

Année de publication : 2020

Jérôme Cros, Nathalie Théou-Anton, Valérie Gounant, Remy Nicolle, Cécile Reyes, Sarah Humez, Ségolène Hescot, Vincent Thomas de Montpréville, Serge Guyétant, Jean-Yves Scoazec, Alice Guyard, Louis de Mestier, Solenn Brosseau, Pierre Mordant, Yves Castier, David Gentien, Philippe Ruzsniowski, Gérard Zalcman, Anne Couvelard, Aurélie Cazes (2020 Feb 5)

Specific genomic alterations in high grade pulmonary neuroendocrine tumours with carcinoid morphology.

Neuroendocrinology : [DOI : 10.1159/000506292](https://doi.org/10.1159/000506292)

Résumé

High grade lung neuroendocrine tumours with carcinoid morphology have been recently reported; they may represent the thoracic counterparts of grade 3 digestive neuroendocrine tumours. We aimed to study their genetic landscape including analysis of tumoral heterogeneity.

Année de publication : 2019

Marina Pinskaya, Zohra Saci, Mélina Gallopin, Marc Gabriel, Ha Tn Nguyen, Virginie Firlej, Marc Descrimes, Audrey Rapinat, David Gentien, Alexandre de la Taille, Arturo Londoño-Vallejo, Yves Allory, Daniel Gautheret, Antonin Morillon (2019 Nov 17)

Reference-free transcriptome exploration reveals novel RNAs for prostate cancer diagnosis.

Life science alliance : [DOI : e201900449](https://doi.org/10.1126/life.201900449)

Résumé

The use of RNA-sequencing technologies held a promise of improved diagnostic tools based on comprehensive transcript sets. However, mining human transcriptome data for disease biomarkers in clinical specimens are restricted by the limited power of conventional reference-based protocols relying on unique and annotated transcripts. Here, we implemented a blind reference-free computational protocol, DE-kupl, to infer yet unreferenced RNA variations from total stranded RNA-sequencing datasets of tissue origin. As a bench test, this protocol was powered for detection of RNA subsequences embedded into putative long noncoding (lnc)RNAs expressed in prostate cancer. Through filtering of 1,179 candidates, we defined 21 lncRNAs that were further validated by NanoString for robust tumor-specific expression in 144 tissue specimens. Predictive modeling yielded a restricted probe panel enabling more than 90% of true-positive detections of cancer in an independent The Cancer Genome Atlas cohort. Remarkably, this clinical signature made of only nine unannotated lncRNAs largely outperformed PCA3, the only used prostate cancer lncRNA biomarker, in detection of high-risk tumors. This modular workflow is highly sensitive and can be applied to any pathology or clinical application.

A Moreira, J Masliah-Planchon, C Callens, S Vacher, C Lecerf, M Frelaut, E Borcoman, N Torossian, F Ricci, S Hescot, M P Sablin, P Tresca, D Loirat, S Melaabi, O Trabelsi-Grati, G Pierron, D Gentien, V Bernard, A Vincent Salomon, N Servant, I Bieche, C Le Tourneau, M Kamal (2019 Oct 9)

Efficacy of molecularly targeted agents given in the randomised trial SHIVA01 according to the ESMO Scale for Clinical Actionability of molecular Targets.

European journal of cancer (Oxford, England : 1990) : 202-209 : DOI : [S0959-8049\(19\)30499-X](https://doi.org/10.1016/j.ejca.2019.09.009)

Résumé

A randomised trial SHIVA01 compared the efficacy of matched molecularly targeted therapy outside their indications based on a prespecified treatment algorithm versus conventional chemotherapy in patients with metastatic solid tumours who had failed standard of care. No statistical difference was reported between the two groups in terms of progression-free survival (PFS), challenging treatment algorithm. The European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of molecular Targets (ESCAT) recently defined criteria to prioritise molecular alterations (MAs) to select anticancer drugs. We aimed to retrospectively evaluate the efficacy of matched molecularly targeted agents (MTAs) given in SHIVA01 according to ESCAT tiers.

Laurence Slembrouck, Lauren Darrigues, Cecile Laurent, Lorenza Mitterpergher, Leonie Jmj Delahaye, Isabelle Vanden Bempt, Sara Vander Borght, Liesbet Vliegen, Petra Sintubin, Virginie Raynal, Mylene Bohec, Cécile Reyes, Audrey Rapinat, Céline Helmoortel, Lynn Jongen, Griet Hoste, Patrick Neven, Hans Wildiers, Ann Smeets, Ines Nevelsteen, Kevin Punie, Els Van Nieuwenhuysen, Sileny Han, Anne Vincent Salomon, Enora Laas Faron, Timothé Cynober, David Gentien, Sylvain Baulande, Mireille Hj Snel, Anke T Witteveen, Sari Neijenhuis, Annuska M Glas, Fabien Reyat, Giuseppe Floris (2019 Sep 13)

Decentralization of Next-Generation RNA Sequencing-Based MammaPrint® and Blueprint® Kit at University Hospitals Leuven and Curie Institute Paris.

Translational oncology : 1557-1565 : DOI : [S1936-5233\(19\)30351-1](https://doi.org/10.1016/j.tron.2019.09.009)

Résumé

A previously developed and centrally validated MammaPrint® (MP) and Blueprint® (BP) targeted RNA next-generation sequencing (NGS) kit was implemented and validated in two large academic European hospitals. Additionally, breast cancer molecular subtypes by MP and BP RNA sequencing were compared with immunohistochemistry (IHC). Patients with early breast cancer diagnosed at University Hospitals Leuven and Curie Institute Paris were prospectively included between September 2017 and January 2018. Formalin-fixed paraffin-embedded tissue sections were analyzed with MP and BP NGS technology at the beta sites and with both NGS and microarray technology at Agendia. Raw NGS data generated on Illumina MiSeq instruments at the beta sites were interpreted and compared with NGS and microarray data at Agendia. MP and BP NGS molecular subtypes were compared to surrogate IHC breast cancer subtypes. Equivalence of MP and BP indices was determined by Pearson's correlation coefficient. Acceptable limits were defined a priori, based on microarray data

generated at Agendia between 2012 and 2016. The concordance, the Negative Percent Agreement and the Positive Percent Agreement were calculated based on the contingency tables and had to be equal to or higher than 90%. Out of 124 included samples, 48% were MP Low and 52% High Risk with microarray. Molecular subtypes were BP luminal, HER2 or basal in 82%, 8% and 10% respectively. Concordance between MP microarray at Agendia and MP NGS at the beta sites was 91.1%. Concordance of MP High and Low Risk classification between NGS at the beta sites and NGS at Agendia was 93.9%. Concordance of MP and BP molecular subtyping using NGS at the beta sites and microarray at Agendia was 89.5%. Concordance between MP and BP NGS subtyping, and IHC was 71.8% and 76.6%, for two IHC surrogate models. The MP/BP NGS kit was successfully validated in a decentralized setting.

Leanne de Koning, Didier Decaudin, Rania El Botty, André Nicolas, Guillaume Carita, Mathieu Schuller, Bérengère Ouine, Aurélie Cartier, Adnan Naguez, Justine Fleury, Vesselina Cooke, Andrew Wylie, Paul Smith, Elisabetta Marangoni, David Gentien, Didier Meseure, Pascale Mariani, Nathalie Cassoux, Sophie Piperno-Neumann, Sergio Roman-Roman, Fariba Némati (2019 Jun 1)
PARP Inhibition Increases the Response to Chemotherapy in Uveal Melanoma.
Cancers : [DOI : E751](https://doi.org/10.3390/cancers11060751)

Résumé

Uveal melanoma (UM) remains without effective therapy at the metastatic stage, which is associated with (BRCA1 associated protein) mutations. However, no data on DNA repair capacities in UM are available. Here, we use UM patient-derived xenografts (PDXs) to study the therapeutic activity of the PARP inhibitor olaparib, alone or in combination. First, we show that the expression and the activity of PARP proteins is similar between the PDXs and the corresponding patient's tumors. In vivo experiments in the PDX models showed that olaparib was not efficient alone, but significantly increased the efficacy of dacarbazine. Finally, using reverse phase protein arrays and immunohistochemistry, we identified proteins involved in DNA repair and apoptosis as potential biomarkers predicting response to the combination of olaparib and dacarbazine. We also observed a high increase of phosphorylated YAP and TAZ proteins after dacarbazine + olaparib treatment. Our results suggest that PARP inhibition in combination with the alkylating agent dacarbazine could be of clinical interest for UM treatment. We also observe an interesting effect of dacarbazine on the Hippo pathway, confirming the importance of this pathway in UM.

Joke G van Bommel, Rafael Galupa, Chris Gard, Nicolas Servant, Christel Picard, James Davies, Anthony James Szempruch, Yinxiu Zhan, Jan J Żylicz, Elphège P Nora, Sonia Lameiras, Elzo de Wit, David Gentien, Sylvain Baulande, Luca Giorgetti, Mitchell Guttman, Jim R Hughes, Douglas R Higgs, Joost Gribnau, Edith Heard (2019 May 29)
The bipartite TAD organization of the X-inactivation center ensures opposing developmental regulation of Tsix and Xist.
Nature genetics : [DOI : 10.1038/s41588-019-0412-0](https://doi.org/10.1038/s41588-019-0412-0)

Résumé

The mouse X-inactivation center (Xic) locus represents a powerful model for understanding the links between genome architecture and gene regulation, with the non-coding genes Xist and Tsix showing opposite developmental expression patterns while being organized as an overlapping sense/antisense unit. The Xic is organized into two topologically associating domains (TADs) but the role of this architecture in orchestrating cis-regulatory information remains elusive. To explore this, we generated genomic inversions that swap the Xist/Tsix transcriptional unit and place their promoters in each other's TAD. We found that this led to a switch in their expression dynamics: Xist became precociously and ectopically upregulated, both in male and female pluripotent cells, while Tsix expression aberrantly persisted during differentiation. The topological partitioning of the Xic is thus critical to ensure proper developmental timing of X inactivation. Our study illustrates how the genomic architecture of cis-regulatory landscapes can affect the regulation of mammalian developmental processes.

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)

Résumé

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)

Résumé

Laura Duciel, 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)

Résumé

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.

Année de publication : 2018

Virginie Maire, Faisal Mahmood, Guillem Rigai, 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)

Résumé

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)

Résumé

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)

Résumé

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)

Résumé

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)

Résumé

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- κ B 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 Rigai, Maïté 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)

Résumé

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.