# COMPUTATIONAL ONCOLOGY JUNIOR GROUP

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## 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 that 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.

**"In our first year of operation we have established computational and laboratory infrastructure that will allow us to observe chromosomal instability at the earliest stages of tumour evolution."**

→ Developing single cell/nucleus sequencing approaches to detect ongoing CIN.

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.





## RESEARCH HIGHLIGHTS

2020 started well for the Computational Oncology Group with the publication of work the group was involved in as part of the pan-cancer analysis of whole-genomes project. However, the onset of the Covid-19 pandemic meant the first year of operations for the Computational Oncology Group did not go as planned. It did, however, make some of the small wins a lot more important!

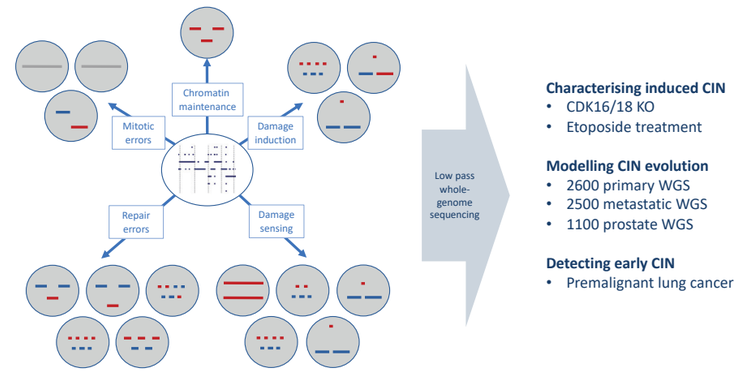
We now have a brand-new laboratory setup designed specifically to interrogate tumour DNA copy number using a low-cost, low-pass whole-genome sequencing strategy. We have established our computational lab and have worked closely with the Bioinformatics Unit to upgrade CNIO's scientific computing infrastructure to handle the imminent influx of sequencing data.

The Group is also slowly growing size – María José García joined from Javier Benítez's Group upon his retirement and has been the driving force behind getting the Computational Oncology Group's laboratory operations up and running. She brings with her a wealth of experience preparing clinical samples for DNA sequencing and her own funded project on DNA mismatch repair in ovarian cancer. Blas Chaves has joined for his Master's project at *Universidad Complutense de Madrid* (*UCM*) and has demonstrated his aptitude in the lab and in front of the computer. He will be characterising different types of chromosomal instability in model systems using copy number signatures.

We have developed collaborations with Marcos Malumbres' laboratory where we will determine the types of CIN caused by knockout of CDKs, and with Felipe Cortés' laboratory looking at CIN induced by etoposide treatment. We have started our project with Sam Janes at University College London (UCL) detecting CIN in premalignant lung cancers. Finally, we have made significant progress characterising pan-cancer patterns of CIN and how they relate to drug response – look out for a publication in 2021!

It looks an exciting year moving ahead with 3 new members and a chance to finally put our new laboratory infrastructure into action to tackle some of the deadliest cancers. ■

**FIGURE** A schematic of the 17 pancancer copy number signatures we have identified using >10,000 tumour samples across 32 tumour types and how we will combine these with low-pass whole genome sequencing to interrogate different types of CIN at different stages of tumour evolution.




### PUBLICATIONS AT OTHER INSTITUTIONS


- Gerstung M, Jolly C, Leshchiner I, Dentro SC, Gonzalez S, Rosebrock D, Mitchell TJ, Rubanova Y, Anur P, Yu K, Tarabichi M, Deshwar A, Wintersinger J, Kleinheinz K, Vázquez-García I, Haase K, Jerman L, Sengupta S, Macintyre G, Malikic S, Donmez N, Livitz DG, Cmero M, Demeulemeester J, Schumacher S, Fan Y, Yao X, Lee J, Schlesner M, Boutros PC, Bowtell DD, Zhu H, Getz G, Imielinski M, Beroukhim R, Sahinalp SC, Ji Y, Peifer M, Markowetz F, Mustonen V, Yuan K, Wang W, Morris QD; PCAWG Evolution & Heterogeneity Working Group, Spellman PT, Wedge DC, Van Loo P; PCAWG Consortium (2020). The evolutionary history of 2,658 cancers. *Nature* 578, 122-128.
- The ICGC and TCGA Pan-Cancer Analysis of Whole, Genomes Consortium (2020). Pan-cancer analysis of whole genomes. *Nature* 578, 82-93.
- Jiménez-Sánchez A, Cybulska P, Mager KL, Koplev S, Cast O, Couturier DL, Memon D, Selenica P, Nikolovski I, Mazaheri Y, Bykov Y, Geyer FC, Macintyre G, Gavarró LM, Drews RM, Gill MB, Papanastasiou AD, Sosa RE, Soslow RA, Walther T, Shen R, Chi DS, Park KJ, Hollmann T, Reis-Filho JS, Markowetz F, Beltrao P, Vargas HA, Zamarin D, Brenton JD, Snyder A, Weigelt B, Sala E, Miller ML (2020). Unraveling tumor-immune heterogeneity in advanced ovarian cancer uncovers immunogenic effect of chemotherapy. *Nat Genet* 52, 582-593.
- C Loveday, K Litchfield, P Z Proszek, A J Cornish, F Santo, M Levy, G Macintyre, A Holryod, P Broderick, D Dudakia, B Benton, M Al Bakir, C Hiley, E Grist, C Swanton, R Huddart, T Powles, S Chowdhury, J Shipley, S O'Connor, J D Brenton, A Reid, D Gonzalez de Castro, R S Houlston, C Turnbull (2020). Genomic landscape of platinum resistant and sensitive testicular cancers. *Nat Commun* 11, 2189.
- Cmero M, Yuan K, Ong CS, Schröder J; PCAWG Evolution and Heterogeneity Working Group, Corcoran NM, Papenfuss T, Hovens CM, Markowetz F, Macintyre G; PCAWG Consortium (2020). SVclone: inferring structural variant cancer cell fraction, *Nat Commun* 11, 730.