Dear Colleagues,

we cordially invite you to attend the lecture of

Professor Henri J. Vial (University of Montpellier 2, Montpellier, France)

Entitled: **Lipids as drug targets for malaria therapy**

To be held at the

Kisterem of the Main Building of the Hungarian Academy of Sciences (Budapest, Roosevelt tér 9.)
on January 13, at 11:00 am.

Beáta Vértessy, Gergely Szakács and János Márki-Zay

on behalf of the AddMal consortium
Lipids as drug targets for malaria therapy

Henri J. Vial

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Glycerophospholipids are the main Plasmodium membrane constituents, with a preponderance of phosphatidyl-choline and -ethanolamine and a massive increase in phosphatidylinositol involved in signaling. These lipids mostly originate from the parasite enzymatic machinery, which relies on the scavenging and downstream metabolism of polar heads and fatty acids serving as building units throughout a bewildering number of pathways. P. falciparum combines metabolic pathways found in bacteria, yeast and plants. The problem is even more complex as rodent and non-rodent malaria parasites differ in their PL metabolic pathways. Extensive research on intraerythrocytic Plasmodium glycerophospholipid metabolism revealed potential targets for chemotherapeutic interference. The most advanced pharmacological approach is based on the use of choline analogs. Their primary interference has been associated with locking the choline carrier, which is considered a limiting step and provides the parasite with the precursor required for phosphatidylcholine synthesis. The potency and specificity of these anti-PL effectors are likely due to their unique ability to accumulate in a non-reversible way inside the intraerythrocytic parasite. In addition their potent antimalarial activity may also be attributed to their compartmentalization within the parasite's food vacuole, where they bind to ferriprotoporphyrin IX. This exciting new class of compounds is currently being developed. Human phase 2 clinical trials of T3/SAR97276 are ongoing for parenteral cures of severe malaria. This clinical candidate is structurally unrelated to existing antimalarial agents and acts through new independent mechanisms of action. Its unique properties are of tremendous interest as anti-infectious agents. The development of choline analogs for innovative antimalarial therapeutics confirms that targeting lipid metabolism is a valuable strategy for the development of new antiparasitic drugs.

Prof. Dr. Henri J. VIAL is a Docteur d'Etat es-Biological Sciences, receiving this degree from the University Claude Bernard and the National Institute of Applied Sciences (INSA) in Lyon (France). He headed a research laboratory, "Molecular Dynamics of Membrane Interactions", jointly run by the CNRS and the University Montpellier 2 (1994-2006), whose activities were mainly focused on cell and molecular biology issues. Currently, he co-manages the "Biogenesis membrane and mechanisms of Invasion in Apicomplexa Plasmodium and Toxoplasma" research team at INSERM (French national medical research institute). The project is geared towards the functional characterization of molecular cellular and membrane events that lead to membrane biogenesis in the development of Plasmodium and Toxoplasma parasites within host cells. The objectives are to clarify the main processes that could be major and/or essential for the differentiation and development of these parasites, and to determine original features in terms of biological processes versus mammalian cells, for example. The programs have resulted in the development of a new chemotherapy strategy against malaria P. falciparum and P. vivax targeting phospholipid plasmodial metabolism. The compounds are currently in development for human treatments, and this will represent a new type of antimalarial whose mechanism of action differs from currently marketed antimalarials. He has published more 160 articles in international scientific journals and is recognized as a co-inventor in 8 patents. He is closely involved in many partnerships in Europe (Network of Excellence BioMalPar and Integrated Project, AntiMal) and with industries (Sanofi-Aventis), and coordinates a multisite European Marie Curie network for training of young researchers. He has chaired Section 23 of the National Committee CNRS "Cell Biology; organization and functions of the cell; pathogens and host/pathogen interactions"
Antimalarial Drug Discovery and Development of New *In Vitro* Assays for the Optimization of Antimalarial Therapy

The spread of drug resistant *Plasmodium falciparum* malaria parasite has led to a significant increase of malarial morbidity and mortality, and a growing crisis in global public health. Thus, a major goal of malaria research is to find drugs with novel targets and a novel mechanism of action. In parallel, more research is needed to elucidate mechanisms of drug resistance, since new drugs should not only be effective, but should also evade mechanisms that contribute to parasite resistance.

The recently funded Add-Mal project is a French-Hungarian bilateral cooperation, which follows these general goals. The partners wish to characterize enzymes of the phospholipid synthesis in the plasmodiums identified as novel antimalaria targets, in order to discover new series of compounds that interact with these targets.

The fate of administered drugs may largely depend on their interactions with transporter proteins, which are present in all major pharmacologically relevant barriers. Such ADME considerations have to be taken into account also by the development of antimalarial drugs characterizing the interaction of candidate antimalarial agents with key human transporters influencing ADMETox properties. Furthermore, transporters are key determinants of antimalarial drug resistance of plasmodiums as well. Therefore, another objective of the project is the optimization of malaria treatment through the development of new *in vitro* test systems serving antimalarial drug discovery projects as well as the diagnosis of malaria. These new assays might facilitate antimalarial drug discovery projects as well as the characterization of plasmodium transporters.

Add-Mal Consortium Members:

F1) UMR5235, CNRS − University of Montpellier 2, Dynamics of Membrane Interactions in Normal and Pathological Cells (Rachel Cerdan, **Henri J. Vial** [project coordinator])

F2) UMR6097, CNRS – University of Nice Sophia-Antipolis, Institute of Molecular and Cellular Pharmacology (Dominique Douguet)

H1) Solvo Biotechnology (János Márki-Zay)

H2) Institute of Enzymology, BRC Hungarian Academy of Sciences (Beáta Vértesy, Gergely Szakács)