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CRP-SANTÉ | ACTIVITY REPORT 2013

FOREWORD BY THE PRESIDENT AND THE DIRECTOR GENERAL

CRP-SANTÉ: WELL PREPARED FOR NEW CHALLENGES

The year 2013 closes the second performance contract with Government. **Results reached the targets and often even outperformed them.** When looking back to 2008, the year when we started our first performance contract, we can now fully appreciate the extent of the improvements we have achieved over the period of the two contracts. Therefore, we are confidently anticipating the new challenges lying ahead.

Overall, CRP-Santé now excels in the **quality of science** as shown by the number and, even more relevant, the increasing quality of our scientific publications. Excellence in science depends crucially on the researchers and their teams. We have carefully recruited **experienced scientists** which can lead the way to future improvements in science, and our research departments will be headed by internationally renowned directors, soon. Excellence in science is also the result of the quality of **research networks**. A single institution, especially in a small country, cannot possess all the needed competences. We actively develop collaborations with outstanding partners, nationally but also internationally. With this in mind, we are looking forward to mature a national strategy plan in biomedicine, as requested by the new Government, and to the novel opportunities in the starting Horizon 2020 program from the European Union.

The students of today are the research work force of tomorrow, and education is an investment in our country's future. CRP-Santé has a good track record in training of master and doctoral students, together with the University of Luxembourg and many universities abroad. In the coming years, we will even pay more attention to the quality of training of our students, and we will further extend the processes needed to guarantee successful training in an efficient manner. Our close participation in the **doctoral schools** of the University of Luxembourg and the University of Strasbourg are essential assets in that regard.

CRP-Santé produces valuable insights in the domain of **public health** which inform the policy decisions of our Government and public administrations. However, a new challenge is looming in public health: chronic non-communicable diseases represent now a significant burden on individuals and healthcare systems. Innovative, cost effective therapeutic approaches are required to provide the best quality of care when prevention fails. While a considerable amount of knowledge has been generated by biomedical research in recent years, the development of new therapies is stagnating, in part due to a lack of clinical validation. CRP-Santé is well equipped to take up that challenge: on one hand, we have a performing department of public health that is able to follow the epidemiology of chronic diseases by implementing **disease registers** and **cohort studies**, and on the other hand, our clinical and epidemiological investigation center is the perfect platform to develop **translational medicine** in these diseases. Both competence domains will be expanded over the next years with the **inception of a health economics research unit**, increased activities in health systems and health



Dr. Jean-Claude Schmit, Chief Executive Officer of CRP-Santé, Dr. Simone Niclou, Management Committee member and Thomas Lentz, Chief Financial Officer.

promotion research, and the transformation of the clinical investigation center into a fully established, national translational medicine unit. Visibly, there is an additional demand for “research clinicians” in this domain. For that reason we are participating with excitement in the current debate on the inception of a medical school in Luxembourg.

We increasingly create **economic value** from our discoveries and inventions, as witnessed by the **number of patent applications** and **private public partnerships** with industry. CRP-Santé has developed a unique strategy to foster value creation: a genuine mix of internal and external competences. Internally, we have created a **tech transfer unit specialized in biomedicine** that helps researchers from CRP-Santé and other national research institutions to identify and protect potential economic value, externally we rely on the exceptional competences of academic (i.e. VIB in Ghent) and private (i.e. Vesalius BioCapital) partners. With this in place we have now to show that the investment in public research brings at the end a satisfying return for the tax payer: first results are promising.

As all institutions in public research, we will have to face these challenges in a context of economic restrictions. The most striking here will be a stagnating basic funding from Government over the next four years, which means that growth can only be achieved from external, third party sources. This will also impact on our plans to have finally an adequate research building on the premises of Centre Hospitalier de Luxembourg. Based on a law voted unanimously in parliament in June 2004, the final plans and authorizations for the building have been approved by the Government in 2013, however, ten years after the vote no budget has been made available yet. CRP-Santé can only maintain and expand its successful activities if appropriate space is at hand.

For the sake of clarity, the following report deliberately highlights only a small range of representative activities by CRP-Santé in 2013. Much more has been achieved!

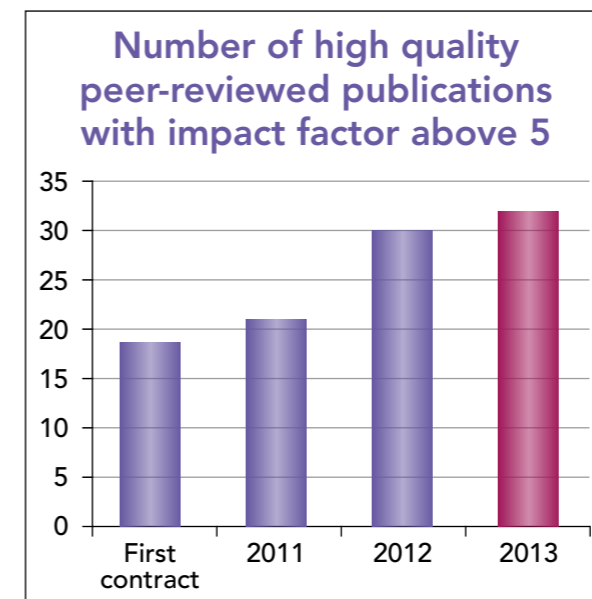
Frank Gansen, President

Jean-Claude Schmit, CEO



EXCELLENCE IN SCIENCE

For more than 26 years, CRP-Santé has been actively contributing to the increasing success of the **biomedical research sector** in Luxembourg. Our aim has always been to offer better diagnosis and treatments to patients and, ideally, to avoid even the emergence of disease by an efficient prevention in healthy people. Therefore, CRP-Santé contributes to the progress in biomedical sciences and develops the best, **new treatments** adapted to the molecular background (e.g. as detected by genomics or proteomics) of each patient. However, **personalized medicine** has always its foundations in excellent science. And excellent science is published in international, peer-reviewed journals with a high impact factor. In 2013, **CRP-Santé published 99 papers in peer-reviewed journal articles with an impact factor above two**. Of special interest is that the high quality papers with an impact factor above 5 increased steadily over the last years (figure), and CRP-Santé researchers were even able to publish 6 articles in outstanding journals with an impact factor higher than 10 in 2013. Some examples of important publications are given below.



TWO IMPORTANT IMMUNE CELL POPULATIONS INTERACT TO DEFEND US AGAINST INFECTIONS AND CANCER



The team around Dr. Tatiana Michel, researcher, and Dr. Jacques Zimmer, senior researcher, from the **Laboratory of Immunogenetics and Allergology (Department Infection & Immunity)** have published in 2013 two papers on NK (natural killer) cell interactions with macrophages. The first paper is a primary research article in the journal "PLOS ONE" showing that macrophages can influence the properties of NK cells in an organ-dependent manner. The second paper, published in the journal "Frontiers in Immunology" which has a distinguished board of editors, is an invited review summarizing current knowledge developed in our laboratory on the bidirectional crosstalk between NK cells and macrophages, which are both important actors in the immune defense against infections and tumors.



A CLOSE COLLABORATION BETWEEN CLINIC AND LABORATORY PROVIDES NEW CLUES FOR FUTURE DRUG DESIGN AND CLINICAL STUDIES IN BRAIN CANCER PATIENTS

A publication by the **Norlux Neuro-Oncology Laboratory** has been published in "BRAIN", one of the leading journals in the field of neurology (Impact Factor 9.5) edited by Oxford University Press. The study was exclusively conducted in the Norlux Neuro-Oncology Laboratory with major contributions from the core facilities in **Flow Cytometry and Genomics** at CRP-Santé and the **Department of Neurosurgery** at the **Centre Hospitalier de Luxembourg** (CHL). The manuscript provides an in-depth analysis of the Side Population (SP) phenotype in human glioblastoma (brain cancer), which represents a measure of drug efflux properties leading to chemoresistance and was previously associated with cancer stem-like cells in a number of malignancies. The data, based on brain tumor patient biopsies and patient-derived green fluorescent protein (GFP) expressing mouse models, showed that all cells with SP properties within patient biopsies are non-tumorigenic, therefore cannot be used as a glioma stem-like cell marker. Importantly, although the efflux properties are not present in glioblastoma

cells, tumor cells are protected by the surrounding stromal endothelial cells carrying the SP phenotype. In addition the laboratory shows that the SP phenotype in endothelial cells is preserved even upon anti-angiogenic treatment. These data will have an important impact on future drug design and clinical trials in glioblastoma patients.



Dr. Anna Golebiewska - Norlux Neuro-Oncology Laboratory

PROTECT YOURSELF AGAINST RUNNING-RELATED INJURIES: THE SHOES MIGHT NOT BE THE MOST IMPORTANT

Work from the **Sports Medicine Research Laboratory** has been published in the "British Journal of Sports Medicine", one of the most renowned journals in the field. The publication focuses on the influence of midsole hardness of standard cushioned shoes on running-related injury (RRI) risk. The Sports Medicine Research Laboratory of CRP-Santé provided 247 runners with standard running shoes having either a soft (soft-SS) or a hard (hard-SS) midsole and followed them for 5 months for running-related injury (RRI) risk. All information about sports practice and injuries was uploaded on a dedicated internet platform and checked for consistency and completeness.

The study concluded that the type of study shoes used for running was not associated with RRIs, despite the hard-SS having a 15% greater overall stiffness in the heel region. The two study groups were similar regarding personal and sports participation characteristics, except for years of running experience, which was higher in the hard-SS group. No between-group differences were found regarding injury location, type, severity or category. Nevertheless, the adjusted regression model revealed positive associations with RRI risk for body mass index, previous injury and mean session intensity. Protective factors were previous regular running activity and weekly volume of other sports activities. The Sports Medicine Research Laboratory concluded that midsole hardness of modern cushioned running shoes does not seem to influence RRI risk.



Dr. Bassam Janji, Senior Researcher at the Laboratory of Experimental Hemato-Oncology

LOW OXYGEN HELPS TUMOR CELLS TO AVOID KILLING BY IMMUNE SYSTEM

The team of the **Laboratory of Experimental Hemato-Oncology** published in 2013 results in the prestigious journal "Proceedings of the National Academy of Sciences of the USA" (PNAS) describing how breast cancer cells can escape from immune cells in a hypoxic (low oxygen) tumor microenvironment, despite an effective immune response. Indeed, when immune cells recognize tumor cells, they deliver a serine protease killer protein called granzyme B, which induces tumor cell death. The research team demonstrated that, under hypoxia, cancer cells are able to activate a process called "autophagy" responsible for the degradation of granzyme B. They provided evidence that inhibition of autophagy under such conditions is sufficient to restore the anti-tumor immune response. This study provides a **cutting edge advance** in our understanding of how cancer cells outmaneuver the immune system and resist immune cell-mediated killing. Furthermore, these results may pave the way for formulating more effective cancer immunotherapy.



WORKING FOR THE HEALTH OF THE LUXEMBOURG POPULATION

THE NATIONAL CANCER REGISTER, AN ASSET FOR LUXEMBOURG, AN ADDED VALUE FOR PATIENTS

On May 15, 2013, **Health Minister Mars Di Bartolomeo** officially launched the **National Cancer Register** during a press conference which was held in the presence of the members of the scientific and organization boards. The National Cancer Register is aimed at providing an objective analysis of the evolution of cancer in the country. Despite all the efforts in prevention and treatment, how many Luxembourg residents are diagnosed with cancer and what is the outcome of their treatments? What exactly is the current situation in comparison with other countries? How could we improve cancer prevention campaigns and treatments in order to support patients and their families? Other European Union countries initiated cancer registers a long time ago; Luxembourg had to catch up. The country has hitherto not gathered

national data related to cancer in one place, which made any comparison with other countries difficult. The National Cancer Register project conducted by CRP-Santé will therefore provide Luxembourg with a unique monitoring tool focusing on lung, prostate, breast, colon, skin cancer and leukemia. Henceforth, Luxembourg will have cancer data based on a clear and objective analysis done in close collaboration with hospitals, foundations and other key actors in the country. In the medium term, the National Cancer Register will allow **health care professionals** and **public authorities** to measure the quality of health care provided to **patients suffering from cancer**. Moreover, the register will be instrumental in improving prevention campaigns and will be a proactive and efficient tool in the monitoring of cancer evolution.



NNC press conference in the presence of the Minister of Health, Mars Di Bartolomeo

THE NATIONAL INJURY SURVEILLANCE SYSTEM RETRACE: ONE MORE STEP TOWARDS PREVENTION

Injuries are one of the major causes of death, hospital admissions and disabilities in Luxembourg.



With 279 annual fatalities, injuries are ranked the fourth cause of death in the general population but remain the major cause of death among children, adolescents and young adults. According to European statistics, for every injury fatality, 28 patients are admitted to hospital, 140 are treated as outpatients in hospitals and 75 patients receive medical treatment outside hospitals. Every year in our country about 55'000 people are injured in traffic, work, sports, home or leisure accidents. In order to implement an injury prevention policy, the Ministry of Health in collaboration with CRP-Santé and the general hospitals of the country, decided to set up a national injury surveillance system named "Retrace". In line with European Injury Data Base standards, "Retrace" gathers exhaustive, continuous and systematic information on causes and circumstances of accidents from injured patients coming to the emergency departments of the five general hospitals in Luxembourg. During the last four months of 2012, about 20'000 injury cases were registered in the emergency departments of all hospitals in the country: 91.7 % were accidents, 3.6 % were consequences of violence, and 0.9 % were self-inflicted injuries. The first results of the injury surveillance system "Retrace" have been officially presented at the conference entitled "Retrace: From injury surveillance to injury prevention" on June 25, 2013.

BEING ABLE TO DETECT VIRUS THREATS RELIABLY: AN IMPORTANT PUBLIC HEALTH ASSET IN AN EPIDEMIC

CRP-Santé's Department of Immunology obtained again a perfect score in the 2013 Proficiency Panel for Avian Influenza and Newcastle Disease and was congratulated by the organizers. Only 7 out of 55 participating national Avian Influenza and Newcastle Disease laboratories had no mistake in their results. The Department of Immunology participates in this proficiency panel since it was launched in 2007 and so far has always had a perfect score. Being able to detect reliably virus threats in animals and humans is a great asset for public health in Luxembourg. CRP-Santé is proud of this performance and its potential contribution to the preservation of the health of people in Luxembourg.



From left to right: Emilie Charpentier, Prof. Dr. Claude P. Muller, Aurélie Sausy, Dr. Chantal Snoeck

ECONOMIC VALUE CREATION AND TECHNOLOGY TRANSFER

CRP-Santé strongly believes that excellence in biomedical research is a key driver for diagnostic and therapeutic innovations that will benefit the population of Luxembourg while strengthening the national economy. In this context, CRP-Santé supported in 2013 its researchers and

inventors to effectively transfer research results to the market place. Furthermore, CRP-Santé increased its involvement in the field of health economics with the preparation of the inception of a Health Economics Unit and the recruitment of a future head of unit.

FACING HEALTH SYSTEM PRESSURE WORLDWIDE

In 2012, CRP-Santé was the organizer in Luxembourg, together with the Fred Hutchinson Cancer Research Center in the USA and the European Commission's – Directorate General SANCO, of a first international conference on health economics in personalized medicine. One year later, a new step has been reached: the European Personalized Medicine Association EPEMED joined the challenge and helped to organize the second edition of the Health Economics Symposium. Moreover Prof. Maarten IJzerman, chairman of the organizing committee of the conference, explained his vision on health economics and the challenges he may have to face if he joins CRP-Santé to set up a health economics research unit. "Luxembourg has chosen personalized medicine as a national strategy for research and development. Personalized or precision medicine aims to be more specific in therapeutic decision-making", explains Prof. IJzerman. "I think this is a unique niche, as many health economic methods are available yet insufficiently adapted to fully evaluate the potential of personalized medicine. In addition, although there may be economic consequences of personalized medicine, there are many societal and ethical challenges as well. For instance, scientific developments in personalized medicine are ongoing, but is

there enough evidence and support to adopt personalized medicine in healthcare? This is an exciting field of research with immediate consequences", concludes Prof. IJzerman.



Prof. Maarten IJzerman



NEW FISH ALLERGEN MOLECULES DISCOVERED AT CRP-SANTÉ ARE EVALUATED FOR DIAGNOSIS OF FISH ALLERGY IN FIVE CLINICAL CENTERS IN FRANCE AND LUXEMBOURG

Dr. Christiane Hilger, Dr. Annette Kuehn and colleagues from the **Laboratory of Immunogenetics and Allergology** (Department Infection & Immunity) have been awarded a competitive grant by the "Société Française d'Allergologie" in 2013. The two-year proof of concept project investigates the correlation between the clinical reactivity and the results of a novel allergen-based diagnosis for patients with fish allergy. For the realization of the diagnostic assay, the researchers use a unique panel of fish allergens from over 15 fish species. The condition for success of the project is the intense collaboration with the clinical partners who are in charge of performing food challenges along with the routine diagnosis. Patients were recruited by the National Unit of Immunology and Allergology of the Centre Hospitalier de Luxembourg (Dr. Morisset, Dr. Hentges) and by four clinical centers from

France located in Strasbourg, Epinal, Bordeaux and Reims. Eventually the project will improve patient care by identifying patients that can tolerate certain fish species, which will be reintroduced into their diet.



THE OTHER FACE OF TECHNOLOGY TRANSFER: A SUCCESS STORY BETWEEN LUXEMBOURG AND RWANDA

Tech transfer is not only occurring between the public and private sectors in Luxembourg or Europe. An import aspect is also tech transfer to Africa. In collaboration with **Lux-Development**, the **national agency for cooperation and development**, the **Laboratory of Retrovirology** at CRP-Santé contributed in 2013 to the evaluation of the **National Laboratory in Rwanda**, which had the goal to obtaining the WHO accreditation as a "National HIV Drug Resistance Laboratory". To transfer competences and knowledge to the National Laboratory, Dr. Gilles Iserentant, researcher, and Manuel Counson, laboratory technician at CRP-Santé, provided training to the Kigali team for ten days. The collaboration between both groups has been ongoing for three years with a continuing exchange between the National Laboratory in Rwanda and the Laboratory of

Retrovirology in Luxembourg to teach the technicians the techniques of HIV genotyping. From now on, Rwandese medical doctors are able to request testing of patients who are considered to be infected with drug resistant HIV. In a joint action plan for accreditation, several key domains were discussed, analyzed and controlled, for instance: i) human resources, equipment and laboratory facilities, ii) quality process set-up, iii) data management, stocks and samples and iv) biosafety and waste management. The Luxembourg team visited the laboratories in Rwanda to **assess the current practices**. The visit was followed by recommendations for required changes and improvements to be put in place. The action plan and recommendations were presented to the general manager of the National Reference Laboratory.



Laboratory of Retrovirology contributing to the evaluation of the National Laboratory in Rwanda

QUALITY IN ALL PROCESSES: ISO 9001 CERTIFICATION FOR THE FIRST SIX UNITS AT CRP-SANTÉ, A PREREQUISITE TO WORK SUCCESSFULLY IN INDUSTRIAL PARTNERSHIPS

After many years of intensive preparation, the first six units of CRP-Santé were officially ISO 9001 certified on December 12, 2013 by the **European Society for Certification of Management Systems (ECCM)**. This certification is the recognition of the huge amount of work that has been done to bring quality assurance to all management processes. The six units which are now certified are the **Center for Health Studies**, the **Competence Center for Methodology and Statistics**, the **Clinical and Epidemiological Investigation Center**, the **Genomics Research Unit**, the **Laboratory of Retrovirology** and the **technical and administrative support unit**. CRP-Santé will extend the certification to other units and will also acquire complementary laboratory or process specific accreditations/certifications.



Accreditations or certifications are increasingly required by private and industrial partners to enter into collaborations.

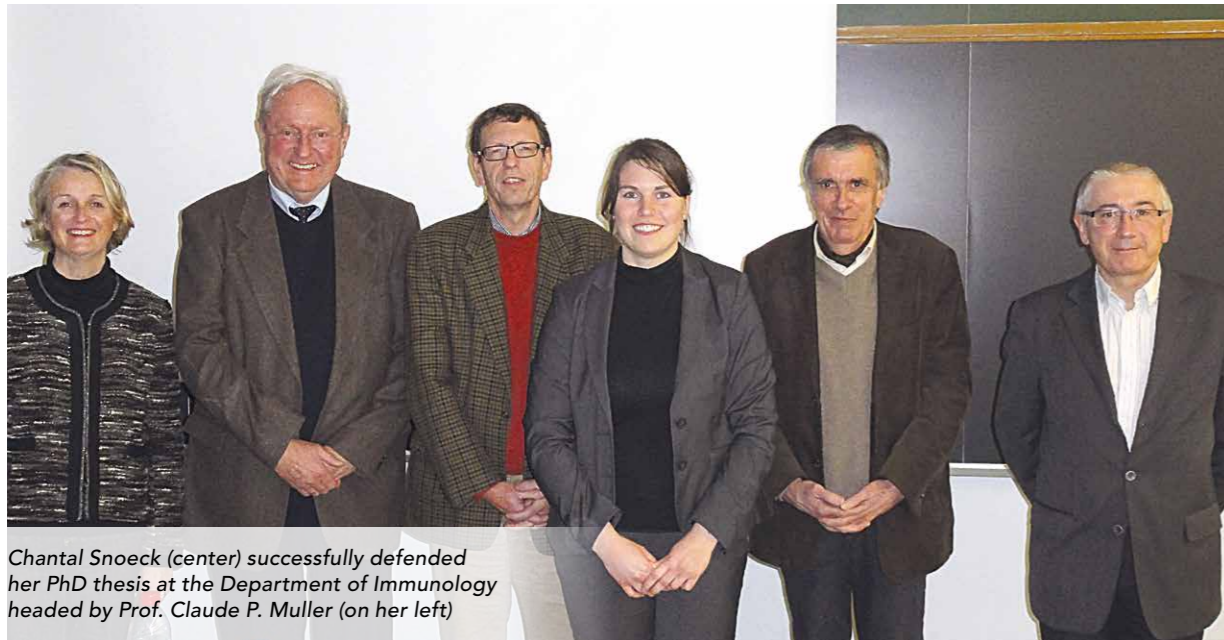


EDUCATING THE NEXT GENERATION OF SCIENTISTS & INFORMING THE GENERAL PUBLIC ABOUT LIFE SCIENCE RESEARCH



Education in science is one of the main missions of CRP-Santé. In 2013, the institution trained numerous PhD students, post-doctoral fellows, master and bachelor students and organized several **outreach activities for the general public**. During the second performance contract (2011-13), CRP-Santé recruited 31 new PhD students and 25 students

successfully obtained their PhD diploma. In September 2013, CRP-Santé and the University of Luxembourg co-organized the **Life Sciences PhD Days**: a unique opportunity for students in training in Luxembourg to exchange on their research. The strong participation of CRP-Santé students highlighted again the high quality of the PhD training provided in our organisation.



Chantal Snoeck (center) successfully defended her PhD thesis at the Department of Immunology headed by Prof. Claude P. Muller (on her left)

DEPARTMENT OF IMMUNOLOGY: EDUCATION IN AN INTERNATIONAL CONTEXT

Chantal Snoeck, a PhD student at the Department of Immunology of CRP-Santé, defended her PhD thesis “Molecular Epidemiology of Avian Influenza Viruses and Newcastle Disease Virus in Western and Central Africa and in Luxembourg” at the University of Lorraine in Nancy, France. She has studied the genetic diversity of Avian Influenza and Newcastle Disease viruses, two of the most important viral diseases for poultry production worldwide, in domestic and wild birds from sub-Saharan Africa and from Western Europe. In Nigeria, she found new avian influenza strains with a re-assorted genome consisting of segments recently introduced from Eurasia and segments originating from Africa, suggesting that avian influenza viruses may actually survive in Africa. She characterized for the first time unique virulent strains of Newcastle Disease virus that are enzootically circulating in Western and Central Africa. She highlighted that trade and movement of animals likely contributed to their spread throughout the region, whereas the contribution of wild birds to their dispersion was probably limited. In Luxembourg however,

wild birds may be an important player for the introduction of Newcastle Disease virus strains. Chantal Snoeck has written or co-authored five publications and two book chapters; three to four other publications are in preparation. She has given a number of oral presentations, both at national and international meetings.

Together with Prof. Claude P. Muller, her PhD supervisor and head of laboratory, Chantal Snoeck regularly represented Luxembourg in the FLU-LAB-NET (www.flu-lab-net.eu), the network of EU National Reference Laboratories for Avian Influenza and Newcastle Disease. She has trained several students from Western and Central Africa in molecular techniques for diagnostic of infectious diseases in livestock. Her PhD work has been sponsored by a fellowship of the Fonds National de la Recherche (FNR), Luxembourg. Chantal will continue as a post-doc in the department, where she will carry on the surveillance and characterization of viral diseases of economic or public health importance in poultry and swine mainly in the Lao People’s Democratic Republic.

PHD STUDENTS IN THE LABORATORY OF RETROVIROLOGY

On June 7, 2013, Martin Mullinge from Kenya successfully defended his thesis at the Université Catholique de Louvain, Brussels, under the supervision of Dr. Jean-Claude Schmit, head of laboratory, Dr. Danielle Perez-Bercoff, researcher and Prof. Patrick Goubau, co-supervisor.

Martin Mullinge’s topic focused on entry and transmission of primary HIV-1 strains in primary target cells for HIV in vivo. In the first part of his work, he validated an in-house recombinant viral assay (RVA) to assess viral co-receptor usage using a wide panel of primary strains of various subtypes. This work showed there was good concordance between phenotypic measurements of tropism and genotypic prediction for subtypes B and C, but also many discordances for other subtypes. This work also led to a collaboration with the Monogram Biosciences Company, USA, who developed another phenotypic assay, and confirmed the accuracy of the in-house assay. In the second part of his work, he addressed the impact of polymorphisms in the cytoplasmic tail of Env (gp41 CT) on viral replication in CD4+ T cells and primary monocyte-derived-macrophages (MDMs). These polymorphisms interfere with viral replication in CD4+ T cells, and the underlying mechanisms are being investigated.

Alain Gras’ thesis focused on pharmacogenetics and the impact of CYP2B6 polymorphisms on the metabolism of two antiretrovirals (efavirenz and nevirapine) in an African population. This project was realized in collaboration with the National Reference Laboratory of Rwanda,

Prof. Uli Zanger from the Dr. Margarete Fischer-Bosch Institute of Clinical Pharmacology in Stuttgart and Dr. Serge Schneider at the Laboratory of Toxicology, Laboratoire Nationale de Santé in Luxembourg. In this project, new single nucleotide polymorphisms (SNP) and alleles of the CYP2B6 gene were identified in the Rwandese population. Their effects on the enzyme activity were characterized in vitro and in silico and several novel or known alleles were further associated with low or high plasma concentrations of efavirenz and nevirapine and their main hydroxy metabolites in a cohort of antiretroviral therapy-treated patients from Rwanda. Alain defended his thesis on June 19, 2013 at the University of Liège in the presence of his supervisor Dr. Carole Devaux.



FIRST BOOK PUBLISHED BY CRP-SANTÉ: "MAIN JOB, MENG PASSIOUN"

In order to inform the general public about jobs in research, CRP-Santé published in 2013 its first book devoted to research careers and entitled "Main Job, Meng Passioun". Through portraits and testimonials, technicians, engineers, students, researchers and nurses speak with **passion about their work**, the **studies** they have conducted thus far, as well as their **personal interests**. Portraits stepped outside traditional paths in order to explain the individual's daily work and to provide the readers with advice in terms of professional orientation. The book has been written in **French, German and Luxembourgish** and has been promoted within the Luxembourgish media and CRP-Santé's website dedicated to the general public. It has been recognized as a relevant and unique tool to promote interest in scientific research.



Furthermore, the book has been widely distributed for free within the schools of Luxembourg. One of the main challenges regarding the inception of the book was the use of the three common languages (Luxembourgish, French, German) as well as popularizing portraits and scientific research. The book has been widely congratulated by **members of government, decision makers and the general public**.



CRP-SANTÉ, A DRIVER IN NATIONAL COLLABORATION PROJECTS

One of CRP-Santé's priorities is to build sustainable national collaborations with other public research centers, the University of Luxembourg as well as the hospitals, foundations (e.g. the "Fondation Cancer", or the **Foundation IBBL**) and the public administrations. In 2013, CRP-Santé achieved this goal. Indeed, two thirds of our research

projects are collaborative, half of them include at least one national partner. In this context, the **Laboratory of Cardiovascular Research**, the **Sports Medicine Research Laboratory** as well as the **Clinical and Epidemiological Investigation Center (CIEC)** are key players that strengthen national collaborations.

THE NORTH POLE PROJECT: A FRUITFUL COLLABORATION BETWEEN THE LABORATORY OF CARDIOVASCULAR DISEASES AND CENTRE HOSPITALIER DE LUXEMBOURG (CHL)

Since 2008, the **Laboratory of Cardiovascular Research** at CRP-Santé collaborates with the Department of Anesthesia and Intensive Care of the Centre Hospitalier de Luxembourg (CHL) on the North Pole project. Cardiac arrest is a devastating condition, with a survival rate of around 10%. The North Pole project aims to improve this outcome and to discover new prognostic biomarkers to guide medical care of patients resuscitated from cardiac arrest. In 2013, the laboratory showed for the first time that microRNAs can be used as biomarkers in cardiac arrest patients, as reported in a publication in

"Critical Care Medicine" (ranked #2 of 26 journals of Critical Care Medicine). This study opens new research perspectives that will be addressed in an international multi-center randomized clinical trial (TTM trial). In 2013, the **Laboratory of Cardiovascular Research** described a novel method to predict outcome after cardiac arrest, combining assessment of a serum protein and of the electric activity of the brain. This method, which is accurate and easily applicable in clinical practice, has been published in the "Journal of the American College of Cardiology" (ranked #2 of 117 journals of Cardiology).



A NATIONAL CLINICAL AND EPIDEMIOLOGICAL INVESTIGATION CENTER (CIEC): BRINGING TOGETHER ACTORS IN CLINICAL RESEARCH AND EPIDEMIOLOGY

The **Department of Public Health** and the **Clinical and Epidemiological Investigation Centre (CIEC)** are major interfaces for national collaborations at CRP-Santé.

Clinical research is a challenge for Luxembourg as international competition in this area is very high. In only a few years, CRP-Santé has successfully developed **expertise** in the field of clinical research and the CIEC was able to establish **close links** with **national hospitals** and to assert its **knowhow** even **beyond Luxembourg borders**.

One of the missions of the CIEC is to provide patients access to **newly developed medications** in various therapeutic areas such as pulmonology, infectious diseases or oncology through the means of clinical studies. In 2013, a total of 694 patients from Luxembourg were able to participate in 18 ongoing international multicenter clinical trials and various local research projects. 24 new studies were initiated in 2013: 6 pharma initiated and 18 academic, local and international, research projects. A growing number of physicians participate in clinical trials in Luxembourg, an interest which also extends to **partners** in the **pharmaceutical industry** and has a positive impact on the **management of patient care**, hospitals and on public health in general. CRP-Santé also conducted several projects in collaboration with IBBL, which collects, stores and analyses biological samples.

In 2013, CIEC involved hospitals in Luxembourg in the celebration of the **International Clinical Trials Day** where CIEC was present in the five main national hospitals to meet patients and their medical and nursing staff. CIEC organized in 2013, the **fifth edition of the Day of Clinical Research**, This special anniversary edition celebrated the CIEC's achievements since its creation in September 2008.



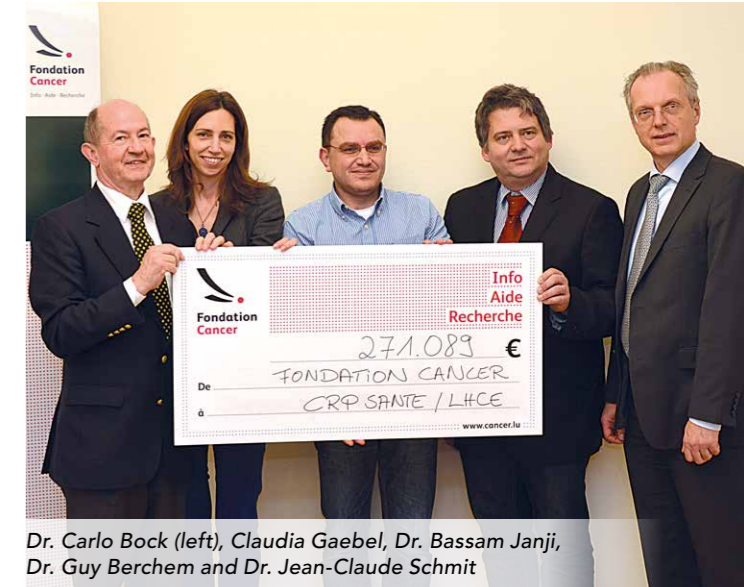
5^e JOURNÉE DE LA RECHERCHE CLINIQUE

The CIEC also co-organized and hosted in Luxembourg the first global conference of the European Society for Translational Medicine. Both conferences have been accredited by the European Union of Medical Specialists (UEMS-EACCME®), accounting for a continuing medical education activity and benefiting from the mutual recognition of this accreditation on European and international level. Last but not least, CIEC trains study nurses, clinical research associates and physicians in clinical research throughout the country, the Greater Region and beyond. In 2013, the CIEC offered the first Luxembourg-based training in good clinical practice.

THE LABORATORY OF EXPERIMENTAL HEMATO-ONCOLOGY COLLABORATES WITH THE "FONDATION CANCER" TO ACHIEVE PROGRESS IN CANCER RESEARCH

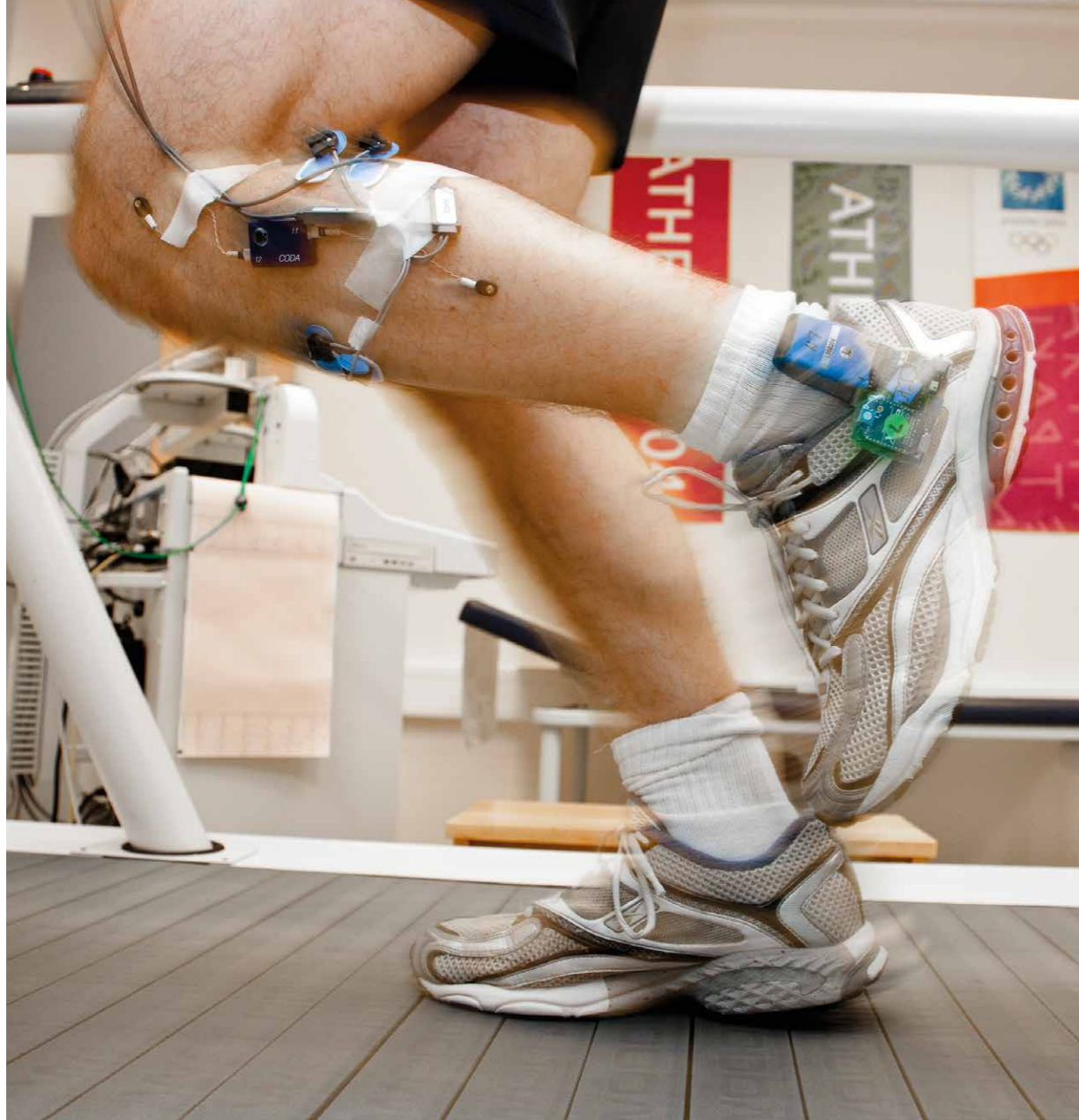
Dr. Bassam Janji, senior researcher at the **Laboratory of Experimental Hemato-Oncology** received financial support of € 271'089 for a project in immunotherapy by the "**Fondation Cancer**". Dr. Carlo Bock, Chairman of the foundation, congratulated Dr. Janji and his team for their important work conducted in the **Laboratory of Experimental Hemato-Oncology** headed by Dr. Guy Berchem.

Tumor immune surveillance relies on the elimination of tumor cells by cytotoxic lymphocytes such as NK (natural killer) cells. This concept is the basis of cancer immunotherapy that is considered a promising new area of cancer therapeutics. NK cells are endowed with several "weapons" that can effectively destroy cancer cells. Serine protease granzyme B, secreted by NK cells, is a formidable weapon capable to enter tumor cells and cause their death. Unfortunately, solid tumors that develop in a hypoxic microenvironment can often outmaneuver the immune surveillance and escape death. Several studies have attributed this tumor resistance to dysfunctional immune cells that infiltrate hypoxic tumors. Immunotherapeutic strategies are primarily based on the reactivation of cytotoxic lymphocytes. However, such strategies may be ineffective if the tumor cells develop their own intrinsic resistance mechanisms to overcome an effective immune response. The team of Dr. Janji has conducted **challenging research work** and obtained results showing that **despite**



Dr. Carlo Bock (left), Claudia Gaebel, Dr. Bassam Janji, Dr. Guy Berchem and Dr. Jean-Claude Schmit

an intact immune response, tumor cells escape NK cell-mediated tumor cell killing by degrading granzyme B via autophagy. They showed that inhibition of autophagy significantly improves the NK cell-dependent immune response in mice. The results of Dr. Janji's team **unraveled an important mechanism** to be considered in the development of more effective clinical immunotherapies for the **treatment of cancer**, which is based on the reactivation of cytotoxic lymphocytes with the simultaneous inhibition of autophagy. Through these results, the Laboratory of Experimental Hemato-Oncology, in collaboration with other laboratories worldwide, paves the way for formulating more effective cancer immunotherapeutic approaches. The financial support from the "Fondation Cancer" contributed to pursue this important project for the treatment of patients suffering from cancer.



NATIONAL SPONSORING: FOREMOST WORK INITIATED WITH SEVERAL WELL-KNOWN PARTNERS

The **Sports Medicine Research Laboratory** conducted in 2013 scientific projects related to **sports injuries** and the influence of physical activity as a treatment for patient groups. In addition, the laboratory gave conferences within companies to promote physical activity and sports. In 2013, national sponsors became part of this collaboration with the Sports Medicine Research Laboratory. The aims of these collaborations were to support the research for new treatments, inform about our web-based **training platform "TIPPS"**, and provide employees of companies with a stronger focus on sports activities as a way to **enhance**



physical and psychological well-being. Partner companies included for instance, Sources Rosport, Sodexo, ING Luxembourg and pharma industry.

BUILDING A WINNING NATIONAL ALLIANCE TO BRING THE FRENCH ARTHROSCOPY SOCIETY (SFA) ANNUAL MEETING TO LUXEMBOURG NEXT YEAR

The meetings of the French Arthroscopy Society (Société Française d'Arthroscopie – SFA) have a long-standing tradition and a high reputation both in the French-speaking world and internationally. They are known for their high scientific standards and innovation in the fields of **arthroscopy**, **minimally invasive surgery** and **regenerative medicine** in traumatic, degenerative and inflammatory joint diseases. Due to continuous improvements over the last three decades, the society's stakeholders have tremendously increased the level of surgical science. In 2013, the annual meeting in Bordeaux gathered **1'100 medical doctors**, orthopaedic surgeons and scientists from **29 countries**.

In 2014, for the first time ever, the SFA meeting will be organized outside France. This will be the **largest medical conference** ever held in Luxembourg. Many efforts had to be deployed years in advance by the conference president, Prof. Dr. Romain Seil, co-head of the **Sports Medicine Research Laboratory** and surgeon at the Centre Hospitalier de Luxembourg, and

staff from CRP-Santé to convince the society's stakeholders to open the meeting to French-speaking neighboring countries. First contacts were made already in 2005. In the following years, the general assembly had to agree upon a change in the society bylaws allowing for the conference to be organised outside of France. At the first application, the Luxembourg bid was rejected, but it was accepted the following year when **Luxembourg was preferred** to the concurring cities of Grenoble and Marseille. Luxembourg had to be promoted actively beforehand. CRP-Santé designed a **specific brochure** and installed an **exhibition booth** at the previous SFA meeting in Bordeaux in December 2013. This turned out to be a **big success**, with more than 800 visitors in two days. The successful promotion of Luxembourg was supported by multiple national partners including Luxair, the City of Luxembourg, the Cercle Cité, LuxExpo, the Ministry of Economy, the Fonds National de la Recherche, the "Cour Grand-Ducale" and the Institut Français du Luxembourg at the French Embassy.



INTERNATIONAL COLLABORATIONS

A modern research institute can only survive in an international competitive environment if it can create successful collaboration links with

the best partners available. In 2013, CRP-Santé was able to further extend its already impressive international network.

COLLABORATION AGREEMENT BETWEEN THE DEPARTMENT OF IMMUNOLOGY AND THE UNIVERSITY OF VIENNA, AUSTRIA

In the framework of the Luxembourg state visit to Austria in 2013, a collaboration agreement between the **Department of Immunology** of CRP-Santé and the **University of Vienna** was signed. The Hygiene Institute of the University of Vienna and the Department of Immunology agreed to collaborate on the development of improved possibilities to diagnose **Lyme disease**. Both in Austria and in Luxembourg the disease plays an increasingly important role. Prof. Gerold Stanek of the Hygiene Institute Vienna is one of the leading scientists in Europe in the field of Lyme disease.

Since 2007, the Department of Immunology is working on pathogens that are transmitted by ticks. In Luxembourg, 8% of the population and even 35% of the risk groups have contact with ticks, although this does not necessarily lead to disease. **Every sixth tick** in Luxembourg is infected with Lyme disease and it regularly happens that the pathogen is transmitted to humans in case of a tick bite. The clinical diagnosis of the disease is complicated because of mostly non-specific symptoms and the lack of reliable laboratory diagnostic tests.



From left to right: Prof. Dr. Hannes Stockinger, Hygiene-Institute, University of Vienna, Prof. Dr. Claude P. Muller, Department of Immunology, Luxembourg, Prof. Dr. Gerald Stanek, Hygiene Institute, University of Vienna

ARTHUR & SONIA LABATT BRAIN TUMOR RESEARCH CENTRE, HOSPITAL FOR SICK CHILDREN – TORONTO, ASSOCIATED TO THE NORLUX NEURO-ONCOLOGY RESEARCH LABORATORY AT CRP-SANTÉ

CRP-Santé and the **Arthur and Sonia Labatt Brain Tumor Research Center** have signed in 2013 a framework agreement for cooperation in neuro-oncology research. This new initiative is an **international recognition** of the scientific expertise of CRP-Santé and its longstanding partner the **University in Bergen**, Norway in the field of brain cancer research. Indeed, both institutions together constitute already one of the largest groups working in glioblastoma in Europe. In the Arthur and Sonia Labatt Brain Tumor Research Center collaborate scientists and clinicians from The **Hospital for Sick Children** and the **University of Toronto**. They have achieved excellence in molecular neuro-oncology research on different tumor types of the central nervous system. The center is led by Prof. Rutka is

a world-renowned neuro-surgeon and researcher. The research at the Labatt Center encompasses all types of malignant brain tumors and focuses on the in depth molecular and genetic characterization of tumors, the targeting of cancer stem cells, and the processes of angiogenesis and invasion.

On March 7, 2013, the collaboration agreement was signed between CRP-Santé and The Arthur and Sonia Labatt Brain Tumor Research Center in the presence of Mr. Etienne Schneider, Minister of Economy, Prof. James T. Rutka, Director of Arthur and Sonia Labatt Brain Tumor Research Center, Dr. Jean-Claude Schmit, CEO of CRP-Santé and Prof. Rolf Bjerkvig, Head of the Department of Oncology, CRP-Santé.



SPREAD: LUXEMBOURG LEADING A EUROPEAN EFFORT IN THE SURVEILLANCE OF TRANSMISSION OF DRUG RESISTANT HIV

SPREAD (Strategy to Control SPREAD of HIV Drug Resistance) is a European HIV drug resistance surveillance program executed under the authority of the **European Society for translational Antiviral Research (ESAR)**. Clinicians, virologists and epidemiologists from 28 European countries are actively involved in the program. The SPREAD program collects representative data, with the aim to characterize newly diagnosed HIV-infected patients and assess transmission of HIV drug resistance over time in Europe. The database is maintained by the **Laboratory of Retrovirology** at CRP-Santé and currently includes over 10.000 patients. With a 3-year grant from the **Fonds National de la Recherche Luxembourg**, the **Laboratory of Retrovirology** is working on improving and extending the current surveillance program and is very actively involved in the analysis of data in collaboration with members of ESAR. In 2013, analysis of patients diagnosed between 2002 and 2010 showed that overall transmission of **drug resistance** in Europe remains stable at around 10%. Resistance mutations associated to the drug class nucleoside reverse transcriptase inhibitors are observed most frequently. Of most concern are resistance mutations associated to non-nucleoside reverse transcriptase inhibitors, which are currently observed in

3.5% of patients. These results have been shared at the **14th European AIDS Conference in Brussels**. A follow-up study to determine clinical implications of infections with a virus that harbors resistance mutations is in progress. In addition, we showed that the degree of late presentation of HIV infection, which is known to be associated with **increased morbidity and mortality**, impaired treatment response and increased costs, is decreasing across Europe. However, public health strategies should focus on vulnerable groups such as migrants, IV drug users and the elderly, as late presentation remains high among these groups.

Furthermore, in 2013 a **new website** was implemented to improve online submission and facilitate automatic verification of data. The surveillance of transmitted drug resistance extended to monitoring of resistance to the new drug class integrase inhibitors. One of the goals for the coming years is to realize continuous submission and real-time analysis, to enable reporting of representative and up-to-date figures of the European HIV epidemic. These figures should become available on the website as an interactive map to better inform public health agencies.

CONFERENCES AND VISITS

Throughout 2013, CRP-Santé organized many events, workshops, seminars, visits and conferences aimed at fostering high-quality

research and promoting scientific exchange within the biomedical research community. We also welcomed many visitors.

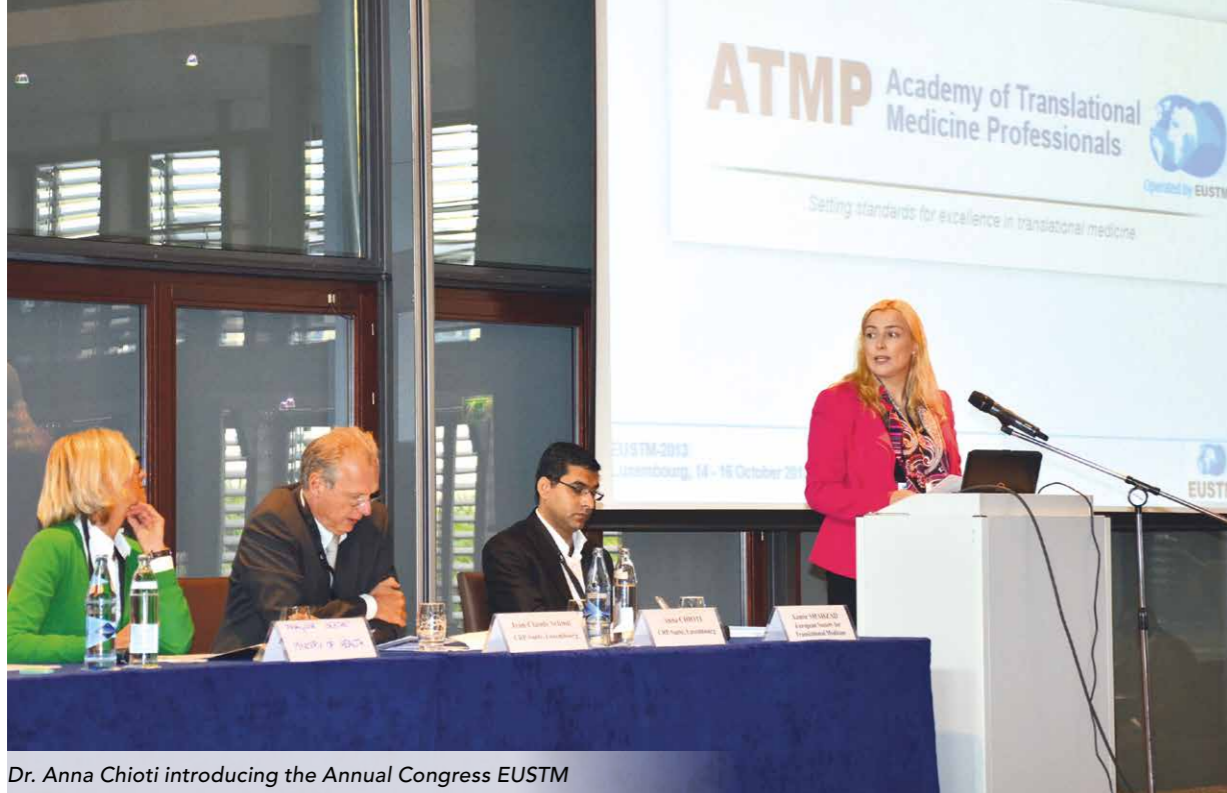
VISIT OF MRS. CATHERINE IVY, PRESIDENT OF THE IVY FOUNDATION, USA

On April 15, 2013, Mrs Catherine Ivy, President of the US based **Ivy Foundation**, visited the Norlux Neuro-Oncology Laboratory at CRP-Santé. The Ben and Catherine Ivy Foundation is a prominent philanthropy organization fully dedicated to improving the survival and quality of life of people diagnosed with brain tumors. The foundation supports

promising research at the forefront of scientific discoveries that will have an impact on patient's life. Touring several European research laboratories in search for promising patient-focused research efforts, Mrs Ivy also took the time to visit and discuss the ongoing projects of the **Norlux Neuro-Oncology team**.



From left to right: Dr. Jean-Claude Schmit, Catherine Ivy, Dr. Simone Niclou, Prof. Rolf Bjerkvig



Dr. Anna Chiotti introducing the Annual Congress EUSTM

TIME FOR A CHANGE: COMBINING RESEARCH AND TRANSLATIONAL MEDICINE IN LUXEMBOURG

Translational medicine is no recent practice in Luxembourg. Using evidence-based medicine to offer **sustainable solutions** for public health problems, translational medicine aims to improve patients' health while giving clinicians the opportunity to apply an idea. Hence, research in Luxembourg has to move towards translational medicine in order to spawn innovative studies focusing on patients' needs. In order to achieve such a challenge, CRP-Santé and IBBL (Integrated Biobank of Luxembourg) decided in 2013 to co-organize the **Annual Congress of the European Society for Translational Medicine & Global Network** Conference on Translational Medicine (EUSTM-2013) from 14 to 16 October 2013 in Mondorf, Luxembourg. With a special focus on public health issues, the conference was supported by multiple national and international organizations including the Austrian Society for Translational Medicine (ASTM), The National Agency for Innovation and Research (Luxinnovation), the Luxembourg Biohealth Cluster, Alstrom Syndrome UK, the Rocky

Mountain Virology Association (RMVA) USA and ImedPub Publishing House, Spain.

EUSTM-2013 brought together world leaders from industry, academic centers, research institutions, regulatory agencies and governments with the aim of discussing translational approaches and tools that could accelerate the research and development of novel diagnostics and therapeutics thereby significantly reducing costs and attrition rates. Participants also included practicing physicians with clinical experience in various therapeutic areas and members of patient organizations. In such a context, EUSTM-2013 offered an interdisciplinary forum to address current challenges in translational medicine and highlighted novel solutions in addition to a unique opportunity for global networking. Pharma and biotech industries, medtech and medical instruments companies, consultancy firms, clinical research organizations and data management companies showcased and exhibited their products and services.

2013: A YEAR AS ANY OTHER. CELEBRATION OF THE INTERNATIONAL YEAR OF STATISTICS

In 2013, we celebrated two important anniversaries in the history of statistics: the 300th anniversary of the publication in 1713 in Basle of **James Bernoulli's "Ars Conjectandi"** and the 250th anniversary of the publication in 1763 in London of **Thomas Bayes's "An Essay towards Solving a Problem in the Doctrine of Chances"**. These two works are not only of fundamental importance but curiously linked. Both authors studied theology, both works were published posthumously, both were considered controversial at the time. To mark these two important events in the history of statistics, the International Statistics Institute has declared 2013 the International Year of Statistics.

Even in a small country like Luxembourg, the range and reach of statistics is impressive. The International Year of Statistics Conference, which was held in November 2013 and organized by the Competence Center for Methodology and Statistics (CCMS) of CRP-Santé, was a collaborative effort of a number of statistics groups within Luxembourg. Between them, they represented a wide range of statistical activities: from **measuring the population of Luxembourg to developing mathematical theories** via purely theoretical research as well as more **applied research** in sociology and health and contract work for industry. This conference, which was organized for the first time in Luxembourg, gathered around 100 participants and was a unique opportunity to showcase some of the very many applications of the broad and fundamental science that is statistics.

Among multiple other aspects, the International Year of Statistics Conference especially stimulated a **better knowledge of statistics issues in Europe**, provided a **working exchange** between researchers with different background and demonstrated the expertise of the various statistical groups in Luxembourg, including the **Competence Center for Methodology and Statistics (CCMS)** of CRP-Santé and made the services they provide more widely known.

Furthermore, a number of the groups involved, are now discussing the possibility of starting a statistical association that can facilitate more regular contact and exchange of ideas between key groups active in statistics in Luxembourg.,



Prof. Stephen Senn, Head of Competence Center for Methodology and Statistics (CCMS)

WORLD HEPATITIS DAY AND OTHER WHO INITIATIVES SUPPORTED BY CRP-SANTÉ

In 2013, CRP-Santé contributed to several disease days from the **World Health Organization (WHO)**. CRP-Santé especially supported the **World Hepatitis Day** on July 27, 2013 by organizing a campaign to raise awareness for this chronic and sometimes deadly disease. At a booth on the market, CRP-Santé volunteers distributed information leaflets and encouraged people to **get tested** for viral hepatitis. The event was attended by local media and was supported by the **World Hepatitis Alliance**.

At CRP-Santé, the Laboratory of Retrovirology is currently working on drug resistance and the molecular epidemiology of hepatitis C virus (HCV) in collaboration with the **“Service National des Maladies Infectieuses”** of the Centre Hospitalier de Luxembourg (CHL). HCV

is among the most common viruses that infect the liver. Every year, 3 to 4 million people around the world are infected with the hepatitis C virus. About 150 million people are chronically infected and at risk of developing liver cirrhosis and/or liver cancer. More than 350'000 people die from HCV-related liver diseases every year. In addition, the **Department of Immunology** of CRP-Santé has been working for 10 years on the hepatitis B virus (HBV). Twenty studies have been published in peer-reviewed scientific journals. These studies focus on the genetic surveillance, on virus transmission channels and the virus molecular evolution in more than 15 countries on 4 continents, particularly in sub-Saharan Africa, in the former Soviet Republic and in Southeast Asia. In Laos, Nigeria, Cameroon and the Central African Republic, the group has found new variants of HBV.



AWARDS AND NOMINATIONS

In 2013, staff members of CRP-Santé have been recognized for their competences and expertise, and have been invited to lead scientific efforts internationally.

DR. JEAN-CLAUDE SCHMIT: MEMBER OF THE F-CRIN SCIENTIFIC BOARD



Dr. Jean-Claude Schmit, currently **CEO of CRP-Santé** and head of the Laboratory of Retrovirology for the past 17 years, has been nominated as a member of the F-CRIN Scientific Board in January 2013. F-CRIN which is the French counterpart of the European Clinical Research Infrastructure Network (ECRIN), a pan-European

support infrastructure for multinational investigator-driven clinical trials.

The F-CRIN infrastructure aims to support French investigators and promoters in the field of **clinical trials**, in order to help them meet new international criteria for attractiveness and efficiency.

During his term as Scientific Board member, Dr. Schmit has contributed to the selection of two methodology platforms in France which will lead all major clinical research efforts. In addition, he contributed to the identification of several high quality research networks in thematic areas where France can become a leader internationally.



DR. ANNA CHIOTI: ADVISORY BOARD MEMBER OF THE EUROPEAN SOCIETY FOR TRANSLATIONAL MEDICINE

Dr. Anna Chioti, head of the **Clinical and Epidemiological Investigation Center** at CRP-Santé has been nominated Advisory Board Member of The **European Society for Translational Medicine (EUSTM)** a global non-profit platform for the advancement and progress of translational medicine.

The society aims to facilitate cooperation and interaction among clinicians, basic life scientists, academia, industry, governments, funding and regulatory agencies, investors and policy makers in order to develop and deliver high quality translational medicine programs and initiatives with overall aim to enhance the health care of European and non-European population.

Dr. Chioti's presence in the advisory board offers the possibility for CRP-Santé to contribute to the society's programs/events including webcasts, webinars, training courses, conferences and also to contribute articles on CRP-Santé's areas of interest in the society's new digital magazine **'New Horizons in Translational Medicine'** available at <http://www.eustranslationalmedicine.org/publications>

PROF. CLAUDE P. MULLER: FIRST AWARDEE OF THE “GRAND PRIX LIFE SCIENCES” OF THE INSTITUT GRAND-DUCAL LUXEMBOURG

In 2013, the Grand Prix of the **Institut Grand-Ducal Luxembourg** has been awarded to **Prof. Dr. Claude P. Muller** to honour more than thirty years of research activity on viruses, which is widely recognised nationally and internationally. He received the first Grand-Prix for Life Sciences sponsored by the Cactus

Group. The award ceremony took place on November 16, 2013 at the Chamber of Commerce. Prof. Muller was honored for his lifetime achievements in scientific research, academic teaching and training, the promotion of scientific culture in Luxembourg and for his social commitment.

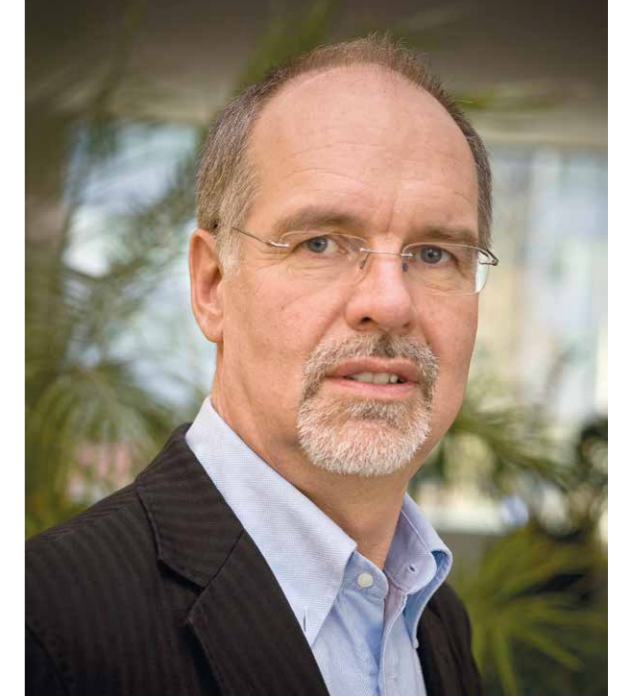


Prof. Claude P. Muller (left) honored for his lifetime achievements in scientific research

PROF. BRUNO DOMON: NEWLY NOMINATED MEMBER OF THE EXECUTIVE COMMITTEE OF THE HUMAN PROTEOME ORGANIZATION (HUPO)

Prof. Bruno Domon, head of the **Luxembourg Clinical Proteomics Center (LCP)** has been elected member of the Executive Committee of the Human Proteome Organization (HUPO).

HUPO is an international scientific organization representing and promoting proteomics through international cooperation and collaborations by fostering the development of new technologies, techniques and training. Prof. Bruno Domon also occupies responsibilities in different working groups of the organization: he is chairing the newly created **Proteome Analyzer Initiative**, which aims to design a new low-cost, high-throughput mass spectrometry-based platform to analyze proteins in biological and clinical samples. In addition, Bruno Domon is co-chair



of the mass spectrometry pillar, one of the components of the **Human Proteome Project (HPP)**, which aims to fully characterize the human proteome, while getting a better understanding of the biology underlying human diseases.

This nomination recognizes the international visibility of the LCP and its leading role in the development of quantitative proteomics approaches based on high-resolution mass spectrometry.

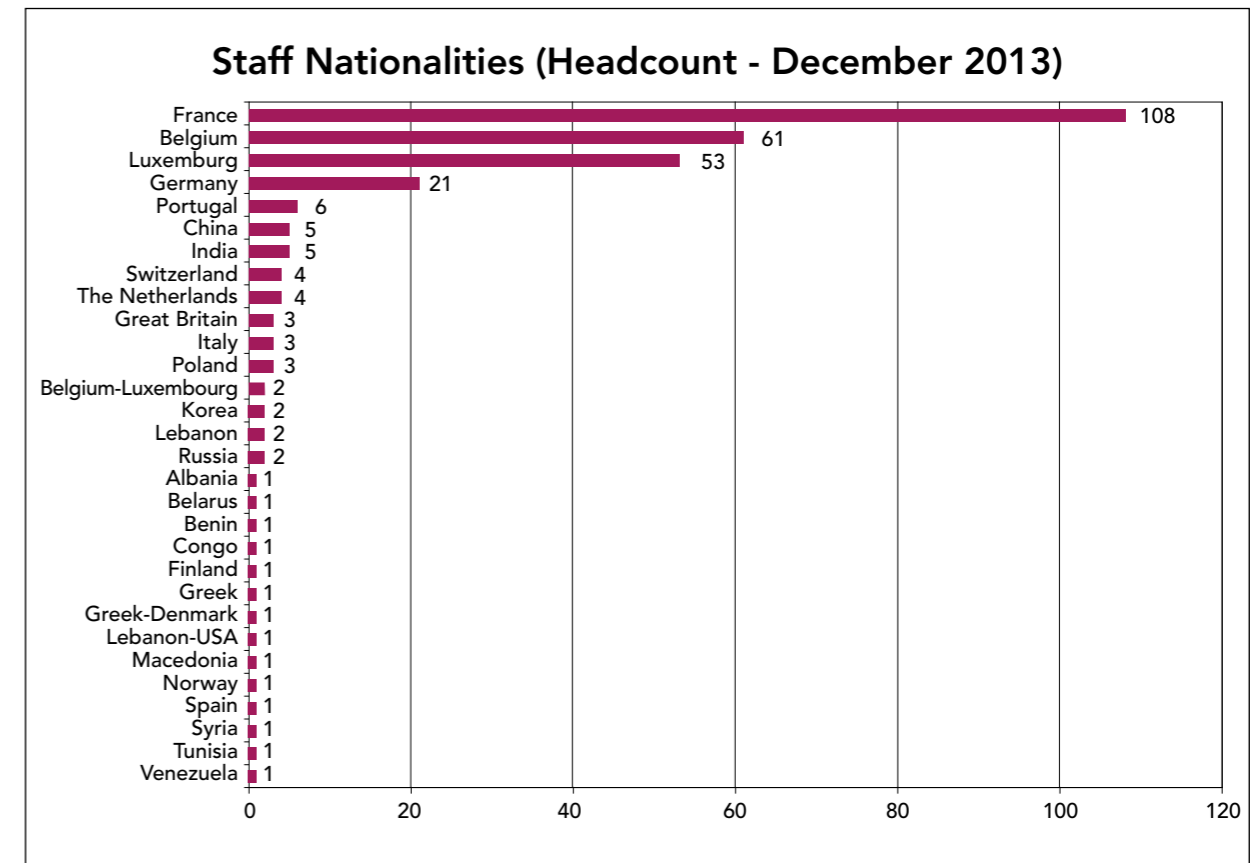
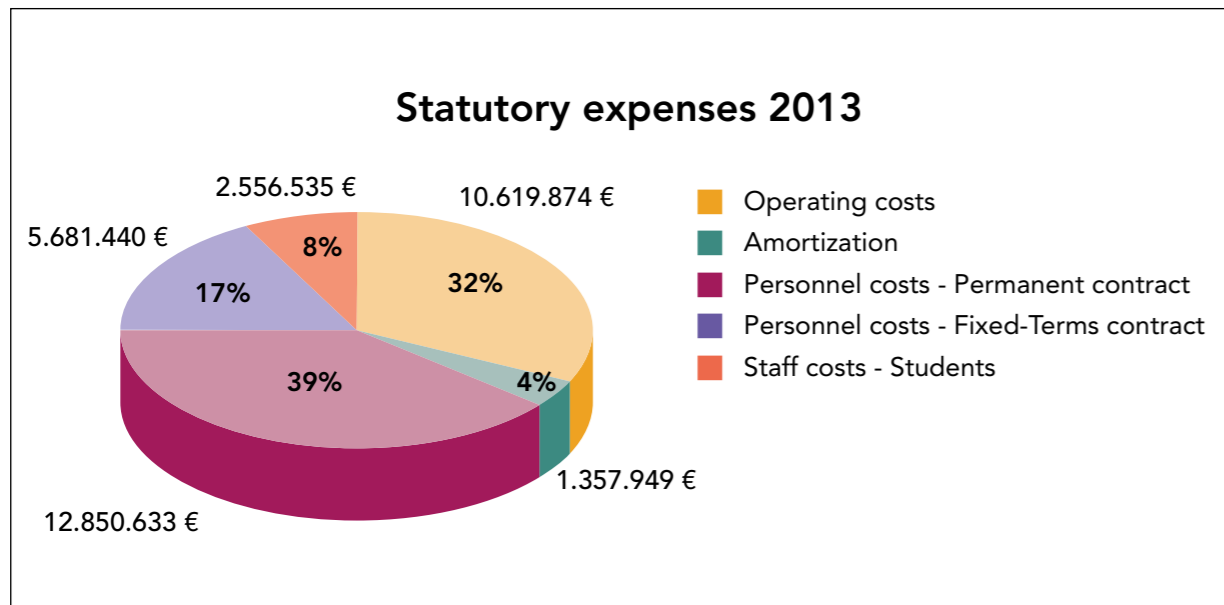
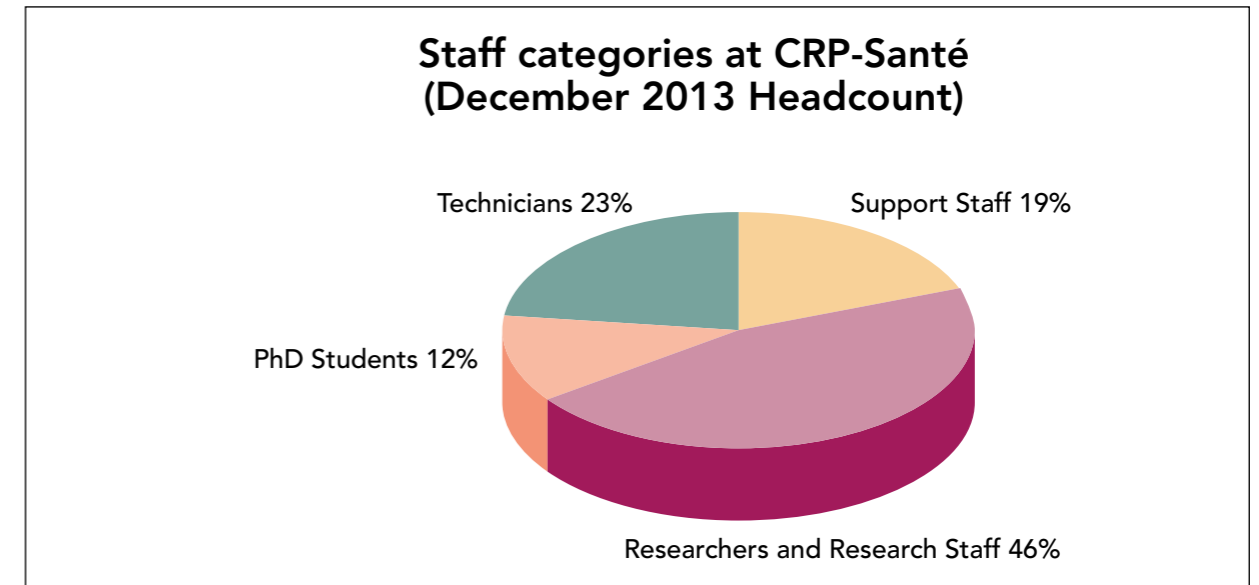
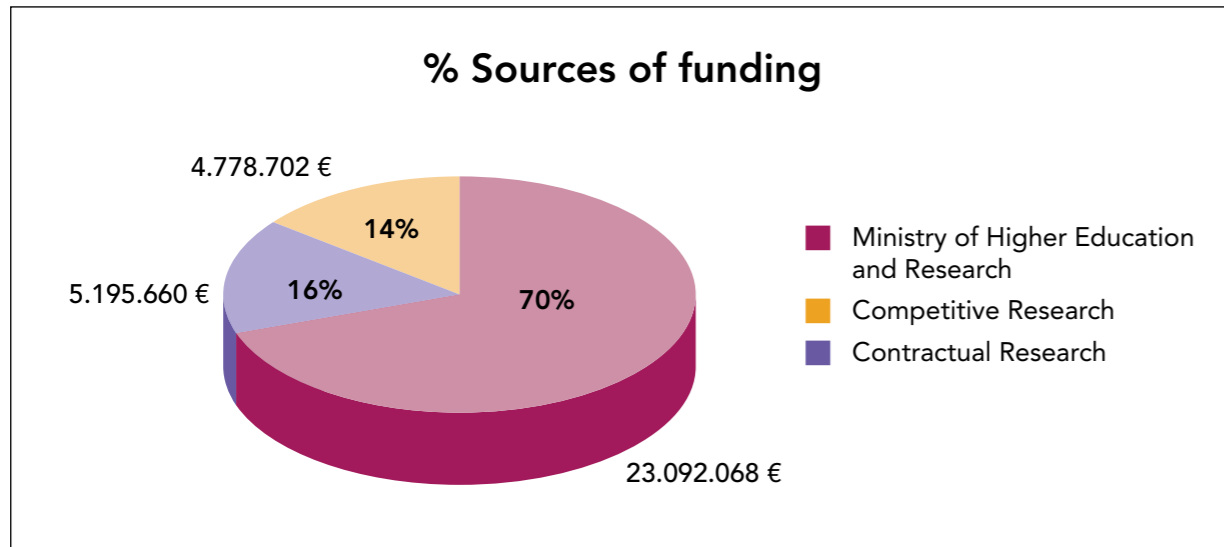
CONFIRMATION OF THE DEPARTMENT OF IMMUNOLOGY AS WHO COLLABORATING CENTER



Left: Dr. Judith Hübschen
Right: Prof. Claude P. Muller

The World Health Organization (WHO) EURO Regional Office located in Copenhagen has nominated in 2013 the **Department of Immunology** for the fourth time as WHO Collaborating Centre for Reference and Research on measles infections with Prof. Claude P. Muller as director. The first nomination goes back to 1998. WHO expects from the Luxembourg Department of Immunology policy and technical support provided to member states in order to enhance their capacity to carry out surveillance and monitoring of all communicable diseases of public health importance.

KEY FIGURES



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