Gerard Roelfes
University of Groningen

Meeting 1
Eindhoven, 26th March 2019

Stratingh Institute for Chemistry

Innovative Training Networks (ITN) – Marie Skłodowska-Curie Actions
H2020-MSCA-ITN-2017 (THERACAT-765497)

Institution description

The mission of the Stratingh Institute for Chemistry is to perform excellent research and teaching in molecular and supramolecular chemistry.

Core activities in the chemical sciences such as bioorganic chemistry, organic chemistry, molecular inorganic chemistry and molecular materials chemistry are embedded in the institute. The research programme is focussed on synthesis, catalysis, functional materials, bio-organic chemistry/chemical biology and systems chemistry/complex molecular systems.

14 research groups

Biomolecular Chemistry & Catalysis – Prof. Gerard Roelfes

Interface Chemistry/Biology, with a focus on bioinspired catalysis

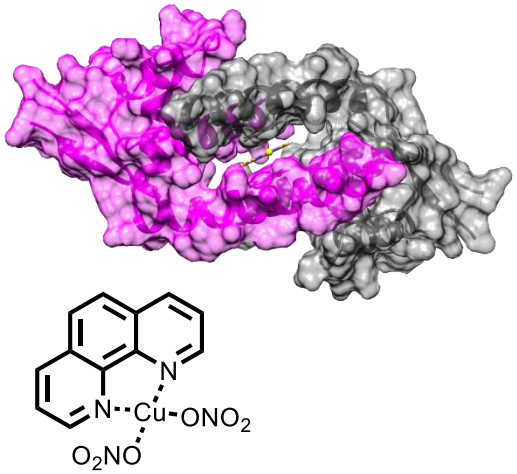
Research topics:

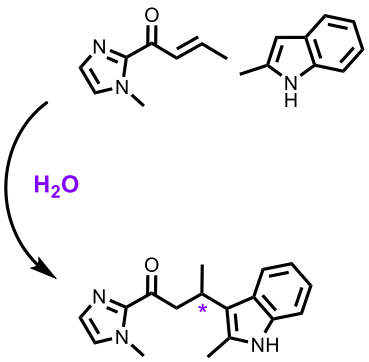
- *Design of (artificial) enzymes*
- *Bio-orthogonal catalysis*
- *Catalytic chemistry in living cells*

Current composition:
1 PI, 7 PhD students,
2 postdocs, 3 MSc students

Selected Past Research Results

Artificial enzymes / enzyme design

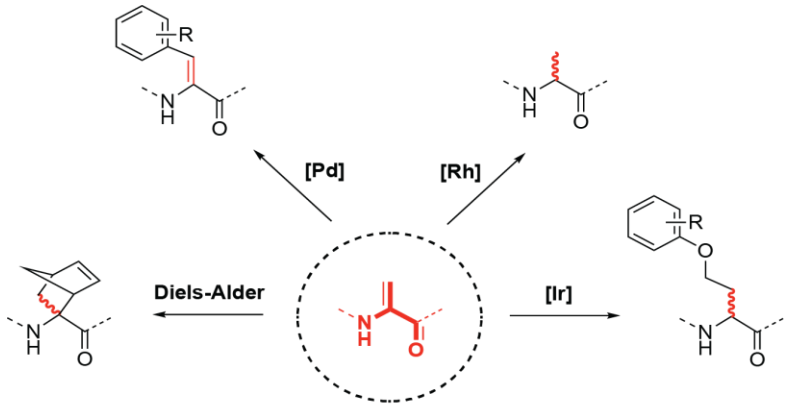




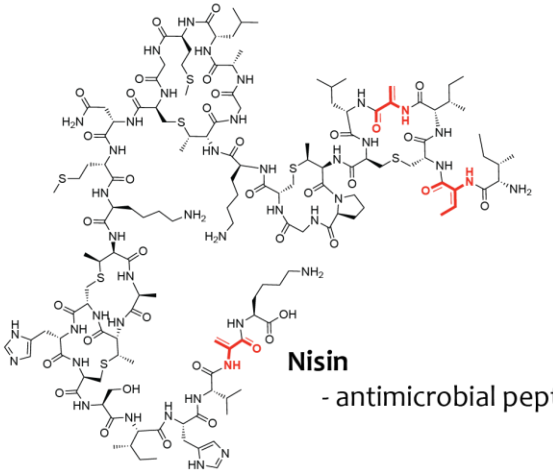
Friedel - Crafts

Acc. Chem. Res. **2019**, *52*, 545.

Bioorthogonal catalysis



dehydroalanine
- natural amino acid
- unnatural catalysts for specific modification



Nisin
- antimicrobial peptide

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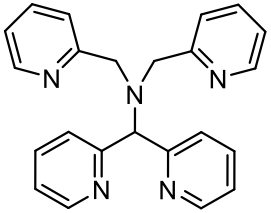
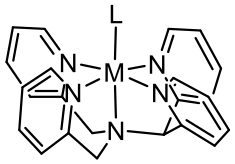


N4Py

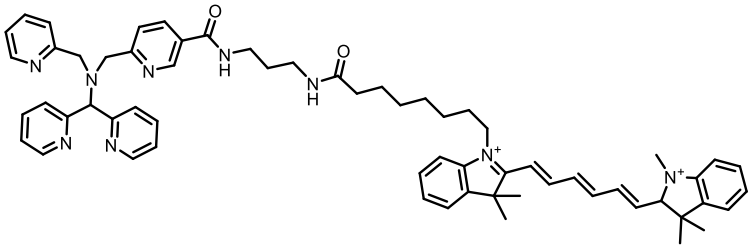


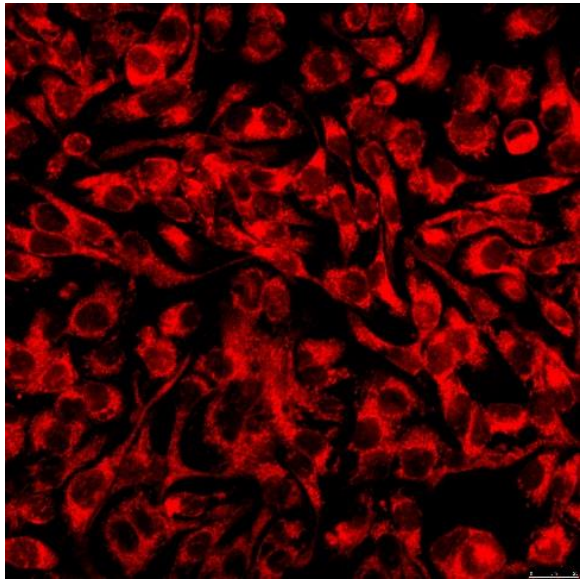
Metal-N4Py complex

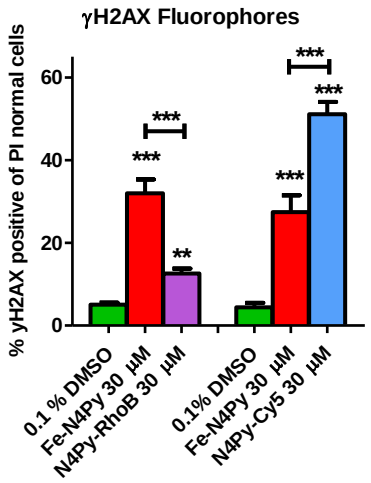
M = Fe(II), Cu(II), Mn(II), Zn(II) ; L = CH_3CN

M = Fe(III) ; L = CH_3O^-

Fe-N4Py produces hROS in cells







With M.G. Rots (University Medical Center Groningen);
ACS Chem. Biol. 2014, 9, 1044;
Inorg. Chem. 2018, 2018, 57, 7748-7756
In preparation.

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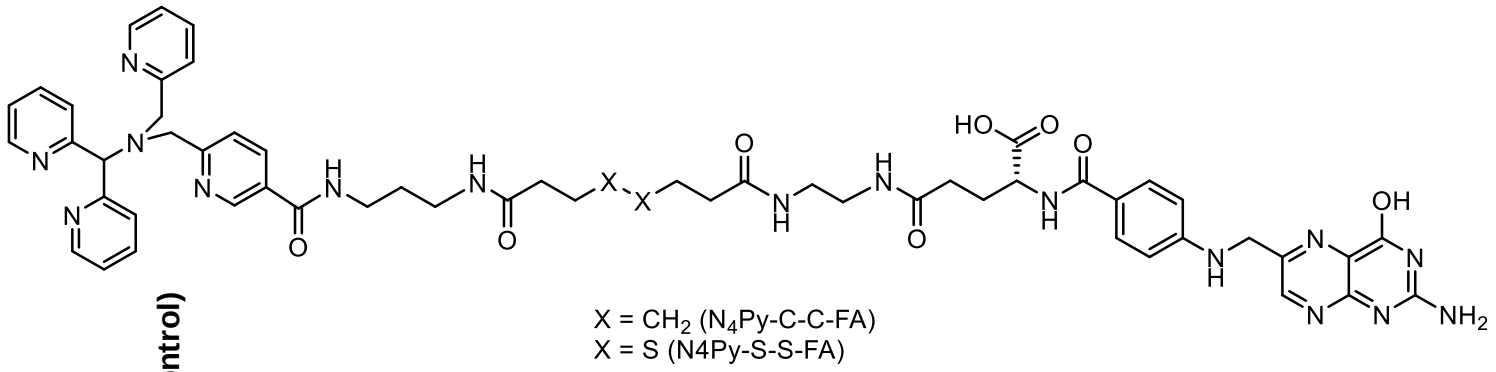
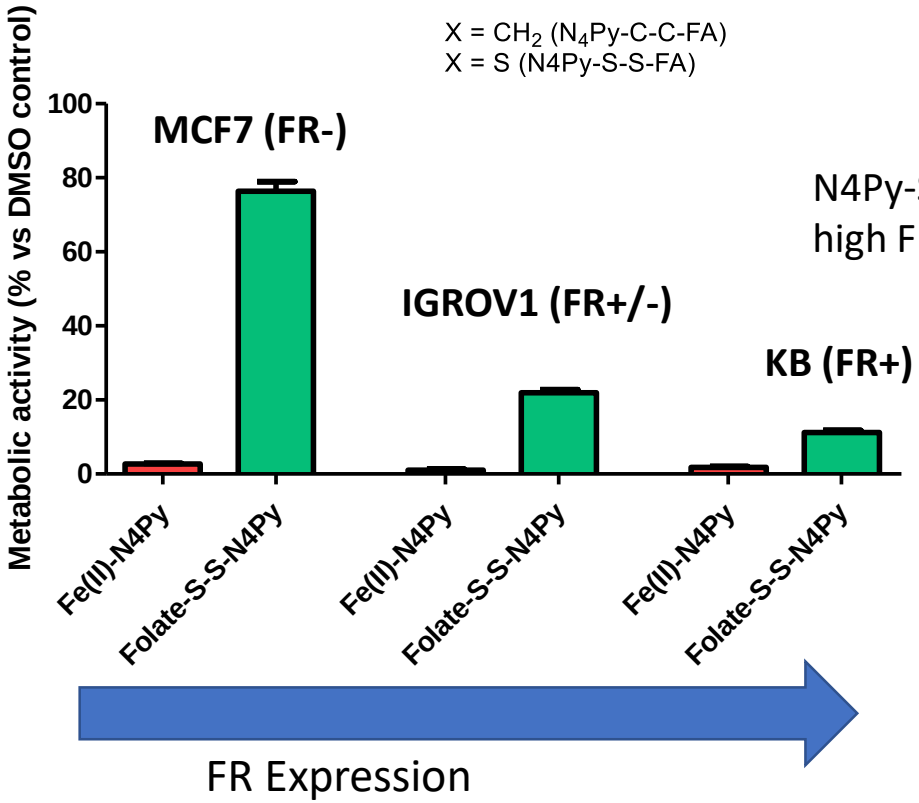
Selected Past Research Results



X = CH_2 (N_4Py-C-C-FA)
X = S (N4Py-S-S-FA)



N4Py-S-S-FA conjugate towards cells with high FR-expression

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Recruitment

ESR1: Bio-orthogonal catalysis for the catalytic activation of cancer drugs

Job position advertised on:

Euraxess: Job id 322936
Websites:
www.academictransfer.com
www.rug.nl
www.noorderlink.nl

Number of Applicants: ~30

Applicants Interviewed: 2 (4 invited)

Name of selected researcher: Michela Vargiu

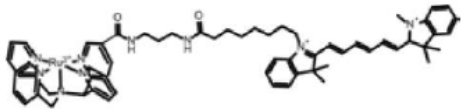
Contract start date: 01/01/2019

Contract end date: 31/12/2022

ESR 1 - GRO	Novel Ru and Pd Complexes of Polypyridine for Catalysis in Living Cells	PhD: Yes	Deliv.: 3.1, 5.1	Start date: M6	Duration 36	WP3

Objectives: **1.** Development of Ru and Pd complexes for catalytic uncaging of prodrugs in cancer cells; **2.** Synthesis of targeted metal complexes by conjugation to targeting moieties; **3.** Development of light activable Ru complexes for spatial and temporal control over catalytic uncaging of prodrugs.

Description: In this project, we aim to develop Ru(II) and Pd(II) complexes of polypyridine ligands for catalytic uncaging of anti-tumour drugs in cancer cells. Metal complexes of polyridyl ligands such as phenanthroline, terpyridine, TPA and N4Py are of interest because of their broad catalytic scope and, as recently shown in our group, are efficiently taken up by cancer cells. Moreover, targeting to specific cellular location can be achieved by conjugation to hydrophobic dyes targeting, for example, the mitochondria. We will prepare a variety of Ru(II) and Pd(II) complexes and investigate them in uncaging of prodrugs, first in model reactions and then in vitro. When required, the complexes will be incorporated in delivery vehicles such as single chain polymer nanoparticles, micelles and lipidic nanoparticles developed in WP3. Finally, light activable variants of active Ru(II) complexes will be prepared and tested by ligation of nitrile ligands to the open coordination sites, which can be dissociated by light irradiation.



Planned secondments: EDI – Prodrug uncaging in vitro (M12, 3 months); **TEVA** – Formulation (M24, 3 months).	**Expected results (deliverables)**: Pd and Ru complexes for catalytic uncaging of prodrugs (D3.1); specific targeting of complexes to cellular location (D5.1); light activable Ru complexes for uncaging of prodrugs (D3.1)

Supervisor: Prof. J.G. Roelfes

Recruitment completed

WP3: Prodrugs design and synthesis

Task 3.1. Synthesis of palladium (TUE) and ruthenium (GROj, ESR 1) complexes for dye/drug uncaging.). **Started**

D3.1 : Novel metal complexes for bio-orthogonal catalysis. *Delivery Month 16*

Schedule of relevant Milestones

Milestone number[18]	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification
MS8	Synthesis of the first catalyst	3 - GRO	18	Spectroscopic characterization and activity test