**First Name / Last name:** Jean-Christophe Barale
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**Unit:** Structural Microbiology Unit, Headed by Pr. Pedro Alzari; UMR CNRS 3528.
**IP Department or IP:** Dpt of Structural Biology & Chemistry
**Secondary affiliation:** Dept of Microbiology
**For JCB:** "Malaria Translational Research Unit", Pasteur International Joint Research Unit, with Malaria Molecular Epidemiology Unit, B. Witkowski, Pasteur Institute in Cambodia

**Main domains 1**: Parasites (*Plasmodium*)

**Main domain 2**: mechanism of resistance, biomarkers, new molecules, alternative strategies, methodological developments.

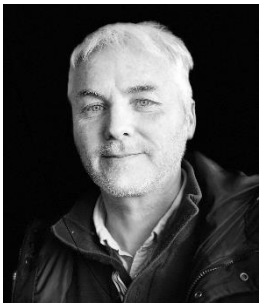
**Attractive synopsis:**
Via combining expertise from the malaria-endemic region where most of resistant parasites have arisen these last decades, namely the Grand-Mekong area, and knowledge-based research relying on multi-disciplinary approaches, we address *P.falciparum*-specific mechanisms of resistance and aim at validating new anti-malarial candidates active on multi-resistant parasites.

**Research projects in relation with AMR:**
Our group's activity, realized in close collaboration with the Malaria Molecular Epidemiology Unit headed by Benoît Witkowski at the Pasteur Institute in Cambodia within the frame of our International Joint Unit "Malaria Translational Research Unit", focuses on:

- Deciphering K13-meditated *P.falciparum* -the most virulent agent of malaria- resistance to artemisinine ($ART^R$), the main active compound composing the first line anti-malarial treatments, known as ACTs (Artemisinin-Combined Therapies). The biological function of *Plasmodium* K13 protein and how some particular mutations trigger $ART^R$ remain poorly understood;
- Explore alternative strategies to define, validate new anti-malarial candidates active on $ART^R$ and targeting the different stages of *Plasmodium* life cycle in human being.

**3 Publications**

- Witkowski B., (…), **Barale J.-C.**, Legrand E., Ringwald P., Fidock D.A., Mercereau-Puijalon O., Ariey F &, Ménard D. (**2017**). "A surrogate marker of piperaquine-resistant *P. falciparum* malaria: a phenotype-genotype association study." *Lancet Infect Dis.*; 17(2): 174–183. PMID: 27818097.
- Giganti D., (…) Alzari P.M. & **Barale J.-C**. (**2014**) "A novel *Plasmodium*-specific prodomain fold regulates the malaria drug target SUB1 subtilase." *Nat. Commun.* 10;5:4833. doi: 10.1038/ncomms5833. PMID: 25204226.
- Bouillon A., (…) Stoven V. & **Barale J.-C**. (**2013**) "*In Silico* screening on the three-dimensional model of the *P. vivax* SUB1 protease leads to the validation of a novel anti-parasite compound." *J. Biol. Chem.* 288(25), 18561-73; PMID: 23653352.



**First Name / Last name:** Didier MENARD
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**Unit:** Malaria Genetics and Resistance Group, Biology of Host-Parasite Interactions Unit

**IP Department or IP:** Department of Parasites and Insect Vectors

**Secondary affiliation:** INSERM U1201 - CNRS ERL9195

**Main domains 1**: Parasites (*Plasmodium*)

**Main domain 2**: Surveillance and epidemiology (*P. falciparum and P. vivax*), Mechanism of resistance and dissemination (*P. falciparum*) Biomarkers and diagnostic (*P. falciparum*)

**Attractive synopsis:** In the context of malaria elimination, our vision is to address new challenges created by the changing epidemiology of malaria, especially the emergence and spread of *P. falciparum* resistance to antimalarial drugs

**Research projects in relation with AMR (non confidential):**

After spending twenty years in the Institut Pasteur Internation Network in Africa (IP Bangui and IP Madagascar) and in Southeast Asia (IP Cambodia), my objectives are to conduct basic science projects on antimalarial drug resistance, generate results that will open new avenues in our knowledge of molecular processes controlling *P. falciparum* antimalarial drug resistance and create a direct continuum between "basic" and "applied" research projects in collaboration with my colleagues from malaria endemic countries. Currently, the risk that *P. falciparum* multidrug resistant parasites invade Africa, as happened with previous generation of antimalarial drugs is a real public health threat. This situation does not only strengthen the need to closely follow the dissemination of these parasites outside Southeast Asia, but also confirm the urgent need to conducting comprehensive biological investigations to decipher mechanisms linked to resistance, optima usage of existing drugs and the development of new, more effective therapies.

**3 Publications**

- Ariey F et al. 2014. A molecular marker of artemisinin-resistant *Plasmodium falciparum* malaria. Nature, 505, 50-55.
- Straimer J, et al. 2015. Drug resistance. K13-propeller mutations confer artemisinin resistance in *Plasmodium falciparum* clinical isolates. Science (New York, N.Y.), 347, 428-431.
- Ménard D et al. 2016. A Worldwide Map of *Plasmodium falciparum* K13-Propeller Polymorphisms. N Engl J Med. 23;374(25):2453-64.

**First Name / Last name:** Brice ROTUREAU
**Contact:** rotureau@pasteur.fr

**Unit:** Trypanosome Cell Biology Unit - Trypanosome Transmission Group
**IP Department or IP:** Parasites and Insect Vectors, IP Paris
**Secondary affiliation:** Cell Biology, IP Paris

**Main domains 1**: Parasites

**Main domain 2**: Surveillance and epidemiology, biomarkers and diagnostic, technological and methodological developments.

**Attractive synopsis:**
Our research investigates the development and transmission of dermal trypanosomes that represent a reservoir of parasites possibly involved in Human African Trypanosomiasis relapses.

**Research projects in relation with AMR:**
African trypanosomes are transmitted by tsetse flies and cause sleeping sickness. Although these protist parasites were considered to reside in the blood, we discovered that they were actually mostly extravascular, with an important population remaining in the skin. Therefore, we are studying the biology of skin-dwelling trypanosomes, including their proliferation, differentiation, motility and interactions with the host tissues and cells by monitoring the infection of a panel of parasite mutants by intra-vital imaging approaches *in vitro* and in mouse models after natural transmission. We are also investigating the epidemiological importance of dermal trypanosomes in the filed in Western Africa. We are especially assessing the trypanocidal efficiency of current drugs and developing diagnostic tools to monitor possible treatment relapses after Human African Trypanosomiasis.

**3 Publications: (not directly related to AMR)**

*Resolving the apparent transmission paradox of African sleeping sickness.* Capewell P, Atkins K, Weir W, Jamonneau V, Camara M, Clucas C, Swar NK, Ngoyi DM, Rotureau B, Garside P, Galvani AP, Bucheton B, MacLeod A. PLoS Biol. 2019 Jan 11;17(1):e3000105. doi: 10.1371/journal.pbio.3000105. eCollection 2019 Jan. PMID: 30633739

*Do Cryptic Reservoirs Threaten Gambiense-Sleeping Sickness Elimination?* Informal Expert Group on Gambiense HAT Reservoirs, Büscher P, Bart JM, Boelaert M, Bucheton B, Cecchi G, Chitnis N, Courtin D, Figueiredo LM, Franco JR, Grébaut P, Hasker E, Ilboudo H, Jamonneau V, Koffi M, Lejon V, MacLeod A, Masumu J, Matovu E, Mattioli R, Noyes H, Picado A, Rock KS, Rotureau B, Simo G, Thévenon S, Trindade S, Truc P, Van Reet N. Trends Parasitol. 2018 Mar;34(3):197-207. doi: 10.1016/j.pt.2017.11.008. Epub 2018 Jan 23. Review. PMID: 29396200

*The skin is a significant but overlooked anatomical reservoir for vector-borne African trypanosomes.* Capewell P*, Cren-Travaillé C*, Marchesi F, Johnston P, Clucas C, Benson RA, Gorman TA, Calvo-Alvarez E, Crouzols A, Jouvion G, Jamonneau V, Weir W, Stevenson ML, O'Neill K, Cooper A, Swar NK, Bucheton B, Ngoyi DM, Garside P, Rotureau B$, MacLeod A$. Elife. 2016 Sep 22;5. pii: e17716. doi: 10.7554/eLife.17716. PMID: 27653219

**First Name / Last name:** Gerald Spaeth
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**Unit:** Molecular Parasitology and Signaling
**IP Department or IP:** Parasites and Insect Vectors

**Main domain 1**: Parasites

**Main domain 2**: mechanism of resistance and dissemination, biomarkers and diagnostic, new molecules, alternative strategies, technological and methodological developments.

**Attractive synopsis:**
Applying population-genetics approaches and conducting evolutionary studies in animals and in culture, we have identified novel mechanisms of *Leishmania* genomic adaptation and fitness gain that are highly relevant for the development of drug resistant phenotypes in the field.

**Research projects in relation with AMR:**
Protozoan parasites of the genus *Leishmania* cause devastating human and animal diseases world-wide. Chemotherapy represents the main intervention strategy in the absence of vaccination. No safe treatment exists and the few anti-leishmanial drugs currently in use are rendered inefficient due to emerging drug resistance. Our understanding on how these parasites evolve towards a drug resistant phenotype is very limited. Together with partners of the LeiSHield consortium (www.leishield.org), our team has recently uncovered that evolutionary adaptation in these parasites relies on genome instability, with frequent and stochastic chromosome and gene amplifications generating a vast phenotypic landscape that drives fitness gains in response to environmental cues, including drug treatment (Prieto et al., Nature Ecol Evol 2017, Bussotti et al., Mbio 2018). We are currently investigating drug resistance mechanisms (i) by analysing the population structure, as well as genotypic and phenotypic variability by single cell sequencing of drug resistant *Leishmania* derived in situ in infected hamsters, (ii) by comparative genomics analyses of drug susceptible and drug resistant field isolates in collaboration with our partners from IP Tunis and IP Algeria, and (iii) by conducting functional genomics screening assays using cosmid libraries (Piel et al Front Cell Infect Microbiol 2018) generated from drug resistant field isolates with the aim to reveal drug resistance loci.

**3 Publications**
Bussotti G, Gouzelou E, Côrtes Boité M, Kherachi I, Harrat Z, Eddaikra N, Mottram JC, Antoniou M, Christodoulou V, Bali A, Guerfali FZ, Laouini D, Mukhtar M, Dumetz F, Dujardin JC, Smirlis D, Lechat P, Pescher P, El Hamouchi A, Lemrani M, Chicharro C, Llanes-Acevedo IP, Botana L, Cruz I, Moreno J, Jeddi F, Aoun K, Bouratbine A, Cupolillo E, **Späth GF**. *Leishmania* Genome Dynamics during Environmental Adaptation Reveal Strain-Specific Differences in Gene Copy Number Variation, Karyotype Instability, and Telomeric Amplification. ***MBio. 2018*** Nov 6;9(6).

- Piel L, Pescher P, **Späth GF**. Reverse Epidemiology: An Experimental Framework to Drive Leishmania Biomarker Discovery in situ by Functional Genetic Screening Using Relevant Animal Models. ***Front Cell Infect Microbiol. 2018*** Sep 19;8:325.
- Prieto Barja P, Pescher P, Bussotti G, Dumetz F, Imamura H, Kedra D, Domagalska M, Chaumeau V, Himmelbauer H, Pages M, Sterkers Y, Dujardin JC, Notredame C, **Späth GF.** Haplotype selection as an adaptive mechanism in the protozoan pathogen *Leishmania donovani*. ***Nature Ecol Evol, 2017*** Dec;1(12):1961-1969.