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New Antiviral strategies: From bench to bedside

April 19th, 2023

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SUMMARY

PROGRAM

9:15 am **Welcome coffee** at Centre François Jacob

10 am **Conferences** at Amphitheater Duclaux – Duclaux Building

10h **Welcome address**
Noël Tordo (SFV, Institut Pasteur) & **Jean-Yves Ortholand** (SCT, Edelris)

10h10-10h40 Opening keynote lecture - *Chair Noël Tordo*

Antivirals, a lot has been achieved, yet a long way to go.
Johan Neyts - KU Leuven, Belgium

Session 1 - The host as a target

10h40 Immunity - *Chair Karine Alvarez*

Biology

Protective antibodies targeting hantavirus glycoproteins
Pablo Guardado Calvo - Institut Pasteur, Paris, France

Chemistry

Activating immune pathways to cure chronic hepatitis B: From the bench to the clinic
Antoine Alam - Evotec ID, Lyon, France

11h20 Vaccins and new technologies - *Chair Muriel Coulpier*

Biology

Title to be communicated
Odile Launay - Centre de vaccinologie de Cochin-Pasteur, Paris, France

Chemistry

Messenger RNA-based modalities as alternatives to conventional approaches to fight infectious diseases
Chantal Pichon - CBM, Orleans, France

12h00 Epitranscriptome - *Chair Julien Sourimant & Prescilla Sutto*

Biology

Viral and cellular epitranscriptomics: New players in RNA virus infections.
Patrick Eldin – IRIM, Montpellier, France

Chemistry

Nucleosides and Oligonucleotides as inhibitors of viral RNA methylation by methyltransferases
Françoise Debart – IBMM, Montpellier, France

12:40 am **Lunch break and Poster session** at Centre François Jacob

2:30 pm **Conferences** at Amphitheater Duclaux – Duclaux Building

Session 2 - Virus as targets

14h30 RNA virus and targets - *Chair Catherine Isel*

Biology

Packaging of the influenza A virus genome: a suitable antiviral target?
Roland Marquet - IBMC Strasbourg, France

Chemistry

From fragment screening to inhibitors of the SARS-CoV-2 RNA genome
Julia Weigand – University of Marburg, Germany

15h10 DNA virus and targets - *Chair Mélanie Ethève-Quelquejeu*

Biology

Preclinical research and development of nanoparticulated TRL2 agonist for the treatment of chronic HBV and HDV infections
David Durantel - CIRI, ENS Lyon, France

Chemistry

G-quadruplexes & Pathogens: targeting nucleic acid unusual structures
Jean-Louis Mergny - Ecole Polytechnique, Paris, France

15h50 Targeting the entry - *Chair Frederic Iseni*

Biology

Screening antibodies and other molecules against SARS-CoV-2 and Mpox virus
Olivier Schwartz - Institut Pasteur, Paris, France

Chemistry

Phenotypic screening: an indirect approach for the discovery of molecules impacting intracellular trafficking.
Jean-Christophe Cintrat – CEA, Saclay, France

16h30 Emergence, identification and detection - *Chair Hélène Munier-Lehmann*

Biology

The Preclinical Study Group (GEPC) of the ANRS-MIE
Xavier de Lamballerie - Université Aix-Marseille, France

Chemistry

From the screening of the Curie-CNRS chemical library to the identification of an anti-HIV drug
Florence Mahuteau-Betzer - Institut Curie, Orsay, France

17h10 Closing remarks

5:30 pm **Cocktail** at Centre François Jacob

SPEAKERS & ABSTRACTS

Johan Neyts

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« Antivirals, a lot has been achieved, yet a long way to go »

Highly potent antiviral drugs are available for the treatment of infections with herpesviruses, HIV, HBV and HCV; a number of drugs are also available for the treatment of influenza infections. Very recently small molecule antivirals have also been approved for the treatment of SARS-CoV2 and monkeypox infections. Yet potent/selective drugs are not available for the treatment of other viral infections, many of which are caused by emerging and neglected viruses. Potent pan-family antivirals will also be important in the context of epidemic and pandemic preparedness. I will discuss the most recent evolutions in the field of small molecule antiviral drug discovery and development. I will focus mostly on the development of novel antiviral molecules based on phenotypic screening followed by hit- and lead optimization. This strategy is of particular interest because it allows to identify also novel molecular targets for inhibition of viral replication. I will document the approach with a number of examples including the development of an ultrapotent pan-serotype dengue drug that targets the NS4B/NS3 interaction (Kaptein et al., Nature 2021, Goethals et al., Nature 2023).

Pablo Guardado Calvo

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« *Protective antibodies targeting hantavirus glycoproteins* »

Hantaviruses are a family of pathogenic airborne viruses that can cause severe disease in humans. Currently, there is no treatment available for hantavirus infections, and patients can only receive supportive care to alleviate their symptoms. These viruses enter host cells by binding to a specific receptor on the cell surface and fusing their membrane with the endosomal membrane at acidic pH. During this talk, I will discuss the unique mechanisms that hantaviruses use to regulate viral fusion and how some monoclonal antibodies exploit them to neutralize the virus. Specifically, I will focus on the neutralization mechanisms of ADI-42898, the only antibody that has been found to neutralize all pathogenic hantaviruses to date, and the strategies we have developed to enhance its potency.

Antoine Alam

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« *Activating immune pathways to cure chronic hepatitis B: From the bench to the clinic* »

Antoine Alam[1], Xavier Marniquet[1], Marion Dajon[1], Julie Montegut[1], Odile Bonnin[1], Gregory Neveu[1], Charlotte Blanc[1], Christelle Marcou[1], Juliette Lavaux[1], V. Yalligara[2], Michel Didier[2], Franck Augé[2], Galina Boldina[2], Céline Lemoine[2], Jacques Dumas[2], Thomas Bouquin[2], Annabelle Milla[1], Hugh Watson[1] Kara Carter[1]

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Type-I interferons (IFN-I) have shown limited ability to cure patients with chronic hepatitis B (CHB), thus more effective treatments are needed to achieve cure in a significant proportion of patients. Previously, we demonstrated that–the simultaneous stimulation of CD40 and IFN-I pathways *in vitro* and *in vivo* HBV infection models increased the antiviral efficacy compared to IFN-I alone. The combination of IFN-I and CD40L, on primary human hepatocytes (PHH) and in AAV/HBV-infected mice, showed a significant increase in anti-HBV activity when compared to either CD40L or IFN-α alone. Fusion of IFN-I molecules to an anti-CD40 agonistic mAb yielded a bifunctional molecule active on both CD40 and IFNR reporter cells capable of delivering both activities to HBV infected hepatocytes in vivo. The fusion molecule is able to reduce viral products from HBV-infected PHH treated for a period of 4 days after infection at picomolar concentrations without cytotoxicity. Stimulation of CXCL10 release and anti-HBV activity in infected PHH treated for 1 day followed by washout period of 3 days was maintained. These results demonstrate the feasibility of combined stimulation of CD40 and IFN-I pathways with a single bifunctional molecule to achieve potent activity against HBV.

Odile Launay

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« Clinical evaluation of new vaccines: from phase 1 to phase 3 trials »

Marketing Authorization for a new vaccine requires documentation on the immunogenicity, efficacy, and safety of the vaccine candidate and administration conditions. That means to conduct a set of studies in a pre-defined order in specialized clinical trials centers.

Sometimes, human infection challenge studies are needed to assess the efficacy of the candidate vaccine before conducting a phase 3 trial, in particular if there is no relevant animal model and if the mechanism of protection is not well established.

Specificities of vaccine trials will be developed.

Chantal Pichon

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« Messenger RNA-based modalities as alternatives to conventional approaches to fight infectious diseases »

The perspective of using messenger RNA (mRNA) as a therapeutic molecule has first faced some uncertainties due to concerns about its instability and the feasibility of large-scale production. The potential of mRNA-based vaccines has been revealed by the success of rapid and adaptable vaccination strategies to fight against COVID-19 pandemic. The achievement of those mRNA vaccines has been made possible through advances in the design of mRNA structure, manufacturing and delivery systems. This success opens up an avenue for the development of innovative mRNA-based vaccines and therapeutics envisioning different applications including various infectious diseases. mRNA-based modalities against variety of infectious diseases have been proposed and few mRNA vaccines are undergoing clinical trials. The development of mRNA formulation is quite challenging due to the peculiar nature of mRNA. Lessons learned from viral infection have been useful to design the delivery systems for crossing multiple biological barriers. Another challenge is to get a targeted delivery which could be reached either by manipulating the lipids composition or using targeting ligands for specific receptors. Issues that we have to face when conducting those two strategies will be discussed. Current knowledge regarding crucial aspects-structure, stability, formulations, cell delivery and *in vivo* applications of mRNA will be summarized. We need a multidisciplinary approach to achieve a rational design of nanomedicine. I will discuss challenges that have to be tackled to fully prove the mettle of mRNA-based modalities and to potentiate their therapeutic applications.

Patrick Eldin

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« Viral and cellular epitranscriptomics: New players in RNA virus infections »

Viral epitranscriptomics is a fascinating field that explores how RNA modifications affect the interactions between viruses and their hosts. These modifications can alter the function, stability and localization of viral and cellular RNAs, and influence the outcome of viral infections. In this talk, I will present some of our findings on how epitranscriptomic marks regulate Zika and SARS-CoV-2 infections, and how they can be exploited for antiviral strategies. I will also illustrate some of the challenges in studying epitranscriptomics, such as the dynamic and specific nature of RNA modifications, the complex interplay between different marks, and the link between epitranscriptomics and human diseases. I hope to convince you that epitranscriptomics is a new and exciting frontier in RNA virus research.

Françoise Debart

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« *Nucleosides and Oligonucleotides as inhibitors of viral RNA methylation by methyltransferases* »

The COVID-19 pandemic caused by the SARS-CoV-2 illustrates what the world faces with emerging viruses in the absence of appropriate treatments or prophylactic vaccines. After three years of pandemic, approved antiviral treatments for CoV-diseases are still limited to molecules targeting the RNA dependent RNA polymerase activity (RdRp) or the Mpro protease activity. Two methyltransferases (MTases), which are engaged in the capping pathway of viral mRNA, are also essential for viral replication. These MTases are responsible for the enzymatic cascade of viral RNA cap methylations: first the N7-methylation of the guanosine by guanine N7-MTase nsp14 and subsequently the 2'-OH methylation of the ribose of the first RNA adenosine by the 2'O-MTase complex nsp10/nsp16. N7-MTase nsp14 was identified as a critical enzyme for the replication of SARS CoV. In this context, our group has developed a rational drug design approach to synthesize competitive bisubstrate inhibitors that occupy both the *S*-adenosylmethionine (SAM) methyl donor binding pocket and the cap-binding pocket of SARS-CoV nsp14. First, we pioneered the synthesis of dinucleosides as mimetics of the SAM, that showed submicromolar inhibition against the SARS-CoV N7-MTase.[1] Then, we developed nucleoside analogues of adenosine, modified in the 5' position by an N-arylsulfonamide group.[2] SARs supported by molecular docking established the optimized 5' scaffold for nanomolar inhibition and the ideal nucleobase, C7-substituted 7-deaza-adenine, to achieve for the first time subnanomolar and selective activity for N7-MTase inhibitors of SARS-CoV-2 nsp14.[3]

To target 2'O-MTases, we developed another approach with modified short cap-oligoribonucleotides (ORN) containing bisubstrate nucleoside analogs mimicking the transition state of the 2'O-methylation of the RNA.

1. Ahmed-Belkacem, R.; Sutto-Ortiz, P.; Guiraud, M.; Canard, B.; Vasseur, J.-J.; Decroly, E.; Debart, F., *Eur. J. Med. Chem.* **2020**, 201, 112557.

2. Ahmed-Belkacem, R.; Hausdorff, M.; Delpal A.; Sutto-Ortiz, P.; Colmant, A.; Touret, F.; Ogando, N.; Snijder, E.; Canard, B.; Vasseur, J.-J.; Coutard, B.; Decroly, E.; Debart, F., *J. Med. Chem.* **2022**, 65, 6231-6249.

3. Hausdorff, M.; Delpal, A.; Barelier, S.; Nicollet, L.; Canard, B.; Touret, F.; Coutard, B.; Vasseur, J.-J.; Decroly, E.; Debart, F., *Eur. J. Med. Chem.* **2023**, under revision.

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« *Packaging of the influenza A virus genome: a suitable antiviral target?* »

Anne-Caroline Jousset[1#], Hardin Bolte[2#], Antoine Hache[1#], Celia Jakob[2#], Béatrice Chane-Woon-Ming[1], Damien Ferhadian[1], Daniel Desiro[3], Gabriel Lencioni Lovate[3], Anne Schweigert[1], Manja Marz[3], Martin Schwemmle[2], Roland Marquet[1]

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Segmentation of the genome of Influenza A (IAV) viruses complicates packaging as IAV particles must contain one copy of each of the 8 vRNAs to be infectious. Packaging signals (PSs) have been identified at the termini of each vRNA and the current model proposes that the 8 vRNAs are packaged as a supramolecular complex maintained by interactions between PSs, but the evidence supporting this model remains limited (1). Recently, several groups identified inter-vRNA interactions using SPLASH and other genome-wide cross-linking methodologies. However, most of these interactions are not located in known PSs and, except for one case, viruses in which interactions were disrupted displayed no phenotype (1). We showed that sequential disruption of SPLAH-identified RNA interactions failed to identify PSs (2). Using SHAPE-MaP, a genome-wide chemical probing approach, we observed that a PS in the PB2 segment adopt a well-defined secondary structure, while a PS in PA is single-stranded (3). Mutations that destroy the secondary structure of the PB2 PS or that induce folding of the PA PS both affect packaging. Our data suggest that mutations in the PB2 PS prevent RNA-RNA interactions in a nearby region and that mutating a single PS results in a complex rearrangement of the RNA-RNA interaction network. Our data also suggest that SHAPE-MaP can be used to precisely map PSs. Interestingly, it was recently shown that locked nucleic acids targeting the PB2 PS display potent antiviral activity *in vitro* and protect mice from lethal IAV infections (4). Thus, SHAPE-MaP has the potential to identify new antiviral targets.

(1) Jakob, C.[#], Paul Stansilaus, R.[#] *et al.* (2022) ***Nucleic Acids Res.*** **50**, 9023-9038.
(2) Jakob, C.[#], Lencioni Lovate, G.[#] *et al.* (2023) under review.
(3) Jousset, A.-C.[#], Hache, A.[#], Bolte, H.[#] *et al.* in progress.
(4) Hagey, R.J. et al. (2022) ***Nature Medicine*** **28**, 1944-1955.

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« *From fragment screening to inhibitors of the SARS-CoV-2 RNA genome* »

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The genome of coronaviruses consists of RNA as information carrier encoding for viral proteins. RNA is able to form secondary or higher structures, which can operate as regulatory *cis*-acting elements through RNA-RNA or RNA-protein interactions and serve essential functions in viral protein synthesis or replication. Since the outbreak of the SARS-CoV-2 pandemic, the genome of RNA viruses and their conserved *cis*-regulatory elements as well as RNA structures gained broad attention as novel targets in the development of antiviral strategies. The linear positive-sense single-stranded RNA-genome of SARS-CoV-2 comprises ~30 kb. Known functional RNA structures are concentrated in the 5'-UTR (untranslated region) and 3'-UTR and between the open reading frames (ORFs) 1a and 1b. Importantly, these secondary structures are highly conserved, not only among the currently upcoming SARS-CoV-2 variants of concern (VOCs), but also between different coronaviruses. The conservation and resistance to occurring mutations underlines the promising role of functional RNA structures as drug targets, especially in the light of future zoonotic events. A possible strategy to target and alter RNA structures is the use of RNA-targeting small molecules, which bind specifically to the viral genome. We created a complete library of SARS-CoV-2 functional RNA elements and characterized their secondary structure by NMR spectroscopy. NMR-based high-throughput screening of a chemically diverse fragment library resulted in a rich dataset for follow-up chemistry and drug discovery campaigns. Currently, we focus on two RNAs controlling viral protein synthesis: the 5'-UTR stem-loop 1 (SL1) and the pseudoknot (PK). The pseudoknot is located in the overlapping region between ORF1a and ORF1b and coordinates the essential -1 ribosomal frameshift during viral genome translation. SL1 plays a key role in the interaction of the viral genome with the non-structural protein 1 (nsp1) during the evasion from cellular translation shutdown in response to viral hijacking of host cells. Using a combination of cheminformatics, medicinal chemistry, *in vitro* RNA binding assays, antiviral testing and *in cell* RNA inhibition assays, we developed drug-like molecules targeting RNA. The presentation will give a short overview of our research methods and will discuss current approaches and challenges in RNA targeting by small molecules.

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« *Preclinical research and development of nanoparticulated TRL2 agonist for the treatment of chronic HBV and HDV infections* »

David Durantel, PHD, HDR

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Pegylated-interferon-alpha (Peg-IFNα), an injectable innate immune protein, is still used to treat chronically HBV (or HBV/HDV co)-infected patients, despite its poor tolerability. Peg-IFNα has the advantage over nucleos(t)ide analogues (NAs) to be administrated in finite regimen and lead to a higher HBsAg loss rate. Yet it would be interesting to improve the efficacy (i.e. while decreasing doses), or replace, this old medicine by novel small molecules/stimulators able to engage innate immune receptors in both HBV replicating hepatocytes and relevant innate immune cells. We had previously identified the TLR2 agonist Pam3CSK4OK, as one of the best PRR agonist to reduce HBV replication, including cccDNA level and activity, in infected hepatocytes (*Lucifora et al., Scientific Rep. 2018*), and have also recently reported a potent anti-HDV activity in *in vitro* models (*Michelet et al., JHEP rep. 2021*). During this lecture, some recent data obtained *in vitro* on the modes of action of this TLR2 agonist will be discussed (*Desmares et al., Antiviral Res. 2022; Michelet et al., JHEP rep. 2021*), as well as our efforts to R&D a nano-formulation of the agonist (*Lamrayah et al., Int J Pharm. 2019*), using *in vitro* and animal models (*Lamrayah et al., Antiviral Res. 2023 & Charriaud et al., in preparation*).

Nano-formulations of TLR2 agonists represent possible assets to improve the rate of HBV/HDV cure in patients. Further evaluations, including regulatory toxicity studies, are warranted to move toward clinical trials.

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«*G-quadruplexes & Pathogens: targeting nucleic acid unusual structures*»

G-quadruplexes ("G4") are unusual nucleic acid structures which can find applications in biology, medicine, as well as biotech- and nano-technologies [1]. G4 can be formed intramolecularly by G-rich DNA or RNA sequences. We are developping tools to understand their folding and polymorphism, both *in vitro* and in cells [2]. In parallel, we proposed a new algorithm for the prediction of G4 propensity [3]. We are now applying this G4-Hunter prediction tool to a number of genomes, including viruses [4]. We recently demonstrated that viruses regularly causing persistent infections are enriched in G4s, while viruses causing acute infections are significantly depleted in these structures [5], including SARS-CoV2 [6]. Interestingly, one of SARS-CoV2 proteins, Nsp3, can bind to G4s. These interactions can be disrupted by G4 ligands. Our results pave the way for further studies on the role of SUD/G4 interactions during SARS-CoV-2 replication and the use of inhibitors of these interactions as potent antiviral compounds. In contrast to SARS-CoV-2, the HIV-1 genome contains evolutionnary conserved G4-forming sequences, and G4 ligand can inhibit HIV-1 infectivity by preventing initiation of reverse transcription [7]. At the DNA level, DNA Topoisomerase 1 represses HIV-1 basal transcription through its interaction with a G4 present in the viral promoter[8].
We are now extending these studies to other viruses. For example, we have analysed genomes of hepatitis B viruses (HBV) for the presence of G-quadruplex-forming sequences [9]. Our work used genomes from ancient and modern HBV stains and represents the first paleogenomic analysis of the propensity for G4 formation in any genome, applied here to the evolution of a life-threatening virus. Our detailed analyses identified G-quadruplex-forming sequences in all HBV genomes. We observed that PQS content in HBV increased over time to become closer to the PQS frequency in the human genome. Our working hypothesis that, for virus causing chronic infections, their PQS frequencies tend to converge evolutionarily with the ones of their hosts, as a kind of genetic camouflage, not to be recognized as foreign material by the host cell.

(1) Mergny & Sen, ***Chem. Rev.*** (2019), *119*, 6290-6325.
(2) Chen *et al,* ***Nucleic Acids Res***. (2021) *49*, 9548; Luo *et al,* ***Nucleic Acids Res.*** (2022), *50*, e93; Luo *et al,* ***Biochimie*** (2023) *in press;* Esnault *et al,* ***Nat Genet*** (2023) *accepted.*
(3) Bedrat *et al,* ***Nucleic Acids Res.*** (2016), 44: 1746; Brázda *et al,* ***Bioinformatics*** (2019), 35, 3493.
(4) Jaubert *et al,* ***Sci Adv.*** (2018) *8*: 8120. Abiri *et al,* ***Pharmacol Rev***. (2021) *73*, 897.
(5) Bohálová *et al,* ***Biochimie*** (2021) *186*, 13-27
(6) Lavigne *et al.* ***Nucleic Acids Res***. (2021) *49*, 7695 ; European patent *EP 20 306606.3 ; also see poster by J. Guillon.*
(7) Amrane *et al.* ***Nucleic Acids Res***. (2022) *50*, 12328.
(8) Lista *et al.* (2023) *submitted.*
(9) Brázda *et al.* (2023) *submitted.*

Olivier Schwartz

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« Screening antibodies and other molecules against SARS-CoV-2 and Mpox virus »

The design and use of antiviral screening assays using field isolates of SARS-CoV-2 and Mpox virus will be discussed.

Jean-Christophe Cintrat

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« Phenotypic screening: an indirect approach for the discovery of molecules impacting intracellular trafficking »

The high throughput screening of chemical libraries on a specified target in a cellular context can sometimes offer opportunities. In this presentation, I will show how we initially started with a screen aiming at identifying compounds that could protect cells against a toxin to finally end up with antiviral compounds. Few compounds were selected from this HTS and after a long journey to decipher their mode of action , new opportunities have emerged in other therapeutic areas for all of them due to impact on cells. This presentation will focus on one compound and will show how we moved from antitoxin activity towards targeting other pathogens (including viruses) highlighting few crucial steps in the development of such compounds into lead compounds. A special emphasis will be on medicinal chemistry and on the respective inputs of chemists and biologists in a very collaborative project.

Xavier de Lamballerie

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« The Preclinical Study Group (GEPC) of the ANRS-MIE »

During the Covid-19 pandemic, the search for therapeutics focused in particular on molecules with antiviral and/or immunomodulatory potential. A large number of known molecules were proposed for direct repositioning in clinical studies, based on simple concepts or summary biological data, causing a harmful "proliferation" of clinical trials on poorly documented grounds. In contrast, new antiviral monoclonal antibody therapeutics have been subject to iterative clinical validation requests for each new variant, with these evaluations frequently taking longer than the duration of dissemination of the variants studied. In both cases, the "weakest link" was the availability of, or ability to take into account, preclinical evaluation data on treatments. This presentation reviews the establishment and work of the ANRS|MIE Preclinical Study Group in this particular context and attempts to draw out guiding principles for the future.

Florence Mahuteau-Betzer

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« From the screening of the Curie-CNRS chemical library to the identification of an anti-HIV drug »

The drug candidate ABX464 has been identified by a hit-to-lead optimization program. The initial screening of the Curie-CNRS chemical library was an *in vitro* test based on the inhibition of HIV RNA splicing whereas, during the hit-to-lead program, the biological activity was evaluated through the monitoring quantification of viral protein (p24) *in cellulo*. We will describe this success story from the screening to the hit-to-lead-optimization, the target identification and the clinical trials carried out in collaboration with Abivax.

POSTER ABSTRACTS

Poster N°1

A platform to identify direct protein-proteins interactions and screen for PPIs-disrupting compounds

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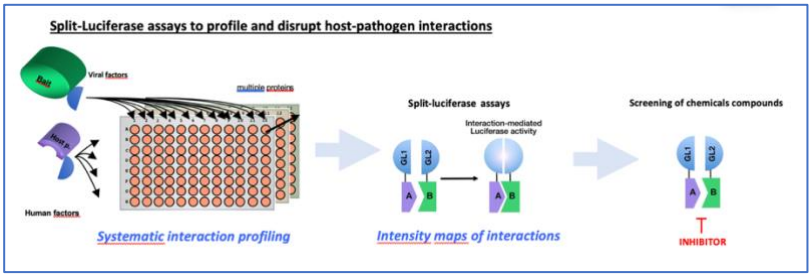
Viruses depend on their ability to hijack and control the cellular machinery to multiply and spread through organisms and populations. Infections are primarily initiated by physical contacts between viral proteins and cellular proteins, that set off molecular rearrangements culminating in the implementation of the viral life cycle. Each step of the viral cycle is mediated by contacts between viral and host molecules that determine functional consequences. Emerging evidence arise that protein-protein interactions (PPIs) are suitable druggable targets, contrary to what was considered earlier. Hence identifying compounds that inhibit the virus's ability to interact with and rewire the host cellular machinery has become a promising path to develop anti-viral therapeutics. We therefore propose a pipeline to identify host/pathogen direct contacts, amenable to screening for PPI inhibiting compounds. Our approach consists in the systematic profiling of binary virus/host PPIs using Protein-Fragment Complementation assay based on luciferase enzymes (split-luciferase assays)[1]. These assays consist in the measurement of direct PPIs via the reconstitution of a fragmented luciferase enzyme (Gaussia *princeps* luciferase or Nano luciferase). Signal intensities reflect the pathogen/Host interaction strength[2], which represents an important asset for prioritizing the most relevant PPIs to be screened for disrupting compounds. Our aim is to identify compounds able to inhibit key host/pathogens PPIs and impact infection. After accurate characterization of the toxicity (EC_{50}), inhibitory activity (IC_{50}) of identified compounds, the most efficient are to be further characterized, and represent attractive targets for host-directed therapeutics.

We applied such pipeline to respiratory viruses (influenza A viruses and SARS-CoV-2) and are providing here an example applied to influenza A virus (IAV). We investigated virus/host PPIs readily detectable by split-luciferase assays and involving host proteins essential for IAV infection (based on literature data). The interaction between the PB2 viral replication protein of influenza A virus ($H1N1_{pdm09}$) and the human protein RAB11A emerged as strongly positive in our assay. This PPI is well characterized (crystal structure of the complex resolved[3]) and well documented for its critical role in the transport of viral genomic segments across the cytoplasm[4]. Taking advantage of its detection by split-luciferase, we undertook the screening of a focused chemical compounds library consisting in ±1000 compounds enriched in potential PPIs disruptors. Our initial results are promising and will be presented here.



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2. Vincentelli, R. *et al.* Quantifying domain-ligand affinities and specificities by high-throughput holdup assay. *Nat Methods* 12, 787–93 (2015).
3. Veler, H. *et al.* The C-Terminal Domains of the PB2 Subunit of the Influenza A Virus RNA Polymerase Directly Interact with Cellular GTPase Rab11a. *J. Virol.* 96, e01979-21 (2022).
4. de Castro Martin, I. F. *et al.* Influenza virus genome reaches the plasma membrane via a modified endoplasmic reticulum and Rab11-dependent vesicles. *Nat Commun* 8, 1396 (2017).

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Poster N°2

Modeling SARS-COV-2-infected central nervous system using human primary neuronal/glial cells to identify antiviral drugs.

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SARS-CoV-2 induces a large range of neurological symptoms even without respiratory manifestations. However, there is still no consensus concerning viral entry and viral tropism in the brain as well as viral-induced inflammation. Here, we used a well-characterized culture of human neuronal/glial cells (hNGCs) differentiated from fetal neural progenitors to provide new arguments about SARS-CoV-2 infection in human brain. We showed that astrocytes were highly permissive to the virus, confirming Andrews et al., (2022) who used human cortical organotypic slices and brain organoids. In hNGCs, viral infection led to a strong alteration of neuronal morphology and to astrocytes death. SARS-CoV-2 infected-hNGCs were then used to screen twenty molecules (viral polymerase inhibitors, statins, antimalaria or antiparasitic drugs, etc…) with either already known or unknown antiviral activity against this virus. Image analyses, quantification of viral RNA and viral particles were used to determine the anti-viral efficiency. We revealed that seven molecules with known anti-SARS-CoV-2 activity in other cell types were inefficient in hNGCs whereas the others were confirmed, which demonstrated that the efficiency of these molecules was cell-type dependent. Among previously unknown antiviral molecules against SARS-CoV-2, we found that small-molecule cyclophilin inhibitors have an antiviral activity in infected-hNGCs. Our data thus demonstrate that human astrocytes are permissive to the virus and that infection strongly affects human neuronal/glial cells. They also outline the importance of using cellular model that are brain specific to question the role of antiviral molecules in this organ.

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Poster N°3

Biochemical and functional characterization of SARS-CoV-2 Nsp3 – RNA G4 complexes and therapeutic properties of G4-ligands inhibiting their formation.

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The multi-domain non-structural protein 3 (Nsp3) is an essential component of SARS-CoV viruses replication complex. Many functions of this protein remain unknown and may be targeted by new antiviral drugs. We have recently shown that the SARS-Unique Domain (SUD) present in SARS-CoV-2 Nsp3 can bind to cellular RNA G-quadruplexes (RNA G4s). These interactions can be disrupted by mutations that prevent oligonucleotides from folding into G4 structures [(a)]. Interestingly, G4-ligands disrupting this SUD/RNA-G4 interaction have antiviral activities on A549-Ace2 cells at sub micromolar range (*European patent 20 306 606.3*).

We are presently characterizing the biochemical and functional properties of the SARS- CoV-2 SUD/Protein/RNA G4 complexes formed in human cells and their impact on viral replication. We will present new data on RNA and protein partners associated with these complexes and on their link with the host translation machinery.

Our project tackles a new viral/host interaction mediated by a protein/RNA G4 complex and pave the way for the use of inhibitors of this interaction as potential antiviral compounds.

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Poster N°4

Access to new SAM cofactor analogues to study viral RNA

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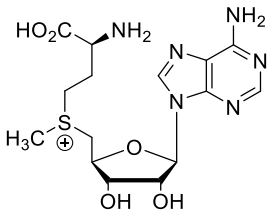
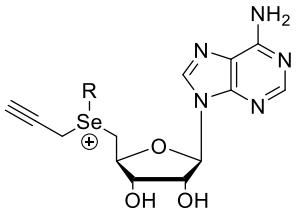
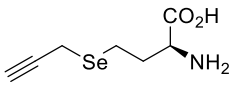
The N^6-methylation of adenosine (m^6A) in RNA is a post-transcriptional mark involved in the regulation of a variety of biological processes in all domains of life. The role of this modification in HIV-1 physiology remains controversial. The methyl group is introduced at the N6 position of adenosine by methyltransferases (MTases) which use the S-adenosyl-L-methionine cofactor (SAM) as the methyl donor. To decipher the influence of the specific methylation identified on gRNA structure, translation, dimerization and trafficking into the cell, we use a chemical biology approach to precisely map the methylated sites of gRNA.[1,2] Here, we present the synthesis of SAM cofactor analogues and methionine analogues to modify RNA *in vitro* and in cell by introduction of a bioorthogonal propargyl group. So far, we have completed the synthesis of stable SAM analogues containing a selenium atom instead of a sulfur and a propargyl group for direct *in vitro* labeling of RNA. The synthesis of propargyl-L-selenohomocysteine was also achieved for metabolic labeling in cells. These tools will be used in combination with click chemistry to detect m^6A and explore its roles in HIV-1 gRNA.



SAM cofactor



SAM cofactor analogues



Propargyl-L-selenohomocysteine

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New inhibitors of the 3CL protease of SARS-CoV-2 discovered by High-Throughput

Screening

Poster N°5

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Since December 2019, the highly pathogenic coronavirus SARS-CoV-2 caused a major outbreak[(a)]. The current pandemic and the risk of emerging coronaviruses highlight the importance to discover new specific therapeutics against coronaviruses.

The main protease ($3CL^{pro}$) is a promising therapeutic target for the development of anti-coronavirus compounds[(b)] because of its crucial role in the viral life cycle, its high conservation among coronavirus species and the absence of human homolog. Two specific antivirals compounds used clinically for the treatment of the COVID-19, nirmatrelvir and ensitrelvir, target this protease.

To discover novel small molecules inhibitors of the 3CL protease to fight SARS-CoV-2 but also future emerging coronaviruses, a high-throughput screening of more than 89,000 small molecules has been designed and performed on the SARS-CoV-2 $3CL^{pro}$. This screening enabled the discovery of several chemical series that entered a hit-to-lead optimization phase. Among them, a new chemotype of potent, covalent and selective inhibitor of the $3CL^{pro}$ of SARS-CoV-2 has been identified[(d)]. Here will be presented the screening and the characterization of this new series of inhibitors.

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Poster N°6

Identification of N-acylbenzimidazoles as new inhibitors of the main protease of SARS-CoV-2

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The Covid-19 pandemic caused by the coronavirus SARS-CoV-2 has led to more than 6 million deaths worldwide. Currently only few specific antiviral treatments against coronaviruses are available and there is a high risk of emergence of new viruses of this family in the future[1]. Thus, effective small molecules with broad spectrum antiviral activity are urgently needed to fight Covid-19 and potential emerging coronaviruses.

The project aims to develop novel molecules that target an essential component for the replication of coronaviruses; the 3CL protease, which is highly conserved within the coronavirus family[2]. This protease is the target of the two specific antiviral compounds used in the clinic; Nirmatrelvir (Paxlovid®) and Ensitrelvir (Xocova®). A high throughput screening of a chemical library of 90,000 compounds was performed in the laboratory on the 3CL protease of SARS-CoV-2 and led to the identification of several chemical series[3]. Here will be reported the optimization and structure-activity relationships of a series of N-Acyl-benzimidazole inhibitors.

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Poster N°7

Cross-reactive memory B cell populations established from the exposure to Japanese encephalitis virus

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To date, characterizing serological responses after flavivirus infections remains a major epidemiological challenge due to the serological crosstalk between DENV and ZIKV or other flaviviruses co-circulating in overlapping geographic regions and sequential co-infections occurring in the population. Human infection results in production of type-specific, sero-complex-reactive and flavivirus group cross-reactive antibodies. In this study, to explore the B-cell immune responses *in vivo* mimicking the sequential exposure of JEV and DENV in human infection, we conducted a prime-boost immunization study wherein mice were immunized with DENV-2 or JEV VLP antigens and evaluated the post-vaccination antibody response for neutralization against homologous and heterologous flavivirus serocomplexes. The result showed that the JEV-JEV VLP prime-boost immunization strategy induced antibodies with elevated levels of cross-neutralizing activities ranging from GMT FRµNT50 titers of 1.4 x 10^2 to 3.5 x 10^3. Notably, homologous JEV VLP prime-boost immunization consistently induced relatively higher neutralization titers not only to the homologous JEV (GMT FRµNT50 = 164) but also to the heterologous flavivirus serocomplexes not encountered (GMT FRµNT50, DENV-1 = 115; DENV-2 = 605; DENV-3 = 961, DENV-4 = 603, ZIKV = 64). To further investigate the memory B-cell (MBC) clones induced by homologous JEV VLP prime-boost immunization, two of the most responsive (FRµNT50 > 120) mice in this group were selected for generating hybridomas using homologous or heterologous antigens, JEV or DENV-2 VLPs, respectively, to stimulate MBC proliferation followed by immediate fusion with murine myeloma cells. Seventy-one percent of the 52 monoclones isolated from the 3D2 polyclone secreted JEV neutralizing mAbs with varying levels of potency at 50% inhibitory concentration (IC50) as strong, moderate, and weak (<1, 1-10, and >10 µg/mL, respectively). On the contrary, polyclonal hybridomas generated from the same homologous JEV VLP prime-boost mice but stimulated by heterologous D2VLP antigens secreted antibodies cross-reactive to JEV, DENV, and ZIKV VLPs. Fifty-eight percent of the 36 monoclones isolated from the 5D5 polyclone secreted JEV, ZIKV, and DENV1-4 cross-neutralizing mAbs, while the rest secreted sub-group, cross-neutralizing mAbs. Most of these mAbs exhibited moderate to weak cross-neutralizing activities. Notably, all 52 mAb from the JEV-VLP stimulation strategy belong to the IgG1 isotype, whereas 36 mAbs from D2VLP stimulation all belong to the IgG3 isotype, demonstrating that the heterologous VLP vaccination model induced the IgG3-focused recall responses. Thus, these findings suggest that heterogeneous MBC populations recognizing different flaviviruses can be established from JEV prM/E VLP antigens, and recalled upon subsequent heterologous VLP antigen exposure resulting in inducing IgG isotype-dependent responses with varying neutralizing activities.

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Poster N°8

Antiviral nucleoside analogues: Set up of phosphorylation tools to support compound characterization

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The current pandemic of SARS-CoV-2 has caused substantial health issues and emphasizes the immediate need of powerful antivirals. For several years, nucleoside analogues have been proving their efficiency as polymerase inhibitors against many viruses (HSV, HIV, HCV...) [(a)] and are a promising strategy against coronaviruses. [(b)] Nucleoside analogues are administered as pro-drug, metabolized intracellularly into their active 5'-triphosphate form and incorporated into the error-prone viral polymerase, by several mechanisms. [(b)]

Thus, to characterize these mechanisms and guide the synthesis of more powerful antivirals, in vitro studies require the access to the active phosphorylated forms. However, their syntheses present several issues, such as a low yield, a poor selectivity and a harsh purification. [(c)] Therefore, the objective of this project is to develop potent and universal tools to phosphorylate the nucleosides, combining enzymatic catalysis and phosphorus chemistry.

Several enzymes have been selected, expressed and purified. Biophysical studies (by DSF) enabled us to pre-screen experimental conditions of the enzymatic reactions and a fast HPLC method, transposable into a semi-preparative method, was developed to monitor the substrate conversion quantitatively. Once the tools developed, they are being used to phosphorylate sequentially and/or in cascade some antiviral nucleoside analogues and assist characterization studies on their therapeutic target. Finally, in order to improve the phosphorylation reactions, enzymes will be immobilized to increase the yield and facilitate the purification of the nucleotides.

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Poster N°9

Set up of an antiviral platform for evaluation of new therapeutics against native SARS-CoV-2 and its VOCs

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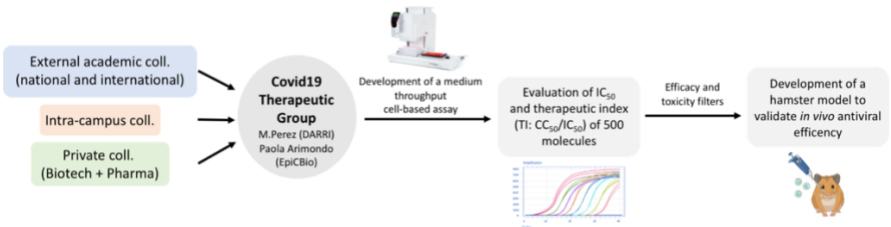
Chemogenomic and biological screening are important steps in the discovery of new medicines and in dissecting molecular pathways and biological networks. The Chemogenomic and Biological Screening Platform (PF-CCB) guides and supports researchers in their drug discovery programs by developing robust bioassays, identifying compounds for drug refinement and development, and addressing the molecular targets of drugs. During the COVID19 pandemic, the PF-CCB had to quickly adapt and set up screening strategies to search for active molecules on the native SARS-Cov-2 virus. A robust medium-throughput screening assay in 384-well format in a BSL3 environment was developed allowing for the evaluation of anti-viral properties (IC50 and CC50) of more than 400 molecules through 24 intra and extra campus collaborations. Among them, potent anti-viral human and camelid antibodies were isolated in collaboration with different research units in Institut Pasteur and the PF-CCB quickly set-up an *in vivo* model on Syrian Hamster to evaluate their antiviral potencies against a multitude of variants of SARS-CoV-2. This led to the development of a therapeutical antibody(a), which is currently under clinical development. This successful therapeutical pipeline can easily be adapted and used for other target of interest in various therapeutic areas.



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Poster N°10

Tick-Borne Encephalitis Virus-infected human neuronal/glial cells identify antiviral drugs

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Tick-Borne Encephalitis Virus (TBEV), a member of the Flaviviridae family, is the major arbovirus of health interest in Central/Northern Europe and North-Eastern Asia. It is responsible for neurological manifestations that may cause permanent disability or death. There is currently no therapeutic treatment for the disease. Although many studies have been conducted using murine models, there is a lack of relevant in vitro human models for neuropathological studies and drug discovery. Here, we infected human neuronal/glial cells (hNGCs) with TBEV and showed that in vitro infection reproduced major hallmarks of TBEV infection in the human brain, such as preferential neuronal tropism, neuronal death and astrogliosis. We then compared the antiviral activity of 8 selected molecules in hNGCs, human neural progenitor cells (hNPCs) and A549 cell line, as 3 models of TBEV infection of different relevance. We showed that most of the molecules had an antiviral activity in A549 but only one was efficient in hNGCs, demonstrating the importance of physiologically relevant models. Next, we developed an image-based phenotypic screen using hNGCs and tested a hundred and ninety compounds for their ability to restrict viral infection. This led to the identification of new antiviral compounds amongst which two may be therapeutically repositioned as they are drugs currently used in human medicine. The antiviral activity of one of them was further confirmed in a newly developed model of human cerebral organoids infected with TBEV. Such physiologically relevant 2D/3D in vitro models of TBEV infection offer a platform that should accelerate the identification of high value antiviral molecules.

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Poster N°11

From plants to the design of antiviral agents

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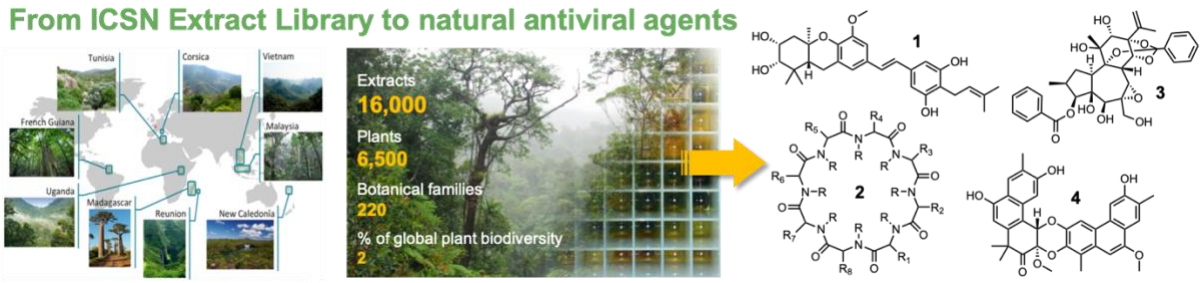
The **plant metabolites group** at the Institute of Chemistry of Natural Substances (**ICSN**) uses integrated approaches to study and valorize specialized metabolites isolated from plants. We develop transversal competencies from natural product isolation and identification to organic chemistry to:

1) explore the chemical diversity of tropical plants;
2) isolate new bioactive natural molecules;
3) improve their activities and properties by developing medicinal chemistry research programs;
4) study their mechanism of action by designing chemical probes.

All our research projects are based on an exceptional plant extract library named **Extractothèque ICSN**. This library gathers **more than 16,000 extracts** prepared from over 6,500 plants collected from areas of rich biodiversity. All the extracts are distributed in multi-well microplates and are available through the Chimiothèque Nationale for screening and hit discovery.

In close collaboration with internal and external partners to ICSN, we evaluate the therapeutic interest of the molecules isolated and synthesized to develop original antitumor agents but also antiviral agents acting against various viruses such as **HIV**, **CHIKV**, **DENV**, or **ZIKV**. Our partners also used these molecules as probes to decipher their mechanism of action and/or to better understand the virus studied. In recent years, this strategy led us to identify and characterize potent natural compounds of different chemical families as stilbene derivatives **1**,[(a)] cyclopeptides **2**,[(a)] phorbol type-compounds **3**,[(b-f)] or phenanthrene dimers **4**.[(c)] In some cases, we have developed synthetic approaches to elaborate libraries of analogs to improve their activities, their pharmacological properties, and their toxicity before potential *in vivo* trials.



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Poster N°12

Does SARS-CoV-2 infection reprogram codon optimality to favor viral RNA translation by altering the tRNA epitranscriptome

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Codon bias analysis of SARS-CoV-2 reveals suboptimal adaptation to the tRNA pool of human cells the virus infects. The precise examination of the codons preferentially used by SARS-CoV-2 shows a strong preference for certain codons (Lys AAA; Gln CAA; Glu GAA) rarely used in the human genome, requiring a modification of the U_{34} wobble position of the corresponding tRNAs ($tRNALys^{UUU}$; $tRNAGln^{UUG}$; $tRNAGlu^{UUC}$) to be efficiently decoded. This mcm^5s^2U modification consists of the gradual addition by a multi-enzymatic complex (ELP1-6, ALKBH8, CTU1/2) of a methoxycarbonylmethyl group in position 5 and of a thiol in position 2 of uracil 34 of these tRNAs. Our preliminary mass spectrometry analyzes show an early increase of the mcm5s2U mark and its intermediates on the tRNAs of human cells (Caco2) during their infection by SARS-CoV-2, and suggest that they may be beneficial to the viral cycle. We propose that the optimal translation of SARS-CoV-2 ORFs requires several adjustments to the host's translation machinery that will allow the highly biased viral genome to reach a more favorable "Ready-to-Translate" state in human cells.

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Poster N°13

Development of Peptide Inhibitors of Influenza Virus by Directed Evolution

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Influenza virus causes hundreds of thousands of deaths every year and can generate serious pandemics. Its high rate of genetic mutation has limited the use of currently available antivirals and creates a demand for new drugs targeting alternative mechanisms. Here we present our development of peptide inhibitors that block the assembly of key protein complexes necessary for influenza virus replication. The first complex targetted is the heterotrimeric influenza virus RNA polymerase (FluPol) that catalyses viral genome replication and transcription. We focused on the protein-protein interfaces between subunits where a natural peptide was shown previously to interfere with assembly[(a)]. A second complex targeted is the host RED-SMU1 complex, building on previous work showing that its transient destabilisation inhibits viral mRNA splicing and thus viral replication[(b)]. We built structure-guided phage display libraries of $>10^8$ random variants of natural interacting peptides and selected for high affinity binders to the partner domain. Multiple hits were characterised using ELISA, NGS and BLI, revealing alternative binding motifs that have never been observed naturally. For both systems, we are now combining biophysical, structural and cell-based methods to understand how these synthetic peptides function, and will seek to improve their performance using chemical optimisation and vectorisation strategies.

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Poster N°14

Inhibition du SARS-CoV-2 et des virus influenza A in vitro par la molécule AM-001, un inhibiteur pharmacologique de la protéine EPAC1

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Dès les prémices de la pandémie de COVID-19, la maladie causée par le virus SARS-CoV-2 (*Severe Acute Respiratory Syndrome Coronavirus 2*), la recherche de nouvelles molécules antivirales est apparue comme l'une des stratégies essentielles pour lutter contre cette infection virale aux multiples formes chez l'Homme.

Les molécules antivirales ciblant l'hôte ont le potentiel de présenter une activité antivirale à large spectre. Elles sont également considérées comme moins susceptibles de sélectionner des variants viraux résistants. Dans cette étude, nous avons évalué l'activité antivirale exercée par la molécule AM-001, un inhibiteur pharmacologique spécifique de la protéine EPAC1 (*exchange protein directly activated by cAMP*). Activée par l'AMP cyclique (AMPc), EPAC1, est fortement impliquée dans de nombreux processus physiopathologiques tels que l'infarctus du myocarde. Si son rôle lors d'infections virales, *in vitro,* par les virus SARS-CoV-1 et MERS-CoV avait déjà été étudié, celui dans l'infection par le SARS-CoV-2 et les virus influenza A n'avait pas encore été démontré.

Notre étude montre ici que l'inhibiteur spécifique d'EPAC1, AM-001, exerce une activité antivirale contre le SARS-CoV-2 (Pre-VOC) dans les lignées Calu-3 (cellules pulmonaires humaines) et VERO E6 (cellules de rein de singe). Nous avons observé une inhibition concentration-dépendante de la production des particules virales infectieuses du SARS-CoV-2 associée à une diminution de l'ARN viral dans les surnageants des cellules traitées par AM-001.

En parallèle, nous avons montré que AM-001 avait également une activité inhibitrice de la réplication du virus influenza A H1N1 (A/PR/8/34) dans les cellules Calu-3. Enfin nous avons montré que cette inhibition n'avait pas d'impact significatif sur la viabilité cellulaire et que la molécule n'avait aucune activité virucide directe sur les virus testés.

L'ensemble de ces résultats suggère que l'inhibition d'EPAC1 pourrait représenter une cible thérapeutique prometteuse contre les infections virales.

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Poster N°15

Evaluation of Pfizer vaccines efficiency against new VOC of SARS- CoV-2: XBB 1.1

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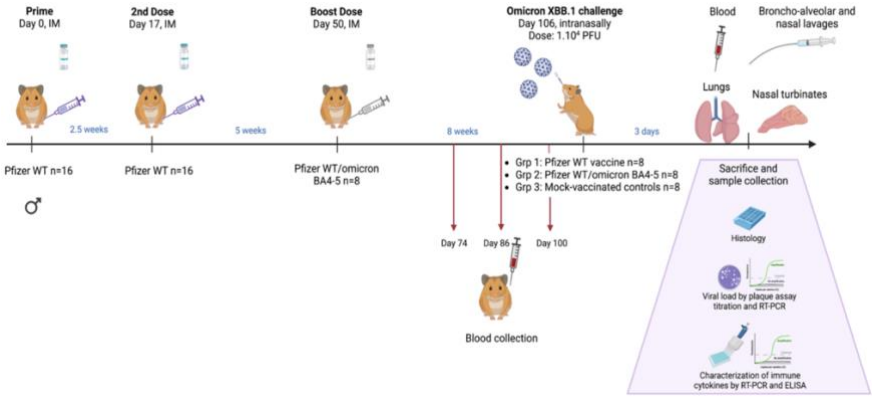
The wide diversity of SARS-CoV-2 variants which have emerged for last months from the different Omicron sub-lineages has been of great concern to the EMERGEN consortium coordinated by Santé Publique France and ANRS-MIE. These new variants of concern (VOC) harbor a large set of mutations in the viral surface protein Spike, giving rise to immune escape and raising concerns about the efficacy of Pfizer vaccines in immunized populations. To this end, we investigated the efficacy of monovalent and bivalent booster (Omicron BA.4/BA.5-containing) mRNA COVID-19 vaccines against the VOC Omicron XBB 1.1 in a Syrian hamster model.

Strikingly, we observed a 1.8- and 4.7- fold decrease of virus load in lungs and a 1.7- and 17.7- fold marked decrease in nasal turbinates after the monovalent vaccine and bivalent booster, respectively. Consistently, we observed that a complete vaccine regimen was required to successfully maintain an appropriate balance between the inflammatory response and robust immune protection. These data were also in agreement with the histopathological evaluation since the vaccinated animals exhibit less lesions and lung damage as compared to unvaccinated ones.

Taken together, these data strongly support the notion that the Pfizer bivalent vaccine displays a significant immune protective effect against the new XBB 1.1 Omicron variant.



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Poster N°16

Synthesis, biophysical and biological evaluation of original heterocyclic ligands as anti-SARS-CoV-2 agents by targeting G4

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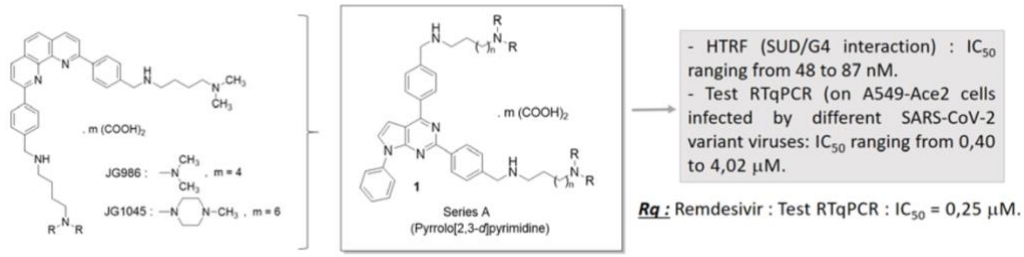
The Covid-19 pandemic caused by the emerging severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is one of the deadliest in human history [1]. There is an urge to develop new antiviral agents, in particular those targeting viral-host interactions. The multidomain non-structural protein 3 (Nsp3) is the largest protein encoded by coronavirus (CoV) genomes and several regions of this protein are essential for viral replication. Our work aims at interfering the interaction between Nsp3 and cellular partners.



Recently, we have shown that SARS-CoV-2 Nsp3 contains a SARS-Unique Domain (SUD), which can bind Guanine-rich non-canonical nucleic acid structures called G- quadruplexes (G4)[2]. These interactions can be disrupted by mutations that prevent oligonucleotides from folding into G4 structures and, interestingly, by molecules known as specific ligands of these G4s. By taking into accounts the various structural parameters required concerning the previously described G-quadruplex ligands, we are currently designing, and synthesizing new bioisoster compounds analogs (Series A) of the first identified bioactive phenanthroline hits [3].

In the present study, we report on the synthesis of these new compounds and their efficient in vitro activities targeting the SUD/G4 interaction (by HTRF) and SARS-CoV-2 replication (in A549-Ace2 cells infected by different variant viruses). We also present promising data on the pharmacological properties of these molecules in cells and small animal models of viral infection.

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Poster N°17

Design and synthesis of naturally inspired SARS-CoV-2 inhibitors

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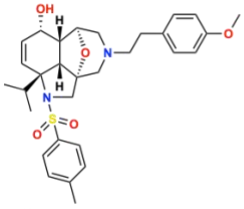
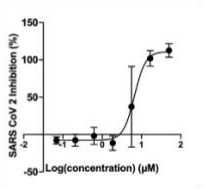
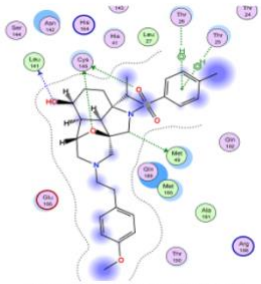
A naturally inspired chemical library of 33 molecules was synthesised guided by 3-D dimensionality and natural product likeness factors to explore a new chemical space. The synthesised chemical library, consisting of fused-bridged dodecahydro-2a,6-epoxyazepino[3,4,5-c,d]indole skeletons, followed lead likeness factors in terms of molecular weight, C-sp3 fraction and clog P. Screening of the 25 compounds against lung cells infected with SARS-CoV-2 led to the identification of hits compound **3b** with antiviral activity (EC_{50} values of 3.7µM) with an acceptable cytotoxicity difference. Computational analysis based on docking and molecular dynamics simulations against main protein targets in SARS-CoV-2 (main protease Mpro, nucleocapsid phosphoprotein, non-structural protein nsp10–nsp16 complex and RBD/ACE2 complex) suggested Mpro (Nsp5) as the possible binding target. Biological assays were performed to confirm this proposition. A cell-based assay for Mpro protease activity using a reverse-nanoluciferase (Rev-Nluc) reporter[(a)] confirmed that **3b** targets Mpro[(b)]. A convergent chemical synthesis was designed to allow further hit-to-lead optimisations. Structure Activity Relationship within this series will be presented.



Compound 3b



SARS-CoV-2 inhibition in ACE-2 A549 cell line



Main interactions of 3b with Mpro catalytic site residues

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Poster N°18

Iso-SATE versus SATE as mononucleotide prodrugs

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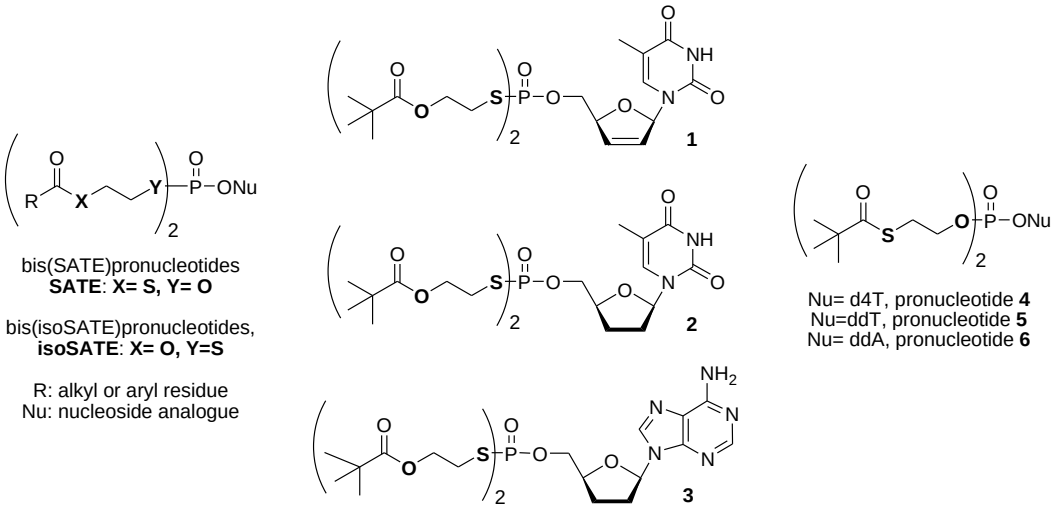
A novel series of pronucleotides, characterized by a phosphorodithiolate structure, and incorporating two O-pivaloyl-2-oxyethyl (isoSATE) substituents as biolabile phosphate protections was investigated on the basis of d4T, ddT and ddA as nucleoside analogue models (Figure).[a] All compounds were obtained following an original one-pot three-step procedure, involving the formation of a phosphorodithioite intermediate which is *in situ* oxidized. Then, comparative anti-HIV evaluation demonstrated that such original prodrugs were able to deliver intracellularly the corresponding 5' -mononucleotide and were as potent as their SATE analogs. Thus, pronucleotide **3** exhibited a very potent antiretroviral effect with EC_{50} (50% effective concentration) values in the nanomolar range in various cell lines. In primary monocytes/ macrophages, this derivative was 500 times more potent in inhibiting HIV replication (EC_{50} 0.23 pM) than the parent compound, and the selectivity index of the prodrug is 50 times higher.

Figure. Structures of the pronucleotides investigated herein.



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Poster N°19

Finding antiviral small molecules that inhibit ACE2-Spike binding: a challenging study

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SARS-CoV-2, the cause of COVID-19 pandemic, led to almost 760 million confirmed cases and more than 6 million deaths, according to WHO. While vaccines against SARS-CoV-2 were successfully developed and distributed, the search for treatment of COVID-19 is still an actual problem. Antibodies work efficiently however the emergence of new resistant variants and their complicated production and high cost leave the need to have small molecule drugs. To date, only two oral drugs received emergency use authorization by FDA and are available on the market to treat COVID-19: Molnupiravir and Paxlovid.

The mechanism of cellular entry of SARS-CoV-2 gave rise to extensive research studies. Its first step consists of binding of viral particle to the ACE2-receptor on the cell surface by receptor binding domain (RBD) of the Spike protein. Our primary goal was to find small molecules that prevent the formation of the tight complex between Spike protein of SARS-CoV-2 and ACE2 receptor and therefore block cell entry of the virus. For this, we developed a robust assay based on Homogenous Time Resolved Fluorescence and screened the oriented Fr-PPIChem library of 10314 small molecules. Strikingly, two hits as well as two their analogues efficiently inhibited infection/replication of native Wuhan SARS-CoV-2 and one of its variants in a cell-based assay with a therapeutic index (CC50/IC50) > 30. The binding of these compounds to both RBD and ACE2 was confirmed by NMR using Saturation-Transfer Difference. However, compounds were not able to efficiently prevent formation of RBD/ACE2 complex as judged by biolayer interferometry. This low competition activity between RBD and ACE2 was further confirmed by new technology called grating-coupled interferometry technology (Creoptix, Malvern Panalytical) since direct binding titration showed that compounds are weak binders of RBD and ACE2.

Next, we performed additional cellular imaging experiments to decipher the mechanism by which these compounds exhibit potent antiviral activities. We showed that the antiviral activity of these small molecules was mainly due to the phospholipidosis, a mechanism which has recently been reported for most of repurposed drugs. [(a)] Altogether, we suggest that combining the phospholipidosis inducing properties and ACE2/Spike binding inhibition could be a promising strategy to further develop a new class of compounds exhibiting high antiviral activity with reduced phospholipidosis.

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Poster N°20

When Two is Better than One: broadly neutralizing antibodies against Zika virus from JEV-immune, dengue-infected individuals

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The re-emergence of Zika virus (ZIKV) among the dengue virus (DENV)-experienced population has raised significant public health alarms due to the increased neurological and congenital disabilities, especially in the Americas[a,b]. However, the low ZIKV transmission and minimal ZIKV-associated microcephaly events in Asia remain poorly understood despite the co-circulation of ZIKV and DENV in the region for decades [c,d]. To our current knowledge, this study provided the first serological evidence of elevated ZIKV-neutralizing antibodies from dengue patients previously exposed to the Japanese encephalitis virus (JEV) infection or vaccination. Using a well-established and clearly-defined cohort of JEV-immune donors with recent dengue infection, the percentage of individuals with elevated DENV and JEV titers and high ZIKV cross-reactive and cross-neutralizing activities was higher than the proportion of individuals with only one immunity. Elevated cross-neutralizing antibodies against ZIKV were also observed among the 50-70-year age group (JEV infected) than in the 20-30-year age classification (JEV vaccinated). Of 31 JEV- and dengue-immune individuals with ZIKV VLP reactive IgGs, 18 (or 58%) individuals showed higher levels of ZIKV VLP-binding IgG3 antibodies. Notably, the magnitude of the humoral responses to ZIKV strongly correlates with the plasma IgG3 antibodies in circulation. The discovery of a rare class of antibodies with superior breadth and potency from individuals with clearly defined DENV and JEV immunity highlights the role of flavivirus pre-immunity to the breadth of humoral response and cross-immunity to ZIKV in the context of the Japanese encephalitis virus, which is endemic in most Asian territories. With this information, administering JEV vaccines in DENV-endemic countries may be a safe and practical approach to mitigate the risk of ZIKV infection during pregnancy and for infants and travelers to ZIKV-endemic territories. Further, the isolation of broadly neutralizing fully human monoclonal antibodies is a promising and rapidly growing therapeutics which, when developed further, may be safe and effective prophylactic or antiviral agents.

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Poster N°21

In vitro assessment of the efficacy of Human Immunodeficiency Virus antiretroviral drugs against Equine Infectious Anemia Virus

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Equine Infectious Anemia Virus (EIAV) is a macrophage-tropic lentivirus belonging to the Retroviridae family, closely related to the Human Immunodeficiency Virus (HIV). Equine Infectious Anemia (EIA) is an almost worldwide disease, characterized by an acute phase with vague clinical signs followed by a chronic phase with recurring febrile episodes and finally an asymptomatic phase, where the asymptomatic carriers never eliminate the virus and become a reservoir.
As EIA has no treatment (vaccines or antiviral molecules approved for equine use), our strategy is to test molecules already characterized as antiretroviral drugs, and explore their effects on EIAV replication. Since HIV and EIAV are both lentiviruses and share steps in their replication mechanisms, we have selected for our study 17 molecules used to fight HIV infection. We evaluated the molecules' cytotoxicity on equine dermis cells. This cell model allowed us to choose the range of molecule concentration to use to test against EIAV infection. As EIAV is a non-lytic virus, to assess the infection, we have developed an *in vitro* EIAV infection protocol on equine cells and set up an RT-qPCR protocol to quantify the EIAV viral replication. Taking advantage of this successful *in vitro* infection model, we tested the 17 selected drugs to assess their potential antiretroviral effects against EIAV. Our results showed that 13 out of the 17 tested drugs importantly decrease (up to 3 logs) the EIAV virion production. We observed that not all viral protein-specific antiretroviral classes are equally efficient against EIAV. These observations could highlight viral proteins similarity and differences between HIV and EIAV to explore. For this purpose, we took advantage of the Alphafold2[(a)] algorithm to predict folding of all EIAV proteins and compare them to HIV-1 proteins thanks to the DALI protein structure comparison server[(b)]. Indeed, there is a low sequence homology between EIAV and HIV-1 proteins but their structures are more similar. We compared them to highlight similarities or differences explaining molecules antiviral activity or not on EIAV multiplication in our *in vitro* model.

These exciting results make us believe that EIAV is an interesting and unexplored research model to contribute in the understanding of the fundamental mechanism of lentiviral infections and help in the antiretroviral drug development following a translational antiviral strategy.

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Poster N°22

Mechanism of action and drug-resistance of Remdesivir, a viral RNA chemical corruptor

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Remdesivir (RDV) is the first FDA approved antiviral treatment for COVID-19. RDV is a nucleotide analogue carrying a ribose 1'-cyano (-CN) group and a pseudo-adenine. Nevertheless, its mode of action (MoA) against SARS-CoV-2 is still unclear. Here, we present a mechanistic analysis with SARS-CoV-2 purified enzymes; active RNA dependent RNA polymerase (RdRp) : nsp12, nsp8, nsp7; and active exonuclease (ExoN) : nsp14, nsp10; on the incorporation and excision of analogues dissecting independent contributions of RDV chemical modifications: RDV-triphosphate [RDV-TP], RDV-TP without 1'-CN [RDV(-CN)-TP], RDV where pseudo-adenine base has been replaced with an adenine base [ATP+CN]. Our biochemical assays show that the 1'-CN group allows and promotes mismatch formations suggesting mutagenic behavior. Once incorporated into RNA, RDV-MP is excised seemingly as well as other RDV analogues or a natural mismatch. The 1'-CN doesn't provide any significant protection against excision. Two RDV resistance mutations selected in infected cells (S759A & A777S) yield RdRp exhibiting modest RDV discrimination but more importantly, an increased stalling during synthesis translating into more time for excision-repair. We conclude that the chemical groups of RDV incorporated into RNA have no direct effect on excision, indirectly supported by the fact that no ExoN resistance mutation has been reported so far. We propose that RDV's success against SARS-CoV-2 is due to multiple factors like low levels of RdRp stalling, inducing misincorporations but mainly due to the synthesis of a chemically corrupted viral RNA disturbing downstream functions in the virus life cycle.

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Poster N°23

Tackling technical issues for the evaluation of vaccine against Human Parvovirus B19: New cell lines allowing Enhanced Detection and Production of B19 infectious particles.

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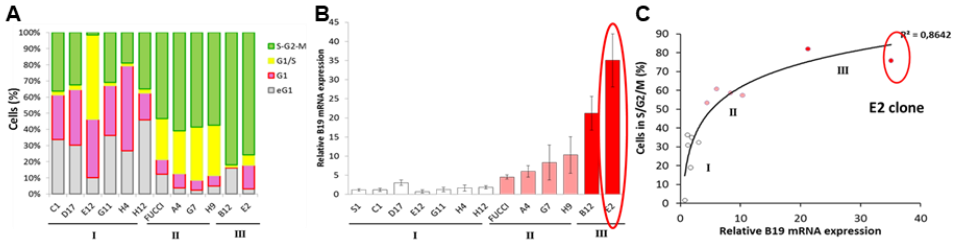
Human parvovirus B19 (B19) is a single-stranded DNA virus responsible for diseases with severities ranging from benign childhood illness to arthropathies, severe anemia or hydrops fetalis, depending on age, health and hematological status of the patients. At present, no vaccine, drugs or monoclonal antibody are available to support preventive or curative therapeutic response, largely due to the lack of a relevant *in vitro* cell model to evaluate and develop specific treatments against B19. Here we report the evaluation of B19 infectious particles production in permissive cells, and improvement of infectious particles detection.

Of all the tested erythroid cell lines, our UT7/Epo cells (named UT7/Epo-STI) showed the highest sensitivity to B19 infection. We generated stable sub-clones, and selected those with the highest permissiveness for B19. Using FUCCI (Fluorescent Ubiquitination Cell Cycle Indicator) expression system, we showed a direct correlation between infectivity and the cell cycle status of the cells (figure below).



New cell lines allowing Enhanced Detection and Production of B19 infectious particles.

***A.** Classification of UT7 clones according to cell cycle profile assessed by FUCCI. **B.** B19 permissivity of UT7 clones. **C.** Relationship between S/G2/M cell cycle status and B19 permissivity.*

Among sub-clones, UT7/Epo-E2 had B19 detection and infectious unit production capacities comparable to those obtained with $CD36^+$ primary erythroid progenitor cells, the natural host cells for B19V: up to 10^9 B19 Genome Equivalent/mL of supernatant were obtained, and the B19 infectious units production reached more than 10^4 $TCID_{50}$/mL. Unsupervised Principal Component Analysis of transcriptomes from several clones with graded B19V permissivity showed that our cell lines were significantly different from the UT7/Epo-S1 reference cell line. Using pairwise differential analysis between clones according to their B19 permissivity, transcriptomic pathways and molecular signatures are analyzed and related to B19V viral cycle.

Altogether, our data propose a simple cell-based method for detecting, quantifying and producing B19 infectious units, and a straightforward suitable new tool for the development of specific treatment against B19.

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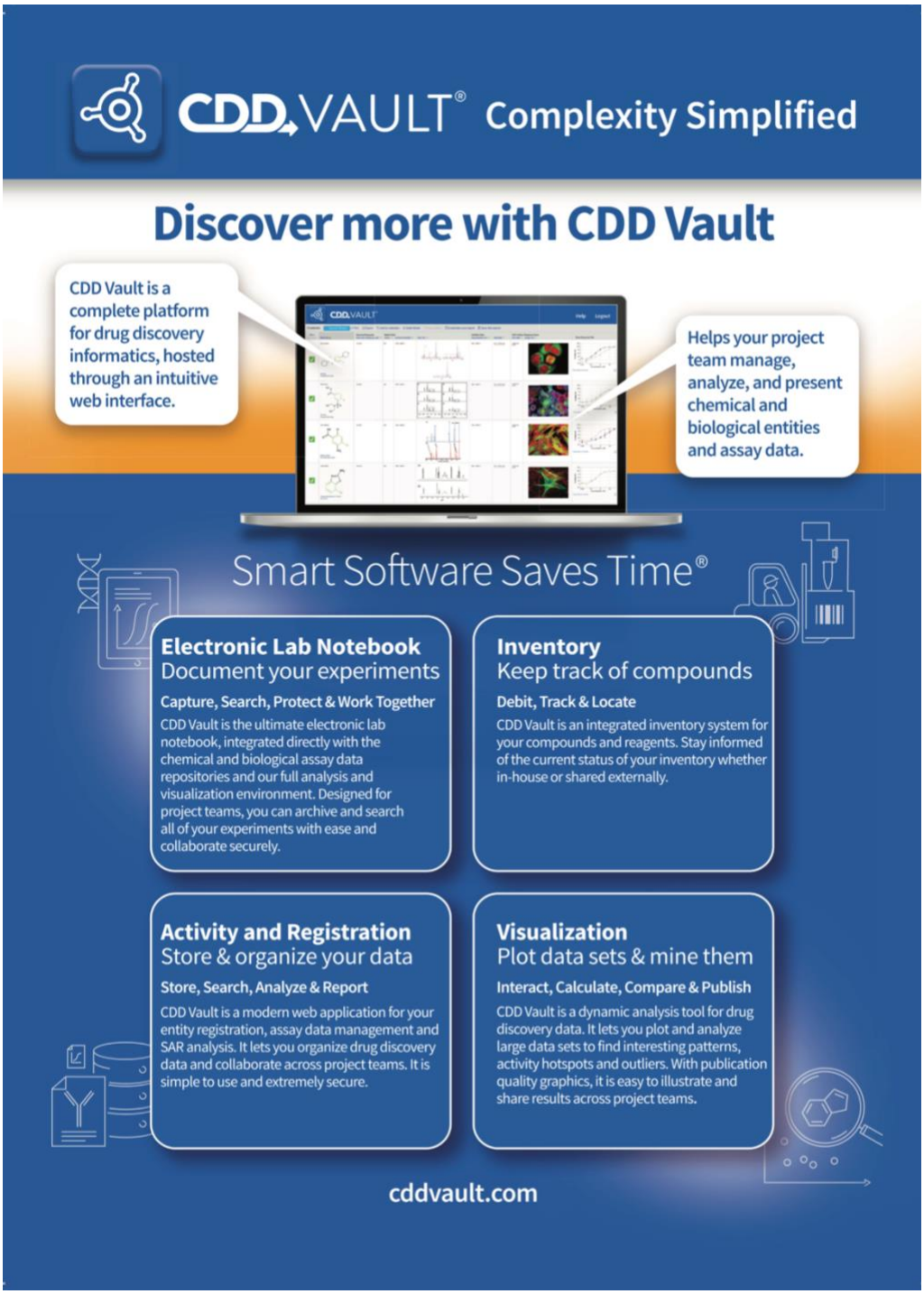

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SPAIS – EID strategic axis

Ever since its very early days, the Institut Pasteur has been committed to tackling emerging infections, and its work has left an extraordinary legacy. Many emerging infectious diseases are zoonoses, in which an animal pathogen has crossed the species barrier to cause disease in humans.

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Coordinators of the Institut Pasteur Emerging Infectious Diseases strategic axis:

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La Société française de virologie (SFV), membre du collège des sociétés savantes, a été créée en 2015. Cette société regroupe un réseau de virologistes provenant de différents laboratoires de France et d'ailleurs. Elle représente toutes les composantes de la virologie allant de la recherche fondamentale à la virologie appliquée et la virologie clinique.
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- organise un congrès annuel, les Journées Francophones de Virologie, qui regroupe près de 500 participants chercheurs, ingénieurs, techniciens, étudiants, pharmaciens, vétérinaires, médecins et professeurs.
- édite le bimensuel Virologie (éditeur JLE), son journal officiel qui propose une revue de la littérature actualisée dans tous les domaines de la virologie animale et humaine, végétale ou bactérienne sous des aspects de recherche fondamentale ou appliquée, pour souligner les découvertes les plus récentes et identifier les défis futurs.

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