The Institute of Clinical Medicine is the largest department of the Faculty of Medicine at the University of Helsinki. There are 130 staff members on the payroll budget — 100 in research and education, with about 30 in support services. In addition, there are 70 to 100 staff members who work in research supported by external funding. The institute comprises ten departments that cover all areas of clinical medicine.

The Institute of Clinical Medicine educates future physicians from the third year of studies until their graduation. There are 560 students annually. With its 43 training programmes in various medical specialities, the institute provides specialist training to meet the needs of the whole country. In addition, further education is provided on an as-needs basis. Institute professors and docents are in charge of the training.

The Institute of Clinical Medicine also provides postgraduate education leading to a doctoral degree, of which 80 are completed annually. High-quality clinical and translational research is conducted in the clinics and laboratories in the Biomedicum building at the Meilahti campus in Helsinki.

The various departments of the Institute of Clinical Medicine conduct high calibre research under the leadership of professors, clinical instructors and docents. Research is an essential component of doctoral education. The institute also hosts a series of doctoral training programmes. Furthermore, several large research groups funded by the Academy of Finland, the Finnish Funding Agency for Technology and Innovation (TEKES), the European Union, NIH or other external sources operate under the auspices of the institute.

Research is conducted in the clinics and the Biomedicum Centre, which accommodates the clinical research laboratories. The institute engages in active co-operation with the other institutes and departments of the Faculty of Medicine as well as with the other faculties of the University of Helsinki. Smooth co-operation with the Hospital District of Helsinki and Uusimaa (Helsinki University Central Hospital) is a prerequisite for clinical research.

The institute’s research has been evaluated by external panels comprising foreign experts appointed by the university. The institute’s research has been rated to be of a high international standard. In fact, within Finnish science, clinical research is among the most productive and successful fields internationally.

The institute’s research focuses on mechanisms mediating cardiovascular diseases, neurological diseases, biomarkers of cancer, metabolic abnormalities and connective tissue disorders. The Faculty of Medicine has five specific research programmes. The recently established Diabetes and Obesity Research Programme is the most clinical programme, and it is expected to generate novel insights into the development of these common diseases.
The Diabetes and Obesity Research Programme started its activities at the beginning of 2013 after a competitive election process.

To date, approximately 300 million people in the world have diabetes. In addition, 540 million adults are obese and 1.6 billion overweight. Over 90% of diabetic patients have Type 2 diabetes (T2D) but the incidence of Type 1 diabetes (T1D) has also increased manifold in most countries since World War II. An alarming concern is the growing presence of obesity and the metabolic syndrome in subjects with T1D and its impact on future cardiovascular risk. Diabetic complications, such as cardiovascular disease outcomes, diabetic neuropathy, amputations, renal failure and blindness result in increasing disability, reduced life expectancy and enormous health costs worldwide.

The mission of this research programme is to elucidate the molecular mechanisms underlying the various forms of diabetes and its complications, the metabolic syndrome and obesity and to translate this knowledge into novel treatment and prevention strategies of these conditions. The overall aim is to assess the role of genetic, environmental and life style factors and their interactions in disease development and outcome in different types of diabetes, metabolic syndrome, and obesity in the context of cardiovascular disease risk and microvascular complications. We aim to design biomarker panels based on specific phenotypes together with genetic and environmental risk factors to predict the development of diabetes/obesity, treatment success and disease complications. We will utilise cross-sectional, prospective and longitudinal epidemiological study cohorts with extensive data on environmental and life style factors and studies based on families with comprehensive information on phenotypes.
Based on our earlier observations among Finnish and Russian Karelian schoolchildren, we embarked in 2008 on the prospective EC-sponsored DIABIMMUNE study recruiting newborn infants and young children in Finland, Estonia, and Russian Karelia. These three countries represent a living laboratory, since they are characterised by conspicuous differences in standard of living and hygiene, i.e. Russian Karelia has a relatively poor standard, Estonia is a country in rapid transition, and Finland has a high standard of living and hygiene. We have screened in each country about 3,000 newborn infants for genetic susceptibility to autoimmunity and recruited three national cohorts comprising each about 330 newborn infants carrying increased predisposition to autoimmune diseases. We are monitoring these children up to the age of three years with sequential study centre visits at the age of three, six, 12, 18, 24, and 36 months. Biological samples including serum, RNA, peripheral blood, nasal swabs, skin swabs and rectal swabs are obtained at each visit. In addition the parents are asked to collect their child’s stool sample once a month up to the age of three years. We have also recruited a cohort comprising about 1,500 three-year-old children in each participating country. These children are also analysed for genetic susceptibility to autoimmunity but all children with parental consent are eligible for participation in the study irrespective of their genotype. These children are re-examined at the age of five years. Based on the three-year results we identify a group of cases characterised by positivity for diabetes-predictive autoantibodies, coeliac disease-associated autoantibodies or at least two allergen-specific IgEs out of eight analysed and a group of control children with no signs of autoimmunity or atopic sensitisation. These cases and controls have an additional study centre visit at the age of four years with a more extensive sampling of biological samples. The expanded sampling procedure is repeated in the case and control children at the five-year visit.

What can we then expect to learn from the DIABIMMUNE study? One essential question which we wish to answer is whether there are specific microbes protecting Russian Karelian children from allergy and autoimmunity or whether the total microbial load in early life is the critical factor. Therefore we are comparing the frequency of various viral and bacterial infections based on objective measurements from the biological samples collected. One possible explanation to the lower frequency of immune-mediated diseases in Russian Karelia is that the Finnish children have an impaired immune regulation as a consequence of their reduced microbial exposure. Circulating regulatory cells appear to play a crucial role in suppressing allergic and autoimmune reactions. Our preliminary data from the DIABIMMUNE study indicate that six-month-old Estonian infants have more active regulatory cells than their Finnish peers. A similar phenomenon was observed when comparing three-year-old Finnish and Estonian children.
The DIPP study was launched in 1994 in Finland. It is based on genetic screening of risk alleles for Type 1 diabetes in newborn infants recruited from the general population in combination with intensive follow-up of those carrying increased susceptibility to Type 1 diabetes.

In the study, newborn infants are screened for increased genetic risk for Type 1 diabetes in three university hospitals. The recruitment is still going on and the risk individuals will be observed up to 15 years of age or to the presentation of clinical diabetes.

The follow-up programme is based on regular study centre visits with an interval of 3-12 months. At every follow-up visit, blood samples are collected for the analysis of the appearance of diabetes-associated autoantibodies. In addition, clinical and physiological data, as well as diverse environmental factors such as infections, diet, allergies, domicile, living habits, and vaccinations are collected. A glucose tolerance test is performed in children who have developed autoantibodies.

To date, more than 160,000 children have been screened for HLA risk alleles. Of those, over 11,500 children carrying increased genetic risk for Type 1 diabetes have joined the follow-up study. More than 300 of them have progressed to clinical diabetes.

The DIPP project aims at clarifying the pathomechanisms in the development of Type 1 diabetes, and there are a series of ancillary studies analysing several potentially important factors contributing to the appearance of beta-cell autoimmunity and overt diabetes. Recently the potential role of vitamin D deficiency and the intestinal microbiota has been explored. Vitamin D deficiency has been implicated as a risk factor for Type 1 diabetes. The data available is, however, contradictory. In the DIPP study we have been unable to observe any association between the development of diabetes-predictive autoantibodies in the offspring and the intake of vitamin D by the pregnant women or by the offspring. In a preliminary study based on four-year-old DIABIMMUNE participants in Finland and Estonia, we noticed that the Estonian children had clearly lower circulating concentrations of vitamin D than the Finnish children. More than half of the Estonian children had insufficient vitamin D concentrations, whereas only one out of 43 Finnish children was in the same situation. This observation does not support a critical role of vitamin D in the development of Type 1 diabetes, since the disease incidence is about three times lower in Estonia than in Finland.

Intestinal microbiota appears to be involved in the pathogenesis of Type 1 diabetes and other immune-mediated diseases. The disease incidence in NOD mice, an experimental model of autoimmune diabetes, does seem to depend on the environment, and there is data indicating that the rate is highest in relatively germ-free environment, and that the intestinal microflora may affect its incidence via modulation of the host innate immune system. Preliminary findings from the DIPP study imply that the diversity of gut microbial composition is indeed diminished in children who later progress to Type 1 diabetes. Sensitive readout of gut microbial variation along with other genetic and environmental factors may also help explain how the gut microbial composition affects host physiology. A recent metagenomics analysis of stool samples from DIPP children, who developed diabetes-predictive autoantibodies and progressed to clinical Type 1 diabetes during prospective observation, and from matched non-diabetic control children showed that genes involved in carbohydrate metabolism, adhesion, motility, phages, prophages, sulphur metabolism, and stress responses were more prevalent in cases whereas genes with roles in DNA and protein metabolism, aerobic respiration, and amino acid synthesis were more common in controls. Mining 16S rRNA data from these datasets showed a higher proportion of butyrate-producing and mucin-degrading bacteria in controls compared to cases, while those bacteria that produce short chain fatty acids other than butyrate were more common in cases. These data suggest that a consortium of lactate and butyrate-producing bacteria in a healthy gut induce a sufficient amount of mucin synthesis to maintain gut integrity. In contrast, non-butyrate-producing lactate-utilising bacteria prevent optimal mucin synthesis, as seen in autoimmune subjects.
The TRIGR study has been designed to provide an answer to the question whether weaning to a highly hydrolysed formula in infancy decreases the risk of future Type 1 diabetes in children with increased genetic risk for Type 1 diabetes. The participants have at least one biological family member (mother, father and/or sibling) affected by Type 1 diabetes and carry in addition HLA-conferred susceptibility to Type 1 diabetes. The participants were given the study formula during their first 6-8 months of life, whenever breast milk was not available. About half of the children received an extensively hydrolysed formula in which the milk proteins had been broken down into smaller peptides, and the other half, the control group, received formula based on untreated cow’s milk.

The recommendation was that the participating infants should be given the study formula for at least two months before the age of eight months. The trial is an international, randomised and double-blinded intervention study. The participants will be observed until the youngest child reaches the age of ten years. The TRIGR study started in 2002, and the recruitment was completed in early 2007. The intervention phase came to an end in August 2007. More than 2,000 children in 12 European countries, USA, Canada and Australia are taking part in the study. Altogether there are 77 local study centres involved. About 20% of the participating children come from Finland being followed in 16 hospitals. The trial has two endpoints. The first is positivity for at least two diabetes-associated autoantibodies out of four analysed and/or clinical diabetes by the age of six years. This endpoint will be reached in 2013. The final endpoint is overt Type 1 diabetes by the age of ten years. This data will be available in 2017. After the child turns two years of age, the participating families visit the study centre once a year for clinical examination of the child and blood sampling. An oral glucose tolerance test is performed at the age of six and ten years to exclude asymptomatic diabetes. All autoantibody analyses are performed in the TRIGR antibody laboratory in Helsinki. Currently, the youngest TRIGR participant is 6 years-old, and the oldest will turn 11 in May 2013. The drop-out rate has remained at a low level being clearly lower than the expected one (20% by the age of ten years). The TRIGR study is the first international large scale intervention study aimed at primary prevention of Type 1 diabetes. The TRIGR study is mainly funded by NICHD and NIDDK.

In the TRIGR pilot study completed in Finland a few years ago we observed that weaning to an extensively hydrolysed casein formula reduced the cumulative incidence of diabetes-predictive autoantibodies to about half by the age of ten years in children with genetic disease susceptibility.
Dutch studies have reported that weaning to a hydrolysed casein diet reduces autoimmune diabetes by 50% in diabetes-prone BB rats. That protective effect was associated with restoration of the impaired intestinal barrier function and a gut microflora characterised by stable *Lactobacilli* levels. We have recently embarked on a study assessing possible mechanisms mediating the protective affect against the appearance of diabetes-predictive autoantibodies conferred by a highly hydrolysed casein formula. In that study funded by NIDDK we randomise infants with increased genetic susceptibility to Type 1 diabetes to be weaned to an extensively hydrolysed casein formula or a regular cow’s milk based formula. The mothers are encouraged to breastfeed as long as possible. The intention is that the participating infants should be exposed to the study formula for at least 90 days before the age of nine months, allowing compliance with the current recommendation of exclusive breast-feeding up to the age of six months. The participating families will have study centre visits when their baby is three, six, nine and 12 months old. Intestinal permeability will be assessed at each visit with the lactulose/mannitol test and we will monitor the number and function of regulatory T-cells in the peripheral circulation. In addition the parents will collect stool samples from their infant once a month starting from the age of two weeks up to the age of 12 months for analyses of the intestinal microbiome.

**Future Prospects**

The disease process leading to Type 1 diabetes starts months and years before any symptoms appear. Deeper insights are needed into the process resulting in clinical disease to be able to develop effective preventive measures. The application of new technologies, including various –omics, provide promising prospects for generating novel knowledge that can be translated into successful prevention and treatment.

The identification of exogenous factors triggering and driving beta-cell destruction potentially offers also means for intervention aimed at the prevention of Type 1 diabetes. Therefore it is important to pursue studies on the role of environmental factors in the pathogenesis of this disease. Environmental modifications are likely to offer the most powerful strategy for effective prevention of Type 1 diabetes.
Type 1 diabetes is the most common serious disease among children and adolescents in the European countries. Globally the incidence is highest in Northern Europe, but the incidence rate is continuously increasing all over our continent.

The number of new cases with Type 1 diabetes among European children younger than five years of age has been predicted to double between 2005 and 2020. The aetiology is largely unknown; no effective primary prevention is available and nobody has so far been cured.

In spite of a heavy treatment with multiple daily insulin injections, adapted to regular meals with suitable content and monitored by several daily blood glucose tests, it is so far in practice impossible to avoid both life-threatening acute complications with sudden unconsciousness, and late diabetes complications affecting kidney, eyes, nerves and heart and leading to disabilities and increased mortality.

The disease process starts months and years before any symptoms of diabetes appear. Deeper insights are needed into the process resulting in clinical disease to be able to develop effective preventive measures.

This must be a priority in diabetes research in the Horizon 2020 programme. New technologies, including various -omics, provide promising prospects for generating novel knowledge that can be translated into successful prevention and treatment.