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Platelets: Helping in coagulation and driving inflammation

ERC Advanced Grant for Bernhard Nieswandt Prof. Dr. Bernhard Nieswandt has been awarded a prestigious ERC Advanced Grant worth 2.5 million euros by the European Research Council for his research on a cellular mechanism in blood platelets that appears to play a crucial role in inflammatory diseases.

Würzburg. In the mid-19th century, they were first observed as small spheres in the blood, and by the turn of the century, their function in blood clotting, known as haemostasis, and the development of thrombosis were discovered. A few years later, the site of their formation in the bone marrow was also identified, where platelets are shed from their giant precursor cells, the megakaryocytes. The biology of these small, nucleus-free cells, which are only one-thousandth of a millimetre in size and of which we have about 250 million in every millilitre of blood, has gradually evolved into a major research area. It has become obvious that platelets have a plethora of functions beyond stopping bleeding or triggering heart attacks. As modulators of the immune system, they also drive inflammatory processes and thereby promote tissue damage in many disease settings.

Thrombo-Inflammation: Inflammatory Processes Triggered by Platelets

Prof. Dr. Bernhard Nieswandt, Head of the Department of Experimental Biomedicine I at the University Hospital Würzburg and Research Group Leader at the Rudolf Virchow Center, has made seminal contributions to these discoveries and coined the term "thrombo-inflammation." For his pioneering work in platelet research, his latest discovery, and further investigations, he has now been awarded an ERC Advanced Grant of 2.5 million euros. The Advanced Grants of the European Research Council (ERC) are part of the EU programme Horizon Europe and target established leading researchers. The grant is one of the most prestigious and competitive scientific awards and research funding instruments of the EU.

PITT-Inflame: Shed Organelles Steering Immune Functions

The award is both recognition and encouragement for Bernhard Nieswandt to keep on trusting his scientific instincts, conducting research at the forefront, and making breakthroughs in the understanding of diseases such as stroke, sepsis, or acute respiratory distress syndrome (ARDS). Platelets play a crucial role in the development of these diseases. And this is also the focus of the new ERC project "PITT-Inflame," an acronym for “Platelet-derived Integrin- and Tetraspanin-enriched Tethers as key effectors in thrombo-Inflammation”. PITTs are comet tail-like organelles shed by platelets that interact with other cells in the vascular system, modulate their function and thereby fuel inflammation and tissue damage.

"We want to analyse a cellular mechanism of platelets that has not been described before and which we discovered rather incidentally in my research group," says Bernhard Nieswandt. "Normally, the life of a platelet ends quickly after its activation and adhesion to injury sites, and it is then removed by phagocytes. However, we observed that non-activated platelets undergo an unexpected process of cellular reorganization in the bloodstream, allowing them to deposit parts of their membrane at sites where inflammatory processes occur, thus fueling them." In the first part of the

ERC project, Bernhard Nieswandt aims to explore the mechanism of this reorganization which makes the platelet shed a small part of its cell body, an organelle filled with communication molecules that control immune functions but also promote inflammatory tissue damage.

100,000 molecules are reorganized

Intriguingly, integrins, specific adhesion receptors connected to the cell's cytoskeleton, can move freely in the membrane and rapidly relocate 100,000 molecules to a specific region of the cell surface (microdomain). "There must be a kind of sorting machine in the cell that reorganizes the entire pool of its most important adhesion receptors along with associated membrane proteins, the tetraspanins, as building blocks for novel cell organelles, the PITTs," says Nieswandt. His research has yielded initial evidence that these organelles are loaded with signalling molecules, ribosomes, and RNA, enabling them to alter the function of their target cells. Having reconstructed the detailed molecular composition and architecture of PITTs and deciphering the underlying signalling networks, Nieswandt in the second part of the project aims to identify PITT-induced effects on target cells and deduce therapeutic strategies from the findings.

"With Covid-19, we have fully learned what thrombo-inflammation actually means"

Many of his findings and patents have already been applied successfully in clinical settings or are on their way there. A good example is ischaemic stroke: Even if a thrombus blocking blood supply to a certain part of the brain is successfully removed, and blood flow is restored, an inflammatory reaction promoting brain damage is still seen in the majority of patients. Bernhard Nieswandt and his team uncovered the mechanisms underlying this inflammatory pathology, driven by platelets, together with colleagues of the Neurology Department of the University Hospital Würzburg. Initial preclinical and clinical studies with inhibitors that suppress this inflammatory reaction showed promising results. Also in acute respiratory distress syndrome, which has affected many people, especially in the COVID-19 pandemic, an excessive immune reaction driven by platelets getting out of control is involved. "With Covid-19, we have fully appreciated what thrombo-inflammation actually means," explains Bernhard Nieswandt. With the glycoprotein VI (GPVI) expressed on the surface of platelets, his research group has identified a promising target for treating such inflammatory disease processes. "By selectively inhibiting GPVI with an antibody, we can prevent the devastating influx of inflammatory cells into lung tissue and significantly reduce the resulting tissue damage in the inflamed lungs, without increasing the risk of inflammatory bleeding," explains Nieswandt. He has not only discovered a mechanism for inhibiting GPVI but also demonstrated how this receptor can be removed from platelets, which could be of considerable therapeutic benefit in the future.

New avenues for treating a wide range of diseases

Back to PITT-Inflame: "Our hypothesis is that circulating platelets have the capacity to use their principal adhesion and signalling machineries in two fundamentally different ways and thereby switch between the haemostatic and thrombo-inflammatory functions. If proven correct, this would implicate a radically new paradigm in platelet biology, and open new avenues for the treatment of a wide range of diseases with major societal impact," summarizes Bernhard Nieswandt.

About Bernhard Nieswandt

Bernhard Nieswandt (born in 1968) studied Biology and Biochemistry in Regensburg and Canterbury (UK). As a doctoral student in Regensburg, the focus of his studies was already on platelets and inflammation, an entirely new research field at this time, and developed the world's first antibodies against mouse platelet receptors, which became important tools in the study of these cells. After completing his PhD in 1997, he moved to the University of Witten/Herdecke, where he completed his habilitation in experimental medicine. In February 2002, he moved to Würzburg, where he has been advancing cardiovascular and neurovascular research with groundbreaking discoveries ever since. He was the first to

establish a research group in the newly founded Rudolf Virchow Center, University of Würzburg, became a professor two years later, and was appointed head of the Chair of Experimental Biomedicine I in 2008. With his team, he has laid the foundation for two medications: a Factor XIIa inhibitor from CSL Behring, which has just been approved by the US Food and Drug Administration FDA and is being evaluated by the European Medicines Agency EMA, and GPVI inhibitors, which have just entered clinical phase III studies.
Bernhard Nieswandt has supervised 26 postdocs, 41 doctoral theses, and 24 master's students in Würzburg so far. Since 1999, he has published over 320 papers, cited more than 26,000 times. Eight patents have been granted, with three more under review. Bernhard Nieswandt lives with his family in Eibelstadt, where he manufactures antibodies for cardiovascular research with his company EMFRET Analytics.

About the ERC Advanced Grants

The ERC Advanced Grants are part of the EU programme Horizon Europe and aim to support groundbreaking research by established leading researchers. The awards are among the most prestigious and competitive in the EU. On Thursday, April 11, the ERC announced the names of a total of 255 outstanding scientists in Europe who will be awarded the ERC Advanced Grant. With the new grants totaling €652 million, research projects in a wide spectrum ranging from natural and life sciences to social sciences and humanities are supported. Germany leads among the successful applicants with a total of 50 awards, followed by France with 37 and the United Kingdom with 28. A total of 1829 applications were submitted. The funding not only supports researchers in breaking new scientific ground but also creates around 2,500 jobs across Europe, says Illiana Ivanova, European Commissioner for Innovation, Research, Culture, Education, and Youth.

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Prof. Dr. Bernhard Nieswandt from the University Hospital Wuerzburg has been awarded a prestigious ERC Advanced Grant for his research on a cellular mechanism in blood platelets that appears to play a crucial role in inflammatory diseases.
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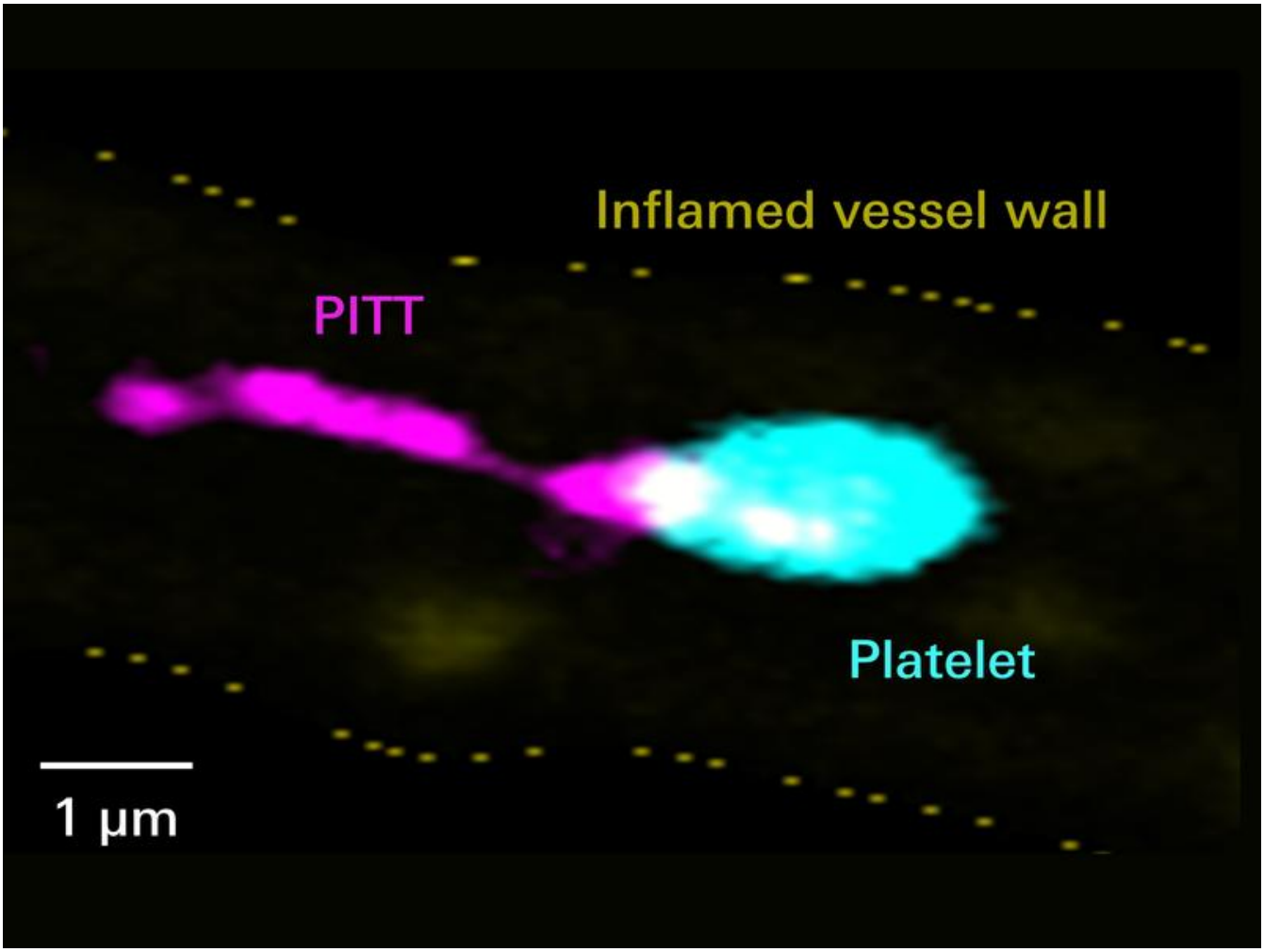

The PITTs - Platelet-derived Integrin- and Tetraspanin-enriched Tethers - observed here in the mouse by Bernhard Nieswandt are comet-tail-like organelles shed by platelets that interact with other cells in the vascular system and modulate their function.
Bernhard Nieswandt