COMPUTATIONAL ONCOLOGY JUNIOR GROUP

Geoff Macintyre
Junior Group Leader

Staff Scientist
Maria José García

OVERVIEW

In the Computational Oncology Group, we are tackling some of the deadliest cancers by targeting the causes of chromosomal instability. Pancreatic, oesophageal, lung and ovarian cancers have some of the lowest survival rates, but they also share a common trait, which we can exploit – extreme chromosomal instability (CIN). By therapeutically targeting CIN, we aim to improve outcomes in these tumours.

Our main research areas include:

- → Using model systems to develop therapeutic strategies to target CIN.
- → Predicting therapy response using genomic signatures of CIN in patient biopsies.
- → Developing single cell sequencing approaches to detect ongoing CIN.

"We have completed a proof-of-concept study showing that different types of CIN can be studied at high resolution, using single cell DNA sequencing, and induced via genome-editing."

We are applying these technologies at the earliest stages of tumour development in patients with premalignant lesions, with the goal of preventing aggressive, difficult to treat cancers.

Post-Doctoral Fellow
Bárbara Hernando (since April)

Graduate Student
María Escobar (since February)

Technician
Alice Cádiz (since April) (PEJ, CAM)*

'Plan de Empleo Joven de la Comunidad de Madrid (Youth Employment Plan, Community of Madrid)

Visiting Master's Students
Blas Chaves (*Universidad Complutense de Madrid*, Madrid, Spain), Agustín Sánchez (February-June) (*E.T.S.I. Agronómica, Alimentaria y de Biosistemas*, Madrid, Spain)

RESEARCH HIGHLIGHTS

2021 saw the Computational Oncology Group shed its pandemic shackles and welcome 5 extremely talented new lab members and complete crucial proof-of-concept experiments.

Both Blas Chaves and Agustín Sánchez completed their master thesis projects: Agustín employed machine learning techniques to explore the relationship between DNA methylation and copy number signatures; and Blas quantified patterns of DNA copy number change at single cell resolution induced by knock-out of CDK18. Agustín has since taken a position in the Marcos Malumbres' Lab, and Blas is continuing as a PhD student building a large collection of induced CIN models in collaboration with the CNIO laboratories of Marcos Malumbres, Ana Losada, Felipe Cortés-Ledesma, Óscar Fernández-Capetillo, Juan Méndez, and Miguel Ángel Quintela-Fandino. As part of this project, Blas and Bárbara Hernando developed the first computational tool to come out of the lab, CNpare, which identifies related cell lines based on their genome-wide copy number profile (preprint here: https://doi.org/10.1101/2021.09.28.462193).

Following on from her excellent master's thesis identifying mismatch repair deficient ovarian cancers (ongoing project led by Maria José), Maria Escobar started her PhD where she will be using ongoing CIN to predict drug response in organoids and predict risk of progression in premalignant lung lesions. Alice Cádiz joined the lab with a training fellowship and is supporting all lab-based projects and keeping our databases in check.

On the computational side, David, a PhD student from Luis G. Paz-Ares' group, joined the team and will work on mutational signatures in lung cancer. Bárbara joined as a post-doc and has developed bioinformatics pipelines to support analysis across all projects; she has also carried out crucial analysis for our pan-cancer copy number signature study (see FIGURE 1) correlating signatures with drug response for 1008 drugs across 297 cell lines.

Our early Christmas present — the cellenONE single cell sorter — now allows us to perform single cell DNA sequencing of human tissue samples, so watch this space for exciting new data in 2022! ■

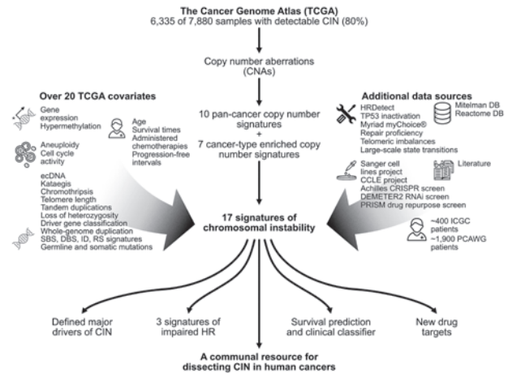

FIGURE 1 A summary of our study where we used DNA profiling of 6,335 tumours to identify copy number signatures of different types of chromosomal instability. We integrated various data sources to propose signature aetiologies and use signatures to predict treatment response and find new drug targets.

PUBLICATIONS AT OTHER INSTITUTIONS

- Dentro SC*, Leshchiner I*, Haase K*, Tarabichi M*, Wintersinger J*, Deshwar AG*, Yu K*, Rubanova Y*, Macintyre G*, Demeulemeester J*, *et al.* (2021). Characterizing genetic intra-tumor heterogeneity across 2,658 human cancer genomes. *Cell* 184, 2239-2254.
- Cmero M, *et al.* (incl. Macintyre G) (2021). Loss of *SNAI2* in prostate cancer correlates with clinical response to androgen deprivation therapy. *JCO Precis Oncol.* doi: 10.1200/PO.20.00337.
- Macintyre G, *et al.* (2021) FrenchFISH: poisson models for quantifying DNA copy number from fluorescence in situ hybridization of tissue sections. *JCO Clin Cancer Inform* 5, 176-186.
- McCoy P, *et al.* (incl. Macintyre G) (2021). MSH2-deficient prostate tumours have a distinct immune response and clinical outcome compared to MSH2-deficient colorectal or endometrial cancer. *Prostate Cancer Prostatic Dis* 24, 1167-1180.

PATENT

- Macintyre G, Drews R, Markowetz F, Hernando B (2021). Method of characterising a DNA sample. *GB 2114203.9*.