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Our goal is to identify genetic and epigenetic events involved in tumor progression and new therapeutic targets. We focus on two carcinomas, bladder and breast cancer, and on retinoblastoma, a pediatric cancer of the retina. We use bioinformatics, based on large-scale transcriptomic, genomic and sequencing data, to identify genes and pathways potentially involved in tumor progression. We then validate candidates experimentally in both cell lines and animal models (xenografts, transgenic mice and/or chemically induced mouse models). Although our work is primarily focused on the understanding of human cancers, the results obtained can be the basis of new treatments, new diagnostic and prognostic markers.

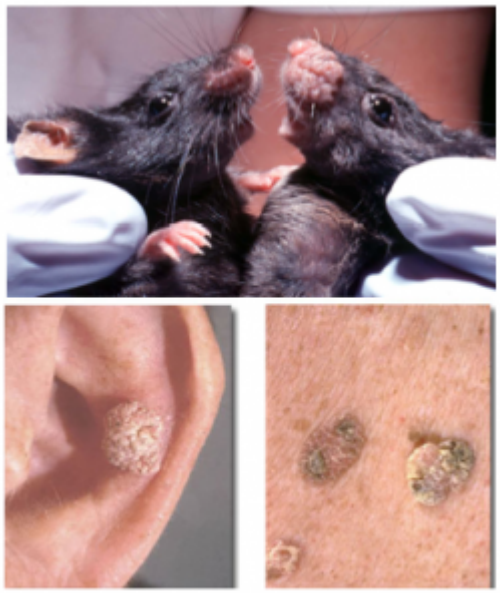

Figure 1: We generated a transgenic mouse model by targeting activated FGFR3 to the epidermis using the keratin 5 promoter. These mice develop severe hyperplasia and can be used to test inhibitors of signalling induced by activated FGFR3 in vivo. They have also been useful for the identification of causes underlying human disease; indeed, their resemblance to seborrheic keratoses has led to the identification of FGFR3 mutations in these frequent human benign skin lesions.

Our work on bladder cancer started many years ago and is based on a strong collaboration with different hospitals in France through a National multidisciplinary program (COBLAnCE project) coordinated by S. Benhamou (CEPH-INSERM). Uropathologists, coordinated by Y. Allory (Henri Mondor hospital), and urologists, coordinated by T. Lebret (Foch hospital), are involved in this program. Bladder cancer is the fifth most common cancer. The only treatment currently available for muscle invasive bladder carcinoma is cystectomy and, despite this treatment, it remains a deadly disease. The identification of new genes and/or signalling pathways involved in bladder tumor progression is therefore of major importance. We identified several kinases (FGFR3, TYRO3, P38a) involved in bladder cancer as well as in other tumour types. Their involvement has been confirmed by functional studies in cell lines and in various animal models. A program for leads identification targeting TYRO3 has been started in collaboration with chemists and structural biologists (Institut Curie, CNRS, INSERM). We identified *CDKN2A* loss as a key genetic event in the progression of *FGFR3*-mutated bladder cancer (which represent 50% of bladder cancer patients at first diagnosis). This finding led to the identification of *CDKN2A* loss as a prognostic marker in *FGFR3*-mutated bladder cancer patients (Rebouissou et al., 2012).

We recently identified and characterized different subgroups of muscle-invasive bladder tumors and identified therapeutic targets for these subgroups (EGFR, PPARG) which have been validated in preclinical models (Biton et al., 2014; Rebouissou et al., 2014).

We also identified a new epigenetic mechanism for gene inactivation, which involves the silencing of whole chromosomal regions by histone modification. Tumours which exhibit this phenotype are particularly sensitive to histone deacetylase inhibitors (Stransky et al., 2006; Vallot et al., 2011; 2014).

We have more recently begun work on breast cancer and retinoblastoma studies, in collaboration with clinicians and biologists. We identified several oncogenes in breast cancer including two new oncogenes, *PPAPDC1B* and *WHSC1L1*, which are overexpressed through amplification of the region 8p12. PPAPDC1B is a phosphatase, and thus could be a potential therapeutic target. These genes are likely to be involved in other cancer types like lung and pancreas (Bernard-Pierrot et al., 2008; Mahmood et al. 2013; 2014).

Key publications

Year of publication 2018

Tom Baladi, Jessy Aziz, Florent Dufour, Valentina Abet, Véronique Stoven, François Radvanyi, Florent Poyer, Ting-Di Wu, Jean-Luc Guerquin-Kern, Isabelle Bernard-Pierrot, Sergio Marco Garrido, Sandrine Piguel (2018 Nov 1)
Design, synthesis, biological evaluation and cellular imaging of imidazo[4,5-b]pyridine derivatives as potent and selective TAM inhibitors.
Bioorganic & medicinal chemistry : 26 : 5510-5530 : DOI : 10.1016/j.bmc.2018.09.031

Year of publication 2014

Sandra Rebouissou, Isabelle Bernard-Pierrot, Aurélien de Reyniès, May-Linda Lepage, Clémentine Krucker, Elodie Chapeaublanc, Aurélie Hérault, Aurélie Kamoun, Aurélie Caillault, Eric Letouzé, Nabila Elarouci, Yann Neuzillet, Yves Denoux, Vincent Molinié, Dimitri Vordos, Agnès Laplanche, Pascale Maillé, Pascale Soyeux, Karina Ofualuka, Fabien Reyal, Anne Biton, Mathilde Sibony, Xavier Paoletti, Jennifer Southgate, Simone Benhamou, Thierry Lebret, Yves Allory, François Radvanyi (2014 Jul 11)
EGFR as a potential therapeutic target for a subset of muscle-invasive bladder cancers presenting a basal-like phenotype.
Science translational medicine : 244ra91 : DOI : 10.1126/scitranslmed.3008970

Anne Biton, Isabelle Bernard-Pierrot, Yinjun Lou, Clémentine Krucker, Elodie Chapeaublanc, Carlota Rubio-Pérez, Nuria López-Bigas, Aurélie Kamoun, Yann Neuzillet, Pierre Gestraud, Luca Grieco, Sandra Rebouissou, Aurélien de Reyniès, Simone Benhamou, Thierry Lebret, Jennifer Southgate, Emmanuel Barillot, Yves Allory, Andrei Zinovyev, François Radvanyi (2014 Jan 25)
Independent component analysis uncovers the landscape of the bladder tumor transcriptome and reveals insights into luminal and basal subtypes.
Cell reports : 1235-45 : DOI : 10.1016/j.celrep.2014.10.035

Year of publication 2013

Ténin Traoré, Andrea Cavagnino, Nicolas Saettel, François Radvanyi, Sandrine Piguel, Isabelle Bernard-Pierrot, Véronique Stoven, Michel Legraverend (2013 Nov 19)
New aminopyrimidine derivatives as inhibitors of the TAM family.
European journal of medicinal chemistry : 789-801 : DOI : 10.1016/j.ejmech.2013.10.037

Year of publication 2012

Sardar F Mahmood, Nadège Gruel, Rémy Nicolle, Elodie Chapeaublanc, Olivier Delattre, François

Radvanyi, Isabelle Bernard-Pierrot (2012 Aug 13)
PPAPDC1B and WHSC1L1 are common drivers of the 8p11-12 amplicon, not only in breast tumors but also in pancreatic adenocarcinomas and lung tumors.
The American journal of pathology : 1634-44 : DOI : 10.1016/j.ajpath.2013.07.028

Year of publication 2011

Sandra Rebouissou, Aurélie Hérault, Eric Letouzé, Yann Neuzillet, Agnès Laplanche, Karina Ofualuka, Pascale Maillé, Karen Leroy, Audrey Riou, May-Linda Lepage, Dimitri Vordos, Alexandre de la Taille, Yves Denoux, Mathilde Sibony, Frédéric Guyon, Thierry Lebret, Simone Benhamou, Yves Allory, François Radvanyi (2011 Sep 30)
CDKN2A homozygous deletion is associated with muscle invasion in FGFR3-mutated urothelial bladder carcinoma.
The Journal of pathology : 315-24 : DOI : 10.1002/path.4017