

Draft programme

Drug Targets in the Ubiquitin Proteasome System

Targetting the ubiquitin system for drug discovery and development

11-12 March, Crowne Plaza, Berlin, Germany

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CQ2172

Pre-Conference Symposium Monday 11th March 2008

Tools for identifying potential drug targets in the UPS

10.00 Coffee and Registration

10.30 Chairperson's opening remarks

10.40 Complexity of the UPS - insights from bioinformatics

The mammalian ubiquitin proteasome system comprises more than 1000 components involved in ubiquitin conjugation, deconjugation and recognition. In terms of complexity, the UPS is rivalled only by the phosphoprotein signalling network. Most UPS components are modular proteins, whose functional elucidation poses a big challenge for bioinformatics.

Hartmut Scheel, *Senior Scientist*, **Miltenyi Biotec GmbH**, Germany

11.20 Chemical tools to study action in the ubiquitin proteasome system

Drug development relies, at least partially, on robust tools that allow scoring for enzymatic action, protein-ligand, or protein-protein interaction. Chemical strategies to investigate action in the ubiquitin proteasome system will be discussed with special emphasis on the chemical design and use of probes directed at various enzymatic activities, including proteasome and DUB activities as well as the chemical and chemoenzymatic synthesis of ubiquitin and ubiquitin-like derivatives.

Huib Ovaa, *Chemical Biology Laboratory*, **Netherlands Cancer Institute**, The Netherlands

12.00 Lunch

14.00 IsoPro, a sensitive assay platform for measuring isopeptidase activity

Progenra has utilised the requirement of certain enzymes to have a free amino terminus for catalytic activity to develop a highly sensitive, reporter based assay platform (IsoPro) for quantitatively measuring ubiquitin and ubiquitin like protein isopeptidase activity. Examples of the ability of the IsoPro platform to enable high throughput screening and rapidly discriminate substrate specificity, as well as comparisons with alternative assay systems will be presented.

Ben Nicholson, *Director of Biology*, **Progenra**, USA

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14.40 Speaker to be confirmed

15.20 Afternoon Tea

15.50 Discussion Forum

Take this opportunity to ask your questions regarding techniques and tools available for identifying potential drug targets in the UPS. Join the day's speakers to assess:

- Assay developments
- Novel screens for identifying potential drug targets in the UPS
- Validating a ubiquitin pathway target
- Identifying substrates for DUBs or ligases (such as E3 ligase substrates)
- Bioinformatics approach to ubiquitin pathway target validation

16.20 Closing remarks from the Chair

16.30 Close of Symposium

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Day One Tuesday 11th March 2008

08.30 Coffee and Registration

09.00 Chairperson's opening remarks

09.10 KEYNOTE PRESENTATION: New insights into proteasome function and new opportunities for drug development

The 26S proteasome is a large proteolytic complex that catalyses the degradation of proteins linked to ubiquitin chains. Dr. Goldberg will review recent insights into its mechanism, regulation, and physiological roles. The core 20S particle contains multiple proteolytic sites that are the targets of the various proteasome inhibitors, including Bortezomib (PS341, Velcade), which is now widely used in the treatment of multiple myeloma. Its 19S regulatory complex binds and disassembles the ubiquitin chains and utilises ATP to unfold protein substrates and translocate them through the narrow gated channel into the 20S particle. This multistep complex process offers many opportunities for drug development.

Professor Alfred Goldberg, *Department of Cell Biology*, **Harvard Medical School**, USA

THE ROLE OF THE UPS IN CANCER

09.50 Targeting of P53 by small molecules: A novel strategy to combat cancer

We have recently identified a low molecular weight compound, named RITA, which reactivates wild-type p53 in tumours via blocking its interaction with MDM-2. The molecular mechanism of action includes binding to p53, which induces conformational change and prevents interaction of p53 with its negative regulators. RITA did not suppress the growth of non-transformed fibroblasts, in spite of the efficient disruption of p53/MDM-2 interaction. This correlated with only transient elevation of p53 levels. In sharp contrast, in tumour cells RITA treatment induced sustained p53 accumulation and expression of p53 target genes. This provides the evidence that RITA is not harmful for normal cells. Indeed, RITA was not toxic for mice *in vivo*. Using human xenografts in scid mice we demonstrated that RITA has significant p53-dependent anti-tumour effect *in vivo*. The specificity of RITA-induced response was demonstrated using DNA microarray analysis comparing the gene expression profiles after RITA treatment in isogenic lines, which differ only in their p53 status. The great majority of differentially expressed genes were observed in wtp53 cells, including a number of known p53 targets. In contrast, gene expression in p53-null cells was largely unaffected by RITA. The major

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efforts for identification of HDM-2 inhibitors are focused towards HDM-2-binding molecules. We show that targeting p53 could be a valuable strategy for its re-activation in tumour. An unexpected mechanism of p53 activation discovered with the help of RITA might help to open completely novel avenues for further research aimed at p53 reactivation.

Galina Selivanova, *Associate Professor, Dept of Microbiology, Tumour and Cell Biology, Karolinska Institute Stockholm, Sweden*

10.30 Morning Coffee

11.00 INDUSTRY CASE STUDY: Small-molecule inhibitors of the p53-MDM2 interaction for cancer therapy

MDM2 is a specific E3 ubiquitin ligase that controls p53 stability and activity through an autoregulatory feedback loop. We have developed selective small molecule

antagonists of p53-MDM2 binding, the Nutlins, which interact with the p53 pocket of MDM2 and free p53 from negative control. Treatment of cancer cells with nutlins stabilises and activates wild-type p53, leading to cell cycle arrest and apoptosis *in vitro* and *in vivo*. By disrupting the p53-MDM2 regulatory circuit nutlins cause p53 and MDM2 upregulation, but may not interfere with other p53-independent functions of MDM2. Our data suggest that elevated MDM2 contributes to antitumor activity of nutlins at least in part by facilitating MDMX degradation. Therefore, inhibition of the p53-MDM2 interaction appears to be a more effective strategy for therapeutic p53 activation than inhibition of MDM2 E3 ligase activity.

Lyubomir Vassilev, *Senior Research Leader, Discovery Oncology, Hoffmann-La Roche Inc., USA*

11.40 DUBs and disease

Deubiquitinating enzymes (DUBs) can counterbalance the action of ligases such as MDM2, similar to the way phosphatases oppose the action of kinases. In this presentation, Dr Huib Ovaa will provide an overview on DUBs and detail the latest scientific advances in this field. Assessments of the avenues for inhibition of DUBs action in oncology and other areas will also be addressed.

Huib Ovaa, *Chemical Biology Laboratory, Netherlands Cancer Institute, The Netherlands*

12.20 Lunch

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THE UPS'S ROLE IN NEURODEGENERATIVE, INFLAMMATORY AND IMMUNE DISEASE

14.00 Diversity of proteasomal missions: fine tuning of the immune response

Substitution of constitutive proteasomal subunits with immuno-subunits leads to conformational changes in the substrate binding channels, resulting in a modified protein cleavage pattern and consequently, in the generation of new antigenic peptides. The recently discovered event of proteasomal peptide splicing opens new horizons in the understanding of additional functions proteasomes apparently possess. Both α -interferon induced immuno-proteasomes and peptide splicing represent two significant events providing increased diversity of antigenic peptides for flexible and fine-tuned immune response.

Professor Michael Groll, *Department of Chemistry, Technical University of Munich*, Germany

14.40 The role of the UPS in antiviral immune response

As part of their immune surveillance system, vertebrate cells display antigenic peptides of defined quality from intracellular pathogens (especially viruses) via MHC class I molecules at the cell surface. The MHC class I/peptide complex can then be recognised by specific cytotoxic T cells for the elimination of infected cells. The UPS and with it the 20S core complex, the proteasome, are the major source for the proteolytic generation of virus derived antigenic peptides. Interferons are major modulators of this antiviral activity of the UPS as evidenced by the induction of proteins, such as immunosubunits, PA28, POMP, conjugating enzymes etc. that directly affect antiviral proteasome function. Using HCV – and bacterial infections as examples we provide experimental evidence on how the UPS can be exploited to suppress the sometimes fatal consequences of infection.

Professor Peter Michael Kloetzel, *Institute for Biochemistry, Charité-Universitätsmedizin Berlin*, Germany

15.20 Afternoon Refreshments and Speed-Networking Session

15.50 Parkin: An E3 ubiquitin ligase implicated in Parkinson's disease

Parkinson's disease (PD) is the most common movement disorder and the second most common neurodegenerative disease after Alzheimer's disease, affecting an increasing number of patients due to the demographic trend towards an aged population. The etiology of sporadic PD is only poorly understood, thus the identification of genes which are associated with familial variants of PD was a major breakthrough. Insight into the function of these genes can promote our understanding

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of the molecular causes of PD and help to focus research on key biochemical pathways. Mutations in the parkin gene, encoding an E3 ubiquitin ligase, are responsible for the majority of autosomal recessive PD. Recent research revealed that parkin has a remarkably wide neuroprotective capacity, preventing cell death under various stress conditions. It will be discussed how parkin can promote neuronal integrity through degradation-dependent or -independent ubiquitylation pathways.

Konstanze Winklhofer, *Department of Biochemistry, Ludwig-Maximilians - University Munich*, Germany

16.30 Discussion Forum – New ideas and future trends

As this field grows and new inhibitors and pathways of the UPS are identified, it is important to consider the possible future direction of this exciting new field. Join us for our end of day discussion forum with the speakers from the day and take this opportunity to ask your questions by emailing the producer at tahira.rashid@informa.com.

17.55 Closing Remarks from the Chair

17.00 Close of Day One

Drinks reception in the Exhibition Hall with the delegates from the four other conferences

Evening Seminar Evening of Tuesday 11th March 2008

This working dinner will begin at 18.00 for a 18.15 start and will finish no later than 21.00. Dinner, wine and refreshments will be provided.

Analysis of the structure of the HECT and RING-finger E3s can reveal insights into the function of these ligases. Join our specially selected speaker panel to discuss this topic and more.

E3 ligases - different architectures, different points of attack

While E1 and E2 enzymes for ubiquitin are structurally rather uniform, the E3 ligases come in different shapes and sizes. Structural and computational biology have shown that for most E3s the two unit functionalities - substrate recognition and ubiquitination - are encoded by different structural domains or different complex subunits. This division of labour allows to target these two processes independently, although

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druggability of E3s is hampered by the nature of the interaction surfaces. Another layer of complexity is introduced by the requirement of certain E3s for modification by Nedd8. The structural aspects of this modification are just beginning to be understood.

Kay Hofmann, *Head of Bioinformatics, Miltenyi Biotec GmbH*, Germany

HECT E3 ligases in human disease

For more information regarding this presentation please refer to our website

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Professor Martin Scheffner, *Laboratory of Cellular Biochemistry, University of Konstanz*, Germany

RING finger E3s as drug targets

Many RING finger containing E3s have been implicated in disease processes including cancer and neurodegenerative diseases. This presentation will assess the function of the RING finger proteins in relation to their structure and will detail how this can provide opportunities for drug development.

Peter Jackson, *Genentech*, USA

Discussion

Day Two Wednesday 12th March 2008

08.30 Coffee and Registration

09.00 Chairperson's opening remarks

PROTEASOME INHIBITORS

09.10 INDUSTRY CASE STUDY: Transcending proteasome inhibition for the treatment of cancer: development of MLN4924 – an inhibitor of NAE

Inhibition of proteasome function in cancer cells has been shown to disrupt protein homeostasis resulting in cancer cell death. The clinical utility of this concept has been demonstrated by the proteasome inhibitor, bortezomib, which is approved for the treatment of multiple myeloma and mantle cell lymphoma. This precedent suggests that compounds targeting other components of the ubiquitin-proteasome system (UPS) could prove useful for the treatment of human malignancies.

The Nedd8-activating enzyme (NAE) has been demonstrated to be an essential component of the Nedd8 conjugation pathway which controls the activity of a subset of UPS E3 ligases that are responsible for the timely ubiquitination and

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subsequent degradation of proteins with important roles in oncogenesis. Millennium has identified novel small molecule inhibitors of NAE, exemplified by MLN4924, that induce apoptosis in human tumor-derived cell lines *in vitro* and result in dramatic tumor growth inhibition in cancer animal models *in vivo*. These preclinical findings represent the foundation to support transition of MLN4924 into human clinical trials.

Joseph Bolen, *Chief Scientific Officer, Millennium Pharmaceuticals, USA*

09.50 INDUSTRY CASE STUDY: Targeting the proteasome with NPI-0052

NPI-0052 is a highly potent proteasome inhibitor derived from a novel marine-obligate actinomycete and is being evaluated for the treatment of multiple myeloma, lymphomas and solid tumors. Due to the success of Velcade™, the proteasome is a high interest drug target. In preclinical studies, NPI-0052 appears superior to Velcade and shows: 1) a broader and longer lasting proteasome inhibition profile; 2) efficacy against Velcade, Revlimid™, Thalomid™ and dexamethasone resistant tumor cells from multiple myeloma patients; 3) efficacy against a wider range of tumors, including many solid tumor models; 4) less cytotoxic to normal cells; 5) a 7 to 10 fold higher *in vivo* potency; 6) potential for administration both orally and by intravenous injection on a once-a-week schedule; 7) marked enhancement of efficacy when used in combination with chemotherapeutics and biologics such as Avastin™, Erbitux™, irinotecan, FOLFOX, FOLFIRI, and oxaliplatin. We will present our latest findings from our Phase I clinical trials.

Michael Palladino, *Senior Vice President, Chief Technology Officer and Scientific Co-founder, Nereus Pharmaceuticals, USA*

10.30 Morning Coffee and Networking Session

11.10 INDUSTRY CASE STUDY: Development of peptide epoxyketone proteasome inhibitors in oncology and autoimmune disease

We have developed a series of mechanistically- and structurally-novel proteasome inhibitors based on the peptide epoxyketone natural product, epoxomicin. Our lead molecule, carfilzomib (PR-171), is a highly potent and selective inhibitor of the chymotrypsin-like activity of the proteasome. Intensive daily dosing schedules with carfilzomib have been found to be well tolerated and efficacious in both preclinical and Phase I clinical studies. Carfilzomib is currently being evaluated in two Phase II trials in multiple myeloma and a Phase Ib/II trial in solid tumors. Additional peptide

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epoxyketone proteasome inhibitors with distinct biochemical and pharmacological properties have been identified. These include two molecules currently under development: PR-047, an orally bioavailable proteasome inhibitor that is well tolerated and efficacious in preclinical xenograft models; and PR-957, a selective inhibitor of the hematopoietically-restricted immunoproteasome that has shown promising activity in preclinical models of autoimmune disease.

Mark Bennett, *Vice President of Research*, Proteolix, USA

11.50 INDUSTRY CASE STUDY: The ubiquitin/proteasome system and androgen receptor function

The role of the ubiquitin/proteasome system in degrading nuclear hormone receptors and regulating their transcriptional function has emerged in recent years. Studies with several nuclear receptors including the androgen receptor (AR) demonstrate that an intact proteasome pathway is necessary for full activity. This can be explained by cyclic recruitment of transcriptional activators and of their cofactors to responsive promoters followed by degradation, as an ultimate and necessary step of the transcription process. This model suggests that new transcriptionally active complexes are formed as long as a sustained response is needed and permits tight control of gene expression. Data on the effects of proteasome inhibitors on AR function will be shown. In addition, the role of ubiquitin-specific protease 10 in modulating

Bernard Haendler, *Principal Scientist, Therapeutic Research Group Oncology*, Bayer Schering Pharma AG, Germany

12.30 Lunch

E3 LIGASE AND DUB INHIBITORS

14.10 INDUSTRY CASE STUDY: Identification and characterisation of ubiquitin-specific protease (USP) small molecule inhibitors: A new class of potential cancer therapeutics

Genome-wide RNAi screens of the catalytically active human USP in cancer relevant cellular models and phenotypic assays identified USP7 and USP8 as attractive cancer targets. Chemical screening and medicinal chemistry based optimisation conducted on these targets led to the identification of a novel series of cyano indenopyrazine derivatives as novel and potent USP inhibitors. One of our lead compounds, HBX 41,108, reversibly inhibits USP7 catalytic

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activity and exhibits dose-dependent antiproliferative activity. Reminiscent of RNAi-mediated USP7 silencing, HBX 41,108 stabilises and activates p53 in a non-genotoxic manner, leading to cell growth inhibition and p53-dependent apoptosis as demonstrated using p53 wild-type and null isogenic cell lines. A related compound displaying exquisite USP8 selectivity in vitro exhibited antiproliferative and pro-apoptotic activities with sub-micromolar GI50 in different cancer cell lines and induced a marked increase in total cell protein ubiquitination, recapitulating the phenotypes observed in USP8 knock-down cells. Preliminary in vivo studies evaluating the anti-tumoral activity of these compounds will be presented.

Frédéric Colland, *Head of Biological Research, Hybrigenics SA*, France

14.50 INDUSTRY CASE STUDY: The search for small molecule inhibitors of E3 ubiquitin-protein ligases

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Nathan Bays, *Senior Research Biochemist, Automated Lead Optimisation, Merck & Co., Inc.*, USA

15.30 Afternoon Tea

16.00 INDUSTRY CASE STUDY: Discovery and characterisation of novel deubiquitinase inhibitors

The aberrant activity of ubiquitin/ ubiquitin like protein isopeptidases has been linked to a number of pathologies, most notably cancer. In particular, the deubiquitinating enzymes USP7 (HAUSP) and USP2a have been validated as anticancer targets. More than 100 isopeptidases have been reported; Progenra has expressed and tested many (~65) of them with its highly sensitive IsoPro assay platform allowing the identification of potent, selective USP7 and USP2a inhibitors. Data for candidate compounds that selectively target USP7 and USP2a for anticancer activity will be presented.

Ben Nicholson, *Director of Biology, Progenra*, USA

16.40 INDUSTRY CASE STUDY: Drugability of DUBs - A case study using UCH-L3

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Martin Renatus, *Expertise Protease Platform, Structural Sciences Unit, Novartis Pharma AG, USA*

17.20 Chair's closing remarks

17.30 Close of Conference

Post-Conference Symposium Thursday 13th March 2008

Protein-Protein Interactions as Drug Targets

09.00 Coffee and Registration

09.30 Opening remarks from the Chair

09.40 Inhibition of protein-protein interactions with small organic molecules

Protein-protein interactions form the basis for most cellular signalling events, and are therefore an emerging class of small-molecule targets in both basic and applied research. Recent developments in the discovery of small-molecule inhibitors in our group will be discussed. These include inhibitors of transcription factors, a family of proteins widely considered to be not amenable to functional modulation by small molecules.

Thorsten Berg, *Junior Group Leader, Max Planck Institute of Biochemistry, Germany*

10.20 Novel PPI inhibitors by Fragment-based Drug Discovery

Protein-protein interactions (PPIs) pose substantial challenges to small molecule drug discovery. However notable examples, such as oral clinical phase II inhibitors of Bcl proteins, indicate that PPIs are drugable. Here we demonstrate how we tackle PPIs by fragment-based drug discovery, namely biochemical and NMR-aided fragment screening followed by crystallographic protein-fragment structure determination and fragment-to-lead chemistry. Our case studies confirm that novel, binding efficient, small molecule inhibitors of PPIs can indeed be identified and optimized towards drug leads. However robust fragment assays sensitive to K_d values above 250 μM, are mandatory to detect such loose PPI binders in the first place.

Dr Marcus Schade, *Vice President NMR Drug Discovery, Evotec AG, Germany*

11.00 Morning Coffee Break

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11.30 Protein-protein interactions in compartmentalized cAMP signalling as potential drug targets

Key players in compartmentalized cAMP signalling networks are A kinase anchoring proteins (AKAP) tethering protein kinase A (PKA), the principal effector of cAMP, and other signalling molecules to cellular compartments. Selective disruption of AKAP-dependent protein-protein interactions in *in vitro*, cell and animal studies has shown that the AKAP-dependent interactions are involved in a variety of physiological processes of which disturbances cause or are associated with a variety of major diseases. Here we demonstrate that AKAP-dependent protein-protein interactions play a role in controlling cardiac myocyte contractility and vasopressin-mediated water reabsorption in renal principal cells. Dysregulation of these cells causes cardiovascular and renal diseases, respectively.

Enno Klussmann, *Group Leader*, **Leibniz Institute for Molecular Pharmacology**, Germany

12.10 Investigation of phosphorylation profiles in cell lysates or tumour homogenates using peptide microarrays

Protein tyrosine kinases are a very important family of enzymes involved in cell signaling. Signals are propagated by phosphorylation of tyrosine, serine and threonine residues in target proteins. We have developed a peptide microarray assay in which up to 256 different target protein-derived peptides are immobilized on a chip. One microarray is the size of a single microtitre plate well, and can be used both in a 4-array as well as a 96-array format. Kinase activity present in a sample incubated on an array results in peptide dependent phosphorylation detected by fluorescence. The unique features of this technology are the convenient mix-and-measure format and the kinetic readout, enabled by the porous nature of the array surface. In a single 96-array experiment several thousand kinetic phosphorylation curves are generated in parallel. This is a convenient and powerful method for investigating kinase activity profiles in cell lines or tumour tissue homogenates. We have used this assay format to investigate, amongst others, the effect of kinase inhibitors on kinase activity profiles. Finally, the alteration of kinase activity in cells after physiological stimulation has been investigated. These microarray-based applications in kinase research and their relevance for drug discovery in oncology will be discussed.

Rinie van Beuningen, *Vice President Technology*, **PamGene International BV**, The Netherlands

12.50 Networking Lunch

14.00 Targeting Chemokine Receptors with Protein Epitope Mimetics (PEM)

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Over the past ten years Polyphor Ltd in collaboration with Prof. John Robinson at the University of Zurich have developed the Protein Epitope Mimetics (PEM) Technology with the aim to discover and develop new selective inhibitors of protein-protein interaction targets of therapeutic value. This talk will show how PEM Technology has been successfully applied to the discovery of novel inhibitors of some chemokine receptors.

A case study describing the discovery and development of potent and selective CXCR4 inhibitors (currently undergoing phase I clinical trials) with therapeutic applications in stem cell transplant, cancer and inflammation, will highlight the full potential of PEM Technology.

Daniel Obrecht, *Chief Scientific Officer, Polyphor Ltd*, Switzerland

14.40 Large-scale human protein-protein interaction maps: A tool for finding the magical bullets against complex diseases?

The assembly of a comprehensive map of human protein-protein interactions, or the so called human interactome, has become a major goal in the post-genomic era. Such a map promises not only to serve as foundation for detailed models of cellular processes, but also as a powerful tool in the rational design of new treatments of complex human diseases. However, the challenges in assembling and analysing the human interactome are considerable due to the intrinsic complexity of molecular networks. In my talk, I will give an overview about the current efforts to construct comprehensive maps of human protein interactions and introduce our database called UniHI (www.mdc-berlin.de/unihi) which provides biomedical researchers a direct and convenient entry gate to the human interactome. Finally, I will discuss approaches how to utilize the assembled data to elucidate human diseases on a systems level.

Matthias Futschik, *Institute for Theoretical Biology, Charite - School of Medicine, Humboldt University*, Germany

15.20 Discussion Forum

Protein-protein interactions regulate a wide variety of important cellular systems and therefore represent a highly populated class of drug targets for drug discovery. Join us and our speakers to discuss the following topics and more in our discussion forum.

- Specificity of protein-protein interactions
- Structural data analysis and application
- Future directions as drug targets

13.50 Closing remarks from the Chair

16.00 Close of symposium and afternoon refreshments