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PUBLICATIONS

*Preclinical exploration of the DNA damage response pathway using the interactive neuroblastoma cell line explorer CLEAN
NAR Cancer, 2024
https://doi.org/10.1093%2Fnarcan%2Fzcad062

ALK signaling primes the DNA damage response sensitizing ALK-driven neuroblastoma to therapeutic ATR inhibition
PNAS, 2023
https://doi.org/10.1073/pnas.2315242121

ALK fusion NSCLC oncogenes promote survival and inhibit NK cell responses via SERPINB4 expression
PNAS, 2023
https://doi.org/10.1073/pnas.2216479120

Novel human-derived EML4-ALK fusion cell lines identify ribonucleotide reductase RRM2 as a target of activated ALK in NSCLC
Lung Cancer, 2022
https://doi.org/10.1016/j.lungcan.2022.07.010

ATR inhibition enables complete tumour regression in ALK-driven NB mouse models
Nature Communications, 2021
https://doi.org/10.1038/s41467-021-27057-2

*Loss of RET Promotes Mesenchymal Identity in Neuroblastoma Cells
Cancers, 2021
https://doi.org/10.3390/cancers13081909

*The coelomic epithelium transcriptome from a clonal sea star, Coscinasterias muricata
Marine Genomics, 2015
https://doi.org/10.1016/j.margen.2015.07.010

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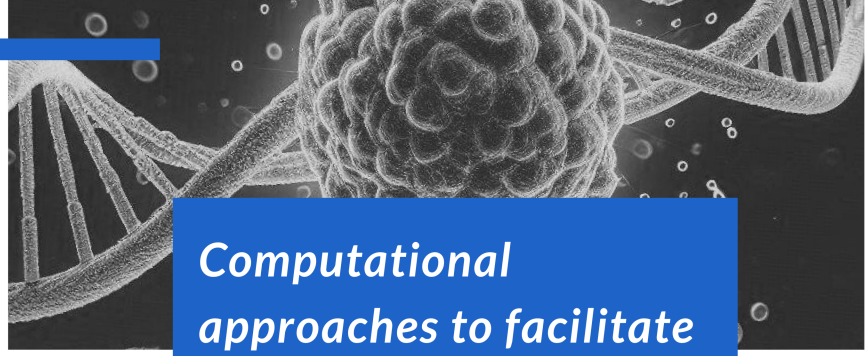


Computational approaches to facilitate the identification of novel therapeutic targets in neuroblastoma and other ALK-driven cancers

GHENT UNIVERSITY,
FACULTY OF MEDICINE AND HEALTH SCIENCES, 2024

JONATAN L. GABRE

Thesis submitted to fulfil the requirements for the degree of "Doctor in Health Sciences".

GHENT UNIVERSITY

FACULTY OF MEDICINE AND HEALTH SCIENCES

Loss of RET Promotes Mesenchymal Identity in Neuroblastoma Cells

OBJECTIVES

Neuroblastoma (NB) is one of the deadliest childhood cancers, accounting for about 15% of all pediatric cancer-related deaths. Tumors develop during early development and arise in the sympathetic nervous system and the adrenal gland.

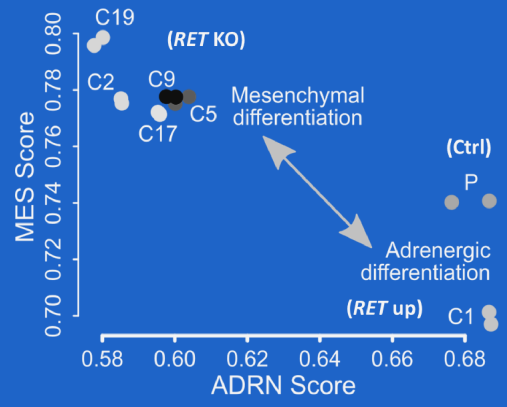
Anaplastic Lymphoma Kinase (ALK) is gene that is mutated in around 10% of all NB tumors and, together with other factors like MYCN Amplification (MNA), drives this cancer. Despite the availability of potent ALK inhibitors, the clinical outcomes for patients harboring oncogenic ALK mutations remain poor. To improve the prognosis for these individuals, this PhD aimed to identify targets for combinatorial treatment with ALK inhibitors, as well as to further our understanding of this protein and its interactors.

In the first part of this PhD, we explored REarranged during Transfection (RET). This protein has been suggested as a potential target for combination with ALK inhibition. It is highly expressed in NB and is critical during development. It has also been identified as a driver in various other cancers, such as lung, breast, and prostate cancers.

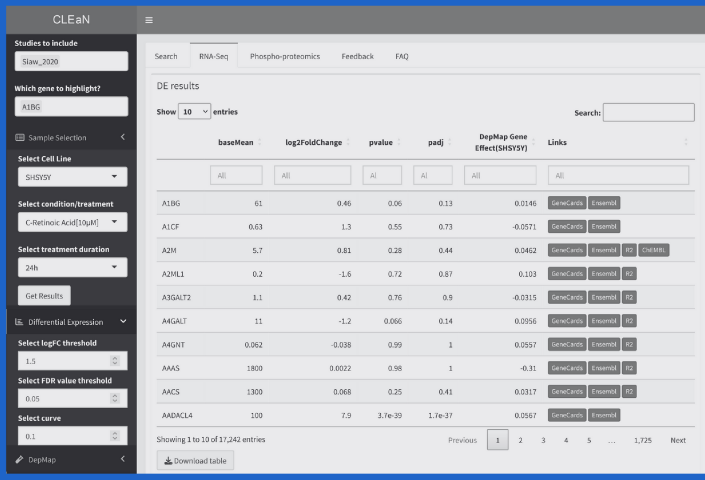
In our study, we uncovered a previously unknown mechanistic relationship between ALK and RET—ALK and RET appear to be co-regulated in NB cells.

We further investigated the effects of disrupting RET activity. By analyzing global gene expression in NB cells where RET was disabled, we observed a phenotypic shift from a state typically associated with better patient prognosis (adrenergic) to a less proliferative but more therapeutically resistant state (mesenchymal).

DISRUPTING RET LEADS TO A SHIFT FROM AN ADRENERGIC (ADRN) TO A MESENCHYMAL (MES) CELLSTATE.



Preclinical exploration of the DNA Damage Response pathway using the interactive neuroblastoma cell line explorer CLEAN



CLEAN IS AN INTERACTIVE WEB APPLICATION FOR EXPLORATION OF HIGH THROUGHPUT NB CELL LINE DATA: HTTPS://CCGG.UGENT.BE/SHINY/CLEAN/

For the study mentioned above, as well as every other study conducted during this PhD, we relied on high-throughput data. Each study generated thousands of data points, many of which remain unaddressed in the original analyses. Additionally, accessing and interpreting this information post-publication often requires bioinformatics expertise, effectively excluding a significant portion of the scientific community from engaging with these datasets. To bridge this gap, we developed the Cell Line Explorer App of Neuroblastoma (CLEAN), an interactive web application that enables users, regardless of computational background, to explore all published preclinical NB cell line data to generate new findings. To illustrate how CLEAN can be used, we demonstrate two use cases focusing on exploration of the DDR.