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3-4 October
Gothenburg SWEDEN
Hosted by AstraZeneca, Gothenburg

http://www.physchem.org.uk/

20th PhysChem Forum

Challenges and Future Directions of Preclinical Characterisation in ADMET and DMPK

Contents

Word from the organizing committee

Dear Participants,

This is really a very special occasion for us, The PhysChem Forum is celebrating its 20th edition!

So… **Welcome to the 20th PhysChem FORUM 2023 hosted by AZ in Gothenburg.**

Since 2005, the PhysChem Forum has hosted an annual two-day meeting covering a variety of topics around the themes of physical chemistry (PhysChem) and Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET; http://physchem.org.uk/index.html).

The focus of the 20th PhysChem Forum is on ***Challenges and Future Directions of Preclinical Characterisation in ADMET and DMPK***. New modalities offer new opportunities in the treatment of diseases, but also generate new challenges, different from well-known small molecules.

Certainly, also for those new compound classes, there is a recognized need within the PhysChem and ADMET industry for a discussion forum; especially for those scientists carrying out practical research and analytical work in the field.

There have been a number of extremely high-quality international meetings covering various aspects of this field. While the papers presented at those meetings have been cutting edge, there has been limited scope for bench scientists to meet in a more informal setting allowing them to present current work, discuss challenges that were overcome and deliberate those yet to be faced. Furthermore, those meetings have generally been expensive, thus precluding multiple attendees from smaller departments. The PhysChem Forum Symposium event series is attempting to address those specify aspects by an adapted, yet very successful proven format. The PhysChem Forum is totally free, and its successful organisation relies on the passion and engagement of many people who dedicate their time and effort to make the PhysChem FORUM a reality.

We would especially like to thank Pion, ACDLabs, The Solubility Company, Fidabio, Selvita, Merck group and SEDA for their kind support, so please visit their booths. Also big thanks to the speakers who are of course the heart of this Forum and agree to share their knowledge with the rest of us receiving no compensation. And lastly, but not least, a big, big special thanks to *Lassina Badolo, Executive Director and Head of eR&I DMPK and Anders Holmén, VP and Head of Pharmaceutical Sciences* who kindly agreed to finance this event and to AstraZeneca for the local support in hosting this event!

Our goal is to generate an environment for informed debate and discussion, in a non-commercial setting, with excellent networking opportunities.

Kind regards,
The PCF203 Organizing Committee

Antonio Llinas, AstraZeneca
Jonathan Burley, University of Nottingham
Shenaz Bunally, GSK
Stephane Rodde, Novartis
Nikita King, Syngenta
Karl Box, Pion
Josep Huerta, Almirall
Linette Ruston, Seda Pharm. Dev.
Stephen Buckley, Novonordisk

PS: To subscribe to our mailing list and receive notifications about upcoming meetings, please e-mail webmaster at physchem.org.uk and follow us on LinkedIn

Programme

Tuesday 3rd October 2023

At the Quality Hotel The weaver, Göteborgsvägen 91, Mölndal

Chair: Antonio Llinas (AstraZeneca)

17.30 - 18.30 **Drinks reception and late registration**
18.30 - 19.30 **Natural Intelligence in Drug Discovery**
Dr. Robert Young (Blue Burgundy, UK)
19.30 - 22.00 **Symposium dinner**

Wednesday 4th October 2023

At the AstraZeneca PGN Conference Center at Pepperedsleden 5, Gothenburg, Sweden. map

Chair: Antonio Llinas (AstraZeneca)

8.30 - 9.00 **Late registration and poster set-up**
9.00 - 9.10 **Welcome by Anders Holmén, VP Head Pharmaceutical Sciences**
9.10 - 9.50 **Design Principles for Balancing Lipophilicity and Permeability in Beyond Rule of 5 Space**
Henrik Moebitz (Novartis, Basel)
9.50 - 10.30 **Bio-mimetic HPLC based protein and phospholipid binding to predict in vivo distribution and toxicity of drug discovery compounds**
Klara Valko (Bio-mimetic Chromatograpy Ltd, UK)
10.30 - 11.00 **Coffee break and poster viewing**

Chair: Shenaz Bunally (GSK)

11.00 - 11.40 **New method for absorption profiling of advanced drug discovery systems**
Christel Bergström (Univ Uppsala)
11.40 - 12.20 **The influence of fluorination on lipophilicity**
Bruno Linclau (Ghent University)
12.20 - 12.40 **Flash poster session (poster authors introduce their posters, no more than 2 minutes each)**
12.40 - 13.40 **Lunch and poster viewing**

Chair: Stephane Rodde (Novartis)

13.40 - 14.20 **Nanomedicine challenges and insights from in vitro LNP screening**
Alan Sabirsh (AstraZeneca Gothenburg)
14.20 - 15.00 **Physicochemical profiling for accelerating drug discovery: a high throughput approach for successful lead optimisation**
Shenaz Bunally (GlaxoSmithKline)
15.00 - 15.30 **Poster prize award, coffee, poster viewing**

Chair: Jonathan Burley (University of Nottingham)

15.30 - 16.10 **Macrocycles in drug discovery - what we know about property-based design**
Jan Kihlberg (Univ Uppsala)
16.10 - 16.50 **Biological-nanoparticles and cell-membrane interaction analysis using label-free surface-sensitive optical microscopy**
Fredrik Höök (Chalmers Uni)
16.50 - 17.00 **Wrap-up and depart**

Biosketches and Abstracts

Dr Robert Young

Principal Blue Burgundy, UK

Email: Rob@blue-burgundy.co.uk

Rob Young joined Wellcome in February 1990, following BA/DPhil degrees at University of Oxford and a Post Doc at Ben May Institute, University of Chicago. His subsequent career navigated changes, mergers and acquisitions and positions of increasing responsibility to become a Scientific Leader and elected GSK Fellow. His career charted significant contributions to six development candidates in antivirals (HIV/HBV/Herpes), iNOS and Factor Xa, before a move to early-stage discovery (2006) fulfilling leadership roles numerous H2L programs, using diverse technologies including HTS, fragments, focussed & designed screens, and DNA-encoded libraries. Expertise in Physical Properties and the Property Forecast Index were developed in a productive partnership with Alan Hill spanning many years. Appointed/co-opted to numerous GSK cross-disciplinary initiatives and communities including in silico predictive modelling, DMPK, Physical Chemistry, Stability and Safety. An author/inventor on more than 100 publications/ patent applications, he continues with writing endeavours with thought provoking perspectives. Rob is an honorary visiting Professor at The University of St Andrews.

Rob took early retirement from GSK in July 2019 and set up Blue Burgundy to pursue medicinal chemistry consulting, training, and educational interests, with an active portfolio of clients encompassing academic institutions and companies of all sizes in many countries.

Natural Intelligence in Drug Discovery design

The PhysChem Forum audience will need no convincing of the pre-eminence of physicochemical properties in drug discovery, whilst it is likely to be fatigued by talk of Artificial Intelligence and prescriptive rules/aspirations in drug discovery. This talk will complement Physical expertise with thinking inspired by natural intelligence, putting blinkered rules are out of their misery in the process. The reasons why naturally-inspired molecules can exploit and expand regions of “chemical space” that purely synthetic chemistry cannot reach will be explored.

Dr Henrik Moebitz

Associate Director Data Science, Global Discovery Chemistry, Novartis, Basel, Switzerland

Email: henrik.moebitz@novartis.com

Dr Henrik Moebitz is an experienced computational medicinal chemist with a track record of successful project delivery and people leadership. Passionate drug hunter integrating physics based property prediction, structure based design and data analysis. Comfortable with ambiguity and able to bridge the interface between chemistry, biology and pharmaceutical development. Broad technical skill set from biochemistry to quantum chemistry. Deep expertise in targeting helicases, kinases and the MAPK pathway.

Design Principles for Balancing Lipophilicity and Permeability in Beyond Rule of 5 Space

An *ab initio* conformational analysis of oral beyond Rule of 5 (bRo5) drugs was complemented with measured permeability and logP(octanol) to derive design principles conferring oral bioavailability. 3D polar surface area (PSA) thresholds for oral bRo5 drugs coincided with those reported for Ro5 space. The majority of oral bRo5 drugs exceeded the Ro5 logP threshold of 5, reflecting a bias for permeability. Above 500 Da molecular weight (MW), oral drugs and highly permeable Novartis compounds occupy a narrow polarity range (topological or TPSA/MW) of 0.1-0.3 $Å^2$/Da, whose upper half coincides with the lower 90 percentiles of the Novartis logP set. This TPSA/MW range and 3D PSA below 100 $Å^2$ define the "Rule of ~$^1/_5$" for balancing lipophilicity and permeability. Neutral TPSA, defined as TPSA minus 3D PSA occurs independent of conformation, intramolecular hydrogen bonds (IMHB) and MW, suggesting it is an intrinsic molecular property. Neutral TPSA increased in the lead optimization (LO) campaigns of three first in class *de novo* designed bRo5 drugs and may be a useful design parameter in bRo5 space.

Dr Klara Valko

Founder Director, Bio-Mimetic Chromatography Ltd. and Honorary Professor at University College London, School of Pharmacy, UK

Email: klara_valko@bio-mimetic-chromatography.com

- PhD in pharmaceutical chemistry and pharmacology, School of Pharmacy at Semmelweis University (1979)
- Head of the Analytical Chemistry section of the Bioorganic Chemistry Department of Central Research Institute for Chemistry, Hungarian Academy of Sciences (till 1991)
- Lecturer and honorary professor at the School of Pharmacy University of London (1991), later UCL School of Pharmacy
- From 1995, 22 years of experience at Wellcome, GlaxoWellcome, GSK in the Physico-chemical Characterization Group in Molecular Discovery Research as principal investigator
- Appointed honorary professor at the University College London's School of Pharmacy since 2004
- Founder CEO, Bio-Mimetic Chromatography Ltd in Stevenage, Herts United Kingdom (2016)
- Author of the book *Physicochemical and Biomimetic Properties in Drug Discovery; Chromatographic Techniques for Lead Optimization* and over 120 peer reviewed publications, over 6000 citations

Bio-mimetic HPLC based protein and phospholipid binding to predict in vivo distribution and toxicity of drug discovery compounds

The chromatographic separation principle is suitable for measuring the physicochemical properties of compounds using generic HPLC methods with standardised retention times. When phospholipids (IAM, immobilised artificial membrane) and proteins (albumin and glycoprotein) are used as stationary phases, the measured data can be used for predicting the toxicity and in vivo distribution of compounds. Thus, compounds' volume of distribution, brain tissue binding, lung retention, skin penetration, phospholipidotic and cardiotoxicity potential can be predicted.
These measurements will be part of an AI / machine-learning (ML) platform developed by AsedaSciences®, which will integrate other high-content cellular and zebrafish embryo toxicity screens. The chromatographic, cellular and zebrafish screening results and associated ML based predictions and visualization will be available on an AWS cloud-based platform called 3RnD®. Scientists from any academic Institution or drug discovery company will be able to compare the results for their own compounds to a library of thousands of compounds, helping to predict toxicity risk earlier. This approach helps scientists select safer scaffolds, understand the impact of SAR and prioritize safer compounds, improving R&D productivity by preventing later stage attrition.

Prof. Christel Bergström

Dept of Pharmacy, Uppsala University, Sweden

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Dr Bergström is Professor in Molecular Pharmaceutics at Uppsala University, Sweden, and adjunct Professor at Monash University, Australia. She is heading a research group of ~25 people focusing on delivery of problematic compounds (poorly solubles, biologics). Her expertise area is within advanced drug delivery systems with focus on biorelevant profiling, computational prediction and novel manufacturing techniques. She is the Center Director of The Swedish Drug Delivery Center – an academic-industry partnership with 16 industrial partners from Sweden, Denmark, Finland and Belgium. Dr Bergström has attracted funding to her research program from highly competitive sources, including the European Research Council (3), the Swedish Research Council (7), the National Institute of Health and the Swedish Foundation for Strategic Research. She has published >130 papers and book chapters and has been cited >7600 times (h-index of 48).

Dr Bergström is a cofounder of the Nordic Pharma Network and an EXCO member of the Nordic University Hub within patient-oriented products (the Nordic POP initiative). She is also an EXCO member of the Globalization Pharmaceutics Education Network. She has founded three companies supporting companies in the drug delivery and development area. In 2017, she was elected Vice Dean of collaboration (Medicine and Pharmacy) at Uppsala University. In this role, she is engaged in outreach activities, identification and establishment of strategic partnerships, interactions with governmental departments of importance for health and education, as well as increasing the academic awareness of the innovation system. In 2018, she became associate editor for the journal Molecular Pharmaceutics and is a sought for member of grant evaluation panels and scientific advisory boards.

New methods for absorption profiling of advanced drug delivery systems

This presentation will focus on new computational and experimental methods to predict and understand intestinal drug absorption from advanced drug delivery systems. A majority of the discovered drug candidates are problematic to deliver to the site of action, why advanced drug delivery systems are needed. In the small molecular space (Mw<500 Da) a large fraction is poorly soluble in water and compounds having aqueous solubility less than that of marble are not uncommon. In the new modality space, the delivery problem is related to poor permeability across cell membranes. For both categories, extensive formulation efforts are demanded to bring them into the clinic. The molecular reasons behind the poor solubility (typically simplified into solid-state effects versus solvation effects) may guide the selection of suitable formulation strategies, whereas size, polarity and hydrogen bond patterns are crucial determinants for poor permeability. In this talk I will describe how methods commonly used in computational chemistry and computational (cell) biology (e.g. Molecular Dynamics simulations and Computational Fluid Dynamics) are useful tools for prediction of formulation strategies and formulation performance of poorly solubles

and poorly permeables. I´ll then present new experimental methods based on dissolution and permeation tools, that nowadays have been developed to better mimic the gastrointestinal tract. These new tools include organoids for better understanding of uptake and permeation processes in the gastrointestinal tract but has also include the development of dissolution/digestion/permeation tools that mimic the gastrointestinal processing and absorption in one assay. The talk hence will summarize some of the new techniques available to better predict and understand performance of advanced oral drug delivery systems.

Prof. Bruno Linclau

Department of Organic and Macromolecular Chemistry, Ghent University, Belgium

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Group web page: https://www.ugent.be/we/orgchem/en/research/bio-organic-synthesis/organic-and-medicinal-chemistry/overview.htm

Bruno Linclau received his PhD in 1996 from Ghent University, followed by a postdoctoral stay with Professor D. P. Curran in Pittsburgh PA (USA) (1997 – 1999). He joined the Chemistry Department at Southampton University as a lecturer in August 1999, followed by a promotion to Senior Lecturer in 2005, to Reader in 2013, and to Professor in 2015. In October 2021, he moved to Ghent University as an Odysseus research professor. His research interests are centred around the modification of molecular properties upon fluorine introduction, especially conformation, lipophilicity and hydrogen bonding. Targets of interest include carbohydrates, amino acids (proline), and small molecules of pharmaceutical interest.
He is a fellow of the Royal Society of Chemistry (RSC) and a regular member of the American Chemical Society (ACS), and of the Society of Chemistry and Industry (SCI). After serving as secretary of the RSC Fluorine Chemistry Group Committee, he became Chair of this Committee in January 2022.

The influence of aliphatic fluorination on lipophilicity

In recent years, the study of lipophilicity of aliphatic compounds has seen a burst of activity involving very different compound classes and fluorination motifs. Our group has contributed to this, in part by introducing an ^{19}F NMR based method that allows measuring lipophilicities of non UV-active fluorinated compounds, albeit with some restrictions regarding log*P*/*D* range.[1] This will be illustrated with recent results of trifluoromethylated oxygenated compounds.
It has already been recognised long ago that the conformations of a molecule have their own physicochemical properties, including lipophilicity. Our NMR-based lipophilicity determination method has allowed us, in specific cases, to directly measure the lipophilicity of individual conformers, which is the first time that this has been achieved.[2] This will be briefly discussed with regards to potential applications in lipophilicity optimisation in drug discovery.In many cases, the log*P* modulation through fluorination can be relatively modest. We wondered whether such lipophilicity changes, as expressed by the octanol-water partition coefficients, are actually equally affecting the membrane partitioning. This has been investigated using a novel solid state ^{19}F NMR MAS methodology employing standard lipid vesicles,[3] the results of which will be discussed in this presentation.

[1] Linclau, B.; Wang, Z.; Compain, G.; Paumelle, V.; Fontenelle, C. Q.; Wells, N.; Weymouth-Wilson, A., Investigating the Influence of (Deoxy)fluorination on the Lipophilicity of Non-UV-Active Fluorinated Alkanols and Carbohydrates by a New log P Determination Method. Angew. Chem. Int. Ed. 2016, 55 (2), 674-678.
[2] Linclau, B.; Wang, Z.; Jeffries, B.; Graton, J.; Carbajo, R. J.; Sinnaeve, D.; Le Questel, J. Y.; Scott, J. S.; Chiarparin, E., Relating Conformational Equilibria to Conformer-Specific Lipophilicities: New Opportunities in Drug Discovery. Angew. Chem. Int. Ed. Engl. 2022, 61 (7), e202114862.
[3] Wang, Z.; Felstead, H. R.; Troup, R. I.; Linclau, B.; Williamson, P. T. F., Lipophilicity Modulations by Fluorination Correlate with Membrane Partitioning. Angew. Chem. Int. Ed. Engl. 2023, 62 (21), e202301077.

Dr Alan Sabirsh

Principal Scientist, Advanced Drug Delivery department, Pharmaceutical Sciences, AstraZeneca, Sweden

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Alan Sabirsh, Ph.D. is a principal scientist in the Advanced Drug Delivery department at Pharmaceutical Sciences. He is a passionate experimentalist who studies the cellular delivery of novel chemical modalities, such as modified mRNA, using nanoparticles. Alan champions the use of biological assays, and high-throughput methods, and data science capabilities within Pharmaceutical Sciences using automation and AI-assisted data acquisition and analysis. He also has decades of drug discovery experience within AstraZeneca and has worked with respiratory, neurological, cardiovascular, metabolic and kidney related diseases. He currently leads the Center of Excellence for Cytometric Imaging at the Gothenburg site

Nanomedicine challenges and insights from in vitro LNP screening

New therapies that require large molecules, like mRNA vaccines or targeted genome editing, have increased the need for effective, safe, and economical delivery systems that are easy to make and to store. Lipid nanoparticles (LNPs) have emerged as one solution for delivering large molecules and these systems became famous during the pandemic. LNPs are, however, expensive and complex to develop because of the multiple interacting components and the need to optimise for many different attributes. To meet this need we developed a comprehensive LNP in-vitro screening workflow that combines throughput with miniaturisation to address a wide range of questions in a multivariate manner. During this talk we will go through this workflow, some of the challenges encountered and, some of our conclusions after systematically testing thousands of nanoparticles

Ms. Shenaz Bunally

Scientific Leader, GSK Associate Fellow , GSK, UK

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Shenaz Bunally obtained her bachelor's degree in Analytical and Medicinal Chemistry from the University Of Hertfordshire. With over twenty years' experience in the pharmaceutical industry, Shenaz is currently the GlaxoSmithKline Scientific lead in the provision of physicochemical solutions to global research programs and is responsible to align physchem support with R&D Chemistry priorities and plan future strategies.
She has a wide range of scientific and interpersonal skills. She has developed and implemented high throughput physchem screening assays and is skilled in the provision, analysis and interpretation of high quality physchem data to improve compound's developability profile. In collaboration with Computational Chemistry, she provides expert guidance to develop in silico models for predicting physchem properties. She works closely with scientists in Drug Development to ensure smart use of physchem data in simulation programs and mechanistic modelling for predicting drug disposition in the human body.
She is experienced in team leadership, management, and matrix/collaborative working. She has contributed to several external and internal publications and gave oral presentations at various conferences, internal and external fora.
Shenaz is a GSK Associate Fellow and a member of the Royal Society of Chemistry. Passionate about promoting Inclusion and Diversity, she provides direction to support Inclusion and Diversity as the departmental champion in GSK. Originally from Mauritius, she speaks English and French fluently and enjoys fitness classes and board games

Physicochemical profiling for accelerating drug discovery: a high throughput approach for successful lead optimization

It has long been recognised that poor physchem profiles are a major contributor to the high attrition rate of drug candidates. During the early phase of drug discovery it is becoming increasingly important to acquire the full physicochemical profile of molecules. For this purpose there is a strong interest in developing platforms for fast and reliable measurements of physchem properties.
Progressing compounds with good developable physicochemical properties during the lead optimisation process is fundamental to GlaxoSmithKline's (GSK) aspirations for Lead and Candidate Molecule Quality.
The Physchem team at GSK have developed assays and in silico models to support medicinal chemistry efforts to guide chemistry projects towards molecules with desirable physicochemical attributes and consequently minimising the likelihood of late stage attrition. Extensive application of automated chromatographic platforms has enabled efficient and cost effective high throughput physicochemical profiling of compounds in early drug discovery. This platform ensures that consistent, comprehensive, and high quality physicochemical property measurements and derived property information for 100's of compounds per week are available alongside potency data at the right time to guide compound progression decisions

Prof. Jan Kihlberg

Prof. Organic Chemistry Uppsala University, Sweden

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Jan Kihlberg holds a chair in Organic Chemistry at Uppsala University, Sweden since 2013. His key research interests are to understand what properties convey cell permeability, aqueous solubility and target binding to drugs in the beyond rule of 5 space and to translate this knowledge into guidelines for design. He has published close to 200 peer–reviewed publications and book chapters. Before moving to Uppsala Prof. Kihlberg spent 10 years at AstraZeneca R&D in Gothenburg, 7 of which as Director of Medicinal Chemistry

Macrocycles in drug discovery - What we know about property-based design

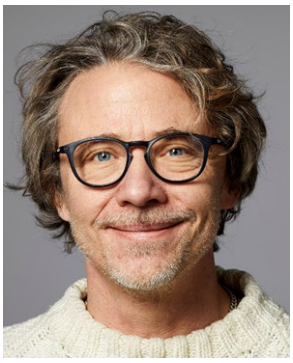
Our recent analysis of FDA-approved macrocyclic drugs clinical candidates revealed that most originate from natural products and identified a chemical space more likely to contain orally bioavailable macrocycles. The ability of macrocycles to adopt disc- and sphere-like conformations was concluded to be essential for allowing them to bind with high affinity to targets that have difficult-to-drug binding sites.

We have studied the conformations of orally absorbed macrocyclic drugs using NMR spectroscopy and by analysis of crystal structures, which revealed that they often behave as molecular chameleons. As a result of the balance between rigidity and flexibility, molecular chameleons combine aqueous solubility, cell permeability and target binding; properties that otherwise would have been mutually exclusive.

Predicting the conformations and properties of molecular chameleons is difficult, but MD simulations using an explicit solvent model, followed by QM refinement of the conformations provided accurate results for moderately flexible macrocycles. Classification models developed by machine learning allowed accurate differentiation of macrocycles that have high or low cell permeability.

Prof. Fredrik Höök

Prof. Biological Physics, Chalmers University of Technology, Gothenburg, Sweden



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Early in his career, **Prof. Höök** contributed to the development of the QCM technique and helped establishing the technology (www.q-sense.com) as a key bioanalytical instrument in fundamental biologically oriented surface science. In collaboration with AstraZeneca, Höök also pioneered TIRF-based equilibrium fluctuation analysis, which is today customized to probe the dynamic interaction between individual viruses and cell-membrane mimics with sub fM sensitivity, which when applied on membrane proteins offers new solutions for drug discovery (www.insingulo.com). Inspired by challenges in medical diagnostics, biomarker discovery, and drug development, Höök's research is presently exploring how novel complementary surface-sensitive microscopy methods can contribute new information with respect to biomolecular and physicochemical characterization of single biological nanoparticles, with the aim to precisely guide bioinspired supramolecular self-assembly processes of functional nanomaterials. In particular, by combining surface sensitive fluorescence and label-free scattering microscopy (www.nanolyze.se), much focus is put on in-depth studies of the interaction between biological nanoparticles, such as viruses, extracellular vesicles, and cell-targeting nanoparticles, with representative cell-membrane mimics, supported by theory, modelling, and advanced image analysis. Höök is member of IVA and KVA, direct the SSF funded industrial research center FoRmulaEx, is vice head of the Department of Physics, Chalmers, for utilization and outreach, and is a Wallenberg scholar.

Biological-nanoparticles and cell-membrane interaction analysis using label-free surface-sensitive optical microscopy

Ionizable lipid nanoparticles (iLNPs) are emerging as a promising formulation for mRNA delivery in the field of RNA therapeutics. However, several challenges must be overcome before this approach can be widely translated into broad clinical applications. In this presentation, I will discuss our recent efforts to address some of these challenges by combining micro- and nanofluidic systems with surface-sensitive optical microscopy techniques. The presentation will primarily focus on the application of these platforms for the visualization of individual biological nanoparticles, such as mRNA-containing iLNPs as well as extracellular vesicles (EVs). One of the approaches combines label-free scattering and fluorescence-based imaging that enables high-resolution characterization with single nanoparticle resolution [1]. Through this approach, we have successfully quantified the refractive index and size of individual iLNPs and EVs, and by employing specific fluorescence labeling, we have established precise correlations between these properties and the cargo content within, and surface markers on both iLNPs and EVs. Our studies have also revealed valuable insights into the role of protein-corona formation in the maturation steps that facilitate cellular iLNP uptake and mRNA delivery [2], which is presently scrutinized by comparing the results with the fusion efficiency of iLNPs with anionic endosomal membrane mimics formed on nonporous silica. Additionally, our recent work on investigating iLNP binding to endosomal membrane mimics [3] has recently been extended by forming the membrane mimics on nonporous silica [4] rather than planar glass substrates. This way,

we have addressed the physicochemical mechanisms that are believed to be responsible for pH-induced of iLNPs with the membrane of endosome during mRNA release. We believe that these investigations will contribute a deeper understanding of nanoparticle heterogeneity and its influence on interactions with cellular membranes, including new insights regarding the endosomal escape mechanism, and hope that our findings will contribute to the rational design of next generation nanocarriers for more efficient oligonucleotide delivery.

[1] Sjoberg, M. et al., Time-Resolved and Label-Free Evanescent Light-Scattering Microscopy for Mass Quantification of Protein Binding to Single Lipid Vesicles. Nano Letters 2021, 21 (11), 4622-4628.
[2] Gallud, M. et al., Time evolution of PEG-shedding and serum protein coronation determines the cell uptake kinetics and delivery of lipid nanoparticle formulated mRNA. bioRxiv 2021: https://doi.org/10.1101/2021.08.20.457104
[3] Joyce, P. et al., TIRF Microscopy-Based Monitoring of Drug Permeation Across a Lipid Membrane Supported on Mesoporous Silica. Angew Chem Int Edit 2021, 60 (4), 2069-2073.
[4] Aliakbarinodehi, N. et al., Interaction Kinetics of Individual mRNA-Containing Lipid Nanoparticles with an Endosomal Membrane Mimic: Dependence on pH, Protein Corona Formation, and Lipoprotein Depletion. ACS Nano 2022, 16 (12), 20163-20173.

Posters

Stephane Rodde, Principal Scientist, Novartis, stephane.rodde@novartis.com
Beyond Rule of 5: Risks and Opportunities in Interpreting High-Throughput Physicochemical Properties

Ferdausi Mazumder, Senior Scientist, GlaxoSmithKline, ferdausi.x.mazumder@gsk.com
EPSA measurements for molecules in the bRO5 chemical space

Merran Bryford, Postdoctoral Research Fellow, AstraZeneca, merran.bryford@astrazeneca.com
Building PROTAC design principles for extended treatment duration

Leonardo De Maria, Principal Scientist, AstraZeneca, leonardo.demaria@astrazeneca.com
Non-natural amino-acids to astronomic scale

Yufei Zhu, PhD student, School of pharmacy, university of Nottingham, paxyz9@exmail.nottingham.ac.uk
Lipid-based drug delivery systems for improved systemic bioavailability and intestinal lymphatic targeting of cannabidiol

Valentyna Pivnytska, Senior Research Scientist, AstraZeneca, valentyna.pivnytska@astrazeneca.com
Miniaturisation of an Aqueous Solubility assay using Acoustic Dispensing and 384-Well Based Workflows

Yoko Shishikura, Bioanalyst, University of Dundee, y.shishikura@dundee.ac.uk
LC/MS/MS cassette analysis for high throughput in vitro metabolic stability assays in drug discovery

Saw Simeon, Post doctoral Research Fellow, Uppsala University, saw.simeon@kemi.uu.se
Macrocyclic Cell Permeability Predictive Models from Different Molecular Representation

Andrius Sazonovas, Head of Development, ACD/Labs, andrius.sazonovas@acdlabs.com
Quantitative Physicochemical Model of P-glycoprotein Efflux Ratio Utilizing Censored Data

Andrius Sazonovas, Head of Development, ACD/Labs, andrius.sazonovas@acdlabs.com
Ionization (pKa) Prediction In Percepta®: v2023 Improvements and Evaluation

Juanitta Julsgart, Business Development, Fidabio, juanitta@fidabio.com
High Throughput Detergent Screening - Membrane Proteins

Kinga Jenei, Master Student, AstraZeneca, kinga.jenei@astrazeneca.com
Multitask model for pKa predictions: an industry perspective

Hugh Walton, Senior Research Associate, Astex Pharmaceuticals, hugh.walton@astx.com
Can Carboxylic Acid Drugs be brain penetrant?

Felix Sheffield, Research Assistant, Imperial College London, f.sheffield18@imperial.ac.uk
Label-free determination of passive membrane permeability for agrochemical and pharmaceutical development pipelines

Rebeca Ruiz, Principal Scientist, pION, rruiz@pion-inc.com
In-vitro Study of the Dissolution rates and Absorption of Adefovir and its co-crystals under GI conditions

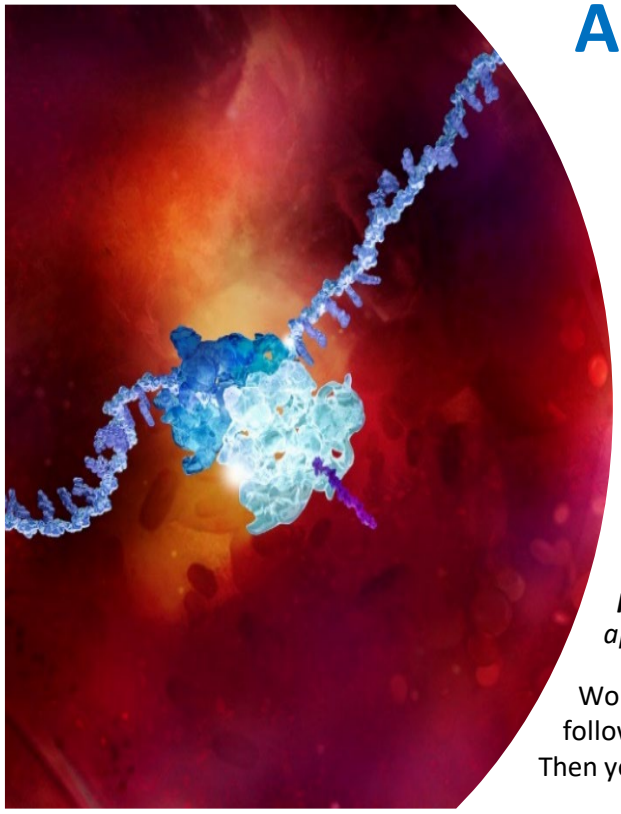
Paul Dyer, Field Application Scientist, Halo Labs, paul.dyer@halolabs.com
High throughput, low volume small molecule solubility determination via membrane filtration and imaging

Madeleine Taylor, PhD Student, University of Strathclyde, madeleine.taylor@strath.ac.uk
Development of molecular descriptors for quantitative structure-retention relationships

Best Poster Prize

One lucky winner will win our Best poster Prize!!

Job opportunities



AstraZeneca eR&I DMPK is looking for:

Biologics Translational PKPD Modeling
&
DMPK Specialist & Preclinical and translational PK & PKPD scientist

Do you have expertise in **DMPK science and PKPD modelling** of **antibody-based therapeutics**?

*Do you have expertise in **mathematical modelling** and/or **pharmacokinetics (PK) and pharmacodynamics (PD)** and its application in **drug discovery**?*

Would you like to apply your knowledge in a global company that follows the science and turns ideas into life-changing medicines? Then you could be the new colleague we are looking for!

The career level can be adjusted to the experience of the successful candidates.

At AstraZeneca we're proud to have an outstanding workplace culture that encourages innovation and teamwork. We are united by our vision to push the boundaries of DMPK science to transform ideas into medicines for R&I patients. Employees are empowered to express diverse perspectives - and are made to feel valued, energized and rewarded for their ideas and creativity toward delivering candidate drugs into late-stage development

Interested? Contact antonio.llinas@astrazeneca.com

Biologics Translational PKPD Modeling

Our team is growing, and we want to hear from you if you are a passionate PKPD modeller and DMPK Scientist to join our DMPK department as a **Biologics Translational PKPD Modelling & DMPK Specialist** within **Early Respiratory and Immunology** (R&I). The R&I DMPK department provides drug metabolism and pharmacokinetic, as well as translational PKPD modeling & simulation support to our portfolio. This position is located at AstraZeneca's vibrant R&D site in Gothenburg, Sweden, one of AstraZeneca's three strategic science centres.

What you'll do

As a Biologics Translational PKPD Modelling & DMPK Specialist you will have the opportunity to drive strategy and provide global leadership in PKPD science across our diverse portfolio, and act as role model, mentoring and guiding less experienced members of the team. You have in-depth knowledge of biologics drug discovery and a keen interest in understanding the translational PKPD of antibody-based therapeutics. In the role you would provide projects with specialist modelling input into exploring PK/PD/Efficacy in preclinical models and use them to guide an understanding of the dosing across different patient populations.

Main Duties and Responsibilities

- Being responsible for setting and implementing the departmental biologics PKPD strategy
- Representing R&I DMPK in projects and providing overall scientific leadership for cross functional collaborations involving DMPK
- Exploring the effects on target and pathway to understand the requirements for efficacy and set a candidate drug target profile (CDTP)
- Ensuring that translational PKPD approaches are embedded at the heart of project strategy and used to support design of appropriate experiments that are aligned to the strategy underpinning human dose prediction and providing input into exposure and pharmacodynamic (PD) biomarker based decision criteria
- Leading and participating in R&I strategic scientific initiatives and continuous improvement projects by providing expert M&S knowledge.
- Having a breadth of influence and impact across AstraZeneca DMPK
- Identifying, championing and developing new ideas
- Leading scientific discipline networks and acting as a focus for debate within the AstraZeneca scientific community
- Develop excellent working relations with key stakeholders within both DMPK and in the project teams, to ensure strategic alignment, strong cross discipline collaboration and communication.
- Responsible for preparing clear presentations of DMPK contributions to internal governance interactions for the projects you support.
- Providing disciplinary scientific leadership and presenting work through publications and lectures

Essential for the role

- PhD (or equivalent industrial experience) in a relevant field e.g. pharmacokinetics, pharmacology, biopharmaceutics etc.
- 7 years of industry experience in Modeling & Simulation, ideally in preclinical/translational setting with a focus on biologics
- Comprehensive understanding of biologics drug discovery, including the PK and PKPD of antibody based therapeutics.
- Experience of DMPK project facing role in pharmaceutical R&D with a variety of therapeutic antibody formats (e.g. mAbs, Fabs, bispecifics, ADCs etc).
- Track record of supporting PK, PKPD and TKPD aspects of projects, with a delivery focus and ability to meet timelines to pre-specified quality and cost
- Excellent interpersonal skills, and ability to work in cross-functional teams as well as strong scientific leadership skills
- Hands on experience of using specialist tools such as WinNonLin/Phoenix, MATLAB, R, Berkely Madonna, SimCYP or similar

Preclinical and translational PK & PKPD scientist

We are interested in hearing from you if uou are a highly skilled and motivated **modelling and simulation scientist** with expertise in mathematical modelling preferably applied in the field of **pharmacokinetics-pharmacodynamics (PKPD)** to join our **drug metabolism and pharmacokinetics department** within **early Respiratory and Immunology (R&I)** at **AstraZeneca's** world-class R&D centre in Gothenburg, Sweden. Working at AstraZeneca means being entrepreneurial, following the science, scrutinizing data and details simultaneously with holistic thinking and through teamwork make progress.

What you'll do

You have a true passion for science and will support our portfolio within the R&I therapeutic area. We believe that you have solid, hands-on experience of PKPD modeling and that you will be able to provide expert advice and interpretation of complex drug discovery data. You will deliver translational quantitative/PKPD input for a broad range of drug modalities from target identification to life-cycle management as an **Associate Principal Scientist (APS**) **or Principal scientist (PS)**, depending on your background, experience and skills.

Main Duties and Responsibilities include:

Identify the appropriate models and conduct analysis/modelling of PKPD data from various sources (from internal lab or external sources). Such models could be e.g. traditional PKPD modelling, non-linear mixed effects modelling or quantitative systems pharmacology to deliver the PKPD insights to influence critical decisions in drug discovery and development

- Inform and influence the design of studies, with PKPD in mind to answer relevant pharmacological questions and report results to project teams and internal governance bodies
- Contribute towards defining safety margins by means of PKPD assessments of efficacy and safety risks in collaboration with other functions
- Predict human pharmacokinetics, efficacious exposure and dosing regimen. This is done in close collaboration with other functions (bio scientists, safety scientists, clinical pharmacologist and clinical pharmacometricians)
- Communicate scientific progress to internal and external stakeholders
- Deliver input and data to projects within agreed timelines and to the right quality that supports/influences compound profiling, project progression and project strategy
- Define and deliver a translational quantitative PKPD strategy in projects, so that effective conclusions can be made
- Prepare clear presentations related to the above for internal governance bodies

Essential for the role

- The successful candidate is expected to have a solid PKPD understanding and hands on experience of mathematical modelling (e.g. empirical PKPD models, in vitro-in vivo translation, non-linear mixed effects models, quantitative systems pharmacology (QSP) models).
- PhD or equivalent in relevant field, with a focus on mathematical modelling of PKPD data, ideally in a preclinical/translational setting with a profound knowledge of drug discovery and development processes
- Specialist in PK and PKPD data analysis, interpretation, and reporting, including hands-on experience with modelling software (e.g. Phoenix WinNonlin, Matlab, Monolix, R, NONMEM, or similar)
- Proven scientific leadership and ability to mentor junior colleagues
- Experience in project leadership and collaborative mindset
- Scientific leadership evidenced by a publication track record and ability to independently lead the drafting and review of publication manuscripts
- Excellent interpersonal skills, and ability to work in cross-functional teams as well as independently
- Proactive and excellent communication skills
- Experience in defining quantitative modelling strategies across several therapeutic modalities (e.g. small molecules, oligonucleotides, peptides, proteins, antibodies)

List of Participants

Name	Company/Institution	Job Title
Abbas Khan	Shanghai Jiao Tong University	Postdoctoral researcher
Alan Sabirsh	AstraZeneca	Principal Scientist
Alice Oram	AstraZeneca	R&D Graduate Scientist
Amy Chang	AstraZeneca	Senior Research Scientist
Anders Bergh	Calliditas Therapeutics AB	Pharmaceutical Development Manager
Anders Holmén	AstraZeneca	VP Pharmaceutical Sciences
Andrius Sazonovas	ACD/Labs	Head of Development, Percepta
Andriy Vdovichenko	Pion-Inc.	Business Development Manager- DACH
Anil kadam	UAB	Research Scientist
Anna Novén	Astra Zeneca	Senior Scientist
Anna-Karin Fransson	Merck Life Science AB	Account Manager
Anne Kaudern	AstraZeneca	Conference Support
Annica Wånge	AstraZeneca	Conference Support
Annika Träff Wergeni	AstraZeneca	Associate Principal Scientist
Anton Hanopolskyi	Preci LLC	CEO
Antonio Llinas	AstraZeneca	Principal Scientist
Arjun Mani	Cytiva / Uppsala University	Intern / MSc student
Bruno Linclau	Ghent University	Professor of Organic Chemistry
Carl Stenbratt	AstraZeneca	Senior Scientist
Christel Bergström	Uppsala University	Professor
Christopher Southan	Medicines Discovery Catapult	Data Scientist
Chrysoula Tsirigoti	AstraZeneca	PostDoc
Chuan-En Lu	AstraZeneca	Postdoc
Dan Lundberg	AstraZeneca	Associate Principal Scientist
Daniel Garcia West	Merck Life Science UK Ltd	Business Development
Dhara Raijada	AstraZeneca	Senior Formulation Scientist
Dong Ye	AbbVie Inc.	Senior Scientist
Felix Sheffield	Imperial College London	Research Assistant
Ferdausi Mazumder	GlaxoSmithKline	Senior Scientist
Giulia Testa	Astrazeneca	Graduate Scientist
Hanna Lavén	AstraZeneca	PT&D Graduate
Hans Lennernäs	Dept of Pharmaceutical Bioscience	Professor
Henrik Moebitz	Novartis Institutes for BioMedical Research	Associate Director

Hugh Walton	Astex Pharmaceuticals	Senior Research Associate
Ibrahim Khadra	Strathclyde University	Reader
Isaure Tetard	Astrazeneca	Biopharmaceutical expert
Ivan Stupák	AstraZeneca	Senior Scientist
Jan Kihlberg	Uppsala University	Professor Emeritus
Jasna Padovan	Selvita	Sr. Director, DMPK
Jeanie Müller	Merck	Key Account Manager
Jessica Larsson	Red Glead Discovery	Head of ADME&Analysis
Joanna Rejmna	AstraZeneca	PhD
Johan Wernevik	AstraZeneca	Associate Director
Jon Greenacre	The Solubility Company	Head of Sales
Jonathan Burley	School of Pharmacy, University of Nottingham	Assistant Professor
Jonathan Rains	Syngenta	Principal Physical Chemist
Juanitta Julsgart	Fidabio	Business Development
Kai Liu	AstraZeneca	Senior Scientist
Kalle Bunnfors	AstraZeneca	Senior Scientist
Karin Angelin Krefting	AstraZeneca	Conference Support
Karl Box	Pion Inc. (UK) Ltd.	Chief Scientific Officer - Europe
Katerina Kleinerova	N/A	N/A
Kinga Jenei	AstraZeneca	Master student
Klara Valko	Bio-Mimetic Chromatography Ltd	Director
Lassina Badolo	AstraZeneca	Executive Director, Head of eR&I DMPK
Laura Setyo	AstraZeneca	Pathologist
Leonardo De Maria	AstraZeneca	Principal Scientist
Linda Fredlund	Astrazeneca	Senior scientist
Linette Ruston	Seda Pharmaceutical Development Services	Director: ADME and Modelling Sciences
Madeleine Taylor	University of Strathclyde	PhD student
Magdalena Kierkowicz	UCB Pharma	Senior Scientist
Markus Kroll	Nuvisan ICB GmbH	Lab Head PhysChem
Martin Hemmerling	AstraZeneca	Prinicipal Scientist
Martina Pannuzzo	Astrazeneca	Associate Principal Scientist
Mateusz Galuszka	Selvita	Senior Director, Business Development
Matthieu Favory	AstraZeneca	Scientist
Meirion Richards	Almac Discovery	Technical Leader
Merran Bryford	AstraZeneca	Postdoctoral Research Fellow
Mohit Tyagi	AstraZeneca	Senior Scientist

Nikita King	Syngenta	Principal Physical Chemist
Nikolas Daskalakis	AstraZeneca	Senior Scientist
Patrick Wehrli	AstraZeneca	DMPK lead
Paul Dyer	Halo Labs	Field Application Scientist
Pavel Gershkovich	University of Nottingham	Associate Professor
Rebeca Ruiz	Pion Inc	Principal Scientist
Richard Visser	ACD/Labs	Account Manager
Rob Young	Blue Burgundy	Principal
Samar	karolinska institute	research assistant
Sami Svanbäck	The Solubility Company	CEO
Sanja Novak Ratajczak	Ryvu Therapeutics	Scientist
Sara Carlert	AstraZeneca	Director
Saw Simeon	Uppsala University	Post doctoral
Shareef Jarvi Antar	Eurofins Villapharma	ADME Team Leader
Shenaz Bunally	GlaxoSmithKline	Scientific Leader
Soma Aref	AstraZeneca	Associate Scientist
Sonia Espinosa	Almirall, S.A.	Senior Scientist
Staffan Berg	AstraZeneca	Senior Scientist Biopharmaceutics
Stephane Rodde	Novartis	Principal Scientist
Stephen Timothy Buckley	Novo Nordisk	Vice President
Tomas Leek	AstraZeneca	Director
Ulrika Ekstrand	AstraZeneca	Conference Support
Ulrika Tehler	AstraZeneca	Senior Director
Valentyna Pivnytska	AstraZeneca	Senior Scientist
Vasanthanathan Poongavanam	Uppsala University	Senior Forskare
Vigneshwari Subramanian	Astrazeneca	Senior Data Scientist
Vijay Kamal	AstraZeneca	Senior Scientist
Viktoriia Meklesh	AstraZeneca	Senior Scientrist
Wagner, Björn	F.Hoffmann-La Roche Ltd.	Senior Scientist
Yoko Shishikura	University of Dundee	Bioanalyst
Yufei Zhu	School of pharmacy, university of Nottingham	PhD student
Yuliia Holota	Enamine	Senior Manager Preclinical Pharmacology
Zulma Santisteban Valencia	AstraZeneca	SRS

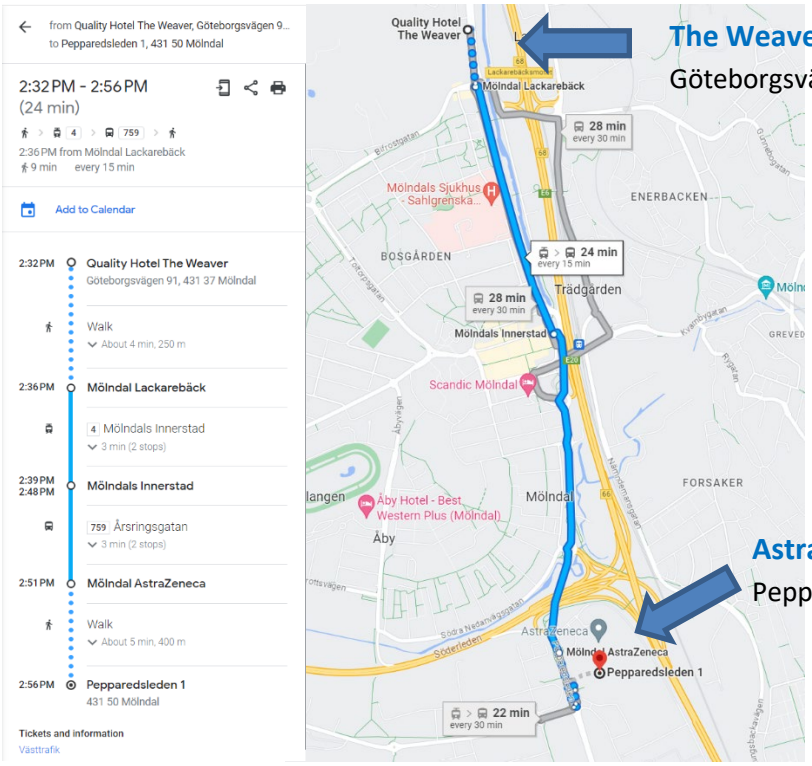
Space for Notes

Maps

Quality Hotel The Weaver, Lat57.6689-Lon12.0150, Göteborgsvägen 91, 43137 Mölndal, Sweden

From hotel The Weaver to AstraZeneca PGN Conference Center, Pepparedsleden 5 Mölndal

A bus is scheduled to depart from the Weaver hotel at 8:10 taking the delegates to the Astrazeneca PGN Conference Center



The Weaver Hotel: Lat57.6689-Lon12.0150, Göteborgsvägen 91, 43137 Mölndal, Sweden

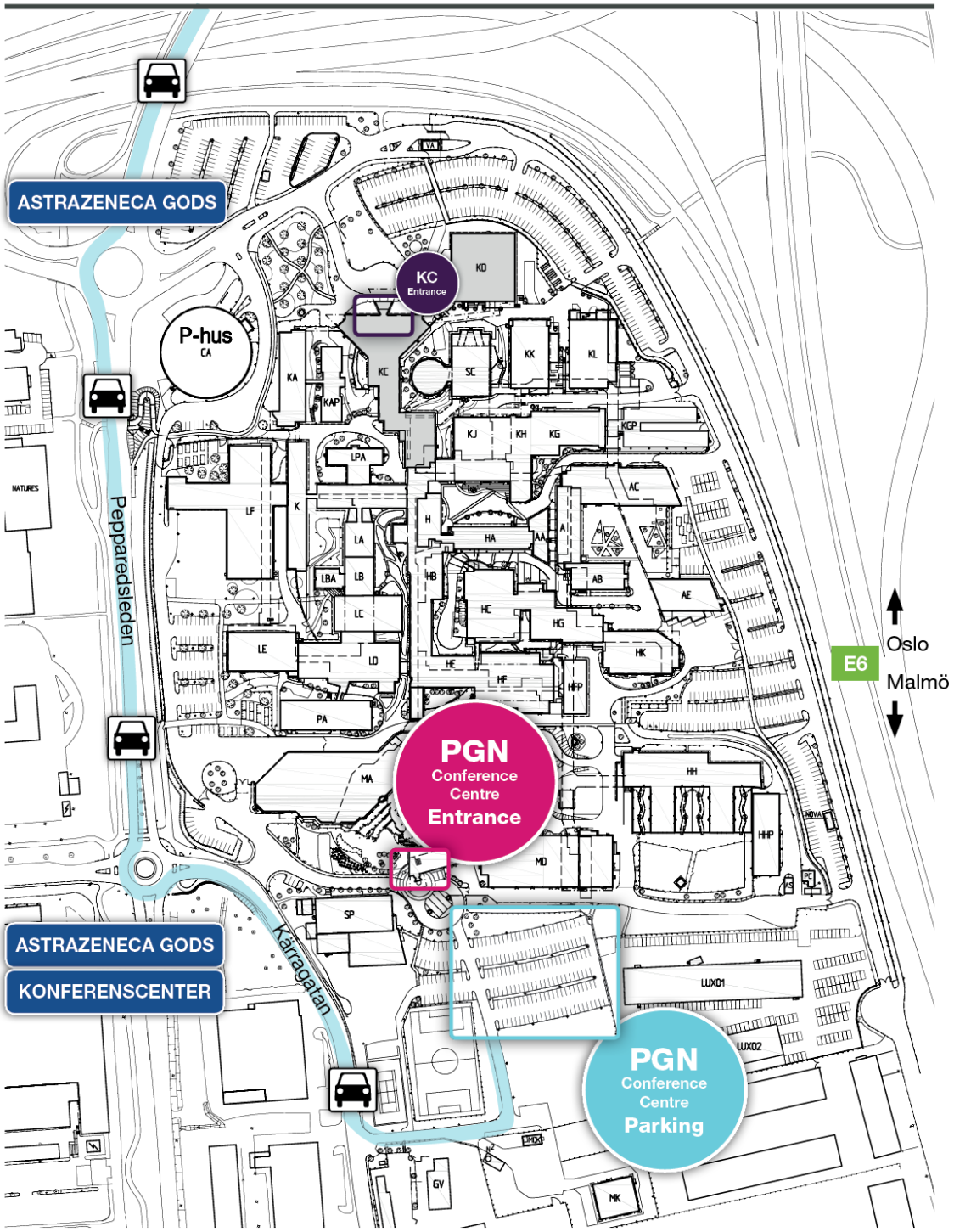
AstraZeneca PGN Conference Center, Pepparedsleden 5 Mölndal: Lat57.6421-Lon12.0211

AstraZeneca PGN Conference Center, Pepparedsleden 5 Mölndal: Lat57.6421-Lon12.0211

Parking available just next to the PGN entrance (see map)

NOTE that the entrance to the PGN center is NOT the main AstraZeneca Entrance called KC

PGN Conference Centre, Pepparedsleden 5, Mölndal



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