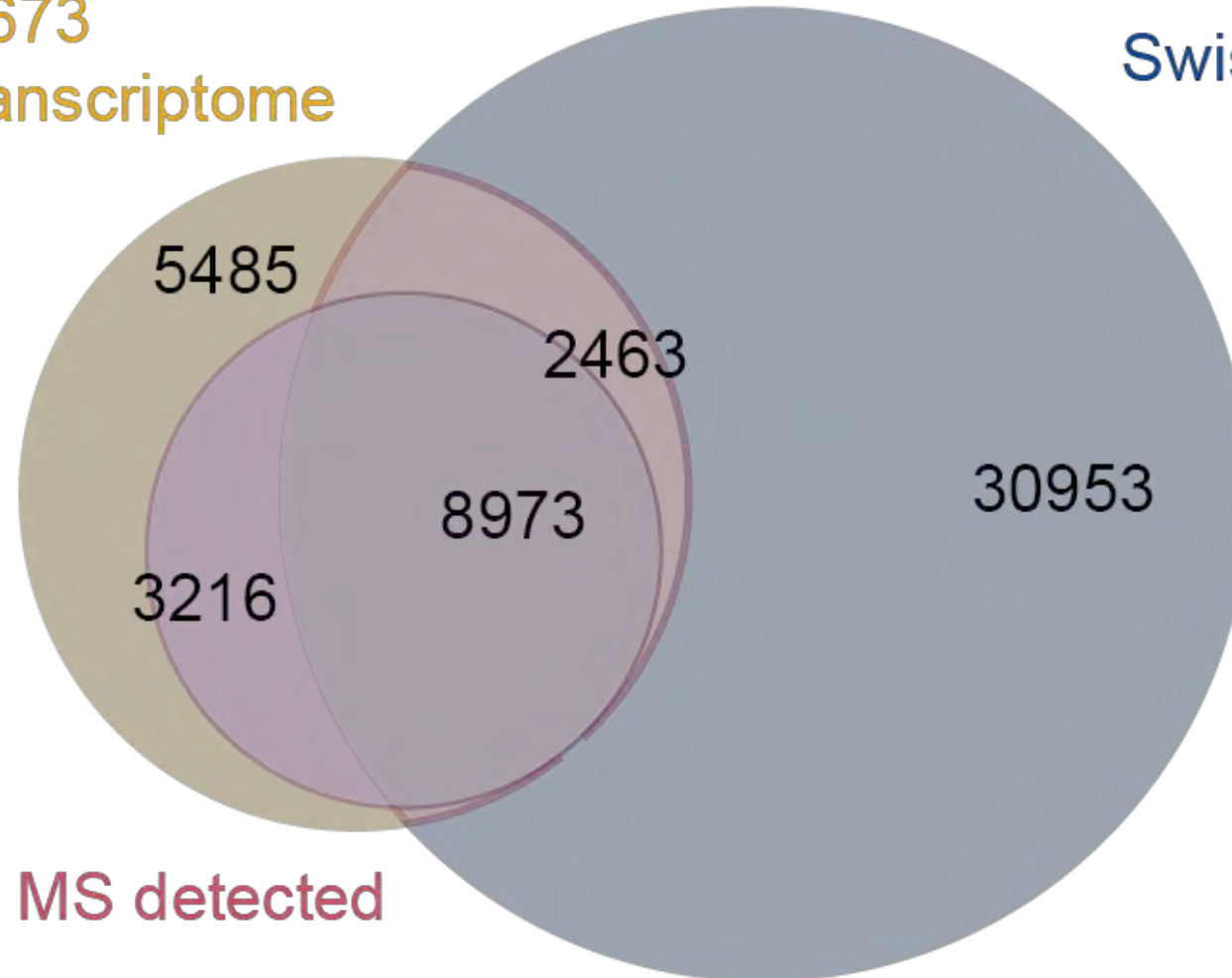


Proteogenomics maximizes proteome coverage

End-to-end proteogenomics of Ewing sarcoma

A673
transcriptome

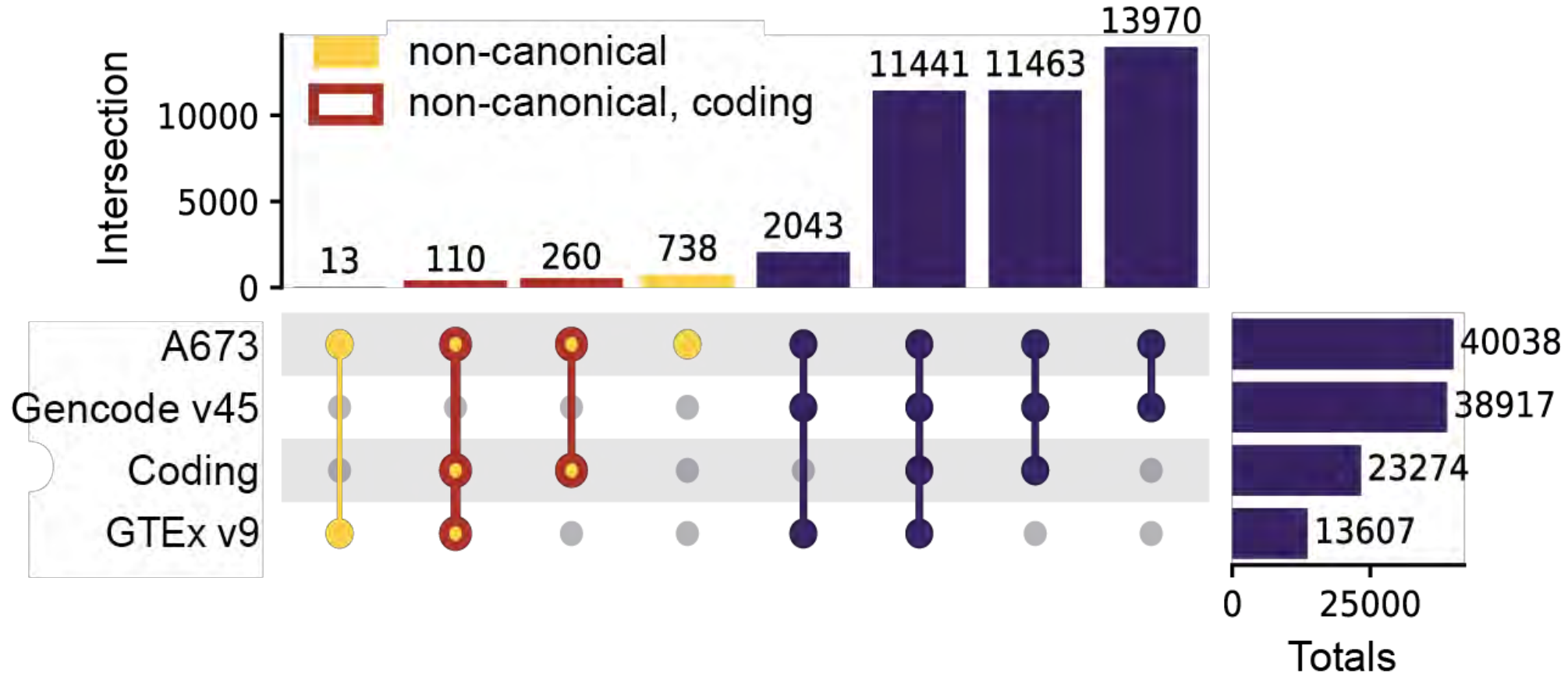
SwissProt



MS detected

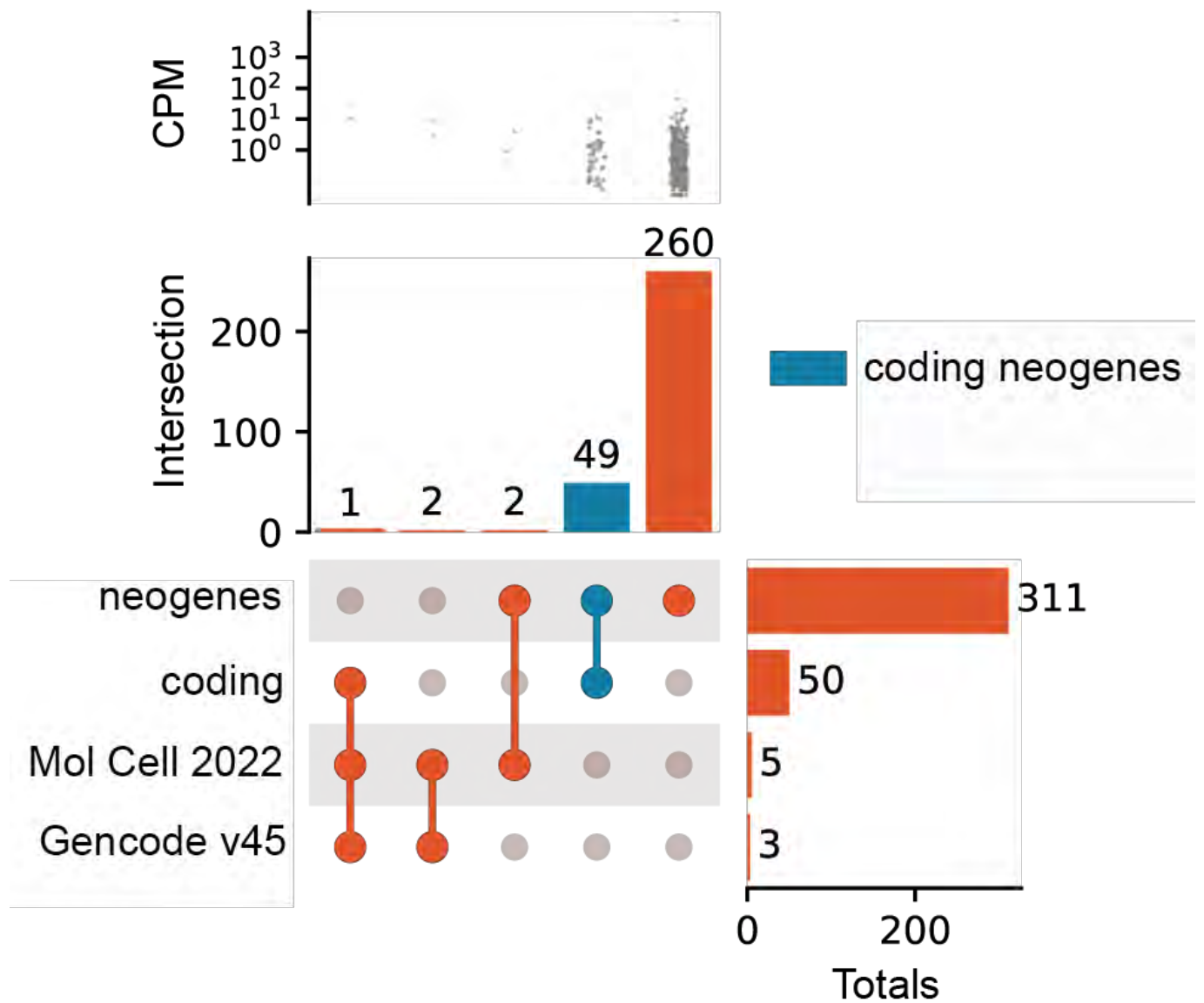
Discovery of individual and non-canonical proteoforms

End-to-end proteogenomics of Ewing sarcoma



Discovery of individual and non-canonical proteoforms

Ewing sarcoma neogenes



Discovery of individual and non-canonical proteoforms

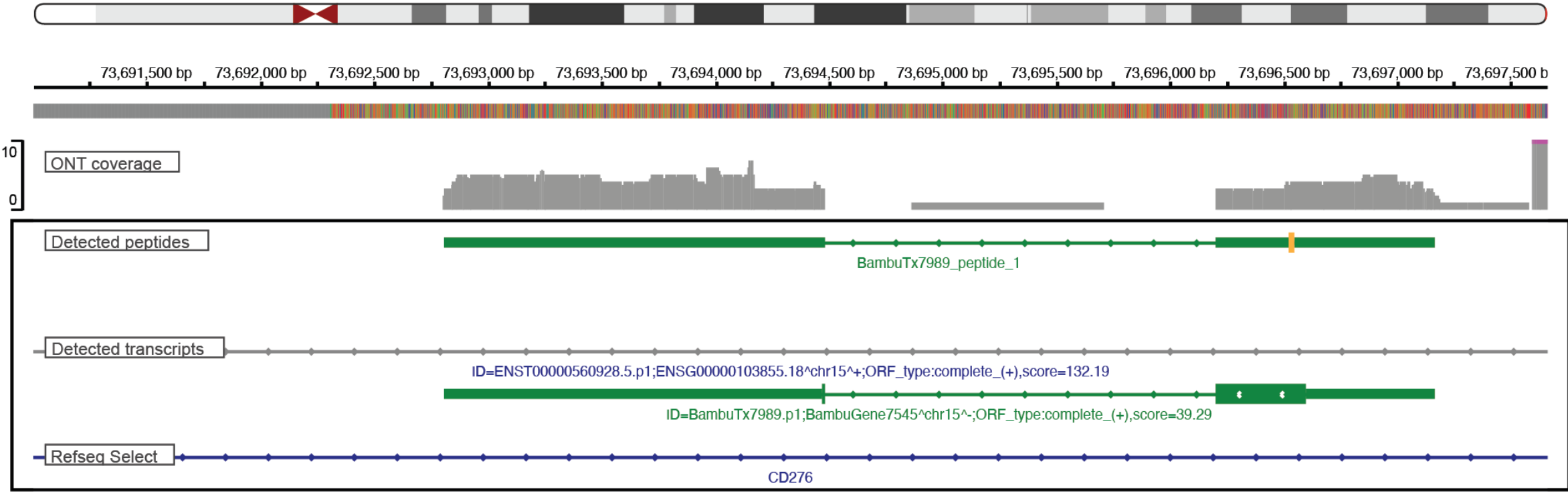
Neogene trans-activated by Ewing sarcoma fusion oncoprotein at polymorphic GGAA repeats



Discovery of individual and non-canonical proteoforms

NeoORF expressed antisense to tumor-specific cell surface CD276 (B7-H3)

chr15:73,691,000-73,697,661



Integrative proteogenomics for the discovery of biomarkers and therapeutics

- Rare childhood cancers can reveal universal mechanisms of oncogenesis and therapeutic vulnerability
- Developmental mutators as causes of young-onset cancers
- Integrative proteogenomics (long-read sequencing + multidimensional MS) maximizes disease-specific discovery, including neogenes and neoORFs
- End-to-end integrative proteogenomics is feasible:
<https://github.com/kentsislab/proteomegenerator3>

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