The TB Working Group meets

The Tuberculosis Working Group, composed of GABRIEL representatives from Bangladesh, France, Haiti, and Ukraine, plus one TB specialist, gathered in Lyon last January 13 and 14 to: 1) explore in greater depth the topics raised at the 2014 GABRIEL Network meeting on the diagnostic tools, epidemiology, biomarkers, and clinical trials that affect TB patients and public health systems, and 2) propose collaborative projects and set up a corresponding action plan. Two of the matters brought up for review were, first, the evaluation of the GeneXpert RIF/TB Ultra cartridge now under development that may be possibly acquired by microscopy laboratories (the sensitivity of this test would be, in fact, improved by the use of the insertion sequence IS6110 as a target), and second, the prospect of evaluating the use of host biomarkers to detect the progress of tuberculosis from its latent to active state, and to follow the effectiveness of treatment. The action plan that was agreed upon has been communicated to members of the Network involved in tuberculosis, and will be subject to deliberation and review at a specifically scheduled session of the upcoming GABRIEL meeting in Vientiane next July. In addition to this, Oksana Ocheretina invited all interested members to undertake a period of observation at GHESKIO Center’s TB laboratory in Port-au-Prince, Haiti, in order to share with participants the laboratory’s experience in terms of organization and best practice.

Jean-Luc Berland, Emerging pathogens Laboratory, Fondation Mérieux (France)
Human papillomavirus (HPV) and cervical cancer in Madagascar: the COFAC-Col network project

Cervical cancer is a leading cause of cancer death in women worldwide with nearly 266,000 deaths and 528,000 new cases in 2012. In developing countries, including sub-Saharan African countries, nearly 231,000 deaths were reported in that same year. In January 2015, the African Consortium on Cervical Cancer Control Research (COFAC-Col) was launched in Dakar, Senegal, by five French-speaking African countries (Cameroon, Gabon, Ivory Coast, Madagascar, and Senegal). France’s National Cancer Institute, acting as a catalyst, is financially supporting the network’s research activities, while the Institut de Cancérologie de Lorraine, France, ensures technical support. The primary goal of COFAC-Col is to provide a working model to implement standardized high-quality research protocols across the five countries and to share knowledge. The specific objectives are 1) to identify the nature of the HPV genotypes associated with high-grade intraepithelial neoplasia lesions and invasive cancers, and 2) to estimate the prevalence of each genotype, including HPV16 and 18, involved in cervical cancers. For each country, the population size required is at least 369 cases. The study, due to end by December 2016, involves the participation of pathologists, clinicians/oncologists, virologists and epidemiologists.

As for Madagascar, the pathological diagnosis of cancer lesions is carried out by the UPFR of Cytology, Anatomy and Cytology Pathology of Ampefiloha Hospital, Antananarivo, and the identification of HPV genotypes is performed by the Charles Mérieux Infectiology Centre of Madagascar, according to standardized and well-defined protocols.

Ultimately, this study is expected (a) to provide epidemiological data that can help update the HPV vaccine in use in each country, and (b) to promote the development of a professional network to maximize resources and skills and standardize management procedures for cervical cancer.

Mala Rakoto-Andrianarivelolo, Rodolphe Mérieux Laboratory, Charles Mérieux Infectiology Centre, Antananarivo University, Tsitohery Francine Andriamampionona, Pathology Ward, UH Tambohobe, Franarantsoa, Madagascar, Nantenaina Randrianajafisamindrakotroka, UPFR of Cytology, Anatomy and Cytology Pathology, Ampefiloha Hospital, Antananarivo, Madagascar
The CML wins two awards for investigations on the etiology of respiratory viruses in China

A research project conducted by the Christophe Mérieux Laboratory (CML) on the applied characterization and etiology of significant and newly identified respiratory viruses was awarded the 1st Science and Technology Grand Prize of the Chinese Preventive Medicine Association for 2015, and the 2nd Science and Technology Grand Prize of the Chinese Ministry of Education for 2015. This is the first time a research prize has been granted for a comprehensive investigation of the etiology of respiratory viral infections in China.

Respiratory viral infections have been a leading cause of mortality and morbidity worldwide. However, the surveillance and prevention of these infections have been impeded by the lack of baseline data on their nature, distribution, and epidemiology. With funding from Fondation Mérieux and the Chinese government, the CML has developed a nationwide network of sentinel hospitals covering locations in China where patients have been recruited and samples collected over the past 10 years. The CML has characterized the space-time distribution of common respiratory viruses in children and adults with an acute respiratory infection. The laboratory was the first to report the epidemics of newly identified and re-emerging respiratory viruses in China, such as rhinovirus C, Saffold cardiovirus 1-3, bocavirus 3, coxsackievirus A21, enterovirus (EV) D68, EV-104, and EV117. It has also elucidated the molecular, epidemiological, phylodynamic and sero-epidemiological characteristics of major emerging respiratory viruses, including the human metapneumovirus, EV-D68, the human coronavirus and human parainfluenzavirus. Its molecular tests developed for the multi-viral detection of infections have been widely implemented in the surveillance network in China and have contributed to the launch of a response to outbreaks of hand, foot and mouth disease, pandemic influenza A H1N1, avian influenza H7N9, etc. A sample bank has been set up for the clinical trials of novel respiratory viruses. The CML has published about 50 papers on these research topics.

In China, science and technology awards are sponsored by academic institutions and the government, and are intended to encourage high quality research projects. In 2015, only two Science and Technology 1st Grand Prizes of the Chinese Preventive Medicine Association were granted among the eight competing candidates. These two awards were in recognition for CML’s contribution and leading role in this field of research in China.

Jianwei Wang and Lili Ren, Christophe Mérieux Laboratory, China
Cholera Battle in Haiti

In 2010, cholera occurred for the first time in Haiti in the aftermath of the earthquake. Now, six years later with more than 800,000 cases and 9,000 deaths, the epidemic remains out of control, despite attempts to improve water supply and sanitation. Different strategies have been developed to control the disease.

Last summer, the GHESKIO cholera treatment center, an innovative architectural structure built by MASS design Group, opened to fill the gap in the public health infrastructure of Haiti. The building conception provides natural light and ventilation for better air circulation and an on-site wastewater treatment facility was incorporated to avoid further recontamination. New vaccines show hope for disease prevention. Recent studies led by GHESKIO in 2012, have established the effectiveness of vaccines to clear cholera from a large field site in Port-au-Prince (70,000 inhabitants). These promising results could unleash the future use of cholera vaccines in other outbreak settings. Indeed, the oral cholera vaccine (OCV) showed an efficacy that approximates 97.5%. Important research questions remained, including the duration of protection, efficacy of one versus two doses in non-endemic areas (a recent study showed that 1 dose is effective), and the impact of herd immunity.

Jean William Pape, GHESKIO centers, Haiti

Diagnostic testing of enteric fevers

Enteric fevers are severe infectious diseases caused by the ingestion of food or water contaminated by Salmonella serovar Typhi (less frequently S. Paratyphi A, B, or C). Without treatment, Typhoid fever is associated with very high mortality and morbidity worldwide, especially in developing countries with limited resources and poor sanitation.

Data on the incidence of the disease is sporadic and unreliable due to the lack of specificity and /or sensitivity of the current gold standard diagnostic methods (blood culture or serological Widal and Felix test). To overcome this issue, Fondation Mérieux, in collaboration with Pasteur Institute in France, the Child Health Research Foundation (CHRF) in Bangladesh, and Fast Track Diagnostics in Luxembourg, was granted by the Bill and Melinda Gates Foundation.
(BMGF) to develop a test adapted to the surveillance and epidemiological studies of typhoid fever.

This test combines a pre-enrichment step of the blood sample in a bile environment with a real-time multiplex molecular detection of the pathogens (S. Typhi and S. Paratyphi A). Trials were run at the Dhaka Shishu Hospital in Bangladesh on children presenting a fever (>38.5 °C) suspected to be typhoid fever. Results have shown that our test has a greater sensitivity than blood culture (93.6% vs. 61.7%) without any loss of specificity. However, the requirement of 5 ml of blood hampers the use of this test in pediatric settings, especially when testing children less than 2 years of age. Consequently, a new trial using 3 ml of blood was performed on a larger cohort of patients of all ages (over 700) either hospitalized or from the community. This study carried out in collaboration with the CHRF and the International Centre for Diarrhoeal Disease Research in Bangladesh (icddr,b) has confirmed prior results and has validated the use of 3 ml of blood sample for the assay.

Furthermore, a number of studies have reported a sharp increase in paratyphoid fever in various regions of the world, especially in Asia and Africa. New funding from the BMGF should enable us to expand our test trials to cover three African countries: Ghana, Malawi, and Burkina Faso.

Data generated should thus allow us to promote this diagnostic test as a reliable means to evaluate the disease burden and vaccines as an effective way to guide typhoid control.

**Stéphane Pouzol and Valentina Picot, Emerging Pathogens Laboratory, Fondation Mérieux (France)**

**A pathogenetic approach to the treatment of severe pulmonary tuberculosis**

Our present research is aimed at improving the efficiency and patient tolerance of multi-agent chemotherapy against multidrug-resistant destructive pulmonary tuberculosis (TB). A total of 250 adult patients with destructive multidrug-resistant pulmonary TB were examined before and after therapy. Our study found increased levels of pro- and anti-inflammatory cytokines: TNF- (38.3-fold increase), IL-6 (24.6-fold increase), IL-2 (2.5-fold increase), and IL-10 (7.1-fold increase). We evaluated the essential components of vegetative disorders: elevated activity of sympathetic components of the autonomic nervous system (a 1.2-fold increased heart rate, and a 1.5-fold greater mode amplitude), a decline of parasympathetic activity (a 1.5-fold decrease in variation range and a 1.2-fold decrease in mode) and a 3.7-fold increase of the voltage index of the autonomic nervous system. This study also showed a high level of oxidative stress and secondary endogenous...
intoxication (a 1.2-fold increase in the levels of spontaneous oxidative modified proteins (OMP)) and a decreased antioxidant status (a 1.7-fold increase in the level of metal-induced OMP).

The study of immunological, biochemical, and autonomic alterations in patients with multidrug-resistant destructive pulmonary TB led us to identify the pathogenetic mechanisms of severe disease progress associated with high levels of serum cytokine markers. We also measured the significant intensity of oxidative stress and sympathicotonia, and we defined the extent of additional pathogenetic treatment needed to correct these alterations (with Glutamyl-Cysteinyl-Glycine Disodium as immune response-modulating medication, Mebicar as anxiolytic medication, Propionate Dihydrate as cytoprotective medication). The restoration of immunological alterations, of autonomic dysfunctions, and of modifications of protein peroxide oxidation coupled with secondary endogenous intoxication (eliminated through supplementary pathogenetic treatment of multidrug-resistant destructive pulmonary TB with the above-mentioned drugs) resulted in improving treatment efficiency by 23.1 %. Greater tolerance to preventive multi-agent chemotherapy was observed by the decrease/elimination of secondary reactions caused by anti-TB drugs which were administered 2.9 times less often.

Olena Raznatovska and Olga Konakova, Zaporozhye State Medical University, Ukraine

since December 2015


