Drug Discovery- Bench to Bedside

Frankfurt 21st & 22nd Sept 2017

Building 23, lecture hall 4, University Hospital Frankfurt, Theodor-Stern-Kai 7, 60590 Frankfurt.

Thursday 21st Sept		
9.00-11.00	Overview of the drug discovery process ▪ Target ID and validation ▪ Assay development ▪ High throughput screening ▪ Hit identification ▪ Lead optimization ▪ Pre-clinical animal testing	Corrado Santocanale
11.00-11.30	*Coffee*	
11.30-13.00	Structural studies for drug discovery	Stefan Knapp
13.00- 14.00	*Lunch*	
14.00-14.30	Question and answer session on careers in industry	Corrado Santocanale, Stefan Knapp, Maximilian Plach, John Patterson, Sandra Healy
14.30 – 15.30	Biophysical analysis for drug discovery	Maximilian Plach
15.30- 16.15	IRE1 drug discovery- Case Study	John Patterson
16.15-16.30	*Coffee*	
16.30-17.30	IRE1 drug discovery-Case Study cont	John Patterson
Friday 22nd Sept		
9.00 – 13.00	Clinical Drug Discovery • Phase I Clinical development • Phase II Clinical development • Phase III Clinical development • Regulatory approval	Marie Mellody
13.00 - 14.00	*Lunch*	
14.00- 15.00	CAR Cells: Engineering patients' immune cells to treat their cancers	Evelyn Ullrich
15.00- 17.00	Case study	Corrado Santocanale

Profiles of course providers

Corrado Santocanale

Professor of Molecular Medicine
NUI GALWAY

Corrado received his Ph.D. in Cellular and Molecular Biology at the University of Milan, Italy, in 1993. His early work focused on the characterization of enzymes required for the duplication of the DNA in the yeast S. cerevisiae. He was then awarded an EU Marie Curie postdoctoral fellowship to work on the molecular mechanisms that control initiation of DNA replication at the Clare Hall Laboratories, Cancer Research UK, London.

He spent eight years in the pharmaceutical industry at the Oncology R&D site in Italy (former Pharmacia then Pfizer and now Nerviano Medical Sciences) both as a group and as a project leader developing protein kinase inhibitors for the treatment of human cancers. His major achievement in Cancer Drug Discovery was to propose and lead a program through all the stages of the pre-clinical drug discovery process delivering a compound with a novel mechanism of action that has entered clinical trials.

He returned to academia in 2007 to pursue his studies. His major achievements in basic cancer research include: - Identification and characterization of the "origin firing checkpoint", a biochemical pathway that is activated in response to the inhibition of DNA replication elongation thus preventing the activation of new replication origins. - Identification of the second "cyclin like" regulatory subunit of the human Cdc7 kinase. - The identification of a biochemical pathway, altered in cancer cells, responding to the inhibition of the Cdc7 kinase. Identification of the gene encoding the first eukaryotic DNA primase large subunit.

Research Interests

Research in his lab is centered on studying the mechanisms of DNA replication in cancer cells and exploiting the results of this research for therapeutic purposes. Active projects focus on understanding the cellular functions and regulation of Cdc7 kinase (A) and on characterizing inhibitors of Cdc7 kinase activity in Multiple Myeloma, Chronic Lymphocytic Leukaemia and Breast cancer (B). Recently his lab has developed a technique that will allow them to study how chromatin assembly is coupled with the duplication of DNA (C).

Selected publications

'An essential role for the Cdc6 protein in forming the pre-replicative complexes of budding yeast'
Cocker JH, Piatti S, Santocanale C, Nasmyth K and Diffley JF. (1996) 'An essential role for the Cdc6 protein in forming the pre-replicative complexes of budding yeast'.
Nature, 379 :180-182

'A Mec1- and Rad53-dependent checkpoint controls late-firing origins of DNA replication'
Santocanale C, Diffley JF (1998) 'A Mec1- and Rad53-dependent checkpoint controls late-firing origins of DNA replication'.
Nature, 395 (6702):615-618

'Drf1, a novel regulatory subunit for human Cdc7 kinase'
Montagnoli A, Bosotti R, Villa F, Rialland M, Brotherton D, Mercurio C, Berthelsen J, Santocanale C (2002) 'Drf1, a novel regulatory subunit for human Cdc7 kinase'.
Embo Journal, 21 (12):3171-318

'Cdc7 inhibition reveals a p53-dependent replication checkpoint that is defective in cancer cells'
Montagnoli A, Tenca P, Sola F, Carpani D, Brotherton D, Albanese C, Santocanale C (2004) 'Cdc7 inhibition reveals a p53-dependent replication checkpoint that is defective in cancer cells'.
Cancer Research, 64 (19):7110-7116

'Identification of Mcm2 phosphorylation sites by S-phase-regulating kinases'
Montagnoli A, Valsasina B, Brotherton D, Troiani S, Rainoldi S, Tenca P, Molinari A, Santocanale C (2006) 'Identification of Mcm2 phosphorylation sites by S-phase-regulating kinases'.
Journal Of Biological Chemistry, 281 (15):10281-10290

'Cdc7 is an active kinase in human cancer cells undergoing replication stress'
Tenca P, Brotherton D, Montagnoli A, Rainoldi S, Albanese C, Santocanale C (2007) 'Cdc7 is an active kinase in human cancer cells undergoing replication stress'.
Journal Of Biological Chemistry, 282 (1):208-21

“A Cdc7 kinase inhibitor restricts initiation of DNA replication and has antitumor activity.”
Montagnoli A, Valsasina B, Croci V, Menichincheri M, Rainoldi S, Marchesi V, Tibolla M, Tenca P, Brotherton D, Albanese C, Patton V, Alzani R, Ciavolella A, Sola F, Molinari A, Volpi D, Avanzi N, Fiorentini F, Cattoni M, Healy S, Ballinari D, Pesenti E, Isacchi A, Moll J, Bensimon A, Vanotti E, Santocanale C.
Nat Chem Biol. 2008 Jun;4(6):357-65

'Cdc7-dependent and -independent phosphorylation of Claspin in the induction of the DNA replication checkpoint'
Rainey, MD,Harhen, B,Wang, GN,Murphy, PV,Santocanale, C (2013) 'Cdc7-dependent and -independent phosphorylation of Claspin in the induction of the DNA replication checkpoint'.
Cell Cycle, 12 :1560-1568

'The Deubiquitinase USP9X Maintains DNA Replication Fork Stability and DNA Damage Checkpoint Responses by Regulating CLASPIN during S-Phase'
McGarry E;Gaboriau D;Rainey MD;Restuccia U;Bachi A;Santocanale C; (2016) 'The Deubiquitinase USP9X Maintains DNA Replication Fork Stability and DNA Damage Checkpoint Responses by Regulating CLASPIN during S-Phase'.
Cancer Research, 76 (8)

Stefan Knapp
Professor & Group Leader
Buchmann Institute for Molecular Life Sciences
Goethe University Frankfurt,

Research Area: Protein Science and Structural Biology
Technology Exchange: Drug discovery and Protein interaction
Keywords: Kinases, Phosphatases, Cancer, Drug design and Crystallography

Stefan obtained his PhD from the Karolinska institute in 1996 and carried out postdoctoral work at the Karolinska and at the University of Paris. He was appointed as a Principal Scientist at Pharmacia Corp in 1999 – 2004. He then became a Principal Investigator at the Structural Genomics Consortium/ University of Oxford, UK where he remained until 2015. He then moved to Frankfurt where he is a group leader at the Buchmann Institute for Molecular Life Sciences at Goethe University Frankfurt.

Research

Cellular functions are tightly controlled by complex signalling networks and dysfunction of these networks often lead to development of diseases. Protein interactions and post-translational modifications such as protein phosphorylation play a key role in signal transduction networks by regulating the assembly of signalling complexes and by controlling the activity of enzymes that regulate signalling flux. Only few components of signalling cascades have been studied in detail and the role of many enzymes and scaffolding proteins in signalling remains therefore enigmatic. Our research group is interested in the molecular mechanisms that regulate cellular signalling networks and how these mechanisms can be exploited for the design of selective inhibitors.

My group at the Structural Genomics Consortium (SGC) determined a large number of high resolution crystal structures that led to a comprehensive structural coverage of large protein families such as protein kinases, phosphatases as well as protein interaction domains. Family wide structural comparison revealed novel and often unique mechanisms of regulation as well as unique binding pockets. We are exploring these regulatory mechanisms for the development of highly selective chemical tool compounds (chemical probes) that can be used to unravel signalling pathways and to explore the utility targeting signalling molecules for the development of novel treatment strategies for diseases.

We are particularly interested in epigenetic reader domains, small protein interaction modules that “read” the epigenetic code in chromatin and play a critical role controlling gene expression programs. Probe development efforts led now to an almost complete chemical tool kit for human bromodomains, a family of acetyl-lysine dependent epigenetic reader domains. In addition, we are developing novel strategies targeting protein kinases, a large superfamily of signalling enzymes that principally control phosphorylation dependent pathways and that are among the most frequently mutated enzymes in cancer.

Selected publications (out of >200)

KNAPP S, ARRUDA P, BLAGG J, BURLEY S, DREWRY DH, EDWARDS A, FABBRO D, GILLESPIE P, GRAY NS, KUSTER B, LACKEY KE, MAZZAFERA P, TOMKINSON NC, WILLSON TM, WORKMAN P, ZUERCHER WJ . 2013. A public-private partnership to unlock the untargeted kinome. *Nat Chem Biol*, **9** (1), pp. 3-6.

FILIPPAKOPOULOS P, PICAUD S, MANGOS M, KEATES T, LAMBERT JP, BARSYTE-LOVEJOY D, FELLETAR I, VOLKMER R, MÜLLER S, PAWSON T, GINGRAS AC, ARROWSMITH CH, KNAPP S . 2012. Histone recognition and large-scale structural analysis of the human bromodomain family. *Cell*, **149** (1), pp. 214-231.

FEDOROV O, MÜLLER S, KNAPP S. 2010. The (un)targeted cancer kinome. *Nat Chem Biol*, **6**(3), pp. 166-169

BARR AJ, UGOCHUKWU E, LEE WH, KING ON, FILIPPAKOPOULOS P, ALFANO I, SAVITSKY P, BURGESS-BROWN NA, MÜLLER S, KNAPP S. 2009. Large-scale structural analysis of the classical human protein tyrosine phosphatome. *Cell*, **136**(2), pp. 352-363.

FILIPPAKOPOULOS P, KOFLER M, HANTSCHEL O, GISH GD, GREBIEN F, SALAH E, NEUDECKER P, KAY LE, TURK BE, SUPERTI-FURGA G, PAWSON T, KNAPP S . 2008. Structural coupling of SH2-kinase domains links Fes and Abl substrate recognition and kinase activation. *Cell*, **134** (5), pp. 793-803.

Maximilian Plach
Chief Scientific Officer
2bind GmbH

2bind is one of the leading service providers for comprehensive biophysical analyses of all kinds of molecular interactions. With a broad set of techniques including MicroScale Thermophoresis (MST), Biolayer Interferometry (BLI), and Isothermal Titration Calorimetry (ITC), 2bind supports start-ups, medium-sized businesses, and big pharma and biotech players in characterizing affinities, kinetics, and thermodynamics of binding reactions in all stages of drug discovery, development, and validation. Since 2012, 2bind has taken part in over 180 early drug discovery projects, mainly in screening and validation approaches, as well as competition assays.

Maximilian has joined 2bind as the Chief Scientific Officer after receiving his PhD from the University of Regensburg in early 2017. During his studies in biochemistry and for his M.Sc., he spent several stints in the R&D department of Roche Diagnostics where he worked on the conjugation and characterization of diagnostic antibodies and developed novel methods for selective antibody cleavage. Maximilian has a strong background in protein-protein interactions, biophysical methods, bioinformatics, and molecular evolution. One main aspect of his PhD work was the identification and characterization of structural elements of protein complex interfaces that determine interaction specificity in large, orthologous protein families. He also designed variants of these elements that change the interaction specificity and behavior of the corresponding complexes, which are often found in pathogenic bacteria. His work received multiple awards, including the renowned Rainer-Rudolph award.

Selected publications

Mapping the Binding Site of an Aptamer on ATP Using MicroScale Thermophoresis
Entzian C., Schubert T., 2bind GmbH
J. Vis. Exp., 2017 Jan 7

Studying small molecule–aptamer interactions using MicroScale Thermophoresis (MST)
Entzian C., Schubert T., 2bind GmbH
Methods, 2015 Aug 31

Review: Studying epigenetic interactions using MicroScale Thermophoresis (MST)
Schubert T., Längst G., 2bind GmbH
AIMS Biophysics, 2015 Aug 21

MicroScale Thermophoresis: Method of Choice
Schubert T., 2bind GmbH
European Biopharmaceutical Review, 2015

The Arabidopsis THO/TREX component TEX1 functionally interacts with MOS11 and modulates mRNA export and alternative splicing events
Brian B. Sørensen, Hans F. Ehrnsberger, Silvia Esposito, Alexander Pfab, Astrid Bruckmann, Judith Hauptmann, Gunter Meister, Rainer Merkl, Thomas Schubert, Gernot Längst, Michael Melzer, Marion Grasser, Klaus D. Grasser.
Plant. Mol. Biol., 2017

John Patterson
Director,
MannKind Corporation

John obtained his BA from the University of California San Diego in 1985 in Cellular Biology and Biochemistry and a PhD from the University of California, Santa Barbara in 1995. He then moved to the Scripps Research Institute to carry out postdoctoral work molecular-viral immunobiology and pathogenesis. In 2000 he moved to the Allecure Corp where he was a Group Leader in Experimental Immunology overseeing diverse projects including vaccines, biologics and small molecules. In 2003 he started working as a principal scientist at Mannkind Corp and over the years he progressed to senior principal scientist, associate director and to his current position of Director of Mannkind Corp.

MannKind Corporation focuses on the discovery, development and commercialization of therapeutic products for patients with diabetes and cancer. It is a development stage business that currently specializes in the inhalable delivery of insulin. In the small molecule field, MannKind has focused on small molecule inhibitors of the IRE1. John works as a Director of MannKind Corp and has responsibility for research programmes across the business. He has a strong background in research and is developing open innovation initiatives to support the continued expansion of the business in this field of ER Stress. MannKind has been awarded one patent for *in vitro* assays and several compositions of matter patents for IRE1 inhibitors. The company has demonstrated proof of concept with IRE1 inhibitors in *in vivo* models of myeloma and collaborates with academic research teams studying the unfolded protein response.
John has extensive expertise in drug discovery related target validation, assay development, high-throughput screening, lead optimization and GLP pre-clinical studies.
His main interests are to discover, optimize and develop novel therapeutics, which impact patients with unmet medical need.

Selected publications

[1] Volkmann et al (2011) Potent and selective inhibitors of the inositol-requiring enzyme 1. J Biol Chem. 286:12743-55;

[2] Virrey et al (2008) Stress chaperone Grp78 confers chemoresistence to tumor-associated endothelial cells. Mol Cancer Res 6:1268-1275;

[3] Dong et al (2005) Vascular targeting and antiangiogenesis agents induce drug resistance effector Grp78 within the tumor microenvironment. Cancer Res 65:5785-91

Marie Mellody

Managing Director
Virtuoso Sarl,
Switzerland

Virtuoso Sarl is a Swiss-based company providing strategic and tactical clinical development consulting and services to the pharmaceutical, medical device and biotechnology industry.

Marie has spent 30 years working in all phases of Clinical Development in the pharmaceutical, biotechnology and contract research industry in the United States, United Kingdom, Ireland and latterly Switzerland.

A science graduate of NUI Galway, Marie has held clinical operations leadership positions at European and Global levels in Hoechst Marion Roussel, Abbott and Serono International S.A. and has service provider experience at the Institute of Clinical Pharmacology, ClinTrials and ICON.

Since 2004, Marie has developed an innovative, pan European clinical research network with the objective of identifying a more streamlined and fit for purpose approach to clinical development and clinical trials.

Since 2005, Marie has been engaged in the provision of lectures and training courses in the non-commercial and academic sector with the Ecole Polytechnic Federal Lausanne (EPFL) in "*Clinical Trial Management & Regulatory Affairs in Pharma and Biotech"* and with National University of Ireland Galway (NUIG) Masters in Clinical Research in Clinical Development. Marie has been a participant in and provides consulting to FP7 and H2020 consortia, as well as being an ethical and research evaluator for H2020, Innovative Medicines Initiative (IMI) as well as national research funding bodies.

Prof. Dr. med. Evelyn Ullrich
Head of the Cellular Immunology Unit,
Frankfurt University Hospital,
Germany

Evelyn studied medicine in Freiburg, obtained her MD degree in 2003 and further specialized in Internal Medicine and Immunology. As a postdoctoral stipend of the "German Research Community" (DFG) followed by a research fellowship of the "Foundation pour la Recherche Medicale" (FRM) she spent several years at the INSERM Unit for Tumor Immunology of Laurence Zitvogel, Institut Gustave Roussy, Paris-Villejuif. There, she qualified as a junior professor at the University Erlangen-Nürnberg where she headed a "Max-Eder Junior Research Group" funded by the German Cancer Aid. Since October 2012, she is professor at the LOEWE Center for Cell and Gene Therapy at the Goethe University Frankfurt. She is head of the Laboratory for Cellular Immunology at the Department of Child and Adolescent Medicine of the University Hospital.

The main scientific interest of the Ullrich lab focuses on cellular immunology and immunoregulation of immune deficiencies, malignant diseases, cancer therapy and stem cell transplantation. Preclinical studies aim to characterize specific functions and the complex interactions of subsets of T cells, dendritic cells (DC), natural killer (NK), cytokine induced killer (CIK) and innate lymphoid cells (ILCs). In the field of translational research, the Ullrich lab performs immunomonitoring studies of cancer patients undergoing specific treatments, autologous or allogeneic stem cell transplantation. Projects with focus on immunoregulation of graft-versus-leukemia (GVL) and graft-versus-host (GVH) effects in allogeneic stem cell transplantation have been supported by the German Cancer Aid and awarded with different international research prizes.

Beyond standard methods of molecular and cell biology, the Ullrich lab is specialized in flow cytometry, cell sorting and advanced in vitro and in vivo imaging methods. By use of these varieties of technics, the group aims to improve the activation and migration of adoptively transferred immune subsets for the optimization of cellular therapeutic protocols.

The overall research aims are the optimization of personalized cellular therapy combined with immunomodulation in patients with advanced malignant diseases.

In this lecture, she will give an update on personalized cellular therapy with focus on gene modified CAR immune cells products.

Selected publications

Wagner J, Pfannenstiel V, Waldmann A, Bergs JWJ, Brill B, Huenecke S, Klingebiel T, Rödel F, Buchholz CJ, Wels WS, Bader P, **Ullrich E**. A Two-Phase Expansion Protocol Combining Interleukin (IL)-15 and IL-21 Improves Natural Killer Cell Proliferation and Cytotoxicity against Rhabdomyosarcoma. Front Immunol. 2017 Jun 12;8:676.

Granzin M, Wagner J, Köhl U, Cerwenka A, Huppert V, **Ullrich E**. Shaping of Natural Killer Cell Antitumor Activity by Ex Vivo Cultivation. Front Immunol. 2017 Apr 26;8:458.

Fischer K, Tognarelli S, Rösler S, Boedicker C, Schubert R, Steinle A, Klingebiel T, Bader P, Fulda S, **Ullrich E**. The Smac mimetic BV6 improves NK cell mediated killing of rhabdomyosarcoma cells by simultaneously targeting tumor and effector cells. Front Immunol. 2017 Mar 7;8:202.

Ullrich E, Salzmann-Manrique E, Bakhtiar S, Bremm M, Gerstner S, Herrmann E, Bader P, Hoffmann P, Holler E, Edinger M, Wolff D. Relation between Acute GVHD and NK Cell Subset Reconstitution Following Allogeneic Stem Cell Transplantation. Front Immunol. 2016 Dec 22;7:595.

Oelsner S, Friede ME, Zhang C, Wagner J, Badura S, Bader P, **Ullrich E**, Ottmann OG, Klingemann H, Tonn T, Wels WS. Continuously expanding CAR NK-92 cells display selective cytotoxicity against B-cell leukemia and lymphoma. Cytotherapy 2017 Feb;19(2):235-249.

Heidkamp GF, Sander J, Lehmann CHK, Heger L, Eissing N, Baranska A, Lühr JJ, Hoffmann A, Reimer KC, Lux A, Söder S, Hartmann A, Zenk J, Ulas T, McGovern N, Alexiou C, Spriewald B, Mackensen A, Schuler G, Schauf B, Forster A, Repp R, Fasching PA, Purbojo A, Cesnjevar R, **Ullrich E**, Ginhoux F, Schlitzer A, Nummerjahn F, Schultze J, Dudziak D. Human lymphoid organ dendritic cell identity is predominantly dictated by ontogeny not tissue microenvironment. Sci Immunol. 2016 Dec 16;1(6).

Scholz A, Harter PN, Cremer S, Yalcin BH, Gurnik S, Yamaji M, Di Tacchio M, Sommer K, Baumgarten P, Bähr O, Steinbach JP, Trojan J, Glas M, Herrlinger U, Krex D, Meinhardt M, Weyerbrock A, Timmer M, Goldbrunner R, Deckert M, Braun C, Schittenhelm J, Frueh JT, **Ullrich E**, Mittelbronn M, Plate KH, Reiss Y. Endothelial cell-derived angiopoietin-2 is a therapeutic target in treatment-naive and bevacizumab-resistant glioblastoma. EMBO Mol Med. 2016 Jan 1;8(1):39-57.

Finkel P, Frey B, Mayer F, Bösl K, Werthmöller N, Mackensen A, Gaipl US, **Ullrich E**. The dual role of NK cells in antitumor reactions triggered by ionizing radiation in combination with hyperthermia. Oncoimmunology. 2016 Jun 7;5(6).

Meinhardt K, Kroeger I, Bauer R, Ganss F, Ovsiy I, Rothamer J, Büttner M. Atreya I, Waldner M, Bittrich M, Lehmann CHK, Rieger MA, Beilhack A, Zeiser R, Edinger M, Dudziak D, Mackensen A, Rehli M, **Ullrich E**. Identification and characterization of the specific murine NK cell subset supporting graft-versus-leukemia- and reducing graft-versus-host-effects. Oncoimmunology. 2015 Feb 3;4(1).

Terme M, **Ullrich E**, Delahaye N, Chaput N, Zitvogel L. NK cell-directed therapies: from unexpected results to successful strategies. Nat.Immunol. 2008;9(5):486-94.