International Helmholtz Drug Discovery Conference

April 28 - 30, 2025 · Berlin, Germany

HDDC 2025

CONFERENCE BOOK

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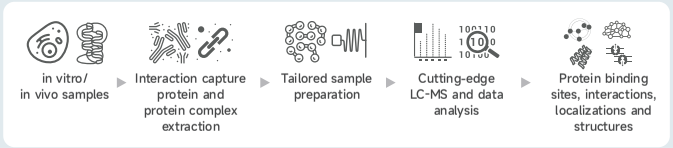

Drug-centric	Protein-centric	Cell-wide
Proteome-wide target and off-target engagment	Targeted interactomes Epitope mapping Disulfide mapping	Disocvering protein and PPI target candidates in intact biological systems

Let's Collaborate

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Welcome Address

We very warmly welcome you to the 4th **International Helmholtz Drug Discovery Conference 2025** (HDDC2025) on the Campus Berlin-Buch.

Campus Berlin-Buch has a rich legacy in biomedical science, with about 100 years of history and numerous success stories in the development of new therapies. The main research institutes on the Campus Berlin-Buch are the Max-Delbrück-Center for Molecular Medicine (MDC) and the Research Institute for Molecular Pharmacology (FMP) which jointly host HDDC2025.

As part of the Health Area within the Helmholtz Association, Max-Delbrück-Center for Molecular Medicine (MDC) aims to elucidate the molecular mechanisms of health and disease, and translate those findings into medical practice. Through academic, clinical, and industrial partnerships, biological discoveries are transformed into clinical applications that detect, treat, and ultimately prevent disease. The MDC harnesses interdisciplinary collaboration to decipher the complexities of disease at the systems level – from molecules and cells to organs and the entire organism. The goal is to create a healthier future through sustainable research in an environment that inspires and nurtures diverse talent.

The Leibniz-Forschungsinstitut für Molekulare Pharmakologie (FMP) aims to broaden the molecular basis of pharmacological therapies at a stage prior to drug development by identifying and characterizing novel active compounds and mechanisms of action. What keeps us healthy and what makes us sick? How does a drug reach the right target in the body? How can viruses and bacteria be prevented from entering cells and tissues? The FMP works on these questions by investigating biochemical processes in cells and organs and by studying the molecular causes of diseases. The FMP also conducts targeted drug research or develop novel diagnostics and therapeutics that form the basis of tomorrow's medicine.

EU-OPENSCREEN, a not-for-profit European Research Infrastructure Consortium (ERIC) for chemical biology and early drug discovery has its central office and compound management laboratory on Campus Berlin-Buch. It is dedicated to advancing chemical biology and provides open access to cutting-edge screening, medicinal chemistry, chemoproteomics, and spatial MS-based omics platforms. EU-OPENSCREEN's mission is to support researchers in developing small molecule modulators, and its compound collection advances the understanding of complex biological systems. By fostering scientific discovery and collaboration, EU-OPENSCREEN aims to improve human health, enhance quality of life, and contribute to addressing global challenges.

To support translation, Campus Berlin-Buch also hosts multiple laboratory buildings for start-ups and is currently home to 76 companies - most of them focused on biomedical innovation. These companies are advancing a broad range of therapeutic modalities, including small molecules, nucleic acids, cell-based therapies, and medical devices.

While these therapeutic approaches are becoming increasingly diverse, small molecules remain a cornerstone of drug development. Alongside RNA-based strategies, they are a central theme of HDDC2025. The meeting will cover cutting-edge developments in drug discovery, including RNA as both a drug and a target, PROTACs, artificial intelligence in drug discovery, and chemoproteomics. The program features keynote lectures from leading scientists around the world, complemented by selected short talks and poster presentations from submitted abstracts. Additionally, there will be a dedicated session for companies to present their innovative research.

The biannual Helmholtz Drug Discovery Conferences organized by the Drug Research Initiative, a consortium of all Helmholtz Centers in the Health Area, have consistently served as dynamic platforms for exchange among researchers from academia, biotech, and the pharmaceutical industry. We are confident that HDDC2025 will follow this tradition.

Michael Bader

MDC

Edgar Specker

FMP

Organization

Local Organizing Committee

Michael Bader	MDC
Edgar Specker	FMP
Oliver Daumke	MDC
Philip Gribbon	EU-OPENSCREEN
Jens von Kries	FMP
Markus Landthaler	MDC
Marc Nazaré	FMP
Ilaria Piazza	MDC
Han Sun	FMP

Helmholtz Drug Research

Mark Brönstrup	HZI
Michael Bader	MDC
Ursula Bilitewski	HZI
Philip Denner	DZNE
Ronald Frank	FMP
Martin Göttlicher	HMU
Kamyar Hadian	HMU
Anna Hirsch	HIPS
Jens von Kries	FMP
Aubry Miller	DZHK
Marc Nazaré	FMP
Oliver Plettenburg	HMU
Michael Sattler	HMU

Conference Office

Matthias Runow
Congress Manager
Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC)
Robert-Rössle-Str. 10
13125 Berlin
Phone: +49 30 94063720

Timkehet Teffera
Congress Manager
Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC)
Robert-Rössle-Str. 10
13125 Berlin
Phone: +49 30 94064255

Lien-Georgina Dettmann
Congress Manager
Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC)
Robert-Rössle-Str. 10
13125 Berlin
Phone: +49 30 94062719

E-Mail: events@mdc-berlin.de

Conference Information

Venue:
Max Delbrück Communications Center (MDC.C)
Robert-Rössle-Str. 10
13125 Berlin-Buch
Germany

Date:
From Monday, April 28th to Wednesday, April 30th, 2025

Reception Desk:
The reception desk will be open throughout the whole meeting.

Talks:
Talks will be held in the room *Axon 1* (1st floor of the MDC.C) and must be uploaded into the presentation computer in Axon 1 in the break before the session at the latest.

Posters:
Posters will be displayed during the whole meeting in building 84 directly adjacent to the MDC.C. The size of a poster should not exceed 1.20m x 1.20m. In this program you will find the number for your abstract and according to these numbers the posters will be mounted in the exhibition room. Mounting material will be available from the registration desk. The Poster session will be held on Tuesday, 29th, from 5:45 to 8:15 pm. Half of this time you should be present at your poster depending on its number as shown in the final program. Poster reviewers will come around and eventually suggest the price winners
5:45 – 7:00 pm
Presentation of posters with odd numbers
7:00 – 8:15 pm
Presentation of posters with even numbers

Social Events for all Participants

Dinner at Alte Pumpe, Lützowstr. 42, 10785 Berlin
Monday, April 28th, 7:00 pm – 9:00 pm
Busses will leave from Max Delbrück Communications Center (MDC.C) at 6:00 pm

Poster Session and Buffet Dinner at MDC.C
Tuesday, April 29th, 5:45 pm – 8:15 pm

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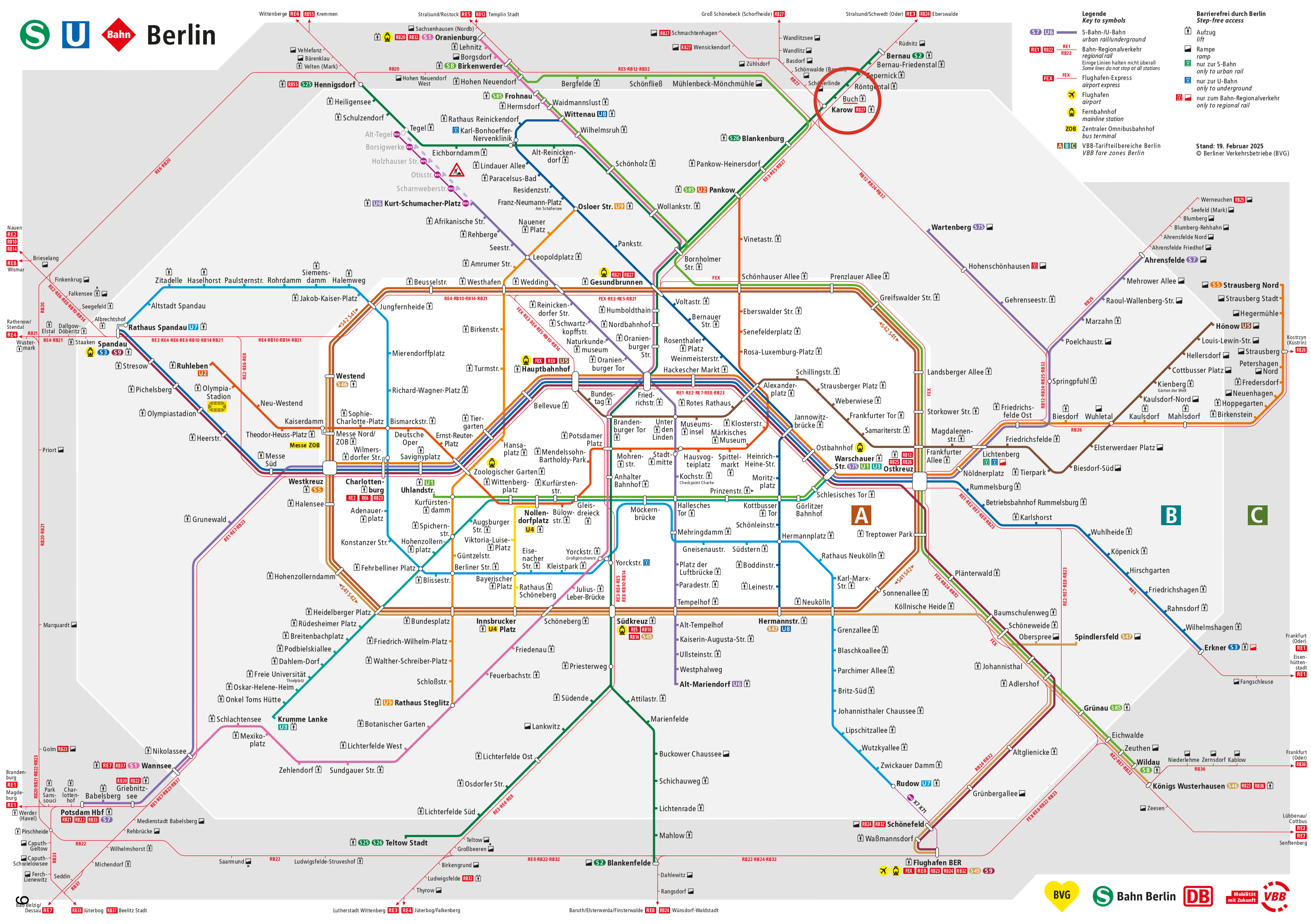

Legende
Key to symbols

- S7 U6 — S-Bahn-/U-Bahn *urban rail/underground*
- RE1 RB22 — Bahn-Regionalverkehr *regional rail*; Einige Linien halten nicht überall *Some lines do not stop at all stations*
- FEX — Flughafen-Express *airport express*
- Flughafen *airport*
- Fernbahnhof *mainline station*
- ZOB — Zentraler Omnibusbahnhof *bus terminal*
- A B C — VBB-Tarifteilbereiche Berlin *VBB fare zones Berlin*

Barrierefrei durch Berlin
Step-free access

- Aufzug *lift*
- Rampe *ramp*
- nur zur S-Bahn *only to urban rail*
- nur zur U-Bahn *only to underground*
- nur zum Bahn-Regionalverkehr *only to regional rail*

Stand: 19. Februar 2025

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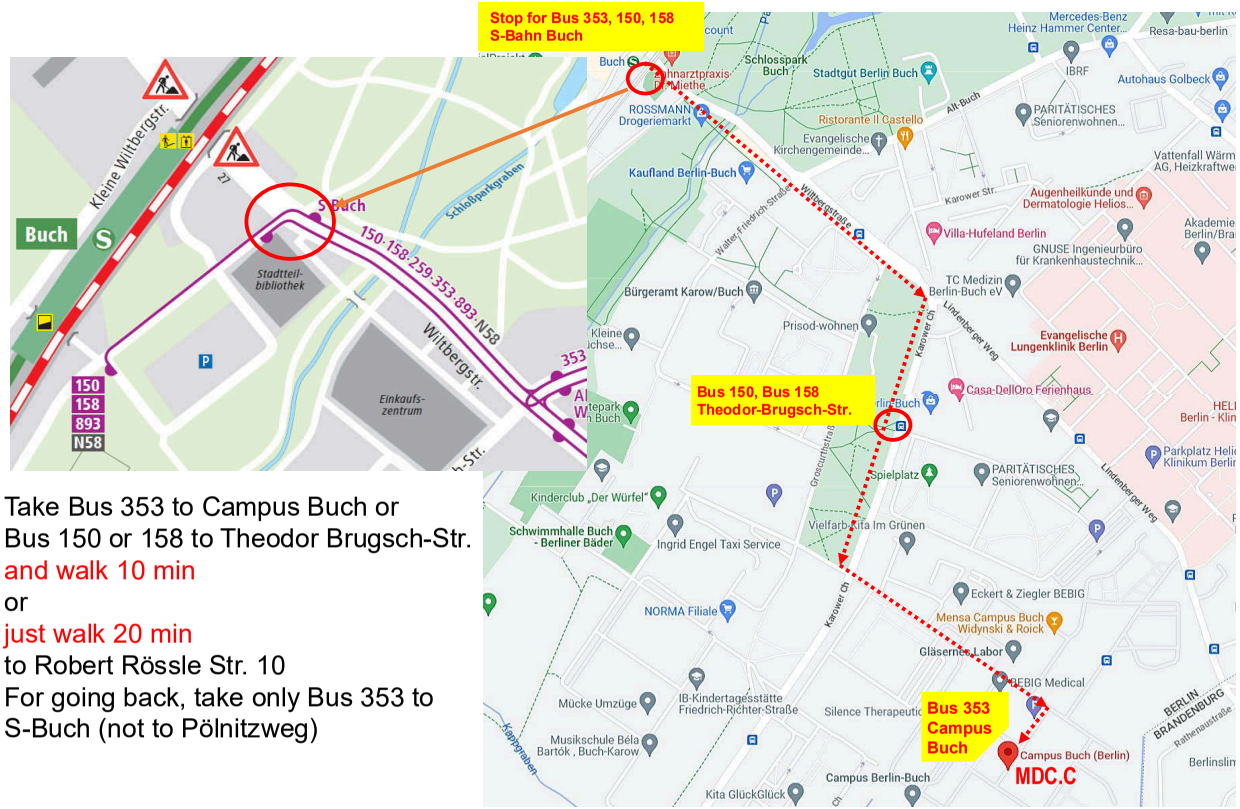
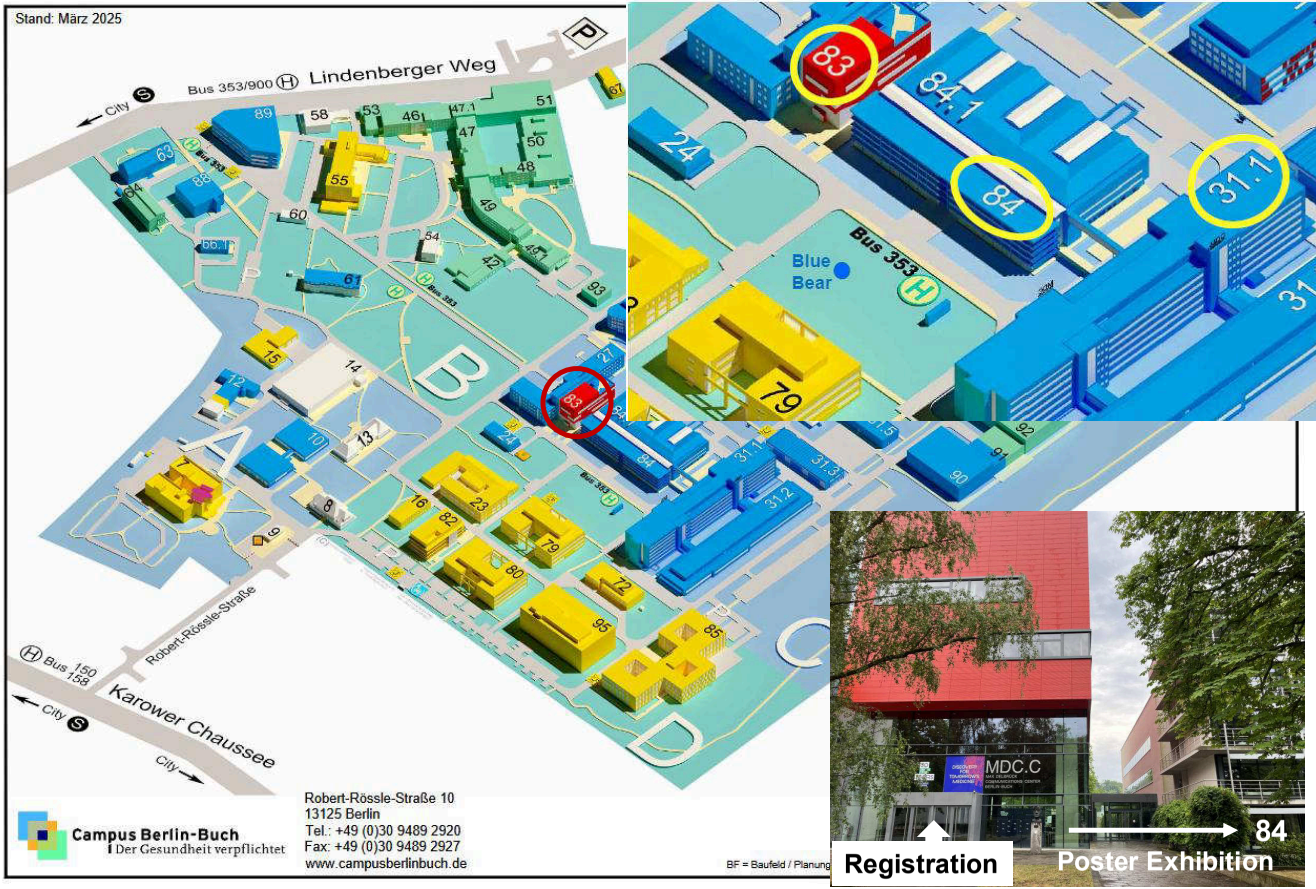
From train station **S Buch** to MDC **Campus Buch**:



Take Bus 353 to Campus Buch or
Bus 150 or 158 to Theodor Brugsch-Str.
and walk 10 min
or
just walk 20 min
to Robert Rössle Str. 10
For going back, take only Bus 353 to S-Buch (not to Pölnitzweg)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Registration
84
Poster Exhibition

Building 83 (red)
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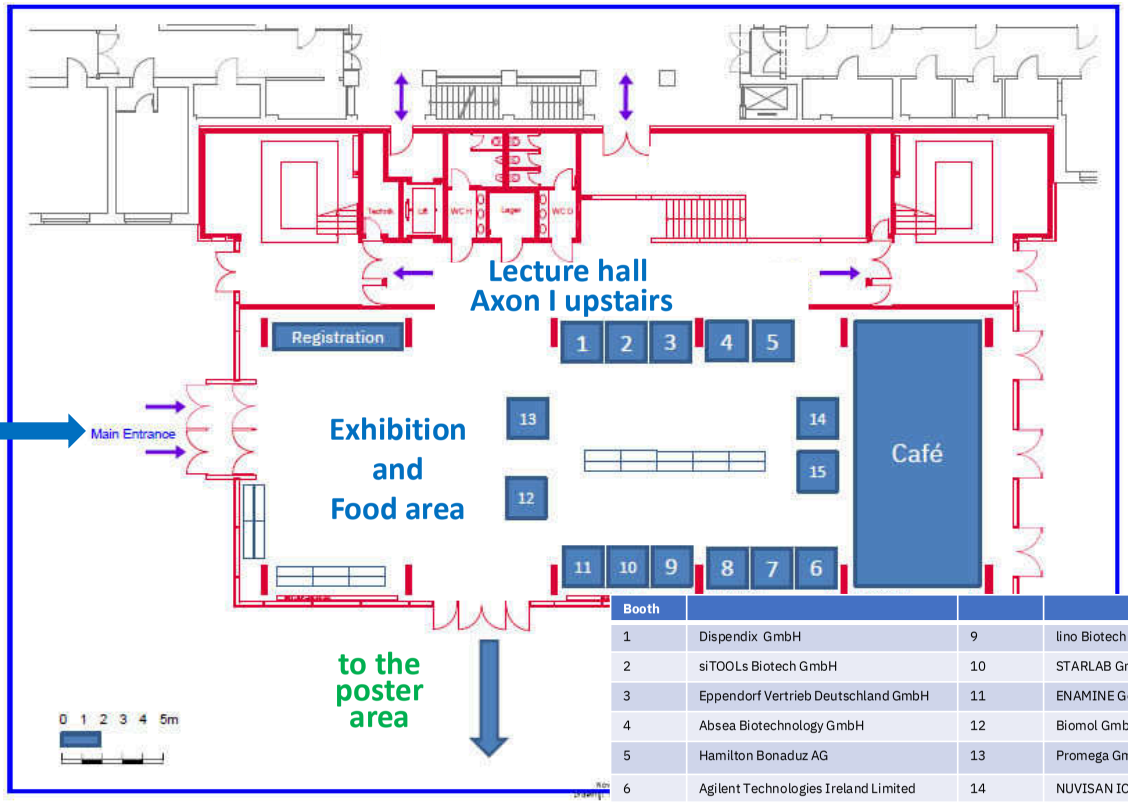


Booth			
1	Dispendix GmbH	9	Iino Biotech AG
2	siTOOLs Biotech GmbH	10	STARLAB GmbH
3	Eppendorf Vertrieb Deutschland GmbH	11	ENAMINE Germany GmbH
4	Absea Biotechnology GmbH	12	Biomol GmbH
5	Hamilton Bonaduz AG	13	Promega GmbH
6	Agilent Technologies Ireland Limited	14	NUVISAN ICB GmbH
7	Medchemtronica	15	ChemBridge Corporation
8	Symeres		

Blue
BEAR

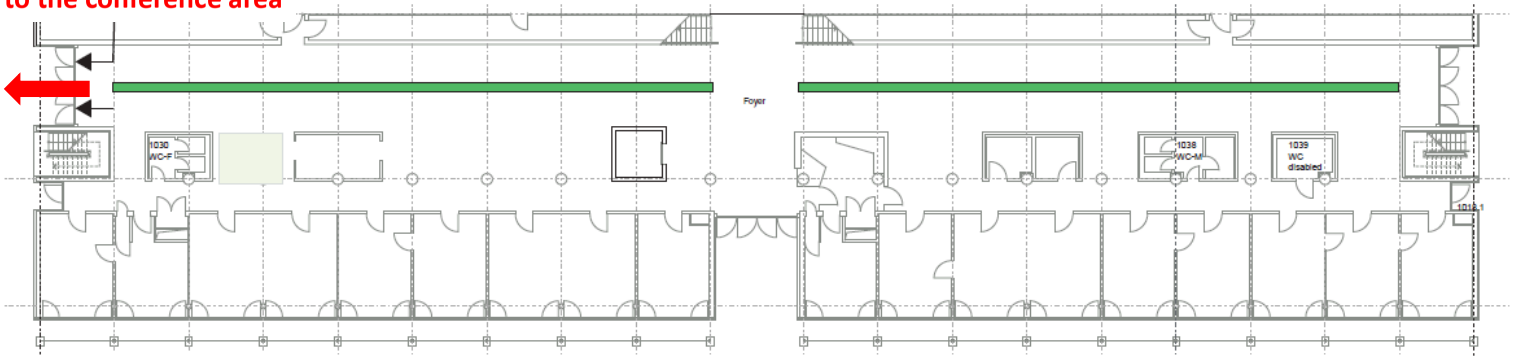
Bus station

Building 84

Building 84
HvH

Poster area

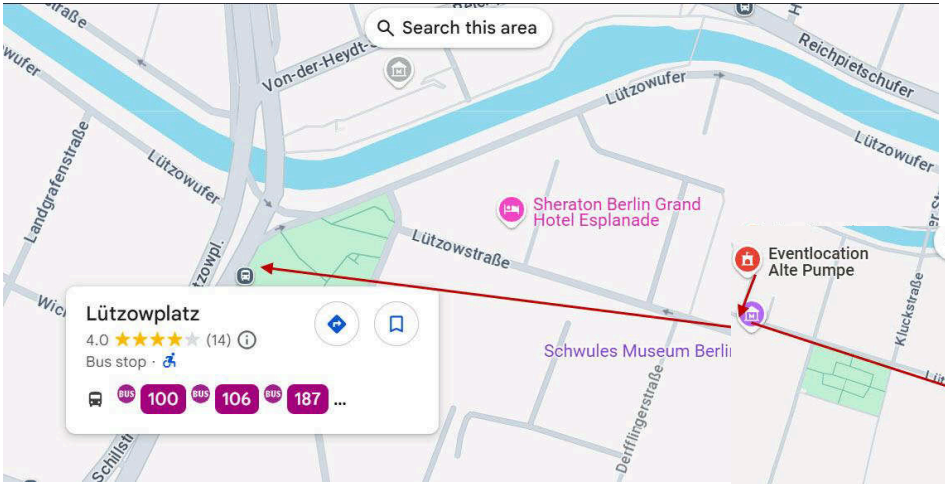
to the conference area



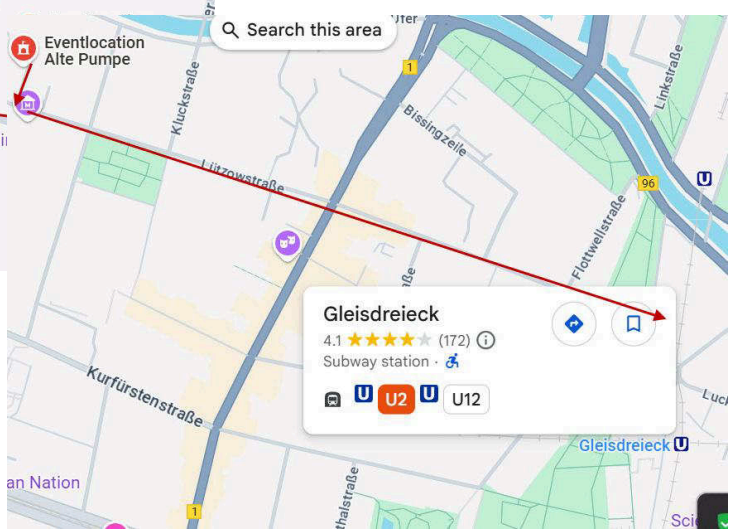
Posterwalls

House 84 (HvH)

From Dinner place **Alte Pumpe (Lützowstr. 42, 10785 Berlin)** to public transport options:



https://www.altepumpe.de/DE/index.html



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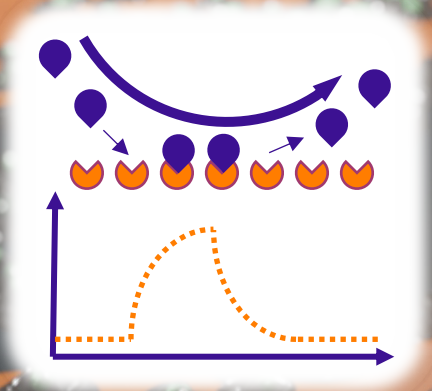

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Program

Monday, April 28th

10:30 – 12:30 EU-OPENSCREEN Workshop on Chemoproteomics and Spatial MS-based Omics

10:30 – 10:40: Introduction to EU-OPENSCREEN and the new Chemoproteomics and Spatial MS-based Omics sites - Philip Gribbon (10 min)
10:40 – 11:00: Proteome-wide approaches for characterizing drug mechanism of action - Bernhard Kuster (20 min)
11:00 – 11:20: Chemical Proteomics at KI: Specialized Proteomics Approaches and Support to Deconvolute Targets, Elucidate MoA, and Map Binding Sites and Conformational Changes - Massimiliano Gaetani (20 min)
11:20 – 11:40: MALDI Imaging applications in pharmaceutical R&D and chemical biology - Carsten Hopf (20 min)
11:40 – 11:50: Break
11:50 – 12:30: Open Discussion (40 min)

12:00 – 13:00 Arrival and Registration

13:00 – 13:20 Opening
Chairs: Michael Bader, Edgar Specker

13:20 – 15:05 Session 1 Chemical Biology
Chairs: Oliver Plettenburg, Jens von Kries

13:20 – 13:50
Helma Wennemers
ETH Zurich, Switzerland
Chemistry in the extracellular matrix for monitoring fibrosis

13:50 – 14:20
Davide Calebiro
University of Birmingham, UK
Dissecting G protein-coupled receptor signalling with light

14:20 – 14:35
Emilia Slugocka[1], Filipe Menezes[2], and Anna Wieckowska[1]
[1]Jagiellonian University Medical College, Faculty of Pharmacy, [2]Institute of Structural Biology, Krakow, Poland
Exploring novel GSK-3β inhibitors for neurodegeneration: structural biology meets quantum mechanics

14:35 – 14:50
Nina-Louisa Efrém[1], Machoud Amoussa[1], Ziqiong Guo[1], Feng Bo[2], Victoria Zeitz[1], Katrin Frank[3], Yvette Roske[4], Silke Radetzki[1], Leonardo Seidl[1], Clemens Alexander Wolf[5], Szymon Pach[5], Noémi Csorba[6], Péter Ábrányi-Balogh[6], Jens-Peter von Kries[1], Oliver Daumke[4], György Keserű[6], Gerhard Wolber[5], Jia Li[2], Hana Algül[3], and Marc Nazaré[1]
[1]Leibniz-Forschungsinstitut für Molekulare Pharmakologie (FMP), Berlin, Germany; [2]Shanghai Institute of Materia Medica (SIMM), Chinese Academy of Sciences; [3]Comprehensive Cancer Center, Institute for Tumor Metabolism, TUM School of Medicine and Health, University Medical Center, TUM, Germany; [4]Max Delbrück Center for Molecular Medicine, Berlin, Germany; [5]Freie Universität Berlin, Molecular Design Group, Germany; [6]Medicinal Chemistry Research Group, National Drug Research and Development Laboratory, HUN-REN Research Centre for Natural Sciences (RCNS), Hungary
From active site- to allosteric SHP2 inhibitors: Discovery and structure-activity relationship of N-aryl-1H-azaindazoles

14:50 – 15:05
Jonathan Franke[1,2], Jan V. V. Arafiles[1], Christian Leis[1,2], and Christian P. R. Hackenberger[1,2]
[1]Leibniz-Forschungsinstitut für Molekulare Pharmakologie (FMP), [2]Humboldt Universität zu Berlin, Germany
Intracellular delivery of native proteins by bioreversible polyarginine modification

15:05 – 15:25 3 min Flashtalks of Gold Sponsors
Chairs: Michael Bader, Edgar Specker

Absea, Agilent, Beckman Coulter, Bruker, Dispendix, Hamilton Bonaduz

Program

15:25 – 15:45 Coffee Break, Posters and Exhibition

15:45– 17:45 Session 2 PROTAC and other Induced Proximity Drugs
Chairs: Marc Nazaré, Aubry Miller

15:45 – 16:15
Ed Tate
Imperial College London, UK
Targeting protein modification: from chemical biology to drug discovery

16:15 – 16:45
Ting Han
Tsinghua University, Beijing, China
Selective degradation of multimeric proteins by molecular glue and PROTAC degraders

16:45 – 17:15
Cristina Mayor-Ruiz
Institute for Research in Biomedicine, Barcelona, Spain
Chemical rewiring of E3 ubiquitin ligases

17:15 – 17:30
Katharina Richter[1], Anne Grapin-Botton[1], and André Nadler[1]
[1]MPI-CBG, Dresden, Germany
Targeted protein degradation to modulate Notch signaling in pancreatic progenitors

17:30 – 17:45
Xinlai Cheng[1]
[1]Goethe University Frankfurt, Germany
Chemical innovations in targeted protein modulation and epigenome editing

17:45 – 18:10 3 min Flashtalks of Gold Sponsors
Chairs: Michael Bader, Edgar Specker

Lino Biotech, Nuvisan, Metabolon, Promega, siTOOLS, Starlabs, Symeres

18:10 Departure of busses to Dinner

19:00 – 21:00 Dinner at Alte Pumpe, Lützowstr. 42, 10785 Berlin

Program

Tuesday, April 29th

09:15 – 11:00 Session 3 RNA / DNA
Chairs: Oliver Daumke, Mark Brönstrup

09:15 – 09:45
Matthew Disney
The Scripps Research Institute, Jupiter, FL, USA
Sequence-based design of small molecules targeting RNA – from binders to degraders

09:45 – 10:15
Juan Valcarcel
Barcelona Institute of Science and Technology, Spain
Networks of alternative splicing regulation in cancer

10:15 – 10:30
Joanna Bogusławska[1], **Aizhan Rakhmetullina[2]**, Alex Białas[1], Małgorzata Grzanka[1], Beata Rybicka[1], Joanna Życka-Krzesińska[1], Tomasz Molcan[2,3], Piotr Zielenkiewicz[2,4], Leszek Pączek[2,5], and Agnieszka Piekiełko-Witkowska[1]
[1]Centre of Translational Research, Centre of Postgraduate Medical Education, [2]Institute of Biochemistry and Biophysics, [3]Institute of Animal Reproduction and Food Research, Polish Academy of Sciences, [4]Institute of Experimental Plant Biology and Biotechnology, University of Warsaw, Poland, [5]Medical University of Warsaw, Poland
miR395e from Cassava: A promising plant-derived miRNA for renal cancer therapy

10:30 – 10:45
Irene Ponzo[1], Wouter Engelen[1], Mareike De Pascali[1], Pablo Porragas Paseiro[1], **Guido Uhlenbrock[1],** Vivien Hafner[1], Ralf Strasser[1], and Ulrich Rant[1,2]
[1]Bruker Biosensors, [2]Kurt-Schwabe-Institute for Bioanalytical Systems, Germany
Biophysical investigation of structural changes as mode of action of drugs targeting nucleic acids and proteins

10:45 – 11:00
Mara Hebeis[1], Thanh Hoang Duc[1], Nina Kirchgässler[2], and Ingrid Span[1]
[1]FAU Erlangen-Nürnberg, [2]HHU Düsseldorf, Germany
Therapeutic DNAzymes for the treatment of HIV-1

11:00 – 11:30 Coffee Break, Posters and Exhibition

11:30 – 13:15 Session 4 RNA / Infection
Chairs: Markus Landthaler, Ursula Bilitewski

11:30 – 12:00
Simone Spuler
Charité University Medicine Berlin, Germany
Multiplex editing of muscular dystrophy causing mutations using CRISPR-RNA and RNP tools.

12:00 – 12:30
Michelle Hastings
University of Michigan Medical School, Ann Arbor, MI, USA
Splice-switching antisense oligonucleotides: from discovery to medicine

12:30 – 12:45
Barak Akabayov[1]
[1]Ben-Gurion University of the Negev, Israel
Combining NMR fragment screening with AI-based cheminformatics to design small molecules targeting RNA for antibiotic development

Program

12:45 – 13:00
Steffen Grimm[1], Melissanne de Wispelaere[1], Charlotte Blanc[1], Gilles- Olivier Gratien[1], Juliette Lavaux[1], Priscilla Rebus[1], Viviane Liziard[1], Pauline Puel[1], Manon Jouvert[1], Anne Tuukkanen[1], Mateusz Mieczkowski[1], Claudia Beato[1], Ghislaine Marchand[1], Stephanie Versluys[1], and Antoine Alam[1]
[1]Evotec SE
Discovery of small molecule antivirals targeting hepatitis B virus epsilon element

13:00 – 13:15
Ayanda I. Zulu[1], Carole Guimard[1], Godfrey Mayoka[1], Niklas Krappel[1], Sari Rasheed[1], Peer Lukat[2], Wulf Blankenfeldt[2], Jennifer Herrmann[1], Rolf Müller[1], Walid A. M. Elgaher[1], and Anna K. H. Hirsch[1]
[1]Helmholtz Institute for Pharmaceutical Research Saarland (HIPS) – Helmholtz Centre for Infection Research (HZI), 66123 Saarbrücken, [2]Helmholtz Centre for Infection Research GmbH, 38124 Braunschweig, Germany
Design and optimization of a new chemical class of inhibitors of the bacterial beta-sliding clamp DnaN

13:15 – 14:30 Lunch, Posters and Exhibition

14:30 – 16:15 Session 5 RNA / Cardiovascular Drugs
Chairs: Anna Hirsch, Enno Klussmann

14:30 – 15:00
Stefan Engelhardt
TU Munich, Germany
Development of a macrophage-targeted RNA therapeutic

15:00 – 15:30
Thomas Thum
MH Hannover, Germany
Use of living human cardiac tissue for next generation drug discovery

15:30 – 15:45
Isabell Drath[1], Malte Feja[1], Sandra Weiß[1], Alexander Ewe[2], Achim Aigner[2], and Franziska Richter Assencio[1]
[1]University of Veterinary Medicine Hannover, [2]University of Leipzig Faculty of Medicine, Germany
Nanoparticle-based nose-to-brain delivery of siRNA or miRNA to reduce alpha-synuclein pathology in a mouse model of Parkinson's disease (Thy1-aSyn)

15:45 – 16:00
Jan Borggräfe[1,2], Laure Gauthé[1,2], Lorenzo Baronti[1,2], Elisa Donati[3], Alejandro Varela Rial[3], Gianni De Fabritiis[3], and Michael Sattler[1,2]
[1]Helmholtz Munich, [2]Technical University of Munich, Germany, [3]Acellera Therapeutics Inc, Barcelona, Spain
Identification and ranking of RNA-binding small molecules by NMR

16:00 – 16:15
Yelena Mostinski[1], Thais Gazzi[1,2], Leonard Mach[1], Anahid Omran[1], Małgorzata Wasinka-Kalwa[1], Jara Bouma[3], Lucia Scipioni[4], Xiaoting Li[5,6], Silke Radetzki[1], David Sykes[7], Maria Schippers[1], Christof van der Horst[3], Benjamin Brennecke[1], Annaleah Hanske[1], Wolfgang Guba[1], Jens P. von Kries[1], Sergio Oddi[4], Tian Hua[5,6], Dmitry Veprintsev[7], Laura Heitman[3], Mauro Maccarrone[8,9], Uwe Grether[2], and Marc Nazaré[1]
[1]Leibniz-Institut für Molekulare Pharmakologie FMP, Campus Berlin-Buch, Germany; [2]Roche Pharma Research & Early Development, Roche Innovation Center Basel, Switzerland; [3]Division of Drug Discovery and Safety, Leiden Academic Centre for Drug Research, Leiden University, 2333 CC, The Netherlands; [4]University of Teramo, 64100 Teramo, Italy; [5]iHuman Institute, ShanghaiTech University, Shanghai 201210, China; [6]School of Life Science and Technology, ShanghaiTech University, Shanghai 201210, China; [7]Faculty of Medicine & Health Sciences, University of Nottingham, Nottingham NG7 2UH, UK; [8]DISCAB at University of L'Aquila, 67100 L'Aquila & CERC at IRCCS Santa Lucia Foundation, 00164 Rome, Italy; [9]European Center for Brain Research/Institute for Research and Health Care (IRCCS) Santa Lucia Foundation, Rome, Italy
Unlocking the Endocannabinoid System (ECS) with Chemical Probes

16:15 – 16:40 Coffee Break, Posters and Exhibition

Program

16:40 – 17:45 Session 6 Startup / company presentations
Chairs: Natalya Baltrukovich (HTGF), Ronald Frank

16:40 – 16:45
Natalya Baltrukovich[1]
[1]HTGF, Germany
Introduction to HTGF

16:45 – 16:55
Marius Arend[1], Charles NJ Ravarani[1], Hannes A Baukmann[1], and Marco F Schmidt[1]
[1]Biotx.ai GmbH, Germany
Scaling Mendelian Randomization to the million genomes era allows for mechanistic models of drug trial success

16:55 – 17:05
Christoph Goletz[1], Mario Avarello[1], Beate Habel[1], and **Hans Baumeister**[1]
[1]FyoniBio GmbH, Berlin, Germany
Quantification of oligonucleotide-based therapeutics in cerebrospinal fluid (CSF) and tissues using high-sensitive hybECLIA-based assays

17:05 – 17:15
Ivana Jaser[1], **Gianluca Luigi Russo**[1], Jan Schnatwinkel[1], and Nathan B P Adams[1]
[1]NanoTemper Technologies GmbH, Munich, Germany
Ultra-high-throughput biophysical screening of MEK1 using the Dianthus uHTS platform

17:15 – 17:25
Hannah Minas[1], Maximilian Bahls[1], Evangelos-Marios Nikolados[1], Irene Wüthrich[1], Steven Schmitt[1], and Kenan Bozhüyük[2]
[1]Myria Biosciences AG; [2]Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), Germany
Harnessing AI and synthetic biology for NRPS-based drug discovery

17:25 – 17:35
Eliot Morrison[1], **Luca Penso Dolfin**[1], Judith Hauptmann[1], Nina Was[1], Wei-Hung Pan[1], and Marie Wikström Lindholm[1]
[1]Silence Therapeutics GmbH
Understanding the limits of hybridization-dependent siRNA: off target interactions

17:35 – 17:45
Peter Sullivan[1], Thomas Hesterkamp[2,3], Ronald Garcia[1], Jennifer Herrmann[1,3], Olga Kalinina[1], and Rolf Müller[1,3]
[1]Helmholtz Institute for Pharmaceutical Research Saarland; [2]Helmholtz Centre for Infection Research, Braunschweig; [3]German Centre for Infection Research, Germany
MyxoTech: offering a hyper-organized library of microbial dark matter chemistry to the pharmaceutical industry

17:45 – 20:15 Poster Session and Exhibition, Dinner

17:45 – 19:00
*Presentation of posters with **odd** numbers*
19:00 – 20:15
*Presentation of posters with **even** numbers*

18:30 Guided lab tour through EU-OPENSCREEN and FMP compound management facilities

Program

Wednesday, April 30th

09:15 – 11:00 Session 7 Artificial Intelligence in Drug Discovery
Chairs: Han Sun, Michael Sattler

09:15 – 09:45
Grzegorz Popowicz
Helmholtz Munich, Germany
Reading your drug target wishes - a structure-aware AI model guiding drug discovery

09:45 – 10:15
Brian Shoichet
University of California San Francisco, CA, USA
Following the rabbit into chemical space

10:15 – 10:30
Ahmet Sarigun[1], and Altuna Akalin[1]
[1]Max Delbrück Center, Berlin, Germany
Do we need Deep Learning for high-throughput virtual screening in protein-ligand docking?

10:30 – 10:45
Daniel Palmer[1], Roberto A. Avelar[1], Claudia Fruijtier[1], and **Georg Fuellen[1]**
[1]Rostock University Medical Center, Germany
Using Large Language Models for assessing drug toxicity and drug efficacy

10:45 – 11:00
Marie Oestreich[1], Erinc Merdivan[2], Michael Lee[1], Shubhi Ambast[1], Joachim L. Schultze[1], Marie Piraud[2], and **Matthias Becker[1]**
[1]German Center for Neurodegenerative Diseases (DZNE); [2]Helmholtz Munich, Germany
DrugDiff: small molecule diffusion model with flexible guidance towards molecular properties

11:00 – 11:30 Coffee Break, Posters and Exhibition

11:30 – 13:00 Session 8 Chemoproteomics
Chairs: Ilaria Piazza, Philipp Gribbon

11:30 – 12:00
Bernhard Kuster
TU Munich, Gemany
Proteome-wide approaches for characterizing drug mechanism of action

12:00 – 12:30
Anne-Claude Gingras
Lunenfeld-Tanenbaum Research Institute, Toronto, Canada
Signal rewiring by oncogenic kinases

12:30 – 12:45
Zehong Zhang[1,3], Mei Wu[1], Max Ruwolt[1], Ying Zhu[1], Pin-Lian Jiang[1], Diogo Borges Lima[1], and **Fan Liu[1,2]**
[1]Leibniz-Forschungsinstitut für Molekulare Pharmakologie (FMP), [2]Charité Universitätsmedizin Berlin, [3]Freie Universität Berlin, Berlin, Germany
AIRPred: A Deep Learning model predictor for peptide intensity ratios in cross-linking mass spectrometry improves cross-link spectrum matching

12:45 – 13:00
Zuzana Demianova[1], Katrin Hartinger[1], Martin Steger[2], Uli Ohmayer[2], Bachuki Shashikadze[2], Björn Schwalb[2], and Garwin Pichler[1]
[1]PreOmics, [2]NEOsphere, Planegg, Germany
Deep proteomic screening platform for targeted protein degradation drug discovery

Program

13:00 – 13:30 Prices and Conclusions

13:30 End of meeting

14:00 Guided lab tour through EU-OPENSCREEN and FMP Compound Management Facilities

15:00 – 17:00 Workshop of Hamilton: Automation for Drug Discovery Assays and Compound Handling

Edgar Specker[1], David Garcia Lopez[2], Victoria Mora[2], Theresa Bamme-Schulz[3], Karim Benyaa[3], Axel Stamme[4]
[1]Leibniz-Forschungsinstitut für Molekulare Pharmakologie (FMP), [2]EU-OPENSCREEN ERIC, [3]Hamilton Germany GmbH, [4]Hamilton Storage

15:00 – 15:05: Introduction to Hamilton Theresa Bamme-Schulz (5 min)
15:05 – 15:20: Introduction to Automation – Axel Stamme/Theresa Bamme-Schulz (15 min)
15:20 – 15:30: Introduction to the compound management of FMP and EU-OPENCREEN – Edgar Specker (10 min)
15:30 – 15:40: Compound Handling with the integrative Hamilton Robotic System – David Garcia Lopez (10 min)
15:40 – 15:50: Biological profiling of the EU-OPENSCREEN academic compound library – Victoria Mora (10 min)
15:50 – 16:05: Break
16:05 – 16:45: Customized solutions for automated drug discovery at Hamilton – Karim Benyaa/Axel Stamme (40 min)
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Keynote Speakers' Abstracts

Dissecting G protein-coupled receptor signalling with light

***Davide Calebiro*[1]**

[1]University of Birmingham, UK

G protein-coupled receptors (GPCRs) are the largest family of membrane receptors and major drug targets. Whereas structural studies have provided major insights into the activation mechanisms of GPCRs, how these receptors operate in our cells to produce specific biological responses remains insufficiently understood. Davide's group develops innovative optical methods based on FRET/BRET and single-molecule microscopy that enable studying GPCR signalling in living cells with unprecedented spatiotemporal resolution. Using these approaches, they were among the first to demonstrate that GPCRs are not only active at the plasma membrane but also in the endosomal compartment, which has challenged the classical model of GPCR signalling. Ongoing work in the Calebiro lab is dedicated to further clarifying the physiological and pharmacological implications of GPCR signalling at intracellular sites, with a particular focus on metabolically relevant GPCRs. In parallel, they have further developed their innovative single-molecule approaches, which previously led to the discovery of receptor-G protein signalling nanodomains at the plasma membrane, to study other fundamental aspects of GPCR signalling such as the mechanisms of β-arrestin recruitment and activation. Altogether, Davide's work has revealed that the molecular events governing GPCR signalling are much more complex and dynamic than previously thought, which has important implications for our understanding of GPCR signalling and the development of 'intelligent' drugs targeting this important family of membrane receptors.

Keynote Speakers' Abstracts

Sequence-based design of small molecules targeting RNA – from binders to degraders

***Matthew Disney*[1]**

[1]UF Scripps, CA, USA

RNA presents significant opportunities as a drug target. The transcriptome—including both coding and non-coding RNAs—offers a vast landscape for therapeutic intervention. RNA plays a crucial role in a wide range of diseases, from viral infections and cancer to incurable genetic disorders. Traditionally, oligonucleotides have been used as therapeutics and research tools to disable RNA, proving transformative as both chemical probes and medicines. However, they do not effectively reach all tissues.

As a complementary approach, efforts have been made to develop small molecules that bind directly to structured regions of RNA, an area not typically targeted by oligonucleotides. Importantly, the structural conformation of RNA in a diseased state is essential for successful small-molecule discovery.

RNA structure can be predicted computationally or with experimental data, but discrepancies between predicted and actual biological structures can hinder progress. Selecting RNA targets with strong genetic or evolutionary validation increases the likelihood of success. Additionally, small molecules must demonstrate intracellular RNA binding—not just in vitro—to confirm their mechanism of action.

In this lecture, I will describe unbiased methods for identifying small-molecule RNA targets in intact cells and leveraging these interactions to infer RNA structure. I will explore how compounds can exert their effects either through direct binding or by recruiting effector mechanisms, such as ribonucleases, to degrade RNA. Furthermore, I will illustrate how small-molecule therapeutics and chemical probes targeting RNA can enhance our understanding of RNA biology and facilitate the translation of basic scientific discoveries into effective medicines. Lastly, I will discuss current challenges in the field, such as the difficulty of lead optimization, and propose ways in which the academic community can accelerate the development of RNA-targeted small-molecule drugs.

Keynote Speakers' Abstracts

Using proximity-dependent biotinylation to understand dynamic cell organization

Anne-Claude Gingras [1,2]

[1] Lunenfeld-Tanenbaum Research Institute, Sinai Health, Toronto, Canada
[2] University of Toronto, Toronto, Canada

Compartmentalization is essential for all complex forms of life. In eukaryotic cells, membrane-bound organelles and a multitude of protein- and nucleic acid-rich subcellular structures maintain boundaries and serve as enrichment zones to promote and regulate protein function, including signalling events. Consistent with the critical importance of these boundaries, alterations in the machinery that mediates protein transport between these compartments have been implicated in several diverse diseases. Understanding the composition of each cellular "compartment" (be it a classical organelle or a large protein complex) remains a challenging task.

Our research, utilizing the proximity-dependent biotinylation approach BioID, has provided a systematic map of the composition of various subcellular structures. This was achieved by using well-characterized subcellular markers as bait proteins. The relationships between the 'prey' proteins detected through this approach offer a unique insight into the protein organization within a cell. This understanding is further enhanced by the use of newly developed computational tools. We will first delve into our map of a human cell, which includes major organelles and non-membrane bound structures, including biomolecular condensates formed through liquid-liquid phase separation. We will demonstrate how this map can be effectively utilized to devise 'compartment sensors' for the exploration of dynamic cell signalling.

We will then describe advances in proximity proteomics that enable large-scale exploration of cancer translocations that involve protein tyrosine kinases. We reveal widespread biomolecular condensate formation by kinase fusions that recruit other enzymes and scaffold proteins to activate signalling outputs. We comment on the specificity of this recruitment and pathway activation, and discuss how therapeutic kinase inhibitor drugs alter the formation of biomolecular condensates and alter the proximal profiles of the kinase fusions.

Together, this work will provide a framework for the understanding of the spatiotemporal parameters of cellular signalling.

This work was primarily funded through the Canadian Institutes of Health Research, the National Science and Engineering Research Council of Canada, the Canadian Foundation for Innovation, and the Government of Ontario.

Keynote Speakers' Abstracts

Selective degradation of multimeric proteins by molecular glue and PROTAC degraders

***Ting Han*[1, 2]**

[1]National Institute of Biological Sciences, Beijing, China
[2]Tsinghua Institute of Multidisciplinary Biomedical Research, Tsinghua University, Beijing, China

Molecular glues are small molecules that induce interactions between target proteins and regulatory proteins that would not normally interact, leading to desirable biological or therapeutic effects. However, the rarity of serendipitous molecular glue discoveries has hindered their broader application in biological research and drug development. Over the past decade, we have identified three distinct molecular glues through phenotype-based screening and unraveled their mechanisms of action using genetic and biochemical methods. My presentation will highlight our latest discovery of a molecular glue targeting multimeric protein complexes while sparing monomeric proteins. Since abnormal protein assemblies drive diseases such as autoimmunity, neurodegeneration, and cancer, our findings demonstrate the potential of multimer-selective degraders as a novel therapeutic strategy to address the root causes of these diseases.

Keynote Speakers' Abstracts

Splice-Switching Antisense Oligonucleotides as Medicines for Neurological Disease

***Michelle L. Hastings*[1]**

[1]University of Michigan, USA

Splice-switching antisense oligonucleotides (SSOs) are short sequences of modified nucleic acids that can be designed to selectively basepair to an RNA target and modulate pre-mRNA splicing. SSOs are a powerful drug platform with clinical success, including therapeutics designed specifically for individuals carrying unique pathogenic variants (n-of-1). We have recently developed an SSO, Zebronkysen, that is now being used in an n-of-2 trial for an ultra-rare case of CLN3 Batten disease, a fatal, pediatric lysosomal storage disease involving neurological and visual degeneration. The development of Zebronkysen occurred over the course of a year and was supported by results from a similar ASO-based approach to treat the most prevalent variant associated with the disease, a large internal deletion encompassing exons 7 and 8 of the gene. Both strategies are based on the correction of mutation-induced open-reading frame shifts through exon skipping. The SSOs reduce neurological disease burden in mouse models of the disease and, in a CLN3 Δex78 pig model, a single intravitreal SSO treatment induced robust exon skipping in the retina for up to 12 months and improved retinal function. The efficacy of SSO-mediated exon skipping in targeting multiple CLN3 Batten disease-causing variants demonstrates a powerful SSO therapeutic approach, applicable to other neurological diseases.

Keynote Speakers' Abstracts

Understanding how drugs work using proteomics

***Bernhard Kuster*[1]**

[1]Technical University of Munich, Germany

Almost all drugs act on proteins, are proteins, make or degrade proteins and it has been known since the days of Paracelsus that drugs exert their effects in a dose-dependent fashion. The molecular processes leading to a drug-induced change in cellular phenotype can be roughly divided into: i) target binding, ii) pathway engagement, and iii) cellular reprogramming to arrive at a new viable state or cell death, together forming the mechanism of action (MoA) of a drug. Today, quantitative mass spectrometry is the most comprehensive approach for the proteome-wide characterization of drugs on all three levels because of its unique ability to assay thousands of proteins and their post-translational modifications in complex cellular backgrounds in parallel.
In this presentation, I will introduce the proteome-wide decryptT, decryptM and decryptE technologies that measure target deconvolution, pathway engagement and cellular reprogramming in a fully dose-dependent fashion respectively. Based on the analysis of >3,000 drugs including small molecules and antibodies, examples for drug characterization at all three levels will be discussed, particularly focussing on unexpected or even surprising findings. These include drug repurposing opportunities for kinase inhibitors, the long elusive MoA or Rituximab and the loss of T-cell receptor components in T-cells in response to HDAC inhibitors.
We have developed CurveCurator do put proteome-wide dose-response measurements on a solid statistical foundation and deposited the millions of dose-response curves and derived cellular EC50 values obtained into proteomicsdb.org for FAIR data sharing and mining by the scientific community. Examples for how the data may be used will be highlighted by ascribing new functions to proteins and phosphorylation sites based on their consistent responses to drugs that target known proteins, signalling pathways or cellular machines. We expect that the various implementations of the general "decrypt" approach will become a standard in drug discovery and pharmacology.

Keynote Speakers' Abstracts

Reading your drug target wishes - AI models understanding molecular structure to guide drug discovery

***Grzegorz Popowicz*[1]**

[1]Institute of Structural Biology, Helmholtz Munich, Germany

Applying machine learning (ML) in structural biology has already transformed the field. Not only because of improved accuracy but also the much better accessibility of structural models to life scientists. Meanwhile, ML models gain accuracy in predicting not only single-domain structures but also multimeric complexes of diverse molecules. Moreover, reverse folding models are able to generate realistic structures with pre-programmed properties without biological templates.
Yet, the progress of structure-based drug discovery seems to lag behind the overall wave of ML developments. This can be attributed to much noise in the training data and poor coverage of nearly infinite chemical combinatorial space by known experimental structures.
We present a set of ML models designed to circumvent these limitations. The approach, called Target Preference Mapping, treats each interface between a biomolecule and a drug as a large set of small microenvironments. They are then used to predict biomolecule preference for specific ligand chemistry. Chemical connectivity and binding energy are not used for the training to avoid overtraining of the model on the known complexes. We show that this approach allows us to predict drug optimization and perform virtual screening at unprecedented speed and accuracy.
A similar approach was recently tested for Protein-protein interactions, we how some preliminary observations on these interactions as well.

Keynote Speakers' Abstracts

Following the Rabbit into Chemical Space

***Brian Shoichet*[1]**

[1]UCSF, CA, USA

Structure-based drug-discovery often begins with screens of compound libraries, using molecular docking. Recently, docking libraries have expanded from three million "in-stock" to over eight billion diverse, stereogenic, and readily available virtual molecules (largely through the work of Enamine). In the last six years, campaigns against over 20 targets have found novel chemotypes with high potencies directly out of docking screens of these ultra-large, "tangible" libraries. As the docking libraries have grown, anecdotal evidence suggests that hit rates and hit affinities have improved, but this has rarely been tested in apples-to-apples experiments. Here I describe wet-lab experiments and simulations where we directly compare the hit-rates and hit affinities of billion molecules vs. million molecule libraries. These results have surprising implications for how we understand docking performance, and for future directions for the technique.

Keynote Speakers' Abstracts

Multiplex editing of muscular dystrophy causing mutations using CRISPR-RNA and RNP tools.

Supriya Krishna[1], Helena Escobar[1], Janine Kieshauer[1], Oskar Gustafsson[2], Samir El Andaloussi[2], ***Simone Spuler[1]***

[1]Muscle Research Unit, ECRC, Charité Universitätsmedizin Berlin and Max Delbrück Center; [2] Karolinska Institute, Stockholm, Sweden

Compound heterozygosity of pathogenic mutations is the most frequent cause of genetic disorders in offspring of non-consanguineous parents. More than 5,000 different diseases result from this mechanism, including the large group of limb-girdle muscular dystrophies (LGMD). LGMDs are monogenic, progressive muscle-wasting disorders caused by mutations in genes that have crucial functions in skeletal muscle cells. Currently, they remain untreatable. Repairing the genetic defect in the diseased muscle through *in vivo* CRISPR-based genome editing or cell replacement therapies with *ex vivo* gene-corrected muscle stem cells offers a potential cure. In the case of autosomal recessive LGMD, it is unclear whether efficient (70-95%) repair of a single mutation would be sufficient to provide adequate gene and protein dosage. Here, we focused on two autosomal recessive LGMD subtypes, LGMDR1 and LGMDR3, caused by loss-of-function mutations in *CAPN3* and *SGCA*, respectively. We delivered SpCas9, ABE7.10, ABE8e, and ABE8e-SpRY to primary human muscle stem cells as mRNA or as ribonucleoproteins using a novel cell-penetrating peptide-based nanoparticle platform. We targeted five *CAPN3* and *SGCA* mutations in muscle stem cells from compound heterozygous patients, including three founder mutations covering 20% of LGMDR1 and >50% of LGMDR3 cases. Following simultaneous or sequential dual delivery of CRISPR enzymes and mutation-specific sgRNAs, we achieved >80% concurrent repair of both compound heterozygous mutations with minimal unwanted indels or bystander edits. Patient-derived muscle stem cells retained their myogenic and proliferative properties and readily fused into multinucleated myotubes following multiplex editing. Dual repair resulted in a robust rescue of Calpain 3 and α-Sarcoglycan protein in patient-derived myotubes, substantially exceeding the levels achieved by repairing only one mutant allele. In sum, our work establishes a highly efficient approach for precise and functional dual correction of compound heterozygous mutations in primary stem cells, with significant implications for cell replacement and *in vivo* gene editing therapies.

Keynote Speakers' Abstracts

Targeting Post-translational Modification for Drug Discovery

Ed Tate[1]

[1]Imperial College London, London, UK

The Tate lab develops novel chemical biology approaches to enable drug discovery against post-translational modification (PTM) pathways and intractable drug targets, including chemical proteomic target identification, screening technologies, and chemical probe discovery for protein-protein interactions and enzymes modulating PTMs. Recent highlights include the first cell-active activity-based probes (ABPs) for deubiquitinases (DUBs), new tools for analysis and discovery of pathogenic secreted protease activities, and the first comprehensive maps of specific classes of PTMs through chemical proteomics. Our research in the field of protein lipidation led to several drug discovery and target validation campaigns, spanning antimalarial and antiviral research to oncology. We are also interested in new modalities including targeted protein degradation and antibody-drug conjugates (ADCs), and translation of technologies and drug candidates through biotech spinouts. These include Myricx Bio (https://myricxbio.com/), building on our discovery of ultrapotent (low/sub picomolar) protein lipidation inhibitors as a unique class of next generation payloads for antibody-drug conjugates (ADCs), and Siftr Bio (https://siftr.bio/), leveraging our platforms for ABP discovery and their application in patient-derived tissues.

Keynote Speakers' Abstracts

Human Living Myocardial Slices: A Translational Platform for Next-Generation Cardiac Drug Development

Thomas Thum[1]

[1]Hannover Medical School, Germany

Cardiovascular drug development has long suffered from a translational gap between preclinical models and clinical outcomes. Traditional in vitro and animal models often fail to replicate the structural, mechanical, and cellular complexity of the human heart, resulting in high attrition rates of drug candidates. Living myocardial slices (LMS), ultra-thin viable sections of human cardiac tissue, present a powerful solution to this challenge by preserving the native multicellular architecture, electrophysiological properties, and contractile behavior of the myocardium.

In this talk, I will introduce the LMS technology and demonstrate its unique advantages as a human-based ex vivo platform for cardiac drug testing. LMS are prepared from human explanted hearts and maintained under biomimetic electromechanical stimulation, enabling chronic culture while retaining functional and molecular fidelity. Using this model, we have tested antifibrotic compounds, revealing dose-dependent suppression of fibrosis-related gene expression, improved contractile relaxation, and minimal cytotoxicity. Moreover, single-nucleus RNA sequencing in LMS treated with established drugs, such as SGLT2 inhibitors uncovered cell-type–specific transcriptional responses, offering insights into drug mechanisms at an unprecedented resolution.

Our data underline the potential of LMS to serve as a translational bridge between cell culture and clinical trials. LMS not only allow functional and molecular assessment of candidate compounds in a human context but also provide a scalable, medium-throughput platform for personalized medicine applications. As cardiac drug development enters an era of precision therapeutics, LMS stand out as a next-generation tool to enhance prediction of efficacy, safety, and patient-specific responses.

Keynote Speakers' Abstracts

Networks of alternative splicing regulation in cancer: therapeutic opportunities

***Juan Valcarcel*[1]**

[1]Center for Genomic Regulation (CRG), Barcelona, Spain

Alternative splicing of messenger RNA precursors expands the information content of the genomes of complex organisms and contributes to gene regulation during development, cell differentiation and homeostasis. Alterations in this process contribute to numerous pathologies, including neurodegeneration and cancer. The spliceosome is one of the most complex molecular machineries of our cells and carries out the splicing reaction through sophisticated conformational and compositional transitions. By systematically knocking down >300 genes encoding spliceosome components and regulators and analyzing the resulting transcriptomes, we have reconstructed regulatory networks relevant for the control of cancer cell proliferation and have used this information to explore potential therapeutic approaches. These include both splice site switching antisense oligonucleotides and small molecule inhibitors of the spliceosome. Therapeutic effects of the modulation of NUMB alternative splicing, a regulator of the Notch pathway, have been observed in four different models of lung adenocarcinoma. Therapeutic effects of inhibitors of the core splicing factor SF3B1 are challenged by widespread effects on alternative splicing leading to toxicity. Transcriptome-wide analyses combined with detailed mechanistic and structural studies reveal ways to generate lead compounds of improved activity and specificity.

Keynote Speakers' Abstracts

Synthetic Collagen Peptides – From Structure to Function

Helma Wennemers[1]

[1]ETH Zürich, Switzerland

Collagen, the most abundant protein in mammals, is a key contributor to the strength and stability of skin, bones, and connective tissue. Collagen formation is thus vital for the integrity of skin, tendons, and the tissue in essentially any organ. Excessive collagen formation is, however, characteristic of fibrotic and malignant diseases, which include major global health issues.

The Wennemers group has used collagen model peptides (CMPs) to understand the stability of collagen at the molecular level and to establish functional synthetic collagen triple helices.[1] These include hyperstable triple helices[2] and heterotrimeric collagen.[3,4] Building on these data, we designed and synthetized a chemical probe for the simultaneous monitoring and targeting of lysyl oxidase (LOX)-mediated collagen cross-linking.[5] The probe allows for the visualization of collagen formation with spatial resolution in vivo and in tissue sections.[5,6]

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Abstract 1

Development of potent FLT3-ITD kinase degraders and their biological evaluation against acute myeloid leukemia cells

Mohamed Abdelsalam[1, 2,*], *Melisa Halilovic*[3], *Matthias Schmidt*[1], *Oliver H. Krämer*[3], and *Wolfgang Sippl*[1]

[1]Institute of Pharmacy, Martin-Luther-University of Halle-Wittenberg, Halle, Germany
[2]Faculty of Pharmacy, Alexandria University, Alexandria, Egypt.
[3]University Medical Center, Mainz, Germany
*Presenting author

Internal tandem duplications of FMS-like tyrosine kinase-3 (FLT3-ITD) are the most common genetic abnormalities in acute myeloid leukemia (AML) and are often associated with resistance to current FLT-3 inhibitors. Targeted protein degradation (TPD) has recently attracted substantial interest as an emerging therapeutic modality to combat specific disease-associated proteins that have been very challenging to target and could overcome drug resistance associated with conventional inhibitors. Here we report a series of potent and selective FLT3-ITD degraders through the application of two different TPD approaches, namely proteolysis targeting chimeras (PROTACs) and hydrophobic tags (HyT). The developed degraders were designed by connecting the FLT3 warhead (Sorafenib-based FLT3 inhibitor) to the von-Hippel-Lindau (VHL) ligand (for PROTACs development) or to the hydrophobic adamantyl scaffold (for HyT development) using various flexible or rigid linkers. Cellular testing demonstrated that several compounds induced the degradation of FLT-ITD in MV4-11 and MOLM-13 AML cell lines with half-maximal degradation concentrations (DC50) in the low nanomolar range. In this range the degraders induce apoptosis of human leukemic cell lines and primary AML blasts with FLT3-ITD, but not of leukemic cells with wild-type FLT3 and normal human immune cells. In addition, mechanistic studies were performed to understand the molecular pathway by which the developed degraders can eliminate this oncoprotein.

Abstract 2

Combining NMR fragment screening with AI-based cheminformatics to design small molecules targeting RNA for antibiotic development

Barak Akabayov[1,*]

[1]Ben-Gurion University of the Negev, Israel
*Presenting author

I will present our strategy for developing novel antibacterial small molecules that specifically target an RNA hairpin located within the ribosomal peptidyl transferase center (PTC). Our approach combines NMR transverse relaxation times (T_2) with computational chemistry to identify a subset of molecules with a common molecular scaffold. By utilizing these small molecules and their binding free energy to the targeted RNA hairpin, we established design principles that guide the optimization of molecular structures for enhanced bioactivity. The molecular optimization involved AI-driven cheminformatics to identify key physicochemical features that provide insights into structure-activity relationships (SAR). The newly designed molecules were synthesized and tested using ribosome inhibition assays, with some showing improved IC_{50} values in comparison to standard antibiotic drugs. Additionally, biochemical and biophysical studies were conducted to clarify the binding mechanism of specific inhibitors to the RNA hairpin.

Abstract 3

Molecularly characterized patient-derived xenograft (PDX) and corresponding cell line models from glioblastoma for drug development and pre-clinical research

Joshua Alcaniz[1,*], *Lars Winkler*[1], *Mathias Dahlmann*[1], *Michael Becker*[1], *Theresia Scheller*[1], *Wolfgang Walther*[1,2], and *Jens Hoffmann*[1]

[1]Experimental Pharmacology and Oncology GmbH, Berlin, Germany
[2]ECRC, Charité Universitätsmedizin Berlin and Max-Delbrück-Center for Molecular Medicine, Berlin, Germany
*Presenting author

Glioblastoma (GBM) is the most common brain tumor in adults, with its complex biology and infiltrative growth limiting success of standard of care (SoC) and new therapeutic approaches. There is a need for models reflecting the tumor's heterogeneity to perform essential steps of pre-clinical drug development - from *in vitro* screenings for target and model validation, to orthotopic *in vivo* models replicating the tumor's various interactions with its microenvironment. GBM patient-derived xenografts (PDX) and corresponding cell lines preserve many of these features and are an essential tool in pre-clinical research.

We established on immune-deficient mice 26 glioblastoma PDX models subcutaneously (s.c.), 15 in addition orthotopically. In an ongoing effort, matching cell lines are established from PDX tumors. *In vivo* and *in vitro* models are screened for their individual sensitivity towards a panel of chemotherapeutics and targeted drugs, and their molecular profile is analyzed by transcriptome sequencing.

Molecular characterization identified all models as IDH-wt with frequent mutations in PARP1, EGFR, TP53, FAT1, and within the PI3K/AKT/mTOR pathway. Expression profiles of PDX resemble mesenchymal, proneural and classical GBM molecular subtypes, with a shift towards the mesenchymal subtype in cell lines. Best treatment responses in s.c. PDX were observed for temozolomide (SoC) and irinotecan, with reduced sensitivity in orthotopic models. Cell lines showed individual sensitivity profiles regarding PI3K/Akt/mTOR inhibition, and an overall high sensitivity towards CDK4/6 and MEK inhibition. Comparison of sensitivities of matching PDX, as well as correlation analyses to identify possible new biomarkers, are ongoing.

In vivo and *in vitro* screenings identified topoisomerase inhibition and targeting CDK4/6 and MEK as alternative treatment options in our GBM models. Our data furthermore demonstrate that our GBM PDX models, complemented by PDX-derived cell lines, retain individual molecular characteristics and sensitivity profiles and are valuable tools in pre-clinical research, target identification and drug development.

Abstract 4

Design, synthesis, and biological characterization of proteolysis targeting chimera (PROTACs) for the Ataxia telangiectasia and RAD3-related (ATR) kinase

Abdallah M. Alfayomy[1, 2, *], *Anita G. Kansy*[3], *Ramy Ashry*[3], *Matthias Schmidt*[1], *Oliver H. Krämer*[3], and *Wolfgang Sippl*[3]

[1]Institute of Pharmacy, Martin-Luther-University of Halle-Wittenberg, Halle, Germany.
[2]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Al-Azhar University, Assiut, Egypt
[3]Department of Toxicology, University Medical Center, Mainz, Germany.
*Presenting author

The Ataxia telangiectasia and RAD3-related (ATR) kinase is a key regulator of the DNA replication stress responses and DNA-damage activated checkpoints. Several potent ATR inhibitors have been reported and four of them are currently in clinical trials as radio- or chemo-sensitizer. Targeted protein degradation (TPD) has recently attracted substantial interest as an emerging therapeutic modality to combat specific disease-associated proteins that have been very challenging to target and could overcome drug resistance associated with conventional inhibitors. Here we report the first-in-class proteolysis targeting chimera (PROTAC) to degrade ATR. Among a synthesized series of compounds, the lenalidomide-based PROTAC **42i** (Abd110) was the most promising candidate when tested in pancreatic cancer cells (MIA PaCa-2). Mechanistic studies confirmed that **42i** (Abd110) selectively degraded ATR through the proteasome, without degrading effects on its related kinases ATM and DNA-PKcs. Applying structure based design we synthesized a larger library of rigidified analogs of **42i** (Abd110) that showed strong degradation of ATR and good selectivity.

Abstract 5

Probing 3-Amino-2H-Azaindazoles as Template to Access Allosteric Inhibitors of the Protein Tyrosine Phosphatase SHP2.

Machoud Amoussa[1,*], *Nina-Louisa Efrém*[1], *Ziqiong Guo*[1], *Victoria Zeitz*[1], *Silke Radetzki*[1], *Jens-Peter von Kries*[1], *Marc Nazaré*[1], *Feng Bo*[2], *Jia Li*[2], *Katrin Frank*[3], *Hana Algül*[3], *Yvette Roske*[4], *Oliver Daumke*[4], *Clemens Alexander Wolf*[5], *Szymon Pach*[5], *Gerhard Wolber*[5], *Noémi Csorba*[6], *Péter Ábrányi-Balogh*[6], and *György Keserű*[6]

[1]Leibniz-Forschungsinstitut für Molekulare Pharmakologie (FMP), Berlin, Germany
[2]Shanghai Institute of Materia Medica (SIMM), China
[3]Klinikum Rechts der Isar, Technische Universität München, Germany
[4]Max Delbrück Center for Molecular Medicine, Berlin, Germany
[5]Freie Universität Berlin, Molecular Design Group, Institute of Pharmacy, Germany
[6]Research Centre for Natural Sciences (RCNS), Hungary
*Presenting author

Src homology 2-containing protein tyrosine phosphatase 2 (SHP2) is a very appealing therapeutic target in oncology and disorders related to immunology. While several allosteric SHP2 inhibitors have already entered clinical trials, none have been approved as drugs to date. Thus, the development of novel potent and selective inhibitors remains a great challenge in drug discovery.
As part of our drug discovery program, we explored a new strategy for the design and synthesis of a series of 3-amino-2H-azaindazoles derivatives, which are considered privileged scaffolds in medicinal chemistry, as potential allosteric SHP2 inhibitors. A rescaffolding approach, and using a palladium-catalyzed domino reaction recently developed by us, gave access to various 3-amino-2H-indazoles to various candidates as potential inhibitors of SHP2.
After an extensive structure-activity relationship (SAR) investigation, we obtained a lead compound with nanomolar potency in a SHP2 biochemical assay and strong efficacy in various cellular models. Structural studies showed that the lead compound binds to the allosteric tunnel site of SHP2 and also revealed a degree of pharmacophore flexibility in the SHP2 allosteric binding site, allowing a unique binding mode as evidenced by the high-resolution crystal structure of the inhibitor in complex with SHP2.
To further optimize this lead compound, we are exploring covalent modification strategies by introducing various reactive electrophilic moieties to selectively target nucleophilic residues present in the SHP2 allosteric site. This approach also aims to improve drug efficacy, selectivity and offer an opportunity to address SHP2 mutant variants, which are a major challenge for current allosteric inhibitors.
Overall, this study introduces 3-amino-2H-azaindazoles as a promising scaffold for designing SHP2 allosteric inhibitors, offering new insight for the further development of new antitumor therapies targeting SHP2.

Abstract 6

Scaling Mendelian Randomization to the million genomes era allows for mechanistic models of drug trial success

Marius Arend[1,*], *Charles NJ Ravarani*[1], *Hannes A Baukmann*[1], and *Marco F Schmidt*[1]

[1]Biotx.ai GmbH, Germany
*Presenting author

As the number of large-scale epidemiologic genome-wide association (GWA) studies increases, evidence grows that drug-targets with genetic variants linked to the treated disease phenotype have a considerably higher chance of success in clinical trials.[1] Recently, Mendelian randomization (MR) has been established as a statistical framework to investigate causal effects between genetically proxied target perturbation and disease risk.[2] To deliver reliable estimates of causal effects, each MR experiment requires independent population genetic studies that measure (i) the drug-target level and (ii) the disease or a linked phenotype.[2]

Here we compiled a large-scale harmonized GWAS resource with 3,124 disease and 1,424,043 gene product datasets. Simultaneously, we improved MR implementations to scale to all pairwise combinations of genes and disease in this resource. For a subset of 25,733 drug-target vs disease combinations we obtained information on drug trial outcomes.[1] In this way we built a framework to systematically assess the predictive power of MR on clinical trial success.

Our results corroborated existing evidence of MR results predicting drug trial success.[3] We found that disease and target features strongly influence the predictive power of MR. Furthermore, we assessed how the choice of instrumental variables and statistical framework can improve the accuracy of MR results. Guided by these insights we trained a machine learning classifier that successfully predicts clinical trial outcomes. Using the full matrix of drug-target vs disease MR results as input to the classifier, we could identify a set of high confidence novel therapeutic targets.

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Abstract 7

Control of organelle biogenesis by the Lipin switch

Paul Carlos Becker[1,*], *Oliver Daumke*[1], *Sebastian Schuck*[2], *Giulia Ruffini*[2], and *Rolf Schmidt*[2]

[1]Max Delbrück Center for Molecular Medicine, Berlin, Germany
[2]Heidelberg University Biochemistry Center (BZH), Germany
*Presenting author

The lipid metabolism is a tightly regulated cellular program that maintains lipid homeostasis and controls organelle biogenesis. Dysregulation of lipid metabolism contributes to disorders such as obesity and lipodystrophy, leading to conditions such as metabolic dysfunction–associated steatotic liver disease (MASLD). An important regulator of the cellular lipid metabolism in eukaryotes is Lipin, a highly conserved enzyme that catalyzes the conversion of phosphatidic acid (PA) into diacylglycerol (DAG). Lipin activity promotes cellular lipid storage in lipid droplets (LDs) by generating DAG while concurrently suppressing genes responsible for phospholipid synthesis. Inhibition of Lipin leads to PA accumulation and derepresses phospholipid synthesis genes, inducing membrane biogenesis at the ER.

This project aims to control LD biogenesis in human cells by regulating the Lipin switch. To achieve this, we purified human Lipin proteins and conducted high-throughput screening to identify small-molecule inhibitors. We identified an initial set of compounds with low micromolar IC50 values. Together with our collaborators, we developed an image analysis pipeline for the automated quantification of LDs and the ER in human cells. Our experiments demonstrated that depletion of Lipin-1/2/3 by RNA interference reduces oleate-induced LD biogenesis in cells. Additionally, we showed that at least one inhibitor reduces LD formation and induces ER expansion, mimicking the effects of Lipin knockdown. These findings suggest that our inhibitors effectively modulate lipid metabolism at the cellular level.

To improve affinity and specificity, we will employ a structure-guided rational drug design approach, integrating structure-activity relationship analysis. LD growth in hepatocytes has been shown to disrupt ER structure, and stabilizing ER sheets can alleviate physiological defects in fatty liver disease, such as impaired protein secretion. Targeting Lipin presents a novel therapeutic strategy for treating obesity, MASLD, and certain cancers reliant on lipid metabolism, offering significant pharmaceutical potential for clinical translation.

Abstract 8

Mass spectrometry imaging of single cells

Hanna Bednarz[1,*], and *Karsten Niehaus*[1]

[1]Bielefeld University, Germany
*Presenting author

The increase in spatial resolution and sensitivity in MALDI MS imaging enables the analysis of single cells. This development opens doors to the investigation of numerous, fundamental and specific aspects, which could not be tackled before by the use of animal models or by analysis of human tissue samples. A striking metabolic heterogeneity can be observed even between cells within one single cultivation. The analysis of cell interactions and individual metabolic responses will surely significantly contribute to our knowledge on cell biology and fuel the biomedical and pharmaceutical research. Similar challenges have already been addressed in the microscopic evaluation of cells, resulting in a variety of methods, tools and approaches. Thereby, the individuality of single cells is the basic element in analysis by flow cytometry, fluorescence microscopy, high-content screening and cell-painting. In order to characterize metabolic individuality, approaches to the analyses of cells as single, individual objects are required in a similar way for MALDI MSI. We have used different software-approaches in order to analyze MALDI MSI measurements of single cancer cells. In addition to cell heterogeneity, the increased spatial resolution shows distinct localization patterns of specific metabolites within the cells, thus moving the entire field in the direction of subcellular single cell metabolic imaging.

Abstract 9

Biaryl Phosphates and Phosphonates as Selective Inhibitors of the Transcription Factor STAT4

Thorsten Berg[1,*]

[1]Institute of Organic Chemistry, Leipzig University, Germany
*Presenting author

Protein-protein interactions regulate most biological processes. A particularly important subgroup of protein-protein interaction domains are the phosphorylation-dependent ones. With 120 representatives in the human proteome, the largest group of phosphotyrosine-binding protein-protein interaction domains are the Src homology 2 (SH2) domains. The conserved nature and similar binding preferences of SH2 domains pose a major challenge for the development of selective SH2 domain inhibitors.

We identified *p*-biphenyl phosphate as an inhibitor of the SH2 domain of the transcription factor STAT4, which is considered a key protein for autoimmune diseases such as multiple sclerosis, rheumatoid arthritis and type 1 diabetes. We synthesized *p*-biphenyl phosphate derivatives and studied their structure-activity relationships. Several newly synthesized *p*-biaryl phosphates showed higher activities and selectivity than the parent compound *p*-biphenyl phosphate. Since phenyl phosphates can be cleaved by intracellular phosphatases, which leads to loss of activity, we also developed phosphatase-stable phosphonate derivatives and optimized their structures. The most potent phosphonate dubbed Stafori-1 selectively stabilized STAT4 against thermal degradation in cell lysates, indicating target engagement. In a human cell line, its cell-permeable prodrug dubbed Pomstafori-1 selectively inhibited STAT4 phosphorylation in the low micromolar concentration range. Our results show for the first time that selective inhibition of the STAT4 SH2 domain by small organic molecules is possible.

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Abstract 10

Development of NIR Contrast Agents for the Detection of Bacterial Biofilms during Fluorescence Guided Surgery

Caroline M. Berrou[1, 2, *], *Matthias Schürmann*[3], *Merle M. Weitzenberg*[1, 2], *Ingo Todt*[3], *Oliver Bruns*[2], and *Oliver Plettenburg*[1]

[1]Institute of Medicinal Chemistry, Helmholtz Munich, Hannover, Germany
[2]Department for Functional Imaging in Surgical Oncology, National Center for Tumor Diseases (NCT/UCC) Dresden, Dresden, Germany
[3]Department of Otolaryngology, Head and Neck Surgery, University Hospital OWL of Bielefeld University, Germany
*Presenting author

The rise in bacterial infections and antibiotic resistance highlights the urgent need for improved diagnostic tools. Early detection remains challenging due to a lack of effective methods. A non-invasive, selective, and sensitive diagnostic approach could aid physicians in making timely treatment decisions.[1]
Fluorescent contrast agents that accumulate at infection sites can be visualized using existing surgical microscopes. Near-infrared (NIR) dyes offer advantages such as reduced tissue autofluorescence and deeper tissue penetration. [2] The novel fluorophore sNIR, developed by the Plettenburg group, outperforms currently available NIR dyes by exhibiting lower nonspecific binding, thereby increasing contrast.
To enable intraoperative differentiation between infected and healthy tissue, we synthesized a small library of NIR fluorescent probes. These probes were assessed for their sensitivity and specificity in labeling Gram-positive planktonic bacteria and bacterial biofilms. A blocking experiment confirmed the selective binding of the targeting moiety, while sNIR exhibited no nonspecific binding. Fluorescence microscopy imaging of sterile and infected human tissue showed a significant fluorescence signal increase in the presence of Gram-positive bacteria. Fluorescence-guided surgery offers a valuable tool for the precise removal of cholesteatoma, a condition affecting the middle ear that becomes more aggressive when associated with bacterial biofilms. By accurately identifying and targeting biofilm infections, this approach reduces recurrence rates and the need for repeat surgeries. [3]

While further validation is needed, we are confident that our fluorescent probes will enhance diagnostic accuracy and improve patient care by enabling precise infection detection.

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Abstract 11

Identification of cyanobacterial metabolites as geroprotectors

Maria Böckmann[1,*], *Jörg Urban*[1], *Philipp Stephan*[2], *Thomas Nöschel*[2], *Heike Enke*[2], and *Jacqueline Franke*[1]

[1]HTW Berlin, Wilhelminenhofstraße 75A, 12459 Berlin, Germany
[2]Simris Biologics GmbH, Magnusstraße 11, 12489 Berlin, Germany
*Presenting author

An important process in human aging is cellular senescence, in which cells undergo an irreversible cessation of proliferation in response to various stress factors. Here, we developed a workflow to validate cyanobacterial metabolites that affected chronological lifespan in a primary screen in yeast. We investigate senescence markers in human dermal fibroblasts and ask whether TOR activity is affected by the cyanobacterial metabolites.

Abstract 12

miR395e from Cassava: A Promising Plant-Derived miRNA for Renal Cancer Therapy

Joanna Bogusławska[1], *Aizhan Rakhmetullina*[2,*], *Alex Białas*[1], *Małgorzata Grzanka*[1], *Beata Rybicka*[1], *Joanna Życka-Krzesińska*[1], *Tomasz Molcan*[2,3], *Piotr Zielenkiewicz*[2,4], *Leszek Pączek*[2,5], and *Agnieszka Piekiełko-Witkowska*[1]

[1]Centre of Translational Research, Centre of Postgraduate Medical Education, Warsaw, Poland
[2]Institute of Biochemistry and Biophysics, Polish Academy of Sciences, Warsaw, Poland
[3]Institute of Animal Reproduction and Food Research, Polish Academy of Sciences, Warsaw, Poland
[4]Institute of Experimental Plant Biology and Biotechnology, University of Warsaw, Poland
[5]Medical University of Warsaw, Poland
*Presenting author

Renal cell cancer (RCC) is the most prevalent type of kidney cancer, with an estimated 300,000 new cases diagnosed worldwide each year. Targeted therapies and immunotherapies, including PD1/PD-L1 inhibitors, are currently regarded as the most effective treatment options for RCC. However, despite positive responses in some patients, up to 75% remain resistant to PD-1/PD-L1 antibodies. Therefore, it is crucial to discover new treatments that can enhance the immune response against cancer.
MicroRNAs (miRNAs) are small, non-coding RNA molecules, 19–24 nucleotides long, that regulate gene expression by targeting mRNAs based on sequence complementarity, resulting in mRNA degradation or translational inhibition. The role of miRNAs in cancer pathogenesis is well established, as they can act either as oncogenes or tumor suppressors, influencing cancer development and progression. Recent studies have highlighted the potential cross-kingdom role of plant-derived miRNAs in regulating human gene expression, suggesting novel therapeutic opportunities in cancer treatment.
We investigated the therapeutic potential of miRNAs from edible plants to modulate Programmed Death Ligand 1 (PD-L1) expression. Using bioinformatic analysis, we identified miR395e, a miRNA derived from *Manihot esculenta* (cassava), as a promising candidate capable of targeting PD-L1. To confirm the regulation of PD-L1 by the predicted plant-derived miRNA, mes-miR395 mimics were transfected into RCC tumor-derived cell lines, and PD-L1 expression was subsequently evaluated through qPCR and Western blot analysis. qPCR analysis showed that mes-miR395e mimics reduced PD-L1 mRNA expression in both primary tumor-derived cell lines (786-O, KIJ265T). Western blot analysis further confirmed a decrease in PD-L1 protein levels in cells transfected with mes-miR395e, compared to those transfected with a non-targeting scrambled oligonucleotide control.
Overall, these results suggest that the mes-miR395e mimic effectively downregulates PD-L1 expression in RCC cell lines derived from primary tumors, highlighting the potential of plant-derived miRNAs as novel RNA-targeting therapeutic agents for RCC treatment.

Abstract 13

Identification and ranking of RNA-binding small molecules by NMR

Jan Borggräfe[1, 2,*], *Laure Gauthé*[1,2], *Lorenzo Baronti*[1,2], *Elisa Donati*[3], *Alejandro Varela Rial*[3], *Gianni De Fabritiis*[3], and *Michael Sattler*[1,2]

[1]Helmholtz Munich, Germany
[2]Technical University of Munich, Germany
[3]Acellera Therapeutics Inc, Barcelona, Spain
*Presenting author

RNA is a rapidly emerging target for development of novel therapeutic approaches given the unique roles in physiological and disease-linked pathways. While the pipeline of possible protein drug targets is reaching exhaustion, a large part of the human genome is transcribed into RNA, where (long) non-coding RNAs offer novel opportunities as potential drug targets. Compared to proteins RNA exhibit different biochemical properties and offers unique challenges and opportunities as drug target. Although RNA adopts a variety of three-dimensional structures to perform their cellular function, its structural diversity is limited due to only four building blocks. Its anionic backbone and dynamic range additional hampers the development of highly selective drugs.
Nuclear magnetic resonance spectroscopy (NMR) is a well-established tool in early-stage drug discovery and offers unique approaches in RNA-targeting drug discovery for characterizing the structure and dynamics of RNAs and for the identification and validation of small molecule inhibitors. Ranking of positive hits based on binding affinity is an important aspect for rational drug design and to support hit selection for structural analysis. Ligand-observed NMR experiments do not require isotope enrichment and relatively small amounts of target RNA, making it a straight-forward approach to study initial hits.
Here, we have identified RNA binding inhibitors by *in silico* screening using mixed-solvent molecular dynamics simulations, followed by a virtual screening and rescoring protocol, and demonstrate the utility of NMR to identify and characterize small molecule inhibitors targeting RNA. We demonstrate our approach with the bacterial flavin mononucleotide (FMN) riboswitch, a key regulator and established target for the development of novel antibiotics. The *in silico* generated inhibitors of FMN riboswitch were tested for binding and ranked by characterizing binding affinities based on NMR transverse relaxation rates. Integrating computational screening and NMR validation is an efficient way to identify and select RNA binding small molecules.

Abstract 14

Our RNA production platform and the associated tools facilitate the development of RNA-based vaccine

Célia Bosso-Lefèvre[1,*], *Erica Cirri*[1], and *Romain Goulay*[1]

[1]Tebubio
*Presenting author

mRNA vaccines have shown their full potential in the Covid-19 pandemic. The application of these technologies for the treatment of cancers represents significant hope, but clinical effectiveness remains to be demonstrated. For this purpose, researchers require high quality production of vaccine mRNA and accurate and cost-saving test tools that are adapted to oncology research. Since 2021, Tebubio has developed a miniscale RNA production platform for providing RNAs (from 100 µg to 1 mg) to researchers around the world. Through an ingenious design, our DNA matrix for mRNA is easily transferable for GMP production for clinical studies. This service is completed by offers on RNA delivery solutions using lipid nanoparticles (LNPs) and cellular tests with biomarker analysis.
We present a complete study on CAP1 capped linear RNA produced from our DNA templates. We assess the stability of two RNAs expressing GFP and the typical tumor antigen, p53, and their relative expression into antigen-presenting cells (APCs). Furthermore, we quantified the response of the APCs expressing p53 by using our biomarker multiplex analysis system. Finally, we present our formulation platform for the encapsulation of mRNAs inside Lipid Nanoparticles (LNP), showing both information regarding the ultrastructure of the LNPs, and RNAs expression in different cellular models. This new type of service and its future developments will constitute a new addition to our pipeline of RNA production and testing for preclinical studies.

Abstract 15

The Role of Structural Biology in Drug Discovery - Search for Novel MALT1 Inhibitors

Matjaž Brvar[1,*], *Isabel Hamp*[1], *Thomas J. O'Neill*[2], *Daniel Krappmann*[2], and *Oliver Plettenburg*[1]

[1]Helmholtz Zentrum München, Institute of Medicinal Chemistry, Germany
[2]Helmholtz Zentrum München, Institute of Molecular Toxicology and Pharmacology, Germany
*Presenting author

MALT1, a human mucosa-associated lymphoid tissue lymphoma translocation protein 1 is a paracaspase and is responsible for the survival, proliferation, and activation of B and T lymphocytes upon antigen stimulation (1). Previously, a transient binding pocket between caspase domain and Ig3 domain was identified, and it has been demonstrated, that binding of the thioridazine inhibitor into this allosteric pocket of MALT1 prevents the conformational change into an active enzyme (2).
Starting from several crystal structures of the protein with a co-crystallized inhibitor (3) we first identified a set of crucial interactions between both binding partners. After successful validation, the pharmacophore models were used in a virtual screen of several million compounds. In the second round, all hits from the pharmacophore screen were additionally docked in the allosteric binding pocket to evaluate their size as well as their geometry and ability to form desired interactions with the enzyme. After the second round of our *in-silico* campaign we chose 35 hits and evaluated their inhibitory activity. Out of 35 compounds 3 showed IC_{50} in a low micromolar range with some additional hits having an IC_{50} of around 50 µM. Overall, we got an excellent more than 10 % hit success.
In our efforts to improve our initial hit compounds we further optimized three discovered hits by repeating the drug-discovery optimization cycle and were able to obtain several compounds with an IC_{50} value in low nanomolar range with the best one having an IC_{50} value of 20 nM and good cell data which was confirmed by inhibition of the MALT1 cellular activity.
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Abstract 16

Chemical Innovations in Targeted Protein Modulation and Epigenome Editing

Xinlai Cheng[1,*]

[1]Goethe University Frankfurt, Germany
*Presenting author

Modern drug discovery is increasingly driven by innovative chemical approaches that enable precise modulation of protein function and epigenetic regulation. Here, we present two complementary studies that advance targeted therapeutic strategies.

In our first study, we focused on reprogramming the binding surface of the E3 ligase CRBN using thalidomide derivatives. A comprehensive proteome-wide analysis identified three derivatives—C5, C6, and C7—that selectively induce degradation of the anti-apoptotic protein BCL-2. AlphaFold-driven molecular modeling, corroborated by experimental data, revealed that key residues (GLY128, ALA131, and THR132) are critical for establishing a unique CRBN-C5-BCL-2 ternary complex. Remarkably, these compounds are capable of degrading BCL-2 mutants resistant to established inhibitor, venetoclax, suggesting a promising approach to overcome drug resistance in cancer treatment [1].

Our second study introduces Chem-CRISPR/dCas9^{FCPF}, a chemically inducible platform for epigenome editing. By incorporating the FCPF-tag into dCas9 and using perfluoro biphenyl (PFB) derivatives, we achieved targeted recruitment of the panBET inhibitor JQ1. The resulting JQ1-PFB conjugate was directed by c-MYC-sgRNA to selectively inhibit BRD4 at the c-MYC promoter regions. This focused inhibition led to effective repression of the intricate transcription networks orchestrated by c-MYC, demonstrating enhanced specificity over traditional chemical inhibitor approaches [2].

Recently, we are developing proteasome-targeting degraders (ProGraders), which mediate ubiquitin-independent protein degradation, thus addressing limitations of conventional PROTACs [3].

Together, these studies underscore the power of chemically induced proximity techniques in redefining therapeutic intervention. By enabling both targeted protein degradation and precise epigenetic modulation, our work provides a versatile platform for developing next-generation treatments against challenging diseases such as cancer.

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Abstract 17

A torch to shed light on the dark kinome. The discovery of PI3K-C2β highly selective inhibitors

Davide Cirillo[1,*], *Wen-Ting Lo*[1], *Marta Diceglie*[1], *Liudmila Perepelittchenko*[1], *Désirée Steimer*[1], *Polina Prokofeva*[2], *Joel Rüegger*[3], *Kristina Puls*[4], *Theresa A. L. Ehret*[5], *Silke Radetzki*[6], *Jens-Peter von Kries*[6], *Gerhard Wolber*[7,8], *Susanne Müller*[1], *Mario van der Stelt*[9], *Stephanie Wilhelm*[10], *Volker Haucke*[1], and *Marc Nazaré*[11]

[1]Leibniz-Forschungsinstitut für Molekulare Pharmakologie (FMP), Berlin, 13125, Germany
[2]Chair of Proteomics and Bioanalytics, Technical University of Munich, Freising, 85354 Germany
[3]Leiden University, Faculty of Science, Leiden Institute of Chemistry, Einsteinweg 55, Leiden, Netherlands
[4]Freie Universität Berlin Institut für Pharmazie Königin-Luise-Str. 2+4, 14195 Berlin
[5]2Institute of Pharmaceutical Chemistry, Johann Wolfgang Goethe University, Max-von-Laue-Str. 9, 60438, Frankfurt am Main, Germany
[6]Leibniz-Forschungsinstitut für Molekulare Pharmakologie (FMP), Berlin, Germany
[7]Freie Universität Berlin, Molecular Design Group, Germany
[8]Institute of Pharmacy, Freie Universität Berlin, Germany
[9]Leiden University, Faculty of Science, Leiden Institute of Chemistry, Einsteinweg 55, Leiden, Netherlands
[10]Chair of Proteomics and Bioanalytics, Technical University of Munich, Freising, 85354 Germany
[11]Leibniz-Forschungsinstitut für Molekulare Pharmakologie FMP, Berlin, Germany
*Presenting author

Phosphoinositide 3-kinase (PI3K) is a family of lipid kinases involved in several cellular signaling pathways and it is of high biomedical interest not only for cancer treatment, but also for non-oncologic diseases such as COPD, and thrombosis. Interestingly, great efforts to develop PI3K inhibitors have been predominantly focused on class I, resulting in drugs reaching the market. In stark contrast, only recently isoform-specific class II PI3K inhibitors have been reported. This is highly surprising given the recent strong links to human diseases and crucial biological roles of PI3K class II isoforms, in terms of vesicular trafficking, primary cilia function and cell signaling. Hence, the identification of a highly selective class II phosphoinositide-3-kinases is pivotal to untangle the future role as potential drug discovery targets. Here, we present the development of active and selective PI3K-C2β inhibitors.
To identify a first-in-class PI3K-C2β inhibitor, we harnessed the off-target activity on the C2β isoform of AZ-3458, a sub-nanomolar, drug-like PI3Kγ inhibitor. Through SAR studies, we have rationalized the structural determinants for PI3K-C2β activity and selectivity, achieving a decisive selectivity switch and thereby abolishing class I PI3K activity. The medicinal chemistry program culminated in the creation of three lead compounds with nanomolar activity on PI3K-C2β and no off-target effect on a panel of 117 kinases. Cellular proof-of-concept studies to demonstrate their viability to probe specific PI3K-C2β functions are ongoing, but initial results indicate that these selective and non-cytotoxic inhibitors are able to recapitulate cellular phenotypes, mirroring genetic PI3K-C2β knockdowns.
Our investigation discloses the first potent isoform specific PI3K-C2β inhibitors and defines key structural determinants necessary for affinity towards PI3K-C2β and for the specificity within the lipid kinase family. These probes will facilitate the elucidation of the role of PI3K-C2β in cell signaling and physiology and are valuable starting points for the development of PI3K-C2β-targeting drugs.

Abstract 18

Deep proteomic screening platform for targeted protein degradation drug discovery

Zuzana Demianova[1,*], *Katrin Hartinger*[1], *Martin Steger*[2], *Uli Ohmayer*[2], *Bachuki Shashikadze*[2], *Björn Schwalb*[2], and *Garwin Pichler*[1]

[1]PreOmics, Planegg, Germany
[2]NEOsphere, Planegg, Germany
*Presenting author

Introduction
Targeted protein degradation (TPD) is an emerging strategy to eliminate disease-causing proteins resistant to conventional drugs. Molecular glue degraders recruit E3 ubiquitin ligases for proteasome-dependent target degradation without direct binding, offering vast therapeutic potential. DIA-MS-based proteomics enhances molecular glue discovery by enabling comprehensive analysis of protein abundance changes, selectivity, potency, and efficacy. Single-shot DIA-MS allows large-scale screening of degrader libraries in endogenous systems. We present a novel workflow that integrates streamlined sample preparation with deep proteomic screening via single-shot DIA-MS for rapid, high-coverage degrader profiling and is optimized for drug discovery.

Methodology
HEK293 cells overexpressing the E3 ligase cereblon were treated for six hours with molecular glues avadomide, iberdomide, and pomalidomide (1 nM–10 µM) in triplicate. PreOmics' iST technology was combined with NEOsphere Biotechnologies' Deep Proteomic Screening platform. Sample preparation was performed using the PreOmics® iST-BCT Kit 96x. Purified peptides (~800 ng/sample) were analyzed by single-shot dia-PASEF® on a timsTOF HT (Bruker Daltonics). Data was processed with DIA-NN v1.8.2 beta 9 and analyzed via NEOsphere's proprietary pipeline.

Results and Conclusions
Our proteomics pipeline achieved deep proteome coverage (~10,300 protein groups across 96 samples) with 99.4% data completeness. Over 95% of proteins showed CVs below 20%, with a median CV <5%. We identified significant protein downregulations (adjusted p ≤0.01), including known (ZMYM2) and novel (PPIL4, PATZ1) avadomide targets. Low-abundance proteins like ZNF653 were reliably detected. DIA-MS enabled precise profiling of degrader selectivity and potency. Iberdomide exhibited higher selectivity than avadomide, sparing ZMYM2 and PATZ1. ZFP91 degradation was most potent with iberdomide (DC50 <1 nM) versus avadomide (5 nM) and pomalidomide (27 nM).
This optimized proteomics workflow enables sensitive detection and precise quantification of molecular glue degraders for rapid selectivity and potency profiling.

Abstract 19

Discovery and Synthesis of Potent and Selective Bax/Bak Inhibitors

Marta Diceglie[1,*], *Jörg Contzen*[2], *Andreas Oder*[1], *Keven Mallow*[1], *Justin Kale*[3], *Arundhasa Chandrabalan*[3], *Jens-Peter von Kries*[1], *David Andrews*[3], *Philipp Mergenthaler*[2], and *Marc Nazaré*[1]

[1]Leibniz-Forschungsinstitut für Molekulare Pharmakologie (FMP), 13125, Berlin, Germany
[2]Charité - Universitätsmedizin Berlin, 10117, Berlin, Germany
[3]Sunnybrook Health Sciences Centre, 2075 Bayview Ave., Toronto, Canada
*Presenting author

Bax and Bak are well-known critical regulators of the apoptosis cascade and their abnormal activation can lead to several pathology developments, such as cardiovascular diseases, neuropathic and neurodegenerative diseases, and viral infections. Therefore, BAX/Bak represent attractive targets for the pharmacological inhibition of pathological cell death. However, the lack of a co-crystal structure and the structural complexity of BAX/Bak protein-protein interaction have made the design of effective inhibitors very challenging. We have conducted a combination of *in silico* and *in vitro* focused screening approaches and identified several EGFR kinase inhibitors with potential activity against Bax/Bak which are already approved or in clinical. We selected two lead compounds for further optimization. The primary objective of our research was to design inhibitors that preserve the advantageous drug-like characteristics of the original EGFR kinase inhibitors, while specifically enhancing the inhibition of Bax/Bak. Moreover, our goal was to minimize the primary EGFR kinase activity and eliminate the inherent covalent mechanism of action associated with the parent compounds. To achieve this, systematic modifications to the core structure were performed, allowing us to elucidate how structural modifications influence biological activity and leading to comprehensive structure-activity relationship (SAR) on BAX/Bak inhibition. Through this effort, we developed a range of novel derivatives with favorable drug-like properties. These compounds further showed enhanced BAX/Bak inhibitory activity (both in vitro and in cells), exhibited no cytotoxicity, and significantly reduced EGFR kinase activity. This series could serve as a promising starting point for the development of improved and potentially therapeutic BAX/Bak inhibitors.

Abstract 20

Nanoparticle-based nose-to-brain delivery of siRNA or miRNA to reduce alpha-synuclein pathology in a mouse model of Parkinson's disease (Thy1-aSyn)

Isabell Drath[1,*], *Malte Feja*[1], *Sandra Weiß*[1], *Alexander Ewe*[2], *Achim Aigner*[2], and *Franziska Richter Assencio*[1]

[1]University of Veterinary Medicine Hannover, Germany
[2]University of Leipzig Faculty of Medicine, Germany
*Presenting author

Potential strategies to develop new treatments for Parkinson`s disease (PD) include targeting alpha-synuclein (aSyn) and the use of non-coding RNAs. Thus, downregulation of the major disease-associated protein aSyn by the therapeutic use of small interfering RNA (siRNA) holds great potential. Further, alterations of PD-associated micro RNAs (miRNAs) are found in patients, making the restoration of physiological levels using miRNA mimics an interesting treatment approach. Nevertheless, efficient delivery of small RNA is challenging due to their instability and the need to bypass the blood-brain barrier. Therefore, we developed a non-invasive nanoparticle (NP)-based approach for intranasal delivery of small RNAs, opening this gene therapy strategy to broad clinical application.
To determine NPs that best distribute the RNAs in the CNS and influence the target protein most efficiently, different AF647-labeled NPs or NPs loaded with siRNA targeting human SNCA mRNA (siSNCA-NPs) were administered intranasally to aSyn overexpressing (Thy1-aSyn) mice on 4 consecutive days. Labeled NPs distributed extensively across the brain and were detectable in different brain regions. Western blot and qPCR analysis showed that siSNCA-NPs significantly reduced aSyn protein levels and SNCA mRNA levels in the brain. RNA sequencing revealed PD-relevant miRNA alterations in the substantia nigra pars compacta of 6-month-old Thy1-aSyn mice. To find appropriate doses for a longitudinal therapeutic intervention, promising miRNAs were complexed with the most efficient NPs and intranasally applied to 6-month-old transgenic mice. After only four days of administration, miRNA-NPs increased miRNA brain levels with a polymer-dependent efficacy. Mice showed no overt adverse behavioral effects nor increased reactive microglia.
We are now exploring whether long-term NP-mediated intranasal application of small RNA can improve motor, cognitive and olfactory dysfunctions, reduce aSyn levels and alter miRNA levels in the brain in our PD mouse model, and could thus be a novel therapeutic approach to treat PD.

Abstract 21

LumiBac: Smart bioresponsive luminescence probes

Michael Dyrks[1,*], *Carolina S. Vinagreiro*[1], *Yelena Mostinski*[1], *Xiang Wang*[2], *Tamara Ilioska*[3], *Mark Brönstrup*[3], *Hai-Yu Hu*[2], and *Marc Nazaré*[1]

[1]Leibniz-Forschungsinstitut für Molekulare Pharmakologie Berlin (FMP), Berlin, Germany
[2]Institute of Materia Medica (IMM), Shanghai, China
[3]Helmholtz-Zentrum für Infektionsforschung GmbH (HZI), Braunschweig, Germany
*Presenting author

Considering the rapid spread of multi-resistant bacteria and the threat posed by these antibiotic-resistant germs, there is an acute need for diagnostic methods for the non-invasive real-time detection of bacterial infections and contaminated surfaces. Once established, such imaging methods could also be used to detect inflammations early before they become systemic and lead to severe damage to the organism.

Nitroreductases (NTRs) are a family of flavin-containing bacterial enzymes that can reduce nitro functional groups and other nitrogen-containing functionalities in the presence of NADH or NADPH. They are present in bacterial pathogens, namely in drug-resistant members of the ESKAPE family, making them a highly relevant diagnostic target for the detection of bacterial infections.

Lanthanide complexes have recently attracted considerable interest since they have several inherent advantages over conventional organic fluorophores, such as long luminescence lifetimes, high photostability, large Stokes shift and fingerprint emission bands. To further increase the signal-to-noise ratio of this system by achieving an increased accumulation of the compound, we functionalized the coordinating DOTAM lanthanoid ion moiety with siderophore units. By this way, we may exploit the “Trojan horse” strategy, which enables active transport of the compound into the bacterial cell by hijacking the prokaryotic iron transport system.

In our study, we have developed an access to a targeted, versatile and robust responsive lanthanoid-based luminescent probe platform for the detection of nitroreductases. In this construct, in the absence of an analyte (NTR), the antenna precursor is not an efficient sensitizer. Upon reaction with the NTR analyte, the antenna is uncaged, enabling efficient excitation and energy transfer for Ln(III) luminescence.

The modular synthetic approach of this turn-on probe serves as the starting point for the development of a toolbox of smart bioresponsive targeted lanthanide probes for the detection of bacterial infections.

Abstract 22

From active site- to allosteric SHP2 inhibitors: Discovery and structure-activity relationship of N-aryl-1H-azaindazoles

Nina-Louisa Efrém[1,*], *Machoud Amoussa*[1], *Ziqiong Guo*[1], *Feng Bo*[2], *Victoria Zeitz*[1], *Katrin Frank*[3], *Yvette Roske*[4], *Silke Radetzki*[1], *Leonardo Seidl*[1], *Clemens Alexander Wolf*[5], *Szymon Pach*[5], *Noémi Csorba*[6], *Péter Ábrányi-Balogh*[6], *Jens-Peter von Kries*[1], *Oliver Daumke*[4], *György Keserű*[6], *Gerhard Wolber*[5], *Jia Li*[2], *Hana Algül*[3], and *Marc Nazaré*[1]

[1]Leibniz-Forschungsinstitut für Molekulare Pharmakologie (FMP), Berlin, Germany
[2]Shanghai Institute of Materia Medica (SIMM), Chinese Academy of Sciences
[3]Comprehensive Cancer Center, Institute for Tumor Metabolism, TUM School of Medicine and Health, University Medical Center, TUM, Germany
[4]Max Delbrück Center for Molecular Medicine, Berlin, Germany
[5]Freie Universität Berlin, Molecular Design Group, Germany
[6]Medicinal Chemistry Research Group, National Drug Research and Development Laboratory, HUN-REN Research Centre for Natural Sciences (RCNS), Hungary
*Presenting author

Src homology domain-containing phosphatase 2 (SHP2) is a cytosolic protein tyrosine phosphatase that has gained much attention as an anticancer drug target thanks to its central role in receptor tyrosine kinase signaling and its potential to modulate the tumor microenvironment. Several allosteric SHP2 inhibitors currently undergo clinical testing, most as part of combination therapies for cancer indications. We have previously developed N-arylated azaindole-based orthosteric inhibitors of SHP2. In an endeavor to identify novel scaffolds for allosteric SHP2 inhibitors, we observed a switch in the mechanism of inhibition of N-arylated azaindole-based inhibitors from active site- to allosteric inhibition upon the exchange of peripheral substituents on the N-aryl azaindole core with privileged allosteric site-targeting substructures. An extensive structure-activity relationship study assisted by co-crystal structures revealed key structural determinants necessary to shift from an orthosteric to an allosteric binding mode. Investigation of a single atom exchange of the azaindole core at various positions led to the identification of N-aryl-1H-azaindazoles as allosteric SHP2 inhibitors with nanomolar potency in biochemical assays and the ability to inhibit key downstream signaling events in cancer cell lines. We are currently investigating whether synergistic inhibition of SHP2 by allosteric and orthosteric inhibitors is a strategy to target clinically relevant activated SHP2 mutants.

Abstract 23

Targeting the moonlighting activity of PQS Response Protein PqsE with small molecule inhibitors

Lea Eilert[1,*], *Sebastian Roman Borgert*[1], *Ursula Bilitewski*[1], *Mark Brönstrup*[1], and *Wulf Blankenfeldt*[1]

[1]Helmholtz Centre for Infection Research, Braunschweig, Germany
*Presenting author

The gram-negative pathogen *Pseudomonas aeruginosa* stands out as one of the most well-known multidrug-resistant bacteria. Therefore, urgent explorations for alternatives to traditional antibiotics in its treatment are needed. Pathoblockers offer a promising alternative to conventional antibiotics.
The interaction between PqsE and RhlR presents an attractive target for the development of pathoblockers. The transcription factor RhlR plays a leading role in the progression of late and chronic infections. However, numerous RhlR-dependent virulence traits require the presence of PqsE, a dispensable thioesterase. Notably, the absence of PqsE halts the production of the prominent virulence factor, pyocyanin. Recently, we have shown that PqsE stabilizes RhlR by forming a 2:2 complex.
This unique moonlighting activity of PqsE provides a new target for development of *P. aeruginosa*-specific pharmaceuticals. To this end, we have developed a FRET-based high-throughput screening system that detects the PqsE and RhlR interaction with high reliability. With this assay in hand, over 30000 compounds were screened for inhibition of the interaction, leading to the identification of 532 potential inhibitors. Subsequent dose-response experiments with the same assay confirmed 167 compounds. A counter screen led to the identification of 13 potent inhibitors, which interestingly exhibited binding to both PqsE and RhlR. These promising lead compounds were subsequently tested in vivo in *P. aeruginosa* and six demonstrated a significant reduction in the production of pyocyanin. Binding mode analysis using protein crystallography is ongoing. The inhibitors offer a starting point for new anti infectives that act as pathoblockers, which may ultimately aid to fight infections with multiresistant *P. aeruginosa*.

Abstract 24

Benzimidazole derivatives as antimalarial agents: Design, Synthesis and Structure-Activity relationship studies

Sidra Eisa[1, 2,*], *Giada Cernicchi*[1], *Felix Boerman*[1], *Antoine Lacour*[1,2], *Patricia Bravo*[3], *Dale Taylor*[4], *Sandeep Ghorpade*[4], *Kathryn Wicht*[4], *Matthias Rottmann*[3], *Mostafa M. Hamed*[1], and *Anna K. H. Hirsch*[1, 2]

[1]Helmholtz Institute for Pharmaceutical Research Saarland (HIPS) – Helmholtz Centre for Infection Research (HZI), 66123 Saarbrücken, Germany.
[2]Department of Pharmacy, Saarland University, 66123 Saarbrücken, Germany.
[3]Swiss Tropical and Public Health Institute, Kreuzstrasse 2, CH-4123 Allschwil, Switzerland.
[4]Drug Discovery and Development Centre (H3D) University of Cape Town, South Africa.
*Presenting author

Abstract
Malaria is still one of the leading cause of morbidity and mortality in the human history. With over 90% of the world's malaria mortality attributed to *Plasmodium falciparum*, this parasite remains a major global health threat, highlighting the need for increased efforts in antimalarial drug discovery.[1-3] This study aims to develop next-generation treatment options to combat malaria. We screened in-house library of compounds and identified HIPS709 as an initial hit with IC_{50} of 470 nM against *Plasmodium falciparum* NF54. After two rounds of Structure-Activity Relationship (SAR) optimization, we successfully identified four compounds with significantly improved activity profiles. Among these, the most promising compound exhibited an impressive ~25 fold increase in activity. The front-runner compounds were subjected to *in vitro* ADMET profiling while mode of action studies are currently in progress.

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Abstract 25

Enhancing small molecule drug discovery through a robust collaborative strategy

Alexandra Ertman,[1] David Garcia Lopez,[1,] Jasmine Harley,[1,*] Robert Harmel,[1] Tanja Miletić[1,*], Victoria Mora,[1] Federica Rossella,[1,*] Yasemin Ucal[1,*] for the EU-OPENSCREEN consortium*

[1]EU-OPENSCREEN ERIC, The European Research Infrastructure for Chemical Biology & Early Drug Discovery, Campus Berlin-Buch, Robert-Rössle-Str. 10, Berlin, Germany
*Presenting authors

EU-OPENSCREEN is a not-for-profit European Research Infrastructure Consortium (ERIC) for chemical biology and early drug discovery. Headquartered in Berlin, Germany, we represent a distributed consortium of over 30 laboratories across Europe, offering access to a wide range of state-of-the-art screening platforms, compound libraries, and expertise in medicinal chemistry and chemoproteomics/spatial MS-based omics. We work with researchers from academic institutions and companies around the world to collaboratively identify and develop novel chemical probes and drug leads. Part of this effort includes developing the European Academic Compound Library (EACL), a collection of compounds submitted by academic chemists from around the world, which we profile for biological activities and integrate into in-network screening campaigns. To maximize the re-use of the data generated within our network, EU-OPENSCREEN operates the open-access European Chemical Biology Database (ECBD, https://ecbd.eu/) [1] a web portal aligned with the FAIR principles (findable, accessible, interoperable, and reproducible) containing the validated bioactivity outputs from in-network screening campaigns. We also collaborate with the structural biology community to expand our capacity in the field of fragment-based drug discovery. EU-OPENSCREEN's operations and services are currently being bolstered under the Horizon Europe initiative IMPULSE (Grant ID 101132028). EU-OPENSCREEN also serves as the coordinator of the Horizon Europe initiative 'RAFIKI: EU-Africa Research Infrastructure Alliance to Foster Infectious Disease research, Knowledge sharing and Innovation' (Grant ID 101188390), an EU-funded project bringing together partners across Africa and Europe to support capacity building for drug discovery and development in sub-Saharan Africa.

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Abstract 26

Intracellular delivery of native proteins by bioreversible polyarginine modification

Jonathan Franke[1, 2,*], *Jan V. V. Arafiles*[1], *Christian Leis*[1,2], and *Christian P. R. Hackenberger*[1,2]

[1]Leibniz-Forschungsinstitut für Molekulare Pharmakologie (FMP), Berlin, Germany
[2]Humboldt Universität zu Berlin, Germany
*Presenting author

Protein-based tools are emerging as innovative solutions to interfere with biological pathways in molecular biology and medicine. They offer advantages over traditional small molecules due to their structural diversity and ability to engage previously inaccessible cellular targets. However, most proteins do not penetrate the lipid bilayer of mammalian cells and are therefore restricted to extracellular targets. Despite recent advances, a universal method for delivery of functional proteins into human cells remains a significant challenge. In this study, we present a bioreversible protein modification strategy using polyarginines, that enables cytosolic delivery of native proteins. We optimized the bioconjugate to achieve fast intracellular and complete restoration of the native protein. In combination with our previously established additive protocol[1], we show superior delivery of fluorescent protein and functional RNase A into the cytosol. In particular, we are able to demonstrate the excellent performance in the presence of serum, thereby broadening the scope for intracellular applications.

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Abstract 27

Quantification of oligonucleotide-based therapeutics in cerebrospinal fluid (CSF) and tissues using high-sensitive hybECLIA-based assays

Christoph Goletz[1,*], *Mario Avarello*[1], *Beate Habel*[1], and *Hans Baumeister*[1,*]

[1]FyoniBio GmbH, Berlin, Germany
*Presenting authors

For oligonucleotide quantification from biological samples, FyoniBio established a highly sensitive and reliable method that is applied in a high throughput manner. This is crucial for investigating the pharmacokinetic and pharmacodynamic properties of oligonucleotide therapeutics, such as antisense oligonucleotides (ASOs) and small interfering RNA (siRNA), during preclinical and clinical development. Although common methods, like chromatography or mass spectrometry allow highly specific quantification of oligonucleotides, they come with lower sensitivity, complex sample preparation, matrix effects, and reduced throughput. Improved sensitivity can be achieved by qPCR-based methods. However, the significant impact of analyte modifications on assay sensitivity and the complex process of method development are disadvantages when it comes to analysis of clinical samples. With this poster we show that the hybridization-based immunoassay (hybECLIA) allows also to quantify oligonucleotide therapeutics in very low-protein matrices, such as CSF and in broad range of tissues with high sensitivity and in a high-throughput manner.

Abstract 28

The Molecule Archive of the Compound Platform: An Infrastructure to promote Open Science and the Sustainability of Chemical Research in Academia

Christoph Grathwol[1,*], *Nicole Jung*[1], and *Stefan Bräse*[1]

[1]Institute of Biological and Chemical Systems, KIT, Karlsruhe, Germany
*Presenting author

The Molecule Archive of the Compound Platform, established in 2009 at the IBCS–FMS, has served as a core facility of the German Research Foundation since 2016. It gathers and preserves chemical substances from academic research, forming a continuously expanding library of over 12,000 compounds from 40 international research groups This screening library is distinguished by its structural diversity and complex molecules unavailable from commercial vendors.

Comparison with FDA-approved drug libraries reveals significant overlap, highlighting the drug-like nature of the archive's compounds. Around 80% comply with at least four of the five extended Lipinski rules. The collection includes privileged drug scaffolds such as steroids, coumarins, indoles, quinolines, pyrimidines, tetrazoles, benzothiazoles, purines, and other N-/S-heterocycles.

Beyond conventional drug-like molecules, the archive enables the identification of exotic bioactive chemotypes, including [2.2] paracyclophanes targeting TRP ion channels and metal-organic compounds as novel antibiotics and antifungals.

The Molecule Archive has fostered a strong network of over 45 international research groups and seven screening centres investigating its compounds for anti-inflammatory, antimicrobial, and cancer therapeutic properties. This collaboration has led to numerous publications and patents.

In addition to archiving, the Molecule Archive supports partners with chemical analysis, automation techniques, and expertise for resynthesis and derivatization of promising screening hits.

Abstract 29

Discovery of small molecule antivirals targeting hepatitis B virus epsilon element

Steffen Grimm[1,*], *Melissanne de Wispelaere*[1], *Charlotte Blanc*[1], *Gilles- Olivier Gratien*[1], *Juliette Lavaux*[1], *Priscilla Rebus*[1], *Viviane Liziard*[1], *Pauline Puel*[1], *Manon Jouvert*[1], *Anne Tuukkanen*[1], *Mateusz Mieczkowski*[1], *Claudia Beato*[1], *Ghislaine Marchand*[1], *Stephanie Versluys*[1], and *Antoine Alam*[1]

[1]Evotec SE
*Presenting author

The hepatitis B virus (HBV) epsilon (ε) RNA element is crucial for viral replication and packaging, making it a potential antiviral target. This study employed affinity selection mass spectrometry (AS-MS) to screen a library of ~50,000 lead-like compounds for ε binders. Initial screening and hit expansion identified 121 active compounds, 75 of which were evaluated for antiviral activity in HepaD38 cells. Small angle X-ray scattering, SHAPE-Map data, and ab initio calculations were used to model ε's tertiary structure. Structure-activity relationship (SAR) studies were initiated on select hits, leading to the identification of a chemical series demonstrating enhanced antiviral activity and desirable physicochemical properties. Analogues with improved profiles were tested in HBV-infected primary human hepatocytes, showing significant effects on intracellular viral RNA accumulation and secretion of viral proteins and particles. Omics-scale assays (kinome, transcriptome, and proteome) indicated promising selectivity and specificity. This project successfully identified novel small molecule binders of the HBV ε RNA, including a promising chemical series with antiviral activity against HBV in primary human hepatocytes. Future work will focus on lead series optimization and conducting mode-of-action studies.

Abstract 30

Lupeol and Betulin from Buxus wallichiana Baill Leaf Extract: A Dual Approach to Attenuating U87 Glioblastoma Cell Line Growth and Enhancing Antioxidant Activity

Sabiha Gul[1,2,*]

[1]Department of Precision Medicine, the University of Campania “Luigi Vanvitelli”, Via de Crecchio 7, 80138 Napoli, Italy
[2]Institute for Biotechnology, Brandenburg University of Technology (BTU) Cottbus-Senftenberg, Senftenberg, Germany
*Presenting author

Objective
The rising interest in natural plant-based compounds for cancer treatment has led to the investigation *Buxus wallichiana Baill* (BW), a plant known for its traditional medicinal uses. This study explores the dual therapeutic potential of lupeol and betulin, two bioactive compounds from *BW* leaf extract, focusing on their ability to attenuate glioblastoma U87 cell growth and enhance antioxidant activity.
Methodology
The chemical composition of the ethanolic extract from *BW* leaves was analyzed using Gas Chromatography-Mass Spectrometry (GC-MS). Lupeol and betulin were identified as major constituents. Antioxidant activity was evaluated through the DPPH (2,2-diphenyl-1-picryl hydrazyl) radical scavenging assay, while anti-cancer activity was assessed using the MTT assay on U87 glioblastoma cells. The data were analyzed using ANOVA followed by Bonferroni’s post hoc test.
Results
The results showed significant antioxidant activity, with the extract effectively scavenging free radicals ($P<0.05$). Additionally, lupeol and betulin significantly inhibited U87 glioblastoma cell proliferation, with IC50 values lower than 30 µg/mL, indicating potential anti-cancer efficacy. The extract exhibited a dual effect of reducing oxidative stress while simultaneously attenuating tumor cell growth.
Conclusion
The findings suggest that *BW* leaf extract, particularly its active constituents lupeol and betulin, possess dual therapeutic potential as an antioxidant and anti-cancer agent. This dual approach makes it a promising candidate for further development as a natural treatment for glioblastoma with minimal side effects.
Keywords: *Buxus wallichiana Baill*, Lupeol, Betulin, Antioxidant, Anticancer, U87 Glioblastoma Cell Line, Phytochemicals.

Abstract 31

Differential KEAP1/NRF2 mediated signaling widens the therapeutic window of redox-targeting drugs in SCLC therapy

Nikolas Gunkel[1,*], *Jana Samarin*[1], *Hana Nuskova*[1], *Aubry Miller*[1], and *Hamed Alborzina*[1]

[1]DKFZ, Heidelberg, Germany
*Presenting author

Small cell lung cancer (SCLC) patients frequently experience a remarkable response to first-line therapy. Follow up maintenance treatments aim to control residual tumor cells, but generally fail due to cross-resistance, inefficient targeting of tumor vulnerabilities, or dose-limiting toxicity, resulting in relapse and disease progression. Here, we show that SCLC cells, similar to their cells of origin, pulmonary neuroendocrine cells (PNECs), exhibit low activity in pathways protecting against reactive oxygen species (ROS). When exposed to a novel thioredoxin reductase 1 (TXNRD1) inhibitor, these cells quickly exhaust their ROS-scavenging capacity, regardless of their molecular subtype or resistance to first-line therapy. Importantly, unlike non-cancerous cells, SCLC cells cannot adapt to drug-induced ROS stress due to the suppression of ROS defense mechanisms by multiple layers of epigenetic and transcriptional regulation. By exploiting this difference in oxidative stress management, we safely increased the therapeutic dose of TXNRD1 inhibitors in vivo by pharmacological activation of the NRF2 stress response pathway. This resulted in improved tumor control without added toxicity to healthy tissues. These findings underscore the therapeutic potential of TXNRD1 inhibitors for maintenance therapy in SCLC.

Abstract 32

Design, Synthesis and Optimization of Orthosteric Inhibitors of Protein Tyrosine Phosphatase SHP2

Ziqiong Guo[1,*], *Nina-Louisa Efrém*[1], *Machoud Amoussa*[1], *Feng Bo*[2], *Victoria Zeitz*[1], *Katrin Frank*[3], *Silke Radetzki*[1], *Tamás Takács*[4], *Jens-Peter von Kries*[1], *András Zeke*[4], *Jia Li*[2], *Hana Algül*[3], and *Marc Nazaré*[1]

[1]Leibniz-Forschungsinstitut für Molekulare Pharmakologie (FMP), Berlin, Germany
[2]Shanghai Institute of Materia Medica (SIMM), Chinese Academy of Sciences
[3]Comprehensive Cancer Center, Institute for Tumor Metabolism, TUM School of Medicine and Health, University Medical Center, TUM, Munich, Germany
[4]HUN-REN Research Centre for Natural Sciences (RCNS), Hungary
*Presenting author

SHP2 is a nonreceptor protein tyrosine phosphatase (PTP) encoded by the PTPN11 gene. It is a key regulator for multiple functions in the cytoplasm downstream of multiple receptor-tyrosine kinases and is involved in numerous oncogenic cell signaling cascades (e.g., RAS−ERK, PI3K−AKT). SHP2 contributes to the programed cell death pathway (PD1/PD-L1) and thereby to cancer immune evasion.

In view of the importance of SHP2 as an anticancer target, the discovery of SHP2 small molecule inhibitors has attracted wide interest. Currently, allosteric modulation of SHP2 has been studied extensively and the allosteric inhibitors have advanced into clinical trials for cancer therapy. However, these allosteric inhibitors exert low efficacy against common strongly activating SHP2 mutations. Therefore, whether SHP2 activity can be efficaciously suppressed in several tumors bearing these mutations in a clinical setting is doubtful. Consequently, developing SHP2 inhibitors underlying a non-allosteric mode of action, by directly inhibiting the active site, is highly desirable.

In our work, we have been exploring the structure optimization of the orthosteric azaindole inhibitors of SHP2 and obtained more potent and in particular, highly soluble inhibitors. Additionally, we present the investigation of introducing a covalent modifier to irreversibly suppressing SHP2.

Abstract 33

Hit Identification and Optimization of Energy-Coupling Factor (ECF) Transporter Inhibitors to Combat Antimicrobial Resistance

Mostafa M. Hamed[1,*], *Eleonora Diamanti*[1], *Ioulia A. Exapicheidou*[1], *Alekesei Tsarenko*[2], *Carole Baumann*[1], *Atanaz Shams*[1], *Jörg Haupenthal*[1], *Jennifer Herrmann*[1], *Rolf Müller*[1], *Dirk J. Slotboom*[2], and *Anna K. H. Hirsch*[1]

[1]Helmholtz Institute for Pharmaceutical Research Saarland, Germany
[2]University of Groningen, The Netherlands
*Presenting author

The rise of antimicrobial resistance among pathogens poses an escalating challenge to global health, emphasizing the urgent need for new anti-infective agents with novel mechanisms of action. Energy-coupling factor transporters (ECF-T) are an underexplored family of transmembrane proteins vital for the uptake of essential nutrients such as vitamins and co-factors. These transporters are crucial for the growth and survival of Gram-positive pathogens and are absent in humans, offering a promising target for novel antimicrobial therapies.[1,2]
Herein, we employed various hit-identification strategies to identify inhibitors targeting the ECF transporters. This yielded hits with promising *in vitro* and cell-based activities, along with favorable *in vitro* ADMET profiles.[3,4] Further medicinal-chemistry optimization and structure-activity relationship studies, coupled with multiparameter optimization, enhanced the potency and broadened the antibacterial spectrum of our compounds while maintaining low cytotoxicity and good *in vivo* PK profile. Additionally, we demonstrated rapid bacterial killing using *Enterococcus faecium* as a representative pathogen and confirmed *in vivo* efficacy of the best compounds in *Galleria mellonella* larvae infection model with *Streptococcus pneumoniae*. These results highlight the therapeutic potential of ECF transporters as novel targets in antimicrobial drug discovery.

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Abstract 34

Development of new anti-infectives targeting the pyocyanin biosynthesis enzyme PhzB in Pseudomonas aeruginosa

Maria Handke[1,2,*], *Marie Thiemann*[1,2], *Moritz Zimmermann*[1,2], *Conrad Kunik*[1], *Wulf Blankenfeldt*[2], and *Matthias Schiedel*[1]

[1]Technical University Braunschweig, Germany
[2]Helmholtz Centre for Infection Research, Braunschweig, Germany
*Presenting author

Antimicrobial drug resistance is an emerging threat in human health care and a major challenge in anti infective drug discovery. A promising strategy to prevent antimicrobial drug resistance is the development of so-called pathoblockers that rather disarm than kill the pathogens by interfering with to biosynthesis or activity of certain virulence factors. Pseudomonas aeruginosa is a Gram negative, opportunistic human pathogen associated with airway infections in cystic fibrosis (CF) patients. The virulence of *P. aeruginosa* is linked to its ability to produce a large repertoire of virulence factors, including the phenazine-derived pyocyanin.[1] Pyocyanin plays a key role in the redox-activity, biofilm formation, and pathogen toxicity of *P. aeruginosa*.[2]
In this project, we developed different compounds targeting the pyocyanin biosynthesis in *P. aeruginosa*. As a target protein, we selected the enzyme PhzB, which is one of the key enzymes in pyocyanin biosynthesis and involved in the rate-determining step during the formation of the phenazine core. Based on the drug repurposing study by Ho Sui et al.,[3] derivatives of the selective estrogen receptor modulator (SERM) raloxifene were synthesized and biologically evaluated. Nano differential scanning fluorimetry (nDSF) was initially used to detect PhzB binding of the synthesized ligands. Subsequently, X-ray co-crystallography helped us to elucidate the binding modes of our novel PhzB ligands at the molecular level and provided new starting points for future structure-based ligand optimization. Furthermore, some of our newly developed PhzB inhibitors evoked an improved inhibition of pyocyanin biosynthesis in *P. aeruginosa* PA14, compared to the parental compound raloxifene.
In summary, our results indicate that PhzB is a suitable drug target to inhibit the biosynthesis of the *P. aeruginosa* virulence factor pyocyanin, thereby providing a new approach for the development of pathoblockers to treat *P. aeruginosa* infections.

Abstract 35

Reverse Design as a Novel Concept for Activatable Fluorescent Turn-on Probes

Annaleah Hanske[1,*], *Axel Hentsch*[1], *Carolina Vinagreiro*[1], *Uwe Grether*[2], and *Marc Nazaré*[1]

[1]FMP Berlin, Germany
[2]Roche Pharma Research & Early Development, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd., 4070 Basel, Switzerland
*Presenting author

The detection and identification of disease-related biomarkers are crucial for early diagnosis, evaluation of disease progression, and the development of innovative therapeutics. Pathologically upregulated or activated enzymes play a pivotal role in disease progression, making them key targets for the visualization and elucidation of underlying pathophysiological processes at a microscopic level. Fluorescence imaging offers a valuable and non-invasive method to visualize such biomarkers with high sensitivity and resolution in real-time. However, monitoring biological processes in vivo requires specific, highly selective imaging methods. Activity-based fluorescence probes – so-called SMART probes – provide a powerful tool for selectively detecting enzymatic activity with high spatial and temporal resolution.
We aim to establish a versatile platform comprising fluorescent, activatable SMART probes targeting hydrolases and thereby enabling real-time disease detection. To design highly specific probes, we use the concept of Reverse Design, thus deriving probes from already established and comprehensively optimized inhibitors to ensure high efficacy and selectivity as well as favorable pharmacokinetic properties. The large number of available inhibitors for high-relevance targets known from the literature enables the establishment of a versatile concept that can be flexibly adapted towards different targets by simple chemical modifications.
In this study, we focus on Monoacylglycerol Lipase (MAGL), a key serine hydrolase in the endocannabinoid system. MAGL hydrolyses the important endocannabinoid 2-arachidonoylglycerol (2-AG) into arachidonic acid (AA) and glycerol. Endocannabinoids are involved in various physiological and pathophysiological processes, including pain, appetite, addiction, and emotion, therefore, MAGL has a significant influence on these processes by regulating 2-AG levels. Moreover, the release of AA is a strong pro-inflammatory signal. The development of small molecule fluorescent probes targeting MAGL could facilitate the visualization of disease-related physiological processes in vitro & in vivo and provide further insights into its functions and activity.

Abstract 36

FASS: A Disruptive Solubility Measurement for Drug Discovery

Robert Harmel [1,], Orly Tarun[2], Damien Bonaudu[3], and Martin Kuentz[4]*

[1]EU-OPENSCREEN ERIC, Berlin, Germany
[2]Oryl Photonics, Lausanne, Switzerland
[3]ALPhANOV, Talence, France
[4]School of Life Sciences FHNW, Muttenz, Switzerland
*Presenting author

Solubility measurement is a fundamental requirement in drug discovery, yet current methodologies suffer from a trade-off between speed, accuracy, and compound consumption. The FASS (Fast and Accurate Solubility for Sustainability) project introduces a disruptive solubility measurement technique based on second harmonic scattering. The underlying principle is based on the Solvent Redistribution method, which detects solubility limits by measuring the dynamic redistribution of solvent molecules at the onset of aggregation. This non-destructive, optical light scattering technique provides an accurate and highly sensitive metric for solubility determination which saves time and resources through its well plate-based format.
Funded through the EIC transition support, a consortium of EU-OPENSCREEN ERIC, Oryl Photonics, ALPhANOV and FHNW tries to transform this early technology into a device that can be used by scientists in academia and industry to optimize formulations or measure aggregation of small molecules in different environments.

Abstract 37

Competitive Molecular Glues and RIPTACs for Challenging Drug Targets and Cell-Type Specificity

Felix Hausch[1,*]

[1]Technical University Darmstadt, Peter-Grünberg-Str. 4, 64287 Darmstadt, Germany
*Presenting author

Proximity-inducing molecular glues and bifunctionals are an emerging class of therapeutics with the potential to unlock fundamentally new properties, incl. gain-of-function pharmacology, cell-type specificity or the targeting of difficult-to-drug proteins. However, the identification molecular glues and the optimization of bifunctionals are far from trivial.[1] Here, we present the discovery of fully synthetic FKBP12-based competitive molecular glues for the FRB domain of mTOR[2] and three neo- targets.[3] Furthermore, the prospect of FKBP12-based RIPTAC-like bifunctionals will be presented. This demonstrated dramatic potency enhancements (CellTrap effect), strict presenter protein dependence, and cell-type specificity in cellular assays. Our findings show that molecular glues are more prevalent than previously thought, provide general insights for their discovery, and support high-expression proteins as preferred presenters for competitive molecular glues and bifunctionals.

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Abstract 38

Therapeutic DNAzymes for the treatment of HIV-1

Mara Hebeis[1,*], *Thanh Hoang Duc*[1], *Nina Kirchgässler*[2], and *Ingrid Span*[1]

[1]FAU Erlangen-Nürnberg, Germany
[2]HHU Düsseldorf, Germany
*Presenting author

DNA enzymes (DNAzymes) are promising candidates for gene-silencing agents and offer great potential for the treatment of inherited genetic disorders, infectious diseases, and cancer. They are considered advantageous over other gene-silencing methods such as short interfering RNA (siRNA) due to their high stability, multiple turnover rates, and ready availability. DNAzymes are single-stranded DNA that adopt unusual three-dimensional structures, which enable them to perform enzyme-like biocatalysis. They consist of a catalytic core and two substrate binding arms, which can be engineered to bind almost any RNA through Watson-Crick base pairing. We have designed and four new variants of the 10-23 DNAzyme that are specific for the mRNA encoded by the gag gene of HIV-1. This mRNA is translated into the Gag polyprotein Pr55Gag, which is later cleaved into functional proteins by a viral protease, including matrix (p17), which supports viral assembly and budding; capsid (p24), which forms the viral core and protects the RNA genome; nucleocapsid (p7), which binds and protects the viral RNA; and protein p6, which is essential for virion release and interaction with host proteins. The bioinformatic design of the DNAzyme takes into account accessibility of the cleavage site in the folded RNA, efficient association with the substrate and rapid dissociation of the cleavage products to ensure catalysis. Activity assays using short RNA strands showed that all DNAzymes are capable of cleaving the substrate. Furthermore, we have generated the full-length RNA sequence by in vitro transcription and demonstrated that the DNAzymes cleave the RNA strand with high specificity at the predicted position. This demonstrates that our approach of designing 10-23 DNAzymes leads to efficient catalysts, which showed different activities, due to the complicated folding of long RNA. Therefore, activity tests of newly designed DNAzymes on full-length RNA are crucial to obtain DNAzymes with high potential as gene-silencing agents.

Abstract 39

Decoding the Structure-Activity Relationship of Novel Synthetic γ-Pyrone Polyketides as potent Anti-HIV Agents

Wiebke Hutwelker[1], *Mark Wever*[1,*], *Matteo Rizzato*[1], *Patrick O'Connor*[1], *Beata Gryzło*[1], *Jenna Labinski*[1], *Sandra Johannsen*[1], *Katharina Rox*[2,3], *Alexander Herrmann*[1], and *Oliver Plettenburg*[1]

[1]Helmholtz Centre Munich, Germany
[2]Helmholtz Centre for Infection Research (HZI), Braunschweig, Germany
[3]German Center for Infection Research (DZIF)
*Presenting author

In the continuous effort to combat human immunodeficiency virus (HIV), the identification and development of new drug candidates remains a top priority. The introduction of combined antiretroviral therapy (cART) has shifted HIV from a certain death sentence to a manageable condition. However, the rise of drug resistance shows the need for development of new therapies with novel mechanisms-of-action. Clinical anti-HIV drugs interfere with steps of the replication cycle catalyzed by HIV enzymes, *i.e.*, protease, integrase and reverse transcriptase. Previously, we published a phenotypic screen of around 10000 natural products, which resulted in the identification of a class of synthetic γ-pyrone polyketides structurally related to the natural product Aureothin.[1] In a first-round optimization, derivative **1** was identified, in which a potentially problematic nitro-substituent was replaced. This analogue has shown potent anti-HIV-1 activity *in vitro*, i.e., IC_{50} = 5 nM. The antiviral effect of **1** was narrowed down to the post-transcriptional and translational steps of the HIV-1 replication cycle. Moreover, **1** inhibits HIV gene expression and synergizes with selected clinical drugs in cell culture experiments. Here, we disclose the design, synthesis and biochemical evaluation of a novel series of synthetic polyketides. Since the disclosure of analogue **1**, more than 100 derivatives have been prepared and evaluated in vitro, to provide rigorous elucidation of the structure-activity relationship (SAR) of Aureothin and related synthetic analogues against HIV-1. During this optimization, the synthetic route has been shortened and potential photo- and chemical liabilities have been removed. In conclusion, this work provides a first step towards development of synthetic γ-pyrone polyketides as potent anti-HIV drugs.

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Abstract 40

Novel Siderophore Conjugates for the Visualization and Treatment of Bacterial Infections

Tamara Ilioska[1,*], *Michael Dyrks*[2], *Yelena Mostinski*[2], *Dr. Marc Nazaré*[2], *Prof. Dr. Haiyu Hu*[3], and *Prof. Dr. Mark Brönstrup*[1]

[1]Helmholtz Center for Infection Research, Braunschweig, Germany
[2]Leibniz-Forschungsinstitut für Molekulare Pharmakologie FMP, Berlin, Germany
[3]Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China
*Presenting author

The rapid rise of multidrug resistance in pathogenic bacteria, such as *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, presents an urgent clinical challenge. In Gram-negative bacteria, the low permeability of the outer membrane reduces the effectiveness of antibiotics with intracellular targets. To address this, we synthetized novel, broad spectrum or species-specific siderophore conjugates designed to overcome the permeability challenge in bacterial pathogens of the ESKAPE panel.
Siderophores are molecules that bacteria produce to scavenge an essential nutrient from their environment - ferric iron (Fe^{3+}). Using a 'Trojan horse' strategy, we exploit the bacteria's need for iron by coupling synthetic siderophores to different payloads that are actively delivered into bacterial cells, overcoming the low permeability of the outer membrane. We developed a synthetic route to obtain four siderophores based on the DOTAM core, bearing catechol and hydroxamate iron binding moieties in different ratios. Their binding affinity for ferric iron was evaluated using the Chrome Azurol S assay and compared to enterobactin. The binding strength increased with the number of catechol moieties. Ongoing studies assess the ability of the siderophores to restore bacterial growth. These experiments will give us insight to which siderophores to use for conjugate formation. With the DOTAM core in hand we rationally designed an enzymatically activatable probe for sensing and imaging of Gram-negative pathogens, which is characterized in cellular assays. Additionally, we have established a synthetic pathway to anguibactins, thermally stable surrogates of the natural acinetobactin oxazoline. The compounds incorporate a functional handle for conjugation and will be used for the specific targeting of *A. baumannii*.

Abstract 41

Ultra-High-Throughput Biophysical Screening of MEK1 Using the Dianthus uHTS Platform

Ivana Jaser[1] *Gianluca Luigi Russo*[1,*], *Jan Schnatwinkel*[1], *and Nathan B P Adams*[1]

[1]NanoTemper Technologies GmbH, Munich, Germany
*Presenting author

The Dianthus uHTS platform revolutionizes biophysical screening throughput, delivering over 250,000 data points daily in 1536-well plates using NanoTemper's Spectral Shift technology. This fluorescence- based readout combines novel probe chemistry and precision optics to detect binding events in solution and in equilibrium, without dependency on mass changes or prior knowledge of the ligand binding site. This allows the characterization of a wide range of target classes and ligand modalities, ranging from PROTACs, molecular glues and fragments, to MDa protein-protein complexes or RNA/ DNA interactions. To showcase Dianthus uHTS in a screening setting, we screened 5112 diverse compounds against MEK1, a key kinase in the MAPK/ERK pathway. MEK1 drives critical cellular processes like proliferation and survival and is implicated in cancers such as melanoma and non-small cell lung cancer, making it a prime target for small-molecule discovery. Using a total of only 0.54 nmol of labeled protein and 90 minutes of total measurement time we were able to perform both a single dose screen in duplicates, and dose-response hit validation in triplicates, identifying 15 confirmed binders out of 5112 compounds, two with affinities of < 100 nM towards MEK1.

Abstract 42

A phenotypic drug discovery platform for combinatorial targeting of cell states and entities

Ben Jiang[1,], Matthias J. Schmitt[1], Maria Pillar Sanchez-Bailon[1], Michela Serresi[1], Gaetano Gargiulo[1]*

[1]Max-Delbrück-Centrum für Molekulare Medizin, Berlin, Germany
*Presenting author

Glioblastoma (GBM) is a highly lethal brain tumor with limited therapeutic options. The blood-brain barrier (BBB) limits the effectiveness and bioavailability of approved therapeutics and the discovery of new ones. Additionally, GBM consists of heterogeneous, highly plastic cellular entities and states conserved across patients. Tumor cell states change and adapt in response to the current standard of care and infiltration of innate immune cells. For example, myeloid cells drive a mesenchymal state in GBM cells that promotes acquired resistance to therapeutics.
Our lab has developed transcriptional reporters for glioblastoma subtypes named synthetic locus control regions (sLCRs), which inform on cell identity and fate transitions *in vitro* and *in vivo*. Using this tool, we established an *in vitro* phenotypic drug discovery (PDD) platform that recapitulates the interaction between GBM and innate immune cells leading to phenotypic transition and a distinct shift in drug sensitivity in a multicellular 3D model. We show that tumor cells and immortalized microglia co-exist under conditions that enable screening for therapeutic effectiveness of individual drugs over days and their combination with the standard of care. We screened close to 1000 small molecules, including lipophilic agents which may possess properties to bypass the BBB. Our platform enables categorization of drug treatments based on tumor cell viability, adaptive cell state changes and the survival of non-transformed innate immune cells. We discovered drugs with the distinct ability to modulate each parameter and novel responses for a clinically relevant drug with potential therapeutic implications.
Hence, our PDD enables data-informed assembly of combinatorial treatments of novel and approved drugs targeting distinct features of the tumor, including a mesenchymal state transition.
Furthermore, we are currently expanding the PDD with additional GBM models of diverse genetic and molecular background as well as additional novel experimental anti-cancer agents.

Abstract 43

Porcine pancreatic ductal organoids for drug screening applications

Christos Karampelias[1,2,*], *Kaiyuan Yang*[1,2], *Michael Sterr*[1,2], *Mireia Molina Van den Bosch*[1,2], *Tatsuya Kin*[3], *Eckhard Wolf*[4,2], *Elisabeth Kemter*[4,2], and *Heiko Lickert*[1,2]

[1]Institute of Diabetes and Regeneration research, Munich, Germany
[2]German Center for Diabetes Research
[3]University of Alberta Hospital, Canada
[4]LMU Munich, Germany
*Presenting author

Exocrine pancreas is a hub for devastating diseases like pancreatitis and pancreatic ductal adenocarcinoma. Given the difficulty to access pancreas tissue from patients and the scarcity of donor material, new and well characterized tools are needed to study pancreatic disease and develop new therapies. Pancreatic organoids derived from exocrine tissue are a great innovation to study disease mechanism and screen for new therapeutics in vitro and in a high-throughput manner. In this work, we characterized porcine pancreatic ductal organoids as an alternative model for high-throughput pancreatic drug screening. Pigs share great similarities in terms of size and metabolism to the human system. We performed an in-depth benchmarking of porcine pancreatic ductal organoids using single cell RNA sequencing against human-derived pancreatic organoids and primary pancreatic tissue and identified the similarities between the systems. We further assessed the range of applications that these porcine pancreatic organoids can be applied for, by assaying organoids derived from distinct developmental stages. Lastly, we used porcine pancreatic ductal organoids to screen FDA-approved drugs as inducers for drug-induced pancreatitis and increased pancreatic ductal proliferation (pancreatic cancer application) and identified causative agents that can induce pancreatic cell death. We translated the most promising primary candidates to the human pancreatic organoid system highlighting the usefulness of this model for translational applications. Our work paves the way for use of an easily obtainable pancreatic exocrine source (porcine ductal organoids) for drug screening applications with comparable results to the hard to obtain human pancreatic tissue.

Abstract 44

DockCADD: A streamlined in silico pipeline for the identification of potent ribosomal S6 Kinase 2 (RSK2) inhibitors

El Mehdi Karim[1,*]

[1]Laboratory of Analytical and Molecular Chemistry, Faculty of Sciences Ben M'Sik, Hassan II University of Casablanca, Casablanca, 7995, Morocco
*Presenting author

The search for innovative therapeutic strategies remains critical in addressing cancer, one of the leading global health challenges. Ribosomal S6 Kinase 2 (RSK2), a serine/threonine kinase, has emerged as a promising target for cancer therapy because it is implicated in oncogenic signaling. Herein, we developed an open-source computational pipeline, identified as DockCADD (available at https://github.com/mehdikariim/DockCADD), which enables the identification of potent RSK2 inhibitors by automated virtual screening, ADME-Tox profiling, and molecular dynamics (MD) simulations. Employing pyran derivatives as the scaffold, top-scoring inhibitors as identified by the pipeline showed scores ranging from -9.46 to -9.89 kcal/mol and binding free energies ranging from -53.731 to -55.193 kcal/mol. Ligands L1, L2 and L3 showed stable binding within the ATP-binding pocket, wherein the compounds undergo slight structural distortions with a favorable van der Waal's interaction. The ligand L3 has exhibited the highest MM-GBSA binding free energy (-55.193 kcal/mol), which so far presents the most promising candidate. These results have pointed out the use of DockCADD as an efficient tool for the fast and low-cost process of drug discovery; L1–L3 should be further validated experimentally for cancer therapy.

Abstract 45

Towards prediction of antibiotic Mode of Action using high-throughput imaging and AI

Felix Knote[1,*]

[1]RVZ Würzburg, Germany
*Presenting author

Antibiotic resistance is fueling a growing global health crisis, necessitating the discovery of antibacterial compounds with novel modes of action (MoAs). The decline in new antibiotic approvals, coupled with the rise of multi-resistant pathogens, highlights the limitations of traditional antibiotic drug discovery. Among them, phenotypic drug screening has proven effective at identifying antibacterial compounds, but requires time-consuming follow-up experiments to determine drug MoA or targets.
Here, we will outline a project aiming to develop a streamlined workflow for predicting antibiotic MoAs from automated microscopy imaging data analyzed by deep learning. The project is based on the hypothesis that MoAs of chemical compounds can be predicted by computationally matching their induced phenotypes to those of genetic mutants. In order to map the phenotypes of essential genes, we use a CRISPRi technique allowing to induce their repression in a finely tuned manner. We will report on our early efforts to create and phenotype these inducible mutants in E. coli. This work contributes to the establishment of a pipeline that will accelerate the search for novel antibiotics against antimicrobial resistant bacteria.

Abstract 46

De novo RNA aptamer against influenza A virus's non-structural protein 1: In silico design, molecular docking, and simulation

Naresh kanna L[1,*], and *Dicky John Davis G*[2]

[1]Genome foundation
[2]Sri Ramachandra Institute of Higher Education and Research, Chennai, India
*Presenting author

Influenza A virus is an infectious respiratory virus that causes seasonal outbreaks and pandemics around the world. The emergence of resistance among strains of the virus to traditional antiviral drugs, such as Oseltamivir, which mostly targets the neuraminidase enzyme, has rendered these treatments less effective. A more promising target is the non-structural protein 1 (NS1), because of its multifunctional mechanism involves viral replication, immune evasion, and pathogenicity. NS1 significance as a therapeutic target has prompted the exploration of alternative strategies, such as RNA-based aptamers. Unlike small molecules or phytochemicals, RNA aptamers can recognize and bind to their targets with high affinity and specificity. They have the potential to target a wide range of biomolecules like proteins, viruses, and small molecules like antibiotics and hormones. This study aims, through a computational approach to develop an RNA-based drug against the target NS1 protein. Although aptamers are traditionally developed through an in vitro process called SELEX, which can be time-consuming and have a low success rate, computational methods offer a faster, more efficient alternative. This approach involves the selection, design, and validation of aptamers against NS1 by leveraging molecular docking and molecular simulation to predict strong binders. The successful development of aptamers through this in silico pipeline could lead to a novel antiviral strategy against Influenza A, especially in the context of drug-resistant strains.

Abstract 47

Advancing iPSC-Based Cardiac Disease Modeling and Drug Discovery at Nuvisan

Skadi Lau[1,*], *Maike Marczenke*[1], *Claudia Noack*[1], *Ekkehard May*[1], and *Norman Liaw*[1]

[1]Nuvisan ICB GmbH
*Presenting author

Cardiovascular diseases such as hereditary cardiac diseases, arrhythmia, cardiomyopathies, cardiac fibrosis, and ultimate heart failure remain a leading cause of morbidity and mortality worldwide. Human induced pluripotent stem cells (hiPSCs) provide a powerful, patient-specific tool for modeling these diseases and developing targeted therapeutics. We introduce here an integrated hiPSC-based platform to generate physiologically relevant cardiac models by either using patient-derived cells or by introducing a disease phenotype through genome editing. Using directed differentiation protocols developed in our laboratories with defined media compositions, we generate iPSC-derived atrial and ventricular cardiomyocytes, cardiac fibroblasts, and cardiac endothelial cells. These cells can be utilized in a variety of assay formats to advance cardiovascular drug discovery including:
• 2D monocultures and co-cultures to investigate cell-specific responses such as cardiomyocyte contractility and beating frequency as measured by multielectrode array (MEA),
• 3D organoids to recapitulate multicellular interactions functionally assessed by organ bath analyses,
• Cellular impedance assays for endothelial barrier integrity studies.
For high-throughput applications, we provide assay-ready 2D cultures in 384-well plate formats, allowing for efficient drug screening and functional validation of lead compounds. Importantly, our iPSC-derived engineered cardiac organoids (ECOs) uniquely resemble the donor/patient, enabling personalized disease modeling. These ECOs:
• Beat spontaneously while responding to external electrical stimuli,
• Function as a syncytium, actively generating measurable contractile forces,
• Serve as myocardial infarction-like models, supporting studies on cardiac injury, fibrosis, and regeneration.
By combining advanced stem cell engineering, biofabrication, and functional phenotyping, our platform enables disease modeling, mode-of-action studies, and preclinical drug evaluation in physiologically relevant cardiac systems.
As full-service contract research, development, and manufacturing organizations (CRO/CDMO), Nuvisan and its affiliates offer a cutting-edge, extended workbench for academic groups and biotech companies developing novel cardiovascular therapeutics.

Abstract 48

It is not crystal clear: Are structural models used to train ML models and in computational studies reliable?

Filipe Menezes[1,*], *Grzegorz Popowicz*[1], and *Michael Sattler*[1]

[1]Institute of Structural Biology, Helmholtz Munich, Germany
*Presenting author

Suppose we wanted to study Axitinib's binding to the BCR-ABL kinase (PDB-ID 4WA9) and its T315I mutant (PDB-ID 4TWP). The models deposited in the PDB would offer an invaluable starting point for the structural backbone and in assigning biologically meaningful protein and ligand protonation states. Following the PDB deposition data and using the experimental IC50's to estimate the relative affinities (doi:10.1038/nature14119), a quantum mechanical (QM) calculation would result in a relative binding enthalpy of over –31.0 kcal/mol and a relative binding entropy of almost –100.0 cal/K/mol.
We developed a quantal-based algorithm, the In-Pocket Analysis (IPA), that analyses biomolecular structures, detects atomic clashes, and suggests changes in protonation and tautomerisation states. Applying IPA to 4WA9 and 4WTP identifies two issues in the former model: 1) atomic clashes involving the indazole group; 2) flipping axitinib's terminal pyridyl ring gives the complex an extra hydrogen bond. Furthermore, calculations using the IPA modified ligand topologies lead to reasonable binding enthalpies and entropies (–9.18 kcal/mol, –26.16 cal/K/mol) and a more sensible chemical state of axitinib in the kinase's pocket.
We previously determined that 20% of the ligands in a popular database were chemically inconsistent (doi:10.1038/s43588-024-00627-2). In this communication, we introduce IPA as a general tool for in-depth chemical analysis of biomolecular structures. IPA identifies the most likely chemical states of ligands in a pockets' environment, irrespective whether it involves proteins, nucleic acids, transition metals, etc. It is also extremely efficient: calculations can be run in standard workstations in a matter of minutes. We benchmark the algorithm on several macrobiological structures and show how IPA can uncover the neglected chemical information from PDB structures. Ultimately, we are convinced that IPA will have a profound impact in how drugs can be optimized or how we train machine learning models.

Abstract 49

Harnessing AI and Synthetic Biology for NRPS-Based Drug Discovery

Hannah Minas[1,*], *Maximilian Bahls*[1], *Evangelos-Marios Nikolados*[1], *Irene Wüthrich*[1], *Steven Schmitt*[1], and *Kenan Bozhüyük*[2]

[1]Myria Biosciences AG
[2]Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), Germany
*Presenting author

Myria Biosciences pioneers drug discovery solutions by integrating high-throughput synthetic biology with cutting-edge, AI-driven design and high-throughput screening to develop transformative small-molecule therapies. Spun out of ETH Zurich, HIPS/HZI, and MPI for Terrestrial Microbiology, Myria leads the way with “Genetically Engineered Modular Molecule Scaffolds (GEMMS)”, smartly engineered synthetic natural products that enable the design and biological production of molecules beyond nature’s constraints.

A proprietary cloning and assembly pipeline, utilizing automated liquid-handling robotics, enables the high-throughput recombination of non-ribosomal peptide synthetase (NRPS)-derived modules, which are subsequently used for the heterologous microbial production of novel synthetic natural products. High-throughput solid-phase extraction and mass spectrometry validate successful compound production.

Additionally, our in silico platform automates the prediction of synthetic natural product structures and enables high-throughput compound searches in mass spectrometry datasets. These datasets are further used to improve the predictive power of computational models for tailor-made NRPS design, closing the loop for the forward design of synthetic natural products.

Abstract 50

EU-OPENSCREEN – An open access initiative to identify new biological activities of your compounds

Victoria Mora[1,*], *Bahne Stechmann*[1]

[1]EU-OPENSCREEN ERIC, Robert-Rössle-Str. 10, 13125 Berlin, Germany
*Presenting author

Compounds and natural products synthesized by chemists represent a rich, untapped source of novel chemical diversity. In many cases, chemists have limited opportunities to systematically test these compounds against a variety of drug targets. These compounds are also often not readily accessible to the biologists who develop suitable assays.

In order to make the invaluable chemistry of local chemistry groups accessible to a broader scientific community, EU-OPENSCREEN offers chemists the opportunity to make their compounds available, in a regulated and transparent framework, to a wider community of biologists, who screen these compounds in suitable bioassays. This opportunity allows chemists to expose their compounds to a range of biological/drug targets to screen for unknown bioactivities, which would otherwise not be feasible in individual one-to-one-collaborations, thereby enabling novel collaborations with EU-OPENSCREEN users from across Europe and beyond.

The submitted compounds are centrally quality-controlled, stored, and reformatted at the EU-OPENSCREEN Central Compound Management Facility in Berlin. Submitted compounds are initially annotated in a suite of cell-based, biochemical and physicochemical assays to analyse their physicochemical and biological properties before being continuously tested and annotated in our screening campaigns. This ‘bioprofiling’ effort is free of charge to the chemist, and the bioactivity data are shared with the respective chemist who submitted the individual compound.

EU-OPENSCREEN is a publicly funded international consortium of approximately 30 academic partner institutes across nine European countries. The consortium supports chemical biologists to implement their drug discovery projects by providing access to high-throughput screening platforms, screening collections and hit-to-lead optimisation support on a collaborative basis.

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Abstract 51

Understanding the limits of hybridization-dependent siRNA:off target interactions

Eliot Morrison[1], *Luca Penso Dolfin*[1,*], *Judith Hauptmann*[1], *Nina Was*[1], *Wei-Hung Pan*[1], and *Marie Wikström Lindholm*[1]

[1]Silence Therapeutics GmbH
*Presenting author

Understanding and predicting off-target interactions is a key element of siRNA design. While high-homology off-target interactions are relatively trivial to identify by traditional alignment-based approaches, capturing low-homology interactions requires extending such searches to allow for additional differences such as bulges (i.e., insertions or deletions) or imperfect base pairing (e.g., G:U wobbles). This typically results in high numbers of false positives when predictions are compared to experimental data. Here, we explore the limits of such low-homology interactions by analyzing the in-silico alignments of miRNAs with their reported targets and siRNA-mediated off-targets identified by RNAseq of treated cells or tissues. A selection of the identified features identified as possibly compatible with direct siRNA-mediated target transcript reduction were then validated experimentally by editing the siRNA target site to induce a low-homology interaction with the target mRNA - e.g., a target bulge-containing interaction – and observing the effect on target mRNA knockdown. The mechanism of off-target activity was further investigated using a recently described cellular system featuring inactive Ago2. Taken together, these analyses can help guide the in silico design of siRNAs by restricting the search space to only include low-homology edits that were experimentally observed, thus minimizing the number of false positives in the in silico predictions.

Abstract 52

Unlocking the Endocannabinoid System (ECS) with Chemical Probes

Yelena Mostinski[1,*], *Thais Gazzi*[1,2], *Leonard Mach*[1], *Anahid Omran*[1], *Małgorzata Wasinka-Kalwa*[1], *Jara Bouma*[3], *Lucia Scipioni*[4], *Xiaoting Li*[5,6], *Silke Radetzki*[1], *David Sykes*[7], *Maria Schippers*[1], *Christof van der Horst*[3], *Benjamin Brennecke*[1], *Annaleah Hanske*[1], *Wolfgang Guba*[1], *Jens P. von Kries*[1], *Sergio Oddi*[4], *Tian Hua*[5,6], *Dmitry Veprintsev*[7], *Laura Heitman*[3], *Mauro Maccarrone*[8,9], *Uwe Grether*[2], and *Marc Nazaré*[1]

[1]Leibniz-Institut für Molekulare Pharmakologie FMP, Campus Berlin-Buch, Germany
[2]Roche Pharma Research & Early Development, Roche Innovation Center Basel, Switzerland
[3]Division of Drug Discovery and Safety, Leiden Academic Centre for Drug Research, Leiden University, 2333 CC, The Netherlands
[4]University of Teramo, 64100 Teramo, Italy
[5]iHuman Institute, ShanghaiTech University, Shanghai 201210, China
[6]School of Life Science and Technology, ShanghaiTech University, Shanghai 201210, China
[7]Faculty of Medicine & Health Sciences, University of Nottingham, Nottingham NG7 2UH, UK
[8]DISCAB at University of L'Aquila, 67100 L'Aquila & CERC at IRCCS Santa Lucia Foundation, 00164 Rome, Italy
[9]European Center for Brain Research/Institute for Research and Health Care (IRCCS) Santa Lucia Foundation, Rome, Italy
*Presenting author

The endocannabinoid (eCB) system is a complex and not yet fully understood signaling network present in vertebrates. Key components of this system include cannabinoid receptors 1 and 2 (CB_1R and CB_2R), endogenous ligands, and enzymes responsible for their synthesis and degradation. Dysfunction in the eCB system has been linked to various disorders affecting the kidneys, cardiovascular, gastrointestinal, pulmonary, and nervous systems, as well as psychiatric disorders, pain, and cancer. Despite its critical role in the (patho)physiology of numerous diseases, the downstream signaling mechanisms of the eCB system are still not well characterized.[1] Furthermore, tissue and cell-type specific expression profiles have remained largely unexplored due to the lack of high-quality, specific biological and chemical tools, such as labeled chemical probes and antibodies. This knowledge gap has hindered drug development programs. Several small molecule modulators of the eCB system have recently demonstrated desired efficacy in preclinical studies. However, none of these promising compounds have achieved clinical approval, largely due to side effects.
To better characterize the eCB system and validate the roles of its main components under inflammatory conditions, we have developed a platform of tool compounds that specifically and selectively target either CB_1R or CB_2R.[2-4] By taking advantage of a reverse-design approach, we designed and synthesized a series of fluoroprobes with varying dyes and recognition elements suitable for diverse biological settings. These probes are used to localize proteins of interest in different systems and measure ligand-binding kinetics and potency of drug candidates. In summary, we present the probe development process from ideation to proof-of-concept applications in drug discovery.

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Abstract 53

The F2X Facility – Crystallographic Fragment Screening At HZB

Melanie Oelker[1,2,*], *Tatjana Barthel*[1], *Laila Benz*[1, 3], *Frank Lennartz*[1], *Uwe Mueller*[1], and *Manfred S. Weiss*[1]

[1]Helmholtz-Zentrum Berlin, Germany
[2]Humboldt-Universität zu Berlin, Germany
[3]Freie Universität Berlin, Germany
*Presenting author

During drug discovery, the identification of suitable starting points for the design process is a key step in the process. Here, fragment-based screening has become a well-established method and X-ray crystallography is one of the major techniques used for the primary screening of the target protein against the fragment libraries. The technical developments and increasing automatization available at synchrotron light sources made it possible to perform whole fragment screening campaigns by X-ray crystallography within a reasonable time frame. At the Helmholtz-Zentrum Berlin (HZB) we have established a dedicated facility, the F2X facility, to enable users to perform their own crystallographic fragment screening (CFS) campaigns at HZB.
Together with a well-established and reproducible crystallization system, provided by the users, the F2X facility provides all required components to perform a CFS campaign. We developed two chemically diverse fragment libraries, the F2X-Entry and F2X-Universal libraries, which are available as ready-to-use plates and allow for high soaking concentrations. Sample preparation is further facilitated by our inhouse developments, the EasyAccess Frame and a crystal tracking software. Furthermore, the option F2X-GO allows sample preparation at the home lab. Afterwards, data collection can be performed at one of our two high-throughput beamlines, 14.1 and 14.2, which allow the collection of up to 240 datasets in 24 hours. For data analysis we develop and provide state-of-the-art analysis software, like the FragMAXapp, as well as dedicated IT infrastructure, which enables data analysis within a few days. Finally, we also aim to support users in their hit-to-lead development process after the CFS campaign with our Frag4Lead workflow.
Overall, based on our many years of experience, we offer a well-established workflow and extensive user support to academic as well as industrial user, who are interested in performing a CFS campaign with their own target protein(s).

Abstract 54

DrugDiff: small molecule diffusion model with flexible guidance towards molecular properties

Marie Oestreich[1], *Erinc Merdivan*[2], *Michael Lee*[1], *Shubhi Ambast*[1], *Joachim L. Schultze*[1], *Marie Piraud*[2], and *Matthias Becker*[1,*]

[1]German Center for Neurodegenerative Diseases (DZNE)
[2]Helmholtz Munich, Germany
*Presenting author

The rising cost/yield ratio of drug development has driven interest in machine learning to accelerate early stages of the development process. In our work, we introduce DrugDiff, a latent diffusion model guided by molecular property predictors to generate novel small compounds with a variety of targeted characteristics. Diffusion models do multi-step rather than one-shot generation, and offer guided generation without explicit conditional training, making them highly suitable for this task. Unlike existing generative modelling approaches focused on proteins and RNA for drug development, our work extends diffusion-based modelling to small molecules. With small molecules making up the majority of drugs but simultaneously being difficult to model due to their elaborate chemical rules, this work tackles a new level of difficulty in comparison to sequence-based molecule generation as is the case for proteins and RNA. Our model architecture is highly flexible, allowing easy addition or removal of considered molecular properties without the need to retrain the model, making it highly adaptable to diverse research settings and it shows compelling performance for a wide variety of targeted molecular properties. Our experiments show successful generation of unique, diverse, and novel small molecules with targeted properties. We used the public ZINC250K dataset, which contains approximately 250,000 small, drug-like, and commercially available molecules from the ZINC database. The code is available at https://github.com/MarieOestreich/DrugDiff.

Abstract 55

Using Large Language Models for Assessing Drug Toxicity and Drug Efficacy

Daniel Palmer[1], *Roberto A. Avelar*[1], *Claudia Fruijtier*[1], and *Georg Fuellen*[1,*]

[1]Rostock University Medical Center, Germany
*Presenting author

As of early March 2025, OpenAI's "Deep Research" Assistant (OAIDR, available since mid-February) was used to generate at least one PhD thesis draft in the humanities, multiple scientific paper drafts, and a DFG grant application draft concerning adverse outcome pathway (AOP) data analytics—an area of growing importance in drug safety assessment. Here, we detail our use of OAIDR to draft the grant application and support toxicity assessments through advanced data analytics. We demonstrate how appropriate prompting enables the analysis of AOP data and discuss OAIDR's ability to propose, execute, and summarise scientific workflows in molecular data analytics. While this automation presents unprecedented opportunities for research, we stress the critical need for rigorous verification of AI-generated content. We also consider how best to ensure engagement in this verification process as AI outputs become more reliable but not infallible.

Abstract 56

Post-translational Regulation in Multiple Myeloma

Kirsten Peter[1,2,*], *Yuen Lam Dora Ng*[1], *Valeriia Sapozhnikova*[1,3], *Thomas Geiger*[4], *Ina Dressel*[4], *Philipp Mertins*[3,5], *Radosław P Nowak*[4], and *Jan Krönke*[6,1]

[1]Charité - Universitätsmedizin Berlin, Berlin, Germany
[2]Freie Universität Berlin, Berlin, Germany
[3]Max Delbrück Center of Molecular Medicine, Berlin, Germany
[4]Institute of Structural Biology, Medical Faculty, University Bonn, Bonn, Germany
[5]Berlin Institute of Health, Berlin, Germany
[6]Universitätsmedizin Greifswald, Greifswald, Germany
*Presenting author

Post-translational regulation plays a major role in cancer biology and therapy. Protein degraders like thalidomide analogs, immunomodulatory drugs (IMiDs), redirect the cereblon (CRBN) E3 ubiquitin ligase for selective degradation of Ikaros (IKZF) transcription factors, which are important for myeloma survival. While IMiDs induce responses in the majority of multiple myeloma patients, most of them acquire resistances, for which the reasons are understood incompletely.
We found CDK6 as a modulator of IMiD sensitivity. Enhanced IMiD-induced IKZF1 and IKZF3 degradation as well as IMiD-sensitivity in multiple myeloma cells were observed upon pharmacological inhibition or proteolysis targeting chimeras (PROTAC)-induced degradation of CDK6. Phospho-proteomics revealed one CDK6-dependent phosphorylation of IKZF1 at T140. This site is located in the linker 1 of zinc finger 1 and 2, which are part of the DNA as well as IMiD-CRBN binding region. Site-directed mutagenesis of T140 revealed that the phospho-ablative mutation Alanine (A) in IKZF1 leads to higher degradation efficacy upon IMiD treatment in a concentration dependent manner in comparison to the phospho-mimetic mutation Aspartic acid (D). This data implicate, that phosphorylation of IKZF alters its binding to the IMiD-CRBN E3 ligase complex, what can be overcome by CDK6 inhibition.
In conclusion, we show that post-translational modification of a substrate protein alters the activity of targeted protein degraders (TPD). These findings may lead to new effective treatment combinations with TPDs in patients.

Abstract 57

Biophysical investigation of structural changes as mode of action of drugs targeting nucleic acids and proteins

Irene Ponzo[1], *Wouter Engelen*[1], *Mareike De Pascali*[1], *Pablo Porragas Paseiro*[1], *Guido Uhlenbrock*[1,*], *Vivien Hafner*[1], *Ralf Strasser*[1], and *Ulrich Rant*[1,2]

[1]Bruker Biosensors
[2]Kurt-Schwabe-Institute for Bioanalytical Systems, Germany
*Presenting author

Structural changes are often essential for the therapeutic effect of small molecules. This was demonstrated by successful developments in structure-based drug discovery. One example is the antibiotic small molecule ribocil, which binds to a bacterial riboswitch causing a change in RNA structure. Another example is the antineoplastic drug rebastinib, which inhibits the conformational switch of a mutant kinase from an inactive to an active state. We investigated these diverse structural effects of small molecules using the biophysical method switchSENSE, a chip-based biosensor technology, employing a versatile array of DNA-based nanolevers. In the first case study, we utilized DNA origami nanolevers to detect small molecule-induced conformational changes in proteins. In a second case study, we investigated nucleic acids as drug targets and elucidated the structural rearrangements within nucleic acids caused by binding of a small molecule. And thirdly, we introduce Y-shaped DNA nanostructures, which can be used to examine induced proximity binding like ternary complex formation by molecular glues and PROTACs. The presented application examples show how biophysical measurements can be used to comprehensively characterize binding-induced structural dynamics in different molecule types.

Abstract 58

Expanding the Horizons of Artificial Siderophores as 68Ga-Complexed PET Tracers for Detection of Bacterial Infections

Pablo Redero[1,*], *Carsten Peukert*[1], *Silav Al-Bazaz*[2], *L. N. B. Langer*[2], *Anna Tutov*[1], *J. P. Bankstahl*[2], *F. M. Bengel*[2], *Tobias L. Ross*[2], and *Mark Brönstrup*[1]

[1]Helmholtz Centre for Infection Research, Braunschweig, Germany
[2]Medical School Hannover, Germany
*Presenting author

Pathogenic bacterial infections are a major cause of severe illness and mortality, posing a serious threat to human health. This challenge is further amplified by the global rise of antimicrobial resistance, which is rendering conventional treatments increasingly ineffective. As resistance continues to spread, this problem is expected to worsen in the coming decades, highlighting the urgent need for novel resistance-breaking antibiotics.
The diagnosis of bacterial infections in deep tissues can be enhanced through noninvasive imaging using positron emission tomography (PET) tracers. In this study, we developed artificial siderophores targeting the bacterial iron transport system for specific labeling. A series of cyclen-based compounds with diverse Fe-chelating motifs was synthesized. These probes incorporate distinct binding sites for both iron and the PET nuclide ^{68}Ga. Probes exhibiting high affinity to iron, radiochemical yield, purity, and stability in vitro and in vivo displayed significant uptake in *Escherichia coli*-infected mice and effectively differentiated infection from lipopolysaccharide-induced sterile inflammation. Their strong iron-chelating properties and ability to complex ^{68}Ga emphasize the potential of these compounds as PET tracers in a Trojan horse strategy for bacterial infection imaging. This, combined with their straightforward and scalable synthesis, establishes cyclen-based artificial siderophores as readily accessible scaffolds for in vivo bacterial imaging.

Abstract 59

Targeted Protein Degradation to Modulate Notch Signaling in Pancreatic Progenitors

Katharina Richter[1,*], *Anne Grapin-Botton*[1], and *André Nadler*[1]

[1]MPI-CBG, Dresden, Germany
*Presenting author

The Notch signaling pathway plays a crucial role in pancreas development, particularly in regulating the fate of pancreatic progenitors. Its inhibition during differentiation promotes the formation of endocrine cells, including insulin-producing β-cells. Additionally, Notch signaling can act as an oncogene when overexpressed in certain cancers. Therefore, tools to precisely modulate this pathway are essential, not only for developmental studies but also for potential therapeutic applications.

While conventional small-molecule inhibitors have been widely used to target Notch signaling, they come with limitations such as incomplete pathway suppression due to the occupancy effect and potential off-target interactions. To overcome these challenges, we employ proteolysis-targeting chimeras (PROTACs), a novel class of molecules that enable spatially and temporally controlled, catalytic degradation of specific target proteins. By harnessing the cell's ubiquitin-proteasome system, PROTACs offer a powerful alternative to traditional inhibition strategies.

In this study, I synthesized a library of PROTAC molecules designed to degrade key components of the Notch pathway and evaluated their efficacy in a high-throughput screening format. The most effective candidates were further optimized in a second-generation library. These molecules were first characterized in 2D cell culture to assess their degradation efficiency, selectivity, and functional impact. Ultimately, they will be applied in spheroid models of pancreatic progenitors to better understand the role of Notch signaling in pancreatic differentiation.

We hypothesize that this PROTAC-based approach will provide deeper insight into the role of specific proteins within the Notch pathway, shedding light on their temporal dynamics during pancreatic progenitor differentiation. This work may offer new strategies for both developmental biology research and targeted therapeutic interventions.

Abstract 60

Do We Need Deep Learning for High-Throughput Virtual Screening in Protein-Ligand Docking?

Ahmet Sarigun[1,*], and *Altuna Akalin*[1]

[1]Max Delbruck Center, Berlin, Germany
*Presenting author

In drug discovery, analyzing protein–ligand interactions is a critical step, making molecular docking essential. Although deep learning–based methods like DiffDock have been developed for blind docking, their application in high-throughput virtual screening—especially for cross-docking on GPUs—often results in prohibitive runtimes and high VRAM usage, along with inaccuracies in conformation sampling and regression. Moreover, deep learning models tend to be less interpretable, limiting our understanding of the underlying docking processes.

To address these issues, we revisited conventional approaches and introduce PocketVina-GPU, a molecular docking tool that not only outperforms deep learning methods in efficiency and accuracy but also provides greater interpretability. PocketVina-GPU is tailored for high-throughput virtual screening and operates as follows:

1. Pocket Detection: Protein pocket centers are identified using p2rank.
2. Region Definition: A cubic region (20 Å along x, y, and z) is defined around each detected pocket.
3. Ligand Preparation: Molecules are converted from SMILES strings into 3D structures.
4. Docking Execution: Docking is carried out on GPUs using QuickVina2-GPU-2-1.

Benchmark comparisons indicate that while DiffDock requires approximately 38 seconds and around 15 GB of VRAM per docking, PocketVina-GPU completes docking in as little as 0.4 to 3 seconds using only about 6 GB of VRAM—making it 10 to 100 times faster and considerably more memory efficient. Furthermore, on PubChem targets, DiffDock struggles to reliably distinguish active from inactive compounds, whereas PocketVina-GPU demonstrates robust discrimination.

Given these significant advantages, PocketVina-GPU offers a powerful and interpretable approach for the early stages of drug discovery. The source code is publicly available at https://github.com/BIMSBbioinfo/PocketVina-GPU.

Abstract 61

New Paths in Peptide Drug Design: Computational Approaches to Overcome Key Challenges

Lara Scharbert[1,*], and *Birgit Strodel*[1]

[1]Forschungszentrum Jülich, Germany
*Presenting author

Although therapeutic peptides currently account for only 5% of the pharmaceutical market, this sector is projected to grow by approximately 10% annually, driven by the increasing prevalence of chronic diseases such as diabetes, obesity, and autoimmune disorders that require biological therapies. Despite rapid advancements in computational techniques, including artificial intelligence models like AlphaFold, the development of novel therapeutic peptides remains a challenge.

Unlike traditional small-molecule drug design, where compounds are screened for their ability to bind well-defined pockets, peptide-protein interactions often involve highly flexible peptides and large, flat binding sites, typical for some viral proteases like SARS-CoV-2 main protease and HIV protease. This structural flexibility is a challenge for standard computational approaches, especially if they are solely based on static methods, like molecular docking. Another limiting factor can be the presence of special elements, such as metal ions in metalloproteins or radiopharmaceuticals, as these require specialized parameters that are often unavailable in standard modeling tools.

Our studies on inhibitors targeting the SARS-CoV-2 main protease and papain-like protease, as well as radiopharmaceuticals binding to PSMA, reveal that molecular docking and AlphaFold-based predictions alone are often insufficient or misleading. To overcome these limitations, we propose a stepwise computational strategy that addresses the challenges of interactions between proteins and their flexible binders. This includes a peptide saturation mutagenesis program that takes into account the dynamic nature of peptide-protein complexes and provides design recommendations, which are subsequently tested in the wet lab. In addition, we developed tools for the parameterization and force-field implementation of metalloproteins and metal ion-containing compounds, which is needed for our work on peptide-containing radiopharmaceutical design.

Abstract 62

Comparison of different crosslinkers in the formulation of chitosan nanoparticles

Evelyn Schnapka[1,*], *Dr. Bernhard Bobusch*[2], *Dr. Alexandra Gruber*[2], *Prof. Dr. Karsten Mäder*[3], *Fitore Mejzini*[3], *Katja Richter*[4], *Dr. Christian Willems*[4], and *Annika Brehmer*[1]

[1]Fraunhofer Institute for Productions systems and Design Technology, Germany
[2]FDX Fluid Dynamix GmbH, Germany
[3]Institute of Pharmacy, Martin-Luther University Halle-Wittenberg, Germany
[4]Heppe Medical Chitosan GmbH, Germany
*Presenting author

Introduction:
Chitosan has emerged as a promising alternative material to lipid nanoparticles for drug delivery. Depending on the cargo, a crosslinker is often required for the encapsulation into chitosan nanoparticles (CNP). The aim of the present study was to compare different crosslinkers (TPP, hyaluronic acid, $NaSO_4$, $MgSO_4$, BSA and mRNA) in the CNP formulation of chitosan 85/20 in terms of particle size and polydispersity index (PDI) to find out the most promising crosslinker for CNP formulation.
Methods:
CNP were freshly formulated using the microfluidic device FDmix with different concentrations of each crosslinker and analyzed by dynamic light scattering (DLS) immediately, 24h and ≥ 4 days after encapsulation.
Results:
While BSA, $MgSO_4$ and $NaSO_4$ were not very fruitful crosslinkers at all concentrations tested, 0.09mg/ml TPP and mRNA (878bp: 0.08mg/ml; 4000bp: 0.06mg/ml) gave promising results regarding particle size and PDI. Whereas mRNA-crosslinked CNP remained stable, TPP-crosslinked particles grew from 62nm to 82nm overnight and reached a size of 89nm after seven days, suggesting the need for post-treatment steps to prevent particle agglomeration. This effect can be explained by differences in molecule size and charge, as TPP is a small molecule with five negative charges and therefore able to fit into small gaps, linking up to five chitosan molecules. In contrast, the mRNAs have more negative charges and require lower concentrations with increasing length. The larger, linear mRNA structure allows more than five chitosan molecules to be crosslinked simultaneously, but provides less flexibility by reaching difficult to access free deacetylated groups of the chitosan due to steric hindrance. Formulation with hyaluronic acid (0.05mg/ml) as crosslinker resulted in CNP with particle size of 141nm and acceptable PDI, but particle growth up to 211nm was observed during the next days, so hyaluronic acid could be a good alternative if CNP ≥ 200nm are also usable.

Abstract 63

High-throughput screens identify novel transcriptional inhibitors of Metastasis inducing genes MACC1 and S100A4

Paul Curtis Schöpe[1,*], *Shixian Yan*[1], *Nina Heisterkamp*[1], *Devin Schütz*[1], *Joe Lewis*[2], *Edgar Specker*[3], *Jens Peter von Kries*[3], *Mathias Dahlmann*[1,4], *Guido Mastrobuoni*[5], *Hector E Sanchez-Ibarra*[1], *Anke Unger*[6], *Mia-Lisa Zischinsky*[6], *Bert Klebl*[6], *Wolfgang Walther*[1,4], *Stefan Kempa*[5], *Marc Nazaré*[3], *Dennis Kobelt*[1,4], and *Ulrike Stein*[1,4]

[1]Experimental and Clinical Research Center (ECRC) of the Charité - Universitätsmedizin Berlin and Max-Delbrück Center, Germany
[2]The European Molecular Biology Laboratory (EMBL), Heidelberg, Germany
[3]Leibniz-Foschungsinstitut für Molekulare Pharmakologie (FMP), Berlin, Germany
[4]German Cancer Consortium (DKTK Partnersite Berlin), Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, Germany
[5]Proteomic and Metabolomics Platform, Berlin Institute for Medical Systems Biology (BIMSB), Max-Delbrück Center (MDC), Berlin, Germany
[6]Lead Discovery Center (LDC), Dortmund, Germany
*Presenting author

In the past decades substantial progress in the overall survival of stage I-III cancer patients has been made. However, little change was achieved for stage IV patients which are faced with distant metastasis. New therapeutic approaches are needed that target causal biomarkers of metastasis. Two such biomarkers are Metastasis-associated in Colon Cancer 1 (MACC1) and S100A4. A high expression of each marker predicts poor metastasis-free survival in CRC patients alone and even stronger in combination. Further, it was shown that MACC1 can induce the expression of S100A4, giving rise to the opportunity of developing therapies which may display beneficial synergy. Recently, two high-throughput screens have been conducted using the compound library of the EMBL in Heidelberg. For each marker a construct consisting of the respective promoter coupled to a luciferase gene was used to identify novel small molecules which can effectively inhibit the respective gene. A lead hit was found for each gene which was then validated on mRNA, protein and phenotypic level in vitro and for their metastasis inhibiting capacity in vivo. Compound 22 and analogues can effectively inhibit the gene expression of MACC1 and reduce functions such as migration in vitro. Further, in CDX metastasis mouse studies Compound 22 and analogues reduced the primary tumor burden and even more importantly inhibited the metastasis formation in the liver. Moreover, these compounds displayed favorable ADMET characteristics and have shown to target the NFκB pathway. E12 was identified in the second HTS as a potent inhibitor of S100A4 gene expression and functions. Furthermore, in a first CDX metastasis mouse model the metastasis formation in the liver and the S100A4 expression was reduced. Taken together, we have identified potent small molecules to restrict the gene expression of the metastasis inducing genes MACC1 and S100A4 which represent promising candidates for anti-metastatic therapy.

Abstract 64

Myxoglucamide: Total Synthesis and Activity-Based Protein Profiling Identifies Aldo-Keto Reductase as Target Protein

Thomas Siemon[1,*], *Vivek K. Mishra*[1], and *Mark Brönstrup*[1]

[1]Helmholtz-Zentrum für Infektionsforschung, Braunschweig, Germany
*Presenting author

Myxoglucamides are a novel class of glycolipopeptides derived from the myxobacterium *Cystobacterineae* sp. MCy9003.[1] Their unique structure features an unprecedented γ-amino acid containing α-ketoamide and vinylic residues, linked to 13-β-D-glucopyranosyl-14-methyl-pentadecanoic acid. We synthesized myxoglucamide A using a convergent strategy that includes enantioselective Brown allylation, Schmidt trichloroacetimidate glycosylation, and direct formation of the α-ketoamide through formal oxidative coupling of an aldehyde with an isocyanide.
Activity-based protein profiling (ABPP) in human lung epithelial cells (A549) with a myxoglucamide-biotin conjugate identified aldo-keto-reductase (AKR) as a target protein family. A comprehensive structure-activity relationship (SAR) study provided insights into the structural basis of protein (AKR1C3) inhibition and improved the IC_{50} value from the low micromolar to the nanomolar range. This study indicated that the glucose and vinylic moieties are not essential for target binding, while the carboxylic acid, ketoamide, and an elongated alkyl chain are crucial for activity. Biophysical characterization and crystal structure analysis will further elucidate the binding interactions.

[1] T. Wang, A. Popoff, M. Hunter, R. Garcia, A. Sikandar, R. Müller, C. Fu, *Manuscript submitted*

Abstract 65

Exploring novel GSK-3β inhibitors for neurodegeneration: structural biology meets quantum mechanics

Emilia Slugocka[1,*], *Filipe Menezes*[2], and *Anna Wieckowska*[1]

[1]Jagiellonian University Medical College, Faculty of Pharmacy, Krakow, Poland
[2]Institute of Structural Biology, Krakow, Poland
*Presenting author

Glycogen synthase kinase-3β (GSK-3β) is a serine/threonine kinase that is overexpressed in the brain of Alzheimer's disease (AD) patients and contributes to the disease progression by promoting amyloid β and tau protein aggregation and neuroinflammation. This renders GSK-3β a promising molecular target for designing inhibitors with implications in treating neurodegenerative diseases. In our study, we have designed, synthesized, and evaluated a new series of GSK-3β inhibitors. The abundant structure-activity relationship (SAR) data has been analysed. Our research uncovered a noteworthy compound **36**, with an IC_{50} of 70 nM against GSK-3β. The crystal structure of compound **36** complexed with GSK-3β was solved by X-ray crystallography. We also provide a thermodynamic mechanism behind compound **36**'s notable activity: the introduction of an oxadiazole ring as an amide bioisoster that is advantageous in terms of protein-ligand shape complementarity, allowing two favourable protein-ligand interaction modes based on the flipping of the oxadiazole group. To rationalize the experimental SAR data and understand which binding elements are key to designing high-affinity ligands, we utilized a series of quantum mechanical calculations and our Energy Decomposition and Deconvolution Analysis (EDDA), an energy partition scheme. Compound 36, the most potent inhibitor in the series, can interfere with processes directly implicated in the onset and progression of AD. Based on pharmacological activities and favourable ADME-tox properties, compound **36** is a promising candidate for in vivo research and a reliable and valuable starting point for further studies. The work has been published in *ACS Chemical Neuroscience* (DOI:10.1021/acschemneuro.4c00365).

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Abstract 66

Structural insight into the binding mode of novel HDAC6 inhibitors

Ingrid Span[1,*], and *Mara Hebeis*[1]

[1]FAU Erlangen-Nürnberg, Germany
*Presenting author

Post-translational modifications are key mechanisms to increase proteomic diversity. One of the post-translational modifications of histones is the reversible acetylation of lysines performed by histone acetylases (HATs) and histone deacetylases (HDACs). The enzyme HDAC6 can shuttle between the nucleus and the cytoplasm, giving it the ability to interact with histones but also with non-histone proteins. It is involved in cellular processes like cell signaling, inflammation, protein degradation, cell motility and cell survival. Overexpression of HDAC6 leads to imbalances in various cellular functions and is therefore associated with neurodegenerative diseases, cancer, and viral infections. To counteract this overexpression, inhibitors have been developed, which currently lack efficiency and specificity. Using X-ray crystallography, we were able to solve high-resolution structures of HDAC6 in complex with two promising inhibitors. The structures allow us to gain insight into the binding mode of these highly active inhibitors to the enzyme and will facilitate the rational design of novel HDAC6-specific inhibitors in the future.

Abstract 67

MyxoTech: offering a hyper-organized library of microbial dark matter chemistry to the pharmaceutical industry

Peter Sullivan[1,*], *Thomas Hesterkamp*[2,3], *Ronald Garcia*[1], *Jennifer Herrmann*[1,3], *Olga Kalinina*[1], and *Rolf Müller*[1,3]

[1]Helmholtz Institute for Pharmaceutical Research Saarland, Germany
[2]Helmholtz Centre for Infection Research, Braunschweig, Germany
[3]German Centre for Infection Research
*Presenting author

Nature is an important source for the pharmaceutical industry. A quarter of all drugs approved over the last four decades are natural products or derivatives of natural products.

Since the 1960s, researchers at the Helmholtz Center for Infection Research (HZI) and its affiliated Helmholtz Institute for Pharmaceutical Research Saarland (HIPS) have built an unprecedented library of myxobacteria (phylum Myxococcota). MyxoTech, a HIPS spin-off, has developed a commercial offshoot of the library available to the pharmaceutical industry. Given these organisms are challenging to culture, myxobacteria effectively exist on the edge of *microbial dark matter*. Greater than 50% of the species, genera, and families in the MyxoTech library do not exist in the public domain or only include strains thus far identified as ‘uncultured’.

While myxobacteria have been minimally prospected in drug discovery, the phylum has proven its pharmaceutical value. Myxo metabolite corallopyronin A is nearing phase 1 clinical trials and three derivatives of metabolites (bengamide B, tubulysin B, and epothilone B) have so far reached clinical trials. Of these, epothilone B semisynthetic derivative ixabepilone was approved by the FDA in 2007 to treat breast cancer.

MyxoTech’s unique selling proposition is novel chemical space with proven bioactivity. Thus, driven to maximize the diversity of this chemical space, MyxoTech is developing an ML-based platform that integrates DNA sequencing and metabolomics data to comprehensively map the distribution of metabolite scaffolds within the phylum. This achieves two objectives: 1) strategic expansion of the library’s unmatched chemical diversity by pre-selection of strains that produce novel scaffolds and 2) systematic tracking of each strain’s contribution to the library’s pool of chemistry.

Novel chemical space is essential for the next generation of therapeutics. With that, MyxoTech is seeking industry partners interested in probing a hyper-organized collection of unprospected natural products.

Abstract 68

Novel Reporter Systems for Ratiometric Measurement of Luminescence

Jörg Urban[1,*], *Jacqueline Franke*[1], and *Klaus Palme*[2]

[1]Hochschule für Technik und Wirtschaft Berlin, Germany
[2]Albert Ludwigs Universität Freiburg, Germany
*Presenting author

Use of absolute levels of luminescence for the quantification of biological processes is hindered by a varying light output and requires measurement of a reference such as cell numbers for comparison between samples. These challenges can be addressed by measuring luminescence ratiometrically, i.e. determining the ratio of light emission in two spectral ranges.

A commonly used ratiometric technique is the detection of protein-protein interactions using bioluminescence resonance energy transfer (BRET). A more broadly applicable approach would be to measure light emission from two co-expressed bioluminescent proteins, which produce spectrally distinct light using the same substrate and and emit light at a relatively constant ratio over time, wherein the first bioluminescent protein provides information about a biological process of interest and the second an internal reference.

We have developed novel reporter systems for ratiometric measurement of luminescence:

• A BRET system with interacting components that comprises an Rluc version and a YFP variant with affinity for Rluc, which yields very high BRET ratios compared to conventional BRET systems when both components are brought into close proximity.

• A dual-color luminescence (DCL) system comprising an Rluc version with blue-shifted emission (Cluc) and a fusion protein containing an Rluc version with red-shifted emission and YFP variant with affinity for Rluc (Yluc), whose components produce light with outstanding spectral separation at a relatively constant ratio.

Validation and application experiments demonstrate the usefulness and applicability of these systems for a wide range of quantification tasks, including recording of time courses.

Abstract 69

Unraveling Neuronal Proteome Dynamics: A SILAC-Based Approach for High-Throughput Drug Screening

Alan An Jung Wei[1,*], and *Matthias Selbach*[1]

[1]Max Delbrück Center for Molecular Medicine, Berlin, Germany
*Presenting author

Induced neurons (iNs) derived from human induced pluripotent stem cells (iPSCs) offer a scalable, reproducible, and physiologically relevant model for drug discovery. To investigate the impact of FDA-approved, blood-brain barrier (BBB)-penetrating drugs on the neuronal proteome, we employ mass spectrometry-based proteomics to capture drug-induced changes. While previous studies have primarily provided a snapshot of steady-state protein abundance, they often fail to distinguish between protein degradation and *de novo* synthesis. To address this limitation, we integrate stable isotope labeling of amino acids in cell culture (SILAC), enabling precise quantification of proteome dynamics. This approach allows us to elucidate drug mechanisms of action, differentiate between protein degradation and synthesis, and identify novel protein targets with potential therapeutic relevance for neurological disorders.

Abstract 70

Nanoparticle-mediated RNA interference to regulate alpha-synuclein expression in an in vitro Parkinson´s disease model

Sandra Weiß[1,*], *Malte Feja*[1], *Isabell Drath*[1], *Alexander Ewe*[2], *Achim Aigner*[2], and *Franziska Richter Assencio*[1]

[1]University of Veterinary Medicine Hannover, Germany
[2]University of Leipzig Faculty of Medicine, Germany
*Presenting author

The development of novel therapeutic strategies against Parkinson's disease focuses on disease-associated proteins such as alpha-synuclein. Small RNAs are a promising approach for suppressing alpha-synuclein expression. However, these have to overcome major hurdles such as the blood-brain barrier and are not sufficiently stable to effectively reach their target site and intracellular compartment. For this purpose, a nanoparticle-based approach for intranasal delivery of small RNAs was developed. It was important to analyse in vitro whether the nanoparticles are taken up by the target cells and if the small RNAs are transported to their intracellular site of action, leading to effective knockdown of the alpha-synuclein mRNA. In this work, the uptake and efficacy of nanoparticles based on polyethyleneimine and polypropyleneimine complexed with small interfering RNAs against alpha-synuclein were investigated. For this purpose, human-derived SH-SY5Y cells were differentiated and transfected with nanoparticles containing fluorescently-labelled siRNA. In addition, doxycyclin inducible, alpha-synuclein overexpressing SH-SY5Y cells were transfected with nanoparticles complexed with functional siRNA. Uptake and knockdown analyses were performed by immunocytochemistry and quantitative RT-PCR, and cytotoxicity was determined by lactate-dehydrogenase release assay. All tested nanoparticles were efficiently taken up by differentiated SH-SY5Y cells and could be detected inside the cells. At the mRNA level, an alpha-synuclein knockdown of 80 % was determined. Increased cytotoxicity as indicated by increased lactate-dehydrogenase release after transfection of the complexes could not be detected. In conclusion, we could prove cellular uptake of complexed siRNA and show efficient downregulation of alpha-synuclein expression at mRNA level by nanoparticles in alpha-synuclein overexpressing SH-SY5Y cells, which substantiates the potential of nanoparticle-mediated RNA-interference as promising therapeutic approach for Parkinson´s disease

Abstract 71

Large scale high content imaging for drug discovery across multiple labs

Christopher Wolff[1], *Martin Neuenschwander*[1], *Maria Ramos*[2], *Alzbeta Srovnalova*[3], *María Varela*[4], *Inmaculada Iáñez*[2], *Divya Sitani*[5], *Pavel Polishchuk*[3], *Katholiki Skopelitou*[6], *Bahne Stechmann*[6], *José Brea*[4], *Petr Dzubak*[3], *Rosario Fernández-Godino*[2], *Martin Lehmann*[1], *Jens-Peter von Kries*[7], *Han Sun*[1], *Philip Gribbon*[8], and *Christopher Schmied*[1,*]

[1]FMP-Berlin, Germany
[2]Fundación MEDINA
[3]IMTM
[4]USC
[5]DZNE
[6]EU-OPENSCREEN
[7]Leibniz-Forschungsinstitut für Molekulare Pharmakologie (FMP), Berlin, Germany
[8]Fraunhofer ITMP
*Presenting author

Morphological profiling with the Cell Painting assay has emerged as a promising method in drug discovery research. The assay captures morphological changes across various cellular compartments enabling the rapid prediction of compound bioactivity. We present a comprehensive morphological profiling resource generated based on more than 100.000 compounds of the EU-OPENSCREEN compound collection. The data is generated across four imaging sites across Europe with high-throughput confocal microscopes using the Hep G2 as well as the U2 OS cell line. We employed an extensive assay optimization process to achieve high data quality across the different sites. An analysis of the extracted profiles validates the robustness of the generated data. We used this resource to compare the morphological features of the different cell lines. By correlating the profiles with overall activity, cellular toxicity, several specific mechanisms of action (MOAs), and protein targets, we demonstrate the dataset's potential for facilitating more extensive exploration of mechanisms of action.

Abstract 72

Targeted Protein Degradation of Aryl Hydrocarbon Receptor (AHR) through Autophagy Pathway

Clara Shania Wong[1,*], *Jacinth Wing-Sum Cheu*[1], *Carmen Chak-Lui Wong*[1,2], and *Clive Yik-Sham Chung*[1,2]

[1]The University of Hong Kong
[2]Centre for Oncology and Immunology
*Presenting author

Aryl hydrocarbon receptor (AHR), a ligand-activated transcription factor, has emerged as a key player in cancer progression, including liver cancer. Its overexpression and heightened activity facilitate tumour growth, immune evasion, and therapy resistance. Hence, targeting AHR should be a promising approach for cancer treatment by inhibiting cancer growth and restoring immune system activity.

Significant effort has been made in the field of targeted protein degradation as a therapeutic approach to silence protein functions through specific eradication of disease-associated proteins. During autophagy, protein cargo is sequestered into the autophagosome for subsequent fusion with lysosomes, leading to its degradation. This pathway can be hijacked therapeutically to selectively degrade proteins of interest for inhibition of oncogenic proteins' activity.

In this study, we developed a heterobifunctional molecule to degrade AHR (CSW20) leveraging the natural degradation machinery, autophagy, aimed to inhibit cancer cells growth while concurrently restoring immune defence. The ability of CSW20 to degrade AHR has been examined in several HCC cell lines, such as HepG2, PLC/PRF/5, and MHCC97-L, and macrophage-like, PMA-stimulated THP-1 cells. Additionally, the anti-cancer effect of CSW20 on HCC cells has been investigated through cell viability assay. On the immune side, treatment with the AHR degrader could promote the repolarization of anti-inflammatory M2 macrophages to pro-inflammatory M1 macrophages. Our findings highlight the potential of CSW20 as a cancer therapy approach by killing cancer cells, while also enhancing the immune responses.

Abstract 73

Mechanistic characterization of PROTACs against Dengue-Virus

Chen-Yu Yang[1,*], *Thomas Siemon*[1], *Srinivasa Allu*[1], *Manon Laporte*[2], *Pieter Leyssen*[2], *Suzanne Kaptein*[2], *Johan Neyts*[2], *Mark Brönstrup*[1,3], and *Katharina Rox*[1,3]

[1]Helmholtz Centre for Infection Research (HZI), Braunschweig, Germany
[2]KU Leuven, Belgium
[3]German Center for Infection Research (DZIF)
*Presenting author

Dengue virus (DENV) is the most prevalent arbovirus globally, with an estimated 390 million infections annually. Despite the availability of two vaccines, the demand for effective antiviral therapeutics remains high due to their limited efficacy. Currently, antiviral drug development for DENV primarily targets NS5-NS3 and NS4B proteins, but no antiviral treatment has been approved yet. Traditional small-molecule inhibitors often act by directly suppressing target protein activity, which can lead to the emergence of resistance mutations, potentially rendering treatment options non-effective again.

In this study, we employ proteolysis-targeting chimeras (PROTACs) as a novel therapeutic strategy. PROTACs function by binding to the protein of interest (POI) with low affinity while recruiting an E3 ligase to facilitate ubiquitination and subsequent degradation via the host's proteasomal machinery. Here, we target a host factor which had been previously proven to be a validated target against flaviviruses.

Initially, we screened PROTACs for target protein inhibition at three different concentrations. Based on these results, we determined the IC_{50} values of selected compounds, which exhibited activity in the upper nanomolar range. In a cell-based assay, we confirmed activity against the target. Further evidence was provided in antiviral efficacy seen against DENV. Furthermore, a first MS/MS-based degradation assay showed significant degradation of the flaviviral target, supporting the hypothesized mechanism of action. Western blot analysis further confirmed that PROTACs facilitated the degradation of the flaviviral target rather than merely inhibiting its function.

In summary, these initial findings validate the innovative approach of employing a host target for PROTACs to combat flaviviruses. Ongoing studies will focus on further mechanistic characterization of the PROTAC and its host target to pave the way toward using PROTACs as antivirals.

Abstract 74

Novel Covalent Ligand Modulates Proteasome Activity and Assembly in Colorectal Cancer

Hillary Yip[1,*], *Tin-Yan Koo*[1], and *Clive Yik-Sham Chung*[1,2]

[1]The University Hong Kong
[2]Centre for Oncology and Immunology
*Presenting author

The global incidence of colorectal cancer (CRC) is increasing, and with the growing resistance to current treatments, there is an urgent need to develop novel anticancer compounds. The ubiquitin-proteasome system (UPS) plays a crucial role in regulating proteins involved in carcinogenesis, primarily through the degradation of unwanted proteins by the 26S proteasome. Since cancer cells typically show higher sensitivity to proteasomal stress compared to normal cells, this makes proteasome inhibition an effective treatment strategy. Here, we have identified the covalent lead compound, CL76, with the ability to modulate the proteasome activity and mediate promising anticancer activities in CRC. Through chemoproteomics experiments and covalent docking analyses, it was determined that a 19S regulatory particle of the proteasome is the protein target of CL76. Following treatment with CL76, a significant inhibition of proteasome activity was confirmed by the Proteasome-Glo™ assay. As characterised from native gel electrophoresis, the binding between our compound and the target site effectively modulates proteasome assembly, which leads to an inhibition in the late stages of autophagy, and eventually cancer cell death. Moreover, CL76 exhibits potent antitumor activity in *in vivo* CRC xenograft model with no observable toxicity. Our study introduces a novel class of proteasome inhibitors with a distinct mechanism of action targeting the 19S regulatory particle, offering a new approach compared to reported proteasome inhibitors that target the catalytic core of the 26S proteasome.

Abstract 75

Optimizing FAP-targeted Radiopharmaceuticals: Novel Ligands and Their Predictive Modeling

Chao Zhang[1,2,*], *Jona Gerhards*[3], *Jens Cardinale*[3], *Frederik L. Giesel*[3], and *Birgit Strodel*[1,2]

[1]Heinrich Heine University Düsseldorf, Germany
[2]Forschungszentrum Jülich, Germany
[3]University Hospital Düsseldorf, Heinrich Heine University Düsseldorf, Germany
*Presenting author

The fibroblast activation protein alpha (FAPα or FAP) is overexpressed on the surface of cancer associated fibroblasts in the tumor microenvironment of many malignancies. Due to its low expression in normal, healthy adult tissues, it offers an attractive target for novel drugs. Radiopharmaceuticals targeting FAP have become a promising novel tool for diagnosis and therapy of many cancer entities.
Our research aims to enhance the selectivity of current FAPIs by exploring novel ligands through computer-assisted radiopharmaceutical design (CARD), subsequent synthesis and testing of the most promising candidates in the wet lab. We designed multiple new ligands informed by existing top-performing FAPIs and conducted molecular docking, molecular dynamics (MD) simulations, and binding affinity calculations to assess their interactions with FAP. The MD simulations indicated that the radioligand vectors can stably bind to the receptor, while the chelators exhibit flexibility within the binding pocket. This new understanding guides our iterative design process, which includes several rounds of CARD, chemical synthesis, and in vitro testing. We will present the most recent results of this approach.

Abstract 76

AIRPred: A Deep Learning Model Predictor for Peptide Intensity Ratios in Cross-Linking Mass Spectrometry Improves Cross-Link Spectrum Matching

Zehong Zhang[1,3,], Mei Wu[1], Max Ruwolt[1], Ying Zhu[1], Pin-Lian Jiang[1], Diogo Borges Lima[1], Fan Liu[*,1,2]*

[1]Leibniz-Forschungsinstitut für Molekulare Pharmakologie (FMP), Berlin, Germany

[2]Charité Universitätsmedizin Berlin, Germany

[3]Freie Universität Berlin, Berlin, Germany

*Presenting author

Cross-Linking Mass Spectrometry (XL-MS) is a powerful tool in structural proteomics, offering insights into protein conformations, interactions and dynamics by linking spatially proximal residues. In drug discovery, XL-MS plays a critical role in identifying protein-protein interactions (PPIs) and mapping binding sites, which are essential for understanding disease mechanisms and designing targeted therapeutics. However, current Cross-Linked Spectrum Match (CSM) scoring methods rely heavily on mass-to-charge ratio (m/z) comparisons, often neglecting fragment ion intensity in-formation, which limits their ability to accurately distinguish true CSMs from false-positives. To overcome this limitation, we present AIRPred, a deep learning model that predicts intensity ratios between cross-linked peptide pairs to improve CSM identification. AIRPred employs Convolutional Neural Network (CNN) blocks to capture peptide fragmentation patterns and an attention layer to model peptide interactions. Our results show that intensity ratios remain consistent across experiments and can reliably differentiate true CSMs from random mismatches. In external validation, AIRPred outperformed traditional methods, demonstrating high accuracy in predicting intensity ratios. This model significantly enhances XL-MS analysis by leveraging intensity data for more accurate peptide identification

Abstract 77

Expanding PBPK modeling techniques towards digital patient-twins

Oliver Zimmer[1,*], and *Angela Relógio*[1]

[1]Institute for Systems Medicine and Faculty of Human Medicine, Hamburg, Germany
*Presenting author

Introduction
Physiology-based pharmacokinetic (PBPK) modeling is frequently relied on to bridge from limited compound data to in vivo behavior in early drug development[1]. However, known PBPK methods come with assumptions, limiting real-world transferability of simulation outcomes: (1) Time-independence of pharmacokinetic (PK) parameters and (2) ideal therapy adherence of patients, both hardly tenable based on published evidence[2,3]. Following our groups ongoing efforts to integrate circadian biology into PK models[4], we developed software-tools to extend the capabilities of PBPK simulations, enabling: (1) To account for circadian fluctuations in PK parameters and (2) to integrate non-ideal therapy adherence by combining discrete event simulation (DES) and ordinary differential equation (ODE) based techniques.

Methods
Based on a compound specific PBPK model[5], we simulated cyclosporin A therapies accounting for circadian fluctuations of CYP3A4 expression and varying degrees of non-adherence by implementing a discrete event-embedded ordinary differential equation simulation (DEe{ODE}S) technique.

Results
Implementing our DEe{ODE}S approach by generating dosage plans as DES schedules - thus, enabling implementation of error parameters - we derived insights on the robustness of cyclosporine A therapy against non-ideal therapy adherence. Running a series of simulations covering a wide space of error parameters, we deduced maximum tolerable non-adherence levels, exceeding which could expose patients to a serious risk of suffering therapy failure. We also investigated how CYP3A4-expression alignment of cyclosporine A therapy regimes affects total drug exposure and, thus, potentially therapy outcome.

Conclusion
The simulations outlined above, demonstrate how our software expands the information derivable from PBPK simulations and thus increase their transferability to real-world scenarios.

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Abstract 78

Design and optimization of a new chemical class of inhibitors of the bacterial beta-sliding clamp DnaN

Ayanda I. Zulu[1,*], *Carole Guimard*[1], *Godfrey Mayoka*[1], *Niklas Krappel*[1], *Sari Rasheed*[1], *Peer Lukat*[2], *Wulf Blankenfeldt*[2], *Jennifer Herrmann*[1], *Rolf Müller*[1], *Walid A. M. Elgaher*[1], and *Anna K. H. Hirsch*[1]

[1]Helmholtz Institute for Pharmaceutical Research Saarland (HIPS) – Helmholtz Centre for Infection Research (HZI), 66123 Saarbrücken, Germany
[2]Helmholtz Centre for Infection Research GmbH, 38124 Braunschweig, Germany
*Presenting author

Antimicrobial resistance poses a continuous serious global health threat and represents a huge burden for society. [1] Hence, there is a need to develop new antimicrobials with novel modes of action to tackle this threat. The β-sliding clamp (DnaN) is an emerging antibacterial target that plays a pivotal role in DNA replication and repair. Its conserved structure across bacterial species and its structural uniqueness from the human counterpart make it an attractive target for producing new antibiotics with novel modes of action. [2,3]

In this work, we report the design, optimization, and biological evaluation of a novel chemical class of small-molecule inhibitors targeting DnaN. Utilizing a structure-guided approach, analogues incorporating key pharmacophores for DnaN binding, were obtained. A detailed structure–activity relationship (SAR) study revealed substitutions in the molecule that are crucial for biological potency and physicochemical properties.

Thus far, several frontrunner compounds with MIC values ranging from 1–4 µg/mL against Staphylococcus aureus were identified. Moreover, the compounds exhibited no activity against eukaryotic cells (Candida albicans). The enzymatic data, STD NMR, and co-crystal structures confirm that the compounds are binding to the target and set the stage for a structure-guided optimization campaign.[4] Our findings establish a novel chemical class of DnaN inhibitors, paving the way for further development in targeted drug discovery.

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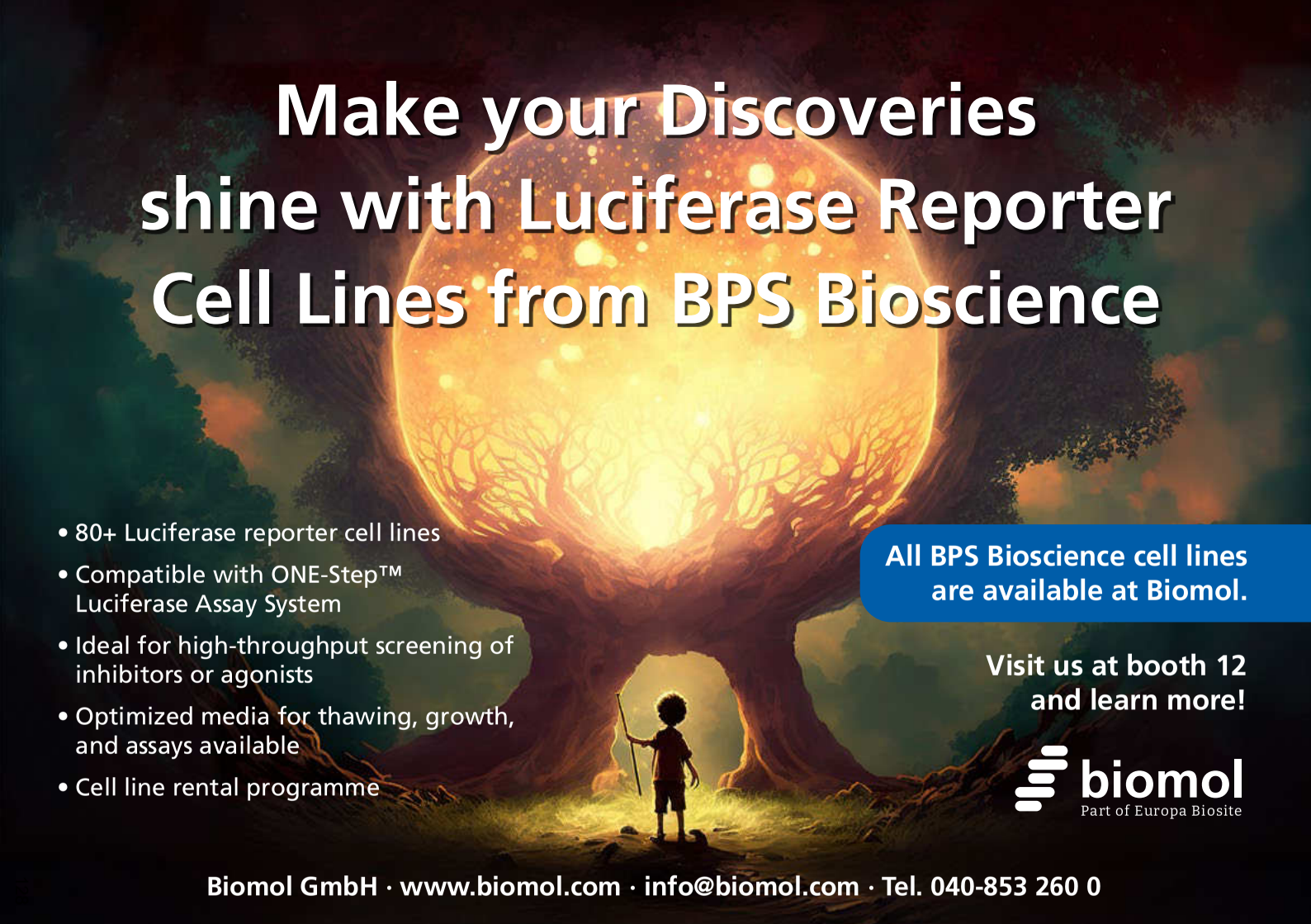
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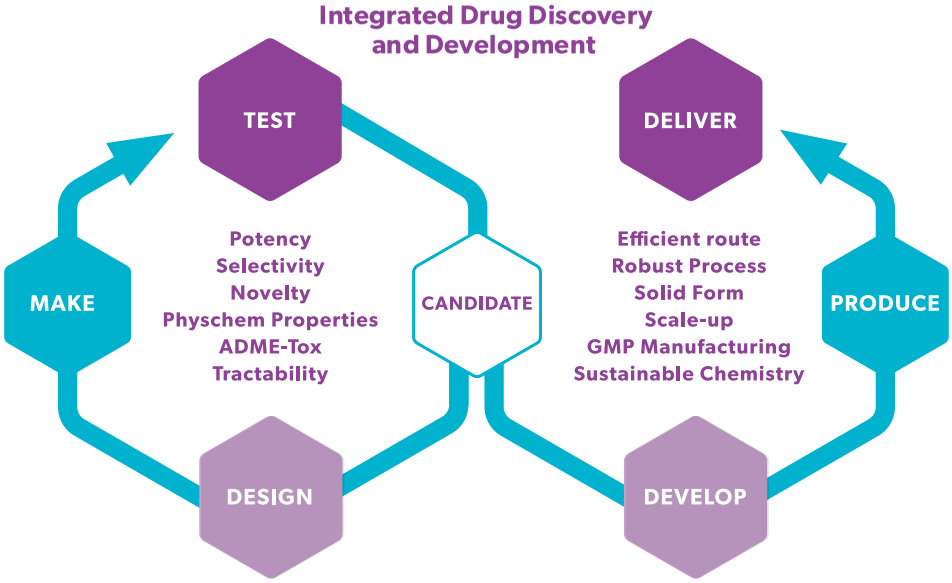

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