Cancer Cell Growth regulation

Finnish Medical Foundation Symposium
24/5/2023
Otto Kauko, MD-PhD

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UNIVERSITY OF TURKU
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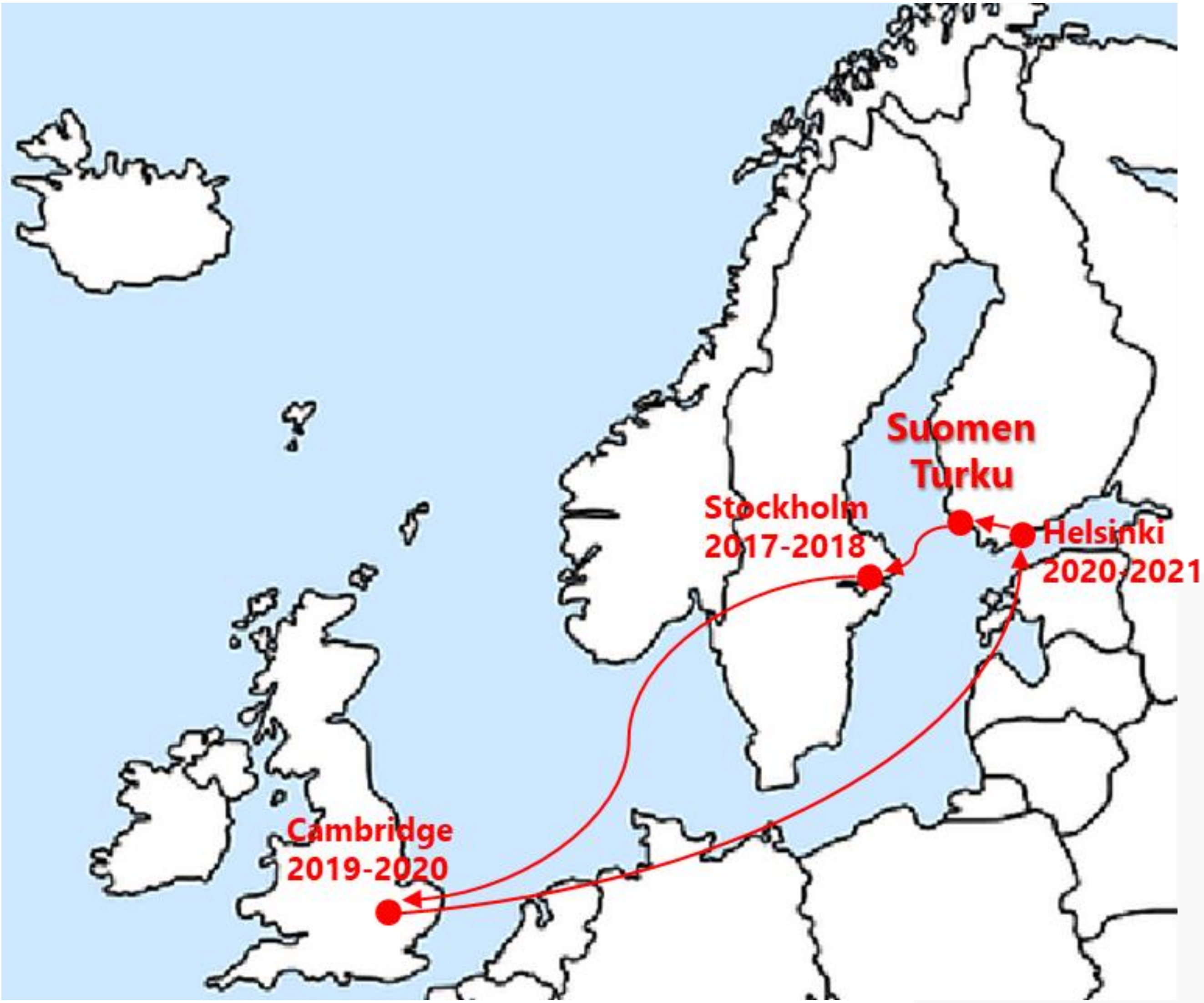

Suomen
Turku
Stockholm
2017-2018
Helsinki
2020-2021
Cambridge
2019-2020

PhD

Prof. Jukka Westermarck's group

University of Turku

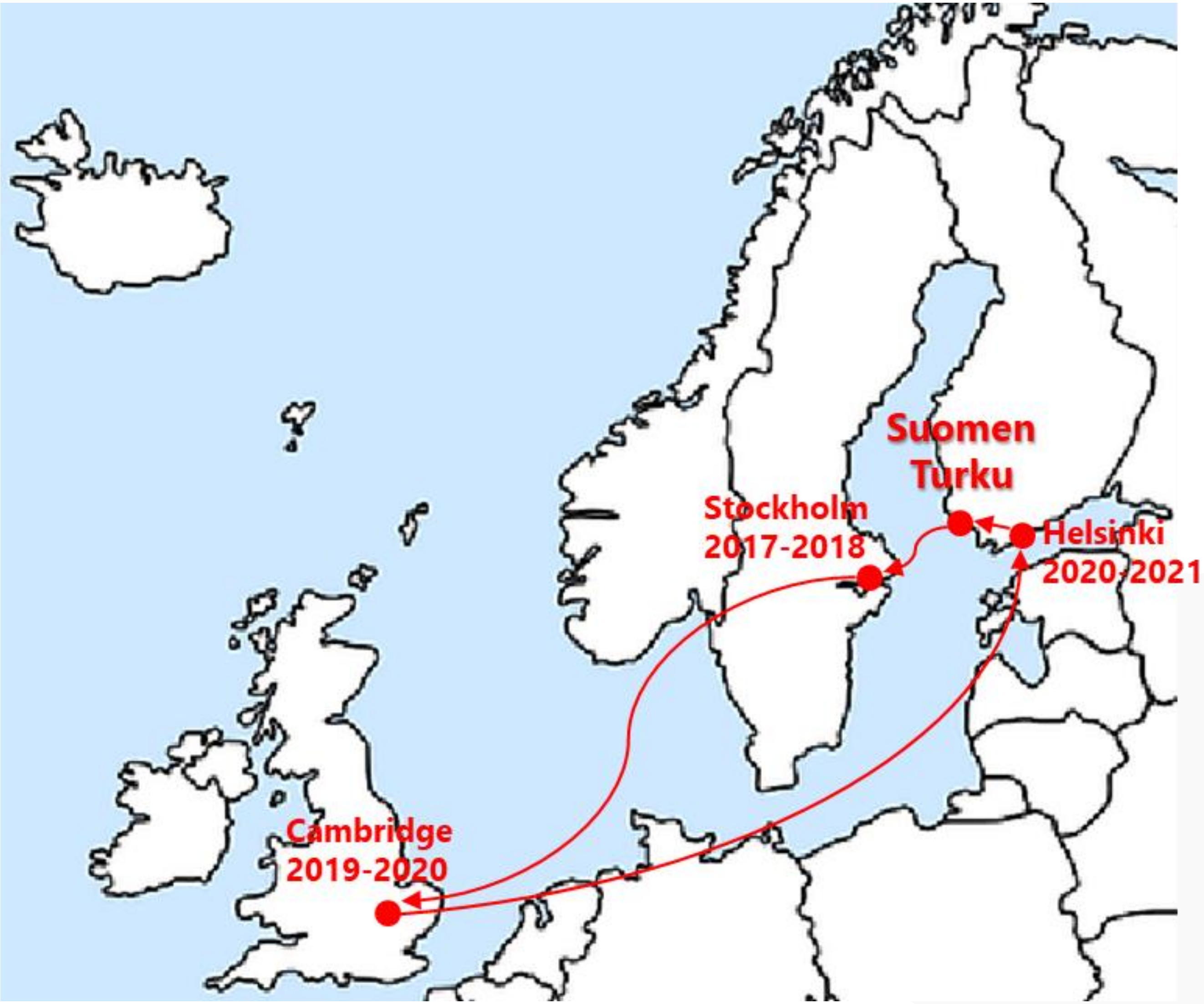
Post-doc

Prof. Jussi Taipale's group

Karolinska Institutet, University of Cambridge, and University of Helsinki

Independent

Head of Turku proteomics facility since 3/2021



PhD

- EKA Grant
- Encouragement Grant
- 8 month working grant

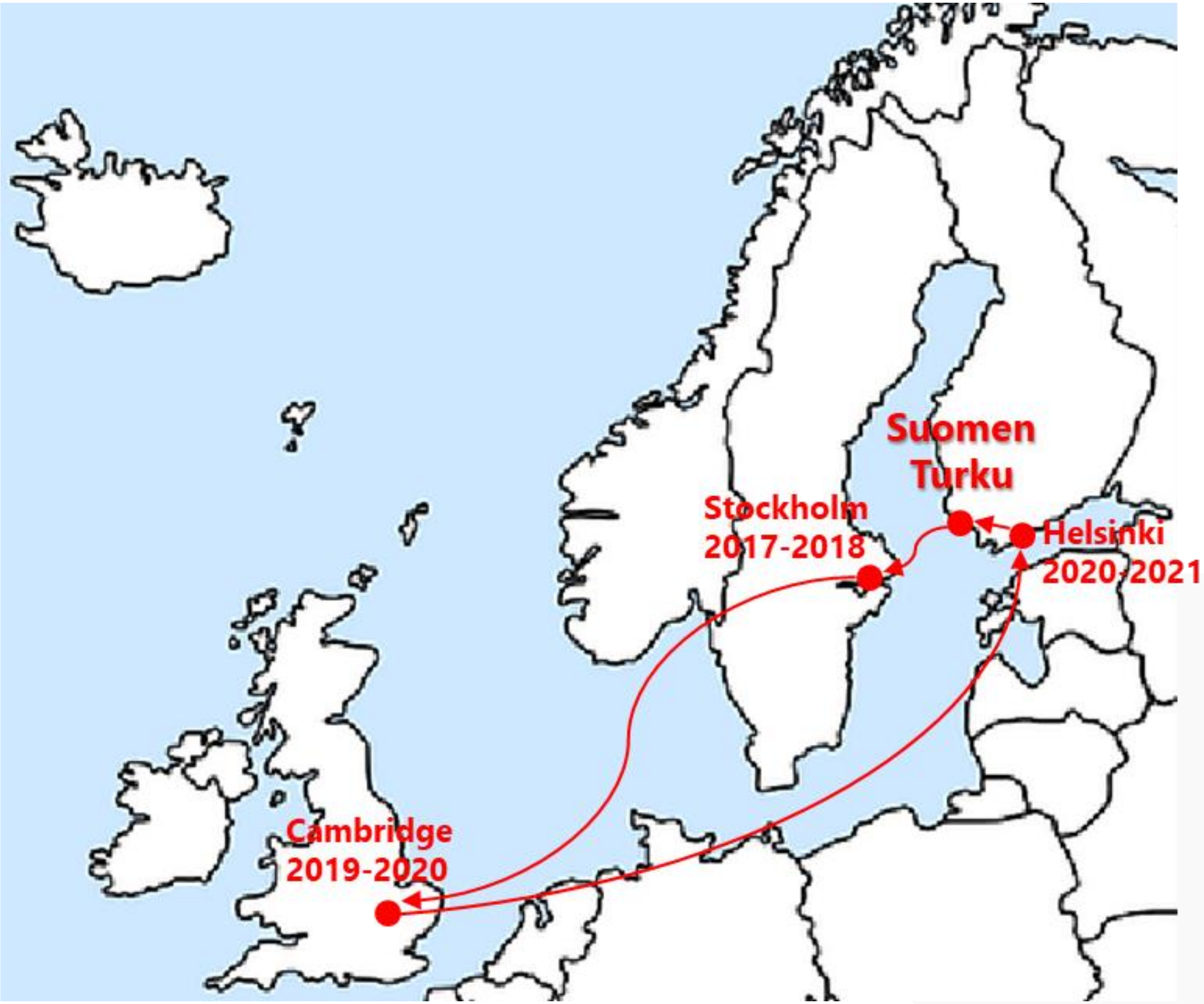
Post-doc

- Returning Researcher Grant

Independent

- Research Group Founder Grant

SUOMEN LÄÄKETIETEEN SÄÄTIÖ

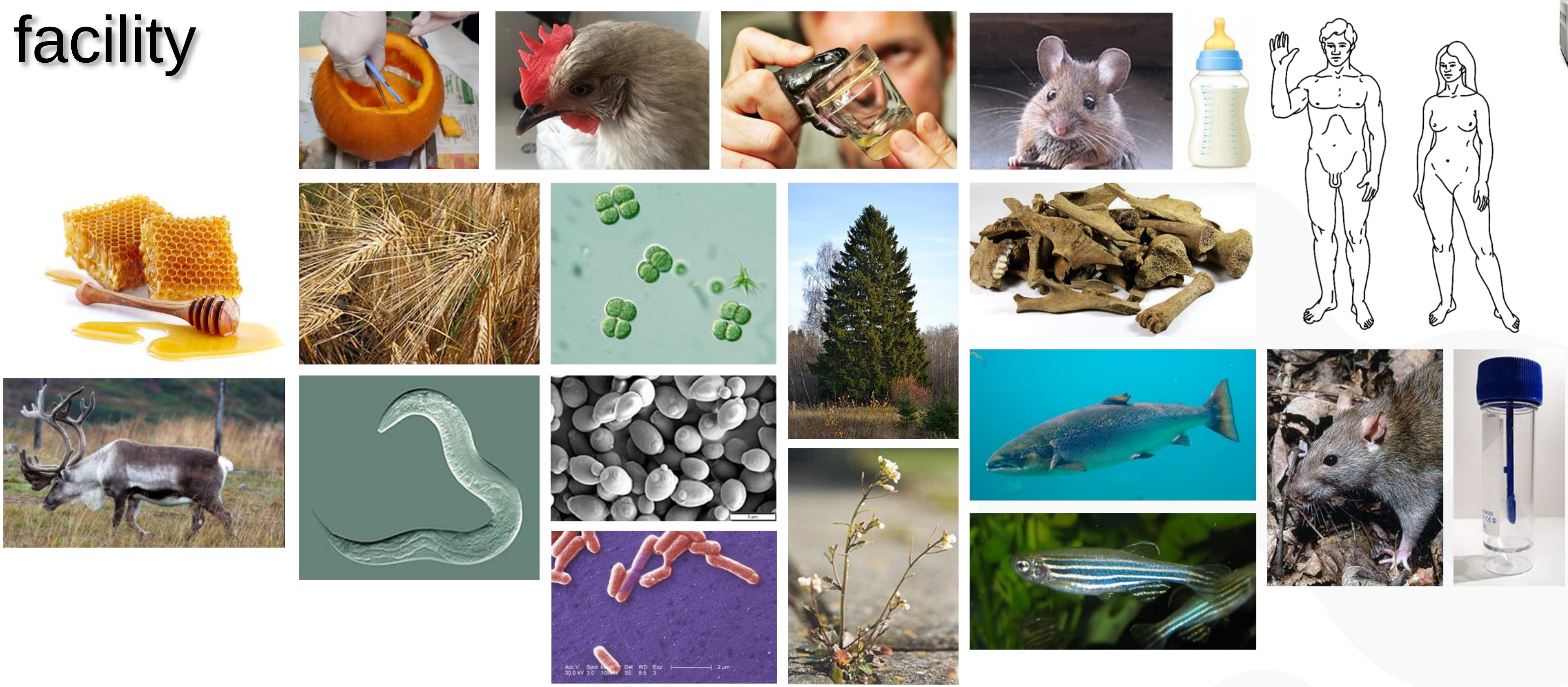


Molecular biology in two international labs

Taipale lab 20th anniversary
4/2023

Westermarck lab 20th anniversary
9/2022

Turku Proteomics facility



Otto Mirva Johannes Arttu Pekka Iris

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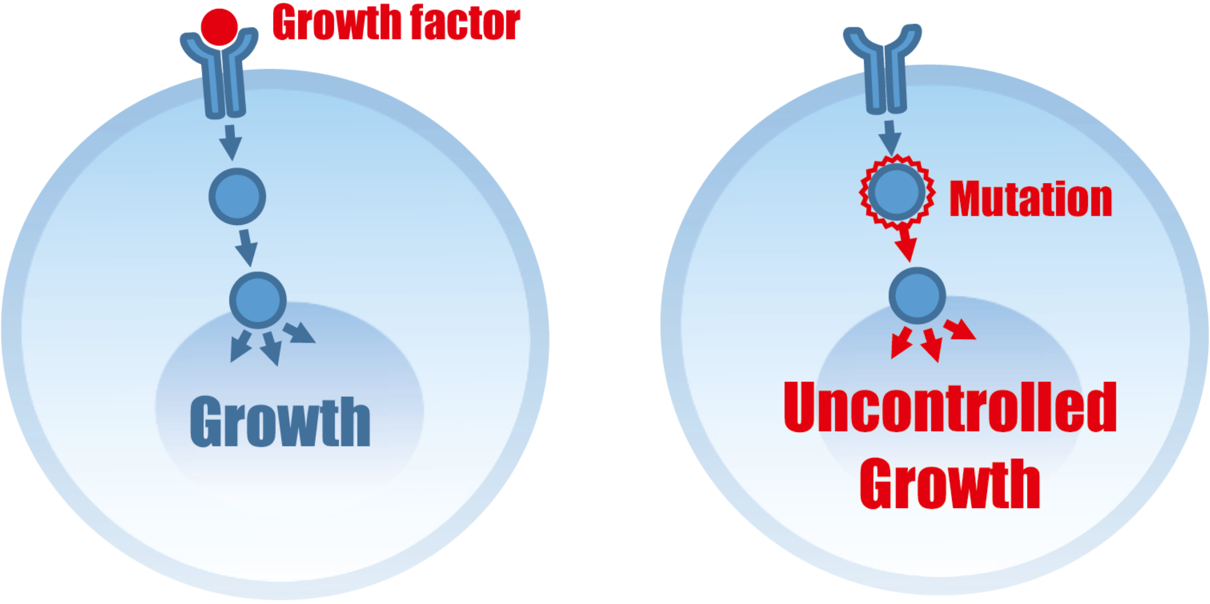
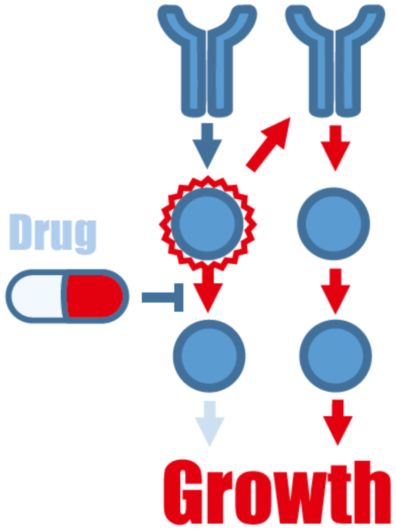
BF Biocenter Finland

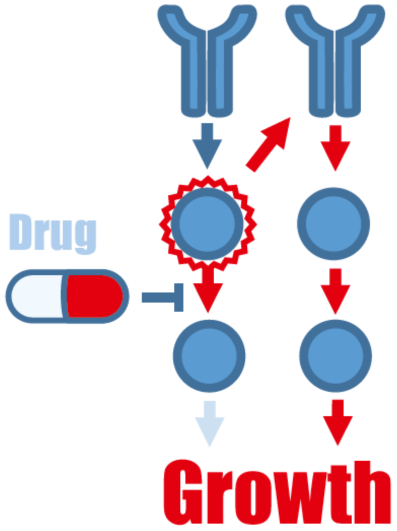


Normal cell

Cancer cell

- Some of the most frequent mutations activate growth regulatory pathways


Drug
Growth



SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

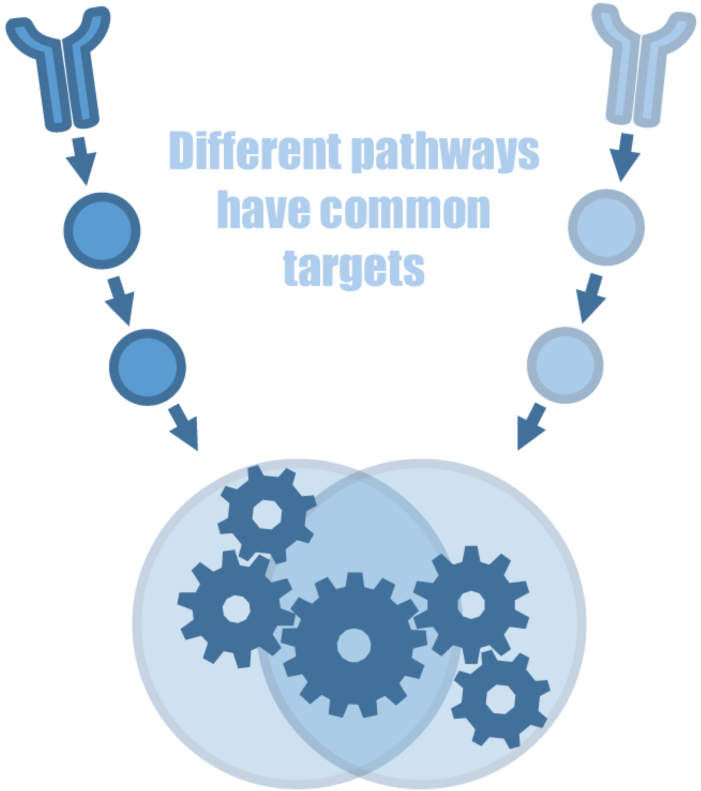
PP2A inhibition is a druggable MEK inhibitor resistance mechanism in KRAS-mutant lung cancer cells

Otto Kauko[1,2,3*], Caitlin M. O'Connor[4†], Evgeny Kulesskiy[5†], Jaya Sangodkar[6], Anna Aakula[1], Sudeh Izadmehr[6], Laxman Yetukuri[1], Bhagwan Yadav[5], Artur Padzik[1], Teemu Daniel Laajala[5,7], Pekka Haapaniemi[1], Majid Momeny[1], Taru Varila[1], Michael Ohlmeyer[6], Tero Aittokallio[5,7], Krister Wennerberg[5‡], Goutham Narla[4§], Jukka Westermarck[1,2§‖]

Cancer heterogeineity and its therapeutic implications (according to ChatGPT-4):

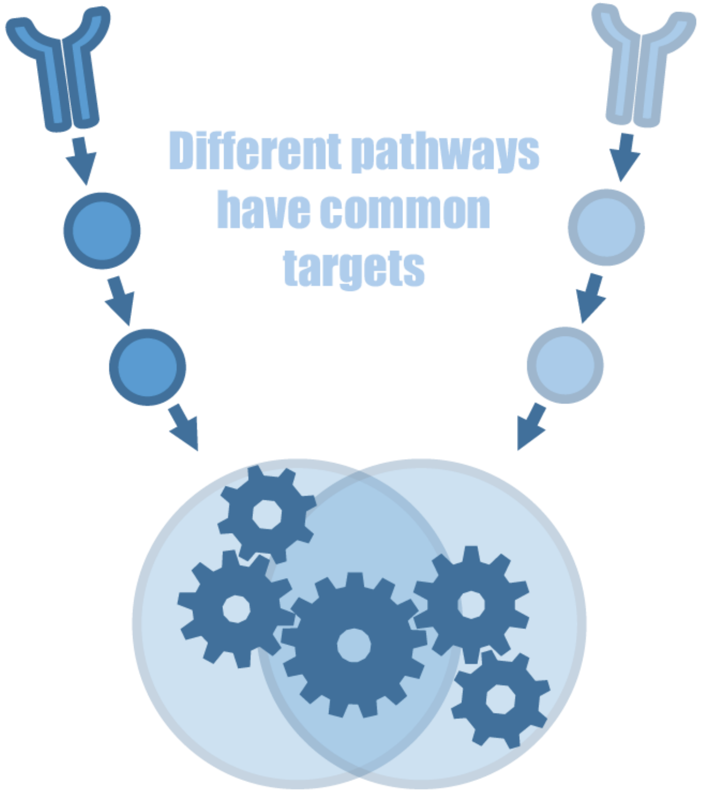
- Cancer heterogeneity refers to variations in genetic, phenotypic, or behavioral characteristics among cancer cells within a single tumor or between tumors.
- This poses significant challenges in treatment as it can lead to therapeutic resistance, diagnostic difficulties, and complications in treatment selection and targeted therapy development.
- To address these issues, strategies like combination therapies, sequential therapies, targeting the tumor microenvironment, and precision medicine are being explored. Understanding and addressing cancer heterogeneity is crucial for the development of innovative new therapies.

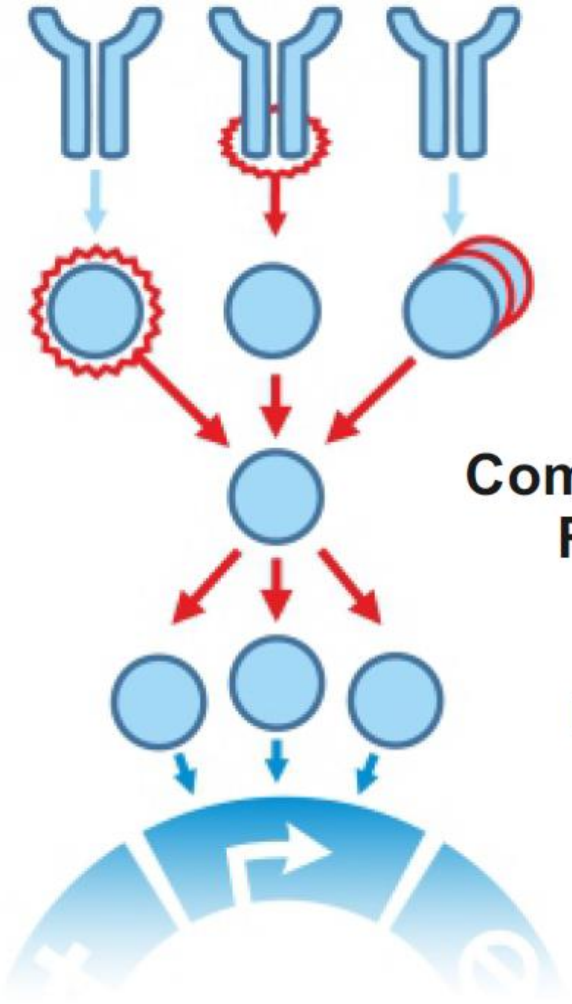
All unhappy families are unhappy in their own way



All unhappy families are unhappy in their own way

But they are
still unhappy





Mutated Drivers

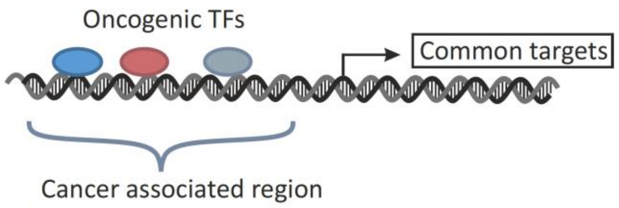
Common Master Regulator

Effectors

Growth

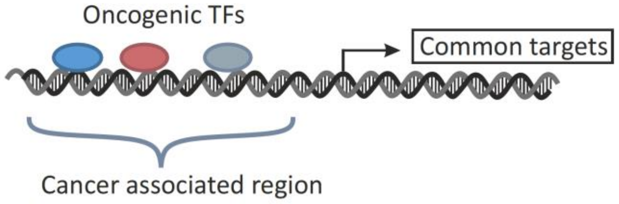
Transcriptional regulation in cancer

ChIP-seq - common targets

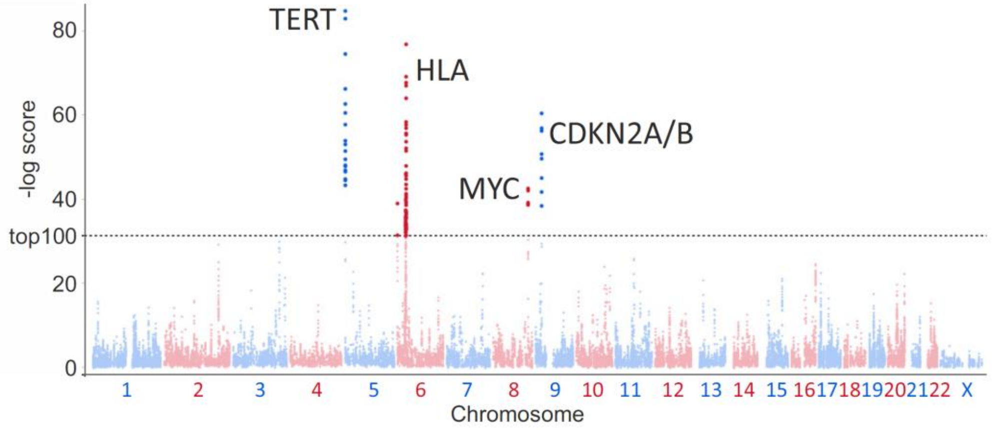


Transcriptional regulation in cancer

ChIP-seq - common targets

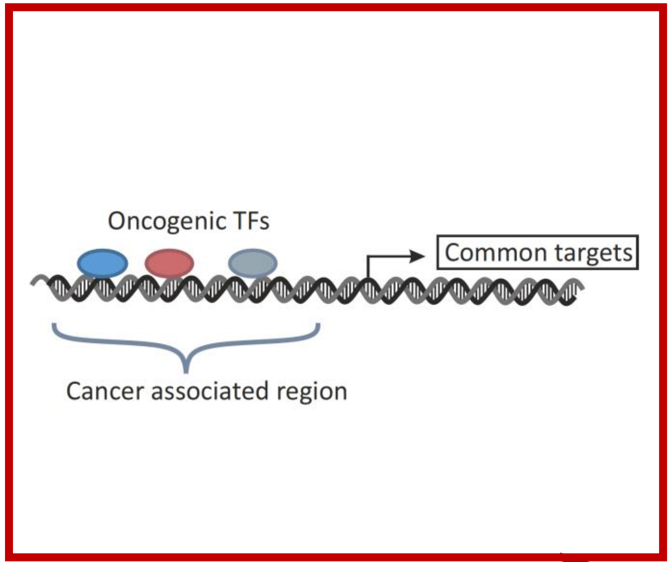


GWAS – pan-cancer association



Transcriptional regulation in cancer

ChIP-seq - common targets



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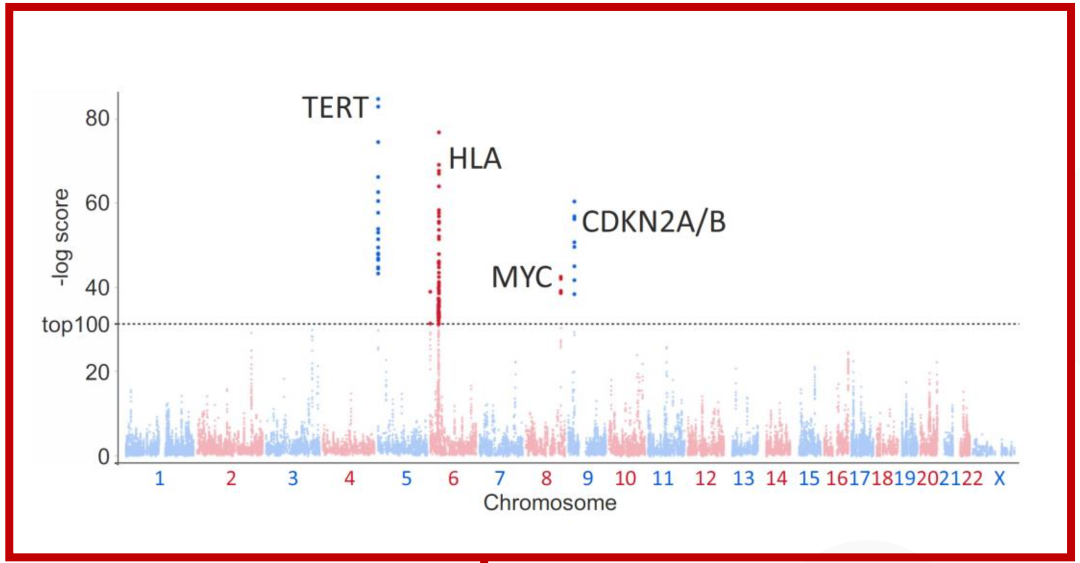
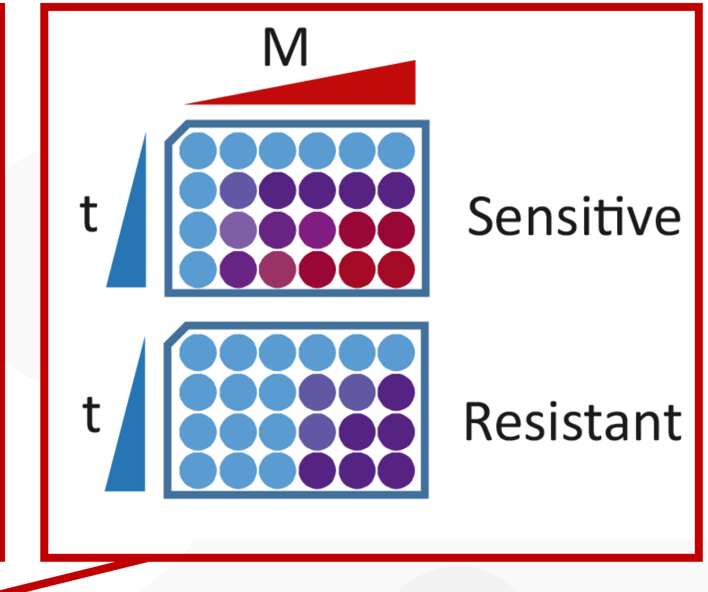


scRNA-seq - drug responses

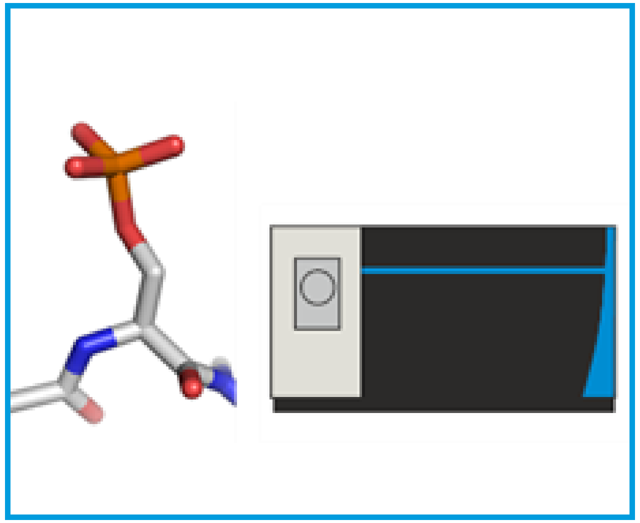


MYC

E2F

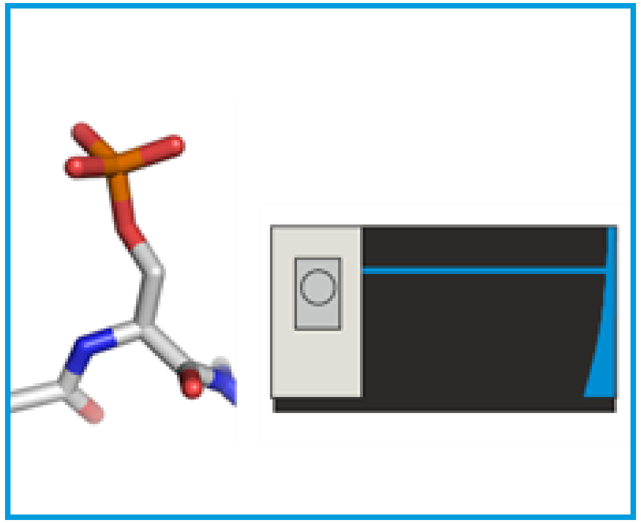
Post-translational regulation in cancer

Phosphoproteomics

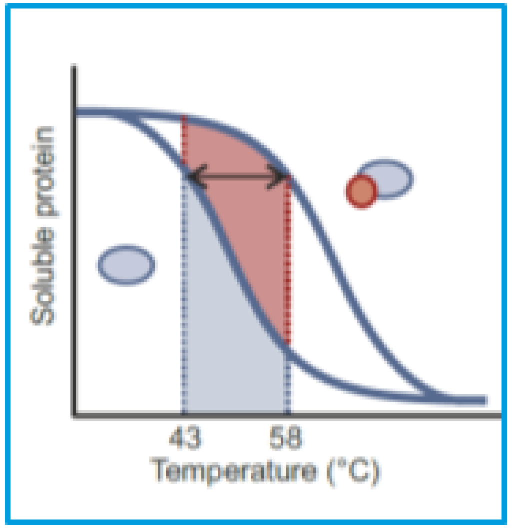


Post-translational regulation in cancer

Phosphoproteomics



Thermal proteome profiling



Post-translational regulation in cancer

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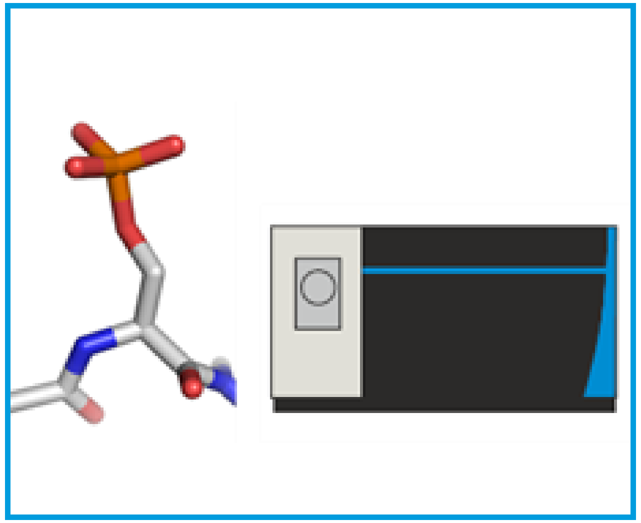

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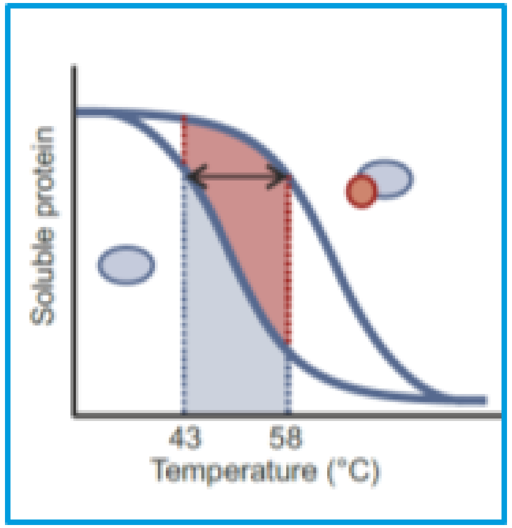
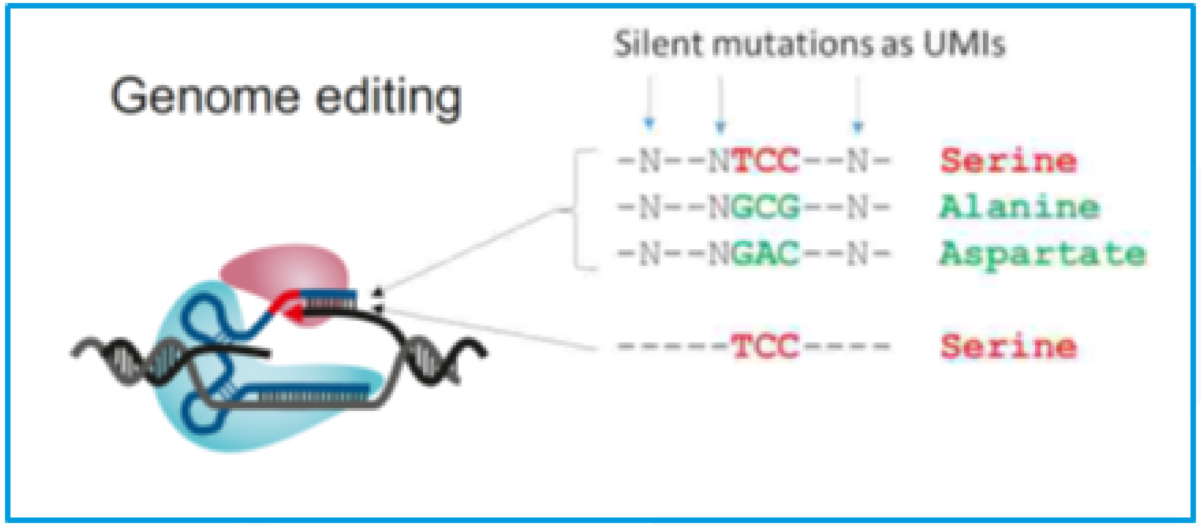
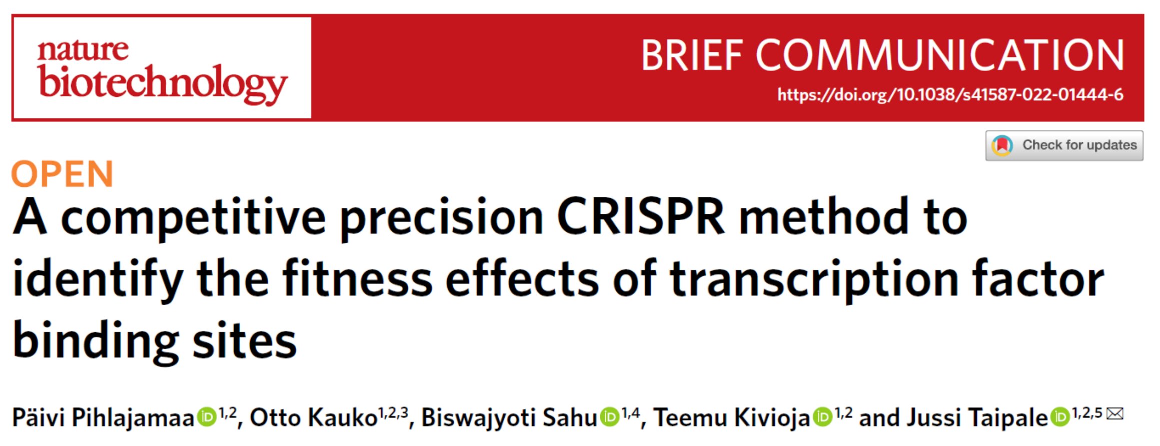


Genome editing





nature biotechnology
BRIEF COMMUNICATION
https://doi.org/10.1038/s41587-022-01444-6

Check for updates

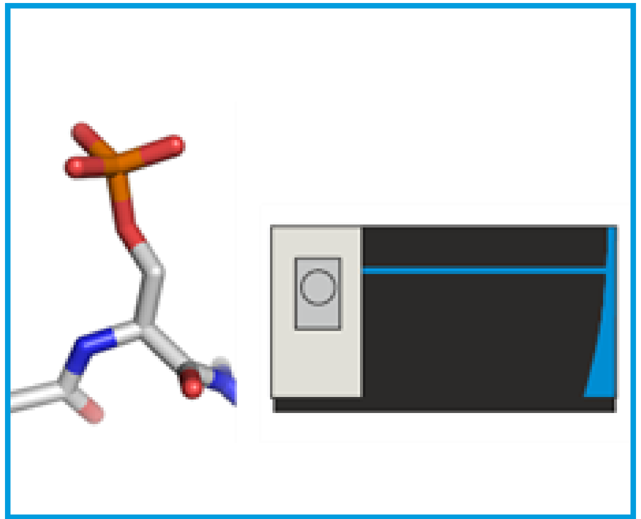
OPEN

A competitive precision CRISPR method to identify the fitness effects of transcription factor binding sites

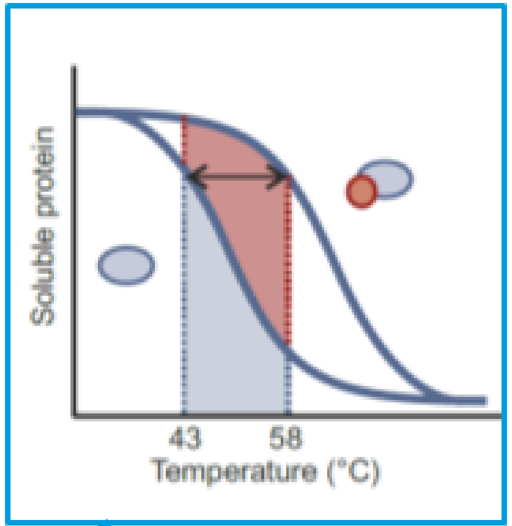
Päivi Pihlajamaa[1,2], Otto Kauko[1,2,3], Biswajyoti Sahu[1,4], Teemu Kivioja[1,2] and Jussi Taipale[1,2,5] ✉

Post-translational regulation in cancer

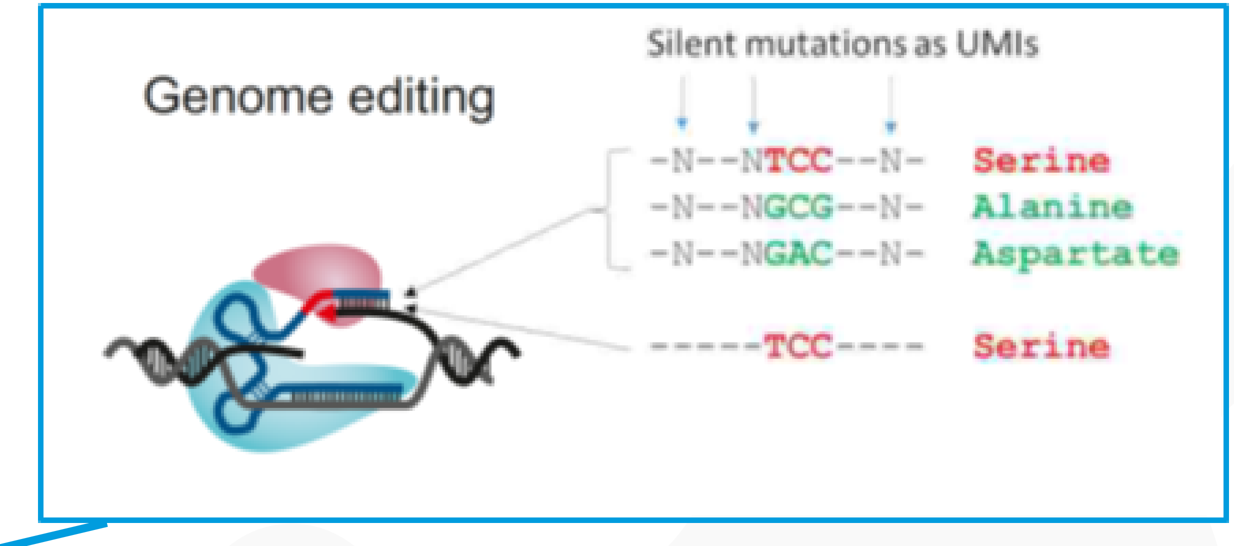
Phosphoproteomics



Thermal proteome profiling

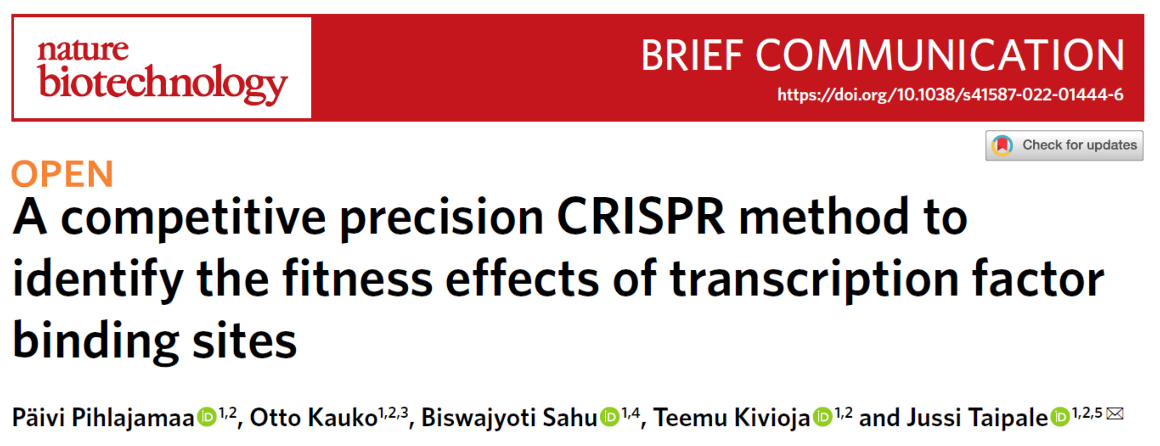


Genome editing



MYC targets

- Ribosome biogenesis
- Translation, Nucleotide synthesis



nature biotechnology

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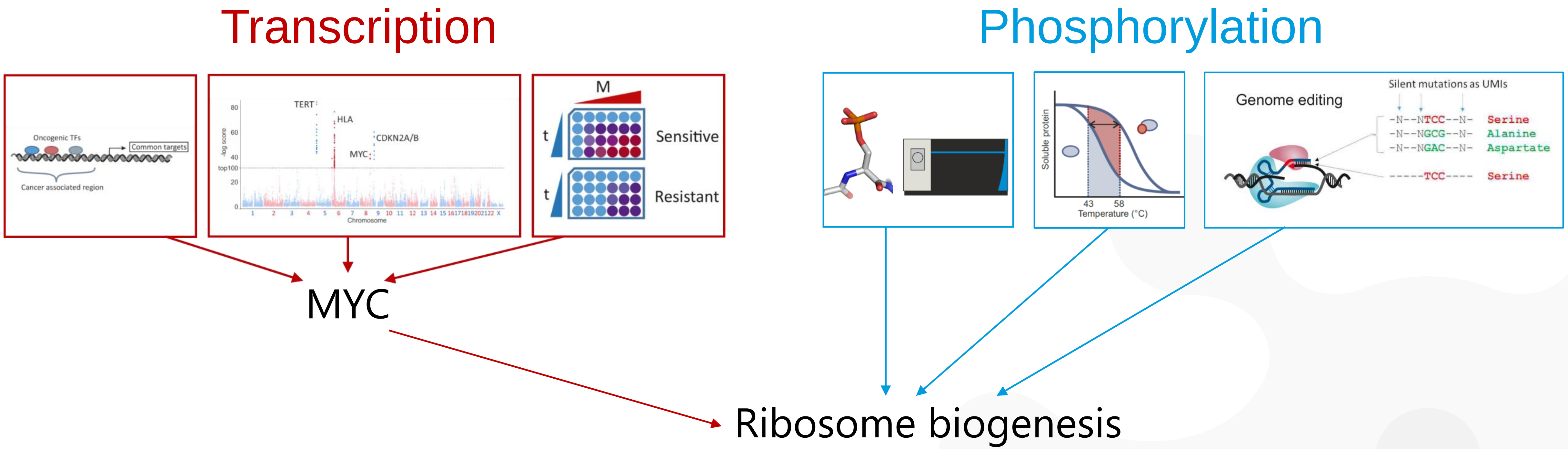
Common growth regulatory mechanism in major forms of human cancer



Transcription

Phosphorylation

Sensitive

Resistant

Genome editing

MYC

Ribosome biogenesis

Kauko et al. BioRxiv **doi:** https://doi.org/10.1101/2022.09.27.509636

rRNA synthesis is the major shared target of transcriptional and post-translational growth regulation

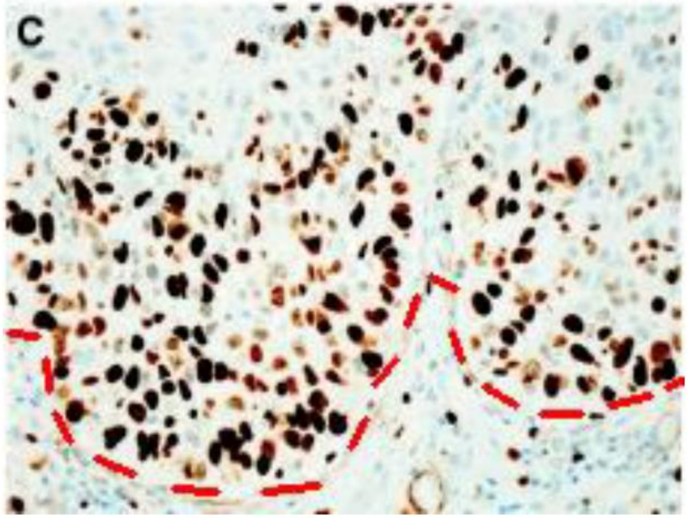
NOLC1, TCOF1,

TCOF1
POLR1C
POLR1D

Treacher Collins syndrome

NOLC1 and TCOF1 define the proliferative compartment in human cancer

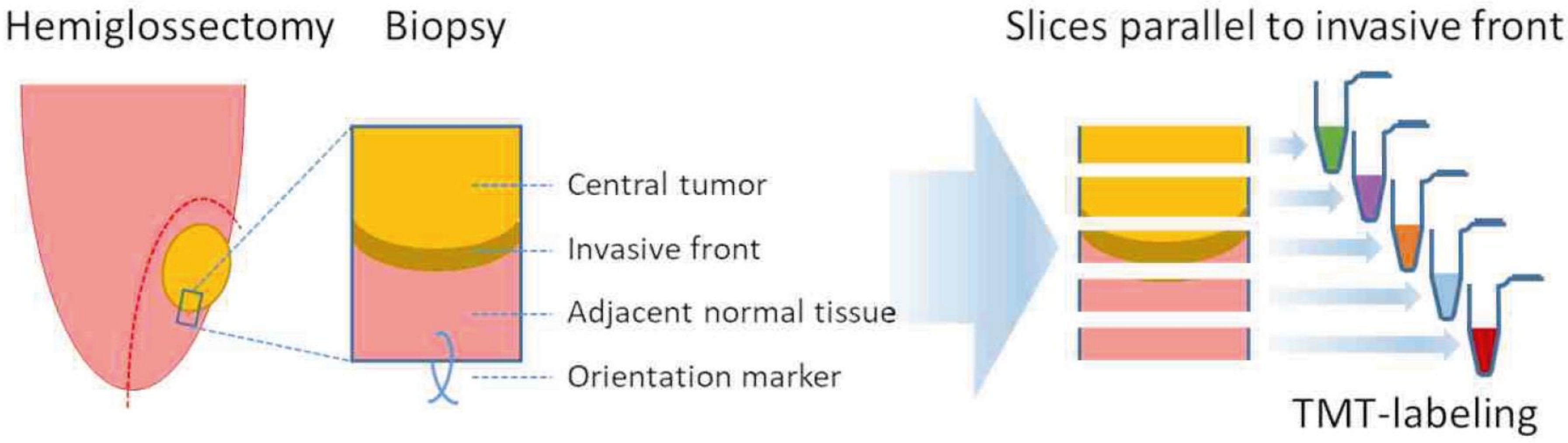
HNSCC invasive front



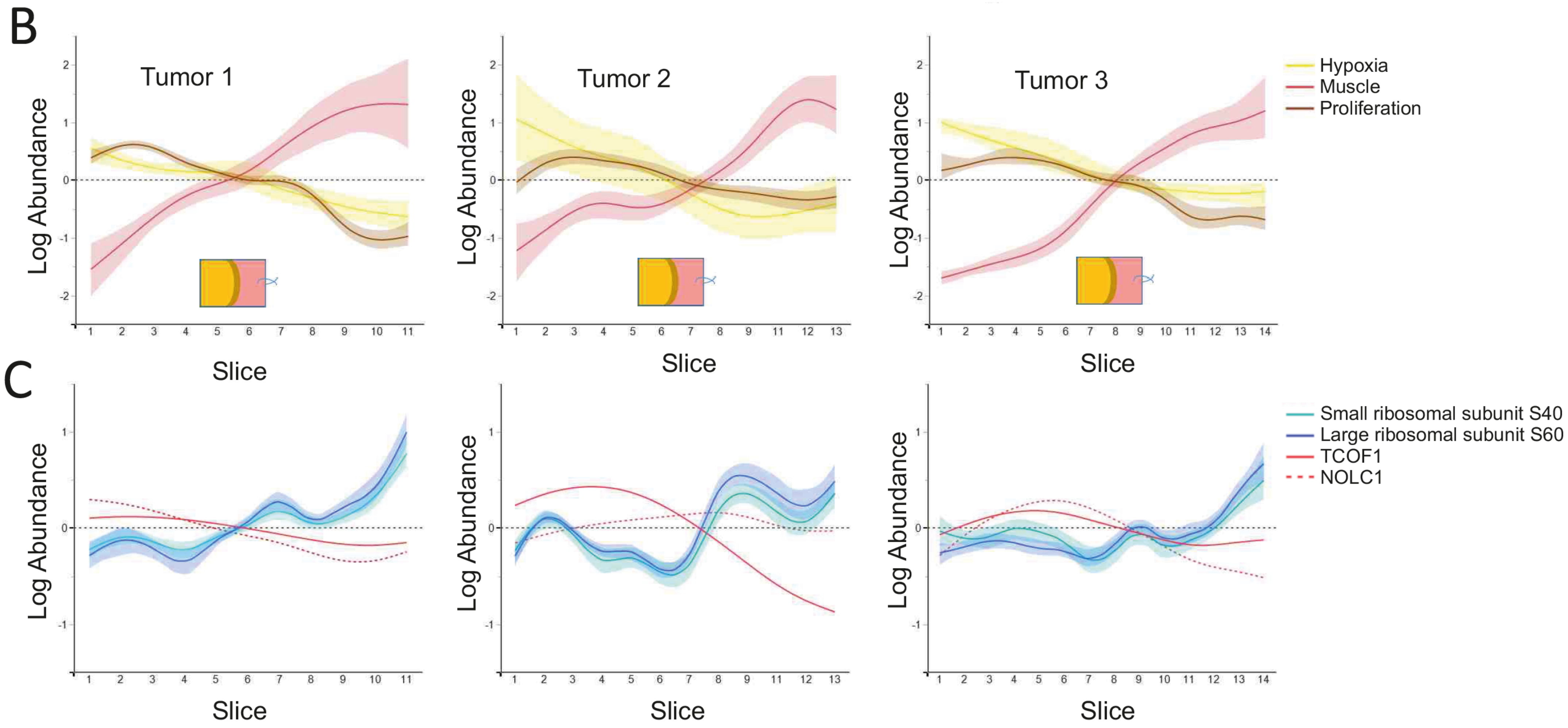
KI67

Adapted from Torres-Rendon et al. Br J Cancer 2009

NOLC1 and TCOF1 define the proliferative compartment in human cancer



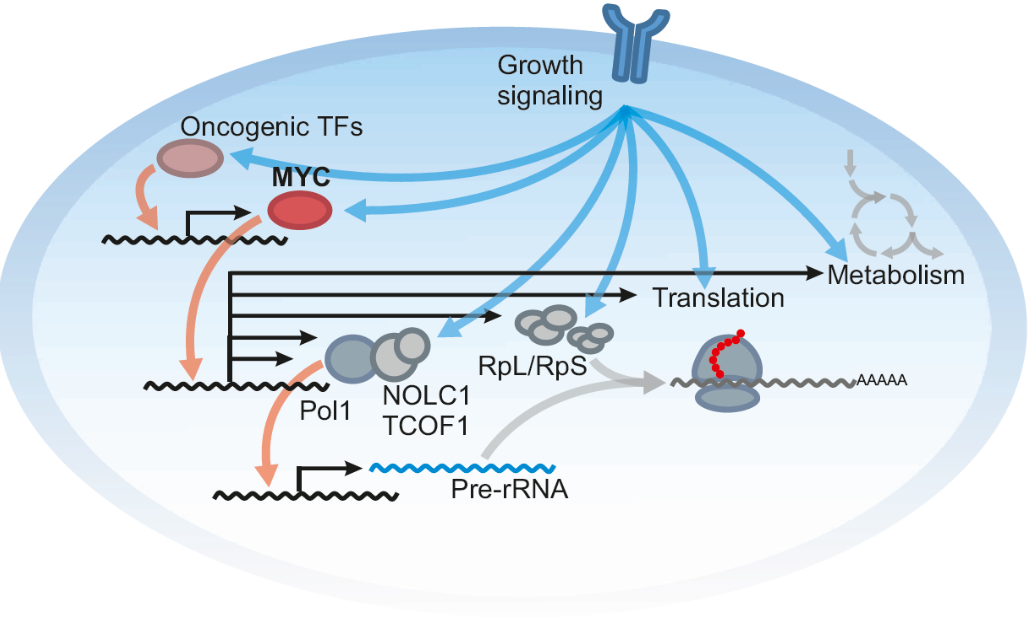
NOLC1 and TCOF1 define the proliferative compartment in human cancer



Conclusions

- **We identified mechanisms of ribosome biogenesis that are specific to cancer cells**

- **Common targets of oncogenic signaling represent therapeutic and cancer prevention opportunities that**
  - **Are less likely to be escaped by collateral pathway activation**
  - **Are active in large fraction of all cancers**



Kauko et al. Submitted
BioRxiv: ***doi:*** *https://doi.org/10.1101/2022.09.27.509636*

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- Taipale lab
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  - Heikki Irjala
  - Johannes Routila

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  - Antti Häkkinen

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  - Rayner Queiroz (Cambridge)
  - Massimiliano Gaetani (KI)
  - Susanna Lundström (KI)
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  - Antonio Murgia

Suomen Lääketieteen Säätiö

Syöpäsäätiö
Niin arvokas on elämä.

Sigrid Juselius Stiftelse

SAKARI ALHOPURON SÄÄTIÖ

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