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International Network on Ectopic Calcification (INTEC)
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Welcome

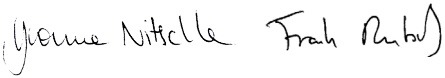
Dear colleagues and friends,

we heartly welcome you to the second INTEC meeting here in Münster. In this year's meeting, we would like to go „one step beyond" ectopic calcification, and we have put together a scientific program focusing on translational aspects. Experts in the field will present results of preclinical studies, clinically relevant endpoints for clinical studies, and ongoing clinical trials for ectopic calcification disorders. Additionally, free communications on all aspects of ectopic calcification will be presented based on selected abstracts.

INTEC is not only a platform for established experts, but also an inclusive community dedicated to nurturing the growth and advancement of emerging researchers. In this respect, for the first time, we offer a career development workshop on the second day of the meeting for young researchers.
We hope that apart from participating to the sessions you use your time to explore the famous city of Münster.

Please also accept our invitation to join our dinner and networking event in the A2 building and sky bar at the Aaseelake on Thursday evening, open to all participants. You will never forget it!

Have fun!



Yvonne Nitschke Frank Rutsch

About INTEC

The International Network on Ectopic Calcification (INTEC) is one of 13 International Thematic Networks which are being supported by Ghent University. These are cooperative networks consisting of Ghent University staff members and international partners concerning a specific topic of excellence in education and research.

INTEC creates a robust network to contribute to the advancement of scientific knowledge and unite international institutions' expertise around ectopic calcification (EC). Ghent University (Hospital) has a strong history concerning connective tissue and EC research, being international leaders for more than three decades. A unique strength of the Ghent partners is the specific capacity for collaboration and integration over different disciplines and teams within the University (Hospital), such as clinics vs. molecular or basic research lab, ...

INTEC uses an interdisciplinary thematic approach to connect the relevant knowledge at Ghent University - fundamental and translational research, clinical and pharmaceutical experts with an established high-impact track record in studying aspects of EC - with an international network of 18 partners who were carefully chosen to represent a diverse base of expertise, to exploit complementarities and to avoid competition. They are internationally recognized leading researchers that acknowledge the need for a collaborative approach to make important progress in the field of EC. Complementarity and diversity are achieved with respect to research expertise and education. In addition, important stakeholders are involved as affiliated members: Genetic Alliance – a coalition of patient organizations, industrial partners (Viforpharma-Sanifit and Elastrin Therapeutics), and VIB.

INTEC contains thus all necessary expertise to address the challenges of EC via excellent and innovative science, to invest in high-quality education of all EC stakeholders, and to establish sufficient impact for the network by dissemination of results. While the fundamental research partners have know-how and technological expertise necessary to accomplish INTEC's research aims, the clinical partners' expertise covers most

tissues where EC occurs. In addition, it allows INTEC to take advantage of the largest cohorts of hereditary EC patients and integration of cohorts with acquired EC. These patients play a crucial role in the translation of basic science results.

INTEC is the largest consortium of experts dedicated to advancing the knowledge on acquired and genetic calcification towards clinical and therapeutic applications by stimulating, facilitating and enhancing cooperation and better transfer of knowledge as it bridges different disciplines (rare versus common disease, genotype versus phenotype, preclinical versus clinical) and sectors (academic research, clinical research and industrial R&D). We are confident that the network will fertilize a multitude of new collaborations and will broaden the perspective of all partners both in terms of internationalization and across sectors. In this respect, it is important that INTEC is an open network that welcomes all stakeholders relevant for EC in aging and disease. INTEC's collaborative ecosystem will reinforce the efficiency of the Research and Innovation on EC by decreasing fragmentation, avoiding duplication, and identifying major research gaps that can be tackled together.

Ectopic Calcification

Ectopic calcification is defined as inappropriate biomineralization occurring in soft tissues. Affecting a wide variety of tissues such as arteries, valves, brain and connective tissues (e.g. skin, joints), EC is highly accelerated in aging, in a wide number of rare hereditary diseases as well as in acquired chronic diseases such as diabetes mellitus, chronic kidney disease (CKD) and rheumatic diseases.

Demographic changes towards an increasingly elderly population result in novel medical challenges, which do not only include improved medical care but also preventive measures and efficacious risk stratification to attain what is referred to as healthy aging. Eighty percent of the +65 population has at least one chronic condition, and among the 10 most prevalent ones, EC was shown to be directly associated to (multi-)morbidity, frailty and mortality. A common theme is vascular calcification (VC); indeed, aging and several pathologic states, such as obesity, diabetes, or CKD, cause degenerative changes of the vascular walls, including inflammation and VC, leading to arterial stiffening which increases mortality risk three-to fourfold. The impact of VC however extends beyond the CV system; e.g. excess VC of retinal blood vessels and thus the age-related stiffness induces a (fast) evolution of age-related macular degeneration (ARMD). VC also increases the incidence of cerebral lacunar infarctions via decreased diastolic flow and increased pulsatility, leading to symptomatic dementia.

Taken everything into account, EC has a significant impact on society; CV disease by itself - the major cause of mortality and morbidity in EU - accounts for 1.9 million deaths and a cost of 210 billion Euro per year. While this highlights the promise of EC as a hitherto overlooked target for risk stratification, diagnosis and preventive intervention, a comprehensive understanding of the causes of EC is still missing. The strength of this ITN is that it will provide a response to the unmet need to understand the mechanisms of EC and that – due to an increasingly elderly population – it will benefit the whole society.

Studies of rare hereditary EC disorders have been instrumental in understanding particular aspects of EC pathophysiology, which are anticipated to be applicable

also to acquired diseases and aging as well. For example, the hallmark multisystemic EC disorder pseudoxanthoma elasticum (PXE), in which we demonstrated accelerated aging processes, has been essential for our understanding of the metabolism of inorganic pyrophosphate (PPi), a calcification inhibitor which is significantly decreased in PXE but also in e.g. CKD patients. In the latter, PPi levels are inversely correlated with CV disease risk and mortality. The liver transporter ABCC6, deficient in PXE, was shown to be the main source of plasma PPi. Further, the retinopathy of PXE bears high similarities with ARMD. Very recently, ABCC6 and systemic PPi were associated with the health of the intervertebral disk and axial skeleton.

Similarly, in progeria syndromes characterized by clinical features mimicking physiological aging at an early age, EC occur in at least one-third of patients. They are considered models for human aging and several molecular mechanisms implicated in progeria such as DNA damage response and epigenetic changes are also involved in EC and in physiological aging.

These examples show that hereditary diseases provide a unique opportunity to identify genetic background, pro-and anti-calcifying molecules, metabolic and epigenetic factors that contribute to the development, phenotypic consequences and severity of EC which are translatable to common disorders and natural aging. However, the role of these factors is still only partially uncovered and needs to be clarified. By integrating and expanding our knowledge on these factors, INTEC offers a unique setting for new discoveries and education. The anticipated research, education and dissemination of results will improve diagnosis and risk stratification in hereditary and common disorders and as such contribute to healthy aging for the general population, based on a deepened understanding of consequences and causes of EC.

Münster

Münster – enchantingly old, excitingly young

1648 – now a long time gone, but a date that still remains charged with historic significance for Münster, and indeed the whole of Europe. However, 1648 is now also a place – one that is still very new, but also very light and bright, and located high above the gables and rooftops of the Old Town .

Stadt Münster/Patrick Schulte

“1648” is the name of a new café situated on the top floor of the Stadthaus building, situated right in the heart of town, and offering a breathtaking panoramic view that reaches far out into the surrounding countryside. It is also a wonderful starting point for obtaining an overview of the shape of this ancient, but at the same time so youthful city. However, you really must then come down and experience at first hand how Münster lives and breathes. All it takes is a few steps across the small, tranquil Platz des Westfälischen Friedens (Square of the Peace of Westphalia) with its famous Chilida sculpture, and you find yourself amid the urban hustle and bustle of the Prinzipalmarkt .

Stadt Münster/Maren Kuiter

And here, in the heart of the 1200-year-old Hanseatic city, you only need to take a look around to understand why Münster numbers among the "Historic Highlights of Germany". After all, European history was written in Münster when, in 1648, the Peace of Westphalia was signed which finally ended the 30 Years’ War. That is why, in testimony to this, Münster’s Historical Town Hall with the Peace Hall – together with its counterpart in the city of Osnabrück – bears the “European Cultural Heritage Label”. The panorama of the proud gabled merchants’ houses on the Prinzipalmarkt, the iron cages suspended from the tower of Lamberti Church that serve as a memorial to the bloody end of

the Anabaptists, a few steps further to the mighty St. Paulus Cathedral, the baroque Schloss that now serves as the headquarters of one of Germany's biggest universities, the magnificent churches and elegant aristocratic houses – they all tell the story of a rich and eventful city history.

Yet in Münster, you never have the sense of being in a museum. Even in the historic centre of the city, you can feel a youthful heartbeat at every step. And no surprise, with 60,000 students at nine universities and institutes of higher education in the city, filling Münster with exuberant life and also new faces every year. Students account for 20 percent of the population – no other German city of over 300,000 inhabitants has such a high proportion.

So old, and at the same time so young – it is therefore no surprise that in this "City of Science and Lifestyle", surprises and seeming mismatches are the order of the day: Take, for example, the only Picasso Museum in Germany with the world's biggest collection of graphics by the artist, located behind the facade of a Westphalian aristocratic town house. Gems of baroque architecture rubbing shoulders with icons of contemporary building design. Or clubs where the in-crowd goes located in old industrial buildings. Elegant up-market shops under the arcades of the Prinzipalmarkt, and latest fashion finds to be made in trendy concept stores – and at the same time, just round the corner, farm produce fresh from the surrounding Münsterland region, organic specialities and delicious Mediterranean foods, all on offer at one of Europe's most attractive outdoor markets. A young woman musico-logist appointed as "Türmerin", one of the city's oldest offices, tasked with watching over the city and blowing her horn nightly from the heights of Lamberti Church tower.

Stadt Münster/Britta Roski

And talking of music: a symphony orchestra with a tradition stretching back more than 100 years – and at the same time a Music School and a Faculty of Music that both keep Münster's sound scene well-supplied with new talent. And then the most unlikely couple of all: a snobbish professor paired with a rough-and-ready St.Pauli football fan. Completely unthinkable! Not in Münster. This duo – Professor Boerne and Inspector Thiel, characters in German TV's "Tatort" crime series – are, along with Wilsberg, the off-beat investigator on the rival ZDF channel, among the city's best-known and best-loved ambassadors.

It is precisely this delightful mix of tradition and modernity that gives Münster its special feeling. It is the same arc that is spanned by the "Courtyard" architecture of the LWL-Museum für Kunst und Kultur – the biggest of Münster's more than 30 museums. Between them, they cover a spectrum ranging from the thousand-year-old Cathedral Treasures, to the very latest works on display in the Kunsthalle or created in or around the Art Academy. And right in the middle: Gerhard Richter's artwork "Two Grey Double Mirrors for a Pendulum" – an oscillating Foucault pendulum, to be experienced in the deconsecrated Dominican Church (Dominikanerkirche), which is due to be closed briefly for renovation; a place of stillness, it has become a magnet for all those seeking a little rest and calm.

Stadt Münster/MünsterView

However, the city owes its reputation on the worldwide arts scene first and foremost to the "Skulptur Projekte", an event staged for the first time in 1977 and held every 10 years since then, that attracts hundreds of thousands of art lovers from the whole world, and whose leitmotiv is "art in public spaces". This motto manifests itself in the over 60 sculptures – including works by Claes Oldenburg, Ilja Kabakov and Henry Moore that can meanwhile be found dotted throughout the city.

But also in other ways, the public spaces in Münster are put to effective use as a stage. For example, when the local tradespeople invite the public to the long table for the traditional Hanseatic Repast. Or when "Schauraum", the Festival of Museums and Galleries, conjures up a cool lounge atmosphere on a red carpet. Or at "Münster mittendrin", the annual city festival, that does all honour to its name – with stages and stands scattered all over the Old Town. And also the cyclists in the Sparkassen Münsterland Giro and the runners in the Volksbank Münster Marathon are always keen to feel the atmosphere of the Prinzipalmarkt on entering the home straight. Alongside these established events, a vibrant young scene constantly finds new niches to use for its experiments: the "Hawerkamp", for example, a former industrial site that has become a hot spot of the nationwide Independent scene, complete with its own clubs and festivals.

But for all the things to see and do, the Münster feeling also means always having air to breathe. Everywhere, whether on foot – and even more so by bicycle, Münster's favourite means of transport – it is possible to find green refuges: on the Promenade, in the paradise of the Botanical Garden behind the Schloss, or by the Aasee Lake, where the outdoor steps and terraces also offer a hint of maritime flair. Or by venturing a little further out, into the park-like Münsterland countryside with its wonderful moated manor houses.

And back in the bustle of town, you can still decide what to do: A guided tour in the footsteps of the Anabaptists, perhaps? And what about this evening – go to the opera or take in the latest avant-garde dance event? Maybe stay in Münster for an extra day? Or make sure to come back again very soon?

Text: Münster Marketing

Programme
Day 1 – September 14, 2023

9.00 Welcome address
Frank Rutsch (Meeting organization) and Olivier Vanakker (INTEC coordinator)

9.20-10.40 **Invited Talks: Preclinical Treatment Models/Studies**
Chairs: Flora Szeri & Georges Leftheriotis

Nanoparticles as possible treatment option for ectopic calcification
Alexander Jones, Elastrin Therapeutics, USA

Pyrophosphate – therapeutic option for different diseases associated with ectopic calcification. An overview.
Viola Pomozi, Research Center for Natural Sciences, Hungary

Activation of the DNA damage response in ectopic calcification diseases – treatment with PARP inhibitors including minocycline.
Lukas Nollet, Ghent University Hospital, Belgium

10.40 Coffee Break

11.10-12.25 **Invited Talks: Clinically Relevant Endpoints and/or Biomarkers for Clinical Studies**
Chairs: Jessica Bertrand & Tamas Aranyi

Vascular calcification as endpoint in ectopic calcification
Wilko Spiering, University Medical Center Utrecht, Netherlands

Eye complications in PXE and current treatment modalities
Bojan Sontacchi, General Hospital Cakovec, Croatia

Programme
Day 1 – September 14, 2023

Calciprotein particles at the interface of bone and vessels (Online-Talk) Andreas Pasch, Calciscon, Switzerland

12.25 Lunch Break

14.00-15.15 **Selected Oral Presentations**
Chairs: Dijana Sontacchi & Hervé Kempf

Reversion and inhibition of porcine aortic valve calcification in vitro using therapeutic nanoparticular formulations and chelating agents
Anja Feldmann, Muenster University Children's Hospital, Germany

Bruch´s membrane calcification in pseudoxanthoma elasticum: comparing histopathology and clinical imaging
Imre Lengyel, Queen's University Belfast, United Kingdom

Evidence that pyrophosphate acts as an extracellular signalling molecule to exert direct functional effects on osteoblasts and vascular smooth muscle cells
Isabel R. Orriss, Royal Veterinary College, London, United Kingdom

Clinical case
Juan Luis Carrillo-Linares, Hospital Virgen de la Victoria, and Instituto de Investigaciones Biomédicas (IBIMA), Málaga, Spain

Inhibition of 5-lipoxygenase reduces valvular calcification by prevention of ferroptosis
Sven-Christian Pawelzik, Karolinska University Hospital, Stockholm, Sweden

Programme
Day 1 – September 14, 2023

15.15 Coffee Break

15.45-17.00 **Invited Talks: Clinical Studies**
Chairs: Vicky McRae & Olivier Vanakker

Therapeutic strategy for Pseudoxanthoma Elasticum ectopic calcification disorder: the PROPHECI study
Georges Leftheriotis, University Hospital of Nice, France

Clinical trials on ENPP1 Enzyme Replacement Therapy
Yves Sabbagh, Inozyme Pharma, USA

Inositol phosphate derivatives as candidate products to inhibit ectopic calcification
Carolina Salcedo, ViforPharma – Sanifit, Switzerland

17.00 Wrap up

19.00 INTEC Network Event

Programme
Day 2 – September 15, 2023

9.00 **Selected Oral Presentations**
Chairs: Viola Pomozi & Lukas Nollet

An ex vivo human calcified tissue explant model to study the response of cells in the cartilage-bone interface to cytokines and TGF-β
Andrea Schwab, Otto-von-Guericke-University Magdeburg, Germany

High frequency of BCP but less CPP crystal-mediated calcification of cartilage and synovial membranes in osteoarthritis patients
Sina Stücker, Otto-von-Guericke-University Magdeburg, Germany

Tracheal calcification: not so crystal clear!
Elodie Baptista, UMR 7365 CNRS-Université de Lorraine Vandœuvre-lès-Nancy, France

Achieving specific vascular targeting via antibody-linked albumin nanoparticles
Franziska Linß, University of Muenster, Germany

10.00 INTEC annual work meeting (for INTEC consortium members)

10.00 Workshop for Young Researchers about Career Development
"Using Individual Development Plans (IDPs) to Plan Your Career"
Dr. Orsolya (Uschi) Symmons, Research manager and certified systemic coach, Brussels, Belgium

13.30 Lunch and end of meeting

Nanoparticles as possible treatment option for ectopic calcification.

Alexander Jones, USA

Ectopic calcification disorders are challenging to treat effectively and carry a high burden of morbidity and mortality, particularly in Generalised Arterial Calcification of Infancy (GACI). There is little evidence that current therapies are able to significantly reverse established calcification, which is particularly important in GACI, where the associated arteriopathy can be advanced by the time of birth, contributing to a high infant mortality rate. Recently, a promising new class of antibody-targeted nanoparticle therapeutics has emerged that can reverse established arterial calcification in animals, restoring arterial elasticity. In one realisation, antibody-targeted albumin nanoparticles carry established chelators, such as ethylenediaminetetraacetic disodium acid, to sites of arterial elastin damage, concentrating the impact of the chelator where it is needed and limiting off-target effects. Such drugs would complement existing and emerging therapies, such as ENPP1 enzyme replacement, that slow or prevent progression of calcification, by offering an opportunity to "reset" arterial health in ectopic calcification disorders.

Pyrophosphate – therapeutic option for different diseases associated with ectopic calcification. An overview.

Viola Pomozi, Hungary

Pyrophosphate was long known to be an endogenous inhibitor of calcification, but since it was believed not to be absorbed, it was not considered as a therapeutic option. Instead, stable analogues (bisphosphonates) have been tested to prevent ectopic calcification in certain conditions.

However, in 2017 it was shown that pyrophosphate – even though with low

bioavailability – was absorbed when given orally. Since that, the inhibitory effect of pyrophosphate on soft tissue calcification has been tested in several in vitro and in vivo models. Animal models of diseases associated with ectopic calcification (e.g. PXE, GACI, diabetes…) have been studied, and based on these experimental results a few clinical trials have already been initiated.

Activation of the DNA damage response in ectopic calcification diseases – treatment with PARP inhibitors including minocycline.

Lukas Nollet, Belgium

The DNA damage response (DDR) is activated in response to DNA strand breaks or base pair alterations, thus maintaining genomic integrity and preventing malignant transformation of cells. However, excessive activation of the DDR is detrimental to cellular homeostasis and drives phenotypic switching of cells towards a disease-causing state. In this presentation, we describe the involvement of excessive DDR activation in the pathophysiology of ectopic calcification diseases, mainly focusing on the hereditary disorder pseudoxanthoma elasticum (PXE). The role of key DDR pathways, including poly(ADP-ribose) polymerase 1 (PARP1) signaling, in PXE pathogenesis will be illustrated based on our previous work in PXE patient-derived cells and tissues. Additionally, we show that pharmacological inhibition of excessive DDR activation using PARP inhibitors such as minocycline significantly reduces ectopic calcification burden in preclinical PXE animal models (Abcc6$^{-/-}$ mice, abcc6a$^{-/-}$ zebrafish). We conclude that pharmacological modulation of DDR mechanisms may be a promising therapeutic option in human patients suffering from acquired or Mendelian ectopic calcification diseases.

Vascular calcification as endpoint in ectopic calcification

Wilko Spiering, Netherlands

New treatment options arise for pseudoxanthoma elasticum (PXE), that need to be evaluated in randomized clinical trials. For this, validated endpoints are needed. As PXE is a slowly progressive disease, characterized by ectopic calcification of the arteries, measuring arterial calcification with imaging techniques is an interesting approach. We studied arterial calcification measured by ^{18}F-NaF PET-CT and standard CT in a randomized controlled trial, and prospectively with standard CT in a natural history cohort. The pros and cons of these techniques will be discussed. We conclude that arterial calcification increases in a linear fashion in PXE and that this can reliably be measured with standard CT. Measuring arterial calcification with standard CT should become the primary endpoint in future clinical trials in PXE.

Eye complications in PXE and current treatment modalities

Bojan Sontacchi, Croatia

Dr. Sontacchi will talk about ocular complications of PXE and the treatment regarding them (anti-VEGF intravitreal injections).

Calciprotein particles at the interface of bone and vessels.

Andreas Pasch, Switzerland

Calciprotein particles (CPP) are naturally circulating nanoparticles in the blood consisting of calcium phosphate crystals and proteins. Similar to lipoprotein particles, which serve to transport and excrete non-soluble lipids, CPP serve to transport and excrete otherwise insoluble mineral crystals. On the one hand, CPP are formed after ingestion of calcium and phosphate, but on the other hand, they are also released from bone. CPP are part of the natural mineral buffer system, which can also be assessed by the T50 test, which measures calcification propensity. CPP have an important physiological role, but may also become pathophysiologically relevant. Understanding CPP biology is expected to provide important insights into the mechanisms how pathological vascular calcification form. These insights could also become the basis for the evelopment of new drugs.

Therapeutic strategy for Pseudoxanthoma Elasticum ectopic calcification disorder: the PROPHECI study

Georges Leftheriotis, France

Pseudoxanthoma elasticum (PXE; OMIM 264800) is a rare inherited disease characterized by ectopic calcification primarily affecting the skin, retina, arteries, and kidneys. PXE is caused by mutations in the ABCC6 gene which encodes an ATP-binding cassette (ABC) transporter mainly present in hepatocytes and renal tubular cells. Calcification in PXE results from low circulating levels of pyrophosphate ([PPi]pl), a major inhibitor of ectopic calcification in soft tissues. Nowadays, the treatment of this debilitating and chronic disease becomes a scientific and therapeutic challenge. Restoration of physiological circulating levels of PPi is envisaged by different approaches, including supplementation with PPi donors and inhibition of PPi hydrolysis by extracellular enzyme systems. Oral administration of PPi salts (e.g. Na or K-PPi) has been demonstrated experimentally in various animal models and human. In humans, the PROPHECI (Pyrophosphate supplementation to fight ectopic calcification – NCT04868578) study is the first randomized, double-blind trial aiming at demonstrating the efficacy and safety of daily oral Na-PPi treatment for 12 months on ectopic calcification in PXE. This ongoing trial aims to include 99 PXE patients from the 2 largest French cohorts (Angers and Nice). Specific calcification biomarkers including calcification scores from CT and PET scans, ophthalmologic changes, arterial function, and PROMS are considered for the study. Preliminary report as well as hopes and pitfalls from the PROPHECI trial will be reviewed.

Clinical trials on ENPP1 Enzyme Replacement Therapy.

Yves Sabbagh, USA

ENPP1 is the major enzyme involved in the generation of pyrophosphate (PP_i), a potent inhibitor of calcification. ENPP1 Deficiency is a rare disorder due to inactivating mutations in the ENPP1 gene. It is characterized by low levels of inorganic PP_i, subsequent pathologic soft tissue calcification, results in ~50% infant mortality and life-long musculoskeletal and cardiovascular morbidities. No targeted therapy exists for this disease. Pseudoxanthoma elasticum (PXE) is a rare mineralization disorder caused by mutations in the ABCC6 gene. The ABCC6 protein transports nucleotides, including ATP, into the extracellular space where it is metabolized by the ENPP1 enzyme to AMP and inorganic PP_i. PXE therefore is associated with reduced levels of PP_i and ectopic calcification. Adults with PXE experience progressive dermatologic, ophthalmologic, and cardiovascular morbidities, and there are no therapies that target the underlying disease process. INZ-701 is a recombinant ENPP1-Fc investigational product which has demonstrated efficacy in preclinical mouse models of ENPP1 and ABCC6 Deficiency. We therefore evaluated INZ-701 in a Phase 1/2, Open-Label, Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics in adults with ENPP1 (NCT04686175) or ABCC6 (NCT05030831) Deficiency. In ENPP1 Deficiency, INZ-701 demonstrated a rapid and sustained increase in PP_i levels in all participants, was well tolerated, and exhibited a favorable safety profile. Improvements in GIC score were observed in 6/8 patients. In ABCC6 Deficiency, a PP_i dose response was observed, and at the highest dose (1.8 mg/kg) mean PP_i remained in the normal range through last data cut. INZ-701 was generally well tolerated and exhibited a favorable safety profile. These ongoing studies will elucidate the impact of INZ-701 on additional clinical and functional endpoints.

Inositol phosphate derivatives as candidate products to inhibit ectopic calcification

Carolina Salcedo, Switzerland

Vascular calcification and its progression are predictors of increased risk of cardiovascular events and mortality. Vascular calcification is a multifactorial and complex process, with the final common pathway, however, consisting of the deposition of solid calcium phosphate within the arteries, mostly in the form of hydroxyapatite. The strategies to inhibit vascular calcification range from managing individual factors that trigger calcification to directly targeting the formation of the hydroxyapatite crystal using crystallization inhibitors like pyrophosphate, bisphosphonates and inositol phosphates.

Inositol phosphates such as SNF472 have shown clinical efficacy in inhibiting cardiovascular calcification. SNF472 is the hexasodium salt of myo-inositol hexaphosphate ($InsP_6$), currently in clinical Phase 3. SNF472 directly inhibits the development and progression of ectopic calcifications by binding to the growing sites of the hydroxyapatite crystal and it showed a significant attenuation of vascular calcification progression in patients with end-stage kidney disease on dialysis. SNF472 is well tolerated, in both healthy volunteers and patients on haemodialysis. Research is ongoing with new approaches around $InsP_6$, by synthesizing new inositol 1, 2, 3, 5-tetraphosphate-4,6-derivatives, such as INS-3001, an inositol phosphate derivative resulting from the PEGylation of inositol tetraphosphate ($InsP_4$) at positions 4 and 6 with polyethylene glycol (PEG) 100 ($InsP_4$ bisPEG). We have developed a screening cascade platform to design, synthetise and test new $InsP_6$ derivatives, not related to PEGylation, to evaluate the effect of lateral chain modifications on the pharmacological, pharmacokinetic and safety properties in silico, in vitro and in vivo.

Selected Oral Presentations

Reversion and inhibition of porcine aortic valve calcification *in vitro* using therapeutic nanoparticular formulations and chelating agents

Anja Feldmann[1], Yvonne Nitschke[1], Franziska Linß[2], Jacqueline Bodes[2], Dennis Mulac[2], Klaus Langer[2], Frank Rutsch[1]

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[2]*Institute of Pharmaceutical Technology and Biopharmacy, Muenster University, Germany*

Pathological calcification within heart valves plays a major role in the development of cardiac diseases such as calcific aortic valve disease, in its end stage leading to aortic valve stenosis limiting heart function. Until today, surgical intervention remains the only option to treat aortic valve stenosis. Aim of this study was combining controlled drug delivery through nanoparticles (NP) and active targeting via antibody conjugation to develop a treatment for pathological calcifications within the aortic valve.

Human serum albumin-based NP were prepared using desolvation technique. The active chelating ingredient diethylenetriaminepentaacetic acid (DTPA) was covalently bound, NP surface was modified by conjugating antibodies (anti-elastin or isotype IgG control). Porcine aortic valves were used to simulate the pathologies mentioned above. Valves were incubated in osteogenic medium to induce calcification *in vitro*. To study reversion of calcification, valves were pre-incubated five days in osteogenic medium. Pure DTPA or specific NP formulations were added to observe an effect on the inhibition or reversal of calcification. Valves were analyzed for calcification (histology and quantification). Calcification could be inhibited with DTPA concentrations of 0.5-5 mg/ml medium. Existing calcification was effectively reversed with 1-5 mg DTPA /ml medium. Success in reversing calcification was further achieved with NP used at the amount of 1 mg DTPA equivalent. The specific anti-elastin antibody NP resulted in significant regression of calcifications compared with the isotype IgG-NP control.

These results represent a significant step towards the development of a novel effective therapeutic option using nanoparticular formulations for the resolution of aortic valve calcifications.

Bruch´s membrane calcification in pseudoxanthoma elasticum: comparing histopathology and clinical imaging.

Sara Risseeuw[1], Matthew G. Pilgrim[2], Sergio Bertazzo[3], Connor N. Brown[2], Lajos Csincsik[2], Sarah Fearn[2], Richard B. Thompson[4], Arthur A. Bergen[5,6], Jacoline B. ten Brink[5], Elod Kortvely[7], Wilko Spiering[7], Jeannette Ossewaarde – van Norel[1], Redmer van Leeuwen[1], Imre Lengyel[2]

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7. Roche Pharma Research and Early Development, Roche Innovation Center Basel, Basel, Switzerland
8. Department of Vascular Medicine, University Medical Center Utrecht, Utrecht University, The Netherlands

We investigated the histology of Bruch's membrane (BM) calcification in pseudoxanthoma elasticum (PXE) and correlated this to clinical retinal imaging.

Six post-mortem eyes from four PXE patients and one comparison eye from an anonymous donor were investigated. Calcification was labelled with OsteSense 680RD and visualized with confocal microscopy. Scanning electron microscopy coupled with energy-dispersive x-ray spectroscopy (SEM-EDX) and time of flight-secondary ion mass spectrometry (TOF-SIMs) were used to analyze the elemental and ionic composition. Findings on cadaver tissues were compared to the clinical imaging of one PXE patient.

Analyses of wholemount and sectioned PXE eyes revealed an extensive, confluent OsteoSense labelling in the central and mid-peripheral BM, transitioning to speckled labelling in the mid-periphery. These areas corresponded to hyperreflective and isoreflective zones in clinical imaging. SEM-EDX and TOF-SIMs analyses identified these calcifications as hydroxyapatite in the BM of PXE eyes. The confluent fluorescent appearance originates from heavily calcified fibrous structures of both the collagen and the elastic layers of BM.

Calcification was also detected in an aged comparison eye, but this was markedly different from PXE eyes and presented as small snowflake-like deposits at the posterior pole. PXE eyes show extensive hydroxyapatite deposition in the inner and outer collagenous and elastic layers in the macula, with a gradual change towards the mid- to far-periphery, which appears to correlate with the clinical phenotype. The snowflake-like calcification in Bruch's membrane of an aged eye used for comparison differed markedly from the extensive calcification in PXE.

Evidence that pyrophosphate acts as an extracellular signalling molecule to exert direct functional effects on osteoblasts and vascular smooth muscle cells

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Extracellular pyrophosphate (PP_i) is a well-known physiochemical mineralisation inhibitor. However, information describing its direct actions on cells remains limited. This study investigated the effects of PP_i (1-100μM) on osteoblasts and calcifying vascular smooth muscle cells (VSMCs). In osteoblasts, PP_i for the whole (0-21d) or latter stages of culture (7-21/14-21d) reduced bone mineralisation by ≤95%. However, PP_i for the differentiation phase only (0-7/0-14d) increased bone formation (≤70%). Prolonged treatment with PP_i resulted in earlier matrix deposition and increased collagen levels (≤2.3-fold). PP_i increased the expression of osteoblast *(RUNX2, Bglap)* and early osteocyte *(E11, Dmp1)* genes along with the mineralisation inhibitors *(Spp1, Mgp)* (≤3-fold). Tissue non-specific alkaline phosphatase (TNSALP) and ecto-nucleotide pyrophosphatase/phosphodiesterase 1 (NPP1) regulate extracellular PP_i levels. PPi reduced NPP1 but increased TNSALP expression (≤2.5-fold) and activity (≤35%). NPP1-mediated breakdown of extracellular ATP represents a key source of PP_i. Osteoblast ATP release was decreased ≤60% by PP_i. In VSMCs, PP_i (≥10≥M) decreased calcification (≤90%) and cell death (40%). PP_i also increased TNSALP activity (65%), reduced NPP1 expression and inhibited ATP release (80%). Pertussis toxin, which prevents $G\alpha_i$ subunit activation, was used to investigate whether G-protein coupled receptor (GPCR) signalling mediates the effects of PP_i. The actions of PP_i on bone mineralisation, collagen production, ATP release, osteoblast gene/protein expression and VSMC calcification were abolished or attenuated by pertussis toxin. PP_i also decreases intracellular cAMP levels (≤35%). Taken together these data show that PP_i directly regulates cell function in many ways and that these actions may be mediated by a $G\alpha_i$-linked GPCR.

CLINICAL CASE

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A 44-year-old male with a history of smoking, childhood dental surgery, and deep venous thrombosis in 2020 attributed to sedentary lifestyle and weight gain. Currently on acenocoumarol treatment.

Physical examination: Blood pressure 129/80 mmHg. Weight 83.5 kg. Height 160 cm. BMI 32.6. No noteworthy alterations.

Laboratory analysis reveals elevated creatinine levels and decreased phosphorus levels.

A CT scan showed calcified paravertebral masses along the entire thoracic and abdominal spine, as well as nephrocalcinosis. An MRI of the spine revealed multiple nodules appearing to correspond to the theoretical region of the spinal ganglion root, with nodular thickening evident at various levels in the cervical segment, particularly affected at C2/C3, and also in the lower cervical area. Virtually present at all dorsal levels, with a relatively uniform size of approximately 1.2 cm. Additionally, nodular formations are identified at lumbar and sacral levels, possibly more evident at the sacral level in all intervertebral foramina, which might correspond to neurinomas or spinal ganglia at that level.

Molecular study confirmed the presence of the c.721C>T (p.Gln241Ter) variant of the FAM20A gene in homozygosity. This variant is a nonsense mutation that predicts the substitution of a Glutamine amino acid with a premature stop codon at position 241. Pathogenic variants in the FAM20A gene have been associated with amelogenesis imperfecta, type IG (AI1G), also known as enamel-renal syndrome (ERS).

Diagnosis: Enamel-Renal Syndrome.

Inhibition of 5-lipoxygenase reduces valvular calcification by prevention of ferroptosis

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Calcific aortic valve disease (CAVD) progresses over time to severe aortic stenosis (AS) with impaired left ventricular outflow, heart failure, and mortality. The etiology of CAVD is unknown, although there is evidence that inflammation of the aortic valve (AV), intravalvular hemorrhage, and oxidative damage play a role. We demonstrated previously that non-heme iron accumulates in the AV, is taken up by valvular interstitial cells (VIC), and actively contributes to calcification. Here, we show that ferroptosis, a recently discovered form of programmed cell death involving iron overload and peroxidation of membrane lipids, is mechanistically involved in CAVD.

Using bioinformatics analyses of a biobank of human AS, we identified 54 ferroptosis-associated genes differentially expressed between non-calcified and calcified AV tissue. Calcified tissue showed significantly lower levels of the key ferroptotic suppressor GPX4, indicating prevalent ferroptosis in CAVD. On the other hand, ALOX5, coding for the inflammatory enzyme 5-lipoxygenase (5-LO), was significantly upregulated and associated with calcification markers.
In an *in vitro* model of induced ferroptosis, we demonstrated that inhibition of 5-LO by zileuton prevented ferroptotic cell death. Importantly, lipid peroxidation occurred also when VIC were cultured under osteogenic conditions, and the ferroptosis inhibitor ferrostatin-1 prevented calcification. Similarly, inhibition of 5-LO, but not of 5-LO activating protein (FLAP), rescued VIC from calcification under osteogenic conditions, indicating a mechanism independent of enzymatic inflammatory mediator formation.
In summary, these results demonstrate a direct 5-LO-induced effect on ferroptosis, and 5-LO inhibition by zileuton may provide therapeutic potential todelay onset, attenuate, or prevent progression of CAVD.

An ex vivo human calcified tissue explant model to study the response of cells in the cartilage-bone interface to cytokines and TGF-β

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The phenotype of cells residing in the calcified cartilage and its role in osteoarthritis disease progression is unknown. Here, we set up an *ex vivo* calcified tissue explant culture model to study the response of the chondrocytes residing in the calcified tissue to external stimuli.

Calcified tissue explants were isolated by cutting off the non-calcified cartilage and subchondral bone harvested from patients undergoing total knee replacement. After enzymatic digestion (protease 0.4% followed by collagenase-B 0.3%) explants (n=4 donors) were cultured in DMEM-LG containing antibiotics and 1% ITS. Non-calcified cartilage tissue explants were used as control group. After pre-culture both explant groups were stimulated (72h) with a cytokine cocktail (TNF-α, IL-1β, INF-γ, 1ng/ml) or TGF-β1 (10ng/ml). Mean values of qPCR data after explant stimulation (n=1-3 replicates per condition and donor) were used for statistical analysis. Gene expression of calcified tissue explants showed higher expression in *COL10A1* (p=0.0410), *SPP1* (p=0.0648), RUNX2 (p=0.0085) and lower expression of *COL2A1* (p=0.0412) and *ACAN* (p=0.0280) compared to non-calcified explants.

Calcified tissue explants responded to TGF-β1 with an increase in *COL10A1* (p=0.0410), non-calcified explants showed an increase in *COL10A1* (p=0.0320) and decrease in *ACAN* (p=0.0636) compared to control media.

Cytokine treatment resulted in an increased expression of *MMP13* (p=0.0065, p=0.0617), and a decrease in *RUNX2* (p=0.0375, p=0.0375), *ACAN* (p=0.0424, p=0.0280) in calcified and non-calcified explants. Non-calcified explants showed a decrease in *COL2A1* (p=0.0412). The calcified tissue explant culture model holds promise to study mechanisms at the cartilage-bone interface after stimulation with growth factors, cytokines, or pharmaceutical drugs.

High frequency of BCP but less CPP crystal-mediated calcification of cartilage and synovial membranes in osteoarthritis patients

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Objective: Ectopic articular calcification is a common phenomenon of osteoarthritic joints, and closely related with disease progression. Identification of the involved calcium crystal types represents an important topic in research and clinical practice. Difficulties in accurate detection and crystal type identification lead to inconsistent data on the prevalence and spatial distribution of BCP and CPP deposition.

Materials and methods: Combining multiple imaging methods including conventional radiography, histology and Raman spectroscopy, this study provides a comprehensive analysis of BCP and CPP based calcification, its frequency and distribution in cartilage and synovial membrane samples of 94 OA patients undergoing knee replacement surgery.

Results: Conventional radiography showed calcifications in 35% of patients. Von Kossa staining detected calcified deposits in 89% and 57% of cartilage and synovial samples, respectively. BCP crystals presented as brittle variably sized deposits on top of the cartilage surface or embedded in synovial tissue. CPP deposits appeared as larger needle-shaped clusters or dense circular pockets below the cartilage surface or within synovial tissue. Spectroscopic analysis detected BCP crystals in 76% of cartilage and 47% of synovial samples. CPP was only detected in 18% of cartilage and 13% of synovial samples, often coinciding with BCP.

Conclusions: BCP is the predominant crystal type in calcified cartilage and synovium while CPP deposition is rare, often coinciding with BCP. Distinct distribution and morphology of BCP and CPP deposits in joint tissues give rise to speculation that different diseases are involved that might need different treatment strategies.

TRACHEAL CALCIFICATION: NOT SO CRYSTAL CLEAR!

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Tracheal mineralization is a rare condition mostly found in the elderly population. However, tracheal calcification is also found in younger individuals suffering from pathological conditions such as Keutel Syndrome (KS), a rare genetic disease caused by loss-of-function mutations in the gene encoding the calcification inhibitor Matrix Gla Protein (MGP). Patients with KS show abnormal hydroxyapatite mineral deposition in most of the cartilaginous tissues, which is accompanied by respiratory complications including infections. In that context, we ought to understand the mechanisms at the origin of tracheal mineralization that has been unexplored so far and investigate the role of MGP in the process.

Our morphological and histological studies show surprisingly that wild-type mice present earlier tracheal mineralization than expected, as calcification appears in the first cartilage rings only 30 days after birth. This mineralization extends in a rostro-caudal pattern, through a process involving terminal differentiation of tracheal chondrocytes overexpressing the hypertrophic marker collagen X. We further demonstrated that *Mgp*$^{-/-}$ mice show signs of calcification in tracheal cartilage rings only 14 days after birth and also exhibit an unexpected and unforeseen calcification of their tracheal lamina propria.

The present study is the first to comprehensively describe mouse tracheal mineralization and provide evidence that calcification of the cartilage rings appears to be a sudden and early physiological event. It also authenticates MGP as a key factor in abnormal mineralization as *Mgp* deficiency accelerates tracheal cartilage mineralization and appears responsible for tracheal epithelium calcification, which could explain respiratory problems found in patients with KS.

Achieving specific vascular targeting via antibody-linked albumin nanoparticles

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Nanoparticles (NP) based on human serum albumin (HSA) represent ideal properties as drug delivery systems. Of crucial importance is the possibility of binding specific antibodies, which enable sufficient active drug targeting [1].
In this study two different ligand binding strategies were used to covalently bind antibodies to the HSA-NP surface. In both cases, coupling chemistry via reactive thiol-groups was used. However, free surface thiol-groups can cause unspecific nanoparticle-cell-interactions, which must be avoided in specific antibody targeting studies [2].

To evaluate these interactions modified NP were incubated with human umbilical vein endothelial cells (HUVECs) as target cells or epithelial human colon cancer cells (HT-29) as a comparative non-target cell line. To gain further insights into the possibility of addressing a vascular target, the interactions were not only investigated statically but also dynamically. As a model, HUVECs were cultivated in slides (Ibidi®) and exposed to a pulsatile laminar flow. The extent of interaction was observed by fluorescence microscopy. Additionally, quantitative confirmation was carried out by FACS analysis. The data clearly showed that free thiol-groups on the NP surface promote unspecific interactions on the tested cell lines. Avoiding free thiol-groups leads to specific binding to the target. This highly selective affinity was also significantly evident in the dynamic model simulating vascular conditions.

Therefore, antibody-linked HSA-NP represent a very promising platform for active drug-targeting within the vascular system.

1. Steinhauser, I. et al.: Biomaterials **2006**, 27 (28): 4975-4983
2. Torres, A., Gait, J.: Opinion **2012**, 30 (4): 185-190

Workshop

Using Individual Development Plans (IDPs) for Career Planing

Orsolya (Uschi) Symmons, Research manager and certified systemic coach, Brussels, Belgium

Navigating the complex landscape of scientific careers can be difficult: the competition for group leader positions is increasing, and there is often a lack of information about so-called "alternative" careers. Uncertainty about future career options in science is a major stress factor for early career researchers at all stages. The goal of this workshop is to eliminate some of this stress, by providing you with the tools to plan your career and design actionable next steps, regardless whether you want to pursue an academic career or look for positions outside of academia.

This workshop will provide you with a set of tools (collectively called "Individual Development Plan") that you can use flexibly for career planning purposes. Using a series of hands-on exercises and group discussions, you will learn how to conduct a structured self-assessment and analyse the assessment to outline career goals and design actionable next steps. As a neutral approach to assess your skills and to set career goals Individual Development Plans can be useful at any stage of scientific training, from BSc to postdoc level.

Topics covered:

- Overview and background of IDPs
- Guided self-assessment and evaluation of results (hands-on exercise)
- Goal setting, based assessment results (hands-on exercise)
- Common roadblocks in career planning and strategies to overcome them (group work)
- Optional: career paths inside and outside of academia (guided discussion)

About the trainer:
Orsolya (Uschi) Symmons is a molecular biologist by training, with research experience in Hungary, Germany, France, the UK and the US. She has been using IDPs for career planning purposes since 2015 (see, for example, here: Career Development: A Plan for Action, Nature 548, 489-490). She regularly works with them when mentoring and supervising early career researchers, who have continued both within and outside of academia. Uschi is certified as systemic coach by the University of Cologne and has been offering workshops on IDPs since 2019.

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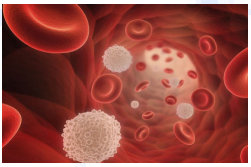
About Elastrin Therapeutics

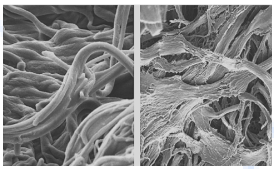
We are a US-based biotechnology startup leveraging a platform technology to develop medicines that restore hardened and damaged arteries and tissues by specifically targeting degraded elastic fiber. Elastin fibers are critical for the homeostasis of tissues around the body, including the skin, vasculature, and pulmonary tissues. As elastin fibers become damaged over time, arterial walls weaken, and the body's physiological response results in aortic wall stiffening, aneurysms, and hypertension. The Elastrin team has developed a platform called DESTiNED that can restore vascular health by removing pathological calcification specifically from sites where elastin has been degraded.

We are dedicated to prevent and reverse damaged elastic fibers

At least **one billion people** have life-threatening conditions linked to damaged elastin fibers.



We restore damaged elastin by using **drug-loaded nanoparticles** targeting damaged elastin.



Healthy elastin in **6-year old** child.

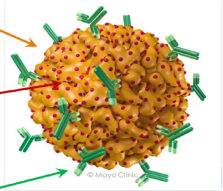
Damaged elastin in a **90-year old** person.

Our proprietary platform can selectively deliver drugs to damaged elastin

Human Albumin Nanoparticle
Safe vehicle to transport drug; charge & size optimized for targeting extracellular matrix; in clinical use for other therapies e.g. Abraxane

Drug
loaded into nanoparticle e.g. EDTA* to reverse calcification and PGG to restore damaged elastin

Humanized Antibody Flexibzumab®
Uniquely recognizes and binds to damaged elastin



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