# Cancer Predisposition and DNA Repair Syndromes

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## DESCRIPTION

This research group works in the field of genetic diseases characterised by a high predisposition to cancer. Many of these syndromes are caused by mutations in DNA repair genes. These genes are therefore crucial in preventing cancer transformation. Research on these syndromes is crucial not only to improve their diagnosis and treatment but also to unravel the mechanisms that protect us from cancer.

Over the past few years, the team has identified and studied several novel genes involved in such syndromes and performed therapeutic research leading to two orphan drug designations by the European Medicines Agency and several academic clinical trials, including gene therapy and drug repurposing. They also investigate DNA repair genes involved in these syndromes as therapeutic targets to induce cancer-specific lethality through synthetic lethality.

There is an increasing number of novel therapeutic strategies based on the deep knowledge of the genetic causes of the disease. Therefore, a proper genetic diagnosis is essential not only to provide adequate genetic counselling and clinical management to patients and their families but also to provide personalised medicine based on genomic information.

## MAIN LINES OF RESEARCH

- Genetics and molecular biology of cancer-prone genetic syndromes with a focus on familial breast cancer and Fanconi Anemia and

related chromosome fragility syndromes such as ataxia telangiectasia. (Bogliolo, Massimo).

- Development of new diagnostic and therapeutic tools in Fanconi anemia, including gene therapy, regenerative medicine and drug repurposing. (Surralles Calonge, Jordi).
- Mechanism of genomic instability and predisposition to cancer. Study of DNA repair mechanism and biological and clinical consequences of DNA repair failure. (Bogliolo, Massimo).
- Fanconi/BRCA pathway in cancer. Implications of Fanconi genes in cancer and their use as therapeutic target against cancer. Development of DNA repair inhibitor against cancer by synthetic lethality. (Surralles Calonge, Jordi).
- Application of next generation sequencing, genome medicine and genome editing to better identify pathogenic mutations and perform functional studies of variants of known significance in rare diseases. (Muñoz Pujol, Gerard).

## SCIENTIFIC CHALLENGES

- Optimisation of our drug candidate to inhibit the FA pathway as a novel anticancer therapy based on cancer-specific synthetic lethality.
- Follow-up of functional assays to classify variants of unknown significance in cancer-predisposing genes.
- As we signed a collaboration agreement with US-based Rocket Pharma Ltd for 10 10-year follow-up of FA patients undergoing gene therapy, we will continue to do so.
- Running of the AFAN clinical trial for the repurposing of afatinib to treat Fanconi anemia patients with advanced head-and-neck cancer.
- Performing a drug screening to find drugs reactivating the Fanconi pathway in cells expressing a FANCA mutant protein.
- Develop and apply advanced genomic medicine tools and pipelines for detecting pathogenic mutations in genes associated with rare diseases.
- Validation of gene candidates identified in a genome-wide CRISPR-Cas screen to identify synthetic lethal and viable interactions with the Fanconi/BRCA pathway.

## ACTIVE & AWARDED GRANTS

- Mora Rodríguez, Angel. Ayudas para contratos predoctorales para la formación de doctores 2022. PRE2022-104819. Ministerio de Ciencia, Innovación y Universidades. Duration: 2024-2028. 111.758,00 €
- Surralles Calonge, Jordi. The Fanconi anemia/BRCA pathway:Genomic medicine and advanced therapies. (FABRAT). PID2021-122411OB-I00. Ministerio de Ciencia e Innovación. Duration: 2022-2025. 417.000,00 €
- Surralles Calonge, Jordi. Ayudas Programa Investigo 2022. 2022 INV-1 00048. Agència de Gestió d'Ajuts Universitaris i de Recerca AGAUR. Duration: 2022-2024. 66.217,84 €
- Surralles Calonge, Jordi. Reposicionamiento de afatinib para HNSCC en pacientes con anemia de Fanconi. ICI22/00076. Instituto de Investigación Carlos III (ISCIII). Duration: 2023-2026. 396.101,20 €
- Surralles Calonge, Jordi. Valorización y prueba de concepto de un inhibidor de la reparación del DNA por la via Fanconi/BRCA para el tratamiento del cáncer por letalidad sintética. PDC2022-133233-I00. Ministerio de Ciencia, Innovación y Universidades (MICIU). Duration: 2022-2024. 149.500,00 €
- Surralles Calonge, Jordi. Genomic medicine and rare diseases group. 2021 SGR 00835. Duration: 2022-2025. 40.000,00 €
- Surralles Calonge, Jordi. AFAN trial. Phase Ib/II study to investigate the safety and efficacy of Afatinib when administered as therapy in Fanconi anemia patients with unresectable and / or metastatic locoregionally advanced squamous cell carcinoma of the oral cavity, oropharynx or hypopharynx or larynx. (FARF) Fanconi Anemia Research Fund. Conv. FARF Research Grant Award (RGA) Program. Duration: 2023-2027. 296.303 €

- Surralles Calonge, Jordi. Genómica funcional: desarrollo e implementación de una plataforma para el estudio de casos de cáncer hereditario sin resolver (IMPaCT_VUSCan). PMP22/00064. Duration: 2023-2025. 352.479,05 €

## DOCTORAL THESES DEFENDED

- Cavero Moreno, Debora. DNA repair in cancer therapeutics: developing a specific inhibitor for tumors and targeted therapies to treat solid tumors in rare diseases. 18/10/2024. Universitat Autònoma de Barcelona. Supervisors: Surralles Calonge, Jordi; Minguillón Pedreño, Jordi. https://hdl.handle.net/10803/692827.

## SCIENTIFIC PRODUCTION

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