# Main Plenary Lecture

## THE RECENT RESOLUTION REVOLUTION & FRIENDLY MEDICINE

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The current global escalation in resistance to antibiotics is a serious threat, as it seems that the world is headed for a post-antibiotic era, in which common infections and minor injuries that have been treatable for decades could become fatal again. Recent studies, taking advantage of revolutions in various methodologies, open novel development in combating or controlling species-specific antibiotics and parasites resistance while preserving the microbiome and minimizing environmental hazards.

**KN1**

## HIGH-RESOLUTION X-RAY CRYSTALLOGRAPHY OF MEMBRANE PROTEINS AND MOLECULAR MECHANISMS OF MEMBRANE TRANSPORTERS

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Cells are surrounded by lipid bilayer, which cannot easily permeate even a water molecule. Membrane channels and transporters embedded in the membrane mediate transport of the target solutes (ions, sugars, metabolites and xenobiotics) across the membrane, which is driven by chemical potential energy of the solutes themselves or partner ions, to maintain the intracellular circumstances. More than 30% of human genes encode membrane proteins, while more than 50% of drug targets are membrane proteins, which suggests membrane proteins are essential not only scientifically but also for medical application. Recently, high-resolution structures of membrane proteins have been getting more and more available, due to the advancement of cutting-edge technologies to improve crystallization of membrane proteins by lipidic cubic phase72 crystallization method, and to collect X-ray diffraction data from micro crystals using micro-focus beam in the synchrotron (BL32XU in Spring-8). These advancements allow us to fully understand the molecular mechanisms of membrane channels and transporters at an atomic resolution; how the transport is driven, how the channel or transporter exclusively selects its target solute and how the transport is regulated. Our recent structural and functional analyses of transporters indicate that bending of transmembrane helices at Pro or Gly residues facilitates the transition between outward-open, occluded and inward-open conformations in the transport cycle, which is triggered by binding of substrates or counter ions.

**KN2**

## ENHANCING THE SUCCESS OF CRYSTALLISING BIOLOGICAL MACROMOLECULES

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Protein crystals play a pivotal role in facilitating rational drug design and other industrial applications. The past decade has seen momentous progress in the miniaturisation, automation and analysis of crystallization experiments. However, production of high quality crystals still presents a major barrier to structure determination; it is often the case that no crystals are formed at all or that clusters of useless crystals are obtained.

There is no 'magic bullet' that will guarantee the yield of useful crystals, hence rational approaches leading to the development of new and improved technologies for attaining high quality crystals is of crucial importance to progress.

This talk will present strategies for increasing the chances of success by highlighting a variety of practical methods that have led to successful crystallization when previous attempts had failed [e.g. 1-6]. Many of the techniques can be automated and adapted to high throughput/nanoscale experiments and several have been patented and commercialised. The design of smart materials and functionalised carbon nano-materials that have produced the first non-protein nucleating agents that can be used for

automated screening and optimization of bio-macromolecules will also be presented.

[1] Chayen and Saridakis (2008) *Nature Methods* 5, 147-153.

[2] Saridakis *et al.* (2011) *Proc. Natl. Acad. Sci. U.S.A*. 108, 11081-11086.

[3] Khurshid *et al.* (2014) *Nature Protocols* 9,Pages: 1621–1633.

[4] Khurshid *et al.* (2015) *Acta Crystallographica* D 71, 534-540.

[5] Govada *et al.* (2016) *Scientific Reports - Nature* 6:20053 DOI: 10.1038/srep20053

[6] http://www.imperialinnovations.co.uk/CRMIP

**KN3**

## THE IMPACT OF CRYSTALS AND CRYSTALLOGRAPHY IN ART AND CULTURE

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Along with the invaluable contribution of crystallography to the advancement of science and technology, the very idea of *crystal* has been highly influential in the world of art and culture. This influence has changed throughout history in correlation with increasing scientific knowledge about crystals. Since the origin of consciousness, hundreds of thousands of years ago, human fascination for crystals has been so deeply rooted in our brains as to shape our perception of patterns. During prehistory, crystals had teleological and theological connotations derived from a hidden power of their singularity among the natural objects. Later on, since the classical world to the emergence of positive science in the eighteenth century, scholars and experts endorsed mineral crystals with healing powers. The sheer beauty of the external forms of crystals and all they evoke fascinated educated people at that time. But the higher impact on mind and cultures started in XIX century. At that time, the extraordinary connection between the external harmony, redundantly beautiful symmetry of crystals, and the perfect internal order, periodic and iterative, was demonstrated. Since then, the word crystal is full of evocations such as purity, transparency, beauty, equilibrium, rationality, intelligence, energy, power . . . The notion of crystal transcended scientific thinking also to inspire the arts, from literature to painting, from architecture to dance, from music to filmmaking. Thus, the existence of a sharp boundary dividing the realm of biology and sensuality and the realm of minerals and cold rationality has pervaded the landscape of arts and philosophy for centuries. Crystals and crystallographic theories have played an important role in the intellectual construction of that proposed boundary. I will explore how well founded is such a centennial controversy between two opposite ways to understand and practice art and what the future holds. I will base the discussion of well-known historical artistic debates in which crystals were central to the controversy, and the last advances in the morphogenesis of crystalline materials.


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KN4

# WHAT BIOCRYSTALLOGENESIS TELLS US – WHAT IS NEEDED IN THE FUTURE

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Protein crystallization dates back to the 19th century, but became only recently a mature science thanks to strong *interdisciplinar* efforts based on physics, chemistry, biology, and associated technologies. Thus, many crystallization methods adapted to proteins were developed, but only a few are systematically used by structural biologists [1, 2]. Nevertheless, the number of successful crystallizations increased tremendously in the last two decades, leading to ~$10^5$ X-ray structures, covering alas only a restricted part of the *macromolecular diversity* and *3D-space* across the tree of life. This relies on idiosyncratic features of biomacromolecules making their crystallization mostly unpredictable, despite it is now well established that biocrystallogenesis is governed by the same physical rules than crystal growth of inorganic molecules. In another perspective, protein crystallization is a *self-assembly* process of particles of more or less defined chemical structure and conformation, with crystals being *supramolecular assemblies*. Empirical observations have shown that crystallizations can occur in the bulk of complex fluids, even *in vivo* for assemblies as large as ribosomes [3], and that purity favours the process [2]. Life also uses *self-assembly* and *supramolecular* processes leading mostly to *transient-* and fewer to *stable* complexes. An integrated view of supramolecularity implies that entities crystallizing or participating in biochemical processes require *determinants* and *anti-determinants*, that favour or disfavour *correct* or *incorrect* associations. Moreover, and as a result of *evolution*, biomacromolecules coexisting in a given biological context show a proper balance between features favouring or disfavouring such associations. If this balance is broken, cellular *disorders/diseases* may occur. Understanding these phenomena is a challenge for the future.

Altogether, these considerations trace the future of biocrystallogenesis research. Crystals covering the missing gaps in structural genomics have to be grown, especially for hydrophobic proteins and macromolecular complexes. Structural *dynamics* ("*4D-structures*" with time as the 4th parameter), conformational *plasticity*, and *allosteric* phenomena underlying biological processes should be better documented. For that, strategies combining X-ray crystallography with alternative technologies, including cryo-EM and computational tools, are needed [4]. Thus, crystallogenesis research remains essential in this quest. Amongst others, analysis of structures of apo- and liganded proteins captured *in crystallo* under different packing / solvent environments will help to understand their structural and functional plasticity. Knowledge of large panels of *thermodynamic compatible* structures, together with precise analysis of packing contacts and contacts within oligomers, will be crucial to decipher the chemical rules governing macromolecule *self-assembly*. This should moderate the recurrent idea claiming that atypical packing polymorphs are useless 'artefacts'. Understanding of crystal growth *in vivo* and under *crowding* conditions is anticipated, and rational-based engineering of biomacro-mo lecule crystallization becomes possible. *Self-assembly rules* will also be the guide for engineering novel biomaterials and, in a wider perspective, their understanding will open the route towards supramolecular biology [5].

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2. R. Giegé, *FEBS. J.*, **280**, (2013), 6456.
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