COMPUTATIONAL ONCOLOGY JUNIOR GROUP

Geoff Macintyre
Junior Group Leader

Research Scientist
Maria José García (until October)

Post-Doctoral Fellow
Bárbara Hernando

Gradutate Students
Blas Chaves, María Escobar, Ángel Fernández (since May), David Gómez

Technician
Alice Nicole Cádiz (PEJ, CAM) *

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

Students in Practice
Diego García (since February) (Master's Thesis, Universidad Politécnica de Madrid, Spain), Sara Vettorazzo (August-December)

(Erasmus + Fellowship, Università di Trento, Italy)

OVERVIEW

In the Computational Oncology Group, we are tackling some of the deadliest cancers by targeting the causes of chromosomal instability (CIN). By therapeutically targeting CIN, we aim to improve patient outcomes.

Our main research areas include:

→ Using model systems to develop therapeutic strategies to target CIN.

→ Predicting therapy response using CIN signatures in patient biopsies.

→ Developing single cell sequencing approaches for ultrasensitive CIN detection.

"We have developed a new computational framework to evaluate the extent, diversity and origin of chromosomal instability pan-cancer."

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

RESEARCH HIGHLIGHTS

2022 was a great year for the Computational Oncology Group. We welcomed a new lab member and saw our senior staff scientist, Maria José Garcia, move to CSIC as a PI! Another key highlight was seeing our CIN signature study published in *Nature*. We also secured the front cover artwork with an abstract interpretation of the research painted by Geoff's cousin Julian Aubrey Smith (FIGURE 1). This study was the culmination of years of computational work during the pandemic period in collaboration with the University of Cambridge. We developed a framework to evaluate the diversity and origin of chromosomal instability pan-cancer, identifying 17 genomic signatures of different types of CIN. Barbara was crucial to the success of the project demonstrating that the signatures can predict drug response and identify new drug targets. The work attracted significant press coverage, including appearing on the front page of *El País*. Barbara is now extending this technology to work at single cell resolution to enable a number of other projects in the lab.

Ángel joined the lab as a computational PhD student to understand how CIN contributes to tumour evolution. Working closely with Barbara, they have recently developed an approach to forecast oncogenic amplification in tumours using the CIN signatures. David is combining this approach with his new method to extract robust copy number profiles from targeted gene sequencing data to forecast MET amplification-driven resistance to EGFR inhibitors in lung cancer.

Maria and Blas were busy performing single cell DNA sequencing of organoids and KO cell lines – expect exciting

FIGURE 1 Our CIN signature article on the cover of *Nature*.

results in 2023! Two masters' students also completed their projects: Diego developed a new method for mis-match repair deficiency prediction, and Sara uncovered new patterns of CIN in premalignant oesophageal lesions.

Much of this work will be submitted in 2023 for publication, so hopefully there will be another great year ahead! ∎

▸ **PUBLICATIONS**

▸ Drews RM, Hernando B, Tarabichi M, Haase K, Lesluyes T, Smith PS, Morrill Gavarró L, Couturier DL, Liu L, Schneider M, Brenton JD, Van Loo P, Macintyre G*, Markowetz F* (2022). A pan-cancer compendium of chromosomal instability. *Nature* 606, 976-983. *Co-corresponding authors.

▸ Cheng Z, Mirza H, Ennis DP, Smith P, Morrill Gavarró L, Sokota C, Giannone G, Goranova T, Bradley T, Piskorz A, Lockley M; BriTROC-1 Investigators; Kaur B, Singh N, Tookman LA, Krell J, McDermott J,

Macintyre G, Markowetz F, Brenton JD, McNeish IA (2022). The genomic landscape of early-stage ovarian high-grade serous carcinoma. *Clin Cancer Res* 28, 2911-2922.

▸ Chaves-Urbano B, Hernando B, Garcia MJ, Macintyre G (2022). CNpare: matching DNA copy number profiles. *Bioinformatics* 38, 3638-3641.

▸ Gallego A, Mendiola M, Hernando B, Berjon A, Cadiz A, Chaves-Urbano B, Heredia-Soto V, Spagnolo E, Hernández Gutiérrez A, Hardisson D, Macintyre G, Redondo A, Garcia MJ (2022). Prognostic markers of inflammation in endometrioid

and clear cell ovarian cancer. *Int J Gynecol Cancer* 32, 1009-1016.

▸ Vias M, Gavarró LM, Sauer CM, Sanders D, Piskorz AM, Couturier DL, Ballereau S, Hernando B, Hall J, Correia-Martins F, Markowetz F, Macintyre G, Brenton JD (2022). High-grade serous ovarian carcinoma organoids as models of chromosomal instability. *bioRxiv*. doi: https://doi.org/10.1101/2022.09.01.506155.

▸ Smith PS, Bradley T, Gavarró LM, Goranova T, Ennis D, Mirza H, De Silva D, Piskorz AM, Al-Khalidi S, Sauer C, Funingana IG, Reinius M, Giannone G, Lewsley LA, Stobo J, McQueen J, Bryson G, Eldridge M,

Macintyre G, Markowetz F, Brenton JD, McNeish IA, The BriTROC Investigators (2022). The genomic landscape of recurrent ovarian high grade serous carcinoma: the BriTROC-1 study. *medRxiv*. doi: https://doi.org/10.1101/2022.10.21.22280992.

▸ **PATENT**

▸ Macintyre G, Drews R, Markowetz F, Hernando B. Method of characterising a DNA sample. PCT application (2022). *PCT/EP2022/077473. WO2023057392A1.*