**Année de publication : 2020**

Thomas Yvorra, Anke Steinmetz, Pascal Retailleau, Olivier Lantz, Frédéric Schmidt (2020 Dec 20)

**Synthesis, biological evaluation and molecular modelling of new potent clickable analogues of 5-OP-RU for their use as chemical probes for the study of MAIT cell biology.**

*European journal of medicinal chemistry* : 113066 : DOI : S0223-5234(20)31038-2

**Résumé**

MAIT cells are preset αβ T lymphocytes that recognize a series of microbial antigens exclusively derived from the riboflavin biosynthesis pathway, which is present in most bacteria. The most active known antigen is unstable 5-(2-oxopropylideneamino)-6-(d-ribitylamino)uracil (5-OP-RU) which is stabilized when bound and presented to MAIT cells by MHC-related protein 1 (MR1). Here we describe the chemical synthesis and biological evaluation of new chemical probes for the study of MAIT cell biology. The two probes were ethinyl functionalized analogues of 5-OP-RU able to react through CuAAC also called « click chemistry ». The molecules up-regulated more MR1 than 5-OP-RU and they efficiently activated iVα19 Vβ8 TCR transgenic murine MAIT cells but not iVα19 TCRα transgenic MAIT cells indicating a surprisingly strong impact of the TRCβ chain. Moreover, the use of these molecules as chemical probes was validated in vitro by efficient and selective binding to MR1 revealed via fluorescence microscopy. This study was also complemented by molecular modelling investigation of the probes and the binary/ternary complexes they form with MR1 and the TCR. These new probes will be crucial to delineate the dynamics of 5-OP-RU at the cellular or whole organism level and to identify the cells presenting 5-OP-RU to MAIT cells in vivo.

Marine Verhulsel, Anthony Simon, Moencopi Bernheim-Dennery, Venkata Ram Gannavarapu, Lauriane Gérémie, Davide Ferraro, Denis Krndija, Laurence Talini, Jean-Louis Viovy, Danijela Matic Vignjevic, Stéphanie Descroix (2020 Dec 11)

**Developing an advanced gut on chip model enabling the study of epithelial cell/fibroblast interactions.**

*Lab on a chip* : 365-377 : DOI : 10.1039/d0lc00672f

**Résumé**

Organoids are widely used as a model system to study gut pathophysiology; however, they fail to fully reproduce the complex, multi-component structure of the intestinal wall. We present here a new gut on chip model that allows the co-culture of primary epithelial and stromal cells. The device has the topography and dimensions of the mouse gut and is based on a 3D collagen I scaffold. The scaffold is coated with a thin layer of laminin to mimic the basement membrane. To maintain the scaffold structure while preserving its cytocompatibility, the collagen scaffold was rigidified by threose-based post-polymerization treatment. This treatment being cytocompatible enabled the incorporation of primary intestinal fibroblasts inside the scaffold, reproducing the gut stromal compartment. We

observed that mouse organoids, when deposited into crypts, opened up and epithelialized the scaffold, generating a polarized epithelial monolayer. Proper segregation of dividing and differentiated cells along the crypt-villus axis was achieved under these conditions. Finally, we show that the application of fluid shear stress allows the long-term culture of this intestinal epithelium. Our device represents a new biomimetic tool that captures key features of the gut complexity and could be used to study gut pathophysiology.

Valentin Partula, Mélanie Deschasaux-Tanguy, Stanislas Mondot, Agnès Victor-Bala, Nadia Bouchemal, Lucie Lecuyer, Christine Bobin-Dubigeon, Marion J Torres, Emmanuelle Kesse-Guyot, Bruno Charbit, Etienne Patin, Karen E Assmann, Paule Latino-Martel, Chantal Julia, Pilar Galan, Serge Hercberg, Lluis Quintana-Murci, Matthew L Albert, Darragh Duffy, Olivier Lantz, Philippe Savarin, Mohamed Nawfal Triba, Mathilde Touvier, (2020 Dec 10)

**Associations between untargeted plasma metabolomic signatures and gut microbiota composition in the population of healthy adults.**

*The British journal of nutrition* : 1-29 : DOI : 10.1017/S0007114520004870

**Résumé**

Host-microbial co-metabolism products are being increasingly recognized to play important roles in physiological processes. However, studies undertaking a comprehensive approach to consider host-microbial metabolic relationships remain scarce. Metabolomic analysis yielding detailed information regarding metabolites found in a given biological compartment holds promise for such an approach. This work aimed to explore the associations between host plasma metabolomic signatures and gut microbiota composition in healthy adults of the Milieu Intérieur study. For 846 subjects, gut microbiota composition was profiled through sequencing of the 16S rRNA gene in stools. Metabolomic signatures were generated through proton nuclear magnetic resonance analysis of plasma. The associations between metabolomic variables and α- and β-diversity indexes and relative taxa abundances were tested using multi-adjusted partial Spearman correlations, PERMANOVAs, and MaAsLins, respectively. A Multiple testing correction was applied (Benjamini-Hochberg, 10%-FDR). Microbial richness was negatively associated with lipid-related signals and positively associated with amino acids, choline, creatinine, glucose, and citrate ($-0.133 \leq$ Spearman's $\rho \leq 0.126$). Specific associations between metabolomic signals and abundances of taxa were detected (25 at the genus level and 19 at the species level): notably, numerous associations were observed for creatinine (positively associated with 11 species, and negatively associated with Faecalibacterium prausnitzii). This large-scale population-based study highlights metabolites associated with gut microbial features and provides new insights into the understanding of complex host-gut microbiota metabolic relationships. In particular, our results support the implication of a « gut-kidney axis ». More studies providing a detailed exploration of these complex interactions, and their implications for host health are needed.

Wolfgang A Weber, Johannes Czernin, Carolyn J Anderson, Ramsey D Badawi, Henryk Barthel, Frank Bengel, Lisa Bodei, Irène Buvat, Marcelo DiCarli, Michael M Graham, Jan Grimm, Ken

Herrmann, Lale Kostakoglu, Jason S Lewis, David A Mankoff, Todd E Peterson, Heinrich Schelbert, Heiko Schöder, Barry A Siegel, H William Strauss (2020 Dec 9)
**The Future of Nuclear Medicine, Molecular Imaging, and Theranostics.**
*Journal of nuclear medicine : official publication, Society of Nuclear Medicine* : 263S-272S : DOI : 10.2967/jnumed.120.254532

**Résumé**

Antoine Vasseur, Nicolas Kiavue, François-Clément Bidard, Jean-Yves Pierga, Luc Cabel (2020 Dec 8)
**Clinical utility of circulating tumor cells: an update.**
*Molecular oncology* : DOI : 10.1002/1878-0261.12869

**Résumé**

The prognostic role of circulating tumor cells (CTCs) has been clearly demonstrated in many types of cancer. However, their roles in diagnostic and treatment strategies remain to be defined. In this review, we present an overview of the current clinical validity of CTCs in non-metastatic and metastatic cancer, and the main studies or concepts investigating the clinical utility of CTCs. In particular, we focus on breast-, lung-, colorectal- and prostate cancer. Two major topics concerning the clinical utility of CTC are discussed: treatment based on CTC count or CTC variations; and treatment based on the molecular characteristics of CTCs. Although some of these studies are inconclusive, many are still ongoing, and their results could help to define the role of CTCs in the management of cancers. A summary of published or ongoing phase II-III trials is also presented.

A-S Cottereau, M Meignan, C Nioche, N Capobianco, J Clerc, L Chartier, L Vercellino, O Casasnovas, C Thieblemont, I Buvat (2020 Dec 5)
**Risk stratification in diffuse large B-cell lymphoma using lesion dissemination and metabolic tumor burden calculated from baseline PET/CT.**
*Annals of oncology : official journal of the European Society for Medical Oncology* : 404-411 : DOI : S0923-7534(20)43174-6

**Résumé**

We analyzed the prognostic value of a new baseline positron emission tomography (PET) parameter reflecting the spread of the disease, the largest distance between two lesions (Dmax). We tested its complementarity to metabolic tumor volume (MTV) in a large cohort of diffuse large B-cell lymphoma (DLBCL) patients from the REMARC trial (NCT01122472).

Silvia Menegatti, Vincent Guillemot, Eleonora Latis, Hanane Yahia-Cherbal, Daniela Mittermüller,

Vincent Rouilly, Elena Mascia, Nicolas Rosine, Surya Koturan, Gael A Millot, Claire Leloup, Darragh Duffy, Aude Gleizes, Salima Hacein-Bey-Abina, , Jérémie Sellam, Francis Berenbaum, Corinne Miceli, Maxime Dougados, Elisabetta Bianchi, Lars Rogge (2020 Dec 3)

**Immune response profiling of patients with spondyloarthritis reveals signalling networks mediating TNF-blocker function in vivo.**

*Annals of the rheumatic diseases* : DOI : annrheumdis-2020-218304

**Résumé**

Antitumour necrosis factor (TNF) therapy has revolutionised treatment of several chronic inflammatory diseases, including spondyloarthritis (SpA). However, TNF inhibitors (TNFi) are not effective in all patients and the biological basis for treatment failure remains unknown. We have analysed induced immune responses to define the mechanism of action of TNF blockers in SpA and to identify immunological correlates of responsiveness to TNFi.

François Anna, Sophie Goyard, Ana Ines Lalanne, Fabien Nevo, Marion Gransagne, Philippe Souque, Delphine Louis, Véronique Gillon, Isabelle Turbiez, François-Clément Bidard, Aline Gobillion, Alexia Savignoni, Maude Guillot-Delost, François Dejardin, Evelyne Dufour, Stéphane Petres, Odile Richard-Le Goff, Zaineb Choucha, Olivier Helynck, Yves L Janin, Nicolas Escriou, Pierre Charneau, Franck Perez, Thierry Rose, Olivier Lantz (2020 Dec 1)

**High seroprevalence but short-lived immune response to SARS-CoV-2 infection in Paris.**

*European journal of immunology* : DOI : 10.1002/eji.202049058

**Résumé**

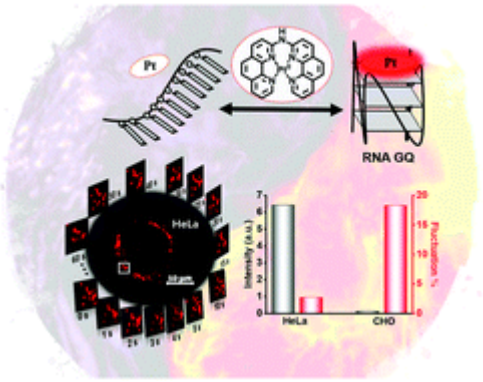
Although the COVID-19 pandemic peaked in March/April 2020 in France, the prevalence of infection is barely known. Using high-throughput methods, we assessed herein the serological response against the SARS-CoV-2 virus of 1847 participants working in three sites of an institution in Paris conurbation. In May-July 2020, 11% (95% CI: 9.7-12.6) of serums were positive for IgG against the SARS-CoV-2 N and S proteins, and 9.5% (CI:8.2-11.0) were neutralizer in pseudo-typed virus assays. The prevalence of seroconversion was 11.6% (CI:10.2-13.2) when considering positivity in at least one assays. In 5% of RT-qPCR positive individuals, no systemic IgGs were detected. Among immune individuals, 21% had been asymptomatic. Anosmia (loss of smell) and ageusia (loss of taste) occurred in 52% of the IgG-positive individuals and in 3% of the negative ones. In contrast, 30% of the anosmia-ageusia cases were seronegative suggesting that the true prevalence of infection may have reached 16.6%. In sera obtained 4-8 weeks after the first sampling anti-N and anti-S IgG titers and neutralization activity in pseudo-virus assay declined by 31%, 17% and 53%, resulting thus in half-life of respectively 35, 87 and 28 days. The population studied is representative of active workers in Paris. The short lifespan of the serological systemic responses suggests an underestimation of the true prevalence of infection. This article is protected by copyright. All rights reserved.

Lei He, Zhenyu Meng, Qianqian Guo, Xiangyang Wu, Marie-Paule Teulade-Fichou, Edwin Kok Lee Yeow, Fangwei Shao (2020 Nov 28)

**Fluorogenic Pt complexes distinguish the quantity and folding behavior of RNA G-quadruplexes between live cancerous and healthy cells.**

*Chemical communications (Cambridge, England)* : 56 : 14459-14462 : DOI : 10.1039/d0cc05622g

**Résumé**




Two Pt complexes with high quantum yields and photostability, and low cytotoxicity, were developed to track RNA G-quadruplexes (GQs) in live cells. Higher number and intensity, and longer lifetime of fluorescent foci in cancer cells than those in healthy cells suggest that the quantity and folding dynamics of RNA GQs could not only correlate to their biological functions, but be two novel biomarkers to characterize cancerous cells.

Leduc A., Chaouni S., De marzi L., Pouzoulet F., Mégnin-Chanet F., Stephan D., Habrand J.L., Sichel F., Laurent C. (2020 Nov 24)

**Biological Effects of Scattered Versus Scanned Proton Beams on Normal Tissues in Total Body Irradiated Mice: Survival, Genotoxicity, Oxidative Stress and Inflammation**

*Antioxidants* : 9 : 1170 : DOI : 10.3390/antiox9121170

**Résumé**

Side effects of proton therapy are poorly studied. Moreover, the differences in the method of dose delivery on normal tissues are not taken into account when proton beams are scanned instead of being scattered. We proposed here to study the effects of both modalities of proton beam delivery on blood; skin; lung and heart in a murine model. In that purpose; C57BL/6 mice were total body irradiated by 190.6 MeV proton beams either by Double Scattering (DS) or by Pencil Beam Scanning (PBS) in the plateau phase before the Bragg Peak. Mouse survival was evaluated. Blood and organs were removed three months after irradiation. Biomarkers of genotoxicity; oxidative stress and inflammation were measured. Proton irradiation was shown to increase lymphocyte micronucleus frequency; lung superoxide dismutase activity; erythrocyte and skin glutathione peroxidase activity;

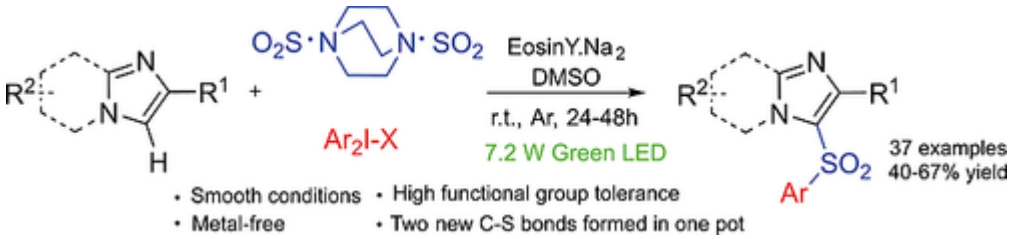
erythrocyte catalase activity; lung; heart and skin oxidized glutathione level; erythrocyte and lung lipid peroxidation and erythrocyte protein carbonylation even 3 months post-irradiation. When comparing both methods of proton beam delivery; mouse survival was not different. However, PBS significantly increased lymphocyte micronucleus frequency; erythrocyte glutathione peroxidase activity and heart oxidized glutathione level compared to DS. These results point out the necessity to take into account the way of delivering dose in PT as it could influence late side effects.

Breton-Patient C., Naud-Martin D., Mahuteau-Betzer F., Piguel S. (2020 Nov 15)

**Three-component C-H bond sulfonylation of imidazoheterocycles via visible-light organophotoredox catalysis.**

*European Journal of Organic Chemistry* : 2020 : 6653-6660 : DOI : 10.1002/ejoc.202001219

**Résumé**




The first entirely visible-light photoredox catalyzed sulfonylation of imidazoheterocycles has been developed. This transformation demonstrates an efficient C-H functionalization for the straightforward synthesis of novel C-3 sulfonylated imidazoheterocycles from various imidazopyridines and diaryliodonium salts with different electronic and steric properties and easy handled DABCO- bis (sulfur dioxide). The reaction proceeds in moderate to good yields under mild conditions at room temperature using the inexpensive organophotocatalyst EosinY.Na 2 and shows a high functional group tolerance (37 examples).

Marie-Judith Saint Martin, Fanny Orlhac, Pia Akl, Fahad Khalid, Christophe Nioche, Irène Buvat, Caroline Malhaire, Frédérique Frouin (2020 Nov 12)

**A radiomics pipeline dedicated to Breast MRI: validation on a multi-scanner phantom study.**

*Magma (New York, N.Y.)* : DOI : 10.1007/s10334-020-00892-y

**Résumé**

Quantitative analysis in MRI is challenging due to variabilities in intensity distributions across patients, acquisitions and scanners and suffers from bias field inhomogeneity. Radiomic studies are impacted by these effects that affect radiomic feature values. This paper describes a dedicated pipeline to increase reproducibility in breast MRI radiomic studies.

Abou-Ghali M, Kusters R, Körber S, Manzi J, Faix J, Sykes C, Plastino J (2020 Nov 6)
**Capping protein is dispensable for polarized actin network growth and actin-based motility**
*Journal of Biological Chemistry* : DOI : 10.1074/jbc.RA120.015009

**Résumé**

François-Clément Bidard, William Jacot, Nicolas Kiavue, Sylvain Dureau, Amir Kadi, Etienne Brain, Thomas Bachelot, Hugues Bourgeois, Anthony Gonçalves, Sylvain Ladoire, Hervé Naman, Florence Dalenc, Joseph Gligorov, Marc Espié, George Emile, Jean-Marc Ferrero, Delphine Loirat, Sophie Frank, Luc Cabel, Véronique Diéras, Laure Cayrefourcq, Cécile Simondi, Frédérique Berger, Catherine Alix-Panabières, Jean-Yves Pierga (2020 Nov 5)
**Efficacy of Circulating Tumor Cell Count-Driven vs Clinician-Driven First-line Therapy Choice in Hormone Receptor-Positive, ERBB2-Negative Metastatic Breast Cancer: The STIC CTC Randomized Clinical Trial.**
*JAMA oncology* : DOI : 10.1001/jamaoncol.2020.5660

**Résumé**

The choice between chemotherapy and endocrine therapy as first-line treatment for hormone receptor-positive, ERBB2 (also known as HER2)-negative metastatic breast cancer is usually based on the presence of clinical features associated with a poor prognosis. In this setting, a high circulating tumor cell (CTC) count (≥5 CTCs/7.5 mL) is a strong adverse prognostic factor for overall survival and progression-free survival (PFS).

Küssau T., Van Wyk N., Johansen M.D., Alsarraf H.M.A.B., Neyret A., Hamela C., Sørensen K.K., Thygesen M.B., Beauvineau C., Kremer L., Blaise M. (2020 Nov 4)
**Functional Characterization of the N-Acetylmuramyl-l-Alanine Amidase, Ami1, from Mycobacterium abscessus**
*Cells* : 9 : 2410 : DOI : 10.3390/cells9112410

**Résumé**

Peptidoglycan (PG) is made of a polymer of disaccharides organized as a three-dimensional mesh-like network connected together by peptidic cross-links. PG is a dynamic structure that is essential for resistance to environmental stressors. Remodeling of PG occurs throughout the bacterial life cycle, particularly during bacterial division and separation into daughter cells. Numerous autolysins with various substrate specificities participate in PG remodeling. Expression of these enzymes must be tightly regulated, as an excess of hydrolytic activity can be detrimental for the bacteria. In non-tuberculous mycobacteria such as Mycobacterium abscessus, the function of PG-modifying enzymes has been poorly investigated. In this study, we characterized the function of the PG amidase, Ami1 from M. abscessus. An ami1 deletion mutant was generated and the phenotypes of the mutant were evaluated with respect to

susceptibility to antibiotics and virulence in human macrophages and zebrafish. The capacity of purified Ami1 to hydrolyze muramyl-dipeptide was demonstrated in vitro. In addition, the screening of a 9200 compounds library led to the selection of three compounds inhibiting Ami1 in vitro. We also report the structural characterization of Ami1 which, combined with in silico docking studies, allows us to propose a mode of action for these inhibitors.