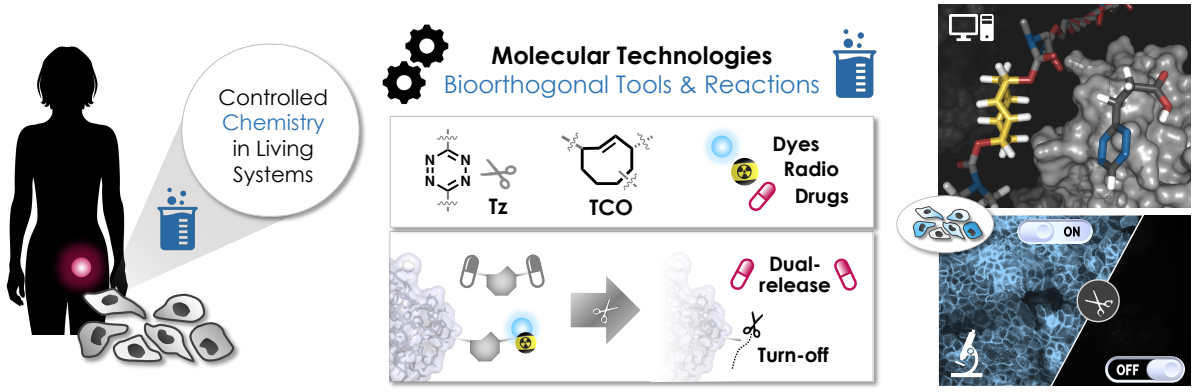
# BIOORTHOGONAL TURN-OFF AND DUAL-RELEASE




## Supervisory Team[1]

**Primary Supervisor:** *Hannes Mikula, Institute of Applied Synthetic Chemistry, TU Wien*

**TU Wien project partners:** *Ruth Birner-Grünberger, Institute of Chemical Technologies and Analytics; Peter Ertl, Institute of Applied Synthetic Chemistry; Martina Marchetti-Deschmann, Institute of Chemical Technologies and Analytics; Gerhard Schütz, Institute of Applied Physics*

**External academic partners:** *Jonathan Carlson, MGH & Harvard Medical School*

**External industry partners:** *Marc Robillard, Tagworks Pharmaceuticals*

## Project Description

This PhD project focuses on the development of bioorthogonal bond-cleavage reactions with unmatched chemical performance and unique capabilities. The candidate will design, prepare and investigate next-generation chemical tools that achieve exceptional reaction kinetics, high stability, selectivity and biocompatibility. These tools will allow the candidate to perform controlled chemical reactions in complex biological environments and thus in situ transformations that drive multiple (bio)molecular technologies to study and control biological systems. Inspired by our recent findings (https://doi.org/10.1021/jacs.0c07922), we aim to achieve ultrafast molecular disassembly in living cells to develop unprecedented methods for cellular profiling. The candidate will moreover design strategies that build on our unexpected discovery of 'dual-release', enabling a new concept in the field of bioorthogonal chemistry, in particular for (i) traceless cleavage and (ii) the targeted activation of caged drug conjugates. This research will be carried out in collaboration with external partners from academia and industry (with optional internships), providing the candidate an outstanding scientific environment to achieve the goals of this interdisciplinary PhD project at the interface of chemistry and biology.

[1] The Early Stage Researchers (ESRs) will be accompanied during their thesis by an individual "Thesis Advisory Committee" (TAC), which will guide the ESR through the graduate studies. The TAC will consist of the thesis primary supervisor, and two additional members of the Supervisory Team selected by the ESR.

## Key Goals and Tasks

The primary aim of this PhD thesis is the **design, synthesis and characterization of new bioorthogonal tools**, in particular modified 1,2,4,5-tetrazines and *trans*-cyclooctenes. The candidate will incorporate these tools into several molecular designs and prepare **chemical probes** to investigate reaction performance and capabilities, with emphasis on kinetics, efficiency and stability. Orthogonal conjugation chemistries will be used to attach fluorescently labeled compounds to targeting ligands such as antibodies or antibody fragments. These constructs will be investigated in **cell culture experiments** (incl. molecular imaging, fluorescence microscopy and *in vitro* assays), aiming for ultrafast (bio)molecular disassembly to achieve **bioorthogonal turn-off** in living systems. The underlying mechanisms of dual-release will be explored in detail, ultimately to develop probes and caged drug conjugates to study **traceless bioorthogonal cleavage and targeted drug activation**.

## Project-specific Requirements

- Completed master studies in chemistry, chemical biology, or a closely related field
- Knowledge on organic chemistry, advanced synthetic methods, functional group transformations, click chemistry, analytical chemistry
- Experience and skills in synthetic chemistry, compound purification/characterization, state-of-the-art analytical techniques (NMR, HPLC, MS, spectrophotometry, etc.), data analysis, chemical software
- Interest in cell culture experiments (mainly human cancer cell lines), *in vitro* assays, fluorescence microscopy, molecular imaging
- Enthusiasm for bioorthogonal chemistry, diagnostics, therapeutics, and, in general, for interdisciplinary research at the chemistry/biology interface
- Affinity for molecular design strategies, unraveling and application of new reaction mechanisms, chemical tool development
- Willingness to travel to project meetings with international collaborators and to present results at scientific conferences. Research visits to partner organizations are optional.
- Highly proficient in spoken and written English
- Personal skills: Ability to work in a team, but also to perform the required research independently; excellent communication, time-management and problem-solving skills