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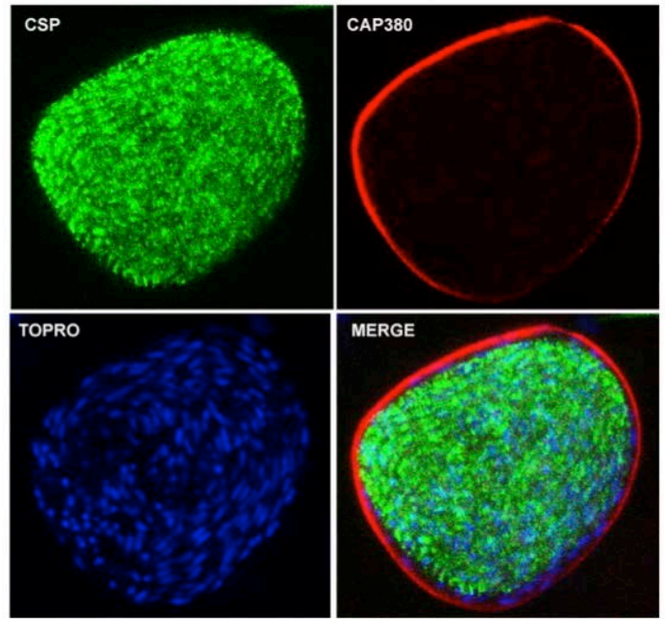
Description of the funded research project

2nd Call for H.F.R.I. Research Projects to Support Post-Doctoral Researchers



Principal Investigator: Chiara Currà, PhD

Title of the research project: Histone-fold domain proteins with divergent functions in *Plasmodium* as target for drug development and malaria transmission blocking strategies

Reader-friendly title: Histone-fold domain proteins with divergent functions in *Plasmodium* as target for drug development and malaria transmission blocking strategies

Scientific Area: Life sciences

Institution and Country: Institute of Molecular Biology and Biotechnology – FORTH, Greece

Host Institution: Foundation for Research and Technology (FORTH) - Hellas

Collaborating Institution(s): Istituto Superiore di Sanità, Rome, Italy; University of Milano, Italy; NCSR "Demokritos", Greece

Budget: euros 180000

Duration:36 months

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Research Project Synopsis

Malaria is a parasitic disease caused by *Plasmodium* parasites and transmitted by *Anopheles* mosquitoes causing every year about 216 million new cases and 445000 deaths in the world (WHO 2018). The difficulty to control the mosquito populations, the lack of an effective vaccine and the development of drug resistance in the parasite highlight the urgent need for new interventions that would both alleviate the symptoms and cure the disease, and also block malaria transmission. The oocyst is the longest stage of the *Plasmodium* life cycle and completion of its development takes about two weeks in the mosquito. Due to the large window of action, the oocyst can be considered an attractive target for anti-malarial strategies. Sporozoites develop inside the oocyst and rupture is an essential step for sporozoites release. Then, infectious sporozoites transfer to the salivary gland from where they are transmitted to a new host. The oocyst is still poorly understood stage due to the difficulty to manipulate infected mosquitoes; I have developed new methods and protocols to circumvent this obstacle. The goal of OOCYSTOP is based on an innovative concept to block malaria transmission by development of new drugs that will be delivered (1) to oocysts in infected mosquitoes and (2) to early stages in human infection by the sporozoite. To this aim I will first investigate the molecular mechanism leading to the rupture of the oocyst and sporozoite egress, identify chemical compounds inhibiting oocyst rupture and delivering into target oocysts.

Project originality

Innovatively OOCYSTOP focus on drugs targeting the oocyst stage: this stage takes 2 weeks to develop thus providing an extended time for use of anti-malarial drugs administered to the mosquito. The preliminary data already obtained can raise new opportunities for the development of molecules that could block the oocyst rupture mechanism and stop malaria transmission. The proposed project includes different aspects of malaria research and several different techniques. The synergy between the expertise in molecular and cellular biology provided by me, the skills in chemistry and structural biology and the proficiency in mosquito stage manipulation provided by the host lab/institution will also lead to the development of new protocols and techniques for *Plasmodium* parasite, such as oocyst purification and co-IPs on oocysts isolated from midguts. In summary, the innovation I will add to the field are: i) details on the mechanisms of the oocyst rupture, largely unknown; ii) develop new methods; iii) develop new drugs against malaria parasite; iv) treatment of infected mosquitoes with "green methods" since the compounds will be given in sugar baits. This innovative project is aiming to develop new and original approaches to block transmission of malaria parasites from the mosquito to the human host. This concept is innovative and completely beyond the state of the art. The development of efficient and ecologically friendly transmission blocking strategies for malaria is an area of uttermost importance for the future goal of elimination of the disease.

Expected results & Research Project Impact

OOCYSTOP will be a great opportunity to reinforce my position as independent researcher at the host institution and continue my career as young group leader. This grant will allow me to work as part of an interdisciplinary collaborative network, both with existing and new collaborations. The project will enhance the experimental and knowledge transfer and the results are expected to lead to new future collaborations. The multifaceted expertise encompassed in OOCYSTOP will provide a wide variety of training and exposure to new technologies. The successful outcome will lead to the development of novel transmission blocking strategies targeting this serious disease. In future, possible trials in field in the endemic African areas where malaria is transmitted, could support these preliminary studies. All the data produced will be disseminated through open access scientific publications and deposition in designated publically accessible databases as to be available to the whole field of malaria research. Furthermore, the solid background and expertise that I have acquired during my research career will be shared with young researchers in my group and in the other groups involved, thus adding to their training. I will also be able to transfer specific concepts and experimental approaches between the labs which will enhance their excellence. The project will enrich my skills and knowledge in a wide range of subjects, which will be crucial for my future research career. To disseminate the results, I plan to publish at least 2 papers in international, peer-reviewed high impact journals. One paper, which will be submitted to Nature Microbiology or Cell Host and Microbes, will describe the mechanisms of interaction of proteins involved in the oocyst rupture mechanism. A second paper, will concern the use of the drugs to block malaria transmission. New protocols such as CO-IP at oocysts stage will be also described.

The importance of this funding

The HFRI funding of my project OOCYSTOP is very important for different reasons. First of all, this innovative and challenging project is aiming to develop new and original approaches to block transmission of malaria parasites from the mosquito to the human host. This concept is innovative and completely beyond the state of the art. The development of efficient and ecological friendly transmission blocking strategies is an area of uttermost importance for the future goal of elimination of the disease. The project will be developed at IMBB-FORTH, in an International environment and high-level infrastructure. The importance of this grant is also relevant to my career. I will have the possibility to set up my own lab at IMBB, to develop an original research as independent scientist, hiring new and young lab members. HFRI funding will also give visibility to our research, promoting new collaborations within Greece and abroad.

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