LECTURES

PL00

LIFE ON THE EDGE: THE NATURE AND ORIGINS OF PROTEIN MISFOLDING DISEASES

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Natural proteins are a highly select group of molecules, and their properties have a number of very special characteristics when compared to random sequences of amino acids, one of which is the ability to fold to unique and often highly intricate structures [C.M. Dobson, *Nature* 426, 884-890 (2003)]. This characteristic has enabled biological systems to generate a vast range of functions and an astonishing degree of specificity in their chemical processes. Great progress has been made recently in defining the conceptual basis and fundamental principles that underlie the folding of natural proteins. Of particular significance have been approaches that bring together biochemical and biophysical experiments with computer simulations to define the characteristics of the ensembles of protein structures that are populated *in vitro* at different stages of the folding process of individual proteins [D.M. Korzhnev, X. Salvatella, M. Vendruscolo, A.A. Di Nardo, A.R. Davidson, C.M. Dobson and L.E. Kay, "Low Populated Folding Intermediates of the Fyn SH3 Domain Characterized by Relaxation Dispersion NMR", **Nature 430**, 586-590 (2004)].

In addition, the roles of a wide variety of cellular processes associated with the folding of proteins *in vivo* are being unravelled, leading to an increasingly detailed understanding of the life cycles of proteins from their synthesis and degradation.

Because proteins are involved in every chemical process taking place within living systems, the failure of proteins to fold, or to remain correctly folded, can give rise to serious cellular malfunctions that frequently lead to disease. One particularly important group of such diseases is associated with the aggregation of misfolded proteins into remarkable thread-like structures known as amyloid fibrils [T.P. Knowles, A.W. Fitzpatrick, S. Meehan, H.R. Mott, M. Vendruscolo, C.M. Dobson and M.E. Welland, "Role of Intermolecular Forces in Defining Material Properties of Protein Nanofibrils", **Science 318**, 1900-1903 (2007)], and includes disorders ranging from Alzheimer's disease to late-onset diabetes, conditions that are becoming increasingly common in our aging populations. The manner in which the normal soluble forms of peptides and proteins can convert into these pathogenic amyloid structures is being uncovered by a wide variety of *in vitro* experimental studies along with theoretical simulations and bioinformatics studies [C.M. Dobson and F. Chiti, *Annu. Rev. Biochem.* 75, 333-366 (2006)]. As with folding, these studies are increasingly being linked to events occurring *in vivo* using a variety of strategies. Of particular interest are experiments an simulations designed to link the principles of misfolding and aggregation to the effects of such processes in model organisms such as *Drosophila* (the fruit fly) [L. M. Luheshi, G.G. Tartaglia, A.C. Brorsson, A.P. Pawar, I.E. Watson, F. Chiti, M. Vendruscolo, D.A. Lomas, C.M. Dobson and D.C. Crowther, "Systematic In Vivo Analysis of the Intrinsic Determinants of Amyloid-beta Pathogenicity", **PLoS Biol. 5**, e290 (2007)]. This talk will draw together some of the ideas that are emerging from recent work in our laboratory including evidence for the extremely narrow boundary between normal and aberrant behaviour [Tartaglia et al., *Trends Biochem. Soc*. 32, 204-206 (2007)], and how this concept sheds light on the origin, current proliferation and potential means of prevention of many of the diseases associated with misfolding.

PL01

CHEMICAL TOOLS FOR THE STUDY OF COMPLEX BIOLOGICAL SYSTEMS

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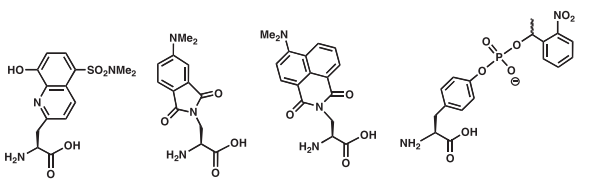
This presentation will discuss the design, synthesis and application of new chemical probes for studying complex biological systems. Due to the pivotal role played by of intracellular protein phosphorylation in all aspects of signal transduction, the focus of recent initiatives in the group has been on protein kinases and the phosphoprotein products of kinase-mediated phosphorylation as key targets for probe development.

In the area of kinase sensor development, novel amino acids including chelation-enhanced fluorophores, such as the sulfonamido-substituted 8-hydroxyquinoline, which is featured in the amino acid Sox, will be presented as robust building blocks for the modular assembly of selective and active chemosensors for a wide array of kinases including both Ser/Thr and Tyr kinases. In particular, recent studies on the semisynthesis and evaluation of highly selective probes for the MAP kinase ERK will be highlighted. Novel amino acids, such as DAPA and 4-DMNA, which include the environment-sensitive phthalimide and naphthalimide fluorophores will also be described together with applications in the diagnosis of peptide/protein and phosphorylation-dependent protein/protein interactions. Finally, the synthesis and application of caged phosphoamino acids, such as cpTyr, for examining phosphorylation-mediated cellular functions in living cells in real time will be highlighted.



Access to novel and versatile chemical probes for monitoring the causes and consequences of protein phosphorylation in living cells will ultimately enable us to define the spatial and temporal characteristics of protein kinases and phosphoprotein mediators in complex cellular pathways.

PL02

DRUG DISCOVERY FOR NEGLECTED DISEASES

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The fundamental role of the pharmaceutical industry is to discover, develop, produce, and deliver innovative products to prevent and cure diseases, to ease suffering, and to enhance the quality of life for patients worldwide. According to the World Health Organization, infectious diseases carry 10 percent of the global disease burden and cannot afford to be neglected any longer. One of Novartis' contributions to help reduce the global disease burden, and contribute to the solution of the problem of access to medicines to poor patients, is The Novartis Institute for Tropical Diseases (NITD). NITD is a drug discovery research institute dedicated to discovering novel therapies and preventive treatments for tropical diseases. In developing countries where those diseases are endemic, the Novartis Group intends to make treatments readily available without profit to poor patients. The investment in the field of tropical disease research is an exception in an industry that has traditionally neglected illnesses seen as endemic within the developing world, and NITD as a research center is the first of its kind to focus solely on drug discovery for infectious disease, using modern pharmaceutical research tools including high-throughput screens, and crystallography/NMR studies. It also houses a state-of-the-art biosafety level 3 lab.

The NITD was set up in 2002 as a public-private partnership between Novartis and the Singapore Economic Development Board. It is currently employing around 100 scientists and its research projects are focused on dengue fever, tuberculosis and malaria. The NITD performs basic and conceptual research for identification of targets, develops high throughput screening assays, and works on synthesis and optimization of compounds up to readiness for clinical testing.

The NITD also intends to become a leading centre for knowledge and education by offering exceptional teaching and training opportunities for biomedical scientists in the world and by transferring Novartis' drug discovery know-how to the developing world.

Starting from the early research activities, through later stages of the drug-development process and successful outreach to patients, the NITD promotes strong partnerships with other institutions and universities on a global scale to leverage its research efforts to bring novel therapies to patients by 2012. Some of the relationships built include leading members of the local, regional, and global scientific and clinical communities, international organizations such as the World Health Organization, and Health ministries of the region, as well as non-governmental organizations including: the Stop TB Partnership, the Drugs for Neglected Disease Initiative, the Global Alliance for TB Drug Development, Médecins Sans Frontières, the Grand Challenges for Global Health Foundation of the National Institute of Health, the Bill and Melinda Gates Foundation, the Wellcome Trust and the Medicines for Malaria Venture. The newest among those partnership initiatives is NITD - Eijkman Institute - Hasanuddin University Clinical research Initiative (NEHCRI) that aims to be effective in driving clinical research in dengue fever and tuberculosis, and possibly other tropical diseases, including malaria. The NITD will contribute its broad expertise in all aspects of drug discovery and development, as well as innovative technologies, financial support and training for the scientists and healthcare staff. The NEHCRI alliance will give researchers at NITD direct access to hospitals and patients in a real-life context on a daily basis. It will also provide a platform to lay the groundwork for the clinical development of new medicines against tropical diseases. Some more details on NITD's research efforts focused on finding antivirals for Dengue fever, new, faster acting antibiotics for tuberculosis that are effective on resistant strains, and new anti-malaria drugs aiming at a one-day cure will be presented.

PL03

STRATEGIES FOR THE DISCOVERY OF INNOVATIVE THERAPEUTICS

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Drug Discovery and Development is a challenging and complex process that involves the dedicated efforts of many multi-disciplinary R&D functions. Compared to the past, today's innovative drug discovery is more costly and time-consuming with fewer novel therapeutics making it to the market place. Traditional Medicinal Chemistry approaches adopted during the 1970s and 1980s were focused primarily on analoging of endogenous ligands and industry leads. Chemistry was low throughput and done iteratively, driven primarily by biochemical observations derived from animal testing. In contrast, the last decade has witnessed an evolution in Medicinal Chemistry approaches wherein automation was utilized effectively in the synthesis of large numbers of analogs Combinatorial Chemistry and rapid screening of large numbers of compounds (HTS).

At the turn of the century, deciphering of the human genome led to an explosion in the "-omics" technologies and, subsequently, the identification and characterization of large numbers of targets. The assimilation of the resulting information and correlation of potential therapeutic

targets with human diseases presents tremendous challenges for drug research. Nonetheless, advances in technology have enabled Pharma to explore multiple medicinal chemistry approaches in support of chemical biology efforts and to identify leads and optimize to drug candidates. These advances include improvements in structure-based design, integrating techniques of x-ray crystallography, computational chemistry and nuclear magnetic resonance spectroscopy, multivariate analysis, parallel synthesis and early pharmaceutical profiling. Additionally, application of these techniques, coupled with the growing field of biosynthetic engineering, precise synthetic methods and the use of high-resolution analytical tools has spurred renewed interest in natural product-based drug research.

The lecture will give a brief overview of the evolution of drug discovery and the various medicinal chemistry approaches from the past and present and with an outlook to the future.

AWARD LECTURES

AL01 - Nauta Award for Pharmacochemistry

CHANGING PARADIGMS IN DRUG DISCOVERY

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The strategies of drug design changed significantly over the past few decades. Whereas chemistry, biological activity hypotheses, and animal experiments dominated drug research, especially in its "golden age" from the 1960's to the 1980's of the last century, many new technologies developed over the past 20 years. A vast amount of new drugs was expected to result from combinatorial chemistry and high-throughput screening; however, the yield of new drugs was relatively poor. Molecular modelling, virtual screening and 3D structure-based design support the selection and rational design of high-affinity protein ligands. But high affinity to a disease-relevant target is only one condition; others are oral bioavailability, favourable pharmacokinetics, and a lack of unacceptable side effects and major toxicity; all these properties are most difficult to predict.

Despite the new technologies we observe a productivity gap in pharmaceutical industry: there is a sharp contrast between the increasing costs of drug research and development and the steady decline in the number of new chemical entities for human therapy. The presentation will shortly discuss the following questions:

- what are the reasons for the productivity gap between R&D costs and the number of new drugs (NCE's)?
- is there a "druggable genome"?
- is target focus always the best strategy?
- are we using the right virtual screening tools?
- is poor ADME the major hurdle in clinical development?
- what are the reasons for poor performance of ADME and toxicity predictions?
- what are the main problems in clinical studies?
- offers pharmacogenomics a hope for the future?

References

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AL02 - UCB-Ehrlich Award for Excellence in Medicinal Chemistry

AUTOMATED OLIGOSACCHARIDE SYNTHESIS AS PLATFORM FOR VACCINE DEVELOPMENT

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Cell surface oligosaccharides and glycosaminoglycans are important for signal transduction processes but also are markers for infectious agents and disease.[1] Described is the development of a fully integrated platform[2] based on automated oligosacharide sythesis[3] and carbohydrate arrays to address biological problems. Particular emphasis in this lecture will be placed on the new automated synthesis platform that will be made available to laboratories around the world. Microreaction systems constructed from etched silicon complement this automated synthesis system and are used for rapid reaction optimization as well as scale up for production.[4]

Based on the automated synthesis platform, carbohydrate arrays an be accessed for use in screening of proteins and blood sera.[5] These diagnostic tools are now beeing applied to correlate glycan expression and disease.