

BIOINFORMATICS UNIT

Fátima Al-Shahrour
Unit Head

Staff Scientist
Michael Tress

Graduate Students
Santiago García (PEJ, CAM)*, María José Jiménez, Laura Martínez, Fernando Pozo, Kevin Troulé (until September)

*Plan de Empleo Joven de la Comunidad de



OVERVIEW

Bioinformatics is a key discipline for understanding the cancer genome and for the future of cancer therapeutics. Bioinformatics-based approaches have the ability to transform the vast amount of biological data into comprehensive models that provide a deep understanding of cancer disease and the complex genotype-phenotype relationships needed to identify molecular cancer-driving alterations and novel therapeutic targets.

The CNIO Bioinformatics Unit (BU) has several objectives: (i) to develop new computational methodologies and bioinformatics tools to enable the integration of biological and clinical data, (ii) to achieve genome analysis in cancer patients' data to identify new biomarkers and drug response mechanisms, (iii) to provide bioinformatics support with data

“We have introduced Beyondcell, the first bioinformatics method to define tumour cell subpopulations of differential drug response at single-cell resolution and have proposed cell-specific anticancer treatments.”

analysis and interpretation using computational and statistical methods, (iv) to maintain the scientific computing facilities at the CNIO, and (iv) to provide training in bioinformatics tools and methods.

Madrid (Youth Employment Plan, Community of Madrid)

Bioinformaticians
Daniel Cerdán (TS) **, Tomas Di Domenico (TS) **, Coral Fustero (TS)**;

Gonzalo Gómez (TS) **, Osvaldo Graña (TS) **, Elena Piñeiro (TS) **, Thomas Anthony Walsh (until April) (TS) **

**Titulado Superior (Advanced Degree)

Students in Practice
Lourdes González (May-December) and Carlos León (May-December) (Master's Programme in Bioinformatics, Personalised

Medicine and Health, ISCIII-ENS, Madrid, Spain)

Visiting Scientist
Paolo Maietta (NIMGenetics, Madrid, Spain)

RESEARCH HIGHLIGHTS

In 2021, the Bioinformatics Unit published more than 22 peer-reviewed articles as a result of our ongoing research projects and scientific collaborations (see the full list of our activities on our website: <https://bioinformatics.cnio.es/>). We studied cancer cell biology and drug response at single-cell resolution. To this end we developed Beyondcell (FIGURE 1), a computational methodology to identify tumour cell subpopulations under drug exposure, thereby revealing sensitive, innate, and acquired drug resistant cancer cells. Through this method we are able to propose possible treatment strategies to overcome such resistance and to identify drug-response markers. Using Beyondcell, we characterised single-cell variability in drug response in 198 cancer cell lines, finding recurrent patterns of drug heterogeneity and their relationship with the cells' functional status. Our software also allowed us to explore inter- and intra-tumour heterogeneity, linking it to clinical drug response data and to successfully predict responders and non-responders to immunotherapy among melanoma

patients (Fustero-Torre *et al.* 2021). Beyondcell is fully accessible at https://gitlab.com/bu_cnio/beyondcell.

During 2021, our group also assessed the clinical importance of tandem exon duplication-derived substitutions (Martínez-Gómez *et al.* 2021) and implemented Bollito (García-Jimeno *et al.* 2021), a comprehensive bioinformatics pipeline that performs basic and advanced single-cell RNA-seq analysis and TRIFID, a method for classifying the functional importance of splice isoforms (Pozo *et al.* 2021). Additionally, the BU served as an active node of the European network ELIXIR (<https://www.elixir-europe.org/>), leading the ELIXIR Cancer Data Focus Group to provide the framework and expertise for the systematic analysis and interpretation of cancer genomes. With regard to academic and knowledge-transfer activities, we co-organised the Master's degree programme in Biocomputing Applied to Personalised Medicine and Health at the National Institute of Health Carlos III (*Máster en Bioinformática Aplicada a Medicina Personalizada y Salud, ENS-ISCIII*). ■

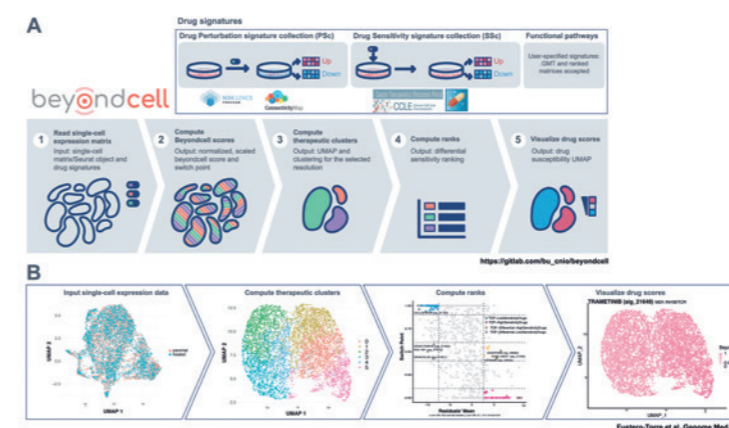


FIGURE 1 (A) Beyondcell workflow. (B) Beyondcell identified the presence of therapeutic clusters (TCs) in BRAF-inhibitor resistant human melanoma cells. Trametinib had a positive Beyondcell score in all TCs, with a higher sensitivity in TC5, showing it could be proposed to target BRAFi-unresponsive cells.

SELECTED PUBLICATIONS*

- Frankish A, Diekhans M, Jungreis I, Lagarde J, Loveland JE, Mudge JM, Sisu C, Wright JC, Armstrong J, Barnes I, Berry A, Bignell A, Boix C, Carbonell Sala S, Cunningham F, Di Domenico T, Donaldson S, Fiddes IT, García Girón C, Gonzalez JM, Grego T, Hardy M, Hourlier T, Howe KL, Hunt T, Izuogu OG, Johnson R, Martin FJ, Martínez L, Mohanan S, Muir P, Navarro

FCP, Parker A, Pei B, Pozo F, Riera FC, Ruffier M, Schmitt BM, Stapleton E, Suner MM, Sycheva I, Uszczyńska-Ratajczak B, Wolf MY, Xu J, Yang YT, Yates A, Zerbino D, Zhang Y, Choudhary JS, Gerstein M, Guigó R, Hubbard TJP, Kellis M, Paten B, Tress ML, Flicek P (2021). GENCODE 2021. *Nucleic Acids Res* 49, D916-D923.

Martínez Gómez L, Pozo F, Walsh TA, Abascal F, Tress ML (2021). The clinical importance of tandem exon duplica-

tion-derived substitutions. *Nucleic Acids Res* 49, 8232-8246.

Fustero-Torre C, Jiménez-Santos MJ, García-Martín S, Carretero-Puche C, García-Jimeno L, Ivanchuk V, Di Domenico T, Gómez-López G, Al-Shahrour F (2021). Beyondcell: targeting cancer therapeutic heterogeneity in single-cell RNA-seq data. *Genome Med* 13, 187.

García-Jimeno L, Fustero-Torre C, Jiménez-Santos MJ, Gómez-López G, Di Do-

menico T, Al-Shahrour F (2021). bollito: a flexible pipeline for comprehensive single-cell RNA-seq analyses. *Bioinformatics*. PMID: 34788788.

Pozo F, Martínez-Gómez L, Walsh TA, Rodríguez JM, Di Domenico T, Abascal F, Vazquez J, Tress ML (2021) Assessing the functional relevance of splice isoforms. *NAR Genom Bioinform* 3, lqab044.

*please see BU's web site for a list of all publications.