Trial to Reduce IDDM in the Genetically at Risk

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TRIGR Family News

Editor's corner

Dear Study families,

Our Principal Investigator Mikael Knip clarifies the current status of the TRIGR Study. He conveys his whole-hearted gratitude to all participants and their families and points out the importance to remain in the study till the end.

Professor Suvi Virtanen presents the TRIGR Asthma and Allergy Ancillary Study that will be implemented through internet. You will soon receive an Invitation to that interesting and important study.

In Science Corner we have two interesting summaries. The first one is how an indoor dog may protect the child against type 1 diabetes and the other one is how to turn stem cells into insulin-producing beta cells.

In Kid's Corner Lorie-Anne from Canada encourages all TRIGR participants to be brave, Oscar from Spain tells about his trip to London and Matilda from Australia tells a story of the Kingdom of Peacocks'.

Matti Koski, Chief Editor

How far we are in the TRIGR Study?

Our TRIGR study has this year turned 12-year-old. If the study would be a human being we could expect to experience a pubertal turmoil at this age. However, as far as I can see the status of the TRIGR study is fortunately quite calm. We will walk together for an additional 2-2.5 years. At this point I wish to thank from the bottom of my heart all participating children and families. You have made a formidable contribution to the efforts aimed at prevention of type 1 diabetes. At the same time I also wish to thank the dedicated TRIGR staff in the 77 participating study centers, in the International Coordinating Center in Helsinki and in the TRIGR Data Management Unit in Tampa and in the TRIGR laboratories.

The final outcome in TRIGR is the proportion of participants who develop type 1 diabetes by the end of the study. After the last study center visit at the beginning of 2017 it will take a few months before all the information compiled during the trial has been checked and the final analyses can be done. In any case we will have the answer to the question whether weaning to a highly hydrolyzed formula is able to reduce the incidence of type 1 diabetes in at-risk children in 2017. The answer is important irrespective of whether it is a yes or a no. If the answer is positive we have together established the first effective modality for preventing type 1 diabetes, which would be a crucial milestone in the fight against this disease. If the answer is negative it tells the world that this kind of dietary intervention is unable to prevent type 1 diabetes, which also indirectly suggests that the age at introduction of cow's milk based formula does not affect the disease risk. Accordingly there would be no need to use special formulas in at-risk babies, when sufficient amounts of breast milk are not available.

As told earlier this year the outcome of the autoantibody analyses by the age of 6 years showed that there was no difference in the appearance of autoantibodies between those participants weaned to the highly hydrolyzed formula and those weaned to a regular cow's milk based formula. This was somewhat surprising, since the pilot study performed earlier in 230 Finnish children showed a reduction in the appearance of autoantibodies by the age of 10 years in the range of 40-60%. So far we have not been able to identify the reason(s) why the current results differ from the previous one. On the other hand we know from experimental studies that weaning to a highly hydrolyzed formula reduces substantially the development of autoimmune diabetes but does not prevent the preceding inflammation of the pancreatic islets (called insulitis), where the insulin-producing cells are located. This suggests that the dietary intervention does not affect the initial inflammation but prevents its progression to clinical disease. In parallel, the TRIGR intervention may prevent the progression from autoan-

tibody positivity to type 1 diabetes in the study participants.

I wish to emphasize that it is extremely important that the TRIGR children and families remain in the study till the end. The last study center visit will be in 2016 for most participants, but a few will have their last visit in 2017, depending on their date of birth. Why is it then essential that you stay in the study? To get an unbiased answer to the study question we need as much information as possible from each participant. Therefore the TRIGR staff is working hard to convince families who have dropped out from the trial to rejoin the study. We are happy to see that almost all families and participants so far invited to continue the follow-up until the youngest participant turns 10 are willing to do so. We count on you. Together we are strong, and we will definitely generate a reliable final answer to the study question.

Mikael Knip
Principal Investigator, TRIGR

TRIGR Asthma and Allergy Ancillary Study

The prevalence of asthma and other allergic diseases in children has been increasing during the last decades in high and middle income countries, although the increase may have leveled off in some. Asthma and other allergic diseases comprise the most prevalent chronic disease group in children and it would be important to find ways how to prevent these diseases.

Allergic diseases are caused by over-reactivity of the human immune system against foreign proteins leading to asthma, rhinitis, conjunctivitis, atopic eczema and food allergies. Parental heredity is a strong risk factor for the development of both asthma and atopic eczema: if one of the parents has an allergic disease the risk is increased at least 2-fold; if both the increase is 3- to 4-fold. However, the rapid increase in the occurrence of such disorders over time indicates that environmental factors are crucial in the development of these diseases. Nutritional factors identified in epidemiological studies as possibly affecting the development of allergic diseases and asthma include breastfeeding, age at introduction of new foods and diversity of complementary foods in infancy, dietary fatty acids and antioxidants, vitamin D, foods which affect gut microbiota, and obesity. In families with parental asthma or allergies, there is evidence that allergies could be decreased by giving hydrolyzed infant formula compared to normal formula. The evidence from children not selected for high risk of asthma and allergies is, however, lacking. The TRIGR study is particularly able to address the question whether extensively hydrolyzed infant formula during infancy would protect from asthma and allergies during childhood in an unselected group of children.

We do hope that all of you will participate in this study and help us to find out whether hydrolyzed infant formula prevents asthma and allergies!

Professor Suvi M. Virtanen, M.D., Ph.D

Science Corner

A dog at home may protect the child against diabetes

The potential health effects of various environmental factors, such as microbial exposures, intrigue researchers. Finnish researchers have now for the first time reported that indoor dog exposure in early infancy may protect the child from type 1 diabetes. The National Institute of Health and Welfare, together with some Finnish universities and university hospitals, carries out extensive research to investigate whether environmental factors, among other things, are associated with the development of type 1 diabetes. More than 3,000 children with genetic susceptibility to type 1 diabetes from the Finnish Type 1 Diabetes Prediction and Prevention (DIPP) study took part in the research. Expo-

sure to both pets, such as dogs and cats, and various farm animals in early infancy were studied. Among these factors, only indoor dog exposure during the first year of life was associated with a reduced risk of development of preclinical type 1 diabetes. Exposure to other animals studied or day care attendance during the first year of life was not associated with type 1 diabetes. While this finding is significant, it needs to be confirmed in further studies. Researchers are yet to discover why and how a dog may protect from type 1 diabetes.

Virtanen SM, et al. Microbial exposure in infancy and subsequent appearance of type 1 diabetes mellitus-associated autoantibodies: a cohort study. JAMA Pediatr. 2014;168:755-763.

Breakthrough in diabetes study

Scientists from Harvard University have figured out the complex series of steps needed to turn stem cells into beta cells. Beta cells are the sugar-sensing, insulin-secreting cells of the pancreas that are missing in patients with type 1 diabetes as a consequence of the body's immune attack on itself. Scientists succeeded in developing a procedure for making large quantities of insulin-producing cells from stem cells. In diabetic mice these cells cured diabetes in less than 10 days. According to Douglas Melton who is the leader of this study, this treatment could be tested in humans in the near future. A remaining problem is, however, how these transplanted cells can be protected from being attacked by the own immune system that has earlier destroyed the patient's beta cells.

http://harvardmagazine.com/print/46591
Cell 2014 Oct 9;159(2):428-39.

Kid's corner

Hello everyone,

My name is Lorie-Anne and I am now 9-year-old. I am part of the TRIGR research program since I was born. As you can see from my picture…

… I don't really like having blood tests but because my father has diabetes, I think that I should help research. This is why year after year, I face my fear and come to the Montreal Children's Hospital for my annual visit. To help me stop crying and to encourage me, my daddy says that I am **HIS NUMBER ONE SUPER HERO**, and he says that one day, because I am brave and with the courage from all the TRIGR children, we will find a cure for diabetes to help the people we love. I hope from the bottom of my heart that those few words of encouragement will help you overcome your fear and allow you to be the SUPER HERO of the people you love. Be brave!

Lorie-Anne, Montreal, Canada

Trip to London

My name is Oscar, I am 10-year-old, and I already was a part of the TRIGR Study even before I opened my eyes.

Last summer I visited London with my family and we had such a good time!

We really enjoyed riding London's typical red double-decker buses. In fact, we always tried to get on the upper floor, right at the front window to have the nicest views of the city and to feel like we were driving the bus! We were always disappointed when we had to get off the bus. It was quite an adventure! One could say that bus drivers were always in a hurry and could hardly wait until we got off the bus. We would have to run downstairs as if we were running a marathon! Once we almost left my father behind on the bus!

We liked the Natural History Museum the best. My youngest brother was allowed to borrow an explorer kit so we felt like real explorers during our visit, seeing the history of our planet, from its origin to present time. We saw so many things but we enjoyed the dinosauruses the most; they came in all shapes and sizes!

Another place that we visited was "Hamleys" on Regents Street. It was the largest toy store we had ever seen and we loved it!

Finally, we had fun dining at the Rainforest restaurant. There are life sized animal figures that move and look so real. We enjoyed a wonderful pizza with the animals moving and making noises around us making us feel like we were in the middle of the jungle!

We had such a great time that we want to go back to London as soon as we can!

Oscar, Bilbao, Spain

Matilda's story of the Kingdom of Peacocks'