First Name / Last name: Hervé Bourhy
Contact : herve.bourhy@pasteur.fr

Unit: Lyssavirus epidemiology and neuropathology, National Reference Centre for Rabies, WHO Collaborating Centre for reference and research on rabies
IP Department or IP: Global Health
Secondary affiliation: Virology

Main domains 1: Virus

Main domain 2: surveillance and epidemiology, new molecules, alternative strategies

Attractive synopsis:
Our project aims at developing a new protocol for rabies post exposure prophylaxis (PEP) and a successful treatment, ultimately improving the probability of survival of patients who have not received adequate PEP and have possibly developed rabies symptoms.

Research projects in relation with AMR:
Rabies is an untreatable disease of humans, which has a case-fatality rate of almost 100% in non-vaccinated individuals. Rabies virus replication and viral RNA capping machinery constitutes a promising antiviral target for the development of therapeutic approaches. In particular, new antiviral compounds active in the brain of infected animals and new human monoclonal antibodies that could advantageously replace the classical serotherapy are investigated. These new developments obtained through a strong collaboration between the academic and the private sectors now allows our unit to consider and work in animals on the proof of concept of a paradigm shift in post exposure prophylaxis and successful treatment of rabies in humans. This research project provides a continuum of activities between fundamental and basic research, development and field applications maintaining the intimate connection with public health problems of interest to the National Reference Centre for Rabies and to the World Health Organization Collaborative Centre for Research and Reference for Rabies, both of whom are housed in the unit.

3 Publications

- De Benedictis P, Minola A, Rota Nodari E, Aiello R, Zecchin B, Salomoni A, Foglierini M, Agatic G, Vanzetta F, Lavenir R, Lepelletier A, Bentley E, Weiss R, Cattoli G, Capua I, Sallusto F, Wright E, Lanzavecchia A, Bourhy H, Corti D (2016). Development of broad-spectrum human monoclonal antibodies for rabies post-exposure prophylaxis. *EMBO Mol Med*. 8(4):407-21.
- Taylor E, Banyard AC, Bourhy H, Cliquet F, Ertl H, Fehlner-Gardiner C, Horton DL, Mani RS, Müller T, Rupprecht CE, Schnell MJ, Del Rio Vilas V, Fooks AR. Avoiding preventable deaths: The scourge of counterfeit rabies vaccines. Vaccine. 2019 Apr 17;37(17):2285-2287.
- Rogée S, Larrous F, Jochmans D, Ben-Khalifa Y, Neyts J, Bourhy H. Pyrimethamine inhibits rabies virus replication in vitro. Antiviral Res. 2019 Jan;161:1-9. doi: 10.1016/j.antiviral.2018.10.016

First Name / Last name: Olivier Gascuel
Contact : olivier.gascuel@pasteur.fr

Unit: Bioinformatique évolutive
IP Department or IP: Computational Biology

Main domains 1: Virus

Main domain 2: surveillance and epidemiology, mechanism of resistance and dissemination

Attractive synopsis:

Phylogeny-, modelling-, and machine learning-based analyses of the emergence and diffusion of drug resistance mutations in HIV.

Research projects in relation with AMR:

Our expertise is mathematical modelling, algorithmics, machine learning, evolutionary biology, phylogenetics, and molecular epidemiology. Our aims are: (1) to discover new drug resistance mutations (DRM) in HIV, depending on the treatment, subtype, risk group, and country/continent; (2) study the epistatic effects among DRMs; (3) establish the mechanisms and conditions of DRM emergence and reversion; (4) determine the fraction of transmitted DRMs and the corresponding populations; (5) apply our models and methods to other pathogens (e.g. TB).

3 Publications

Zhukova A, Cutino-Moguel T, Gascuel O, Pillay D. The Role of Phylogenetics as a Tool to Predict the Spread of Resistance. J. Infectious Diseases, 216(suppl_9):S820-S823, 2017.

VILLABONA-ARENAS CJ, VIDAL N, GUICHET E, SERRANO L, DELAPORTE E, GASCUEL O, PEETERS M, “In-depth analysis of HIV-1 Drug Resistance Mutations in HIV-infected individuals failing first-line regimens in West and Central Africa”, AIDS, 30(17):2577-2589, 2016.

Mourad R., Chevennet F., Dunn D.T., Fearnhill E., Delpech V., Asboe D., Gascuel* O., Hue* S., “A phylotype-based analysis highlights the role of drug-naive HIV-positive individuals in the transmission of antiretroviral resistance in the UK”, AIDS 29 (15), 1917-1925, 2015.

First Name / Last name: Michaela Müller-Trutwin (head), Asier Saez-Cirion (team leader)
Contact : mmuller@pasteur.fr

Unit: HIV, Inflammation and Persistence
IP Department or IP: Virology Department
Secondary affiliation: Immunology Department

Main domain 1: Virus

Main domain 2: *in order of priority:* mechanism of dissemination and its control, new host targets, biomarkers, alternative strategies, methodological developments.

Attractive synopsis:
We search for host-directed therapies aiming to kill HIV-infected cells or durable control HIV infection in order to contribute to the development of a cure for HIV.

Research projects in relation with AMR:

Since the discovery of HIV, tremendous progress has been made in preventing and treating HIV infection. However, a vaccine and a cure are still missing. We search for unprecedented mechanisms of HIV control and protection against HIV-associated non-AIDS morbidity and mortality. Our approach consists in learning from HIV-infected individuals who control HIV replication, either spontaneously or after an antiretroviral treatment (HIV remission) and in some very rare animal models of spontaneous protection. We have identified innate immune and metabolic factors involved in HIV control. Based on the discoveries, we develop novel host-directed therapies that are tested in pre-clinical trials. On the longer term, the studies shall help to define scalable approaches for a durable HIV remission. In addition, the studies are designed to allow for the screening of biomarkers of inflammation and HIV remission.

3 (max) Publications

- Huot N, Jacquelin B, Garcia-Tellez T, Rascle P, Ploquin M, Madec Y, Reeves RK, Derreudre-Bosquet N & Müller-Trutwin M. NK cells migrate into and control SIV replication in lymph node follicles in African green monkeys. **Nat Med**. 2017 Nov;23(11):1277-1286.
- Valle-Casuso JC, M Angin, S Volant, C Pereira Bittencourt Passaes, V Monceaux, K Bourdic, V Avettand-Fenoel, F Boufassa, M Sitbon, O Lambotte, M Thoulouze, M Müller-Trutwin, N Chomont and A Sáez-Cirió. Cellular metabolism is a major determinant for the seeding of the HIV-1 reservoir in CD4+ T cells. **Cell Metabolism**. 2019. pii: S1550-4131(18)30734-4.
- Saez-Cirion A, Müller-Trutwin M. The yellow brick towards HIV Eradication. **Trends Immunol**. 2019 May 6. pii: S1471-4906(19)30093-6.

First Name / Last name: Nadia Naffakh
Contact : nadia.naffakh@pasteur.fr

Unit: Molecular genetics of RNA Viruses
IP Department or IP: Virology
Secondary affiliation:

Main domains 1: Virus

Main domain 2: new molecules, alternative strategies

Attractive synopsis:
We recently demonstrated the potential of synthetic molecules that destabilize the RED-SMU1 splicing complex as an antiviral, host-directed therapy which could be active against a wide range of influenza viruses and be less prone to drug resistance.

Research projects in relation with AMR:
Influenza virus is a serious threat to global public health and there is a critical need for innovative anti-influenza drugs. Two broad, non-exclusive approaches to inhibit viral replication are possible, either targeting directly viral proteins or targeting host proteins essential for the viral life cycle. We are taking the second approach, which is more likely to counter the problem of drug-resistant virus emergence. We are focusing on cellular partners of the influenza virus polymerase (the RED-SMU1 splicing complex, the cellular RNA polymerase II and associated transcription factors).

3 Publications

• Ashraf A, Tengo L, Le Corre L, Fournier G, Busca P, McCarthy A, Rameix-Welti MA, Gravier-Pelletier C, Ruigrok R, Jacob Y, Vidalain PO, Pietrancosta N*, Crépin T*, Naffakh N*. Destabilisation of the human RED-SMU1 splicing complex as a basis for host-directed anti-influenza therapy. **Proc Natl Acad Sci USA, in press**

• Lukarska M, Fournier G, Pflug A, Resa-Infante P, Reich S, Naffakh N, Cusack S. Structural basis of an essential interaction between influenza polymerase and Pol II CTD. **2017. Nature** 541(7635):117-121. doi: 10.1038/nature20594.

• Fournier G[#], Chiang C[#], Munier S, Tomoiu A, Demeret C, Vidalain PO, Jacob Y, Naffakh N*. Recruitment of RED-SMU1 complex by Influenza A Virus RNA polymerase to control Viral mRNA splicing. **2014. PLoS Pathog** 12;10(6):e1004164. doi: 10.1371/journal.ppat.1004164.

First Name / Last name: Félix Rey
Contact : felix.rey@pasteur.fr

Unit: Structural Virology
IP Department or IP: Virology
Secondary affiliation: Structural Biology and Chemistry

Main domains 1: Viruses (and also gamete fusion of eukaryotic parasites *Trypanosoma, Plasmodium*)

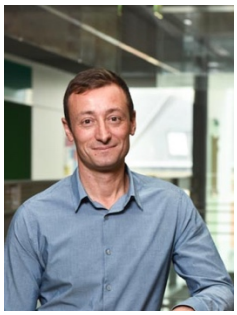
Main domain 2: Antibody neutralization of viruses – Virus evolution

Attractive synopsis:
We study the tree-dimensional organization of virus particles and certain viral replication enzymes. But we mainly focus on enveloped viruses and the envelope glycoproteins anchored in the viral membrane. All enveloped viruses have a specialized protein that induces the merger of the viral envelope with the membrane of the cell for entry, and one main emphasis in the Unit is to understand the molecular mechanism involved, as well the evolutionary links with proteins driving the fusion of eukaryotic cells, for instance the fusion of sperm and egg.

Research projects in relation with AMR:
Among other results, we have characterized the interaction of broadly neutralizing antibodies against flaviviruses, especially antibodies that potently neutralize all four circulating dengue viruses as well as Zika virus. These studies are important as the presence of poorly neutralizing antibodies against dengue virus has been shown to correlate with the severity of the disease. We are currently trying to understand how to use the structural results to inform the design of better immunogens to confer immunity against all four dengue viruses simultaneously.
In parallel, we are characterizing the structure of the envelope proteins of New World hantaviruses, agents of the deadly hantavirus pulmonary syndrome, and their interactions with antibodies. We have also studied the fusion protein of the Rift Valley Fever virus, and identified a specific lipid binding pocket that can be used to derive specific antiviral compounds.

3 Publications

- Hellert J, Aebischer A, Wernike K, Haouz A, Brocchi E, Reiche S, Guardado-Calvo P, Beer M*, Rey FA* *Orthobunyavirus* spike architecture and recognition by neutralizing antibodies. **Nat Commun**. **2019** Feb 20;
- Guardado-Calvo P*, Atkovska K, Jeffers SA, Grau N, Backovic M, Pérez-Vargas J, de Boer SM, Tortorici MA, Pehau-Arnaudet G, Lepault J, England P, Rottier PJ, Bosch BJ, Hub JS, Rey FA* *A glycerophospholipid-specific pocket in the RVFV class II fusion protein drives target membrane insertion.* ***Science*** **2017** 358:663-667
- G. Barba-Spaeth, W. Dejnirattisai, A. Rouvinski, M.-C. Vaney, I. Medits, A. Sharma, E. Simon-Lorière, A. Sakuntabhai, V.M. Cao-Lormeau, A. Haouz, P. England, K. Stiasny, J. Mongkolsapaya, F.-X. Heinz*, G.R. Screaton* and F.A. Rey* *Structural basis of potent Zika-dengue virus antibody cross-neutralization*. ***Nature*** *2016* 536:48-53



First Name / Last name: Marco VIGNUZZI
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Unit: Populations virales et pathogenèse
IP Department or IP: Virology

Main domain 1: Virus

Main domain 2: mechanism of resistance and dissemination, alternative strategies, evolution

Attractive synopsis:
We study how viruses evolve and how they adapt to new environments; as such, we identify the ways that viruses can evolve to escape antiviral approaches and develop ways to counter these measures through evolutionary concepts.

Research projects in relation with AMR:
We study RNA viruses in general. The viruses currently used in our lab include influenza virus; the enteroviruses (poliovirus, Coxsackie virus, rhinovirus, enterovirus 71); the alphaviruses (Sindbis, Chikungunya, Mayaro, O'nyong'nyong, Ross River); the flaviviruses (dengue, Zika, Usutu). Our research seeks to identify how these viruses can evolve to adapt to new environments, or escape from selective pressures, including antimicrobials. We evaluate new antiviral compounds and determine whether resistance can emerge. We use mathematical modelling to help determine the likelihood of resistance emergence, and to design treatment regimens that reduce this risk.

3 Publications

- Moratorio G, Henningsson R, Barbezange C, Carrau L, Bordería AV, Blanc H, Beaucourt S, Poirier EZ, Vallet T, Mounce BC, Fontes M, Vignuzzi M* (2017). Attenuation of RNA viruses by redirecting their evolution in sequence space, *Nature Microbio*, 2017 Jun 5;2:17088. doi: 10.1038/nmicrobiol.2017.88....
- Mounce BC, Cesaro T, Moratorio G, Hooikaas PJ, Yakovleva A, Werneke SW, Smith EC, Poirier EZ, Simon-Loriere E, Prot M, Tamietti C, Vitry S, Volle R, Khou C, Frenkiel MP, Sakuntabhai A, Delpeyroux F, Pardigon N, Flamand M, Barba-Spaeth G, Lafon M, Denison MR, Albert ML, Vignuzzi M*. Inhibition of polyamine biosynthesis is a broad-spectrum strategy against RNA viruses. *J Virol.* 2016 Aug 17. pii: JVI.01347-16.
- Beaucourt S and Vignuzzi M*. (2014) Ribavirin: a drug active against many viruses with multiple effects on virus replication and propagation. Molecular basis of ribavirin resistance. *Curr Opin Virol*. May 17;8C:10-15. doi: 10.1016/j.coviro.2014.04.011

Name / Last name: Sylvie van der Werf
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Unit: Molecular Genetics of RNA Viruses

IP Department or IP: Virology

Main domains 1: Virus

Main domain 2: surveillance and epidemiology, mechanism of resistance and dissemination, alternative strategies, technological and methodological developments.

Attractive synopsis:
Our research focus on the mechanisms of virus evolution and virus-host protein-protein interactions as well as the large collection of influenza and other respiratory viruses of the National Reference Center for Respiratory viruses, provides a unique setting for the evaluation of the potential of emergence of antiviral resistance, identification of new antiviral targets with reduced potential for viral escape and assessment of the performance of new antiviral inhibitors.

Research projects in relation with AMR:

- genotypic and phenotypic surveillance of the emergence upon treatment and potential for dissemination of influenza viruses with reduced sensitivity to antivirals
- evaluation of potential new inhibitors for other respiratory viruses (e.g. MERS-CoV)
- high-throughput interactomics methods for the identification of novel drug targets based on disruption of virus-host protein interactions also amenable for drug screening
- evaluation of potential for variation of new drug targets

3 Publications

- LeGoff J, Rousset D, Abou-Jaoudé G, Scemla A, Ribaud P, Mercier-Delarue S, Caro V, Enouf V, Simon F, Molina JM, **van der Werf S**. *I223R mutation in **influenza** A(H1N1)pdm09 neuraminidase confers reduced susceptibility to oseltamivir and zanamivir and enhanced resistance with H275Y.* PLoS One. 2012;7(8):e37095.
- Rameix-Welti MA, Enouf V, Cuvelier F, Jeannin P, **van der Werf S**. *Enzymatic properties of the neuraminidase of seasonal H1N1 influenza viruses provide insights for the emergence of natural resistance to oseltamivir.* PLoS Pathog. 2008 Jul 25;4(7):e1000103.
- Biquand E, Poirson J, Karim M, Declercq M, Malausse N, Cassonnet P, Barbezange C, Straub ML, Jones L, Munier S, Naffakh N, van der Werf S, **Jacob Y**, Masson M, Demeret C. *Comparative Profiling of Ubiquitin Proteasome System Interplay with Influenza A Virus PB2 Polymerase Protein Recapitulating Virus Evolution in Humans.* mSphere. 2017 Nov 22;2(6). pii: e00330-17.