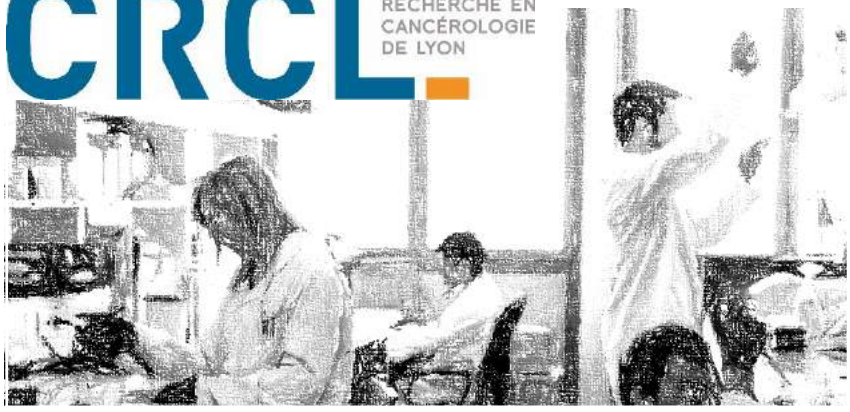
CRCL CENTRE DE RECHERCHE EN CANCÉROLOGIE DE LYON



CRCL Newsletter N°31

May – June, 2020

1st CRCL Retreat

As announced at the beginning of the year, there are still plans to organize the first CRCL retreat on the 16th thru 18th of September, 2020 in the Azureva holiday village at the Karellis resort, located in Maurienne.

This center retreat, which replaces the department retreats and the CRCL's scientific day, will allow for us to meet and exchange around science, discuss cross-cutting themes and to also share convivial moments together in order to get to know each other better, all in a remarkable setting!

The Organizing Committee, made up of team members and support services, is gradually refining the course of the3 days retreat and now offers you a provisional program full of surprises, which are sure to leave us with many memories!

Deadline for registrations postponed to July 14
https://forms.gle/MFkzYTxygmT8bnbm9

Thank for filling in the scientific animations form:
https://forms.gle/1Wkd98Lea3ZLMUJG9

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FOCUS ON

Presentation of the "Epigenetics, microenvironment and liver cancer" team, Dir. M. Levrero

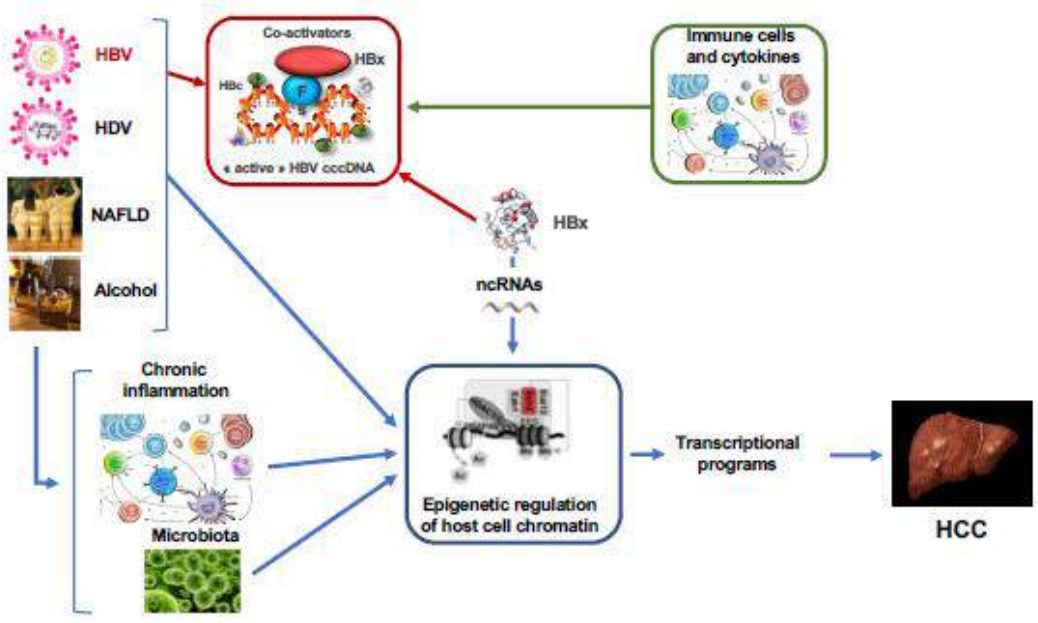
After joining the CRCL from Rome (La Sapienza University and the Italian Institute of Technology – ITT) Massimo Levrero, Prof. of Hepatology and Gastroenterology (PUPH UCBL/HCL), has started his research activity together with 1 PhD student (Océane Floriot) in March 2015 and created his own research team "Epigenetics and epigenomics of hepatocellular carcinomas [EpiHep]" in January 2016 to become more recently "Epigenetics, microenvironment and liver cancer [EpiLiCan]". The team is located in the Inserm Cours Albert Thomas (CAT) building.

Since 2016, the team has steadily increased its workforce by recruiting PhD students, postdocs and technical staff. In 2017, Dr. Marie-Laure Plissonnier has integrated the team as a research engineer (IR) and Dr. Mirjam Zeisel (CRCN Inserm) has joined the team from Strasbourg (Inserm U1110). In 2018, Dr. Francesca Guerrieri has joined the team first as visiting scientist and then as staff scientist. The composition of the team has further evolved in 2019 with the integration of Dr. Claude Caron de Fromentel (DR2 Inserm), Dr. Jean-Claude Cortay (CRCN Cnrs) and Prof. Philippe Merle (PUPH) from the CRCL team Chemin/Merle, as well as Prof. Jean-Yves Mabrut (PUPH), Prof. Kayvan Mohkam (PHU), and Prof. Mickael Lesurtel (PUPH) from the Hepatobiliary Surgery and Liver Transplantation team of the Hôpital de la Croix Rousse, Lyon.
At the moment the team also includes 2 post-docs (Francesca Casuscelli di Tocco, Vincenzo Alfano), and 4 PhD students (Yasmina Chouik, Xavier Muller, Alexia Paturel, Margot Thirion).

The EpiLiCan team focuses on hepatocellular carcinoma (HCC), one of the major causes of cancer death worldwide. About 90% of HCC cases can be associated with a well-characterized underlying risk factor, including chronic infection with hepatitis B, D and C viruses (HBV, HDV, HCV), ethanol consumption and non-alcoholic fatty liver disease (NASH). Despite the fast rise in obesity and NASH-related HCCs in Western countries, chronic HBV infection remains the first cause of HCC and a major public health problem worldwide, with 240 million individuals concerned. Although the risk of developing HCC can be reduced in patients by treatment of the underlying cause, e.g. by HCV clearance, suppression of HBV replication, or alcohol abstention, effective strategies to prevent cancer development in patients with advanced fibrosis and established cirrhosis are still lacking. Patients with advanced HCC carry a very poor prognosis and despite recent improvements, treatment options remain largely unsatisfactory.

Driving forces in hepatocyte transformation, HCC development and progression are chronic inflammation, DNA damage, epigenetic modifications, senescence and telomerase reactivation, chromosomal instability and early neo-angiogenesis. All "etiologic" factors seem to act through similar mechanisms (i.e. point mutations, chromosomal aberrations, epigenetic changes) that converge to affect common pathways.

The Levrero team in Rome and at the CRCL has been at the forefront of the research on the epigenetic control of the HBV minichromosome (cccDNA) activity, the identification of novel viral/host targets for HBV cure, the identification of viral and immunological determinants of HBV persistence and the impact of HBV viral proteins on host genes expression in chronic HBV infection and HCC development.



In the past years, the team's research efforts enabled to gain new knowledge on i) the epigenetic changes that precede and accompany HCC development and progression; ii) the interaction of HBV, HDV and HCV on the host epigenome; iii) the molecular and immunological basis of viral pathogenicity and persistence in the setting of HBV and HDV chronic liver diseases.

The team continues to work on the epigenetic changes in virus- and non virus-related HCCs focusing on 2 main axes: 1) histone methyl-transferases (HMTS) as HCC epi-drivers and therapeutic targets; 2) HBV and HDV proteins as epigenetic modulators in viral pathogenicity and HCC development

These research efforts profit of a vast network of national and international collaborations with access to large cohorts of HBV/HDV, HCV and HCC patients and of the direct participation of EpiLiCan members to the strong clinical research program at the Hôpital de la Croix Rousse.

Building on his experience and expertise at the IIT in Rome, M. Levrero has created a next-generation sequencing platform on the CAT site (contact: Marie-Laure Plissonnier; E-mail: marie-laure.plissonnier@inserm.fr). It is dedicated to epigenetics projects and available for the whole CRCL as well as external collaborations. The platform includes a MiSEq from Illumina, a nCounter Sprint from Nanostring, an IP-Star from Diagenode, a Biomek 4000 from Becton Dickinson, a QiaCube from Qiagen, a Maxwell Extractor from Promega, a Bioruptor from Diagenode and a Bioanalyzer from Agilent.

Beyond their scientific tasks, EpiLiCan team members are actively involved in the education of young scientists through their teaching activities at the local, national and international level (medical students, Master students). The team also contributes to disseminate information on chronic liver diseases and liver cancer to national and local patient associations as well as to the general public. Moreover, team members contribute actively to the life of the CRCL (Institutional Research Center Council, Department animation committee, ...).

CRCL PUBLICATIONS

IFN-III Is Selectively Produced by cDC1 and Predicts Good Clinical Outcome in Breast Cancer

Margaux Hubert, Elisa Gobbini, Coline Couillault, Thien-Phong Vu Manh, Anne-Claire Doffin, Justine Berthet, Céline Rodriguez, Vincent Ollion, Janice Kielbassa, Christophe Sajous, Isabelle Treilleux, Olivier Tredan, Bertrand Dubois, Marc Dalod, Nathalie Bendriss-Vermare, Christophe Caux, Jenny Valladeau-Guilemond

Science Immunology, 17 Apr 2020, Vol. 5, Issue 46

https://DOI:10.1126/sciimmunol.aav3942

CD163 + Tumor-Associated Macrophage Accumulation in Breast Cancer Patients Reflects Both Local Differentiation Signals and Systemic Skewing of Monocytes

Rodrigo Nalio Ramos, Céline Rodriguez, Margaux Hubert, Maude Ardin, Isabelle Treilleux, Carola H Ries, Emilie Lavergne, Sylvie Chabaud, Amélie Colombe, Olivier Trédan, Henrique Gomes Guedes, Fábio Laginha, Wilfrid Richer, Eliane Piaggio, José Alexandre M Barbuto, Christophe Caux, Christine Ménétrier-Caux, Nathalie Bendriss-Vermare

Clin Transl Immunology. 2020 Feb 13;9(2):e1108.

https://doi.org/10.1002/cti2.1108

Hyperprogression and Impact of Tumor Growth Kinetics After PD1/PDL1 Inhibition in Head and Neck Squamous Cell Carcinoma

Andy Karabajakian, Thibaut Garrivier, Carole Crozes, Nicolas Gadot, Jean-Yves Blay, Frédéric Bérard, Philippe Céruse, Philippe Zrounba, Pierre Saintigny, Charles Mastier, Jérôme Fayette

Oncotarget, May 2020

In this cohort of 120 patients treated with PD-1/PD-L1 inhibitors alone or in combination with anti-CTLA4 or anti-KIR antibodies, we evaluated the frequency of 'Hyperprogressive disease' (HPD) using Tumor Growth Kinetics (TGK). We found that hyperprogression was frequent (18%) and correlated with a high Neutrophil-to-Lymphocyte Ratio (NLR). TGK of HPD patients were similar to rapidly progressive screen-failure patients that did not receive immune checkpoint inhibitors (ICI), suggesting that the published rates of HPD might be due to natural disease behavior, at least in some cases. Furthermore, we found that patients who had a tumor growth deceleration ($TGK_R < 1$) on ICI had much better outcomes on salvage chemotherapy than those with a tumor growth acceleration ($TGK_R > 1$).

https://doi.org/10.18632/oncotarget.27563

JNJ-56136379, an HBV Capsid Assembly Modulator, Is Well-Tolerated and Has Antiviral Activity in a Phase 1 Study of Patients With Chronic Infection

Zoulim F, Lenz O, Vandenbossche JJ, Talloen W, Verbinnen T, Moscalu I, Streinu-Cercel A, Bourgeois S, Buti M, Crespo J, Pascasio JM, Sarrazin C, Vanwolleghem T, Shukla U, Fry J, Yogaratnam JZ

Gastroenterology. 2020 Apr 25:S0016-5085(20)30519-9

https://doi.org/10.1053/j.gastro.2020.04.036

ERα-36 Regulates Progesterone Receptor Activity in Breast Cancer

Konan HP, Kassem L, Omarjee S, Surmieliova-Garnès A, Jacquemetton J, Cascales E, Rezza A, Trédan O, Treilleux I, Poulard C, Le Romancer M

Breast Cancer Res. 2020 May 19;22(1):50

https://doi.org/10.1186/s13058-020-01278-7

Neogenin neutralization prevents photoreceptor loss in inherited retinal degeneration.

Charish J, Shabanzadeh AP, Chen D, Mehlen P, Sethuramanujam S, Harada H, Bonilha VL, Awatramani G, Bremner R, Monnier PP

J Clin Invest. 2020 Apr 1;130(4):2054-2068

https://doi.org/10.1172/JCI125898

CDYL2 Epigenetically Regulates MIR124 to Control NF-κB/STAT3-Dependent Breast Cancer Cell Plasticity

Maha Siouda, Audrey D Dujardin, Laetitia Barbollat-Boutrand, Marco A Mendoza-Parra, Benjamin Gibert, Maria Ouzounova, Jebrane Bouaoud, Laurie Tonon, Marie Robert, Jean-Philippe Foy, Vincent Lavergne, Serge N Manie, Alain Viari, Alain Puisieux, Gabriel Ichim, Hinrich Gronemeyer, Pierre Saintigny, Peter Mulligan

iScience, 2020, May 6;23(6):101141

https://doi.org/10.1016/j.isci.2020.101141

Generation of a conditional transgenic mouse model expressing human Phospholipase A2 Receptor 1

Jaber S, Goehrig D, Bertolino P, Massemin A, Bihl F, Chabry J, Lambeau G, Vindrieux D, Bernard D.

Sci Rep. 2020 May 18;10(1):8190.

https://doi.org/10.1038/s41598-020-64863-y

The JAK1/2 inhibitor Ruxolitinib delays premature aging phenotypes

Griveau A, Wiel C, Ziegler D, Bergö M, Bernard D

Aging Cell. 2020 Mar 20:e13122

https://doi.org/10.1111/acel.13122

Failed Apoptosis Enhances Melanoma Cancer Cell Aggressiveness

Kevin Berthenet, Camila Castillo Ferrer, Deborah Fanfone, Nikolay Popgeorgiev, David Neves, Philippe Bertolino, Benjamin Gibert, Hector Hernandez-Vargas, Gabriel Ichim

Cell Reports, Volume 31, ISSUE 10, 107731, June 09, 2020

https://doi.org/10.1016/j.celrep.2020.107731

How Can Immune Checkpoint Inhibitors Cause Hyperprogression in Solid Tumors?

Morgane Denis, Michael Duruisseaux, Marie Brevet, Charles Dumontet

Front Immunol. 2020; 11: 492. Published online 2020 Mar 20

https://dx.doi.org/10.3389%2Ffimmu.2020.00492

Tissue-nonspecific alkaline phosphatase is an anti-inflammatory nucleotidase

L Bessueille, A Briolay, J Como, S Mebarek, C Mansouri, M Gleizes, A El Jamal, R Buchet, C Dumontet, EL Matera, E Mornet, JL Millan, C Fonta, D Magne

Bone. Author manuscript; available in PMC 2020 Apr 27.

https://dx.doi.org/10.1016%2Fj.bone.2020.115262

Breast Cancer Stem Cells: Therapy Resistance and Novel Therapeutic Targets

Nora Jung, Véronique Maguer Satta and Borisd Guyot

Cancers 2019, 11(9), 1351;

https://doi.org/10.3390/cancers11091351

Estrogens are major regulators of the mammary gland development, notably during puberty, via estrogen receptor (ER) activation, leading to the proliferation and differentiation of mammary cells. In addition to estrogens, the bone morphogenetic proteins (BMPs) family is involved in breast stem cell/progenitor commitment. However, these two pathways that synergistically contribute to the biology of the normal mammary gland have also been described to initiate and/or promote breast cancer development. In addition to intrinsic events, lifestyle habits and exposure to environmental cues are key risk factors for cancer in general, and especially for breast cancer. In the latter case, bisphenol A (BPA), an estrogen-mimetic compound, is a critical pollutant both in terms of the quantities released in our environment and of its known and speculated effects on mammary gland biology. In this review, we summarize the current knowledge on the actions of BMPs and estrogens in both normal mammary gland development and breast cancer initiation, dissemination, and resistance to treatment, focusing on the dysregulations of these processes by BPA but also by other bisphenols, including BPS and BPF, initially considered as safer alternatives to BPA.

CRCL NEWS

Creation of the CRCL Young Researchers Association - CLYRA

The initial idea was born during a meeting with doctoral students, postdocs and Patrick Mehlen earlier this year.

The primary goal of CLYRA will be to represent young CRCL researchers by bringing together PhD students, postdocs, engineers and technicians. The main actions will be to implement young researchers in shaping the scientific life of the center (seminars, workshops, etc.), to encourage the dissemination of scientific knowledge, to promote the reception and integration of new CRCL members, to enhance and promote doctoral and post-doctoral training and finally to generate a link between current and former members of the CRCL community.

CLYRA will also be responsible for organizing events accessible to all CRCL members, such as the popular afterwork gatherings.

A temporary office, which is represented by Dorian Ziegler (president), Simon Durand (vice-president), Noémie Lopez-Ramirez (treasurer), Pia Gamradt (vice-treasurer), Amélie Massemin (secretary) and Anaïs Eberhardt (vice-secretary), has already tackled their new challenges.

For those who would like join them and the other 20 founding members and become part of the association, do not hesitate to contact them!

The board of the association. From left : Pia Gamradt, Dorian Ziegler, Amélie Massemin, Anaïs Eberhardt, Noémie Lopez-Ramirez, Simon Durand

CRCL's website redesign project

The CRCL website, www.crcl.fr will be completely redesigned and modified. As an important showcase for activities at CRCL and it's research teams, this brand new site will aim to promote the image of an excellent research center, dynamic and of international scope. For this, it will notably be a question of responding to new uses of the web, both in terms of design and user's experiences.

The objective is to put this new site online at the beginning of 2021, in order to be concomitant with the start of the 2021-2025 five-year CRCL contract.

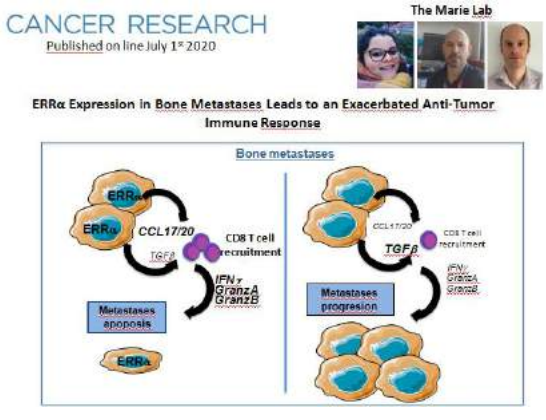
To achieve this, a working group, made up of team members and support services, created specifications which were validated by the CRCL board of directors. Providers, specialized in the creation of websites, will be contacted during the summer. One of them will be selected in September to work with the working group on the creation of the new website.

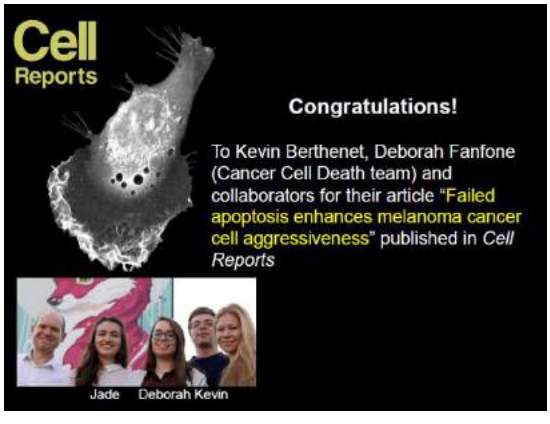
The dynamic display system is operational

As you may have noticed, display screens are now fitted at the entrance halls of the 4 Cheney buildings, as well as the Cours Albert Thomas. After a period of testing, the system is now fully operational at CLB (test phase in progress at the CAT) and allows a large amount of information to be passed on. The display system will show information related to the internal life of the CRCL: announcement of seminars, thesis defenses, important publications, etc .

Cheney D screen

If you wish to display a publication, please send the information you wish to communicate on a powerpoint slide to:
pierre.chaumont@lyon.unicancer.fr





Examples of displayed publications

CONGRATULATIONS !

PhD Thesis Defense

Paul GIROUD (Team Caux), Ciffre thesis in collaboration with Elsalys Biotech, « Expression of TAM receptors in human immune cells and identification of MerTK as a therapeutic target in the tumor microenvironment », May 25.

Fleur CHAPUS (Team Zoulim), « Role of the viral Core protein and the associated helicases in the biology of the hepatitis B virus minichromosome », May 28.

Muhammad ZAWWAD RAZA (Team Jordhheim/Dumontet), "Role of 5'-nucleotidases in the biology of human lung cancer cells and their response to different external stress conditions", April 30.

Anna Rita REDAVID (Team Mehlen), « Role of Netrin-1 in the tumor microenvironment », June 30.

Publishing director: Patrick Mehlen
Redaction : Pierre Chaumont - Blandine Bruneel / Translation from French : Brigitte Manship – Quynh Chuong