GENETIC AND MOLECULAR EPIDEMIOLOGY GROUP

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Ramón Tejedor (National Institute of Health Carlos III, Madrid, Spain), Mónica Cabrera (Pompeu Fabra University, Barcelona, Spain)

Visiting Scientists
M. Ángeles Jiménez (until June) (*Centro Nacional de Microbiología*, National Institute of Health Carlos III, Spain), Kristel Van Steen (Liège University, Belgium)

OVERVIEW

The scope of research carried out by our Group ranges from the identification of aetiological agents and mechanisms, to the translation of the findings into the clinical and Public Health domains, focusing on bladder, pancreatic, and breast cancers.

We employ a wide variety of biomarkers to better characterise exposures, genetic susceptibility patterns, and cancer outcomes. *Omics* data provide a unique opportunity in this regard and the Group explores its integration in epidemiologic studies.

The strategic goals of the Group are to:

- → Identify non-genetic and genetic factors, as well as their interactions, associated with cancer development and progression and with its molecular/*omics* subphenotypes.
- → Develop and apply statistical/informatics tools to model the risk, prediction, and clinical course of patients with cancer by integrating epidemiologic with *omics* information.
- → Assess clinical and public health strategies for cancer control using current genomic tests and data.

"We have undertaken in-depth analyses integrating *omics* and non-*omics* data to predict pancreatic and bladder cancer risk and outcome, and have assessed the challenges that epidemiology faces in this endeavour."

RESEARCH HIGHLIGHTS

Research findings

During 2016, the Group mainly focussed its research on pancreatic and bladder cancers.

Regarding **pancreatic cancer** (PC), we have further analysed the epidemiological and clinical data from the PanGenEU Study and have characterised the risk of PC associated with diabetes, multimorbidity patterns and family history of cancer, among others. We have completed the genome-wide association study (GWAS) and, in collaboration with the international consortia, we are now replicating the primary findings. We are exploring, in collaboration with experts in the field, genome-wide methylation data generated with the Illumina 850K array in cases and controls. We also participated in a study that identified 3 new pancreatic cancer susceptibility signals on chromosomes 1q32.1, 5p15.33 and 8q24.21. Regarding **bladder cancer** (BC), we showed that common SNPs have a limited role in predicting BC outcomes and reported, for the first time, a heritability estimate for disease outcome by assessing the predictive ability of the models, including up to 171,304 SNPs for tumour recurrence and progression. We have also provided proof of concept for the joint effect of genetic variants in improving the discriminative ability of clinical prognostic models by using innovative analytic approaches, and demonstrated that SNPs in inflammatory-related genes were associated with BC prognosis (FIGURE 1). Through international collaborations, the Group has participated in the exploration of common germline variants in the APOBEC3 region associated with BC and breast cancer risk, and observed a tissue-specific role of environmental oncogenic triggers. In line with this study, mutations in cancer driver genes were primarily found in high-risk BC, together with APOBEC-related mutational signatures. We also participated in the development of a urine-based peptide biomarker and a combined methylation&mutation panel for detecting both primary and recurrent BC.

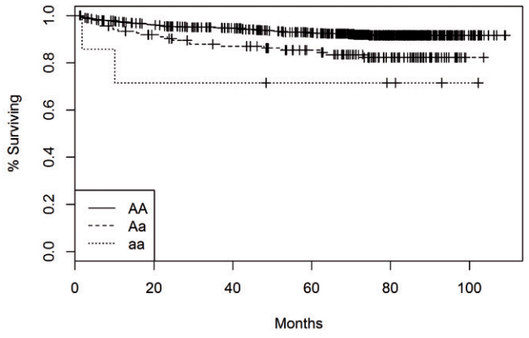

Figure 1 Progression-free survival of the 822 non-muscle invasive BC patients according to CD3G-rs3212262 genotypes. Five-year progression free survival was 92% for AA, 85% for Aa and 71% for aa genotypes (log rank p-value=8.4x10-4, adjusted Cox p-value = 0.023).

Methodological contributions

We have proposed an epidemiological-based integration of *omics* and non-*omics* data by considering the 'massive' inclusion of variables in the risk assessment and predictive models (FIGURE 2). We also discussed the numerous challenges imbedding this type of research and have proposed analytical strategies that allow considering both *omics* and non-*omics* data used in the models towards a personalised prevention. Furthermore, we have adapted Bayesian sequential threshold models in combination with LASSO and applied them to time-to-event and the censoring nature of data, in order to study 822 BC patients followed-up more than 10 years.

Translational activities

We coordinate the COST Action BM1204 *EUPancreas (www.eupancreas.com).* This Action includes 250 multidisciplinary members from 22 EU countries, EU governmental and nongovernmental institutions, and private companies. Several scientific, training, and dissemination activities have been conducted during 2016. By endorsing the Pancreatic Cancer Europe (PCE) multi-stakeholder platform, we have actively participated in several activities aimed at increasing the awareness of PC in the general population, the medical community, and among health policy makers. The Group has actively participated in setting up a European-based clinical registry of PC (PancreOS) jointly with the EPC, the Joint Research Centre from the European Community, and the European Network of Cancer Registries. The Group has also contributed to the development of recommendations for a state strategy for personalised/precision medicine, led by the Roche Institute. Another area our Group contributed to was the identification of different sources of big data and the importance of unstructured data for potential future uses in drug discovery; the main practical and ethical challenges to unravel the full potential of big data in healthcare were discussed. ■

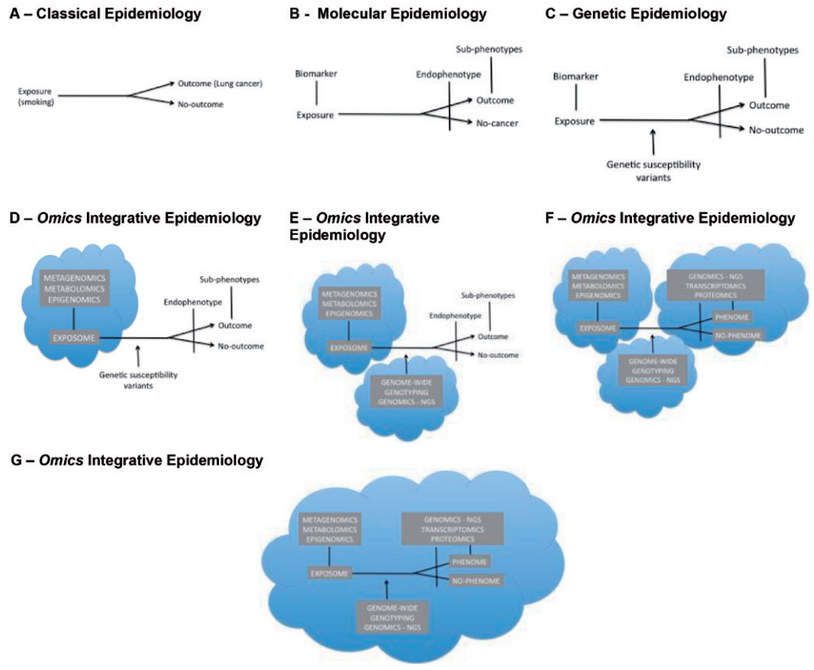

Figure 2 Conceptual association models applied in classical (**A**), molecular (**B**), genetic (**C**) and *omics* integrative epidemiology (**D**, **E**, **F**, and **G**).

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AWARDS AND RECOGNITION

- Founder and Board Member of Pancreatic Cancer Europe.
- Member of the Working Group 'Recomendaciones para un plan de Medicina de Precisión', *Fundación Instituto Roche*, Spain.