Infectious disease research at Riga Stadins University

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Riga Stradins University, Division of Medicine is the major educational institution in the field of medical sciences in Latvia. With almost 100 FTE researchers, it is also the largest Latvian institution with research activities in various areas of medical sciences such as biomedical, clinical, regulatory and health systems. The RSU is currently amongst the top 3 Latvian Institutions considering research outputs such as patents. RSU is one of the top 3 institutions that receive the highest funding for research in Latvia. RSUDM is also the leading Latvian institution for developing research-based evidence in medicine, which provides major input for regulatory authorities, expert panels and policy measures. A.Kirchenstein Institute of Microbiology and Virology (KIMV) of Riga Stradiņs University is an academic unit with scientific activities in the fields of microbiology, virology and biotechnology.

Morbidity and mortality from several infectious diseases has been restricted or fully eliminated by the introducing new and effective vaccines, improving the system of epidemiological supervision, and by effectively coordinating international action in terms of dealing with epidemics. At the same time the outbreak of SARS in 2003, the spread of the pandemic influenza in 2009, and the outbreak of poliomyelitis in Central Asia in 2010 demonstrated that infectious diseases still pose a significant threat to the public health. Due to demographical, environmental, technological, economic and social factors, infectious diseases and related morbidity and mortality are spreading with an increasing speed. Latvia is one of EU countries with high prevalence of HIV infection, proportion of AIDS patients has increased to 4.3 cases per 100,000 inhabitants (2009), which is the highest morbidity rate in the EU countries. According to WHO data, Latvia still belongs to the eighteen high priority countries in the European region for TB control and is one of 27 countries in the world with the highest level of multi-resistant TB, with MDR-TB incidence increasing by every year. Recent surveys showed that 1.7% of the Latvian population (1,714 per 100,000 population) are chronically infected with the hepatitis C virus (HCV) with the perspectives of development of liver fibrosis, cirrhosis and eventually hepatocellular carcinomas. Long-term consequences of persistent infections present a serious public health threat, as chronic inflammation processes translate into cardiovascular, oncological, liver, pulmonary diseases, and lead to the disfunction of the immune system manifested by allergies and autoimmunity. KIMV/RSU conveys research on chronic viral infections and concomitant inflammation, highly actual and promising field providing strong grounds for competitive international collaboration.

KIMV/RSU research covers the following areas: The role of viruses in emerging and re-emerging diseases; Viruses as health threatening factors; Viruses as factors influencing biological aging and life quality; New developments in early and non-

invasive diagnostics; Novel anti-viral therapies; Development of nanotechnology-based approaches in cell biology and medicine to target drug delivery to tumour cells; New natural substances for the treatment and prevention of diseases; New methods in virology, immunology and medical technology.

A paraphly of research projects hosted at KIMV/RSU investigate the involvement of persistent virus infections in the development of systemic autoimmunity. Chronic viral infections poise high risk for development of autoimmune disorders, including multiple sclerosis (MS), scleroderma and Hashimoto thyroiditis (AITD), rheumatoid arthritis (RA), systemic lupus erythematosus, anti-phospholipid syndrome (APS), systemic sclerosis and vasculitis. We have established links between infection with parvovirus B19 and development of RA (Kozireva et al., 2008), and HHV-6A/B infections and MS, and AIDT (Chapenko et al, 2003; Nora-Krukle et al, 2011). Currently, we are investigating the molecular mechanisms by which HHV6/7 and parvovirus B19 infections influence the clinical course RA and osteoarthritis (OA), with the final aim to identify new host and viral biomarkers for the prognosis of autoimmune disease progression. This would allow early introduction of preventive therapeutic interventions for stabilization of the immune system. The wide range of host parameters include the expression on PBMCs of chemokine receptors CCR1 and CCR2 (by FACS); of local tissue mediators as growth factors (TGF-beta etc.), regulators of extracellular matrix rearrangement (as metalloproteinases) , proinflmmatory cytokines IL-6, IL-10 and TNF-alpha, and chemokines CCL2 and CCL1 (by ELISA). The involvement of HHV-6 in the development of autoimmune thyroiditis is analysed by assessing the presence of viral infection activity markers in patients' PBMCs manifested by the expression in the thyroid gland tissues of mRNA corresponding to U41, U89/90, U60/66, U79/80 and U95 ORFs of HHV6 ORFs and correlation of the expression to the immunomodulation indices. Better understanding of the mechanisms of immunomodulation by parvovirus B19, HHV6 and HHV7 would allow a motivated choice of antiviral and immune therapies preventing the development and aggravation of autoimmune disorders. Insufficiency of new cost effective diagnostic and treatment methods is a general problem, particularly in Latvia, where health care budget is limited. Development and timely applications of the innovative treatment regimens will lead to the improvement of public health of the Latvian population.

Molecular mimicry between host and viral proteins is considered to be the main mechanism in the autoimmune processes (Lunardi et al., 2008). Taking into account the molecular mimicry aspect, one could suggest that the virus as the trigger for autoimmune mechanism leaves footprints in the autoantibody profile. Identification of these footprints may point at the initial autoimmunity-inducing pathogen. To test this hypothesis, we are studying the autoantibody profiles in the groups patients with autoimmune diseases as RA, OA, AITD compared to the apparently healthy individuals. An accent will be made on autoantibodies against cellular lipids. Immune response against a unique sequence within parvovirus B19 VP1 protein has been shown to experimentally induce anti-phospholipid antibodies, explaining correlation between B19 infection and APS (Tzang BS, Lee YJ, 2007; Chen DY, 20100). Lipids serve as mediators of viral entry for several human pathogens as flaviviruses, hence,

presence of these antibodies could modulate host susceptibility to viral infections providing new insights into the mechanism(s) of natural resistance to viral infections.

Importantly, KIMV/RSU hosts the 7th Framework programme founded Coordination and support action project BALTINFECT. The objective of the project is to strengthen multidisciplinary infectious diseases research in Baltic, European and global dimension as a critically important part of health research by unlocking the research potential of RSU in the area of infectious, immunological and rare diseases. This will be achieved by establishing two new laboratories: a digital immunological visualisation laboratory and an infectious diseases modeling laboratory; by up-scaling research personnel capacity by employing experienced incoming researchers; and by organizing a series scientific workshops and conferences in the field of in the area of infectious, immunological and rare diseases.

KIMV/RSU is seeking partners to jointly study the molecular epidemiology of life-threatening infections in the Baltic region, including pathogens affecting children; uncover host determinants of resistance versus susceptibility to infection with RNA viruses; perform the autoimmune population profiling; and study the mechanisms of immune modulation and autoimmunity in viral infections.