

Summaries of the five proposals in grant preparation

AdjustEBOVGP-Dx

Title: Biochemical Adjustments of native EBOV Glycoprotein in Patient Sample to Unmask target epitopes for rapid diagnostic testing

Reference: RIA2018EF-2081

Duration: 12 Months

Requested Budget: 500,000 Euro

Abstract

Background: Ebolavirus and Marburgvirus (EBOV and MARV, respectively) are two genera of the negative sense RNA virus family Filoviridae, order mononegavirales. Filoviruses cause rare but fatal viral haemorrhagic fevers (VHF) in equatorial Africa, with potential for regional and international urban spread. Filovirus VHFs present with a similar prodrome; mimicking several tropical infectious diseases. Early detection is important for response and control. Existing technologies for filovirus detection are, however, not suited for point-of-care (POC). While 2 rapid diagnostic tests (RDTs) for EBOV have recently emerged, there are no pan-filovirus targeted RDTs.

Preliminary data: Our group—with prior funding from Grand Challenges Canada and now EDCTP –, has synthesized, tested and validated monoclonal antibodies-mAbs and synthetic analogues of 3 conserved epitopes of filovirus glycoprotein (GP) for capture of (i) recombinant zaire EBOV GP (cloned and expressed in HEK cells), and (ii) IgG antibody (in gamma irradiated serum of EVD survivors from the 2000 Gulu and Masindi outbreak, UVRI). However, none of the best performing sandwich EIAs detected native Gp on vero-expressed zaire EBOV virions, or patient samples in the P4 laboratory.

Hypothesis: Post translational modifications of EBOV glycoprotein (GP) mask target epitopes from detection by mAbs.

Objective(s): The overall goal of this project is to develop biochemical treatments that adjust native EBOV GP in patient sample as a target for rapid diagnostic testing. Five specific aims are contingent to this goal, viz: (i) In-silico studies of filovirus GP 3-D crystal structural and post-translational modifications, (ii) In-vitro testing of pre-treatment with various mixtures (namely a. glycosidases to remove glycans, b. endopeptidases to denature secondary structure, and c. reducing agents to break disulfide bond) to expose target conserved epitopes, (iii) Optimization of concentrations of sample pre-treatment buffer mixture (iv) Prototype testing within the P4 and NICD using samples from the on-going EVD outbreak in Kivu, Democratic Republic of Congo-DRC, and (v) ROC-characterization of the optimized sandwich EIA for filovirus rapid diagnostic testing.

Approach: In-silico bioinformatics and computational biology, In-vitro experiments tailored to aims within the P4 Lab at the CEZD, NICD, Johannesburg, SA and pre-clinical testing on samples collected from the on-going Kivu EVD outbreak, DRC.

Potential Impact: This project could yield the 1st ever prototypes of RDTs for the duo-detection of EBOV and MARV. Pan-filovirus RDTs are required to ensure early detection, response and control of the on-going and future outbreaks. Moreover, the mAbs presented are candidate therapeutics.

EPIRISK-EBOV

Title: Epidemic preparedness and risk assessment for Ebola Virus Disease outbreaks in the Republic of Congo

Reference: RIA2018EF-2082

Duration: 24 months

Requested budget: 500,000 Euro

Abstract

Background: This year, two epidemics outbreaks of Ebola virus disease (EVD) took place in the Democratic Republic of the Congo (DRC), one along the Congo River and the second one in further North in the Great Lakes region, increasing the threat of spill-over of EVD cases into neighbouring countries notably in the Republic of Congo (RoC).

Since RoC is in the preparedness approach and a network assistance has been formally requested by the RoC Government, the pilot study proposed here is therefore aimed at assessing the EBOV cross-sectional seroprevalence as well as the incidence of a longitudinal seroconversion. The presence of EBOV and possible additional pathogens will be determined via pan-domain molecular approaches following a pathogen enrichment method.

Objectives:

The specific objectives are:

1. To conduct Ebola-seroprevalence study for Ebola virus across along the border with DRC and compare with a 'negative control' population from Brazzaville.
2. To investigate in seropositive individuals, the biological functions of Ebola-specific antibodies and T cells.
3. To conduct questionnaire-based interviews to identify Ebola virus infection risk factors among the resident population.
4. To detect and identify the most prevalent viruses and bacteria in human collected samples by using very sensitive molecular diagnostic tools including PCR and metagenomic
5. Capacity development. In addition to the scientific objectives, training of local staff will be one of the most crucial objectives of EPIRISK-Ebov. Personnel from the Fondation Congolaise de la Recherche Medicale (FCRM) and the Laboratoire National de Sante Publique (LNSP) will be enrolled in training on diagnostics, biosafety, serology (ELISA) and flow cytometry. The social science training will be strengthened by UCL and CERMEL and staff from all the DRC surrounding countries including representatives of DRC will be invited to CERMEL to participate in a training workshop.

This proposal is fully in line with the call text:

1. It addresses the diagnostic for screening and identifying affected individuals in the risk areas of the Congo river corridor.
2. It will provide high quality data on Ebola surveillance and epidemiological characteristics of viral, bacterial and parasite genotypes as well as data on humoral and cellular immune responses to EBOV antigens in individuals living in the study zones.

The Ministry of Public Health of the Republic of Congo will be informed of the results by means of regular meetings and by involving its key personnel in this project as well. These two years activities will be fully integrated in the country surveillance activities.

CAPA-CT-II

Title: Leveraging capacity for early phase clinical trials for filoviruses in Uganda

Reference: RIA2018EF-2083

Duration: 18 Months

Requested Budget: 500,000 Euro

Abstract

Objectives: The CAPA-CT 2 project aims to generate knowledge relevant to the potential spread of the EVD outbreak in Democratic Republic of the Congo (DRC) to the Republic of Uganda. The project:

1. aims to improve knowledge of the mechanism of action of a prioritised drug by generating local clinical pharmacokinetic data that is needed for interpretation of pharmacokinetic data generated through MEURI, drug interactions with antiretroviral drugs and to inform future treatment optimisation approaches.
2. seeks to use diagnostic approaches to strengthen surveillance for especially dangerous pathogens in Uganda.
3. will describe a capacity building model for rapid acquisition of competencies for enhanced laboratory biosafety and infection prevention and control for case management using a low-cost mentorship strategy, while contributing to the national response. The costs and effectiveness of this strategy will be evaluated. A communications/social science work package will be implemented in support of

activities across the work packages.

The project leverages prior and ongoing investments by EDCTP (CAPA-CT, VirTUAL and TMA2015-1166) for a clinical pharmacokinetic study and an ongoing project in collaboration with investigators at Johns Hopkins University for a surveillance research project.

CAPA-CT 2 is aligned to national priorities and ongoing capacity building and research Global Health Security Agenda investments in Uganda. The CAPA-CT 2 project consortium institutions from Uganda, United Kingdom and Italy.

PEAU-EBOV-DRC

Title: Improved management of Ebola Virus Disease in emergency situations in the Democratic Republic of Congo: from MEURI protocol to randomized controlled trials [originally submitted in French as: Prise en charge améliorée de Maladie à Virus Ebola en situation d'urgence en République Démocratique du Congo : du protocole MEURI aux essais randomisés contrôlés]

Reference: RIA2018EF-2087

Duration: 24 Months

Requested Budget: 490,000 Euro

Abstract

Background: Up until the end of 2017, the Democratic Republic of Congo (DRC) had experienced eight outbreaks of Ebola Virus Disease (EVD). In 2018, two complex epidemics of EVD occurred successively in West Bikoro) and for the first time in East Mangina, bringing the total number of epidemics to ten. The case-fatality rate of EVD cases in the DRC remains high. It was 61% in the Bikoro epidemic and is currently 46% in eastern DRC. If the diagnosis is made early and an optimal standard of care is applied, this case-fatality rate could be reduced. Several therapeutic and diagnostic tools have been developed to combat epidemics of EVD in recent years in West Africa. These have provided opportunities for substantial improvements in the early diagnosis/detection and therapeutic management of patients with EVD.

The Institut National de Recherche Biomédicale (INRB), the DRC's national public health laboratory, has been given the task of coordinating research on experimental emergency interventions for EVD by the Ministry of Health.

Objective(s): The overall objective of this project is to improve the management, both therapeutic and diagnostic, of patients with EVD through the application of an optimal standard of care. This objective will be achieved through the four work packages. In response to the emergency created by the May 2018 EVD outbreak, INRB developed an EVD research plan on the recommendation of the DRC Ministry of Health. This plan identified 12 research priorities, including "Coordinate the design and support the rapid implementation of efficacy trials to evaluate therapeutic product candidates". This application directly supports this national priority through work package 2. It will contribute to improving the quality and interpretability of safety data on experimental therapies used in MEURI protocols and will strengthen the national capacity to conduct randomized controlled trials of experimental therapies in EVD.

A second priority identified in the EVD research plan is to "Strengthen the DRC's capacity for the safe handling, diagnosis and reporting of major diseases caused by Haemorrhagic Fever Viruses (HFVs)". Work packages 3 and 4 will address this priority.

MobEBO-DRC

Title: Mobile point of care diagnostic testing for Ebola virus disease in DRC

Reference: RIA2018EF-2089

Duration: 24 Months

Requested Budget: 498 507 Euro

Abstract

Background: A mobile suitcase laboratory for EBOV point-of-care detection at Ebola treatment centres was successfully implemented in Guinea during the large Ebola virus disease (EVD) outbreak in West-Africa 2014-2015. It was shown that isothermal amplification (Recombinase Polymerase Amplification (RPA)) could be efficiently used to test suspect EVD cases and local teams were trained in and successfully deployed with this fast method.

Objective(s): In the frame of this project we want to train teams in DRC and expand RPA testing capacity to the differentials recommended by the WHO. Existing RPA assays for all parameters will be included into a multistrip for simultaneous use. This will be integrated with a simple biosafe extraction method. The project team consist of experts in the development of mobile molecular assays and a track record of their use in outbreak response.

By extending cooperation into DRC this programme will enable local teams in DRC to provide response capacity for future EVD outbreaks. Additionally, a wider outbreak response network of African teams with state of the art point-of-care tests is formed. This proposal falls directly into the scope of this EDCTP call addressing urgent diagnostic needs in alignment with the national priorities of the DRC and neighbouring countries. The international team pairs up with the most important Ebola virus research group in DRC and will strengthen their capacity to respond to EBOV outbreaks. It is therefore also in alignment with the WHO R&D blueprint for rapid activation of R&D activities during epidemics. The team has a good record of working according to all required ethical standards. Data will be published in peer reviewed scientific journals which require open access and data sharing.