

Year of publication 2019

F Coussy, L de Koning, M Lavigne, V Bernard, B Ouine, A Boulai, R El Botty, A Dahmani, E Montaudon, F Assayag, L Morisset, L Huguet, L Sourd, P Painsec, C Callens, S Chateau-Joubert, J-L Servely, T Larcher, C Reyes, E Girard, G Pierron, C Laurent, S Vacher, S Baulande, S Melaabi, A Vincent Salomon, D Gentien, V Dieras, I Bieche, E Marangoni (2019 Mar 13)

A large collection of integrated genomically characterized patient-derived xenografts highlighting the heterogeneity of triple-negative breast cancer.

International journal of cancer : [DOI : 10.1002/ijc.32266](https://doi.org/10.1002/ijc.32266)

Summary

Triple-negative breast cancer (TNBC) represents 10% of all breast cancers and is a very heterogeneous disease. Globally, women with TNBC have a poor prognosis, and the development of effective targeted therapies remains a real challenge. Patient-Derived Xenografts (PDX) are clinically relevant models that have emerged as important tools for the analysis of drug activity and predictive biomarker discovery. The purpose of this work was to analyze the molecular heterogeneity of a large panel of TNBC PDX (n=61) in order to test targeted therapies and identify biomarkers of response. At the gene expression level, TNBC PDX represent all of the various TNBC subtypes identified by the Lehmann classification except for immunomodulatory subtype, which is underrepresented in PDX. NGS and copy number data showed a similar diversity of SMGs (Significantly Mutated Gene) and SCNAs (Somatic Copy Number Alteration) in PDX and TCGA TNBC patients. The genes most commonly altered were TP53 and oncogenes and tumor suppressors of the PI3K/AKT/mTOR and MAPK pathways. PDX showed similar morphology and immunohistochemistry markers to those of the original tumors. Efficacy experiments with PI3K and MAPK inhibitor monotherapy or combination therapy showed an antitumor activity in PDX carrying genomic mutations of PIK3CA and NRAS genes. TNBC PDX reproduce the molecular heterogeneity of TNBC patients. This large collection of PDX is a clinically relevant platform for drug testing, biomarker discovery and translational research. **KEYS WORD:** Triple-negative breast cancer, targeted therapies, patient-derived xenograft (PDX), integrated genomic analysis. This article is protected by copyright. All rights reserved.

Maud Blanluet, Julien Masliah-Planchon, Irina Giurgea, Franck Bielle, Elodie Girard, Mamy Andrianteranagna, Stéphane Clemenceau, Christine Bourneix, Lydie Burglen, Diane Doummar, Audrey Rapinat, Badreddine Mohand Oumoussa, Olivier Ayrault, Celio Pouponnot, David Gentien, Gaëlle Pierron, Olivier Delattre, François Doz, Franck Bourdeaut (2019 Mar 9)

SHH medulloblastoma in a young adult with a TCF4 germline pathogenic variation.

Acta neuropathologica : [DOI : 10.1007/s00401-019-01983-4](https://doi.org/10.1007/s00401-019-01983-4)

Summary

Laura Duciél, Océane Anezo, Kalpana Mandal, Cécile Laurent, Nathalie Planque, Frédéric M Coquelle, David Gentien, Jean-Baptiste Manneville, Simon Saule (2019 Mar 1)

Protein tyrosine phosphatase 4A3 (PTP4A3/PRL-3) promotes the aggressiveness of human uveal melanoma through dephosphorylation of CRMP2.

Scientific reports : 2990 : [DOI : 10.1038/s41598-019-39643-y](https://doi.org/10.1038/s41598-019-39643-y)

Summary

Uveal melanoma (UM) is an aggressive tumor in which approximately 50% of patients develop metastasis. Expression of the PTP4A3 gene, encoding a phosphatase, is predictive of poor patient survival. PTP4A3 expression in UM cells increases their migration in vitro and invasiveness in vivo. Here, we show that CRMP2 is mostly dephosphorylated on T514 in PTP4A3 expressing cells. We also demonstrate that inhibition of CRMP2 expression in UM cells expressing PTP4A3 increases their migration in vitro and invasiveness in vivo. This phenotype is accompanied by modifications of the actin microfilament network, with shortened filaments, whereas cells with a inactive mutant of the phosphatase do not show the same behavior. In addition, we showed that the cell cytoplasm becomes stiffer when CRMP2 is downregulated or PTP4A3 is expressed. Our results suggest that PTP4A3 acts upstream of CRMP2 in UM cells to enhance their migration and invasiveness and that a low level of CRMP2 in tumors is predictive of poor patient survival.

Year of publication 2018

Virginie Maire, Faisal Mahmood, Guillem Rigaiell, Mengliang Ye, Amélie Brisson, Fariba Némati, David Gentien, Gordon C Tucker, Sergio Roman-Roman, Thierry Dubois (2018 Dec 22)

LRP8 is overexpressed in estrogen-negative breast cancers and a potential target for these tumors.

Cancer medicine : 325-336 : [DOI : 10.1002/cam4.1923](https://doi.org/10.1002/cam4.1923)

Summary

Triple-negative breast cancer (TNBC) is the breast cancer subtype with the worst prognosis. New treatments improving the survival of TNBC patients are, therefore, urgently required. We performed a transcriptome microarray analysis to identify new treatment targets for TNBC. We found that low-density lipoprotein receptor-related protein 8 (LRP8) was more strongly expressed in estrogen receptor-negative breast tumors, including TNBCs and those overexpressing HER2, than in luminal breast tumors and normal breast tissues. LRP8 depletion decreased cell proliferation more efficiently in estrogen receptor-negative breast cancer cell lines: TNBC and HER2 overexpressing cell lines. We next focused on TNBC cells for which targeted therapies are not available. LRP8 depletion induced an arrest of the cell cycle progression in G1 phase and programmed cell death. We also found that LRP8 is required for anchorage-independent growth in vitro, and that its depletion in vivo slowed tumor growth in a xenograft model. Our findings suggest that new approaches targeting LRP8 may constitute promising treatments for hormone-negative breast cancers, those overexpressing HER2 and TNBCs.

Houda Benhelli-Mokrani, Zeyni Mansuroglu, Alban Chauderlier, Benoit Albaud, David Gentien, Sabrina Sommer, Claire Schirmer, Lucie Laqueuvre, Thibaut Josse, Luc Buée, Bruno Lefebvre, Marie-Christine Galas, Sylvie Souès, Eliette Bonnefoy (2018 Oct 16)

Genome-wide identification of genic and intergenic neuronal DNA regions bound by Tau protein under physiological and stress conditions.

Nucleic acids research : [DOI : 10.1093/nar/gky929](https://doi.org/10.1093/nar/gky929)

Summary

Tauopathies such as Alzheimer's Disease (AD) are neurodegenerative disorders for which there is presently no cure. They are named after the abnormal oligomerization/aggregation of the neuronal microtubule-associated Tau protein. Besides its role as a microtubule-associated protein, a DNA-binding capacity and a nuclear localization for Tau protein has been described in neurons. While questioning the potential role of Tau-DNA binding in the development of tauopathies, we have carried out a large-scale analysis of the interaction of Tau protein with the neuronal genome under physiological and heat stress conditions using the ChIP-on-chip technique that combines Chromatin ImmunoPrecipitation (ChIP) with DNA microarray (chip). Our findings show that Tau protein specifically interacts with genic and intergenic DNA sequences of primary culture of neurons with a preference for DNA regions positioned beyond the ± 5000 bp range from transcription start site. An AG-rich DNA motif was found recurrently present within Tau-interacting regions and 30% of Tau-interacting regions overlapped DNA sequences coding for lncRNAs. Neurological processes affected in AD were enriched among Tau-interacting regions with *in vivo* gene expression assays being indicative of a transcriptional repressor role for Tau protein, which was exacerbated in neurons displaying nuclear pathological oligomerized forms of Tau protein.

P Cottu, V D'Hondt, S Dureau, F Lerebours, I Desmoulins, P-E Heudel, F P Duhoux, C Levy, M-A Mouret-Reynier, F Dalenc, J-S Frenel, C Jouannaud, L Venat-Bouvet, S Nguyen, J-M Ferrero, J-L Canon, J Grenier, C Callens, D Gentien, J Lemonnier, A Vincent-Salomon, S Delalogue (2018 Oct 12)

Letrozole and palbociclib versus chemotherapy as neoadjuvant therapy of high-risk luminal breast cancer.

Annals of oncology : official journal of the European Society for Medical Oncology : [DOI : 10.1093/annonc/mdy448](https://doi.org/10.1093/annonc/mdy448)

Summary

Palbociclib is a CDK4/6 inhibitor with demonstrated efficacy and safety in combination with endocrine therapy in advanced luminal breast cancer (LBC). We evaluated the respective efficacy and safety of chemotherapy and letrozole-palbociclib (LETPAL) combination as neoadjuvant treatment in patients with high-risk LBC.

Camille Tlemsani, Eric Pasmant, Pascaline Boudou-Rouquette, Audrey Bellesoeur, Julien Even,

Frédérique Larousserie, Cécile Reyes, David Gentien, Jérôme Alexandre, Michel Vidaud, Philippe Anract, Karen Leroy, François Goldwasser (2018 Jul 26)

BRCA2 Loss-of-Function and High Sensitivity to Cisplatin-Based Chemotherapy in a Patient With a Pleomorphic Soft Tissue Sarcoma: Effect of Genomic Medicine.

The American journal of the medical sciences : [DOI : S0002-9629\(18\)30174-5](https://doi.org/10.1002-9629(18)30174-5)

Summary

We report the case of a patient with a BRCA2 germline mutation who developed a localized pleomorphic soft tissue sarcoma of the leg with poor prognostic features. BRCA2 germline mutations were not previously reported to be associated with pleomorphic sarcoma. BRCA2 loss-of-heterozygosity was found in the tumor, resulting in a complete BRCA2 loss-of-function. BRCA2 deficiency is associated with sensitivity to cisplatin-based chemotherapy in breast and ovarian cancer patients. We used a cisplatin-based chemotherapy. A rapid major partial response was obtained, which allowed a curative and conservative surgical resection of the sarcoma followed by adjuvant irradiation. This case illustrates that sarcoma patients may present unexpected but targetable genetic abnormalities and that BRCA2 loss-of-function may be targetable in sarcoma as it is associated with enhanced sensitivity to cisplatin. Our observation emphasizes the input of genomic medicine in clinical practice, its importance for treatment decisions, and the overlap between constitutional and somatic genetics.

Sandrine Tury, Franck Assayag, Florian Bonin, Sophie Chateau-Joubert, Jean-Luc Servely, Sophie Vacher, Véronique Becette, Martial Caly, Audrey Rapinat, David Gentien, Pierre de la Grange, Anne Schnitzler, François Lallemand, Elisabetta Marangoni, Ivan Bièche, Céline Callens (2018 Jun 8)

The iron chelator deferasirox synergizes with chemotherapy to treat triple negative breast cancers.

The Journal of pathology : [DOI : 10.1002/path.5104](https://doi.org/10.1002/path.5104)

Summary

To ensure their high proliferation rate, tumor cells display an iron metabolic disorder with increased iron needs, making them more susceptible to iron deprivation. This vulnerability could be a therapeutic target. In breast cancers, the development of new therapeutic approaches is urgently needed for patients with triple negative tumors which frequently relapse after chemotherapy and suffer from a lack of targeted therapies. In this work, we demonstrated that deferasirox (DFX) synergizes with standard chemotherapeutic agents such as with doxorubicin, cisplatin and carboplatin to inhibit cell proliferation and induce apoptosis and autophagy in triple-negative breast cancer (TNBC) cell lines. Moreover, the combination of DFX with doxorubicin and cyclophosphamide delayed recurrences in breast cancer patient-derived xenografts without increasing the side-effects of chemotherapies alone or altering global iron storage of mice. Antitumor synergy of DFX and doxorubicin seems to involve down-regulation of the PI3K and NF-κB pathways. Iron deprivation in

combination with chemotherapy could thus help to improve the effectiveness of chemotherapy in TNBC patients without increasing toxicities. This article is protected by copyright. All rights reserved.

Sylvie Maubant, Tania Tahtouh, Amélie Brisson, Virginie Maire, Fariba Némati, Bruno Tesson, Mengliang Ye, Guillem Rigauill, Maité Noizet, Aurélie Dumont, David Gentien, Bérengère Marty-Prouvost, Leanne de Koning, Sardar Faisal Mahmood, Didier Decaudin, Francisco Cruzalegui, Gordon C Tucker, Sergio Roman-Roman, Thierry Dubois (2018 Jun 2)

LRP5 regulates the expression of STK40, a new potential target in triple-negative breast cancers.

Oncotarget : 22586-22604 : [DOI : 10.18632/oncotarget.25187](https://doi.org/10.18632/oncotarget.25187)

Summary

Triple-negative breast cancers (TNBCs) account for a large proportion of breast cancer deaths, due to the high rate of recurrence from residual, resistant tumor cells. New treatments are needed, to bypass chemoresistance and improve survival. The WNT pathway, which is activated in TNBCs, has been identified as an attractive pathway for treatment targeting. We analyzed expression of the WNT coreceptors LRP5 and LRP6 in human breast cancer samples. As previously described, LRP6 was overexpressed in TNBCs. However, we also showed, for the first time, that LRP5 was overexpressed in TNBCs too. The knockdown of LRP5 or LRP6 decreased tumorigenesis and , identifying both receptors as potential treatment targets in TNBC. The apoptotic effect of LRP5 knockdown was more robust than that of LRP6 depletion. We analyzed and compared the transcriptomes of cells depleted of LRP5 or LRP6, to identify genes specifically deregulated by LRP5 potentially implicated in cell death. We identified serine/threonine kinase 40 (STK40) as one of two genes specifically downregulated soon after LRP5 depletion. STK40 was found to be overexpressed in TNBCs, relative to other breast cancer subtypes, and in various other tumor types. STK40 depletion decreased cell viability and colony formation, and induced the apoptosis of TNBC cells. In addition, STK40 knockdown impaired growth in an anchorage-independent manner and slowed tumor growth . These findings identify the largely uncharacterized putative protein kinase STK40 as a novel candidate treatment target for TNBC.

Sarah Huet, Bruno Tesson, Jean-Philippe Jais, Andrew L Feldman, Laura Magnano, Emilie Thomas, Alexandra Traverse-Glehen, Benoit Albaud, Marjorie Carrère, Luc Xerri, Stephen M Ansell, Lucile Baseggio, Cécile Reyes, Karin Tarte, Sandrine Boyault, Corinne Haioun, Brian K Link, Pierre Feugier, Armando Lopez-Guillermo, Hervé Tilly, Pauline Brice, Sandrine Hayette, Fabrice Jardin, Fritz Offner, Pierre Sujobert, David Gentien, Alain Viari, Elias Campo, James R Cerhan, Gilles Salles (2018 Feb 25)

A gene-expression profiling score for prediction of outcome in patients with follicular lymphoma: a retrospective training and validation analysis in three international cohorts.

The Lancet. Oncology : [DOI : S1470-2045\(18\)30102-5](https://doi.org/10.1016/S1470-2045(18)30102-5)

Summary

Patients with follicular lymphoma have heterogeneous outcomes. Predictor models to distinguish, at diagnosis, between patients at high and low risk of progression are needed. The objective of this study was to use gene-expression profiling data to build and validate a predictive model of outcome for patients treated in the rituximab era.

Elisabetta Marangoni, Cécile Laurent, Florence Coussy, Rania El-Botty, Sophie Château-Joubert, Jean-Luc Servely, Ludmilla de Plater, Franck Assayag, Ahmed Dahmani, Elodie Montaudon, Fariba Nemati, Justine Fleury, Sophie Vacher, David Gentien, Audrey Rapinat, Pierre Foidart, Nor Eddine Sounni, Agnès Noel, Anne Vincent-Salomon, Marick Lae, Didier Decaudin, Sergio Roman-Roman, Ivan Bièche, Martine Piccart, Fabien Reyat (2018 Feb 22)

Capecitabine Efficacy Is Correlated with TYMP and RB1 Expression in PDX Established from Triple-Negative Breast Cancers.

Clinical cancer research : an official journal of the American Association for Cancer Research : 2605-2615 : [DOI : 10.1158/1078-0432.CCR-17-3490](https://doi.org/10.1158/1078-0432.CCR-17-3490)

Summary

Triple-negative breast cancer (TNBC) patients with residual disease after neoadjuvant chemotherapy have a poor outcome. We developed patient-derived xenografts (PDX) from residual tumors to identify efficient chemotherapies and predictive biomarkers in a context of resistance to anthracyclines- and taxanes-based treatments. PDX were established from residual tumors of primary breast cancer patients treated in neoadjuvant setting. TNBC PDX were treated by anthracyclines, taxanes, platins, and capecitabine. Predictive biomarkers were identified by transcriptomic and immunohistologic analysis. Downregulation of was performed by siRNA in a cell line established from a PDX. Residual TNBC PDX were characterized by a high tumor take, a short latency, and a poor prognosis of the corresponding patients. With the exception of BRCA1/2-mutated models, residual PDX were resistant to anthracyclines, taxanes, and platins. Capecitabine, the oral prodrug of 5-FU, was highly efficient in 60% of PDX, with two models showing complete responses. Prior treatment of a responder PDX with 5-FU increased expression of thymidylate synthase and decreased efficacy of capecitabine. Transcriptomic and IHC analyses of 32 TNBC PDX, including both residual tumors and treatment-naïve derived tumors, identified RB1 and TYMP proteins as predictive biomarkers for capecitabine response. Finally, knockdown in a cell line established from a capecitabine-responder PDX decreased sensitivity to 5-FU treatment. We identified capecitabine as efficient chemotherapy in TNBC PDX models established from residual disease and resistant to anthracyclines, taxanes, and platins. RB1 positivity and high expression of TYMP were significantly associated with capecitabine response. .

Year of publication 2017

Barbara Piasecka, Darragh Duffy, Alejandra Urrutia, H el ene Quach, Etienne Patin, C eline Posseme, Jacob Bergstedt, Bruno Charbit, Vincent Rouilly, Cameron R MacPherson, Milena Hasan, Benoit Albaud, David Gentien, Jacques Fellay, Matthew L Albert, Llu s Quintana-Murci, (2017 Dec 29)

Distinctive roles of age, sex, and genetics in shaping transcriptional variation of human immune responses to microbial challenges.

Proceedings of the National Academy of Sciences of the United States of America : E488-E497 :

DOI : [10.1073/pnas.1714765115](https://doi.org/10.1073/pnas.1714765115)

Summary

The contribution of host genetic and nongenetic factors to immunological differences in humans remains largely undefined. Here, we generated bacterial-, fungal-, and viral-induced immune transcriptional profiles in an age- and sex-balanced cohort of 1,000 healthy individuals and searched for the determinants of immune response variation. We found that age and sex affected the transcriptional response of most immune-related genes, with age effects being more stimulus-specific relative to sex effects, which were largely shared across conditions. Although specific cell populations mediated the effects of age and sex on gene expression, including CD8T cells for age and CD4T cells and monocytes for sex, we detected a direct effect of these intrinsic factors for the majority of immune genes. The mapping of expression quantitative trait loci (eQTLs) revealed that genetic factors had a stronger effect on immune gene regulation than age and sex, yet they affected a smaller number of genes. Importantly, we identified numerous genetic variants that manifested their regulatory effects exclusively on immune stimulation, including a-specific master regulator at the locus. These response eQTLs were enriched in disease-associated variants, particularly for autoimmune and inflammatory disorders, indicating that differences in disease risk may result from regulatory variants exerting their effects only in the presence of immune stress. Together, this study quantifies the respective effects of age, sex, genetics, and cellular heterogeneity on the interindividual variability of immune responses and constitutes a valuable resource for further exploration in the context of different infection risks or disease outcomes.

Jean-Philippe Jais, Thierry Jo Molina, Philippe Ruminy, David Gentien, Cecile Reyes, David W Scott, Lisa M Rimsza, Georges Wright, Randy D Gascoyne, Louis M Staudt, Corinne Haouin, Herve Tilly, Philippe Gaulard, Gilles A Salles, Fabrice Jardin, Karen Leroy (2017 Jul 7)

Reliable subtype classification of diffuse large B-Cell lymphoma samples from GELA LNH2003 trials using the Lymph2Cx gene expression assay.

Haematologica : DOI : [haematol.2017.166827](https://doi.org/10.1182/haematol.2017.166827)

Summary

Wilfrid Richer, Julien Masliah-Planchon, Nathalie Clement, Irene Jimenez, Laetitia Maillot, David

Gentien, Benoît Albaud, Walid Chemlali, Christine Galant, Frederique Larousserie, Pascaline Boudou-Rouquette, Amaury Leruste, Celine Chauvin, Zhi Yan Han, Jean-Michel Coindre, Pascale Varlet, Paul Freneaux, Dominique Ranchère-Vince, Olivier Delattre, Franck Bourdeaut (2017 Apr 22)

Embryonic signature distinguishes pediatric and adult rhabdoid tumors from other SMARCB1-deficient cancers.

Oncotarget : 34245-34257 : [DOI : 10.18632/oncotarget.15939](https://doi.org/10.18632/oncotarget.15939)

Summary

Extra-cranial rhabdoid tumors (RT) are highly aggressive malignancies of infancy, characterized by undifferentiated histological features and loss of SMARCB1 expression. The diagnosis is all the more challenging that other poorly differentiated cancers lose SMARCB1 expression, such as epithelioid sarcomas (ES), renal medullary carcinomas (RMC) or undifferentiated chordomas (UC). Moreover, late cases occurring in adults are now increasingly reported, raising the question of differential diagnoses and emphasizing nosological issues. To address this issue, we have analyzed the expression profiles of a training set of 32 SMARCB1-deficient tumors (SDT), with ascertained diagnosis of RT (n = 16, all < 5 years of age), ES (n = 8, all > 10 years of age), UC (n = 3) and RMC (n = 5). As compared with other SDT, RT are characterized by an embryonic signature, and up-regulation of key-actors of de novo DNA methylation processes. Using this signature, we then analysed the expression profiling of 37 SDT to infer the appropriate diagnosis. Thirteen adult onset tumors showed strong similarity with pediatric RT, in spite of older age; by exome sequencing, these tumors also showed genomic features indistinguishable from pediatric RT. In contrary, 8 tumors were reclassified within carcinoma, ES or UC categories, while the remaining could not be related to any of those entities. Our results demonstrate that embryonic signature is shared by all RT, whatever the age at diagnosis; they also illustrate that many adult-onset SDT of ambiguous histological diagnosis are clearly different from RT. Finally, our study paves the way for the routine use of expression-based signatures to give accurate diagnosis of SDT.

Sébastien Schaller, Dorothée Buttigieg, Alysson Alory, Arnaud Jacquier, Marc Barad, Mark Merchant, David Gentien, Pierre de la Grange, Georg Haase (2017 Mar 9)

Novel combinatorial screening identifies neurotrophic factors for selective classes of motor neurons.

Proceedings of the National Academy of Sciences of the United States of America : E2486-E2493 : [DOI : 10.1073/pnas.1615372114](https://doi.org/10.1073/pnas.1615372114)

Summary

Numerous neurotrophic factors promote the survival of developing motor neurons but their combinatorial actions remain poorly understood; to address this, we here screened 66 combinations of 12 neurotrophic factors on pure, highly viable, and standardized embryonic mouse motor neurons isolated by a unique FACS technique. We demonstrate potent, strictly

additive, survival effects of hepatocyte growth factor (HGF), ciliary neurotrophic factor (CNTF), and Artemin through specific activation of their receptor complexes in distinct subsets of lumbar motor neurons: HGF supports hindlimb motor neurons through c-Met; CNTF supports subsets of axial motor neurons through CNTFR α ; and Artemin acts as the first survival factor for parasympathetic preganglionic motor neurons through GFR α 3/Syndecan-3 activation. These data show that neurotrophic factors can selectively promote the survival of distinct classes of embryonic motor neurons. Similar studies on postnatal motor neurons may provide a conceptual framework for the combined therapeutic use of neurotrophic factors in degenerative motor neuron diseases such as amyotrophic lateral sclerosis, spinal muscular atrophy, and spinobulbar muscular atrophy.