

## The CoRD study – can cord blood prevent type 1 diabetes?

The CoRD study is an Australia-wide pilot trial which will investigate whether cord blood can be used to prevent or delay the development of type 1 diabetes. The study is being led by Associate Professor Maria Craig, a paediatric endocrinologist at the Children's Hospital at Westmead, in Sydney.

### Study rationale

To date, no intervention has successfully prevented type 1 diabetes, but there is increasing evidence that immune therapies, particularly those based on restoration of peripheral immune tolerance, may prevent autoimmune diseases such as type 1 diabetes.

Abnormalities of regulatory T cell (Treg) function and/or number have been identified in people with type 1 diabetes. Umbilical cord blood contains highly functional populations of Tregs and therefore may have a role in immunomodulation. In the non-obese diabetic (NOD) mouse model of type 1 diabetes, infusion of Tregs prevented the development of type 1 diabetes. However, no studies in humans have examined whether cord blood can prevent type 1 diabetes.

Thus, the **primary hypothesis** for the study is that infusion of autologous cord blood will restore immune tolerance in children with islet autoimmunity and delay or prevent the progression to type 1 diabetes.

### Study objectives

The primary aim is to assess the feasibility of reinfusion of autologous cord blood in children at high risk of T1D.

The secondary aims are to:

1. confirm the safety of reinfusion of autologous cord blood in this pre-diabetic population; and
2. establish and refine protocols for participant identification, recruitment, investigation and cord blood reinfusion, which will inform a definitive randomised controlled trial.

### Study Population

Children aged 1-12 years, at high risk of developing T1D, with available autologous cord blood (CB) banked, with Cell Care.

### Study design

There are two phases to the study:

1. Screening for high risk children, defined as those with antibodies to > 2 islet antigens

In the screening phase, we will invite approximately 600 children whose cord blood was collected at birth (and stored in a private cord blood bank), who have a first degree relative with type 1 diabetes, to participate in the study.

2. Treatment: infusion of autologous cord blood in high risk children and follow up

Those who are confirmed to have antibodies to  $\geq 2$  islet antigens will be invited to receive an infusion of their cord blood. We estimate approximately 20 children will receive the infusion. As this is a pilot trial,

there is no randomisation. All infusions will be performed at the Children's Hospital at Westmead. Participants will be followed for three years or until they develop diabetes. Follow-up will be 3 monthly visits for the first year and 6 monthly visits until the end of the study.

### **Study outcomes**

#### Primary:

1. Feasibility of recruitment and screening of children who have stored and have a first or second degree relative with T1D, or have previously been tested for islet antibodies.
2. Prevalence of islet autoimmunity in children with a first or second degree relative with T1D.

#### Secondary:

1. Safety (adverse event profile after reinfusion).
2. Development of dysglycaemia or diabetes as defined by the American Diabetes Association (ADA) criteria.
3. Changes in immunological markers including islet autoantibody titres, cytokine levels and regulatory T-cell (Treg) phenotype and function.
4. Differences in inflammatory markers, vitamin D and prevalence of viral infection in antibody positive versus negative children.

### **What will the study involve?**

The screening phase will involve testing for Insulin, GAD, IA2 and ZnT8 autoantibodies. We will also measure haemoglobin A1c and random glucose at screening.

If two or more antibodies to islet antigens are present, conferring a high risk of progression to type 1 diabetes, the child will be invited to participate in the treatment phase of the study. Participants will receive a single intravenous infusion of autologous cord blood containing  $>5 \times 10^6$  Total Nucleated Cells /kg recipient body weight. Cord blood will be reinfused over a period of 1 hour. All of the cord blood will be used.

Those with negative antibodies will be invited to return for repeat screening in 12 months.

### **Are there any risks?**

Many millions of cord blood samples have been collected and cryopreserved around the world in both public and private banks. In Australia, the collection, storage and release of umbilical cord blood is regulated by the Therapeutic Goods Administration (TGA). Over 10,000 cord blood transplants, and hundreds of thousands of other haematopoietic stem cell transplants, have been performed using frozen samples of cord blood; these products have a very good safety profile.

### **Other information**

The study sponsor is The Children's Hospital at Westmead. The study will be overseen by a steering committee which contains experts in diabetes, immunology and epidemiology. Study monitoring will be performed by the Diabetes Vaccine Development Centre (DVDC).

The study being funded by a grant from Australia's largest private cord blood bank, Cell Care Australia.

The study co-ordinator is Ms Phuong Phan, 02 9845 1233.

The chief investigator is Assoc Prof Maria Craig 02 9845 3907

**This project has been approved by The Sydney Children's Hospital Network Human Ethics Committee. If you have any concerns about the conduct of the study, please do not hesitate to contact the Secretary of the Ethics Committee (02 9845 1253) and quote approval number 11/SCHW/211.**