

## **Establishing an 'immuno-metre' to measure the strength of the immune system**

**Interview: Dr Gregor Bond explains how leading European researchers are exploring a novel way to individualize care for kidney transplant recipients.**

Dr Bond is an Associate Professor at the Medical University of Vienna's Department of Nephrology and Dialysis. He is also a consulting physician in nephrology and intensive care medicine at Vienna's University Hospital (Allgemeines Krankenhaus), one of Europe's largest medical centres.

Dr Bond is among the leading researchers from 13 academic hospitals in Austria, the Czech Republic, France, Germany, the Netherlands and Spain who are working to break new ground in care for kidney transplant recipients. With support from the EU's Horizon research and innovation programme, they are exploring using the Torque Teno virus (TTV) to monitor a kidney transplant recipient's immune system response, and thus tailor drug therapies to the individual to reduce the risk of infection, rejection and side-effects. The kidney is the most transplanted organ in the EU, with more than 15,000 grafts performed each year on average.

As Dr Bond explains, TTV is found in nearly all humans and research shows it is harmless. While current trials focus on kidney transplant recipients, being able to guide drug treatment on an individual basis could significantly improve patient care in other medical fields.

**Question: This clinical study began in August 2022. What has your research shown so far?**

**Dr Bond:** Let me start with the general clinical problem we would like to address. Not only in transplantation, but in medicine in general, we have no tool to measure the ability of the human immune system to control pathogens – the viruses, bacteria and other microorganisms that can cause diseases.

In certain clinical scenarios, we must suppress the immune system. In the case of kidney transplantation, the patient receives a kidney from a foreign donor that has a unique pattern on its surface, and the immune system recognizes it as foreign and attacks it. We have to prohibit that, and we do this by using immuno-suppressive drugs. There is a careful balancing act here. On the one hand, you want to suppress the immune system so the body accepts the new organ. But if the immune system is suppressed too much, it cannot do its intended work: it cannot fight pathogens, so you will have more infections; and it cannot fight cells in your own body that turn malignant, so you will be prone to malignant diseases.

In other words, we need an optimal immuno-suppressant that provides a balance – a 'golden middle'. Today, this is a clinical challenge. What we are trying to do in our EU-funded project is to establish an 'immuno-metre' to measure the strength of the immune system.

**The word 'virus' normally has a bad connotation – think about the coronavirus. Are suggesting that a virus, in this case TTV, can help you optimize drug therapies?**

**Dr Bond:** Exactly. This virus was first described about 20 years ago. It is interesting because it lives in almost every mammal species and every individual. We believe it is apathogenic, which means it doesn't cause any disease. It is somehow controlled by the immune system, but is never completely eradicated. Every part of our body is colonized by bacteria, and they are not always bad: some protect us from more harmful bacteria.

We believe there is a link between TTV and the strength of the immune system. If your immune system is very active, it can fight the virus and contain it. But if your immune system is weaker or suppressed by immuno-suppressants, such as those we use in solid organ transplantation, then your immune system is not prepared to fight this virus very well and the copy number of this virus rises. The copy number in your blood reflects how strong your immune system is. In other words, a low TT virus level means a stronger immune system, while a high concentration in the blood means a weaker immune system. Our EU project sets out to prove this concept – that if there is a low level of TT virus in the blood, the immune system is very active, and if the virus is high, the immune system is very suppressed.

### **If your theory is correct, how does this help kidney transplant recipients?**

**Dr Bond:** We want to prove that if we measure TTV to guide immuno-suppressive drugs, we can optimize the patient's outcomes – we can have a personalization of the immuno-suppression. We have very good immuno-suppressive drugs, and we know they work. But now it is time to personalize them, to help reduce the risk of infection and rejection in each transplant recipient.

### **How does this differ from current methods used to guide drug therapies?**

**Dr Bond:** Large clinical trials tell us that there is an average level you must target for kidney transplantation. But we don't know if these levels are right for every individual. Every patient is different.

Our research focuses on individualising the number of drugs given based on TTV levels. If the TTV in a single person is too high, or above the optimal range, their immune system may be over-suppressed. As I said a moment ago, this can lead to complications such as higher risks of infection. On the other hand, if the TTV level is below the optimal threshold, your immune system may be *too* strong, and you need more immuno-suppressive drugs to help the body accept the transplant.

We believe that by using TTV as a guide, we can create a full picture of the immune system to help determine if the patient needs more or fewer immuno-suppressant drugs. Our ultimate goal is to reduce infection, reduce the risk of tumours developing, and to reduce organ rejection.

### **Is detecting TTV a complicated clinical procedure?**

**Dr Bond:** We use a specially designed PCR test to measure TTV levels in the patient's blood. It is easy to perform and relatively cost-efficient. They are very similar to the PCR tests used

for coronavirus, except that nasal swabs were used to detect corona, while TTV is detected in the blood.

### **Thirteen leading hospitals in six EU countries are taking part in this study. How do these trials work?**

**Dr Bond:** We are using a randomized control trial, which is the gold standard for proving theories in the clinic. We have 260 kidney transplant recipients who have agreed to participate in the trials, divided into two groups of 130 each, all of whom receive immunosuppressive drugs. One group is being monitored through conventional clinical practice, the other, the experimental group, is monitored using TTV measuring.

We want to prove, first and foremost, that using TTV in clinical practice is safe, and then prove that the principal works. After this early phase, we may want to repeat this study on other continents and regions outside the European Union to ensure that all ethnic groups are included.

### **Can TTV guidance be used for all kidney transplant recipients?**

**Dr Bond:** So far, our results suggest that TTV can be used in at least 90 per cent of kidney transplant patients. But we are still in trials, and we should have better data later on.

### **Are there potential safety risks involved in using a virus as an 'immuno-metre'?**

**Dr Bond:** The study in general is very low risk. There are no new drugs involved and we are not using any additional interventions. Of course, there are possible risks in everything you test, and that is why we have an independent data and safety monitoring board, which meets regularly to look at the trial data to see if there are safety concerns. Additionally, in the experimental group, the one using TTV to measure immune levels, there are safety rules in place and investigators do not have to go above or below a certain agreed drug dose level.

### **You mentioned that TTV was first identified only about 20 years ago. Are other researchers looking into its potential for other types of organ transplants?**

**Dr Bond:** The link between TTV and organ rejection has been shown by other groups as well. In fact, there is a lung transplant group here at the Vienna University Hospital that is doing a similar study. However, our study goes further because our end point is to look at ways to use TTV as an immuno-metre to reduce the risk of rejection, infection and death.

### **Does your research have possible benefits beyond organ transplantation?**

**Dr Bond:** This is of potential interest in almost the whole medical field. Interest in TTV is starting to grow because the immune system influences so many areas. For example, we are beginning to see interesting data for oncological diseases. The old-school drugs are very toxic and more or less burn most rapidly dividing cells in the body, targeting the tumour but also a lot of the body's other cells. A new, more effective way is to activate your own immune system by using immune modulators, and these will become more and more important in the coming years. Here, TTV may come into play to measure the strength of the

patient's immune system and help determine whether he or she needs immune modulators to strengthen the immune system at an early stage to fight the tumour.

**What happens if your efforts to use the TT virus to help create more individualized therapies for kidney transplant recipients are not successful?**

**Dr Bond:** You always learn a lot from clinical trials even if they do not bring clear benefits, and these efforts may very well help other researchers. Even if the efficacy of the trial is negative, but the safety profile is OK, then we will still have a tool in the clinic to use as one piece of the puzzle. The work, the funding and the contributions of the trial participants aren't wasted, and maybe this project turns out to be the first domino.

**What made you think about this very promising research project in the first place?**

**Dr Bond:** It was like love at first sight! The head of our virology department here in Vienna, Dr Elisabeth Puchhammer-Stöckl, was one of the first interested in this topic and our lung transplant department was already looking at TTV. She proposed to analyse how this could be useful in kidney transplants, where we have higher numbers of patients. I said it sounds perfect and began working on the topic. From then on, I was hooked and am motivated by the idea of optimizing and working on something completely new. It is an honour to be working with some of the best kidney transplant experts and institutions in the EU, and to help advance Europe's lead in medical research and innovation.