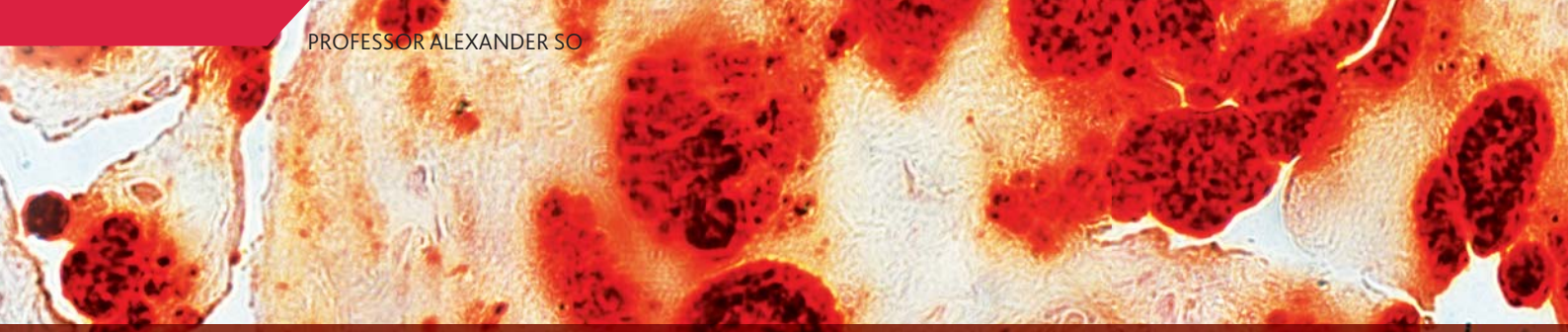


A joint effort in joint research

Crossing traditional discipline frontiers, the **European Crystal Network** is promoting and facilitating collaborative research efforts across Europe, aiming to deliver solutions to common rheumatic diseases

INFLAMMATORY DISEASES HAVE little regard for boundaries, crossing geographical borders and socioeconomic groups with ease. Scientists and healthcare practitioners throughout Europe have long struggled to solve the mysteries of common inflammatory conditions, such as gout, osteoarthritis and atherosclerosis, but now a new collaboration known as the European Crystal Network may just hold the key to improving our understanding of how these diseases work and what novel solutions may be within our grasp. Set up as a COST action, the Network's focus is to unite currently fragmented European research and to facilitate the pooling of research efforts.

One of the main goals of the Network is to build out knowledge of biological microcrystals, which are now known to be a major cause of inflammatory diseases. Whilst scientists do know that biological microcrystals probably share similar biological pathways, it is acknowledged that the way that these crystals are formed, breakdown and engage with the human body is not well understood. Seeking to cross the more conventional research boundaries to help create novel strategies for therapeutic intervention for inflammatory diseases, the Network are specifically addressing a number of key research areas. Some of these include researching how tissues react to crystals and how the mechanics of inflammation work, delving into crystal genesis and looking at how homeostasis and crystals actually form.

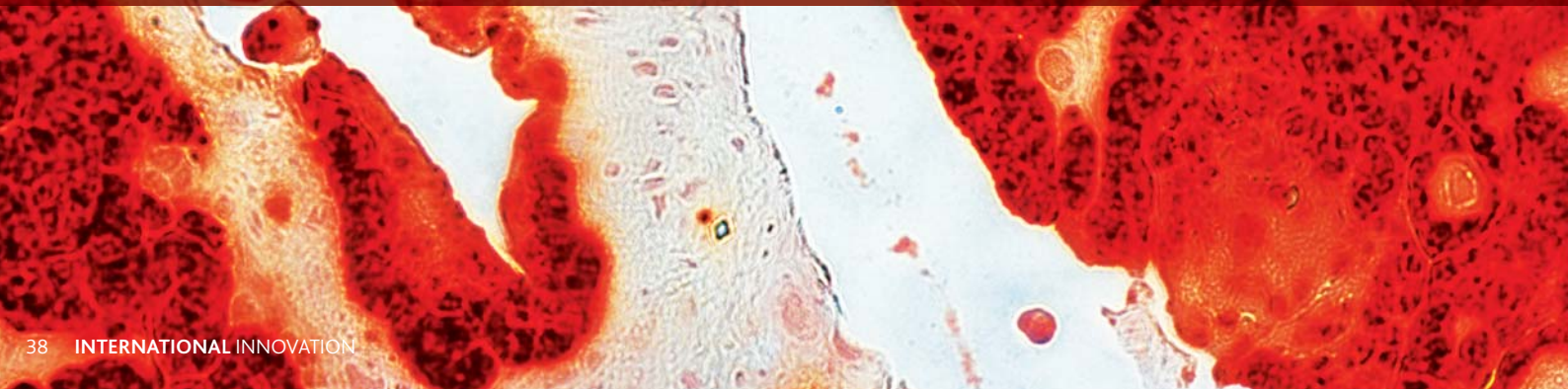
A EUROGOUT GENETICS CONSORTIUM

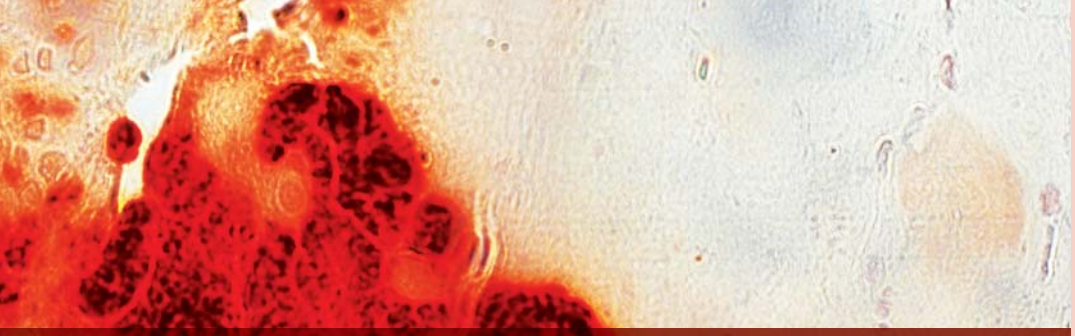
Professor Alexander Kai-Lik So from the Service de Rhumatologie of the University Hospital of Lausanne in Switzerland is one of the scientists responsible for leading the European Crystal Network. He explains that this European collaboration has been formed in order to support the exchange of scientific resources and personnel between different institutions across many countries, but to also help develop mutually beneficial interdisciplinary research. One of the Network's priorities that is of particular interest to him is looking at the role calcium containing microcrystals play in disease pathogenesis, specifically the way it affects osteoarthritis progression. From So's perspective, the Network will be key to helping him answer many of the questions arising from some of his latest research objectives: to better understand the mechanisms that underlie gout and to study the contribution of crystals in osteoarthritis. Gout, in particular, is one inflammatory disease with global reach and some of the latest epidemiological studies have drawn attention to the rate at which this disease is increasing throughout Europe and America. It is caused by an excess of uric acid, which may also have an impact on health by its effects on the cardiovascular and renal systems. With the support of the Network, So is establishing a cohort of gout patients in Europe and also setting up a consortium of genetics experts (EuroGout) which it is hoped will help to facilitate genetic and metabolomic analysis of this disease. So tells us that the inflammation that is associated with gout is understood to be triggered by the formation of monosodium urate (MSU) crystals, which is the result of persistent hyperuricemia: "As hyperuricemia is also linked to a number of other diseases, the EuroGout cohort will provide the perfect opportunity to study how disorders, like the metabolic syndrome and cardiovascular disease, interact with hyperuricemia on a genetic and biochemical level".

THE INNER WORKINGS OF CALCIUM CRYSTALS

The increasing research efforts going into microcrystals is not surprising given the significant burden on healthcare systems resulting from many of the chronic diseases for which these crystals are responsible. Whilst the research has been fragmented, it is clear that microcrystals hold one of the keys to pathological conditions and improving our knowledge of the mechanics of how these conditions are triggered will help with managing and treating inflammatory diseases.

The term microcrystals means particles that have originated from biological components that come in a micrometre size, such as urate, cholesterol and basic calcium phosphate (BCP). Whilst microcrystals are made up of different biochemicals, it is thought that the effect they have on cells and tissues are common across many types. For example, acute inflammatory responses can be caused by microcrystals due to the release of IL1b, a powerful inflammatory cytokine. A joint effort in research, crossing traditional discipline frontiers, the European Crystal Network, aims to promote and facilitate collaborative research efforts across Europe. One aim is to deliver solutions to three





The EuroGout cohort will provide the perfect opportunity to study how metabolic syndrome and cardiovascular disease interact with hyperuricemia on a genetic and biochemical level

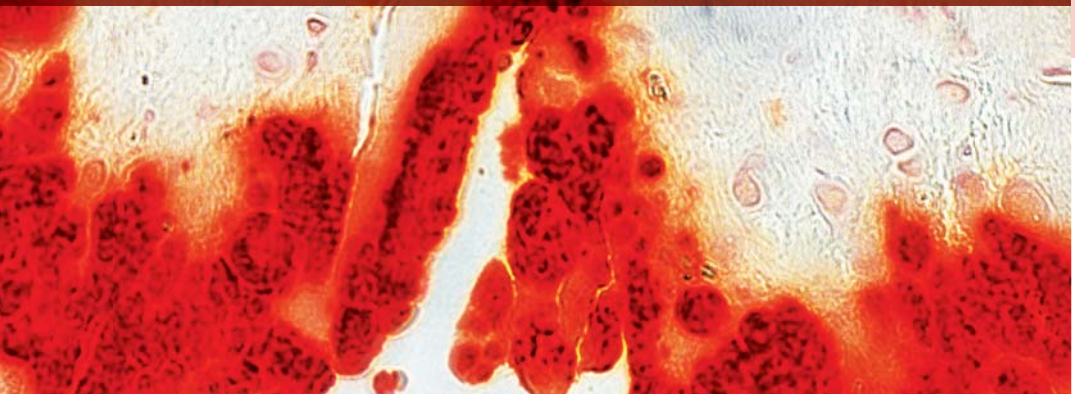
common rheumatic disease conditions that have now been clearly linked to the deposition of microcrystals, gout, calcium pyrophosphate and BCP crystals. BCP and pyrophosphate crystals are found in the cartilage of patients with osteoarthritis and may hold the key to explain why osteoarthritis progress differently in different individuals. Another key objective of the research collaboration is to share new data on the formation and effects of different biological microcrystals.

TARGETING THE CRYSTALS CAUSING INFLAMMATION

So's team is working on a project funded by the Swiss National Science Foundation which is specifically looking at what factors may modulate the effects of monosodium urate crystals on cells leading to inflammation. Titled 'Micro-crystal-induced joint inflammation, joint damage and the inflammasome', this research project is expected to identify the mechanisms that cause arthritis as well as the protective factors that can help to reduce inflammation. Their identification will hopefully lead to future targeted therapies. Part of the research strategy is the use of experimental animal models and genetically modified strains of mice in order to study how crystals impact on inflammatory processes, and how they modify the process of osteoarthritis.

Through these investigations, the common pathways in the human body which mediating not just joint inflammation but also other crystal-induced diseases can be found. The ultimate goal for any medical research project is to deliver real-life applications, and So looks forward to the day that his results can be used on human patients, however there are some hurdles to be overcome before this can be a reality: "To be able to apply our results in humans, the models that we are working on need to be refined to identify key pathways, which will then be addressed by targeted inhibitors or drug development to look for novel therapies".

One of the obvious benefits of pooling resources is that it means scientists have easy access to various other scientific disciplines, which they can then turn to for support and knowledge to help piece together their own research puzzle. But the Network is more than just a one-way street; it also provides an opportunity for scientists to access other research that is underway around Europe thus open the door for other potential applications. This work has numerous implications for a wide range of medical investigations, including research on hypertension, vascular disease and orthopaedics. Without the Network in place, these disciplines may not previously have known So's work. For example, the mechanisms regulating IL1β release are likely to be relevant to chronic diseases such as diabetes, atherosclerosis and pulmonary diseases. In addition, the Network is setting up an educational and training programme that it is hoped will stimulate young researchers to enter the field and help to enhance and build European capacity in this kind of research, thus laying the pathway for resilient and sustainable Europe-wide inflammatory disease research capabilities.



INTELLIGENCE

MICRO-CRYSTAL-INDUCED JOINT INFLAMMATION

OBJECTIVES

This research is focused on two main areas:

- The genetics of hyperuricemia and gout, for which a EUROGOUT genetics consortium has been established through members of the European Crystal Network
- The mechanisms of cellular activation of microcrystals and their participation in joint diseases, which includes studying how osteoarthritis in humans is modified by microcrystal deposition and looking at pathways that can be inhibited by targeted therapies in animal models

KEY COLLABORATORS

European Crystal network members: **Frédéric Lioté, Paris; Michael Doherty**, Nottingham • **Dominique Bazin**, Paris • **Ed Rooney**, Keele • **Michel Burnier** and **Bernard Thorens**, Lausanne • **Leo Joosten** and **Peter van Lent**, Nijmegen • **Tony Merriman**, New Zealand • **Naomi Schlesinger**, New Jersey

FUNDING

Swiss National Research Foundation • Fondation Novartis • Fondation Warnery • Fondation de l'association IAR (Institute of Arthritis Research) • Various pharmaceutical sponsored research grants

CONTACT

Professor Alexander So
Research Leader

Service de Rhumatologie
Department de l'Appareil Locomoteur
Avenue Pierre-Decker 4
CH-1011 Lausanne, Switzerland

T +41 21 314 14 50
E alexanderkai-lik.so@chuv.ch

ALEXANDER SO obtained his medical training in the UK. After qualifying from Cambridge University, he trained in internal medicine and rheumatology and pursued a PhD on the genetics of the HLA system at University College, London. He was appointed Senior Lecturer in Rheumatology at the Royal Postgraduate Medical School in London in 1990. In 1994, he was appointed Professor of Rheumatology at the University of Lausanne in Switzerland and currently directs a clinical department and laboratory research team.

Centre hospitalier universitaire vaudois

UNIL | Université de Lausanne