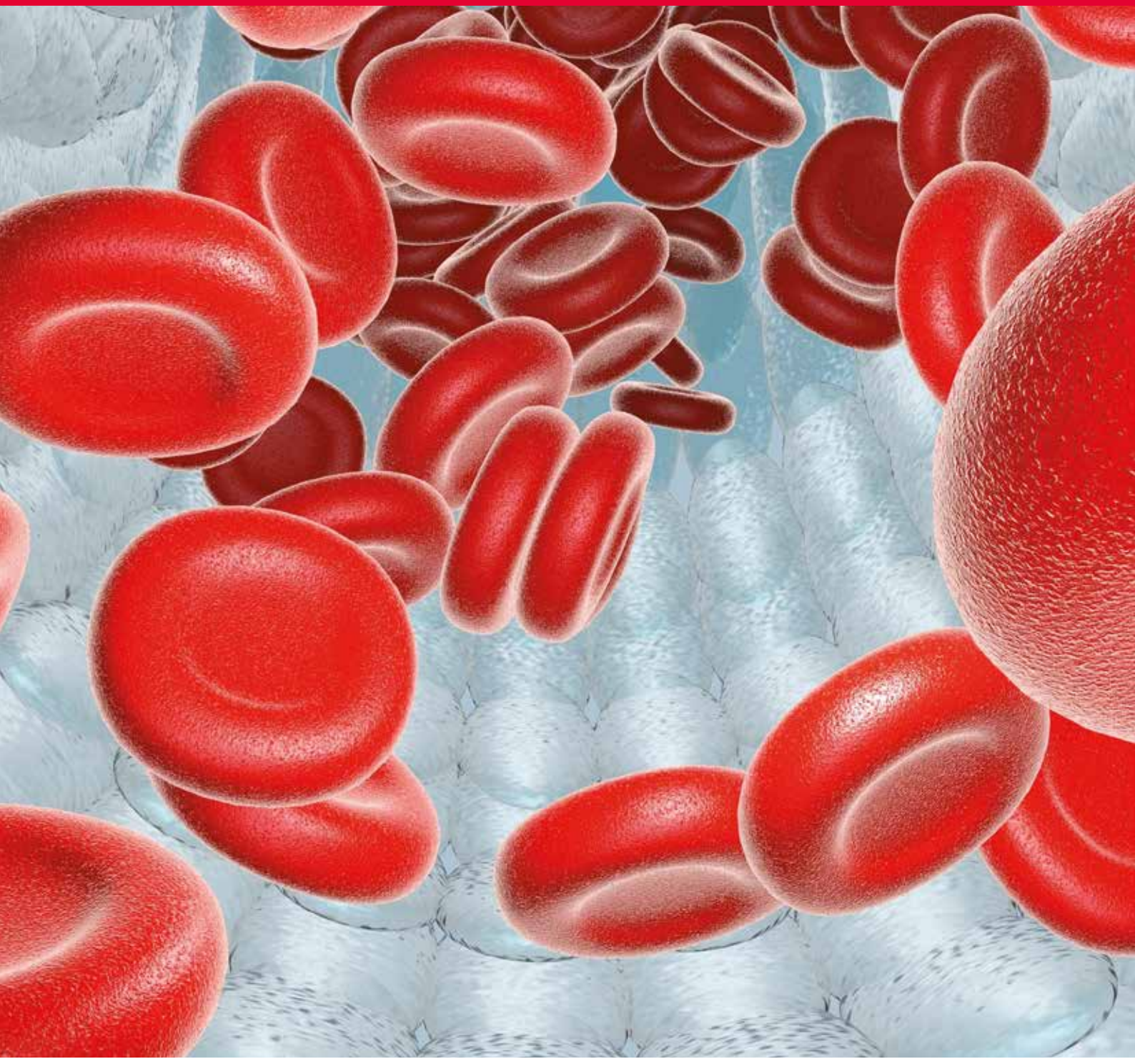
IMPACT

A RESEARCH MODEL FOR THE FUTURE



HORIZON 2020

http://relevance.arivis.com/
www.researchgate.net/profile/Anna_Bogdanova

A research model for the future

One of the main problems with complex medical research projects is the need to ensure consistency in the method of investigation, and failure to approach these subjects homogenously can miss essential data, to the detriment of the final outcome. The ***Relevance*** *project seeks to redress this*

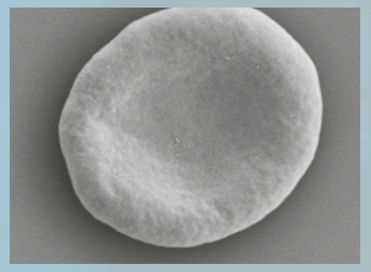
According to World Health Organization (WHO) statistics, anaemia affects around 1.62 billion people around the globe, representing 24.8 per cent of the population. By any measure, this is a serious proportion, with the greatest prevalence found in non-pregnant women. Generally defined clinically as a reduction in the total amount of red blood cells within the body, the condition can also relate to a reduction in the ability of the red blood cells to transport oxygen. The onset of anaemia can be rapid and is accompanied by symptoms such as shortness of breath, confusion, increased thirst and loss of consciousness.

Impaired red blood cell production, increased destruction of them, and blood loss or fluid overload have been cited among the causes of anaemia, however, several of these may interplay to cause the condition in a patient. Indeed, the most common cause of anaemia tends to be blood loss, but this is usually short-lived and usually does not cause any lasting symptoms unless a relatively impaired red blood cell production develops in turn, most commonly, by iron deficiency.

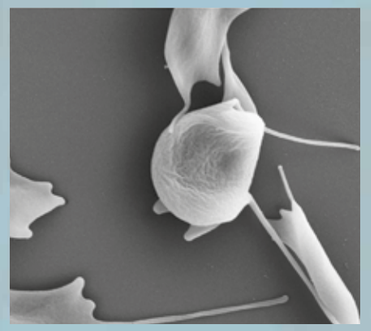
UNDERSTANDING THE PROBLEM

The Relevance project seeks to further our understanding of the causes of anaemia. Relevance is an international consortium of 13 partners representing academic research centres, diagnostic labs, blood supply centres and small industries that combine basic and translational research to improve prognostic, diagnostic and therapeutic approaches to red blood cell production, function and clearance in healthy humans and patients.

Part of the problem with understanding this complex disease is that researchers don't have a common background or standard investigative methodologies, and this is what the Relevance project hopes to change. Key to the project are 15 Early Stage Researchers (ESRs), who will not only exhaustively investigate the causes of anaemia, but will establish a common platform for future researchers to work from, ensuring a standardised working methodology. This will create an environment where researchers can focus on the problem itself – in this case, the causes of anaemia – rather than the fundamental problems of how to research and report out. The current project hopes to demonstrate how research can be fed into high quality publications in a standardised way, making it available to anyone.



Red cell of healthy human: scanning electron microscopy Picture taken by Greta Simionato, an ESR on the RELEVANCE project from Saarland University, Germany during her secondment at the University of Zurich, Switzerland



Red cell of a patient with sickle cell disease: scanning electron microscopy. Picture taken by Greta Simionato

BUILDING ON PREVIOUS RESEARCH

Relevance grew from the CoMMiTMenT project, which will conclude in 2018. CoMMiTMenT itself sprung from the need to understand the growing anaemia problem in Europe, and formed a five-year fully funded plan, which focused on microscopy techniques. The main aim of the research was to investigate rare anaemia treatments and develop new tools for identification and potential treatment of the condition. Following the successful development of that project, it became apparent that previous research into the causes of anaemia were in part being undertaken in a fairly haphazard way (incomparable methodology, lack of attention to the blood handling and shipment conditions), and this lack of research standardisation was a detriment to the seriousness of the condition. Funding was sought for a new project in which ESRs would be trained in consistent ways to be able to address the open questions that were put forward in the CoMMiTMenT project.

But Relevance is far more than a simple training programme. Split into five separate work packages (WP), each will address fundamental issues surrounding anaemia and the medical issues the condition raises. WP1 focuses on the development of new and novel diagnostic tools using blood samples for pathophysiologic and genetic studies, which can be used to help characterise anaemia. This will be completed with the assistance of commercial partners and is predicted to result in the shaping of industry standard tools for the investigation of anaemia and for future use in clinical labs.

WP2-WP4 consist of detailed investigations into red blood cells as treatment targets in pathophysiological conditions, cell interactions with other cells and tissues, and red blood cell transfusions with a specific focus on *in vitro* generation of red cells to transfuse, storage and conservation of the material. WP5 is designed to consider the question of red blood cells in the context of patient exercise and physical training,

> *'Relevance is far more than a simple training programme'*

and will examine the role and effects of erythropoietin and the potential increased risk of thrombosis and the changes in rheological properties of native and auto-transfused red blood cells.

FUNDAMENTAL ISSUES

The issues surrounding anaemia are not as straightforward as many previously considered. It is known that the basic principle of anaemia stems from the imbalance between production of red cells and the rate of their removal from the circulatory system. The underlying reason for this imbalance is often clear. In a healthy body, around one per cent of the senescent red blood cells are replaced with new and healthy cells every minute. That equates to around 100 million blood cells being replaced in an adult human, and the body has the ability to increase that production rate by as much as 10 times that amount in cases of high blood loss. Thus, we are well equipped to avoid chronic anaemia and conditions would need to be particularly detrimental to override this high degree of system stability.

Searching for the causes of hereditary anaemia has so far focused on the role of mutated genes and a subsequent damage in the corresponding proteins which compromise red cell survival. However, there is growing evidence that there are meaningful roles played by other factors, such as shear stress to which the cells are exposed in circulation, inflammatory factors, hyper-activation of protein cleaving enzymes, and even intracellular calcium ions (Ca^{2+}) which play a vital role in the pathophysiology underlying rare anaemia in patients. Relevance partners join efforts to bridge aberrant genes and cellular function to the severity of disease manifestation.

A COMMON RESEARCH PLATFORM

Plainly there is much research work needed in this complex subject, and the Relevance project is not only seeking to address all of the current unknowns, but to do so in a consistent way which will become a model for other researchers. Making the next step from bench to bed, Relevance is also keyed towards practical use of academic knowledge, and the commercial process and applications. The ESRs are also receiving training in business aspects such as Intellectual Property (IP) rights and legislation, and commercial development. As well as being researchers, the ESRs will become fully consummate with the applied and commercial perspectives of their work.

Under the guidance of Relevance partners coordinated by Professor Anna Yu Bogdanova, the 15 ESRs will become research leaders in the field, and will set the pathway for future research into many different areas of science, medicine and high-tech industry. By creating a structured route to the understanding of this common yet underestimated research and medical issue in the field of hematology, Bogdanova and her team are moulding methods of R&D, which can be applied to any medical field and are designed to achieve maximum academic and commercial impacts.

The Relevance project is already demonstrating significant results, as presented at the recent 22nd meeting of the European Red Blood Cell Research Society, held in Heidelberg, Germany, and hopes to present even greater achievements at the 23rd meeting in spring 2019. With the ESRs now fully enveloped in their research, a full understanding of anaemia is becoming clear, and that can only be good news for the vast proportion of the planet's population who suffer from the condition.

Project Insights

FUNDING

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 675115-RELEVANCE-H2020-MSCA-ITN-2015/ H2020-MSCA-ITN-2015.

COLLABORATORS

Lars Kaestner, University of Saarland, Germany • Marieke von Lindern and Robin van Bruggen, Sanquin Blood Bank Supply, Netherlands • Tim Ryan, Epigem Ltd, UK • Giampaolo Minetti, University of Pavia, Italy • Ashley Toye, University of Bristol, UK • Richard van Wijk, University Medical Center Utrecht, Netherlands • María del Mar Mañú Pereira and Josep Carreras, Leukaemia Research Institute, Spain • Stéphane Egée, Biological Station Roscoff, France • Andrew Rafael Banas, Optorobotix, Denmark • Wassim El Nemer, INSERM, France • Andrea Brueggemann and Markus Rapedius, Nanion, Germany • Christian Götze, Arivis AG, Germany

CONTACT

Professor Anna Yu Bogdanova
Project Coordinator

T: +41 44 6358811
E: annab@access.uzh.ch
W: http://relevance.arivis.com/ and www.researchgate.net/profile/Anna_Bogdanova

PROJECT COORDINATOR BIO

After completing her Master's in Chemistry at Leningrad State University, Russia, **Professor Anna Yu Bogdanova** continued her education in experimental biophysics at the Humboldt University in Germany. She made further advancements in animal and human physiology at the University of Turku, Finland and later at the University of Zurich, Switzerland.

Impact Objectives

- Develop a greater understanding of red blood cells so as to improve prognostic, diagnostic and therapeutic approaches to red blood cell production, function and clearance
- Establish a common platform and standardised working methodology for future researchers to work from, thus creating a R&D environment where researchers can focus on the problem itself
- Ultimately aid the 1.62 billion people around the world living with anaemia

Seeing red

__Professor Anna Yu Bogdanova__ is lead coordinator of the __Relevance__ project, which is seeking to understand and unravel the finer details of the structure and function of red blood cells and use this knowledge to help patients. Here she explains the key objectives of the project and the importance of collaborating with industry

Can you talk about the problems associated with establishing a reason for the reduction in red blood cells' number, a condition known as anaemia?

Putting to one side acute blood loss or dietary problems with amino acids and/or iron deficiency, facilitated loss of red cells is often caused by mutations in a number of genes. These genes may code globin-proteins forming O_2-carrying pigment haemoglobin, or proteins forming elastic yet firm carcass underneath the cell membrane known as cytoskeleton. Yet more proteins that, when not working, compromise red cell survival, are those regulating red cell volume and protect the cell form oxidative stress. These hereditary diseases related to red cell instability and premature destruction, may only be treated symptomatically. Unique analytical procedures "from the laboratory bench" may help to avoid mistakes in choosing individual therapeutic strategies.

The project has five key objectives; are these mutually independent or do some require certain parts to be completed before they can be started?

They are not at all mutually independent and hence require very intensive interaction between the work package leaders and individual partners, each of whom is a unique expert in their own field. In order to achieve our goals we need to understand how red cells are born, how they mature, how they adapt to stress conditions and how they age and signal to other cells that they are ready to be removed. To address all these questions we have to join our intellectual forces and share unique methodologies available at partners' sites, for example precise age detection of red cells or conditions required to produce red cells from precursors in a test tube.

A fundamental part of the project is looking for novel treatments for anaemia. Do you see this as a major stumbling block with the project?

I guess the major challenge is to think "out of the box" and try to identify several "master regulators" and "master targets" that are the cause of multiple down-stream events typical for pathological state in more than one type of rare anaemia. Targeting these master-switches, one can develop a therapy covering a broad spectrum of symptoms. Our pilot data indicates that such an approach may be successful before gene medicine will be introduced to the clinics.

The 15 ESRs were trained in issues related to intellectual property. Do you expect this novel research to identify many new processes and innovations?

Relevance is a science-driven consortium and science is about discovering new molecular players in physiological and pathological processes, suggesting new methodological approaches and generating new theories. So we cannot miss new discoveries. Our expertise and research tools multiply as we join forces to investigate mechanisms behind red cell diseases and adaptation to stress conditions. We are further reinforced by the SMEs helping us with novel designs of bioreactors and microfluidic chips, automating electrophysiological measurements and red cell image analysis.

Red blood cells (RBCs) are neither simple, nor easily obtainable in a pure form. Will part of the project investigate the development of processes to routinely produce pure RBCs in suspension?

Red cells were becoming more and more "complex", as red cell research was unravelling more details in terms of their structure and function using new tools and approaches. Pure red cell population can be obtained in culture by way of targeted transformation of precursor cells to red cells. Obtaining pure population of red cells free from white blood cells and platelets is a demanding task that is addressed by the group of Giampaolo Minetti at the University of Pavia, Italy.

Dealing with 13 academic and industrial partners in different geographical locations takes a great deal of project management. How has the team handled potential issues?

We are all experts in our own fields, and none of these 13 partners are specialists in project management. Therefore, we are supported by a great team of experts from Eurice GmbH.