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# SUMMIT & so forth

ADDRESSING THE URGENT NEED FOR NEW TREATMENTS TO TACKLE DIABETES COMPLICATIONS THAT CAUSE DAMAGE TO EYE, KIDNEY, AND BLOOD VESSELS

## Helping IMI2 achieve its goals for faster and better medicines

*Horizon 2020 is a European Union new financial programme for research and innovation. Running from 2014 to 2020 with a € 80 billion budget, it aims at supporting joint technology initiatives as well as creating new jobs and growth in Europe. The EU will contribute up to €1.725 billion from Horizon 2020 to the new Innovative Medicines Initiative 2 (IMI2).*

The new IMI2 is a Joint Technology Initiative expected to start in January 2014 and end in 2024. It will bring together public and private sectors in the sphere of research, technological development and innovation. Through these joint initiatives, IMI2 will strengthen the collaborations between pharmaceutical companies, universities, and innovative SMEs needed to tackle the growing health problems that affect all Europeans. In particular, IMI2 aims at delivering new and approved diagnostic markers for immunological, respiratory, neurological and neurodegenerative disease, increase the success rate of clinical

trials, and ultimately speed up the development of safer and more effective medicines and treatments for patients.

IMI2 budget estimated € 3.45 billion is based on nearly equal contributions from the new EU's Horizon 2020 programme and the European Federation of Pharmaceutical Industries and Associations (EFPIA). An additional input is also expected from life science industries, non-EFPIA organizations, and SMEs.

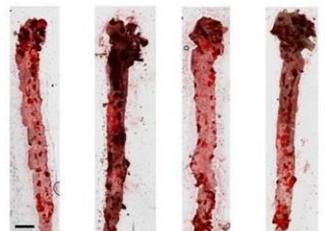
The former IMI initiative established in 2007 and financed under EU FP7 programme is an example of success.



IMI has offered exciting opportunities to the diabetes community by creating a Diabetes Platform consisting of three consortia: SUMMIT, IMIDIA, and DIRECT, with the aim of improving diabetes care and management. The generation of the first ever human pancreatic beta cells that can survive in test tubes exemplifies a valuable tool for developing new therapies.

Learning from and drawn on the successes and experiences of the current IMI, the successor IMI2 partnership is expected to lead the way in finding innovative solutions for patients, biomedical research and development.

[www.imi.europa.eu](http://www.imi.europa.eu)

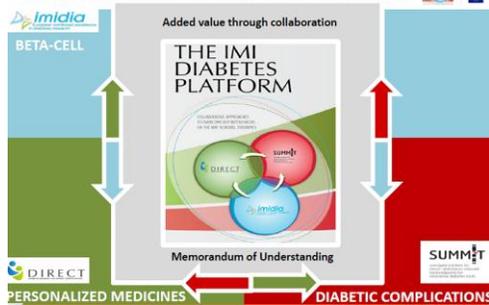


## Hot off the Press

Researchers at Lund University in Sweden have made a giant step toward unraveling the riddle of atherosclerosis in diabetic mice. The team led by Prof. Maria Gomez has demonstrated that "targeting Nuclear factor of activated T-cells (NFAT) signaling may be a novel and attractive approach for the treatment of diabetic macrovascular complications."



THE IMI DIABETES PLATFORM: FILLING THE GAPS  
TO BRING NEW THERAPY OPTIONS FASTER TO THE PATIENT



## A compelling mosaic of diabetes research: impressions from the 1<sup>st</sup> Symposium of the IMI Diabetes Platform in Barcelona

*On the occasion of this year's EASD Annual meeting IMI's three diabetes projects SUMMIT, IMIDIA and DIRECT met in Barcelona to jointly present their latest research on diabetic complications, the pancreatic  $\beta$ -cell and personalized medicines to the public. With thousands of diabetes stakeholders coming to town the stage was well set to attract a wide audience. Among the welcoming speakers were EASD President Andrew Boulton and IMI Executive Director Michel Goldman. SUMMIT, IMIDIA and DIRECT together constitute the IMI Diabetes Platform - one of the most holistic discovery approaches in diabetes research to date.*

### Destination diabetes

It is late September. Like every year you find yourself sitting in an airplane heading for one of Europe's major capitals. Of course, you chat with your next seat neighbors. Like in every plane seats, diabetes is the only point discussed. The community's pilgrimage to the annual meeting of the European Association of Diabetes (EASD) has just started again.

This September the plane's destination was Barcelona, the lively Catalan metropolis on the northeast coast of the Iberian Peninsula. Again thousands of diabetes stakeholders were coming to town - some of them flying in a day earlier for a reason: to get firsthand information on recent results from SUMMIT, IMIDIA and DIRECT, the three public private diabetes partnerships within the Innovative Medicines Initiative (IMI), which together constitute the IMI Diabetes Platform. Titled "OPENING UP A NEW CHAPTER IN DIABETES RESEARCH" the three projects held their 1<sup>st</sup> joint symposium on the occasion of the EASD's 49th Annual meeting in the afternoon of Sunday, September 22<sup>nd</sup>.

### A long nourished plan

Open to the public, a broad audience was invited. The organizers addressed not only diabetes researchers, clinicians and health care providers but also patient organizations and decision takers. "The scientific opportunities of our projects are immense. The key to success is the collaborative approach we are following. Now that we are harvesting the fruits from our work we want to share them with everybody interested" Michael Mark (Boehringer Ingelheim), the co-ordinator of the SUMMIT consortium informed over a cup of coffee during the break, only to go on "Today we are putting into action a long nourished plan. What better stage

than the annual meeting of the EASD can be imagined to reach all relevant stakeholders at the same time".

### A warm welcome

When Werner Kramer (Sanofi), the coordinator of the IMIDIA consortium opened the symposium at exactly 1:30 pm, close to a hundred guests had arrived, amongst them several researchers from the three hosting consortia, taking the opportunity to meet their colleagues from the other diabetes projects. Others, like participating representatives from the Juvenile Diabetes Research Foundation (JDRF), travelled as far as from the US.

The guests welcomed and the day's agenda introduced, Werner Kramer handed over the microphone for welcome addresses by the EASD and IMI. Andrew Boulton, EASD president, highlighted the 15<sup>th</sup> anniversary of the UKPD landmark study and informed about the various activities and functions of the EASD. Holding up a leaflet handed out to announce SUMMIT's numerous oral and poster presentations selected for the upcoming EASD conference, he acknowledged the IMI diabetes projects for their achievements. However, generating results is only one side of the medal, dissemination of relevant outcomes the other. Hence, Michael Goldman, Executive Director IMI, thanked the organizers for their efforts to organize the symposium before informing the audience about the IMI's goals and achievements.

### Filling the gaps

The Diabetes Platform describes itself as one of the most holistic discovery approaches in diabetes research. Michael Mark took on the challenge to introduce the concept behind to the audience. While each of the three IMI diabetes projects has its own research

focus, they perfectly complement each other in filling the gaps on the way to faster develop innovative therapies for improved patient care, he informed. However, he added, although current symptomatic treatment has improved substantially over recent decades, still there remains an urgent need for slowing down disease progression, better understanding disease heterogeneity and, last but not least, better treatment and prevention of severe diabetic complications. IMIDIA, DIRECT and SUMMIT are addressing exactly these hurdles in today's drug development process. With a combined budget of 100 Mio € and the involvement of more than 300 leading experts in diabetes from all over Europe, the IMI diabetes platform is one of today's leading initiatives in diabetes research. Importantly, he went on, the 54 partners involved signed recently a Memorandum of Understanding (for more information see News in Brief on page 5). This new collaboration framework enables an even tighter interaction across all three projects and enables the comprehensive utilization of platform synergies.

### Talking science I

"Make good science and talk about it" - referring to the meeting's unofficial motto the organizers reserved the better part of the afternoon for science. In three dedicated sessions the projects introduced their key objectives, addressed next steps and future benefit for the patients and, most importantly, presented an impressive selection of research highlights.

The SUMMIT session "Approaching diabetes complications" being first, work package leaders Mark McCarthy (University of Oxford) and Helen Colhoun (University of Dundee) presented novel findings, biological

insights and translational opportunities from genetic and non-genetic biomarker analyses on behalf of the consortium. Though additional indications are under investigation, the day's focus was set on diabetic nephropathy (DN) and cardiovascular disease (CVD).

SUMMIT's key objective is to develop procedures, technologies and tools to make clinical trials testing of novel medications in diabetic complications shorter and more focused. Linked to these goals Maria Gomez (Lund University) addressed the urgent need for animal models better replicating diabetes complications. Glad about what was achieved in a joint effort of SUMMIT's animal research group, she described three interesting models now identified for DN and CVD. Importantly, these well-characterized animals cover both, the early and late stages of the disease Maria Gomez pointed out, emphasizing at the same time that it is this complementarity, what makes them so interesting for pre-clinical intervention studies.

And there was more to present – imagin(e)g to “Make cardiovascular disease visible”. Along these line and, perceived with great interest, Jan Nilsson (Lund University) presented a novel device for ultrasound-based carotid plaque structure analysis, the so-called UPSA-system (see interview with Isabel Goncalves on page 4). The UPSA, Jan Nilsson explained to his audience, can detect high-risk vulnerable atherosclerotic lesions. This feature makes it a possible novel non-invasive, low cost and safe method to identify individuals prone to stroke and to monitor response to interventions.

Impressed – and some in the audience afterwards said, even a bit moved – Leif Groop (Lund University), who chaired the SUMMIT session together with his counterpart from industry, Michael Mark, summarized that SUMMIT is creating the largest database on diabetic complications ever – a goldmine for diabetes research. Saying, “Our public private partnership has opened new possibilities and improved exchange between academia and industry” he closed the SUMMIT session.

### Talking science II

Coffee break - and afterwards IMIDIA and DIRECT. Under the heading “The pancreatic  $\beta$ -cell: the key to diabetes” IMIDIA colleagues presented an im-

pressive series of achievements on novel human  $\beta$ -cells for drug discovery research, the creation of a unique biorepository of human  $\beta$ -cell samples and the bioinformatical identification of novel biomarker modules as well as the visualization of insulin turnover in the pancreatic  $\beta$ -cell. On the other hand, Ewan Pearson (University of Dundee) from the DIRECT consortium addressed “Personalized medicines in type 2 diabetes” showing first results from retro-perspective sample analysis.

At the end of the day, when Hartmut Rütten (Sanofi), the DIRECT co-ordinator, made his final remarks, the three platform projects had presented a compelling mosaic of achievements in diabetes research to their audience. The article format only allows for some flashlights on the sessions. Much more was shown – and what was shown was only a selection of the many achievements the projects had made so far. In any case, it was worth coming to Barcelona, the home of late Catalan architect Antoni Gaudí.

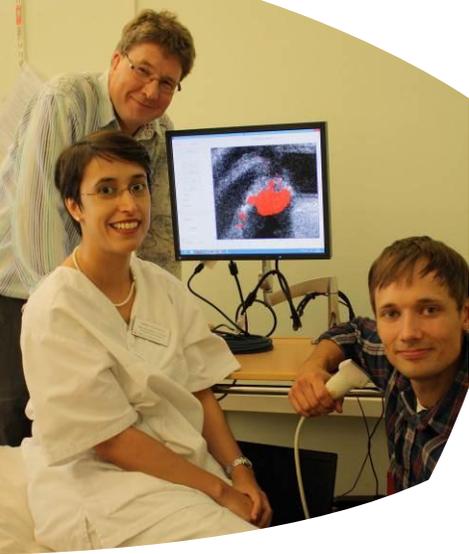
### More than a research project

Like Gaudí's opus magna, the Sagrada Família, also the mission of the IMI Diabetes Platform is not yet completed – there is more to come. However, you can already imagine the beauty of it and, like Gaudí, SUMMIT, IMIDIA and DIRECT are dedicated to make a difference. Sharing the great architects passion and ambition to study and integrate every detail of his work and his capability to introduce new techniques and skills, the three projects of the IMI diabetes platform bring together all the different bits and pieces, which in the end will give the full picture or – to stay with Gaudí – mosaic display.

Més que un club – more than just a club is the slogan of the world's most popular and successful soccer team that re-invented the game, the FC Barcelona. Més que un proyecto de investigacion – more than just a research project, the IMI Diabetes Platform, a private public partnership dedicated to develop game changing solutions in diabetes research.

After a successful meeting the only thing left to say is “Thank you” to all speakers and especially the EASD Executive Office for making the 1<sup>st</sup> Symposium of the IMI Diabetes Platform possible.





## Four people with one great idea: developing a revolutionary ultrasound device that staves off life-threatening diseases

*Isabel Gonçalves, cardiologist at the University Hospital in Malmö-Skåne has together with engineers Tobias Nilsson and Magnus Cinthio at the Faculty of Engineering of Lund University developed a groundbreaking ultrasound imaging technique that has the potential to predict when the atherosclerotic plaque that causes heart attacks and strokes can be dangerous. An interdisciplinary collaboration within SUMMIT is the key to the discovery.*

**The SUMMIT correspondent Klodiana Jani reports on the interview with Isabel Gonçalves**

### **Q1. How would you explain your research focus to the general lay public?**

Atherosclerosis – the process of plaque formation due to the accumulation of fatty material inside the blood vessel wall - affects preferentially some regions of the arterial tree such as the vessels that supply blood to the heart – coronary arteries – and to the brain – carotid arteries. The danger arises when the atherosclerotic plaque breaks up or ruptures. As a result, a blood clot is formed. The clot may block the blood vessel and consequently reduce or even cut off/stop the blood flow within the vessel. The clot forming at coronary arteries obstructs the blood flow at the heart muscle. People may therefore have a heart attack. If the affected vessels are the carotids, people can have a stroke. These conditions are nowadays the leading causes for death and disability.

The plaques that are “prone to rupture” have certain features in their compositions. They are very inflamed and have fat inside them. The inflammation can cause the thin covering over the plaque to crack, thus forming a clot large enough to block the artery. We therefore aim at developing an imaging technique that enables identification and visualization of the inflammatory atherosclerotic plaque plus predict when it can be dangerous and harmful. This technique is based on non-invasive ultrasound imaging is called UPSA, Ultrasound-based Plaque Structure Analyses.

### **Q2. Why it has been created? Why should you put money into it? And how does it fill a gap in the market?**

At the moment there are no non-invasive imaging techniques capable of observing the inflammation in the vessel wall or determining which plaques are most likely to rupture. Intravascular ultrasound developed in the recent years gives some information about the vessel wall and plaques. It is only used in the coronaries because it is too dangerous to bring it close to the brain. Besides, it is quite expensive and may present significant risks for the patients. First, you need to go inside the vessel of the patient plus use of contrast agents, radiation, catheters, wires and other procedures that may cause trauma and pain to the patient.

Our strategy attempts to use ultrasound to characterize the plaque structure and detect

inflammation or fat, in other lesions in the blood vessels of the neck – carotids arteries. Patients with carotid plaques have an increased incidence of coronary artery disease. Therefore, it is highly possible that patients with carotid plaques are at risk of having heart attack too. So, in some way, one is studying the disease in different regions.

Our method is non-invasive; it is used by the bed of the patient, requires no contrast, no X-ray, no needles, no magnetic fields. In principle, it can be used everywhere, in primary care units, by someone capable of handling ultrasound machines, just like the ultrasound for pregnant women. With such a user-friendly technique, the clinicians can competently identify patients at high risk for heart attack or stroke and follow them up. As such, it can prevent lots of diseases including heart attacks and strokes.

### **Q3. How long does it take to come to a statistically significant conclusion that leads to being published?**

At the moment, the method has been evaluated in 50 patients. We got significance already in 20 patients. We have also collected more images from the remaining patients, and we’re currently validating the results. Within the SUMMIT consortium, the technique is currently being validated in a multi-centre study involving 500 diabetic patients with cardiovascular disease, 500 diabetic patients without cardiovascular disease and 500 non-diabetic control patients. These patients are recruited by the SUMMIT partners based at universities of Dundee, Exeter, Lund and Pisa.

### **Q4. Who is the creator of the invention? Where is it based? Are there any partners based anywhere else?**

Our team is composed of four experts: myself, Jan Nilsson, Professor of Experimental Cardiovascular Research at Lund University, PhD-student Tobias Nilsson and the associate Professor Magnus Cinthio, both engineers at Electrical Measurements, Faculty of Engineering of Lund University. We had the idea all together. Whereas Tobias and Magnus designed the signal processing for the ultrasound imaging, Jan and myself did the method validation on patients and focused on the applications. Therefore the inventors for the patent application are the four of us: Tobias,

We are closely collaborating with Piero Tortoli, Professor in Electronics at University of Florence, and his team who has developed the research ultrasound scanner to collect the images data, providing the needed information for Tobias and Magnus to design the methods. The probe looks just like the regular ultrasound, similar to the one being rubbed onto pregnant mom’s belly. In reality our ultrasound method is much more complex. Moreover, the SUMMIT partners of Pisa, Dundee, and Exeter universities are currently using the same research scanner and collecting prospective data on the cohorts too.

These collaborations have been absolutely essential to develop our new invention. In a typical scenario, the researchers first develop the technique and then look for centers that collect information from patients with the disease of interests. In our case we have been doing it very fast because of the SUMMIT network. SUMMIT provides all necessary services, support including the cohorts and funding. The Florence crew has built four research ultrasound scanners, one for each SUMMIT center. As such, it will be much faster to collect the data from all the centers.

### **Q5. What is the impact of your discovery on the diabetes patients?**

Diabetic patients have much higher risks of having stroke and heart attack. Our technology was created within the SUMMIT consortium and is currently being used in patients with diabetes. However, it is also intended for broader applications.

### **Q6. Patent application is a key step which enables the transitions of research from the bench to the commercial product. Is your recent discovery licensed?**

We have submitted the application for the patent in June 2013. We are hoping to get a first response to our patent application by the end of the year. In my view our innovation is going to be a big hit if it continuous giving positive results in the rest of the tests.

*As this discovery is pending patent approval, we could also agree that it is an example of an innovation, in which the invention will certainly ride one great wave of change in the diagnostics and treatments of patients with diabetes and vascular disease.*



## The 'culprit' that brings atherosclerosis to a halt in diabetic mice

Researchers at Lund University in Sweden have made a giant step toward unraveling the riddle of atherosclerosis in diabetic mice. The team led by Prof. Maria Gomez has demonstrated that "targeting Nuclear factor of activated T-cells (NFAT) signaling may be a novel and attractive approach for the treatment of diabetic macrovascular complications."

The tempting hypothesis put forward by this team is coherent with the observation that NFAT activated by elevated sugar in blood turns on a sequence of events that damage the blood vessels and speeds up the development of atherosclerosis.

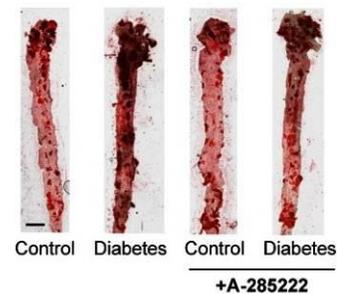
It has long been shown that inflammation is a pivotal contributor to all stages of atherosclerosis, from initial lesion to the ruptured plaque. Both elevated glucose and lipids contribute to increased inflammation and diabetes is associated with an increased inflammatory state. Given of the inflammatory base of atherosclerosis and the observation that NFAT is activated by elevated sugar, Gomez and her team members examined the NFAT activity in aorta and other organs of diabetic mice. Of all the organs examined, NFAT activity was selectively augmented in the aorta of diabetic mice. Besides, a significant increase of a number of inflammation markers was observed in the aortic

wall of diabetic mice when compared to controls.

Since crucial pieces needed to be pieced together, the researchers targeted in vivo the NFAT signaling/activity by administrating a NFAT blocker originally developed as an immunosuppressant. To their excitement, the NFAT blocker completely abolished diabetes-induced activation of NFAT in the aorta as well as reduced the expression of all established players in atherogenesis. The inhibition seemed to exclusively affect diabetes-driven atherosclerosis in non-diabetic mice, suggesting potentially different mechanisms underlying plaque formation under diabetic and non-diabetic conditions.

This finding breaks exciting new ground in the field of diabetes research and provides new evidence on the role of NFAT in the development of athero-

sclerosis in diabetes. The researchers also believe that that NFAT signaling pathway could constitute a novel therapeutic target that can reverse the diabetic macrovascular complications.



Diabetic female mice treated for 4 weeks with the NFAT blocker completely counteracted the effect of diabetes on lesion area.

**Citation:** Anna V. Zetterqvist et al., "Inhibition of Nuclear Factor of Activated T-Cells (NFAT) Suppresses Accelerated Atherosclerosis in Diabetic Mice." *PLoS ONE*, 2013; 8 (6): e65020 DOI: [10.1371/journal.pone.0065020](https://doi.org/10.1371/journal.pone.0065020)

**Image:** Publication image, *PLoS ONE* (citation above).

## News in Brief

**The IMI Diabetes Platform:**  
Opening a new chapter in diabetes research  
PRESS RELEASE ... PRESS RELEASE ... PRESS RELEASE ...

**The IMI Diabetes Platform: SUMMIT, IMIDIA & DIRECT open up new opportunities for collaboration in diabetes**



**Prof. Leif Groop will receive this year's Fernström Foundation Nordic Prize**

On September 23<sup>rd</sup> SUMMIT, IMIDIA & DIRECT announced the signature of a new Memorandum of Understanding (MoU). The MoU provides the framework for taking collaborative activities between the three public private diabetes partnerships within the Innovative Medicines Initiative (IMI) one step further – formally implementing the IMI Diabetes Platform and bundling of expertise, knowledge and findings across the projects. With a combined budget of 100 Mio € and the involvement of over 300 leading experts in diabetes, the Diabetes Platform is of the world's leading initiatives in diabetes research focusing on overcoming key bottlenecks for novel therapies and improved disease management. For additional information please see the official press release @ [www.imi-summit.eu](http://www.imi-summit.eu).

Leif Groop, M.D., Ph.D., Professor at Lund University, Director of Lund University Diabetes Centre and a partner in SUMMIT, has received the Fernström Foundation Nordic Prize awarded annually to an outstanding Nordic scientist in medicine. The Nordic price is one of Scandinavia's most prestigious medical prizes. In 2012 Leif Groop already received the Norwegian Anders Jahre Senior Medical Prize for his ground breaking re-search on diabetes, especially his identification of hereditary factors predisposing to the disease.



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What you need  
to know about  
SUMMIT...

**SUMMIT**

surrogate markers for  
micro- and macro-vascular  
hard endpoints for  
innovative diabetes tools

SUMMIT is one of the three IMI-funded Diabetes projects. It aims at promoting faster development of new treatment options for diabetes micro- and macro-vascular complications by identifying novel markers that enable detection of patients at high risk for complications and monitoring their response to therapy. To this end, SUMMIT has established an integrated framework of expertise involving 19 European academic institutions, one small and medium-sized enterprise (SME) along with 6 Pharma partners. The team combines competencies from a wide range of disciplines including molecular and cellular biology, genetics, animal models, bioinformatics and imaging technologies.