GENOMICS CORE UNIT

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OVERVIEW

The Genomics Unit provides on-demand scientific services to the CNIO research community. Cutting-edge technologies have the capacity to interrogate whole genomes in a single assay, such as next-generation sequencing (NGS). These methodologies reveal the genetic diversity of cancer and contribute to dissect its molecular processes. Structural features, such as mutation landscapes, DNA-binding of protein factors, variations in chromatin structure, as well as functional activation states reflected on changes of transcriptomic profiles (mRNA, miRNA), are being elucidated with these technologies in order to uncover basic mechanisms, therapeutic targets and prognostic biomarkers. We offer a broad range of applications, including powerful solutions such as exome mutational landscapes, protein location analysis by ChIP-seq analysis and transcriptome profiles by RNA-seq technologies, besides from the more traditional microarray platform – suitable for whole genome gene expression, array comparative genomic hybridisation (aCGH) – and capillary DNA sequencing. Among other side activities, we also provide a very active transgenic mouse genotyping service.

"The genetic and genomic services provided by the Genomics Unit to assist CNIO's scientists all help to contribute towards the understanding of the molecular processes of cancer at different levels of biological complexity."

Ángeles Rubio, Delfina Sanguino (until September), Marco De Mesa, Laura Conde (since November)

RESEARCH HIGHLIGHTS

The Genomics Unit contributes to the advancement of research projects carried out by multiple CNIO Research Groups. It provides services that survey different levels of complexity. A wide genomic level is addressed mainly by deep-sequencing (NGS) techniques and their applications. NGS permits a variety of different explorations, such as whole genome or whole exome tumour sequencing, transcriptome analyses – long non-coding RNA included – or location of interacting protein factors or RNA binding sites on chromatin. This year, the demand for NGS services has been stable and the number of samples processed has been similar to that of 2017. At a more focused single locus level, other services, such as the traditional DNA capillary sequencing service, are also provided; this service is used to find and confirm mutations in candidate genes, or in the verification of cloned genes or inserts. The Unit also provides a transgenic mouse genotyping service, based on allele-specific quantitative PCR for a quick and efficient turnaround time. The genotyping service has a catalogue of about 120 genetic modifications and 2018 has seen a steady increase in demand over that of former years.

Some of our activities have contributed to two research reports being published in 2018, with the authorship of some of the members of the Unit. When searching for the genetic causes of resistance to antiangiogenic therapies in a metastatic colorectal cancer patient, a collaborator's project sought to recapitulate the tumour exome from circulating tumour DNA (ctDNA). An L840F somatic mutation in the *KDR/VEGFR2* gene was found as the cause of the resistance. This tumour mutation blocks the angiogenic inhibitors' binding to VEGFR2. This study demonstrates new opportunities for analyses on ctDNA in order to explain therapy resistance mechanisms and to detect prognostic biomarkers (Toledo RA *et al.*).

RAS proteins are mostly known as oncogenic factors, but they also play a key role in pluripotency. The second report shows how embryonic stem cells devoid of RAS genes are unable to abandon pluripotency (Mayor-Ruiz C *et al.*), a feature that depends on the phosphorylation state and subsequent activation of inhibiting transcription factor ERF. Relative to cancer, this work further suggests the possibility that selective RAS inhibitors, which could eventually be used in therapy, would promote the emergence of resistance mechanisms through the inactivation of mediators such as ERF. ■

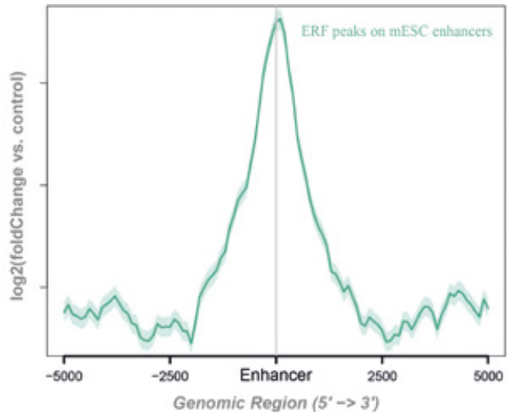

Figure The enrichment of ERF chromosomal location in Ras^{less} OHT-treated mESCs, at or nearby enhancers, suggests a role for ERF in the global rewiring of the transcriptional gene expression programme associated with pluripotency (Mayor-Ruiz *et al.*, *Genes Dev*, 2018). Figure prepared with ngs.plot (Shen *et al.*, *BMC Genomics*, 2014).

PUBLICATIONS

- Toledo RA, Garralda E, Mitsi M, Pons T, Monsech J, Vega E, Otero Á, Albarran MI, Baños N, Durán Y, Bonilla V, Sarno F, Camacho-Artacho M, Sanchez-Perez T, Perea S, Álvarez R, De Martino A, Lietha D, Blanco-Aparicio C, Cubillo A, Domínguez O, Martínez-Torrecuadrada JL, Hidalgo M (2018). Exome sequencing of plasma DNA portrays the mutation landscape of colorectal cancer and discovers mutated VEGFR2 receptors as modulators of antiangiogenic therapies. *Clin Cancer Res* 24, 3550-3559.
- Mayor-Ruiz C, Olbrich T, Drosten M, Lecona E, Vega-Sendino M, Ortega S, Dominguez O, Barbacid M, Ruiz S, Fernandez-Capetillo O (2018). ERF deletion rescues RAS deficiency in mouse embryonic stem cells. *Genes Dev* 32, 568-576.