PanCanRisk

Personalised Bioinformatics For Global Cancer Susceptibility Identification & Clinical Management

Personalized bioinformatics for global cancer susceptibility identification and clinical management

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CRG Centre for Genomic Regulation

institutCurie Together, let's beat cancer.

Dexeus Salud de la mujer

EMBL

Fundación Pública Galega de Medicina Xenómica

ProteinLogic Pattern-based medicine

This project has received funding from the European Union's H2020 research and innovation programme under grant agreement No 635290

Hypothesis: Patients with common cancer types carry a convergence of rare variants in a reduced number of genes of cancer related pathways

Objectives

1/ Discovery and selection of *potential cancer predisposition genes and variants* in WGS and WES pan-cancer datasets (ICGC and TCGA) with powerful bioinformatics approaches

2/ To scale ***rare variant association studies to pan-cancer data*** of all tumour types, as part of the TCGA/ICGC and PCAWG studies, to identify cancer associated germline mutations

3/ To identify ***regulatory risk variants and eQTLs***, integrating germline and somatic mutations and phenotypes, and characterize the ***functionality of risk regulatory variants***

4/ To translate ***multi-gene targeted sequencing*** panels of cancer predisposition genes (cancer-risk genes), carrying variants of different levels of penetrance, to cohorts of patients for clinical diagnostic purposes

5/ To develop and evaluate ***biomarkers of cancer susceptibility and clinical course*** identified in the context of combination of genetic variants that accumulate in specific genes and pathways to provide high cancer risk

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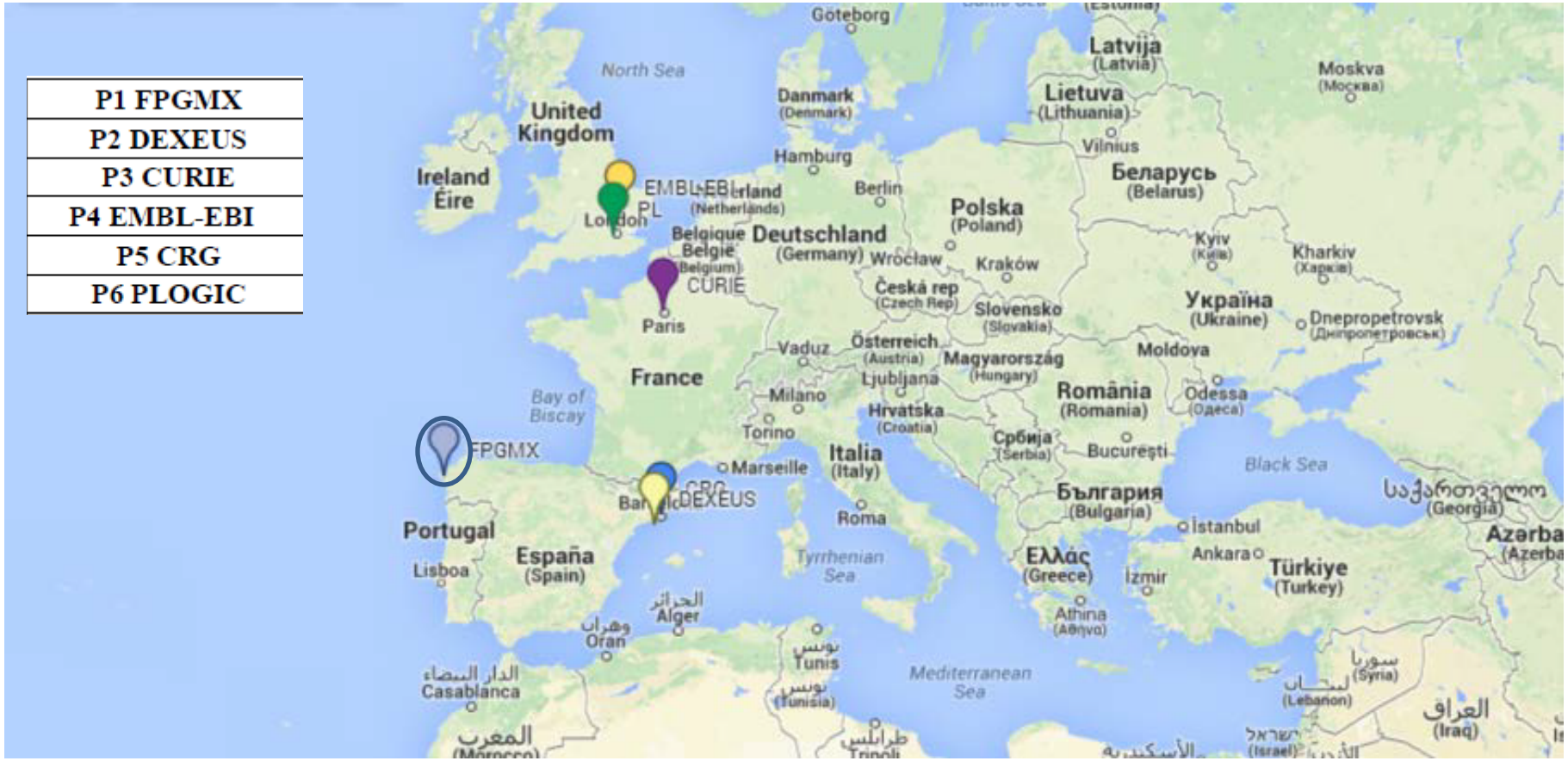
P1 FPGMX
P2 DEXEUS
P3 CURIE
P4 EMBL-EBI
P5 CRG
P6 PLOGIC



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WP1 - Development of a Computational Platform for Sequencing-Based Cancer Risk Analysis (Ossowski-CRG, Stegle-EBI)

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- Implementing a **distributed analysis platform** for the analysis of ICGC/TCGA whole-exome-sequencing cancer samples (eDiVA-Cancer)
- **Cloud-based implementation** of eDiVA-Cancer with secure restricted access and a highly intuitive user interface for use in clinics
- Generate **high-quality variant set** by Pan-cancer-cohort analysis
- Comprehensive **functional annotation** of germline variant set
- Identification of **somatic variants** to facilitate correlation analysis with germline variants
- **Improved methods** for identification of indels and CNV in WES data

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WP2- Tools for rare and common variant association analyses in cancer studies (Estivill-Ossowski, CRG)

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- Utilize large-scale cancer cohorts from PCAWG (WGS) and ICGC/TCGA (WES) to dramatically increase the power of sequencing based cancer risk association studies *(Stegle, Ossowski-participating in the development of bioinformatic tools for PCAWG)*
- Develop and test a flexible model for rare variant association analysis that incorporates variant-, gene- and patient-specific characteristics and population effects
- Utilize tissue-specific protein-interaction networks and expression data to group genes for rare variant association tests in order to improve statistical power and biological relevance of associations
- Identification of germline cancer risk variants for validation

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WP3-Identification of regulatory variants and eQTLs, integrating germline and somatic mutations (Stegle EBI-Ossowki CRG)

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- Derive methods to comprehensively map **regulatory variants**
- Combining evidence form
  - genotype-gene expression relationships (eQTLs)
  - epigenetic information, readouts and marks
- Innovation of new methods and analysis approaches

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WP4-Replication and Clinical Validation in cancer and non-cancer cohorts (Carracedo FPGMX, Abuli-Dexeus)

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1. ***Replication studies by multi-gene targeted sequencing and targeted genotyping*** of cancer predisposition genes and variants in breast and colorectal cancer and non-cancer cohorts.

2. ***Clinical validation of cancer predisposition genes and variants*** in breast and colorectal cancer-risk population cohorts that are screened for breast or colorectal cancer.

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Replication studies

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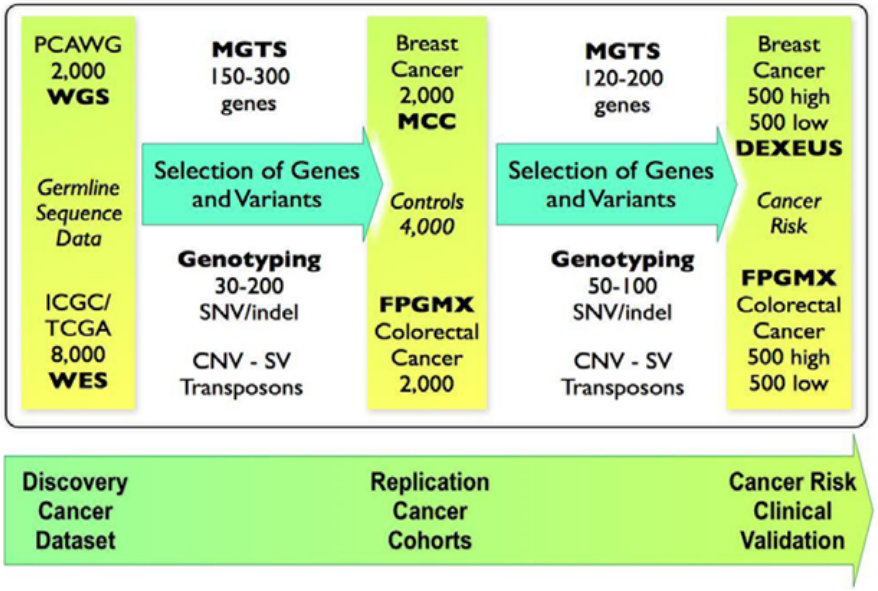
4,000 cancer patients
4,000 controls
Spanish Caucasian origin



FPGMX cancer cohort
1,000 BC patients
1,000 CRC patients
2,000 controls

MCC-SPAIN cohort
1,000 BC patients
1,000 CRC patients
2,000 controls

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Clinical Study: Design

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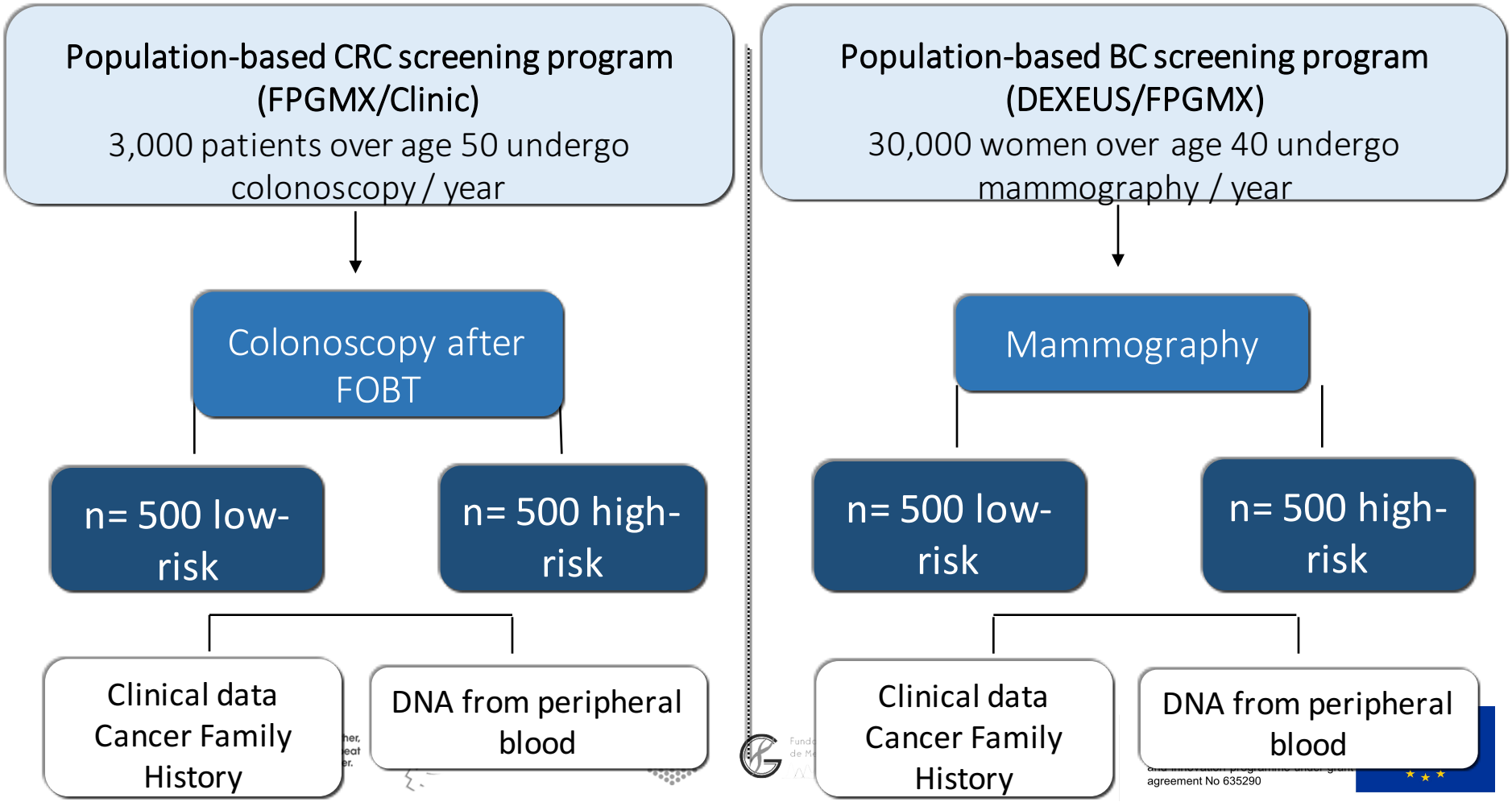
Recruitment: *Cancer risk clinical validation studies*



agreement No 635290

WP5 Functional study of identified risk genes and regulatory variants (Carreira-Curie)

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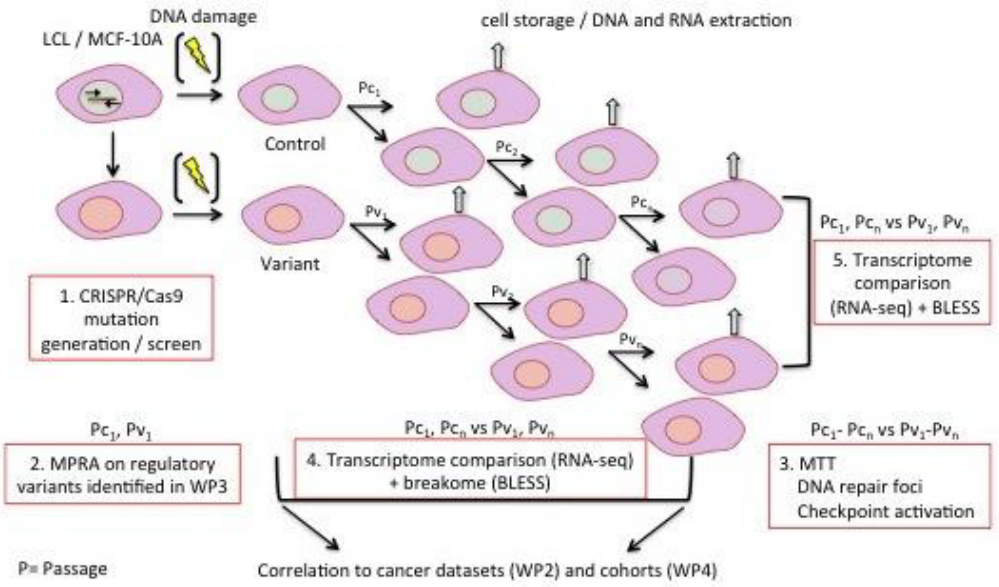
- Generation of knock-in cell clones carrying the variant of interest by genome editing (CRISPR/Cas9)
- Classify variants depending on their gene of origin to define the panel of specific tests to use
- Gene (and protein) expression profile and mutational signature



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