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We are interested in DNA repair and its link to tumorigenesis.

In particular, we study BRCA2, a tumor suppressor involved in DNA repair by Homologous Recombination. Mutations in this gene cause susceptibility to breast and ovarian cancer.

Homologous Recombination

In humans, the central player of the HR process is RAD51; it catalyzes the homology search in the intact copy of the sister chromatid and the strand exchange required to repair the DNA lesion. Through its interaction with RAD51, BRCA2 controls RAD51 function by locating it to the DSB (**Figure 1**). Thus, defects in BRCA2 lead to genomic instability, a hallmark of tumorigenesis.

Figure 1: Our current model for the role of BRCA2 in homologous recombination

We use biochemical, cell biology and recently also genomic and proteomics approaches to understand BRCA2's function in HR and other pathways. Our approach consists on searching for new BRCA2 protein partners and studying the phenotype of BRCA2 mutations identified in breast cancer patients to elucidate the mechanisms that contribute to tumorigenesis in a *BRCA2* or HR defective background.

The main projects of the lab include:

1) Identifying new functional domains of BRCA2: BRCA2 comprises 3,418 aa. This protein is known to interact with several partners such as RAD51 or PALB2 however; there are a priori "unstructured" regions of the protein that are mostly unexplored. We have used a proteomic approach to identify novel interacting partners of the unstructured part of the protein, the N-terminal region, enriched under DNA damage. This strategy can reveal functions in other RH related processes such as cell cycle regulation, chromatin remodeling, etc.

Importantly, these interactions may be used as targets to develop new anticancer therapy tools, which we also plan to exploit.

We have recently revealed a second DNA binding site in BRCA2 that promotes the recombination activity of RAD51 (**Figure 2**). This study opens new questions about the interplay of the two DNA binding domains in cells.

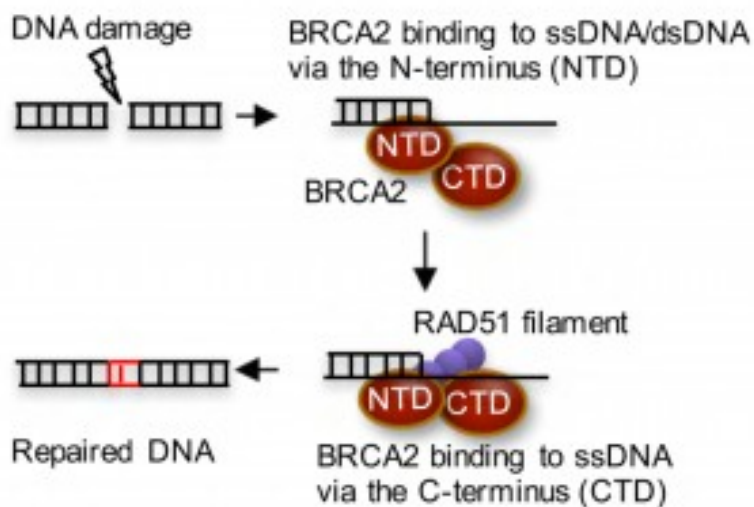


Figure 2. Working model for the role of the N-terminal DNA binding domain of BRCA2 (NTD).

2) Functional characterization of BRCA2 missense variants identified in breast cancer patients. Using an interdisciplinary and systematic approach our goal is to accurately evaluate the impact of variant of missense variants of unknown clinical significance (VUS) on BRCA2 function and to determine their clinical relevance for the benefit of patients. For example, in a collaborative work, we have identified BRCA2 hypomorphic mutations that confer moderate risk of breast cancer. In turn, studying the phenotype of these variants will also serve to find new functions of BRCA2 protein (objective 1).

3) BRCA2 haploinsufficiency and cancer predisposition

Inactivating germline monoallelic mutations in the BRCA2 gene are associated with an increase risk in breast cancer. However, the precise link between BRCA2 mutation and tumorigenesis remains elusive. We are trying to address this question using functional genomics.

Thus, we expect to contribute to identify the genetic signature(s) that predispose to tumour formation in a BRCA2-mutation context.

In addition, as part of the [PanCanRisk consortium](#), we plan on using the same tools to uncover

variants predisposing to cancer in other genes and regulatory regions.

Key publications

Year of publication 2017

Hermela Shimelis, Romy L S Mesman, Catharina Von Nicolai, Asa Ehlen, Lucia Guidugli, Charlotte Martin, Fabienne Mgr Calleja, Huong Meeks, Emily Hallberg, Jamie Hinton, Jenna Lilyquist, Chunling Hu, Cora M Aalfs, Kristiina Aittomaki, Irene L Andrulis, Hoda Anton-Culver, Volker Arndt, Matthias W Beckmann, Javier J Benitez, Natalia Bogdanova, Stig E Bojesen, Manjeet K Bolla, Anne-Lise Borresen-Dale, Hiltrud Brauch, Paul Brennan, Hermann Brenner, Annegien Broeks, Barbara Brouwers, Thomas Bruning, Barbara Burwinkel, Jenny Chang-Claude, Georgia Chenevix-Trench, Ching-Yu Cheng, Ji-Yeob Choi, J Margriet Collée, Angela Cox, Simon S Cross, Kamila Czene, Hatef Darabi, Joe Dennis, Thilo Dork, Isabel Dos Santos Silva, Alison M Dunning, Peter A Fasching, Jonine D Figueroa, Henrik Flyger, Montserrat Garcia-Closas, Graham G Giles, Gord Glendon, Pascal Guenel, Christopher A Haiman, Per Hall, Ute Hamann, Mikael Hartman, Frans B L Hogervorst, Antoinette Hollestelle, John L Hopper, Hidemi Ito, Anna Jakubowska, Daehee Kang, Veli-Matti Kosma, Vessela Kristensen, Kah-Nyin Lai, Diether Lambrechts, Loic Le Marchand, Jingmei Li, Annika Lindblom, Artitaya Lophatananon, Jan Lubinski, Eva Machackova, Arto Mannermaa, Sara Margolin, Frederik Marme, Keitaro Matsuo, Hui Miao, Kyriaki Michailidou, Roger L Milne, Kenneth Muir, Susan L Neuhausen, Heli Nevanlinna, Janet E Olson, Curtis Olswold, Jan C Oosterwijk, Ana Osorio, Paolo Peterlongo, Julian Peto, Paul D P Pharoah, Katri Pylkäs, Paolo Radice, Muhammad U Rashid, Valerie Rhenius, Anja Rudolph, Suleeporn Sangrajrang, Elinor J Sawyer, Marjanka K Schmidt, Minouk J Schoemaker, Caroline M Seynaeve, Mitul Shah, Chen-Yang Shen, Martha J Shrubsole, Xiao-Ou Shu, Susan L Slager, Melissa C Southey, Daniel O Stram, Anthony J Swerdlow, Soo Hwang Teo, Ian Tomlinson, Diana Torres, Therese Truong, Christi J van Asperen, Lizet E van der Kolk, Qin Wang, Robert Winqvist, Anna H Wu, Jyh-Cherng Yu, Wei Zheng, Ying Zheng, Jennifer Leary, Logan C Walker, Lenka Foretova, Florentia Fostira, Kathleen Claes, Liliana Varesco, Setareh Moghadasi, Douglas F Easton, Amanda B Spurdle, Peter Devilee, Harry Vrieling, Alvaro N Monteiro, David E Goldgar, Aura Carreira, Maaïke P G Vreeswijk, Fergus J Couch (2017 Jun 1)

BRCA2 hypomorphic missense variants confer moderate risks of breast cancer.

Cancer research : [DOI : 10.1158/0008-5472.CAN-16-2568](https://doi.org/10.1158/0008-5472.CAN-16-2568)

Year of publication 2016

Catharina von Nicolai, Åsa Ehlén, Charlotte Martin, Xiaodong Zhang, Aura Carreira (2016 Sep 15)

A second DNA binding site in human BRCA2 promotes homologous recombination.

Nature communications : 12813 : [DOI : 10.1038/ncomms12813](https://doi.org/10.1038/ncomms12813)

Juan S Martinez, Catharina von Nicolai, Taeho Kim, Åsa Ehlén, Alexander V Mazin, Stephen C Kowalczykowski, Aura Carreira (2016 Mar 29)

BRCA2 regulates DMC1-mediated recombination through the BRC repeats.

Proceedings of the National Academy of Sciences of the United States of America : 3515-20 : [DOI : 10.1073/pnas.1601691113](https://doi.org/10.1073/pnas.1601691113)

Year of publication 2015

Juan S Martinez, Céline Baldeyron, Aura Carreira (2015 Nov 13)

Molding BRCA2 function through its interacting partners.

Cell cycle (Georgetown, Tex.) : 3389-95 : [DOI : 10.1080/15384101.2015.1093702](https://doi.org/10.1080/15384101.2015.1093702)

Year of publication 2014

Martin Dutertre, Sarah Lambert, Aura Carreira, Mounira Amor-Guéret, Stéphan Vagner (2014 Mar 1)

DNA damage: RNA-binding proteins protect from near and far.

Trends in biochemical sciences : 141-9 : [DOI : 10.1016/j.tibs.2014.01.003](https://doi.org/10.1016/j.tibs.2014.01.003)

Lucia Guidugli, Aura Carreira, Sandrine M Caputo, Asa Ehlen, Alvaro Galli, Alvaro N A Monteiro, Susan L Neuhausen, Thomas V O Hansen, Fergus J Couch, Maaïke P G Vreeswijk, (2014 Feb 1)

Functional assays for analysis of variants of uncertain significance in BRCA2.

Human mutation : 151-64 : [DOI : 10.1002/humu.22478](https://doi.org/10.1002/humu.22478)