

**Année de publication : 2021**

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Cong Trung Nguyen, Stefano Caruso, Pascale Maillé, Aurélie Beaufrère, Jeremy Augustin, Loetitia Favre, Anaïs Pujals, Camille Boulagnon-Rombi, Rami Rhaïem, Giuliana Amaddeo, Luca Di Tommaso, Alain Luciani, Hélène Regnault, Raffaele Brustia, Olivier Scatton, Frederic Charlotte, Isabelle Brocheriou, Daniele Sommacale, Patrick Soussan, Vincent Leroy, Alexis Laurent, Van Ky Le, Van To Ta, Hong Son Trinh, Thi Lan Tran, David Gentien, Audrey Rapinat, Jean-Charles Nault, Manon Allaire, Sébastien Mulé, Jessica Zucman-Rossi, Jean-Michel Pawlowsky, Christophe Tournigand, Fouad Lafdil, Valérie Paradis, Julien Calderaro (2021 Nov 17)

**Immune profiling of combined hepatocellular-cholangiocarcinoma reveals distinct subtypes and activation of gene signatures predictive of response to immunotherapy.**

*Clinical cancer research : an official journal of the American Association for Cancer Research :*

[DOI : clincanres.1219.2021](https://doi.org/10.1158/1078-0432.CCR.211111)

**Résumé**

Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a rare malignancy associated with an overall poor prognosis. We aimed to investigate the immune profile of cHCC-CCA and determine its impact on disease outcome. We performed a multicenter study of 96 patients with cHCC-CCA. Gene expression profile was analyzed using nCounter PanCancer IO 360 Panel. Densities of main immune cells subsets were quantified from digital slides of immunohistochemical stainings. Genetic alterations were investigated using targeted next generation sequencing. Two main immune subtypes of cHCC-CCA were identified by clustering analysis: an « Immune High » (IH) subtype (57% of the cases) and an « Immune Low » (IL) subtype (43% of the cases). Tumors classified as IH showed overexpression of genes related to immune cells recruitment, adaptive and innate immunity, antigen presentation, cytotoxicity, immune suppression, and inflammation ( $p < 0.0001$ ). IH cHCC-CCAs also displayed activation of gene signatures recently shown to be associated with response to immunotherapy in patients with HCC. Immunostainings confirmed that IH tumors were also characterized by higher densities of immune cells. Immune subtypes were not associated with any genetic alterations. Finally, multivariate analysis showed that the IH subtype was an independent predictor of improved overall survival. We have identified a subgroup of cHCC-CCA that displays features of an ongoing intra-tumor immune response, along with an activation of gene signatures predictive of response to immunotherapy in HCC. This tumor subclass is associated with an improved clinical outcome. These findings suggest that a subset of patients with cHCC-CCA may benefit from immunomodulating therapeutic approaches.

**Année de publication : 2020**

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Bogdan Badic, Stéphanie Durand, Flaria El Khoury, Pierre De La Grange, David Gentien, Brigitte Simon, Catherine Le Jossic-Corcos, Laurent Corcos (2020 Oct 12)

**Prognostic impact of cancer stem cell markers and in colorectal cancer.**

*American journal of translational research* : 5797-5807

**Résumé**

Colon cancer develops according to a defined temporal sequence of genetic and epigenetic molecular events that may primarily affect cancer stem cells. In an attempt to identify new markers of such cells that would help predict patient outcome, we performed a comparative transcriptome analysis of colon cancer stem cells and normal colon stem cells. We identified 162 mRNAs, either over- or under-expressed. According to Cox multivariate regression with our set of 83 colorectal cancers, low expression of , tumor size and the presence of distant metastases were predictive factors for overall survival. Combined expression of and was a significant predictor for overall survival in our cohort, which was confirmed by external validation in 221 colorectal cancers from the Cancer Genome Atlas (TCGA) portal. Tumor size, lymph node involvement and expression were also independently correlated with disease-free survival. Taken together, our results suggest that molecular markers of colorectal cancers and are prognostic factors in colorectal cancer patients. It can be proposed that surveying expression of these marker genes should help better characterizing CRC prognosis, and help selecting the best therapeutic options.

David Gentien, Laure Piqueret-Stephan, Emilie Henry, Benoît Albaud, Audrey Rapinat, Serge Koscielny, Jean-Yves Scoazec, Philippe Vielh (2020 Oct 4)

**Digital Multiplexed Gene Expression Analysis of mRNA and miRNA from Routinely Processed and Stained Cytological Smears: A Proof-of-Principle Study.**

*Acta cytologica* : 1-11 : [DOI : 10.1159/000510174](https://doi.org/10.1159/000510174)

**Résumé**

Although transcriptomic assessments of small samples using high-throughput techniques are usually performed on fresh or frozen tissues, there is a growing demand for those performed on stained cellular specimens already used for diagnostic purposes.

Elodie Montaudon, Joanna Nikitorowicz-Buniak, Laura Sourd, Ludivine Morisset, Rania El Botty, Léa Huguet, Ahmed Dahmani, Pierre Painsec, Fariba Nemati, Sophie Vacher, Walid Chemlali, Julien Masliah-Planchon, Sophie Château-Joubert, Camilla Rega, Mariana Ferreira Leal, Nikiana Simigdala, Sunil Pancholi, Ricardo Ribas, André Nicolas, Didier Meseure, Anne Vincent-Salomon, Cécile Reyes, Audrey Rapinat, David Gentien, Thibaut Larcher, Mylène Bohec, Sylvain Baulande, Virginie Bernard, Didier Decaudin, Florence Coussy, Muriel Le Romancer, Guillaume Dutertre, Zakia Tariq, Paul Cottu, Keltouma Driouch, Ivan Bièche, Lesley-Ann Martin, Elisabetta Marangoni (2020 Aug 15)

**PLK1 inhibition exhibits strong anti-tumoral activity in CCND1-driven breast**

**cancer metastases with acquired palbociclib resistance.**

*Nature communications* : 4053 : [DOI : 10.1038/s41467-020-17697-1](https://doi.org/10.1038/s41467-020-17697-1)

**Résumé**

A significant proportion of patients with oestrogen receptor (ER) positive breast cancers (BC) develop resistance to endocrine treatments (ET) and relapse with metastatic disease. Here we perform whole exome sequencing and gene expression analysis of matched primary breast tumours and bone metastasis-derived patient-derived xenografts (PDX). Transcriptomic analyses reveal enrichment of the G2/M checkpoint and up-regulation of Polo-like kinase 1 (PLK1) in PDX. PLK1 inhibition results in tumour shrinkage in highly proliferating CCND1-driven PDX, including different RB-positive PDX with acquired palbociclib resistance. Mechanistic studies in endocrine resistant cell lines, suggest an ER-independent function of PLK1 in regulating cell proliferation. Finally, in two independent clinical cohorts of ER positive BC, we find a strong association between high expression of PLK1 and a shorter metastases-free survival and poor response to anastrozole. In conclusion, our findings support clinical development of PLK1 inhibitors in patients with advanced CCND1-driven BC, including patients progressing on palbociclib treatment.

Coussy F, El-Botty R, Château-Joubert S, Dahmani A, Montaudon E, Leboucher S, Morisset L, Painsec P, Sourd L, Huguet L, Nemati F, Servely JL, Larcher T, Vacher S, Briaux A, Reyes C, La Rosa P, Lucotte G, Popova T, Foidart P, Sounni NE, Noel A, Decaudin D, Fuhrmann L, Salomon A, Reyat F, Mueller C, Ter Brugge P, Jonkers J, Poupon MF, Stern MH, Bièche I, Pommier Y, Marangoni E. (2020 Feb 19)

**BRCAness, SLFN11, and RB1 loss predict response to topoisomerase I inhibitors in triple-negative breast cancers**

*Science Translational Medicine* *Science Translational Medicine* : [DOI : 10.1126/scitranslmed.aax2625](https://doi.org/10.1126/scitranslmed.aax2625)

**Résumé**

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 Ruszniewski, Gérard Zalzman, 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

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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/10.1093/life/liaa049)

#### 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/10.1093/ejco/ezy304)

#### 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 Helsmoortel, 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/10.1186/s12936-019-30351-1)

#### **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](#)

### 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* : 51 : 1024-34 : [DOI : 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 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)

## 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 an 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

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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)

## 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



## Publications **Génomique**

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.