



# VACTRAIN



## TWINNING ON DNA-BASED CANCER VACCINES

This project has received funding from the European Union's Horizon 2020 Research and innovation programme under grant agreement No 692293

# TWINNING ON DNA-BASED CANCER VACCINES



RĪGA STRADIŅŠ  
UNIVERSITY



Karolinska  
Institutet



University of  
**LODZ**



R.E. Kavetsky Institute of  
Experimental Pathology, Oncology,  
and Radiobiology



**The objective** - to significantly strengthen the research in Riga Stradiņš University in the smart specialization area of Latvia “bio-medicine, medical technologies, and biotechnologies” with application to immunotherapy of cancer.

## TASKS:

Train essential steps of research aimed to deliver new anti-cancer remedies based on the novel promising vaccine platform employing naked DNA:

- Defining the target(s) of cancer vaccine,
- Designing respective immunotherapeutical,
- Construction and characterization,
- Delivery to vaccine recipients
- Testing of activity in preclinical trials
- Connecting to a clinical trial.

## VACTRAIN INCLUDES THE FOLLOWING ACTIVITIES:

- Coordination of staff exchange, workshops, and schools
- Trainings and experimental laboratory courses
- Expert Visits, short-term on-site training
- Conferences attendance and publications
- Dissemination and outreaching activities
- Project management

- Project acronym: VACTRAIN
- Grant Agreement No 692293
- Contribution of EC : 999 475 EUR
- Duration : 01.01.2016. – 31.12.2018.
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**THE COORDINATOR - RĪGA STRADIŅŠ UNIVERSITY, LATVIA**



**RĪGA STRADIŅŠ  
UNIVERSITY**

**Project partners:**

Department of Microbiology, Tumor and Cell Biology  
(MTC) at Karolinska Institutet, Sweden



**Karolinska  
Institutet**

University of Lodz, Poland



University of

**LODZ**

R.E.Kavetsky Institute of Experimental Pathology,  
Oncology and radiobiology of National Academy of  
Sciences of Ukraine, Ukraine



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of Experimental  
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**RĪGA STRADIŅŠ  
UNIVERSITY**

RSU is an advanced institution of higher medical education in Latvia and also one of the leading in Europe. RSU offers several levels of education, starting from Bachelor and Master lines up to Phd Programmes in all fields of medicine. RSU has an excellent teacher-student ratio with approximately 6500 students to 400 academic staff members. 21% students are international, with 89 in ERASMUS out-going, and 56 in ERASMUS in-going projects. The majority of students are enrolled in the faculties of Medicine, Law, Rehabilitation and Public Health and Social Welfare.

Another key RSU activity is the continuation of education and professional development programmes for the medical doctors and healthcare practitioners. There are five doctorate study programmes operating at RSU – medicine, pharmacy, sociology, law, political science and seven doctorate councils: with bases in medical science, internal medicine, surgery, medicinal biomechanics, dentistry, pharmacy, and sociology. RSU hosts the 2nd level professional education programme "Residency in Medicine" in the form of full-time 3 to 6 year studies, depending on the chosen programme or speciality. The teaching personnel are the country's leading specialists with remarkable experience and broad cooperation with their colleagues in many European countries. Teaching is offered in the recent theories of disease pathogenesis, modern methods of early diagnostics and modern principles of complex treatment.

Furthermore, Rīga Stradiņš University holds a unique place in Latvia's scientific field, providing a full research cycle from laboratory to hospital bed. This applies particularly to such research fields of public importance as oncology, infections, paediatrics, rehabilitation and dentistry. RSU is a leading academic research institution in the fields of medicine, pharmacy, dentistry, rehabilitation and nursing sciences. Scientific activity is centred around 62 professors and 30 leading researchers. RSU processes are ISO 9001:2008 certified (Bureau Veritas). Due to this, RSU possesses a managerial capacity required by complex projects.

Since 2008, Rīga Stradiņš University research activities have been organized within the following RSU priority research directions:

Ageing: biological ageing factors and quality of life in Latvian population;  
Structural biology, functional and biomechanical studies for new diagnostic tools and new therapeutic interventions;

Endogenous and exogenous risk factors in Latvia, comprehensive analysis of public health determinants;

Modern approaches to infection agents, their role in infections relevant for Latvia  
Mortality and disability factors during childhood;

Immunochemical, radiological and clinical methods in research on dentofacial and maxillofacial deformities and anomalies;

Clinical epidemiology of functional limitations caused by health disturbances;

Social dimension of medicine, effects of globalization.

One specific field is engulfing the topic of current project proposal, namely:

Cancer: research on clinical and molecular characteristics and their advancement for prevention, early diagnosis and improvement of treatment strategies.

Proposed project will be coordinated by the Research Department of RSU.

RD/RSU is an administrative entity dealing with the co-ordination, monitoring and support of research activities under the direct jurisdiction of the Vice-Rector for Science. Employees of the Research Department are responsible for the development of science at the university. RD/RSU activities lie in the support of the effective research activity strategies and the implementation of RSU science policies. An ever-increasing attention is paid to the transfer of knowledge and technologies by integrating knowledge in the basic functions of the University. In short, RD/RSU implements the following activities:

Provision of RSU scientific activity;

Evaluation of the complex results of scientific activities;

Co-ordination of the scientific projects of RSU structural units;

Support in up-grading the qualifications of the researchers;

Support in the international collaborative research;

Representation of RSU in the external communications on scientific activity issues;

Support of RSU scientific publications;

Intellectual property registration.



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## Karolinska Institutet

KI/MTC focuses the research on immunology, infection biology and cell and tumor biology. The research interests are centered on the genetics and molecular biology of virus, bacteria and parasite replication, the role of gene products in abnormal cell growth, the use of microbes as probes for the study of signal transduction, transcription, translation, cell cycle regulation, cell differentiation, and cell death. Specific research areas include the biochemical mechanisms of cell growth control, transformation, signal transduction, and transcriptional regulation, the molecular genetics, molecular biology and molecular pathogenesis of latent, persistent and cytolytic infections, the characterization of receptor interactions and the mechanisms of cell entry, the interaction with cells involved in innate and adaptive immune responses, the pathogenesis of infection and rational drug design. Research at MTC is carried out in several scientific areas, this generates a diversified environment where cross-fertilization between different fields has the potential to generate novel and groundbreaking concepts. Specific area in focus with the current proposal is Cancer, and Tumor Biology. It consolidates the research on the basic mechanisms causing tumors and tumor progression, host responses to tumor, genetic factors predisposing to or on contrary preventing development, protein products of these factors, such as oncogenes, cell cycle regulating genes, signal transduction genes, growth factors, apoptosis and cell aging controls, and suppressor genes and susceptibility genes. This area also includes studies on genetic cancer susceptibility and familiar cancers, related molecular epidemiology, on the interplay between malignant and normal cells, cell adhesion, angiogenesis, metastasis formation, aspects on tumor regression, and research on the relationship between infections and tumor development, as well as related bioinformatics and biom complexity. The application of this knowledge in the development on experimental treatments, such as gene and immunotherapy, and preventive measures is also included in this area of research.

MTC offers several levels of education. Today MTC offers Third cycle (doctoral) education programs in the research areas, including Immunobiology, Infection Biology, Cell Biology, Tumor Biology, Vascular biology, Infectious Diseases and Microbiology. It provides a dynamic research environment for approximately 100 or so postgraduate students engaged in many research activities. All students are registered for a PhD in Medical Science. Besides, MTC leads bachelor student education in Biomedicine including basic immunology covering morphology and general functions of the immune cells, proteins and organs of the immune system; maturation, interactions and regulation of innate and adaptive immune responses. It includes also clinically orientated immunology covering autoimmunity, allergy and transplantation immunology, morphology, taxonomy, genetics and metabolism of bacteria.

Current proposal is driven by a laboratory at MTC working on genetic vaccines against HIV and cancer. The laboratory conveys studies and educational activities in the field of the design, preclinical and clinical testing of DNA vaccines. Genetic vaccines have generated wide-spread interest for many applications, since DNA encoding a microbial or tumor-specific gene results in in vivo expression of the desired gene, protein production and presentation as an endogenous foreign antigen. The laboratory headed by Prof Wahren explores genetic vaccination against a protein abundant in human tumors, namely carcinoembryonic antigen (CEA). Studies were initiated in 2006. Preclinical evaluation results were published in 2007 (Haller malm K et al. Pre-clinical evaluation of a CEA DNA prime/protein boost vaccination strategy against colorectal cancer. Scand J Immunol. 2007 Jul;66(1):43-51), and clinical trials were initiated in 2009. Active immunization approach was applied. Since then, the laboratory has tested two genetic CEA vaccines (wild type and mutated) and one glycoprotein vaccine in patients who are radically operated against colorectal cancer, with a primary surgical finding of Dukes B or C, diagnoses that confer around 50% risk for progression within 2-5 years. The CEA vaccines are tested in joint studies with H Mellstedt, Radiumhemmet, Karolinska Hospital, Stockholm. The laboratory also develops new tools for in vivo evaluation of passive-active vaccination efficiency. In parallel, the laboratory has constructed HIV genes covering the highly variable sites of HIV envelopes and structural genes of Gag, subtypes A-E, the less variable parts of HIV regulatory genes and enzymes.



University of  
**LODZ**

The University of Lodz (LU) is one of the strongest scientific and research centres in the country. The University is repeatedly ranked among the top higher education institutions in Poland, and it especially excels in such fields of study as management, biology, law and economics. The 12 faculties of the University provide programs in 40 fields of study and 170 specializations for more than 40,000 students. LU has gained experience and reputation as a reliable project coordinator and project partner, as well as a strong international science and research centre.

The Faculty of Biology and Environmental Protection is one of the strongest faculties of LU. Research carried on at the faculty is of pure, applied and methodological character. The scientific problems studied by the research staff focus on three main themes: biological environment, structure and functions of plant, animal and microorganism cells, and biomedical and biotechnological topics. Scientific schools created by faculty professors include among others: biochemical, biophysical, zoological, ecological, anthropological, neurophysiological, microbiological and immunological.

The Department of General Biophysics has been studying a novel group of polymers called dendrimers for over 15 years, being actively present in this field from the very beginning. The main areas of interest are: (i) application of dendrimers in medicine, especially as carriers of anticancer drugs and anti-amyloid agents; (ii) interaction of dendrimers with various molecules like proteins, nucleic acids, membranes; (iii) biophysical characterization of complexes of dendrimers with biomolecules (dendriplexes); (iv) in vitro toxicity studies of dendrimers and dendriplexes. Members of the Department are authors of over 260 scientific papers published in peer reviewed journals.

Main research topics of the Department:

- Interactions of various dendrimers (PAMAM, PPI, PPI modified with sugar residues, viologen-phosphorus, phosphorus, carbosilane) with biomolecules: nucleic acids, proteins, model and biological membranes;
- Characterization of formed dendriplexes, their physico-chemical properties, morphology, size, zeta potential and stability in time, temperature, pH;
- Toxicity of dendrimers and dendriplexes against various cell lines and blood cells. Applications of dendrimers in medicine, especially as: carriers of anticancer drugs, factors influencing the process of fibril formation in neurodegenerative diseases and carriers of antisense oligonucleotides and siRNAs (HIV infection, cancer)/



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## R.E. Kavetsky Institute of Experimental Pathology, Oncology, and Radiobiology

KIEPOR of National Academy of Science of Ukraine (NASU) is a strong academic center with more than 50 years of experience in the field of experimental and clinical oncology.

The main topic of research at KIEPOR is a work on biology of tumor cell and the tumor microenvironment, and a study on molecular mechanisms of oncogenesis with the aim to develop personalized medicine. Another aspect of the work is an investigation of molecular features of metabolic regulation in cancer with the aim to develop the biotechnological approaches and sorption-based technologies for the anti-cancer treatment. Yet another field of research is to find out the molecular and cellular markers of the initiation, promotion and progression of tumors, and create panels of markers for the early diagnostics and prognosis of the course of disease. Among important directions of research are studies on the influence of potentially carcinogenic environmental factors (chemical carcinogens, ionizing and non-ionizing radiation) on carcinogenesis and development of the agents that can counteract these factors. Under an umbrella of translational medicine, researchers are working on innovations in diagnostics and anti-cancer treatment, including the development of anti-cancer vaccine. The Scientific Council and the Specialized Dissertation Advisory Council (D.26.155.01) at KIEPOR has the right to grant degrees of Doctor of Science (Dr Sci, Dr Hab) and PhD in Medical and Biological Sciences with the specialty 14.01.07 (Oncology). The international journals "Experimental Oncology" (founded in 1979) and "Oncology" (founded in 1999) are issued by KIEPOR. At KIEPOR, the bank of cell lines is created that consists of more than 35 000 cell cultures. This bank has the status

of the National Heritage of Ukraine from 2001. KIEPOR is a member of the Organization of European Cancer Institutes (OEIC-EEIG). Leading researchers of KIEPOR are members of numerous international organizations, such as American Society of Clinical Oncology (ASCO), the British Association for Cancer Research (BACR), the European Association for Cancer Research (EACR), the European Society For Medical Oncology (ESMO), the European Society for Hyperthermic Oncology (ESHO), the International Network For Cancer Treatment and Research (INCTR), the European Society Gynaecologic of Oncology (ESGO), and EBV-association. KIEPOR has hosted numerous national and international scientific forums.

An Ukrainian team leads research in the field of the molecular and cell biology of cancer, with the aim to reveal molecular mechanisms of oncogenesis. Recently it was shown by the team members, in collaboration with Professor George Klein, that the human mitochondrial ribosomal protein MRPS18-2 (S18-2) could bind RB1 protein, preventing association of RB1 with E2F1 and promoting the S-phase (Snopok et al., 2006; Kashuba et al., 2008). Moreover, overexpression of S18-2 protein led to immortalization of primary rat embryonic fibroblasts and induced expression of embryonic stem cell markers (Kashuba et al., 2009). We have also shown that pathways, that are characteristic for rapidly proliferating cells, were upregulated in the S18-2 immortalized cells depending on overexpression of S18-2 protein. Elevated expression of S18-2 in stem cells (our findings and the analysis of the published microarray data) raises a question whether this protein can be a promising target for anti-cancer vaccine.

These unique findings are the base for the proposed project aimed to propose the new markers for early diagnostics and/or prognosis of the course of cancer disease. No doubt, that some markers could be the promising targets for anti-cancer vaccination.

The Twinning project gives us an opportunity to widen the expertise of our group towards the field of the immunotherapy of cancer. In the result of the Twinning project the members of Ukrainian team will get the possibility to extent their research network, take part in the training (both in wet lab and during meetings), and exchange with their expertise during workshops based in Kyiv and other countries.