## 17 Doctoral Candidate Positions within the MSCA Doctoral Network

# MC4DD – Macrocycles for Drug Discovery

Subject to the successful signing of the EU Grant Agreement, a call for 17 DC (Doctoral Candidate) positions is open within the context of the Doctoral Network (DN) project MC4DD.

The Doctoral Network **MC4DD** "MC4DD – Macrocycles for Drug Discovery", funded within the framework of the Marie Skłodowska-Curie Actions (MSCA), follows an interdisciplinary and cross-sectoral approach by bringing together leading experts in macrocyclic drug discovery from academia and industry from the fields of organic synthesis, medicinal, high-throughput and computational chemistry, pharmacological and structural analytics, and modelling.
Eight academic research groups and five industrial partners, coordinated by Technische Universität Darmstadt in Germany, join forces in **MC4DD** to create a mobility and training platform for young scientists by means of cross-site, interdisciplinary research projects. The DCs will work on individual research projects to expand the opportunities of macrocycles as next-generation drug modalities.

**Eligibility criteria**
**Supported researchers** must be doctoral candidates, i.e. not already in possession of a doctoral degree at the date of the recruitment.

**Mobility Rule:** researchers must not have resided or carried out their main activity (work, studies, etc.) in the country of the recruiting beneficiary >12 months in the 36 months preceding their recruitment date.

**Monthly allowances (employee gross):**
Living allowance*: 3400 €
Mobility allowance: 600 €
Family allowance**: 660 €

*adjusted by country correction coefficient*
***if applicable*

QR code

MSCA Guide for Applicants

## What we offer

The project offers the DCs research and training excellence in medicinal and drug discovery. The partners of **MC4DD** are leading research groups in this field and their research institutes actively **promote young researchers.** The **8 academic research groups** and **5 industry partners** join forces in **MC4DD** to create a **platform of intersectoral and multidisciplinary mobility and training**.

To complement the academic and scientific goals of the DCs, the project offers customized research projects, structured interdisciplinary local and network-wide transferable skills training activities, and **secondments at top-ranking European universities and industry partners.**

## Candidate profile:

- MSc or equivalent in Chemical, Pharmaceutical or Life Sciences
- Research experience with organic, medicinal, analytical, computational or bio-chemistry
- Scientific interest, dedication to research, and career goal to work in drug discovery
- Appreciation for interdisciplinarity and proactive drive to collaborate across fields
- Proficiency in English, good communication skill and social competence

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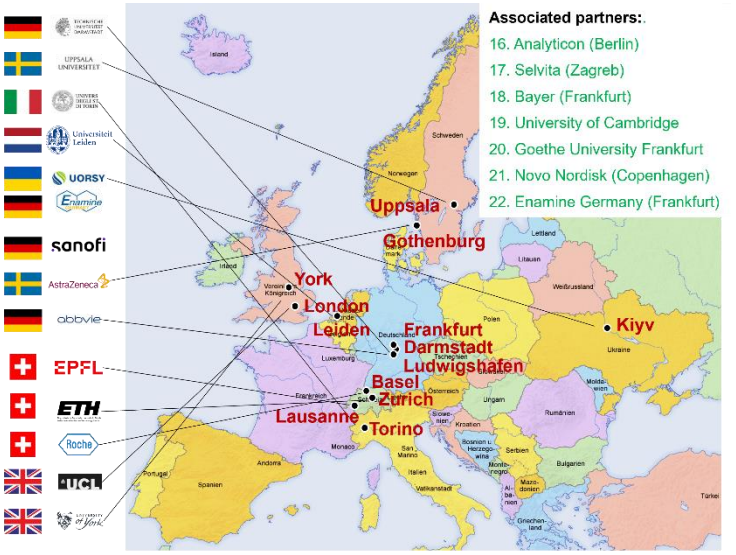
# MC 4 DD

## Applications:

- Complete applications are written in **English** and include a **CV, copies of transcripts of any obtained degrees**, as well as contact details of **two possible referees**.
- Applications should be sent directly to the contact provided below for each specific project
- Applicants should not apply to more than three different projects
- Applications should be sent via e-mail as a **single pdf** file until **31.08.2024**
- The individual DC projects are expected to start between 01.11.2024 and 31.05.2025

## Network (Main supervisors and sites):

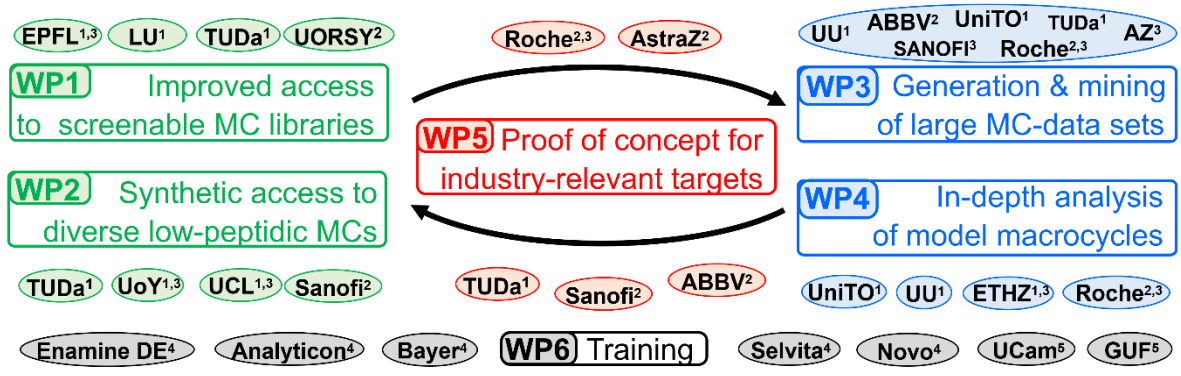
1. Felix Hausch (Technical University Darmstadt)
2. Mate Erdelyi/Jan Kihlberg (Uppsala University)
3. Giulia Caron (University of Torino)
6. Sebastian Pomplun (Leiden University)
7. Serhiy Ryabukhin (UORSY, Kiyv)
   Research carried out at Enamine (Frankfurt)
8. Sven Ruf (SANOFI, Frankfurt)
9. Werngard Czechtizky (AstraZeneca, Mölndal)
10. Frauke Pohlki (Abbvie, Ludwigshafen)
11. Christian Heinis (EPFL)
12. Sereina Riniker (ETHZ)
13. Carsten Kroll (Roche)
14. Alethea Tabor (University College London)
15. Will Unsworth (University of York)



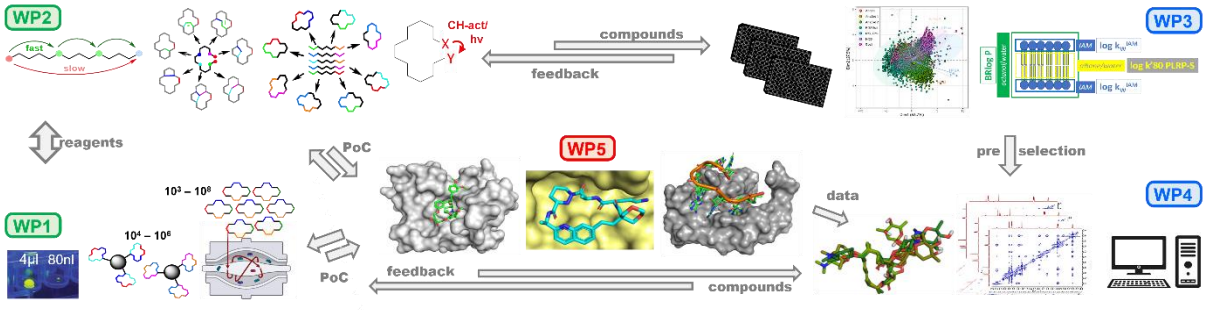

**Associated partners:**

16. Analyticon (Berlin)
17. Selvita (Zagreb)
18. Bayer (Frankfurt)
19. University of Cambridge
20. Goethe University Frankfurt
21. Novo Nordisk (Copenhagen)
22. Enamine Germany (Frankfurt)

## Research areas:




## Scientific Integration:





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# Individual DC projects:

| Fellow: DC1 | Host institution: TU Darmstadt | Apply to: kornelia.graefing@tu-darmstadt.de |
|---|---|---|
| **Supervisor:** *F. Hausch* | **Prospecive Co-Supervisor:** *K. Schmitz* | **Prospective Industry Mentor:** *F. Pohlki* |
| **Project Title (related to WP1&3):** On-bead screening and deconvolution nonpeptidic MC libraries | | |
| **Objectives:** (1) Demonstrate that MCs can be synthesized on solid support and identified by mass spectrometry; (2) Identify target protein binders in a one-bead-one-MC library (3) Validate, characterize, and optimize screening hits.<br>**Methodology**: (1) Test orthogonally cleavable building blocks; (2) incorporate into FKBP or Cyp-preferring scaffolds; (3) Build one-bead-one-compound MC librariesy by mix-and-split synthesis; (5) Screen with fluorescently labeled target proteins; (6) deconvolute after cleavage by MS; (7) Resynthesize and characterize affinity, selectivity and binding mode. | | |
| **Expected Results:** 1) Versatile method for deconvolution of one-bead-one-MC libraries; (2) Identification of improved FKBP and cyclophilin ligands; (3) Transfer to other industry-relevant targets, e.g. RNA. | | |
| **Planned secondment(s):** (1) **ABBV**, *S. Vuklevic*, M18-19: ADME studies. (2) **EPFL**, *C. Heinis*, M23-24: adaption to nanoscale; (3) **ETHZ**, *S. Riniker*, M31-32: Modelling of advanced MCs. | | |

| Fellow: DC2 | Host institution: TUDa | Apply to: kornelia.graefing@tu-darmstadt.de |
|---|---|---|
| **Supervisor:** *F. Hausch* | **Co-Supervisor:** *K. Schmitz* | **Industry Mentor:** *S. Ruf* |
| **Project Title (related to WP2&5):** Synthesis and exploration of multifunctionalized linkers for nonpeptidic MCs | | |
| **Objectives:** (1) Explore linker side chains in MCs to improve key properties (selectivity, permeability, solubility, MetStab), compared to simple linkers; (2) Develop a tool box for assembly of functionalized linkers and sets of building blocks.<br>**Methodology**: (1) Generation of functionalized C3-building blocks; (2) Conversion to mono-protected C3-diols; (3) Combinatorial pairwise assembly to ether diols; (4) Incorporation into FKBP or Cyp-preferring scaffolds; (5) Characterize affinity (by FP), selectivity (FKBP & Cyp panel), intracellular binding (nanoBRET), and binding mode (X ray). | | |
| **Expected Results:** 1) Versatile method & tool set for macrocyclization via non-peptidic, function group-rich linkers; (2) Insight into preferred side chains; (3) improved FKBP and cyclophilin ligands; (4) Transferability to other target classes. | | |
| **Planned secondment(s):** (1) **ACD**, *L. Haustedt*, M13-14: Adaption to external scaffolds. (2) **UCam**, *D. Spring*, M21-22: Incorporation of additional reactions; (3) **Sanofi,** *M. Mendez & S. Ruf*, M23-24: Combination with photo/electrochemistry. | | |

| Fellow: DC3 | Host institution: University of Uppsala | Apply to: |
|---|---|---|
| **Supervisor:** *M. Erdelyi* | **Co-Supervisor:** *J. Kihlberg* | **Industry Mentor:** *S. Vucelić* |
| **Project Title (related to WP3):** Predicting and understanding MC cell permeability by ML | | |
| **Objectives:** (1) Use ML to develop fast and accurate classification and regression models for prediction of the Caco-2 cell permeability of MCs; (2) Use and improve state-of-the-art ML technologies for identification of the most important descriptors contributing to the output from the models.<br>**Methodology**: (1) Determine cell permeability of selected 1000 MCs across Caco-2 cell monolayers; (2) Use PCA and other ML methods to select the most informative 2D and 3D descriptors for model building; (3) Build models for cell permeability using different ML methods; (4) Use data analysis approaches such as PLS, PCA, and clustering to provide insight into the effective set of descriptors governing the output from the models. (5) Determine to what extent selected macrocycles behave as molecular chameleons. | | |
| **Expected Results:** (1) Robust models for prediction of the cell permeability of MCs of diverse structures; (2); ML models that are easy to interpret by medicinal chemists and allow facile use to design MCs; (3) Dissemination to industry partners. | | |
| **Planned secondment(s):** (1) **ABBV**, *S. Vukelic/C. Hoft*, M7-M14: Determination of cell permeability across Caco-2 cells; (2) UniTO, *G. Caron*, M24-M26: Characterize MCs chromatographically to assess lipophilicity, polarity & chameleonicity. | | |

| Fellow: DC4 | Host institution: University of Uppsala | Apply to: |
|---|---|---|
| **Supervisor:** *M. Erdelyi* | **Co-Supervisor:** *J. Kihlberg* | **Industry Mentor:** *W. Czechtizky* |
| **Project Title (related to WP4):** NMR characterization of MC conformational dynamics in solution at atomic level | | |
| **Objectives:** Development of a solution NMR algorithm for the atomic level description of solution ensembles by combined use of (1) orientational (residual dipolar coupling, scalar coupling) and distance (nuclear Overhauser effect, pseudocontact shift, paramagnetic relaxation enhancement) restrains; (2) Identification of the conformational ensemble of MCs generated/identified in WP1, 2 or 3; (3) Development of a paramagnetic NMR method for determination of binding mode.<br>**Methodology**: (1) Determination of NOE build-up rates, scalar couplings in isotropic as well as of residual dipolar couplings (alignment media or paramagnetic tagging) pseudocontact shifts and paramagnetic relaxation rates (paramagnetic tagging); (2) Computational generation of a theoretical conformational pool; (**3**) Order matrix analysis by singular value decomposition, identification of solution conformers and their populations. | | |
| **Expected Results:** (1) Development of algorithms to handle a series of isotropic and anisotropic NMR observables simultaneously; (2) Improvement of NMR-based characterization of small and midsize MCs' structure and dynamics; (3) Understanding of selected MCs conformation in solution, in membranes and in their protein binding sites. | | |
| **Planned secondment(s):** (1) **ABBV**, *S. Vuklevic/C. Hoft*, M15-17: Determination of cell permeability across Caco-2 cells; (2) **ETHZ** *S. Riniker*, M25-M30: Computational generation of conformational ensembles, method development. | | |

| Fellow: DC5 | Host institution: University of Torino | Apply to: |
|---|---|---|
| **Supervisor:** *G. Caron* | **Co-Supervisor:** *G. Ermondi* | **Industry Mentor:** *S. Kostrun* |
| **Project Title (related WP3&4):** Physicochemical profiling of macrocycles | | |

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**Objectives:** (1) Measuring ionization, lipophilicity, polarity, chameleonicity and solubility descriptors to characterize the physicochemical profile of selected MCs from WP3; (2) Build global and local lipophilicity predictors and local polarity, chameleonicity and solubility models; (3) In depth analysis of chameleonicity data for drug design purposes.
**Methodology**: (1) Potentiometry; (2) Chromatographic methods based on different stationary/mobile phases combination; (3) Shake-flask to measure thermodynamic solubility; (4) Machine learning to build models and (5) molecular modeling tools for the implementation of chameleonicity in drug design.

**Expected Results:** (1) Dataset of experimental physicochemical data; (2) Setting-up of lipophilicity calculators; (3) Polarity, chameleonicity and solubility local predictors; (4) Rules to apply chameleonicity in drug design; (all specific for MCs

**Planned secondment(s):** (1) **UU**, *M. Erdelyi*, M16-M18: conformational studies by NMR to highlight chameleonic behavior; (2) **Roche,** *C. Kroll*, M21-M24: extensive polarity determination; (3) **Selvita**, S. Kostrun, M31-33: intracellular/lysosomal accumulation using Selvitas high-throughput imaging assay

| **Fellow: DC6** | **Host institution: University of Torino** | **Apply to:** |
|---|---|---|
| **Supervisor:** *G. Caron* | **Co-Supervisor:** *G. Ermondi* | **Industry Mentor:** *C. Hoft* |

**Project Title (related to WP4):** Identification of druggable regions in the MC chemical space

**Objectives:** (1) Describe the MC chemical space with different pools of descriptors; (2) Locate the different classes of MCs generated in WP3 within the chemical space; (3) Identify druggable regions using descriptors also obtained in WP3 and WP4; (4) Offering recommendations on a) areas to prioritize for synthetic exploration and b) regions to obtain new MCs with a favorable drug-like profile.
**Methodology**: (1) chemoinformatic methods to build and analyze chemical space and (2) infographic tools to generate informative readout to share with the industrial partners.

**Expected Results:**. (1) MC chemical space; (2) Indication for future MC synthetic efforts

**Planned secondment(s):** (1) **ABBV**, *C. Hoft*, M16-18: High throughput cell permeability measurements; (2) **ETHZ**, *S. Riniker*, M36-38: In silico modelling of selected macrocycles

| **Fellow: DC7** | **Host institution: University of Uppsala** | **Apply to:** |
|---|---|---|
| **Supervisor:** *M. Erdelyi* | **Co-Supervisor:** *J. Kihlberg* | **Industry Mentor:** *Nele-Johanna Hempel* |

**Project Title (related to WP4):** Determination solution ensembles of cell permeable large macrocyclic peptides (MCPs)

**Objectives:** (1) Participation in the synthesis of approximately 10 large (MW >>1000 Da) MCPs based on a potent and permeable hit, and in the determination of their cell permeability and target binding; (2) Determination of the solution ensembles of MCPs in an aqueous environment as well as in a membrane-like, low dielectric environment. A series of 3-5 MCPs that vary in cell permeability will be studied; (3) Determination of the solution ensembles of a reference MCP in aqueous and membrane-like environment.
**Methodology**: (1) Prepare MCPs by solid-phase synthesis; (2) Get experience of the determination of cell permeability of MCPs across Caco-2 cell monolayers; (3) Determination of NOE build-up rates, scalar couplings (isotropic media), residual dipolar couplings and pseudocontact shifts (alignment media or paramagnetic tagging); (4) Computational generation of a theoretical conformational pool; (5) Identification of solution conformers and their populations, using NMR data and the conformational pool as input.

**Expected Results:** (1) Understanding of selected MCPs conformation in aqueous solution, in membranes and in their protein bound states. (2) Improvement of NMR-based characterization of large MCPs' structure and dynamics; (3) Mechanistic understanding of how large MCPs cross cell membranes, and what structural features that are important.

**Planned secondment(s):** (1) **Novo Nordisk**, N.-J. Hempel, M3-5: Synthesis and characterization of MCPs (2) **ETHZ** *S. Riniker*, M20-22: MD simulations for one or two of the MCPs studied by NMR spectroscopy.

| **Fellow: DC8** | **Host institution: UORSY/Enamine** | **Apply to:** |
|---|---|---|
| **Supervisor:** *S. Ryabukhin* | **Co-Supervisor:** *F. Hausch* | **Industry Mentor:** *I. Kondratov* |

**Project Title (related to WP1):** Design and producing of building blocks for the synthesis of macrocycles using non-amidic disconnections

**Objectives:** (1) design several sets of building blocks for the synthesis of macrocycles based on non-amidic disconnections (Grubbs reaction etc); (2) elaborate efficient cost-effective procedures for designed building blocks producing and determine their scope and limitation; (3) generate the database of building blocks based on common starting materials and elaborated procedures and synthesize the necessary examples in 1-10 gram amounts for further combinatorial chemistry uses.
**Methodology**: (1) The design will perform using our in-hose experience in the synthesis of polyfunctional small molecules with several orthogonal or protected functionalities; (2) The elaboration of the methodologies and determination of their scope and limitations will provide using various synthetic chemistry technics depends on their efficacy for the appropriate scheme with further functional group protection/deprotection/interconversion; (**3**) Based on a predicted structural features and elaborated procedures for combinatorial synthesis the set of building blocks will be synthesized in 1-10 g amount.

**Expected Results:** (1) Available sets of target compounds appropriated for project needs; (2) Available a 10-20 methodologies with determined scope for cherry picking and generation of final BB set; (3) 100-200 Compounds for combinatorial libraries' synthesis are produced and ready for further utilization.

**Planned secondment(s):** (1) TUDa, F. Hausch, M16-21: Incorporation of building blocks into FKBP- and Cyp-focussed libraries; (2) LU, S. Pomplun, M22-24: Adaption of high-throughput chemistry to ASMS library generation and deconvolution.

| **Fellow: DC9** | **Host institution: Leiden University** | **Apply to:** |
|---|---|---|
| **Supervisor:** *S. Pomplun* | **Co-Supervisor:** *C. Heinis* | **Industry Mentor:** *W. Czechtizky* |

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| **Project Title (related to WP1 ):** Ultrahigh throughput property screening of self-encoded MC libraries | | |
| **Objectives:** (1) Generate a general synthesis and screening workflow for combinatorial macrocycle libraries (incl. tandem MS-based decoding strategy). (2) Produce a diverse set of tandem MS encoded MC libraries (10^3 – 10^8 members). (3) Combinatorial screen of building block related properties with the 1000-member libraries (cell penetration via PAMPA and proteolytic stability). (4) Affinity enrichment of binders for disease relevant RNA-binding proteins.<br>**Methodology**: (1) Establish solid phase synthesis and macrocyclization of the libraries. (2) Develop robust quality control assays for the in-solution libraries (3) Develop MSMS based decoding (combining nanoLC-MS/MS on an Orbitrap and *de novo* MS decoding software such as PEAKS or Sirius). (4) Establish property screening assays (e.g. PAMPA with 1000 compounds at a time) (5) Perform affinity selection against RNA binding properties and validate hit compounds | | |
| **Expected Results:** (1) Improved understanding which building blocks and chemistries in macrocycles lead to 'druglike' properties (2) High affinity binders for disease relevant RNA binding proteins and immunophilins | | |
| **Planned secondment(s):** (1) **UCL**, *A. Tabor*, M15-16: Multi-protection chemistry for library generation; **EPFL**, *C. Heinis*, M29-M30: MC chemistry for libraries; (2) **AZ**, *W. Czechtizky*, M31-M32: Test MCs on AZ-relevant RNA-protein targets. | | |

| **Fellow: DC10** | **Host institution: Sanofi** | **Apply to:** |
|---|---|---|
| **Supervisor:** *S. Ruf* | **Co-Supervisor:** *F. Hausch* | **Industry Mentor:** *M. Mendez Perez* |
| **Project Title (related WP):** Late-stage functionalization methodologies for the synthesis and derivatization of MCs (WP2) | | |
| **Objectives:** (1) Systematic exploration of C-H activation, photochemical and electrochemical methods for the synthesis of MC, especially the macrocyclization step; (2) Selective modification of aliphatic or heteroaromatic residues in MCs and introduction of side chains by late-stage functionalization; (3) Deliver matched molecular pairs of MCs based on variations in linkers to assess the impact on ADME properties, exemplified for FKBP and Cyp-based scaffolds.<br><br>**Methodology:** (1) Photoinduced decarboxylative radical addition; (2) Photo-redox Ni catalyzed C-N cross coupling; (3) Novel electrochemical reaction protocols; (4) Late-stage functionalization methodologies via electro-/photochemical approaches to introduce $CF_3$-substituents; (5) Introduction of methyl groups, fluorine atoms and explore C-H activation by Rh-catalyzed additions of carbene residues; (6) In-silico analyses of conformational ensembles of the MCs. | | |
| **Expected Results:** (1) Novel late-stage functionalization toolbox of photo-/electrochemical reactions for the rapid construction and derivatization of MCs; (2) Improved macrocyclic inhibitors for FKBPs or Cyps; (3) Transfer of methods to other target classes. | | |
| **Planned secondment(s):** (1) **UoY**, *W. Unsworth*, M11-12: Combination of photo/electrochemical synthesis with cascade-ring expansion approaches; (2) **GUF**, *S. Knapp*, M23-24: Application of photo/electrochemistry to macrocyclic kinase inhibitors; (3) **TUDa**, *F. Hausch*, M37-38: Testing and co-crystallization of synthesized MCs for binding to FKBPs & Cyps | | |

| **Fellow: DC11** | **Host institution: AstraZeneca** | **Apply to:** |
|---|---|---|
| **Supervisor:** *W. Czechtizky* | **Co-Supervisor:** *J. Kihlberg* | **Industry Mentor:** *S. Schiesser* |
| **Project Title (related to WP5):** Expanding the druggable space of MCs to protein/RNA interactions – identify suitable protein/RNA interfaces and discover MCs which can bind and modulate disease-associated RNAs | | |
| **Objectives:** (1) Discover and optimize macrocyclic inhibitors of disease-associated RNA/protein interactions. (2) Investigate binding mode and cellular potency of MCs.<br>**Methodology**: (1) Select RNAs with peptide/protein interfaces, where the protein/peptide can be mimicked by a MC; (2) *De novo* synthesis of MCs, VS within AZ and collaborator´s MC library, or phage display selection of macrocyclic binders to selected RNA structures; (3) Validation of discovered binders via SPR/ITC/ASMS; (4) Investigation of MC/RNA binding site using NMR and/or X-ray crystallography; (5) Affinity optimization of macrocyclic hit to RNA; (6) Biologic effect assay(s) and benchmarking against state-of-the-art methodologies to modulate RNA biology. | | |
| **Expected Results:** (1) Learn how to analyze peptide/protein-RNA interfaces regarding binding motifs and pharmacophore patterns; (2) Understand if we can *de novo* design or experimentally identify MCs that mimic proteins or peptides in their binding to RNA; (3) Demonstrate binding and functional effect of macrocyclic binders to RNA; (4) Generate a better understanding if we can design macrocyclic modulators of RNA function. | | |
| **Planned secondment(s):** (1) **TUDa**, *F. Hausch*, M34-35: Affinity optimization of discovered MCs; (2) **UU**, *M. Erdelyi/J. Kihlberg*, M36-42: Elucidation of NMR structure of MC-RNA complexes & solution conformation of MCs. | | |

| **Fellow: DC12** | **Host institution: Abbvie** | **Apply to:** |
|---|---|---|
| **Supervisor:** *F. Pohlki* | **Co-Supervisor:** *F. Hausch* | **Industry Mentor:** *C. Hoft* |
| **Project Title (related to WP3):** Brain penetrant MCs for CNS Drug Discovery | | |
| **Objectives:** (1) Systematically explore the effect of key structural and physicochemical parameters such as ring size, ring conformation, hydrogen bond donors and acceptor count and lipophilicity on brain penetration of macrocyclic model substrates; (2) Generate a comprehensive set of in silico and in vitro parameters for a set of MCs and selected acyclic analogues; (3) Investigate brain pharmacokinetics of selected compounds with appropriate properties.<br>**Methodology**: (1) Define a set of macrocyclic model substrates spanning a range of key structural and physicochemical parameters; (2) Characterize structural and physicochemical properties in silico and experimentally (NMR-based structure conformational studies in collaboration with Mate Erdelyi for a subset of MCs); (3) Generate in vitro data on permeability and efflux substrate properties using cellular models: Caco2, MDCK (+MDR1 & BCRP efflux transporters); (4) for a selected subset of compounds, use mouse PK cassette studies to determine in vivo brain/plasma ratio, absolute brain and plasma compound levels, and determine unbound free fraction in brain homogenate to calculate Kp,uu,brain. (5) Determine the desired property space for brain penetrant macrocycles by analyzing relationships between endpoints determined above, e.g. SAR | | |

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| (relationship between structural or physicochemical properties and in vitro permeability / efflux or in vivo brain penetration), and in vitro – in vivo (relationship between in vitro permeability / efflux and and in vivo brain penetration) |
| **Expected Results:** (1) Improved understanding of structural and physicochemical parameters, as well as in vitro properties determining brain penetration of macrocyclic drugs; (2) dataset for efflux properties of MCs |
| **Planned secondment(s):** (1) **UniTO**, *G. Caron*, M16-18: Measurement of chameleonicity of brain-permeable MCs. (2) **TUDa**, *F. Hausch*, M31-33: Synthesis of analogues of brain-permeable MCs. |

| **Fellow: DC13** | **Host institution: EPFL** | **Apply to:** |
|---|---|---|
| **Supervisor:** *C. Heinis* | **Co-Supervisor:** *S. Pomplun* | **Industry Mentor:** *W. Czechtizky* |
| **Project Title (related to WP1):** Synthesis and screening of large MC compounds libraries | | |
| **Objectives:** (1) Identify MCs for challenging targets (e.g. FKBPs, Cyps, RNA). (2) Optimize obtained MCs into drug leads. **Methodology**: (1) Design and synthesis of target-tailored libraries comprising ten-thousands of MCs using an approach recently developed in the Heinis group (combinatorial synthesis of MCs at a nanomole-scale using acoustic reagent transfer, and screening of crude reactions); (2) Screening the MC libraries against relevant model targets using biochemical assays; (3) Characterize the MCs (affinity, selectivity, membrane permeability, cellular activity). | | |
| **Expected Results:** (1) Validation/improvement of methods for combinatorial synthesis of large MC compound libraries; (2) High affinity inhibitors of multiple protein-protein interaction targets; (3) Drug leads for important disease targets. | | |
| **Planned secondment(s):** (1) **AZ**, *S. Schiesser*, M16-M18: Testing of macrocyclic libraries for RNA binding; (2) **TUDa**, *K. Schmitz*, M33-M36: Structural & biochemical characterization of macrocyclic libraries & hits for FKBPs and cyclophilins. | | |

| **Fellow: DC14** | **Host institution: ETHZ** | **Apply to:** |
|---|---|---|
| **Supervisor:** *S. Riniker* | **Co-Supervisor:** *M. Erdelyi* | **Industry Mentor:** *C. Kroll* |
| **Project Title (related to WP4):** Computational characterization of MCs conformations and connection to permeability | | |
| **Objectives:** (1) Characterization of the structure-permeability relationship of the (peptidic and non-peptidic) MCs in the selected subset (from WP3) using extensive MD simulations in different environments and comparison with NMR data (with UU Erdelyi); (2) Development of novel conformation- and environment-dependent 3D descriptors based on the MD simulations; (3) Refinement of models for permeability prediction for MCs using the novel MD-based descriptors. **Methodology**: (1) MD simulations in different environments (mono/biphasic, membrane); (2) Extraction of relevant features to describe dynamics; (3) Construction of kinetic models and comparison with experimental NMR, solubility and permeability data; (4) Development of MD-based 3D descriptors; (5) Training of ML models to predict permeability of MCs using MD-based descriptors. | | |
| **Expected Results:** (1) Generalized computational workflow to characterize the conformational behavior of peptidic as well as non-peptidic MCs; (2) MD-based 3D descriptors for MCs; (3) Refined ML approach for permeability prediction of MCs. | | |
| **Planned secondment(s):** (1) **Roche**, *C. Kroll*, M10-M12: Experimental determination of PAMPA permeability coefficients for MC library. (2) **UU**, *M. Erdelyi*, M18-M24: Conformational studies by NMR experiments. (3) **Bayer**, *D. Barber*, M31-33: Conformational sampling of MCs. | | |

| **Fellow: DC15** | **Host institution: Roche** | **Apply to:** |
|---|---|---|
| **Supervisor:** *S. Kroll* | **Co-Supervisor:** *S. Riniker* | **Industry Mentor:** *S. Schadt* |
| **Project Title (related to WP3&4):** Refinement of *in silico* methods for permeability prediction of peptidic MCs through experimental validation | | |
| **Objectives:** (1) Generate data (PAMPA, logD) for MC library in WP3; (2) Apply models and methods that aid optimization of MCs for drug-like properties, especially permeability; (3) Increase throughput of computational methods, e.g. by combining with trained AI/ML models to enable design of entire libraries with privileged properties; (4) Increase predictivity of computational calculations (e.g. 3D-PSA) to act as surrogates for actual assays. **Methodology**: (1) Synthesize MC derivatives with known biological activity (e.g. from WP1) and assess permeability in assays such as PAMPA, Lipophilic Permeability Efficiency, ePSA, cellular permeability; (2) Combine obtained data with short MD simulations and structural descriptors to train AI models for permeability prediction; (3) Iteratively improve predictions and derive design principles; (4) Generate novel molecules based on newly derived design principles. | | |
| **Expected Results:** Demonstrate impact on project-relevant MCs with biological activity, ideally derive generalizable design principles that hold across series. | | |
| **Planned secondment(s)**: (1) **ETHZ**, *S. Riniker*, M.13-15: 3D conformation-based computational methods. (2) **UU,** J. Kihlberg & M. Erdelyi, M25-27: Define design principles & experimental analysis of conformation. | | |

| **Fellow: DC16** | **Host institution: University of York** | **Apply to:** |
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| **Supervisor:** *W. Unsworth* | **Co-Supervisor:** *A. Tabor* | **Industry Mentor:** *S. Vuklelić* |
| **Project Title (related to WP2):** High throughput synthesis and screening to identify cell permeable MCs | | |
| **Objectives:** Use of novel cascade ring expansion methods to prepare MCs with skeletal diversity. **Methodology**: (1) Synthesis of precursors with suitable starting functional groups to prepare macrocycles containing, e.g. lactone, lactam, amine and aza heterocyclic motifs ; (2) Exploration of cascade ring expansion conditions with focus on broad applicability; (3) Exploration of building block approaches for faster assembly on substrates and MCs; (4) Generation of focused libraries of MCs; (5) Optimization after property (WP3 & 4) and activity (WP5) feedback. | | |
| **Expected Results:** (1) Versatile platform for MC generation and diversification; (2) Library of high-quality MCs as a resource for WP3 and future screenings; (3) Novel cell-permeable MCs with improved properties. | | |

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| **Planned secondment(s):** (1) **ABBV**, *S. Vuklelić*, M20-M22: ADME measurements for cascade ring-expanded MCs; (2) **UCam**, *D. Spring*, M23-M25: Integration of diversity-oriented chemistry into cascade ring expansion syntheses. | | |
| | | |
| **Fellow: DC17** | **Host institution: University College London** | **Apply to:** |
| **Supervisor:** *A. Tabor* | **Co-Supervisor:** *W. Unsworth* | **Industry Mentor:** *S. Güssregen* |
| **Project Title (related to WP2):** Low-peptide MC libraries displayed on privileged scaffolds for cell permeability | | |
| **Objectives:** Methodology development, generation, screening and analysis of low-peptide, cyclophilin-targeted MCs<br>**Methodology:** (1) Synthesis of orthogonally protected building blocks containing thioether linkages to give Cyp-targeted scaffolds by solid phase macrocyclization; (2) synthesis of precursors with functional groups to give sangliferin-inspired Cyp-targeted scaffolds; (3) solid-phase synthesis of scaffolded MC displaying tripeptide and depsipeptide sequences, including Cyp-preferring piperazic acid and ΨPro; (4) generation and screening of diverse scaffolded MC libraries. | | |
| **Expected Results: (**1) novel, versatile MC libraries combining privileged non-peptidic scaffolds with minimal peptide display; (2) improved Cyp ligands (resource for WP5); (3) datasets with structural and ADME data for WP3. | | |
| **Planned secondment(s):** (1) **UU**, *M. Erdelyi*, MD simulations & NMR characterization of selected MC, M23-M24; (2) **Sanofi,** *S. Güssregen*, Modelling of constraint MCs, M29-M30; (3) **LU**, *S. Pomplun*, Scaffold-MCs for ASMS, M31-M32. | | |

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