School of Molecular Sciences
Arizona State University

SMS Fall 2023 Seminar Series

Wednesday August 9 | 3:00 pm | Biodesign Auditorium

Automation + Miniaturization = Acceleration

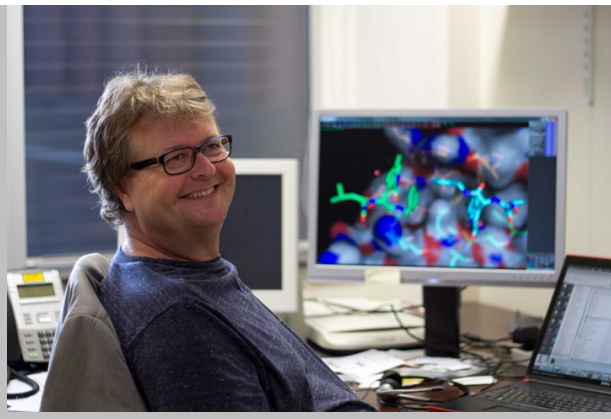
The mantra 'Automation + Miniaturization = Acceleration' is successfully applied in many research areas and technologies, but not in synthetic chemistry, which is largely believed to be not automatable. However, with the potential to accelerate discoveries while flattening costs, increase safety, streamline data generation, enhance reproducibility, and lower the environmental footprint, automation and miniaturization are two promising approaches to synthesis and are worthwhile to invest in.

Since 2018 we have introduced acoustic droplet ejection (ADE) and iDOT for the automated synthesis of small molecules on nanoscale. [1] We showed that organic chemistry can be generally performed on nanoscale e.g. by producing large numbers of novel boronic acids, [2] isoquinolines, [1] quinazolines, [3] iminopyrrolidines [4], and covalent inhibitors. [5] Moreover, we showed that libraries based on multiple chemistries in parallel can be performed on the ADE platform, approaching degrees of diversity comparable to large screening libraries. [6] Notably, the synthesis of 1536 unprecedented drug-like small molecules based on 16 different scaffolds consumed only 20 mg of building blocks inclusive solvent. Thus, ADE is suitable to considerably reduce the ecological footprint of synthetic chemistry. Clearly, running reactions on a small scale is not only more *sustainable* and *greener*, *safer*, producing *less waste*, but also more *rapid* and *economical*.

Highly automated and miniaturized synthesis at a nanoscale can also be incorporated into drug discovery: we realized for the first time the incorporation of HT synthesis and HT protein crystallography for the discovery of potent covalent SARS-CoV-2 3CLpro inhibitors; [7] we showed the discovery of menin-MLL antagonists; [8] and most recently we discovered Crbn degrading glues with extraordinary cellular potency. [9] We strongly believe that early medicinal chemistry will depart from currently mostly performed manual mmol scale synthesis towards automated and highly miniaturized synthesis and will help to accelerate future drug discovery.

Prof. Alexander Dömling

Professor, Palacky University Olomouc



Prof. Alexander Dömling (ERA Chair of Innovative Chemistry Group at the Palacky University Olomouc) devotes his academic life to the design and discovery of bioactive compounds for difficult targets such as protein protein interactions, transcription factors, or RNA. He studied multi-component reactions with Ivar Ugi at the Technical University Munich (PhD), and with Barry Sharpless at The Scripps Research Institute (PD). At the University of Pittsburgh, he became associate and full professor and he introduced the "google-like" web-based technology ANCHOR.QUERY together with Carlos Camacho. ANCHOR.QUERY can screen very large (billions) of virtual compounds in just seconds for pharmacophores and based on key interacting fragments, e.g. large amino acid side chains of amino acids (in PPIs). Interestingly the resulting virtual hits can be instantaneously synthesized using convergent and fast multicomponent reaction chemistry in order to test the virtually generated hypothesis. Another development is the technology platform **A**utomated, **m**ini**a**turize**d** and acc**e**lerated dr**u**g di**s**covery (AMADEUS) which was recently rewarded by an ERC Advanced grant. Here a fundamentally novel approach towards preclinical drug discovery and development is introduced by blending Instant Chemistry, nL dispensing, HT purification, HTS and machine learning. The indication areas Alexander Dömling is interested in are cancer immunology, infectious diseases and metabolic disorders. He has published more than 300 scientific articles, reviews and applied for >70 patents. Additionally, Alexander Dömling is a serial entrepreneur trying to make the expression "from bench to bedside" become true. - alexander.domling@upol.cz

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