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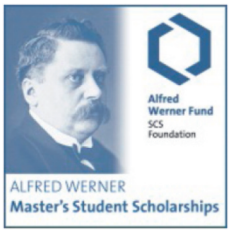
ALFRED WERNER FUND MASTER'S STUDENT SCHOLARSHIPS



In this report, the Alfred Werner Scholars' class of 2023–2025 present their Master Thesis research projects. There are four scholars of this class who completed their studies earlier this year. The fifth scholar of this class is expected to complete his studies next year. One student of the class of 2022–2024 presents his research only now, but for a very good reason: With his research, he contributed to a patent application, which was filed in late 2024.

The *Alfred Werner Fund* of the SCS Foundation, established in 2013, supports master's degree studies for excellent students from foreign countries in Chemistry or Biochemistry at a Swiss University or at a Federal Institute of Technology. The Foundation offers scholarships in the amount of CHF 30'000 for international students nominated by the Swiss partner universities.

The scholarship program is supported by the Swiss chemical and pharmaceutical industry and several private donors.

So far, eighty-eight scholarships have been granted to students from over thirty countries, about two thirds of them continuing their career in Switzerland. This also applies to the five scholars presented here: Two went abroad again to pursue doctoral studies and to explore more of the world (Austria and Denmark), whereas the three other scholars continued their studies here in Switzerland. Two of those who decided to stay in Switzerland did change university (EPFL to ETHZ and ETHZ to University of Geneva). There is more information about the scholars in the section 'Future Plans' of the reports.

About one half of the eighty scholars who completed their master's studies are now pursuing doctoral studies, most of them at Swiss universities. So far, nine scholars were permanently hired by one of the program supporting companies.

To learn more about the Alfred Werner Scholars, please visit the Gallery of alumni at https://foundation.scg.ch/scholarships/scholar-gallery or download the Alfred Werner Program Impact Report 2013-2021 from the same Web site.

Alfred Werner Master's Scholarships 2025–2027

The Allocation Committee of the Alfred Werner Fund, consisting of representatives from the program supporting companies and the partner universities, granted stipends to the following international students:

Claire J. Benedict, University of Bern
Hope College, Holland (MI), USA
Loïc Carrier, EPFL Lausanne
University of Montréal, Canada
Manca Mursa, ETH Zurich
Ruprecht Karl University of Heidelberg, Germany
Shourav Saha, University of Zurich
USC, Los Angeles (CA), USA
Feriha Mesra Aktas, EPFL Lausanne
Boğaziçi University, Istanbul, Turkey
Adam Hoško, EPFL Lausanne
University of Chemistry and Technology, Prague, Czech Republic
Marjan Moradkhan, University of Geneva
Kharazmi University, Tehran, Iran

Alfred Werner Fund Master's Scholarships 2022–2025

Pau Reolid Coll
Nationality: *Spanish*
Bachelor: *University of Barcelona*
Master at: *UNIGE/EPFL*
Master Thesis Supervisor: *Prof. Nicolas Thomä*

Characterization of KBTBD4 Interactions: Insights into Corepressor Regulation

Medulloblastoma (MB) is the most common malignant brain tumor in children, frequently leading to long-term disabilities. Recent studies identified KBTBD4, an E3 ubiquitin ligase, as a recurrently mutated driver in Group 3 and Group 4 MB. As part of the ubiquitin system, KBTBD4 mediates post-translational protein modification crucial for maintaining cellular homeostasis. This work explores how KBTBD4-mediated ubiquitination of chromatin regulators contributes to the molecular mechanisms underlying medulloblastoma progression.

Medulloblastoma (MB) is the most common malignant brain tumor in children and often results in long-term physical

disabilities.[1] Extensive genetic studies worldwide have sought to uncover the mechanisms underlying the development of distinct MB subgroups. In a seminal study, KBTBD4 was identified as a recurrently mutated driver gene in Group 3 and Group 4 MB.[2] KBTBD4 functions as an E3 ubiquitin ligase, a component of the ubiquitin system – a multi-enzymatic cascade (E1, E2, and E3) that attaches the small protein ubiquitin to specific substrate proteins (Fig. 1).[3] This post-translational modification regulates key cellular processes such as protein stability, localization, and activity, and its dysregulation is often associated with various diseases, including cancer.

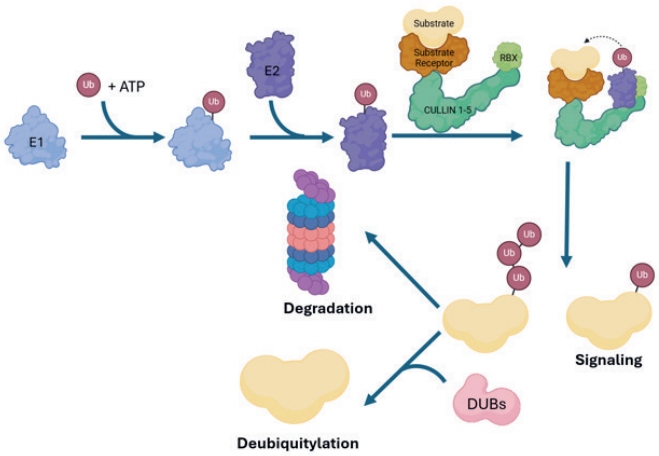


Fig. 1. Overview of the ubiquitin–proteasome system, illustrating the E1–E2–E3 enzymatic cascade leading to substrate ubiquitination which can lead to multiple outcomes. Fig. generated with Biorender.

Subsequent studies have shown that KBTBD4 mutations promote a neomorphic ubiquitin-mediated degradation of the CoREST complex,[4] a chromatin-modifying corepressor, and that compounds like UM171 can mimic this effect,[5] further implicating KBTBD4 in chromatin dysregulation and tumor biology (Fig. 2). However, the physiological substrates of KBTBD4 and how corepressor degradation influences medulloblastoma progression and development remains a mystery.

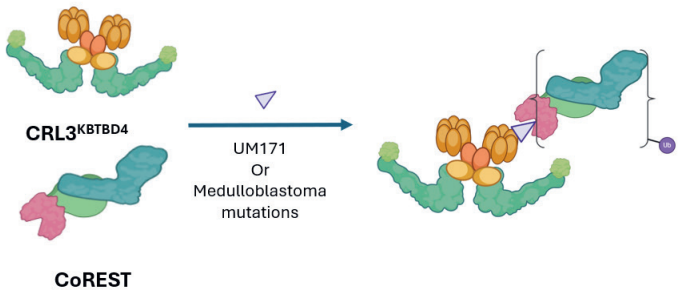


Fig. 2. KBTBD4-mediated ubiquitination of the CoREST complex, enhanced by UM171-induced surface modifications or medulloblastoma-associated mutations. Fig. generated with Biorender.

My thesis aimed to answer these questions through the biochemical characterization of KBTBD4 and its interactions. After extensive optimization of the purification protocol, I characterized its interactions with several reported and novel transcriptional corepressors, mainly HDAC-containing complexes. Using insect cell expression systems, I established protein purification pipelines and performed domain mapping through truncation analyses and pulldowns. I reconstituted corepressor complexes *in vitro* and developed biochemical assays, including ubiquitination and deacetylation assays, to investigate their activity and regulation by KBTBD4.

[1] P. A. Northcott, G. W. Robinson, C. P. Kratz, D. J. Mabbott, S. L. Pomeroy, S. C. Clifford, S. Rutkowski, D. W. Ellison, D. Malkin, M. D. Taylor, A. Gajjar, S. M. Pfister, *Rev. Dis. Primer* **2019**, *5*, 11, https://doi.org/10.1038/s41572-019-0063-6.
[2] P. A. Northcott, I. Buchhalter, A. S. Morrissy, V. Hovestadt, J. Weischenfeldt, T. Ehrenberger, S. Gröbner, M. Segura-Wang, T. Zichner, V. A. Rudneva, H.-J. Warnatz, N. Sidiropoulos, A. H. Phillips, S. Schumacher, K. Kleinheinz, S. M. Waszak, S. Erkek, D. T. W. Jones, B. C. Worst, M. Kool, M. Zapatka, N. Jäger, L. Chavez, B. Hutter, M. Bieg, N. Paramasivam, M. Heinold, Z. Gu, N. Ishaque, C. Jäger-Schmidt, C. D. Imbusch, A. Jugold, D. Hübschmann, T. Risch, V. Amstislavskiy, F. G. Rodriguez Gonzalez, U. D. Weber, S. Wolf, G. W. Robinson, X. Zhou, G. Wu, D. Finkelstein, Y. Liu, F. M. G. Cavalli, B. Luu, V. Ramaswamy, X. Wu, J. Koster, M. Ryzhova, Y.-J. Cho, S. L. Pomeroy, C. Herold-Mende, M. Schuhmann, M. Ebinger, L. M. Liau, J. Mora, R. E. McLendon, N. Jabado, T. Kumabe, E. Chuah, Y. Ma, R. A. Moore, A. J. Mungall, K. L. Mungall, N. Thiessen, K. Tse, T. Wong, S. J. M. Jones, O. Witt, T. Milde, A. Von Deimling, D. Capper, A. Korshunov, M.-L. Yaspo, R. Kriwacki, A. Gajjar, J. Zhang, R. Beroukhim, E. Farenkel, J. O. Korbel, B. Brors, M. Schlesner, R. Eils, M. A. Marra, S. M. Pfister, M. D. Taylor, P. Lichter, *Nature* **2017**, *547*, 311, https://doi.org/10.1038/nature22973.
[3] D. Komander, M. Rape, *Annu. Rev. Biochem.* **2012**, *81*, 203, https://doi.org/10.1146/annurev-biochem-060310-170328.
[4] Z. Chen, R. M. Ioris, S. Ruchardson, A. N. Van Ess, I. Vendrell, B. M. Kessler, F. M. Buffa, L. Busino, S. C. Clifford, A N. Bullock, V. D'Angiolella, *Cell Death Differ.* **2022**, *29*, 1955, https://doi.org/10.1038/s41418-022-00983-4.
[5] J. Chagraoui, S. Girard, J.-F. Spinella, L. Simon, E. Bonneil, N. Mayotte, T. MacRae, J. Coulombe-Huntington, T. Bertomeu, C. Moison, E. Tomellini, P. Thibault, M. Tyers, A. Marinier, G. Sauvageau, *Cell Stem Cell* **2021**, *28*, 48, https://doi.org/10.1016/j.stem.2020.12.002.

Future Plans

After successfully completing my MSc thesis in the laboratory of Prof. Thomä, I had the opportunity to continue my research under his guidance. I am deeply grateful to the Alfred Werner Scholarship Program and all its partners for enabling me to pursue my MSc studies in Switzerland and for the chance to grow within such a vibrant and inspiring scientific community.

Patrick Domke
Nationality: *German*
Bachelor: *Friedrich-Alexander-Universität Erlangen-Nürnberg*
Master at: *EPFL*
Master Thesis Supervisor: *Prof. Bill Morandi* (ETHZ)

Award: Syngenta Monthey Prize for the best average grade in the Master's program in Molecular and Biological Chemistry at EPFL

Electrochemical Degradation and Valorization of Persistent Organic Pollutants (POPs)

POPs are chemicals produced on a megaton scale over the past century, primarily for use as pesticides and flame retardants. These substances typically feature strong carbon-halogen (C–X) bonds, making them unusually resistant to biodegradation. An adequately scalable, cost-effective, and resource-efficient solution to remediate the vast quantities of remaining stockpiles and POP-contaminated soils has hitherto remained elusive. Herein, a new electrochemical protocol is described, which fully dehalogenates four of the most concerning POPs, including lindane and DDT, affording useful hydrocarbons and table salt.

Persistent Organic Pollutants (POPs) are highly recalcitrant and toxic compounds that pose a profound threat to ecosystems across the world. One of the most notorious representatives of this class of chemicals is hexachlorocyclohexane (HCH) – a known human carcinogen – a specific isomer of which was used as the insecticide Lindane. While the 2001 Stockholm Convention outlawed the manufacture and use of HCH and other POPs, millions of tons of production wastes throughout Europe alone are still left untreated in warehouses and landfills. Significant research has been carried out on thermal, microbial, chemical (usually base-promoted), photo-, mechano-, and electrochemical approaches to remediate such POP wastes. However, high cost, non-scalability, and the formation of ecotoxic by-products have hitherto stymied the application of these methods on industrially meaningful scales.[1]

In 2021, the groups of Morandi and Waldvogel disclosed a vicinal dihalide shuttle reaction under electrochemical conditions, with which HCH could be fully dechlorinated.[2] In the present work, instead of transferring chlorine to another molecule, we sought to sequester it as an innocuous inorganic chloride salt, which is preferable for large-scale application.[3] This was achieved with a uniquely efficient protocol using inexpensive graphite electrodes and DMSO as the solvent, which also acts as a sacrificial reductant. A key discovery was that using alternating current (AC) instead of conventional direct current (DC) unwanted side reactions were suppressed and, crucially, maintained the structural integrity of the electrodes throughout the electrolysis. Preliminary mechanistic studies suggest that the beneficial effect of AC arises from its ability to suppress the formation of superbasic species around the cathode. Furthermore, we show that with slight modifications, our conditions are also applicable to the complete dehalogenation of other POPs such as DDT, HBCD, and methoxychlor. Currently, we are looking for an industrial partner to deploy our method for the large-scale remediation of contaminated sites.

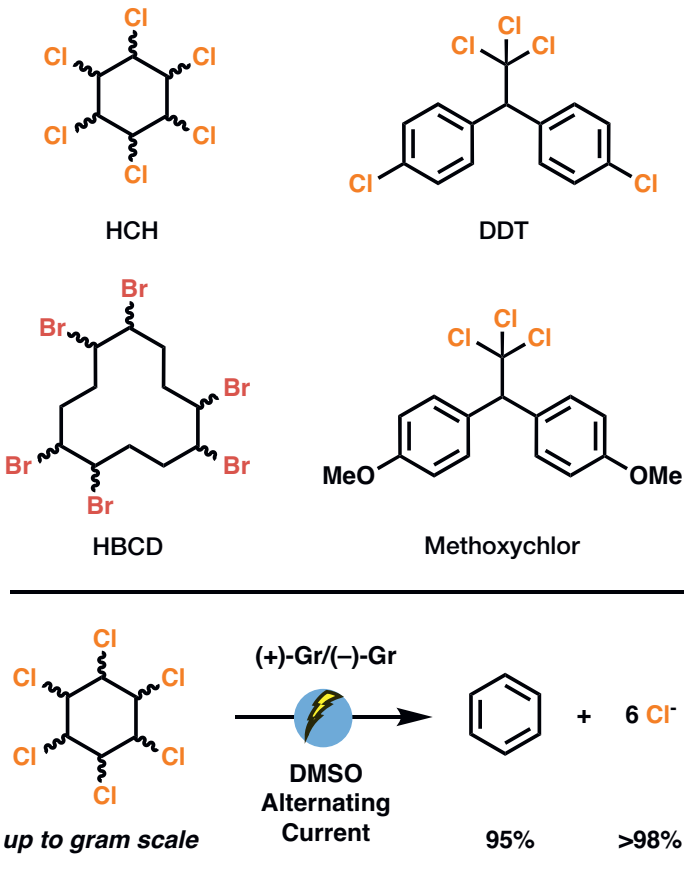


Fig. 1. Top: Chemical structures of the POPs investigated in this project. Bottom: Overview of the optimized conditions for the dechlorination of HCH.

[1] a) J. Vijgen, B. de Borst, R. Weber, T. Stobiecki, M. Forter, *Environ. Pollut.* **2019**, *248*, 696, https://doi.org/10.1016/j.envpol.2019.02.029. b) R. Weber, G. Aliyeva, J. Vijgen, *Environ. Sci. Pollut. Res.* **2013**, *20*, 1901, https://doi.org/10.1007/s11356-012-1247-8. c) E. T. Martin, C. M. McGuire, M. S. Mubarak, D. G. Peters, *Chem. Rev.* **2016**, *116*, 15198, https://doi.org/10.1021/acs.chemrev.6b00531. d) M. Vega, D. Romano, E. Uotila, Directorate-General for Internal Policies of the European Parliament, **2016**, https://www.europarl.europa.eu/RegData/etudes/STUD/2016/571398/IPOL_STU(2016)571398_EN.pdf, accessed October 30, 2025.

[2] X. Dong, J. L. Roeckl, S. R. Waldvogel, B. Morandi, *Science* **2021**, *371*, 507, https://doi.org/10.1126/science.abf2974.

[3] A. F. Garrido-Castro, P. T. Domke, B. Morandi, Patent Appl. No. PCT/EP2025/079986, **2025**, manuscript in submission.

Future Plans

Following my Master's thesis, I completed a six-month internship in medicinal chemistry at Novartis, where I worked on developing a new method to access complex indolin-3-ones. In July 2025, I returned to the group of Prof. Bill Morandi as a doctoral student, focusing on the development of novel, electrochemically-driven synthetic methodologies. I sincerely thank the Alfred Werner Scholarship Program for allowing me to pursue my Master's degree in Switzerland and facilitating crucial connections to the program-supporting companies.

Lucas Paul Grobon
Nationality: *French*
Bachelor: *McGill University*
Master at: *EPFL*
Master Thesis Supervisor: *Prof. Vassily Hatzimanikatis*
Co-examiners: *Dr. Peter H. Winegar and Prof. Jay D. Keasling*

Total Microbial Biosynthesis of Steroidal Alkaloids in Engineered Saccharomyces cerevisiae

Steroidal alkaloids (SAs) have emerged as a diverse class of bioactive natural products with promising therapeutic potential. However, they remain underutilized because it is difficult to scale their native biosynthesis or chemical synthesis. To address this challenge, we established S. cerevisiae as a microbial chassis for biosynthesis of SAs from simple sugars. This work highlights the potential of engineered yeast as a sustainable platform to produce structurally diverse and complex natural and new-to-nature SAs.

Steroidal alkaloids (SAs) are a class of bioactive products from plants (*e.g. Liliaceae*, *Apocynaceae*, *Buxaceae*, *Solanaceae*) and marine organisms.[1] Plants produce SAs for constitutive and inducible defense responses against biotic stressors.[2] Despite their historical association with toxicity in improperly consumed food, SAs have garnered significant interest due to their broad pharmacological properties, including anti-cancer, anti-diabetes, and anti-inflammatory.[3] Select SAs are FDA-approved therapeutics (e.g. abiraterone acetate) and others are under ongoing investigation as potential therapeutics (*e.g.* cyclopamine). Nevertheless, this promising class of natural products remains underutilized, largely due to challenges with scaling production economically and sustainably. Biosynthesis in engineered microorganisms offers a promising strategy to address these constraints by enabling renewable and scalable production of natural compounds from simple sugars (Fig. 1). *S. cerevisiae* proves an optimal chassis for biosynthesis of natural molecules

due to its eukaryotic capacity to functionally express plant-derived enzymes with complex post-translational requirements. To achieve the total *in vivo* synthesis of novel SA targets, we designed novel microbial synthetic pathways by integrating heterologous genes from plants into the *S. cerevisiae* genome *via* CRISPR-Cas9 cleavage and homologous recombination (Fig. 1). Enzyme expression levels and subcellular localization were characterized using proteomics and fluorescent confocal microscopy, respectively. Biosynthesized secondary metabolites were characterized using HR-LC-MS^n.

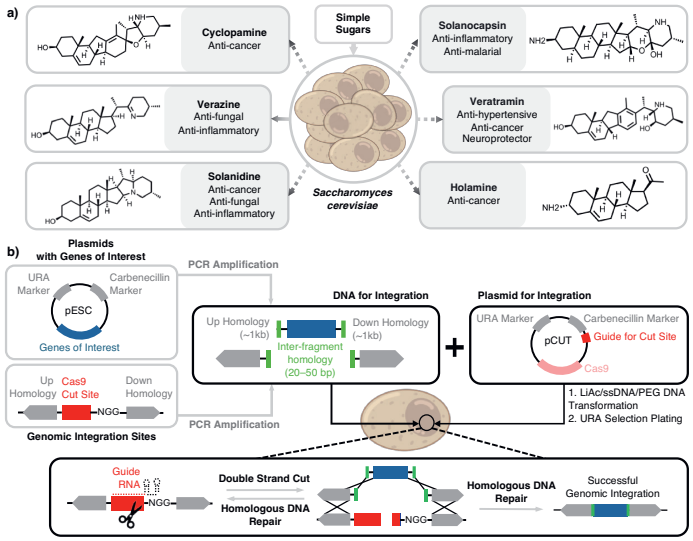


Fig. 1. Microbial platform for biosynthesis of relevant SAs. a) Selected SA targets for production in yeast from simple sugars, some of whose properties are shown for context. Dashed arrows refer to molecules not yet synthesized in a microbial chassis. b) Integrated CRISPR-Cas9 workflow for *S. cerevisiae* engineering. Guide RNAs direct Cas9 cleavage at genomic NGG PAM sites followed by homology-directed recombination. Exogenous DNA was inserted through LiAc/ssDNA/PEG protocol.

Our work reports the first total *in vivo* biosynthesis of previously unsynthesized SA secondary metabolites in *S. cerevisiae*. We reprogrammed yeast sterol metabolism and demonstrated transferability of key enzymatic activities across non-canonical SAs. Our engineered yeast chassis provides a scalable platform for producing high-value natural and new-to-nature SAs to advance drug discovery and sustainable biomanufacturing.

[1] M.-L. Xiang, B.-Y. Hu, Z.-H. Qi, X.-N. Wang, T.-Z. Xie, Z.-J. Wang, D.-Y. Ma, Q. Zeng, X.-D. Luo, *Nat. Products Bioprospect.* **2022**, *12*, 23, https://doi.org/10.1007/s13659-022-00345-0.
[2] S. Chowański, Z. Adamski, P. Marciniak, G. Rosiński, E. Büyükgüzel, K. Büyükgüzel, P. Falabella, L. Scrano, E. Ventrella, F. Lelario, S. A. Bufo, *Toxins* **2016**, *8*, 60, https://doi.org/10.3390/toxins8030060.
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Future Plans

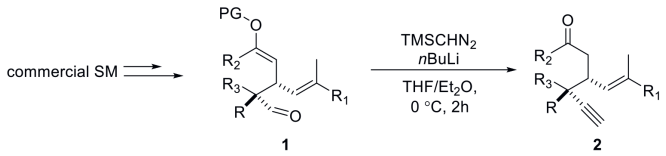
My MSc degree in Chemical Engineering and Biotechnology at École Polytechnique Fédérale de Lausanne (EPFL) included an internship at dsm-firmenich and a thesis at UC Berkeley; after completing this degree, I will begin a PhD in enzyme design at the Technical University of Denmark (DTU) in partnership with International Flavors & Fragrances. I am deeply grateful to the Alfred Werner Scholarship Program and the Swiss Chemical Society Foundation for their invaluable support of my academic training.

Martymianov Den
Nationality: *Ukrainian*
Bachelor: *V. N. Karazin Kharkiv National University*
Master at: *ETHZ*
Master Thesis Supervisor: *Prof. Erick M. Carreira*

Synthetic Studies Towards the Total Synthesis of a Caged Sesquiterpenoid

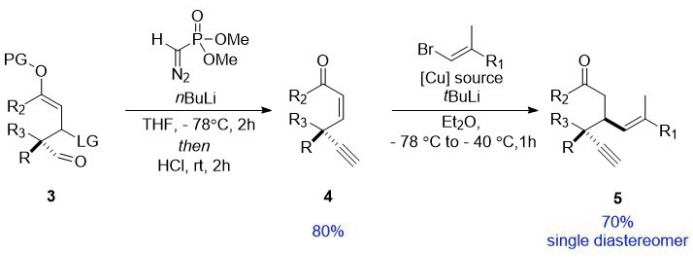
Natural products have long attracted the attention of chemists because of their diverse and potent biological properties. Despite significant advances in synthetic methodology and complex-molecule assembly, the construction of caged terpenoid frameworks remains highly challenging due to pronounced ring strain, dense functionalization, and severe stereochemical congestion. In this work, strategic approaches toward the synthesis of a caged diterpenoid were explored, and an 5-endo-dig cyclization of a 1,5-enyne system was proposed to form a key cyclic conjugate diene.

The goal of this project was to investigate alternative synthetic strategies towards the key cyclic intermediate en route to the caged diterpenoid. To achieve this, we began by evaluating homologation protocols for aldehyde **1**, which was prepared from commercial starting materials. Both the Ohira–Bestmann and Seyferth–Gilbert homologations led to decomposition of the starting material, whereas only the modified Colvin conditions afforded intermediate **2** in 40% yield.[1,2]



Scheme 1. Synthetic route towards **3**.

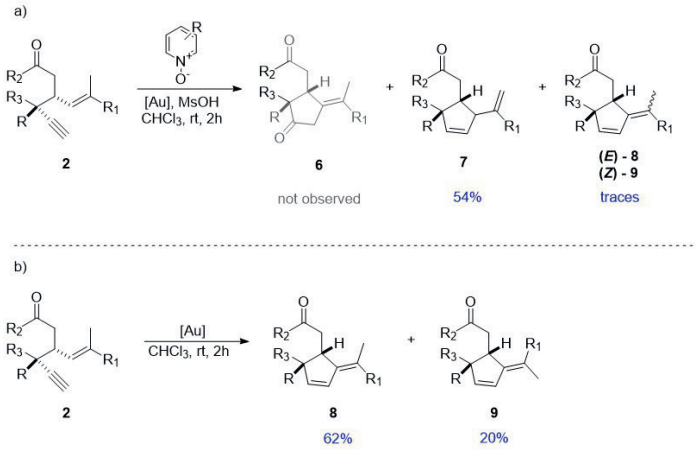
We hypothesized that introducing the alkyne functionality at an earlier stage of the synthesis would improve the overall yield of intermediate **2** and enhance the efficiency of the synthetic sequence. The investigation commenced with the screening of homologation conditions. Various protocols were tested; employing the Semmelhack variation of Seyferth-Gilbert rearrangement delivered **4** in 80% yield over two steps (Scheme 2). To our regret, subsequent conjugate addition produced exclusively the undesired diastereomer **5**.



Scheme 2. Alternative route leading to the undesired diastereomer **4**.

With **2** in hand, drawing inspiration from the work of Zhang *et al.*, we undertook an investigation into the Au(I)-catalyzed

N-oxide-mediated alkyne-oxidation/C–H insertion cascade to form the key cyclic ketone **6** (Scheme 3).[3]



Scheme 3. (a) Initial results for Au-catalysed *5-endo-dig* cyclization; (b) Optimized reaction conditions.

Unexpectedly, rather than achieving the anticipated C–H insertion to form **6** the reaction proceeded *via* a *5-endo-dig* cyclization.[4] To validate these results, the reaction was repeated in the absence of the *N*-oxide source. To our delight, this confirmed the previous observations, in this instance yielding the conjugated dienes **8** and **9** as a 3:1 mixture of *E* : *Z* isomers.

Alternatively, we investigated various electrophilic activators for the alkyne group. It was found that the use of NIS in the presence of a base promotes an electrophile-mediated *5-endo-dig* cyclization,[5] although further optimization of the reaction conditions is required.

[1] (a) S. Ohira, *Synth. Commun.* **1986**, *19*, 561, https://doi.org/10.1111/j.1944-9720.1986.tb01051.x; (b) S. Müller, B. Liepold, G. J. Roth, H. J. Bestmann, *Synlett* **1996**, 521, https://doi.org/10.1055/s-1996-5474; (c) J. C. Gilbert, U. Weerasooriya, *J. Org. Chem.* **1982**, *47*, 1837, https://doi.org/10.1021/jo00349a007. (d) E. W. Colvin, B. J. Hamill, *Chem. Soc. Perkin Trans.* **1977**, *1*, 869, https://doi.org/10.1039/p19770000869.

[3] Y. Wang, Z. Zheng, L. Zhang, *J. Am. Chem. Soc.* **2015**, *137*, 5316, https://doi.org/10.1021/jacs.5b02280.

[4] E. Jimenez-Nunez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326, https://doi.org/10.1021/cr0684319.

[5] Y. Wang, A. Genoux, S. Ghorai, H. Chen, R. Todd, L. Zhang, *Adv. Synth. Catal.* **2016**, *358*, 1417, https://doi.org/10.1002/adsc.201600027.

Future Plans

I am grateful to the Alfred Werner Foundation for supporting my studies at ETH Zürich. After completing my Master's degree, I commenced my doctoral research in the Winssinger group at the University of Geneva. My research interests include, but are not limited to, the development of synthetic methodologies for bioconjugation and the total synthesis of biologically active natural products, with the aim of expanding the chemical tools available for studying and modulating biological systems.

Polina Nikolaeva Foteva
Nationality: *Bulgarian*
Bachelor at: *University of St Andrews, UK*
Master at: *University of Geneva, Switzerland*
Master Thesis Supervisor: *Dr Carlos Moreno-Yruela and Prof. Beat Fierz*

Revealing the Link Between Sirt7 Catalysed Deacylation Kinetics and Substrate Specificity

Sirtuin 7 (Sirt7) is a chromatin-modifying enzyme and a potential drug target in certain types of cancer. Ongoing research at the lab determined the structure of Sirt7 bound to the nucleosome and identified key Sirt7-nucleosome interactions. Here we demonstrate how these interactions influence the enzymatic activity in cells and the in vitro deacylation kinetics.

Epigenetics encompasses different pathways that regulate gene expression without causing mutations in the DNA. A key mechanism involves the post-translational modifications (PTMs) of chromatin. Chromatin is a complex between DNA and histone proteins with a basic unit called the nucleosome. Sirt7 is an enzyme involved in the epigenetic regulation of gene expression through its histone deacetylation activity (removal of acetyl-lysine PTMs). Notably, Sirt7 is often overexpressed in cancer, where it maintains the tumor state.[1]

Existing deacetylase activity assays are not suitable for Sirt7, because unlike other sirtuins, it deacetylates histones only in the presence of nucleosomes. Using a mechanism-based cross-linking strategy and cryo-EM our lab identified two enzymatic domains responsible for this high substrate specificity.[2] The Sirt7 *N*-terminal domain (NTD) provides nanomolar nucleosome affinity (Fig. 1. **II** and **III**), while a key loop at the catalytic site fine-tunes substrate selectivity *in vitro* (Fig. 1. **I**).

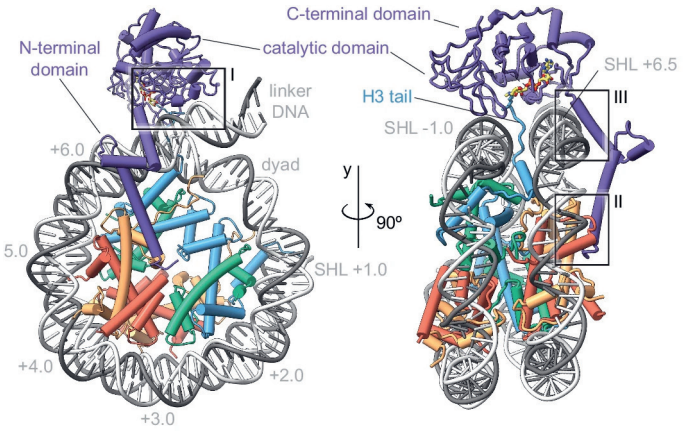


Fig. 1. **Sirt7 (violet) bound to the nucleosome**. Key functional domains are indicated. (I) Loop region; Interacting sites with the (II) acidic-patch and (III) linker-DNA. Adapted from Moreno-Yruela *et al*.[1]

To test the effect of these domains on histone acetylation in cells, I cloned a truncated Sirt7 mutant with a deleted NTD and a loop mutant, where 3 lysine residues, interacting with nucleosome DNA, were mutated to alanine. The plasmids were transiently transfected into Sirt7 knock-out cells. The cells were fixed, stained against histone 3 lysine 18 or 36 acetylation mark (H3K18ac or H3K36ac) and imaged (Fig. 2a). Quantitative immunofluorescence validated the preliminary *in vitro* data and additionally revealed the importance of multivalent interactions between Sirt7 and the nucleosome in cellular substrate recognition

(Fig. 2b). The truncated mutant showed lower activity due to inefficient substrate binding, while the loop mutant had higher specific activity towards H3K18 residue. These findings were published earlier this year.[2]

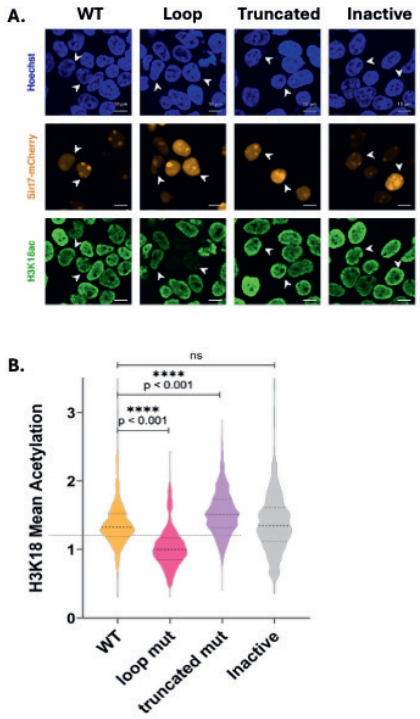


Fig. 2. **Sirt7 mutants exhibit different H3K18ac deacetylation activity compared to the wild type**. A) Confocal microscopy of fixed cells, expressing fluorescently-tagged mCherry-Sirt7 and stained with Hoechst to visualise DNA and with H3K18ac antibody. B) Quantification of the fluorescence signal from microscopy images, corresponding to the H3K18-acetylation level. Higher acetylation level correlates with lower activity.

Considering the role of Sirt7 in tumor maintenance, small molecules modulating Sirt7 activity are potential candidates for cancer therapy. The second part of the project focused on optimizing an unpublished fluorescence-based assay, developed at our lab. The high sensitivity and reproducibility of the assay enabled me to kinetically characterize wild-type Sirt7 and the two mutants. The still unpublished results provided mechanistic insight into the effect of Sirt7 interactions with the nucleosome on deacylation kinetics at the molecular level.

Having a controlled assay, complemented by an endogenous activity readout, highlighted the distinct role of Sirt7 domains in enzyme kinetics and substrate specificity in cells.

[1] C. Moreno-Yruela, B. E. Ekundayo, P. N. Foteva, D. Ni, E. Calvino-Sanles, H. Stahlberg, B. Fierz, *Nat. Commun.* **2025**, *16*, 1328, https://doi.org/10.1038/s41467-025-56529-y.

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Future Plans

The fluorogenic assay is currently being adapted to a multi-well format for high-throughput compound screening. Successful validation of this method would enable the discovery of molecules that specifically regulate Sirt7 activity on nucleosomes and rescue disease phenotype.

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