



Horizon Breakthrough Projects

Granted Projects- Seventh Call

Bacteria on Sex Hormones

Dr. R (Robert) van der Geize (m), 30-05-1970, University of Groningen - Department of Microbiology

Estrogens are highly bioactive steroid hormones mainly entering the environment via waste water treatment effluents, which is of major environmental concern. Estrogens have immune-modulating functions and have been proposed to play a role in resistance to bacterial infections. Transcriptome analysis will be performed to elucidate the enigmatic microbial estrogen catabolic pathway.

Druggable DUBs in trypanosomes

Dr. B. (Boris) Rodenko (m), 5-2-1975, Netherlands Cancer Institute - Division of Cell Biology

Sleeping sickness threatens millions of people in Africa and causes about 70,000 deaths each year. Also livestock suffers from this disease, which frustrates local economy. Current drugs are difficult to administer, have severe side effects and drug resistance is emerging rapidly. Clearly, there is an urgent need for new and safe medication. Sleeping sickness is caused by the parasite *Trypanosoma brucei* and in this project we will explore a class of proteins, so called deubiquitinating enzymes, as new targets for therapeutic intervention.

Metabolite imaging using FRET-based sensors

Dr. S.F.J. (Stan) van de Graaf (m), 18-08-1977, University Medical Centre Utrecht - Metabolic and Endocrine diseases

Better insight into metabolite profiles of tissue, body fluids and cells is essential for our understanding of human (patho)physiology. Nature has devised proteins that can sense metabolites in a sensitive and specific manner. In this project researchers utilize these proteins to create sensors that enable sensitive, dynamic measurement of specific metabolites at single cell, or even subcellular resolution.

Targeted, quantitative, multiplex imaging mass spectrometry

Dr. L.A. (Liam) McDonnell (m), 4-6-1975, Leiden University Medical Centre - Department of Parasitology, Biomolecular Mass Spectrometry Unit

Modern biomolecular analytical techniques have identified a large number of proteins that are associated with specific diseases, so called biomarkers. Conservative estimates for the three most common cancers in the Netherlands are breast cancer (37), colorectal cancer (65), and prostate cancer (36).

Simultaneous analysis of just 4 breast cancer biomarkers has demonstrated improved diagnostic capabilities, so developing tests incorporating many biomarkers could lead to improved patient diagnosis for a variety of diseases. Simultaneous (multiplex) imaging of multiples biomarker could also help illuminate the roles of the different cell types often found in a tumour. Here we will establish the capabilities of a new method, based on mass spectrometry, for quantitative multiplex imaging of protein biomarkers, which has the potential to allow multiplex analysis of >30 biomarker proteins.



Healthy brains as treasure trove of ADHD genes

Dr. A. (Alejandro) Arias-Vasquez (m), 22-6-1975, Radboud University Nijmegen Medical Centre - Departments of Psychiatry & Human Genetics

Abnormalities of the volume of brain structures have been documented in many psychiatric disorders and genetic factors explain a considerable part of the variability of these structures. In this project we want to test the hypothesis that the identification of common genetic variants (single nucleotide polymorphisms [SNPs] and copy number variants [CNVs]) related to the change in the volume of brain structures in healthy individuals can serve as a powerful tool to identify risk factors for psychiatric disorders, in this case Attention Deficit/Hyperactivity Disorder (ADHD). In order to accomplish this aim, we will first assess the association between SNPs/CNVs and the volume of brain structures as estimated by Magnetic Resonance Imaging (MRI) in a population of 1000 healthy participants of the Brain Imaging Genetics (BIG) study. Second, we will test if the SNPs/CNVs associated with brain volumes (found in step 1) are associated with the risk for ADHD using the information provided by ADHD studies performed in children and adults and, third, we will evaluate if the variants associated with brain volumes and ADHD risk have an effect on brain function.

Massive parallel sequencing for extreme genomes

Dr. R. (Richárd) Bartfai (m), 23-5-1975 Radboud University Nijmegen

Deciphering genomes has been a major challenge to biologist for decades. The current development in sequencing technologies revolutionized genome research, but has its limitations especially if the sequence composition is unusual. The genome of the human malaria parasite provides one such example of an extreme genome that severely hinders its exploration and exploitation. This project aims at the adaptation of the deep sequencing technology to extreme genomes that will enable the investigation of regulatory mechanism that govern parasite growth and pathogenicity. Knowledge and technological advances gained during the project could ultimately help us to identify new drug candidates and combat this and possible other devastating diseases.

A promoter resource to study the effect of genome duplication on regulatory sequences

Dr. U.G. (Ulrike) Jacobi (f), 9-3-1979, Radboud University Nijmegen, Nijmegen Centre for Molecular Life Sciences

The clawed frog *Xenopus* is an animal model that enables researchers to study diseases and complex processes in whole organisms and can be used to mimic the situation in humans. Strikingly, one member of the *Xenopus* family, *Xenopus laevis* has doubled its genome during evolution which makes it also an interesting model for evolutionary processes. This research project aims to identify DNA sequences that play an important role in switching genes on and off. The obtained regulatory sequences enable researchers to apply genomic techniques and will be analyzed to reveal new insight into the effect of genome duplication. Additionally, the identified regulatory sequences can be used by all researchers working with *Xenopus laevis*.



Using zebrafish to explore miRNAs as drug targets for bone related diseases.

Dr. R.F. (René) Ketting (m), 19-05-1971, Hubrecht Institute

In our aging society, bone-related diseases represent an ever-increasing medical problem, for which few effective treatments are available. We will explore to what extent small RNA molecules, also named microRNAs, are effective targets for the development of new drugs that can be used to treat bone related diseases, as microRNAs have been shown to be relatively easy and effective drug targets. We will identify the microRNAs that are present in the cells that make bone, and what their effects are on the functions of these cells. Based on these results we will judge which ones might be useful as novel drug targets. To achieve this, we will use zebrafish embryos as a model, because gene function, including microRNA function, can be easily manipulated and bone development can be easily followed in living embryos.

A chemical emergency switch for plants

Dr. C.S. (Christa) Testerink (f), 20-10-1973, UvA University of Amsterdam, Swammerdam Institute for Life Sciences (SILS), Mass spectrometry of Macromolecules

Phosphatidic acid (PA) is an important signaling lipid. In plants, it is essential for survival under adverse conditions. In this breakthrough project, we will engineer a chemical switch to make PA at will in plant cells. We will then turn on the switch and investigate the proteome-wide consequences. The ultimate goal is to find protein targets that can be exploited in plant breeding to enhance stress tolerance.

An inflammasome genome screen to detect novel disease genes in hereditary autoinflammatory disorders

Dr. M.E. (Marielle) Van Gijn (f), 21-2-1970, University Medical Centre Utrecht - Division of Biomedical Genetics

For a large percentage of the patients with hereditary autoinflammatory disorders, such as Familial Mediterranean Fever and Muckle-Wells syndrome, the underlying cause of the disorder remains unexplained. This raises the question which gene(s) are responsible for these disorders. This project will screen 120 potential disease related genes in these patients for disease associated mutations using state of the art techniques. The identification of genes, which are causing the above mentioned diseases will not only help diagnostics and the development of future therapies but has also implications for other multifactorial autoinflammatory disorders.

Bacterial virulence gene discovery using phage display technology

Dr. P.J.A. (Pieter-Jan) Haas (m), 20-8-1974, University Medical Center Utrecht - Department of Medical Microbiology

Pathogenic bacteria use different ways to evade the host immune defenses through the production of immune evasion molecules in order to cause colonization and infection. Identifying these immune evasion molecules is a time consuming and inefficient process. In this project we functionally select secreted bacterial proteins using the power of phage display technology. This novel approach greatly enhances the identification of these immune evasion molecules. Understanding bacterial immune evasion will lead to better understanding of infection and inflammation and novel strategies in the treatment of infectious and inflammatory diseases.



The tomato RNA degradome in fruit development and domestication.

Dr. R.B. (Rumyana) Karlova (f), 13-4-1978, Wageningen University and Research Centre - Department of Molecular Biology

Tomato is an important crop as well as a model system for studying fleshy fruits in plants. During the domestication process beneficial alleles underlying yield and quality of the cultivated plant compared to its wild relatives were selected. Through domestication, research and breeding activities that were implemented by scientist and breeders worldwide, modern tomato varieties have been developed in a variety of shapes, colors and sizes. In this project we would like to study the role of small regulatory RNAs and their conservation during the domestication process by comparing different wild species and natural mutants with a focus on fruit ripening

A novel screening method to identify human adipokine-receptor interactions

Dr. J.W. (Johan) Renes (m), 25-11-1971, Maastricht University, Faculty of Health, Medicine and Life Sciences - Human Biology

Aim of this project is the establishment of a novel method to detect interactions between secreted cellular proteins from one cell and receptor proteins on other cells. Fat cell secreted proteins (adipokines) are chosen as a model since they play a major role in the development of obesity-related disorders by targeting other non-fat tissues like liver and muscle. Here, liver cells are chosen as target cells. Since this novel method is not restricted to adipokines and liver cells, but applicable to any secreted protein and target cell, it will open a new area in explorative research with respect to inter-cellular communication.

Dissecting the fruit formation transcriptional regulatory network

Dr. ir. R.G.H. (Richard) Immink (m), 13-3-1973, Wageningen University and Research Centre - Plant Sciences Group

Fruits are one of the major sources of our daily food. Understanding how genes orchestrate fruit formation is essential for optimizing fruit production. In this research novel genomic tools will be developed to decipher the function of individual genes at different stages of fruit development.

BAC TransgeneOmics-based Systems Microscopy for Predictive Toxicology

Dr. Ir. B.H.A. (Bram) Herpers (m), 04-04-1979, Leiden University, LACDR - Division of Toxicology

Safety assessment of new drugs relies on end-point measurements by tradition. Toxicity is a time-dependent multi-step process in which proteins react by changing their intracellular location. By tagging these responsive proteins with fluorescent tags in their natural environment, the researcher aims to develop microscopy tools that can predict drug safety *in vitro*.

miRNA expression as a new tool for sepsis diagnosis in Intensive Care

Dr. C.W. (Catharina) Wieland (f), 7-3-1978, Academic Medical Centre Amsterdam (AMC)

The reaction of the body to infection (sepsis) is still a prominent cause of morbidity and mortality in the intensive care unit. New tools that can distinguish between critically ill patients and patients with sepsis are necessary to avoid inadequate treatment. Within this project, we will search for specific miRNAs in whole blood that discriminate between critically ill patients and sepsis patients. Whole blood is easy to obtain and no further time consuming purifications are necessary. This approach could provide a first step to a fast and easy miRNA based diagnostic tool for sepsis.



Analyses of the role of small virus-derived RNAs in human antiviral immune responses

Dr. P.C.J. (Joost) Haasnoot (m), 20-10-1971, Academic Medical Centre Amsterdam (AMC), Centre for Infection and Immunity Amsterdam (CINIMA), Laboratory of Experimental Virology, Department of Medical Microbiology

All organisms have specific mechanisms to protect themselves against invading viruses. In plants, insects and nematodes a special mechanism called RNA interference (RNAi) plays an important role in antiviral defenses. Although RNAi also exists in mammals, it is unclear whether it has an antiviral function. In this project we will study the role of RNAi in controlling HIV-1 replication in human cells. For this we will use novel highly sensitive sequencing technology.

Discovery of stem cell markers in the regenerating flatworm *Macrostomum lignano*

Dr. E. (Eugene) Berezikov (m), 7-7-1975, Hubrecht Institute - Generegulation

Stem cells hold great promise for regenerative medicine and various disease therapies, and have attracted a lot of research interest in recent years. Due to technical reasons some fundamental questions concerning stem cell biology can be best addressed in invertebrate experimental model organisms like flatworms, which have an astonishing regeneration capacity. Regeneration in flatworms is facilitated by a population of stem cells called neoblasts, which are the only proliferating cells within the organism and perform a crucial role during development, regeneration and tissue homeostasis. In the proposed project I aim to use next-generation sequencing technologies to identify genes that are specifically expressed in the neoblasts of the free-living flatworm *Macrostomum lignano*, and thus could have relevant roles in regulation of neoblast dynamics. Identification and verification of these stem cell-regulating genes should form a fundamental toolbox for further research on how stem cells are maintained in an undifferentiated state or induced to go into differentiation using *M. lignano* as a model organism.

Conditional and rapid inactivation of nuclear factor functions by 3A technology (Advanced-Anchor-Away)

Dr. E. (Eric) Soler (m), 14-11-1976, Erasmus MC - Department of Cell biology

Transcription Factors (TFs) are nuclear proteins controlling gene regulatory networks, governing cellular identity, proliferation and differentiation. We propose to analyze the roles specific TF play on gene expression by developing a new technology allowing very fast and inducible TF inactivation (within minutes) through their sequestration in the cytoplasm ("spatial knock-out"). Due to its speed, this system (called 3A) will allow for the first time to dissect the very early and specific effects TF play on gene expression.

Ultra-high throughput analysis of insertional mutations to study collaborating cancer genes and genetic networks in mouse tumors

Dr. J.M.M. (Jos) Jonkers (m), 16-5-1965, Netherlands Cancer Institute - Molecular Biology

Cancer is a genetic disease caused by accumulation of mutations in oncogenes and tumor suppressor genes. Identification of these cancer-related mutations may yield novel targets for anti-cancer therapeutics. Retroviral or transposon-based insertional mutagenesis screens in mice are an effective way to identify large numbers of cancer-related mutations. We will use massively parallel sequencing methods for ultrahigh-throughput analysis of insertional mutations in mouse models of breast cancer. Our method enables unbiased and quantitative analysis of clonal and subclonal mutations in genetically heterogeneous tumors and facilitates identification of co-occurring mutations.



Functional genomics of antiviral defense in insects

Dr. ir. R.P. (Ronald) van Rij (m), 17-09-1972, Radboud University Nijmegen Medical Centre - Medical Microbiology

Humans and other vertebrate animals have a sophisticated and complex immune system for the defense against pathogens, such as viruses. Invertebrate animals are also infected by viruses, yet, little is known about the invertebrate immune system. Using the fruit fly, *Drosophila melanogaster*, as a model organism, the researchers will identify novel genes for the defense against viruses in insects.

Autoimmune disorders looking: for common grounds using uncommon methods.

Dr. M.J.H. (Marieke) Coenen (f), 9-10-1975, Radboud University Nijmegen Medical Centre - Department of Human Genetics

Autoimmune disorders are caused by the dysregulation of the immune system resulting in destruction of normal tissue. This common mechanism suggests the existence of shared risk factors for different autoimmune disorders. Using a novel method (Bayesian Variable Selection Method) we will identify shared genes and pathways underlying four autoimmune diseases: rheumatoid arthritis, Crohn's disease, ulcerative colitis and psoriasis.

State-of-the art sequencing technology to identify genes for hearing loss in the Dutch population

Dr. ing. M. (Margit) Schraders (f), 9-12-1978, Radboud University Nijmegen Medical Centre - Department of Human Genetics

Hearing loss is the most common sensory disorder and has a tremendous negative impact on the quality of life in our complex society which relies on rapid communication. Defects in more than 100 different genes can cause early onset hearing loss, however, less than one third of the causative genes have been identified. This project aims at the identification of the genes that are involved in early onset hereditary hearing loss in the Dutch population with a novel technology for DNA sequencing. The results will be translated into patient care and for many patients and families the question on the cause of the hearing loss can be answered as a result of this study and follow-up studies.

Identifying biomarkers for immune-related diseases using genome-wide ribosomal-associated RNA expression profiles

Dr. C.C. (Cleo) van Diemen (m), 13-11-1979, University Medical Centre Groningen - Genetics

The diagnosis of diseases can be difficult because symptoms may be non-specific and because many environmental and genetic factors can influence the disease. It would be useful to have an easily assessable marker, such as a protein in blood, for each disease (so-called biomarkers) to diagnose and monitor patients. Every protein is generated through the process of translation of an mRNA molecule by ribosomes, with the number of mRNA molecules and how much mRNA is translated into protein being tightly regulated. We think that differences in the number of mRNA molecules bound to ribosomes may well reflect the amount of protein produced and thus may reflect the disease status of a patient. In this project we aim to find new biomarkers for patients with two types of inflammatory bowel disease (Crohn's disease and ulcerative colitis) as a proof-of-principle by assessing the levels of ribosome-associated mRNA.



SQIL, a new method to measure the impact of gene acquisition on bacterial evolution

Dr. M. (Marian) Llamas Lorente (f), 13-11-1973, VU Medical Centre - Department of Medical Microbiology

Bacteria multiply asexually by binary fission, which implicates that bacteria are in fact clonal. However, bacteria also show horizontal gene transfer, a process by which genes from another strain or another species are acquired. This process plays an important role in the evolution of new bacterial species, including new bacterial pathogens. In this project we will develop a new tool which will allow to measure exactly the effect of horizontal gene transfer on a genome-wide scale. This tool will be used to study the evolution of pathogenic bacteria and to identify new targets for antibiotics.

High-throughput miRNA-mRNA target identification

Dr. P.A.C. (Peter-Bram) 't Hoen (m), 17-1-1975, Leiden University Medical Centre, Centre for Human and Clinical Genetics

MicroRNAs (miRNA) are important regulators of gene expression in biological systems by either inducing degradation of their target RNAs or repressing the production of their targets into protein. To fully understand the roles miRNAs have on cellular processes, their target transcripts need to be identified. In current protocols the one-to-one relation of the miRNA and the target RNA that exists in the regulatory complex is lost, which impairs target identification. We intend to develop a new method in which the miRNA and its target identity are maintained in a one-to-one ratio and subsequently measure these interactions by using next generation sequencing techniques.

Signaling pathways in tuberculosis: elucidating mechanisms of macrophage recruitment to granulomas

Dr. A.M. (Anna) Zakrzewska (f), 28-6-1975, Institute Biology Leiden, Molecular Cell biology

One third of the human population is infected with latent ("sleeping") tuberculosis caused by mycobacteria. Granuloma, a structure comprising infected and uninfected host immune cells, is the main characteristic of this disease. Mycobacteria can survive within the granulomas for many years. This project will investigate communication between immune cells within a single granuloma to expose the mechanisms that allow for survival of mycobacteria in the host.

The role of retinoic acid in regulation of gene expression during lymph node formation.

Dr. S.A. (Serge) van de Pavert (m), 19-9-1971, VU Medical Centre - Molecular Cell biology and Immunology

Autoimmune diseases are often associated with chronic inflammation and formation of lymphoid structures. Retinoic acid plays an important role in lymph node development by altering the gene expression profile of cells involved. I will explore how retinoic acid affects the gene expression profiles of these cells, which could help to find drugs that efficiently treat chronic (auto-)inflammatory diseases.

Small circulating RNAs as predictors for bone loss

Dr. ing. B.C.J. (Bram) van der Eerden (m), 1-11-1970, Erasmus MC - Department of Internal medicine

Osteoporosis is characterized by bone loss and elevated risk for fracture and its incidence is rising. It has a strong impact on the health care budget and personal life due to pain and disability. Therefore, early, easy detectable markers for bone loss are needed to be able to prevent damage later on. A novel exciting group of molecules in the circulation that may serve as a risk indicator are small RNA molecules (miRNAs). In this project, profiles of blood-based small RNAs from osteoporotic patients and healthy controls will be compared, which may lead to the identification of novel biomarkers for the diagnosis of osteoporosis.



Stromal transcriptomes from development to disease

Dr. T. (Tom) Cupedo (m), 4-5-1976, Erasmus MC - Department of Hematology

Our immune system battles infections and cancer from lymphoid organs called lymph nodes. These lymph nodes are packed with immune cells that continuously interact with supportive stromal cells. The researchers will define the transcriptomes of the specialized stromal cells in human lymph nodes in order to understand how these cells coordinate both the development of the node and the fight against infections.

Stochastic gene expression in the human pathogen *Streptococcus pneumoniae*:

Regulation of translational noise

Dr. J. (Jan-Willem) Veening (m), 26-12-1978, University of Groningen - Department of Molecular Genetics

The human pathogen *Streptococcus pneumoniae* is a leading cause of bacterial pneumoniae and causes millions of deaths in young children each year. Interestingly, many people carry this bacterium without getting ill. In this project we will investigate the role of so-called biochemical 'noise' as a potential source that causes this bacterium to switch from its harmless mode to its pathogenic mode.