We have continued to decipher the genetic bases of hereditary and sporadic breast cancer. In addition, we participated in a project that combines the genotype and the phenotype in order to stratify and select women at high risk of developing breast cancer. Other families with rare tumours are also the object of our studies, for example, testicular cancer whose genetic bases are unknown. More recently, we started working on a study to elucidate the common genetic origin of different autoimmune-originated pathologies: gastric neuroendocrine tumours or chronic atrophic gastritis plus different immune diseases in other tissues, such as thyroiditis, diabetes or arthritis. We have identified several genes thereby opening up new avenues for new treatments. Finally, we have progressed in understanding the role of glycosylase genes as modifiers of hereditary breast cancer and their role along the cell cycle.

“We have discovered 3 new genes that confer susceptibility to testicular cancer and a moderate breast cancer susceptibility gene. A whole pathway with several genes associated to gastric neuroendocrine tumours or chronic atrophic gastritis plus several immune diseases, has been identified.”
Deciphering the role of rare variants in breast cancer

The European project BRIDGES, in which we participate, has 3 main phases. The first one was the study of 36 candidate genes in 60,000 breast cancer cases and controls in order to determine their role as possible moderate susceptibility genes. The second phase, which is currently performing a screening in a large number of patients carrying these variants, will involve whole exome sequencing we identified several candidate genes, 3 of them (PLEC, EX05 and DNAH5) were validated in a large case-control association study (Paumand et al., 2018). We then continued the study with more cases and separated 2 main histologic groups, seminomias and sporadic cases, which will be analyzed in another study. Several gastrointestinal pathologists, pathologists and endocrinologists are collaborating in this project.

During the past few years, we have been collecting families with testicular cancer and also sporadic tumours. We conducted a first study in 17 families with over 71 members and by whole exome sequencing we identified several candidate genes, 3 of whom (PLEC, EX05 and DNAH5) were validated in a large case-control association study (Paumand et al., 2018). We then continued the study with more cases and separated 2 main histologic groups, seminomias and sporadic cases, as well as seminomas from non-seminomias. We then continued the study in depth and discovered a biomarker that differentiated familial, bilateral and sporadic cases, as well as seminomas from non-seminomias.

Breast cancer susceptibility genes

In a whole-exome sequencing study of 4 BRCA families we identified a mutation in the moderate susceptibility gene ATM as being responsible for the disease in one of the families (Tavera-Tapia et al., 2017). In a second family, we found a deleterious mutation in an excellent candidate gene RCQ4LS that belongs to a family of DNA helicases that have a role in the Homologous Recombination (HR) DNA repair pathway. Using a combination of targeted next-generation sequencing and functional assays, we identified 7 deleterious or likely deleterious mutations in the gene in a series of 700 BRCA cases and only 1 deleterious mutation in 700 controls, suggesting that the gene could actually explain a small percentage of the BRCA families (Tavera-Tapia et al., submitted).

SNPs and the BER pathway

We investigated the molecular basis underlying the effect of an SNP in the glycosylase UNG as an ovarian cancer risk modifier in BRCA2 mutation carriers (Baquero et al., submitted). Our results suggest that an SNP rs14209 is associated with significant UNG down-regulation and a better performance of the enzyme, measured by a lower accumulation of uracil at the telomeres in BRCA2 mutation carriers. Our findings could help to explain the association of this variant with a lower cancer risk in BRCA2 mutation carriers. In addition, we want to study the role of this and 2 other glycosylases previously studied, OGG1 and NEIL2, across the cell cycle.

Familial cancer exome project

In 2015, we identified a gene responsible for families with cardiac tumours (POT1) (Calvete et al., 2015). Recently, we described its relation not only to cardiac tumours but also to other types of different tumours (Calvete et al., 2016). We investigated if the malignancy of this gene involves not only abnormal telomere length but also to generate different tumour types in different individuals in a similar way as P13. We analysed the somatic changes in several cardiac tumours with and without POT1 mutations and have concluded that the inhibition of POT1 gene function, and the damage-response mechanism, would activate ATR-dependent DNA damage signalling, which would trigger cell cycle arrest in asymptomatic tissues and might interfere the apoptosis mechanism, this would permit the further acquisition of somatic mutations in the VEGF/angiogenesis pathway (POT1 deregulation) and other angiosarcomas (mutations in damage-signalling), which drives tumour formation. The same observation was made in sporadic cardiac lesions (Calvete et al., submitted).

In 2015, we published the identification of the AT44 gene as being responsible for families with gastric neuroendocrine tumours (Calvete et al., 2015). In 2017, we extended this study to a new family that presented the same lesion along with hypothyroidism and arthritis. The family presented 2 mutations in BRCA1 (one digenic model (Calvete et al., 2017). We further explored the apparent relation of gastric autoimmune disease (gastric neuroendocrine tumour or chronic atrophic gastritis) plus a second immune disease; we found several mutations in new candidates involved in homeostasis and genetic function (solute carriers) altering AT44 function. We have designed a panel of 15 genes from this pathway and we are currently performing a screening in a large number of patients carrying these variants. Several gastrointestinal pathologists, pathologists and endocrinologists are collaborating in this project.

During the past few years, we have been collecting families with testicular cancer and also sporadic tumours. We conducted a first study in 17 families with over 71 members and by whole exome sequencing we identified several candidate genes, 3 of whom (PLEC, EX05 and DNAH5) were validated in a large case-control association study (Paumand et al., 2018). We then continued the study with more cases and separated 2 main histologic groups, seminomias and non-semimomas. We differentiated several altered pathways and the spermatogenesis pathway was significantly altered. We studied this pathway in depth and discovered a biomarker that differentiated familial, bilateral and sporadic cases, as well as seminomas from non-seminomias.