Hands on manipulation of molecules in a PDB structure using a novel PYMOL version

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Abstract: Structure-based drug design (SBDD) leverages 3D protein structures but often requires using multiple separate tools for essential tasks. To address this fragmentation, we present PyMOL Fitter, a plugin integrating key SBDD workflows directly within the widely used PyMOL visualization environment. PyMOL Fitter offers a user-friendly interface for an automated pipeline including protein and ligand preparation (from PDB/mmCIF and SMILES/SDF respectively), `smina`-based docking, OpenMM-driven post-docking energy minimization, and virtual screening capabilities.
The core workflow utilizes `smina` for docking, featuring automatic binding site detection guided by a reference ligand, alongside robust MD-quality energy minimization of complexes using OpenMM with Amber and OpenFF Sage force fields in implicit solvent. Virtual screening across multiple ligands is also supported. Importantly, all generated results, including docked poses and minimized structures, are loaded directly back into the PyMOL session. This seamless integration allows for immediate visualization and analysis within a familiar environment, offering a practical and efficient tool for researchers engaged in drug discovery to rapidly assess and optimize protein-ligand interactions.

Deciphering Immune and Metabolic Signatures in SCLC Patients: Linking Peripheral Blood Mononuclear Cells to Chemoimmunotherapy Response

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Small cell lung cancer (SCLC) is currently treated with a combination of chemotherapy and immunotherapy. However, not all patients benefit from this regimen, and alternative therapies are limited. A pressing need exists for predictive biomarkers to identify high-risk patients. Our group and others have demonstrated that activation of innate immune pathways in lung cancer, such as the canonical cGAS/STING signaling pathway, is a good predictor of antitumor immune response. Additionally, exceptionally long-term responders among SCLC patients harbor germline variants in DNA damage Repair (DDR) genes. We also demonstrated that activation of the cGAS-STING signaling pathway in peripheral blood mononuclear cells (PBMCs) from SCLC patients may serve as a novel potential predictive immunotherapy biomarker, with high levels being correlated with a better response to treatment.

We conducted RNA sequencing of PBMCs from best responders (BR) and non-responders (NR) SCLC patients and found significant changes in interferon and innate immune sensor activation in the BR cohort. Interestingly, DDR and innate immune sensor enrichment occurred alongside a significant downregulation of the transcription of genes which are related to L-arginine methylation and Choline metabolism, suggesting an interplay between DDR, immune response and metabolic pathways. Metabolomics profiling using prospectively collected PBMC samples before and after cisplatin treatment identified metabolites associated with chemoresponse in the choline pathway. These findings suggest a novel association between choline levels and treatment outcomes in SCLC patients receiving chemoimmunotherapy. Our results could facilitate the development of predictive biomarkers that enhance personalized treatment strategies in SCLC.

Overcoming cancer therapy resistance: the role of arginase inhibitors

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The overexpression of two isoforms of arginase (ARG), ARG1 and ARG2, contributes to the development of several diseases, including cancer. To clarify the specific roles of ARG1 and ARG2 without disrupting their physiological functions, it is essential to develop selective and effective ARG inhibitors with low toxicity and an appropriate pharmacokinetic profile. A promising medicinal chemistry strategy that could be useful in this context is molecular hybridization. This approach could exploit the distinct subcellular localization of the two isoforms to enhance specificity for ARG1 and ARG2, potentially leading to improved therapeutic outcomes, especially in cancers such as gastric cancer, where ARG's hyperactivity has not yet been fully elucidated.

Ugi reaction to generate stable polypeptoid particles from amino acid derivatives

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The Ugi multicomponent reaction (Ugi-4CR) is a powerful tool for the synthesis of functional polymers, allowing precise incorporation of diverse chemical functionalities. In this work, we exploit the Ugi reaction to generate stable polypeptoid particles using amino acid derivatives as key building blocks. The resulting polypeptoids exhibit tunable properties, making them attractive for applications in drug delivery, antimicrobial coatings, and biomaterials. By carefully selecting the starting materials, we can control the particle size and morphology leading to a versatile platform for material design. Our approach leverages the efficiency and modularity of the Ugi reaction to construct well-defined, bioinspired polymeric architectures in a one-pot process. This strategy offers an alternative to traditional polypeptide and peptoid synthesis, enabling rapid access to novel materials with tailored properties. Additionally, the formation of stable colloidal suspensions without the need for extensive post-synthetic modifications highlights the robustness of this method. The potential biomedical and environmental applications of these polypeptoid-based materials make them an exciting avenue for future research. This presentation will cover the synthetic methodology, characterization of the resulting materials.

New butyric acid-releasing glucosamine derivatives for the treatment of inflammatory-based diseases

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Butyric acid (BA), a short-chain fatty acid naturally found in common foods, has been shown to be a potent modulator of various intestinal and extra-intestinal functions, playing a crucial role in controlling inflammation and pain. However, dietary intake of BA is often insufficient to promote optimal intestinal health and fully harness its numerous physiological and pharmacological benefits. Despite its potential, the clinical application of BA is limited due to its unfavorable physicochemical properties and unpleasant organoleptic characteristics, such as taste and odor.
To meet the growing demand for BA derivatives, the prodrug approach, which involves chemically modifying a parent drug molecule to optimize its physicochemical and pharmacological properties, could represent an effective strategy in medicinal chemistry. The application of this strategy to synthesize new BA derivatives has led to improvements in pharmacokinetic properties, maintained a good atoxicity profile, and allowed further exploration of the role of these derivatives in pain treatment, particularly in nociception modulation.

Eco-Friendly Synthesis and Molecular Modelling of 2-Phenylimidazo[1,2-b]pyridazine Derivatives: *In Vitro* and *In Vivo* Studies for Lead Optimization

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7-methyl-2-phenylimidazo[1,2-b]pyridazin-3-carboxylic acid (DM1) and 6-methoxy-2-phenylimidazo[1,2-b]pyridazin-3-carboxylic acid (DM2) have emerged as promising human (h) $Cav_{3.1}$ voltage-gated calcium channel blockers with notable anti-absence seizure activity *in vivo*, positioning them as potential antiepileptic drugs. The main objective of this study was to develop cost-effective and environmentally friendly synthetic procedures for preparing 2-phenylimidazo[1,2-b]pyridazine derivatives. Optimized synthetic routes were achieved through green technologies, including microwave and ultrasound-assisted methods. The antiepileptic efficacy of DM1 and DM2 was then evaluated in two established animal models: CD-1 ICR mice after pentylenetetrazol administration and DBA/2 mice with seizures induced by audiogenic stimuli. Additionally, their neuroprotective potential against oxidative stress was assessed *in vitro* using C6 rat brain glioma cells. Both compounds exhibited potent anti-seizure effects in both animal models and demonstrated significant *in vitro* neuroprotective activity by reducing reactive oxygen species release. To support future structure-based drug design, molecular docking studies were conducted to explore the binding modes of DM1 and DM2 with $hCav_{3.1}$ channels. The predicted interactions showed partial overlap with the binding profile of Z944, a known selective $Cav_{3.1}$ blocker, providing valuable insights for lead optimization.

Beyond Venetoclax: Exploring BCL-2 Family Member Degraders for Neuroblastoma Therapy

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BCL-2 overexpression, which enables cancer cells to evade apoptosis, is common in neuroblastoma. However, tumor models often exhibit only partial sensitivity to the clinically approved BCL-2 inhibitor venetoclax, highlighting the challenge of therapy resistance. PROTACs offer a promising strategy by degrading oncogenic proteins and potentially overcoming resistance mechanisms associated with small-molecule inhibitors. In this study, we preclinically evaluate the efficacy of various experimental degraders targeting BCL-2 and related family members in neuroblastoma models. We compare their efficacy with both clinical and preclinical BH3-family inhibitors to assess their potential as therapeutic options for treatment-resistant neuroblastoma

Development of a Novel Abemaciclib-based PROTAC Degrader with Potent Anti-Proliferative Effect in Neuroblastoma

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Cyclin-dependent kinases (CDKs) are essential regulators of both the cell cycle and transcription, making them excellent targets to interfere with MYCN-driven oncogenic signalling and the deregulated cell cycle, specifically the G1/S-phase transition, in high-risk neuroblastoma (NB). Since many CDK inhibitors have not lived up to their promise, we hypothesize that protein degraders, like proteolysis targeting chimeras (PROTACs) can improve potency by disrupting kinase-dependent and -independent functions, overcome resistance mechanisms, and elicit tumor-selective effects. We have selected abemaciclib, the most efficacious CDK4/6 inhibitor with a broader inhibitory profile, to exacerbate its inhibitory effects in high-risk NB via cereblon (CRBN)-based protein degrader technology. Via viability screening of a library of novel abemaciclib-based PROTACs in a panel of NB models, QW719 was identified as the most potent, outperforming CDK4/6 inhibitors and commercially-available CDK4/6 PROTACs. Effective target degradation was dependent on the ubiquitin-proteasome system and ternary complex formation and occurred swiftly at low nanomolar concentrations. Using binding affinity analysis (KINOMEscan) and proteomics, we identified the directly degraded target proteins, besides CDK4/6, to be CDK9, GSK3α/β, AAK1, and TTK. Additionally, CRBN-based neosubstrates were mostly spared. On a transcript and protein level oncogenic signalling was greatly reduced via extensive downregulation of MYCN, and hampered cell cycle progression mediated by degradation of CDK9 and CDK4/6, respectively. The role of the other protein targets in the anti-proliferative effect is currently being characterized. Additionally, favourable *in vivo* pharmacokinetics was observed for QW719 after intraperitoneal administration in healthy BALB/c mice, but no oral bioavailability. In conclusion, QW719 is a highly potent CDK4/6/9 PROTAC degrader exerting a strong anti-proliferative effect in NB and shows the potential of targeting multiple kinases simultaneously. The acquired results warrant further *in vivo* efficacy and toxicological testing of QW719, and more in-depth characterization of its mechanism of action.

Engineering Bioluminescent Biosensors for Drug Discovery Targeting Protein–Protein Interfaces

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The inherent structural features of protein–protein interfaces (PPIs)—including their large, relatively flat, and dynamic surfaces—have long rendered them "undruggable" targets in pharmaceutical development. Addressing this challenge requires sensitive and scalable methods for the real-time detection of PPIs under physiologically relevant conditions.

Split-luciferase complementation assays provide a powerful solution by enabling the visualization and quantification of protein interactions through bioluminescence. In this approach, luciferase is divided into two inactive fragments, each fused to a protein of interest. Upon interaction, these fragments reconstitute enzymatic activity, producing a bioluminescent signal compatible with high-throughput screening.

The split-luciferase complementation strategy has been broadly applied across diverse biological systems and disease pathways, including apoptosis, inflammation, necroptosis, autophagy, and, more recently, oncogenic signaling. These applications underscore the versatility of split-luciferase biosensors in facilitating both functional analysis and pharmacological targeting of PPIs, thereby advancing the development of next-generation therapeutics.

The Silent Threat: Antibiotic Resistance and Its Global Consequences

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Antibiotic resistance is one of the most pressing global health threats of our time, silently undermining decades of medical progress. This presentation explores the mechanisms behind antibiotic resistance, highlighting the role of misuse and overuse in its rapid emergence. The consequences are severe—ranging from untreatable infections to a growing economic burden that threatens healthcare systems worldwide. As resistance continues to rise, the urgency to develop new antibiotics and alternative treatments has never been greater. We will examine strategies to combat resistance, including responsible antibiotic use, policy reforms, and public awareness initiatives. Finally, we will look ahead to the future of antibiotic resistance, discussing potential innovations and the role individuals can play in mitigating this crisis. By understanding the magnitude of the problem and recognizing actionable solutions, we can collectively work towards preserving the efficacy of antibiotics for generations to come.

Next-generation anticoagulants: Selective covalent inhibitors targeting coagulation factor XIIa

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Coagulation factor XIIa (FXIIa) has emerged as a promising therapeutic target for safe anticoagulation, as its inhibition suppresses pathological thrombosis without disrupting hemostasis. Recent advancements include the discovery of orally bioavailable, small-molecule covalent inhibitors that demonstrate sub-nanomolar potency and high specificity over related coagulation factors (e.g., factors Xa and XIa). Preclinical studies highlight their efficacy in reducing thrombosis in murine models and suppressing contact activation-driven clotting in extracorporeal systems, such as artificial lungs, without increasing bleeding risk. For example, the covalent inhibitor FXII900, a macrocyclic peptide, achieved prolonged anticoagulation in rabbits and pigs with no adverse bleeding events, underscoring its potential for acute medical applications. Structural optimization of triazole-based compounds has further yielded submicromolar inhibitors with enhanced selectivity, paving the way for orally administered therapies. These innovations address a critical unmet need in anticoagulation by decoupling antithrombotic effects from bleeding complications, positioning covalent FXIIa inhibitors as transformative candidates for treating thromboembolic diseases, perioperative interventions, and medical devices requiring blood compatibility. Building on these advances, and by leveraging structure-based drug design and MCR chemistry approaches, we aim to create highly potent and selective covalent FXIIa inhibitors for achieving safe anticoagulant effects. Our efforts will address the current gap in the availability of small-molecule covalent FXIIa inhibitors and contribute to the next generation of safe and effective anticoagulant therapies.

RNA aided drug discovery of small molecules

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For many years, RNA has been largely overlooked as a pharmaceutical target in favor of proteins. Since the first protein structure was crystallized and deposited in the Protein Data Bank (PDB) [1], more than 92% of the deposited structures have been proteins, whereas only 3% are RNA structures—and even fewer are RNA–small molecule complexes—highlighting a significant underrepresentation. Despite the completion of the Human Genome Project, only a small fraction of the genome has been successfully drugged. Approximately 1.5% of the genome encodes proteins (roughly 20,000 in total), and it is estimated that only 10–15% of these (~2,000–3,000, representing 0.2% of the genome) are disease-related. Currently, fewer than 700 of these proteins (~0.05% of the genome) are targeted by therapeutic drugs [2–4]. Targeting RNA could substantially expand the druggable portion of the genome, as potential RNA targets include messenger RNAs encoding disease-related proteins—particularly those considered "undruggable"—as well as various non-coding RNAs (e.g., microRNAs, riboswitches, ribosomal RNAs, and long non-coding RNAs) implicated in disease processes.

This work presents **ACRADIS**, a platform designed to accelerate the discovery of small molecules targeting RNA, thereby opening new avenues for drug development. In collaboration with industrial and academic partners, and supported by the ERC-funded **AMADEUS** platform—which embraces the "miniaturization and automation" approach—this project aims to establish a high-throughput RNA crystallography pipeline. The in vitro transcription of two riboswitches from *Staphylocuccus Aureus* and *Streptococcus Pneumoniae* and the poison exon 20N of *SCN1A*, implicated in Dravet syndrome, is described, along with preliminary data from an internship conducted in collaboration with the Helmholtz Zentrum Munich. By integrating chemistry, structural biology, and machine learning approaches, **ACRADIS** seeks to overcome current limitations in RNA-targeted drug discovery, expedite structural determination, and ultimately contribute to the advancement of RNA-focused therapeutics.

BIBLIOGRAPHY

1. Epp, O., Lattman, E. E., Schiffer, M., Huber, R. & Palm, W. Molecular structure of a dimer composed of the variable portions of the Bence-Jones protein REI refined at 2.0-Å resolution. *Biochemistry* **14**, 4943–4952 (1975).
2. Hopkins, A. L. & Groom, C. R. The druggable genome. *Nat Rev Drug Discov* **1**, 727–730 (2002).
3. Warner, K. D., Hajdin, C. E. & Weeks, K. M. Principles for targeting RNA with drug-like small molecules. *Nat Rev Drug Discov* **17**, 547–558 (2018).
4. Dixon, S. J. & Stockwell, B. R. Identifying druggable disease-modifying gene products. *Curr Opin Chem Biol* **13**, 549–555 (2009).

Triazolopiperazines Enabled By High Throughput Experimentation

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The triazolopiperazine scaffold, present in various drugs, offers a valuable framework for medicinal chemistry due to its unique structural features. We developed an innovative one-pot multicomponent reaction (MCR) synthesis of triazolopiperazines that overcomes limitations of traditional multistep methods, such as lengthy procedures, use of expensive catalysts, and limited variability. This MCR approach allows for the efficient synthesis of diverse triazolopiperazines with three positions for substitution. The reaction conditions are being optimized using high-throughput experimentation (HTE). This novel methodology provides a rapid and versatile route to triazolopiperazines, opening new avenues for drug discovery.

Innovative Design of K-Ras G13C Covalent Inhibitors.

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KRAS G13C is the second most common KRAS mutation in cancer, but unlike the well-studied G12C mutation, it has remained undrugged due to the challenge of targeting its highly conserved and GTP-occupied binding pocket. This research focuses on developing the first covalent inhibitors specifically targeting KRAS G13C by designing small molecules that mimic GTP and selectively bind to the cysteine at position 13. The approach aims to overcome the high binding affinity and intracellular concentration of GTP by covalent modification. Key challenges include developing stable, cell-permeable GTP mimics and achieving selective C13 reactivity. Using structure-based design and protein mass spectrometry screening, this work seeks to deliver the first drug-like G13C inhibitors, with broader potential for targeting other GTPases in disease.

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Structure-Guided Strategies for p53 Y220C: Echo Chemistry and Drug Design

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p53 is a crucial tumor suppressor protein, often referred to as the "guardian of the genome" for its role in maintaining genomic integrity. Mutations in p53 are found in more than half of human cancers, frequently disrupting its ability to regulate cell cycle arrest, apoptosis, and DNA repair. Among these, the Y220C mutation replaces a tyrosine with a cysteine residue, creating a surface cavity. This newly formed, druggable pocket offers a unique opportunity for therapeutic intervention.

In this work, two complementary approaches are explored. First, carbazole-based PROTACs (Proteolysis Targeting Chimeras) are designed to selectively degrade the mutant p53 by recruiting E3 ubiquitin ligases, reducing its dominant-negative effects. Second, covalent inhibitors are synthesized to target the cysteine exposed within the cavity, aiming to stabilize the mutant conformation and restore wild-type-like DNA binding and transcriptional activity. Several carbazole derivatives have already demonstrated promising results in reactivating p53 Y220C by enhancing its thermal stability.

Compound synthesis will be performed using the Echo 655 acoustic liquid handler, a high-throughput, non-contact technology that allows for precise nanoliter-scale transfer, enabling rapid and efficient library generation. Together, these strategies showcase how structure-guided drug design, combined with advanced synthesis technologies, can pave the way for novel cancer therapies targeting mutant p53.

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Targeting DYRK1

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DYRK1A is a challenging but promising target in neurodegeneration and cancer. We present a modular multicomponent reaction (MCR) strategy to develop selective covalent inhibitors based on a triazolopiperazine scaffold. This core is further diversified into tetrazole derivatives, enabling fine-tuned binding and potential macrocyclization for enhanced pharmacokinetics. Our approach offers a streamlined path to structurally diverse, drug-like candidates with improved selectivity and stability.

With High-Throughput Experimentation Towards Novel Antibiotics

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The global escalation of antimicrobial resistance (AMR) threatens the effectiveness of current antibiotics and underscores the urgent need for novel therapeutic strategies. To address this, we are employing high-throughput experimentation (HTE) to accelerate the discovery and optimization of innovative antibiotics targeting both novel bacterial enzymes and re-engineered legacy drugs.

One focus of our work is MraY (phospho-MurNAc-pentapeptide translocase), a membrane-associated enzyme critical to bacterial cell wall biosynthesis and absent in humans. MraY represents an attractive, underexploited antibacterial target. By leveraging HTE, we rapidly synthesize and evaluate structurally diverse small molecules to identify potent MraY inhibitors and define clear structure–activity relationships.

In parallel, we are modifying the structure of streptomycin, a well-established aminoglycoside antibiotic, to overcome its known limitations, including resistance, ototoxicity, and low oral bioavailability. Using a high-throughput semi-synthetic approach, we generate libraries of streptomycin analogs aimed at enhancing potency, evading resistance mechanisms, and improving pharmacokinetic profiles.

This dual strategy targeting both novel mechanisms and improving established scaffolds demonstrates the power of HTE to streamline early-phase antibiotic discovery. By integrating automated synthesis with parallel screening, we significantly reduce development timelines and improve the likelihood of identifying clinically relevant candidates.

Overall, our approach contributes to revitalizing the antibiotic pipeline with next-generation compounds equipped to combat drug-resistant bacterial infections.

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Enhancing Acoustic Droplet Ejection: Workflow and Solvent Exploration

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Acoustic Droplet Ejection (ADE) is emerging as a powerful tool for high-throughput, miniaturized synthesis at the nano- and microliter scale, offering an efficient and sustainable alternative to conventional liquid handling methods. While its use has largely been restricted to aqueous and DMSO-based systems, expanding ADE to broader areas of organic synthesis requires testing solvents with a wider range of physicochemical properties. In this presentation, we outline our streamlined workflow for automated synthesis and analysis using ADE, and discuss an ongoing solvent screening effort designed to identify new compatible options. Both traditional and green solvents are being evaluated in terms of acoustic transfer efficiency and suitability, aiming to highlight how ADE can be further leveraged to access a wider chemical space while aligning with green chemistry principles.