UniBas Presentation

Thomas R. Ward
https://www.chemie.unibas.ch/~ward

Meeting 1
Eindhoven, 26th March 2019

Institute for Bioengineering of Catalonia
Nanoscopy for nanomedicine group

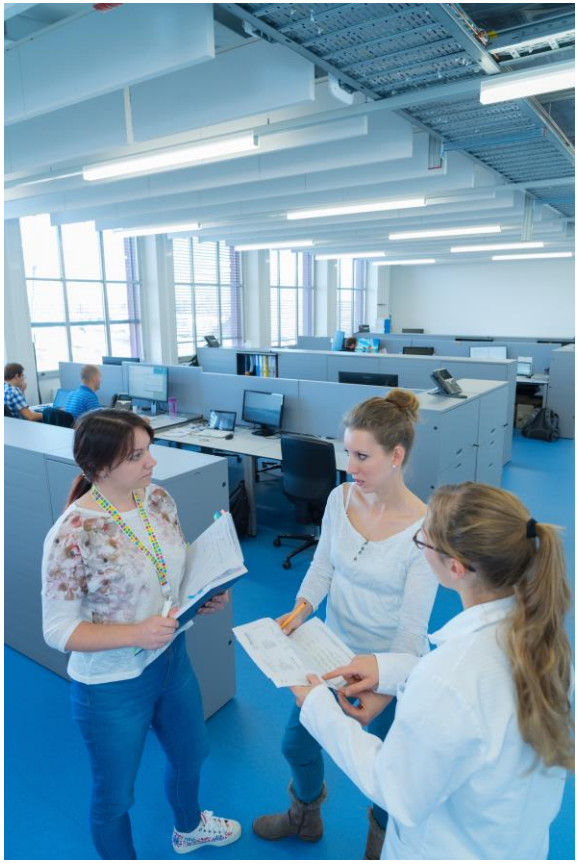
Innovative Training Networks (ITN) – Marie Skłodowska-Curie Actions
H2020-MSCA-ITN-2017 (THERACAT-765497)

The University of Basel

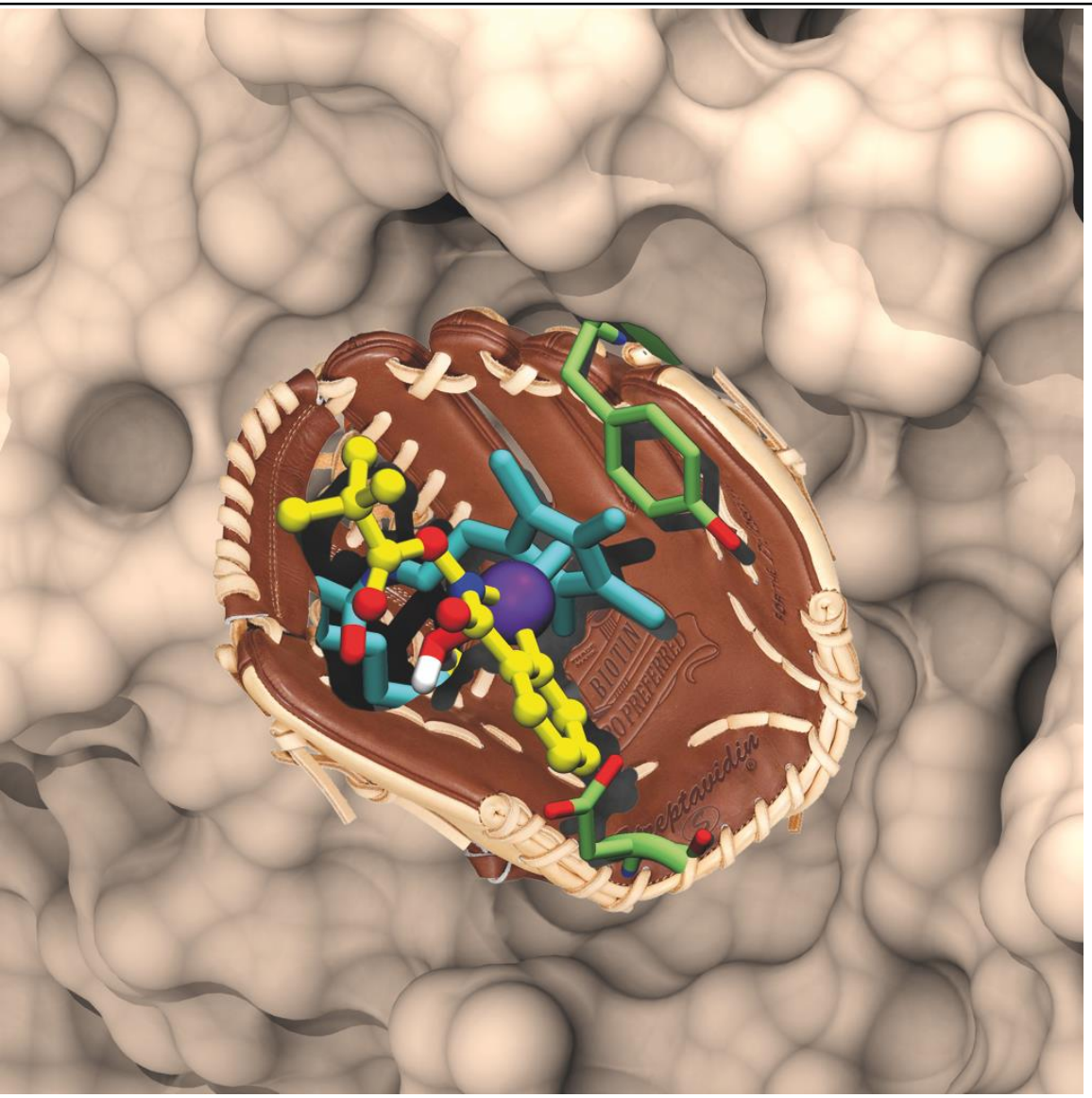
- The Basel Hub is the World's Headquarter of Life Sciences: Roche, Novartis, Actelion, Lonza, Syngenta etc
- University of Basel: oldest in Switzerland from Paracelsus to Wüthrich via Reichsten
- Dpt Chem. 15 Professors with a heavy focus on Life Sciences and Nanotechnology (15 mio CHF/year external funding); exceptional infrastructure, including newly renovated building
- Strong collaboration with the Bio-Systems Science Engineering Dpt of the ETHZ D-BSSE)
- Leading House of a National Centre of Competence in Research "Molecular Systems Engineering" (joint with the D-BSSE)
- Ward Group: 20 coworkers, (12 postdocs). Focus on *in vivo* catalysis and artificial metalloenzymes (Director of the NCCR Molecular Systems Engineering)

NCCR
Molecular Systems
Engineering

The University of Basel



The Ward Group in Short



- The Ward group is in the business of Artificial Metalloenzymes
- Rely on supramolecular interactions to accumulate a non-natural cofactor in a protein of interest
- Target a protein that is overexpressed on the surface of cancer cells to accumulate the abiotic cofactor
- The cofactor catalyzes the uncaging of a protected drug
- Multiple turnovers of the immobilized cofactor allow to selectively treat the cells that overexpress the protein of interest
- Currently, we focus on human Carbonic Anhydrase IX

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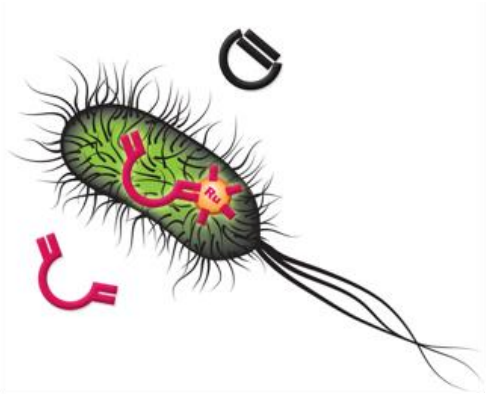
LETTER

doi:10.1038/nature19114

Directed evolution of artificial metalloenzymes for *in vivo* metathesis

Markus Jeschek[1], Raphael Reuter[2], Tillmann Heinisch[2], Christian Trindler[2], Juliane Klehr[2], Sven Panke[1]§ & Thomas R. Ward[2]§



Organic & Biomolecular Chemistry

PAPER View Article Online View Journal

CrossMark

Cite this: DOI: 10.1039/c5ob00428d

Carbonic anhydrase II as host protein for the creation of a biocompatible artificial metathesase†

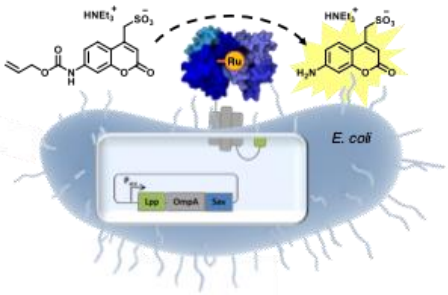
Chemical Science

EDGE ARTICLE

Cite this: DOI: 10.1039/c8sc00484f

E. coli surface display of streptavidin for directed evolution of an allylic deallylase†

Tillmann Heinisch,‡[a] Fabian Schwizer,‡[a] Brett Garabedian,[a] Eszter Csibra,[b] Markus Jeschek,[c] Jaicy Vallapurackal,[a] Vitor B. Pinheiro,[b] Philippe Marlière,[d] Sven Panke[c] and Thomas R. Ward*[a]



ARTICLE

DOI: 10.1038/s41467-018-04440-0 OPEN

A cell-penetrating artificial metalloenzyme regulates a gene switch in a designer mammalian cell

Yasunori Okamoto[1], Ryosuke Kojima[2,3], Fabian Schwizer[1], Eline Bartolami[4], Tillmann Heinisch[1], Stefan Matile[4], Martin Fussenegger[2] & Thomas R. Ward[1]

Recruitment at UniBas

ESR10: Targeting human Carbonic Anhydrase IX for Drug Release via Metathesis

Job position advertised on:

Euraxess: Job Offer id: 313142
Website:
https://www.chemie.unibas.ch/

Number of Applicants: 39

Applicants Interviewed: 3

Name of selected researcher: **Boris Lozhkin**

Contract start date: 1/12/2018

Contract end date: 30/11/2021

Supervisor: **Prof. Thomas R. Ward**

Recruitment completed

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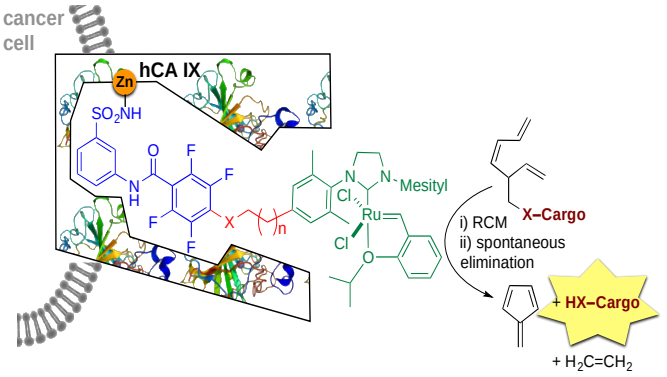
Recruitment at UniBas

ESR 10 - BAS	Targeting Human Carbonic Anhydrase IX for Drug Release via Metathesis	PhD: Yes	Deliv.: 3.1, 3.3	Start date: M9	Duration 36	WP3

Objectives: **1.** Identify metathesis catalyst activated upon binding to hCA IX; **2.** Uncage cargo (fluorophore or drug) by ring-closing metathesis; **3.** Fluorophore- or Drug-release by ring-closing metathesis on the surface of cancer cell overexpressing hCA IX.

Description: In the past decade, the Ward group has developed a series of artificial metalloenzymes for a variety of bio-orthogonal reactions. For this purpose, a catalyst precursor (green) is activated upon incorporation within a host protein (ribbon display) via a high affinity anchor (blue). We have shown in the past that i) hCA II is an outstanding host for the creation of artificial metathases and ii) artificial metathases are fully biocompatible, air stable and can be performed *in vivo*.[4] To target the tumour site, it is proposed to exploit hCA IX to specifically accumulate and activate a metathesis catalyst on the surface of cancer cells. With this goal in mind, the fluorinated sulfonamide anchor will be linked via a spacer (red) to a metathesis catalyst. Initial experiments will be carried out with diallyl-*N*-tosylamide as model substrate. Having identified an active metathesis catalyst for incorporation within hCA IX, the artificial metathase will be screened for its RCM activity towards an heptatriene substrate bearing either a caged fluorophore or a caged drug. Upon RCM, a spontaneous elimination occurs via an aromatic transition state, thus uncaging the fluorophore or the drug. For the synthesis of the triene substrates, ESR10 will spend three months at EDI. Having identified a suitable precatalyst, activated upon incorporation in hCA IX, experiments will be performed in the presence of cells overexpressing hCA IX on their cell surface. To facilitate its delivery to cancer cells, the catalyst precursor will be non-covalently incorporated in a variety of delivery vectors including:, hydrogels, micelles, SCNPs, lipidic NPs. For this purpose, ESR10 will spend 3 months at TEVA to adapt their NPs to the delivery of the metathesis catalyst.



Planned secondments: **EDI** – synthesis of caged prodrugs (M27, 3 months); **TEVA** – encapsulate catalyst in lipid NP (M36, 3 months).	**Expected results (deliverables)**: synthesis of five metathesis catalysts (D3.1); reactivity profile of two caged fluorophores and one drug uncaged upon RCM (D3.3); reactivity profile upon incorporation within hCA IX (D3.3)

Supervisor: **Prof. Thomas R. Ward**

Network Training Event in Basel

2 – Chemical synthesis & catalysis	M18, 5 days	2 ECTS	BAS
Content: This event will introduce the ESRs to the fundamental principles of designing the structure and synthesis of the prodrugs and the catalysts that will be studied throughput the project. It will also include an important chemical safety session.			
Catalysts and catalysis: from the synthetic utilization to artificial enzymes	**BAS** (T.Ward)	SCI	1 day
Prodrugs: design principles, synthesis and preliminary evaluation	**EDI** (A.Unciti-Broceta)	SCI	1½ day
Safety in chemical laboratories and research in industry and academia	**TUE** (A.Palmans)	LAB	1 day
How can we do better in bringing new molecules to the market: scaling up, formulations, regulations, procedures and economical aspects	**TEVA** (H.Barash)	SCI COMP	1 day
Entrepreneurship and translation: IP and commercial exploitation	**IBEC Tech Transfer**	COMP	1 day

- 23-27 September at Bildungszentrum in Basel: https://bz21.ch
- Workshops offered by Anja Palmans (24 IX 2019), Asier Unciti-Broceta (25 IX), Bianca Avramovitch (26 IX), Tom Ward (23 IX) + Tech Transfer (27 IX)
- PI meeting (25 IX)?

Update on UniBas Research Activities

WP3: In vitro delivery and imaging

Task 3.1. Synthesis of catalyst carriers bearing targeting ligands (UniBas-ESR10). **Started**

Task 3.3. Test the efficacy of prodrug conversion in 2D and 3D cancer models ligands (UniBas-ESR10).

WP4: In vivo evaluation

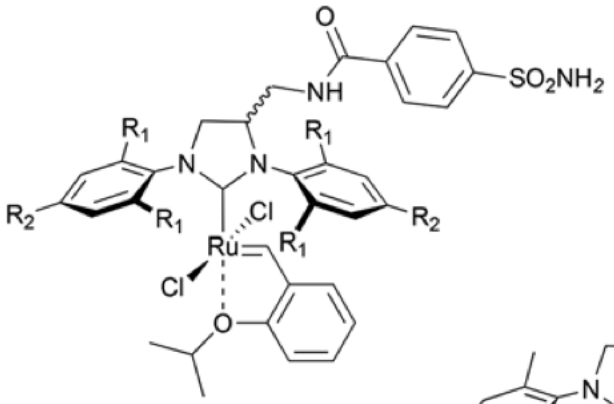
Task 4.3. Use intravital optical and PET imaging to study catalyst localization and efficacy (UniBas-ESR10).

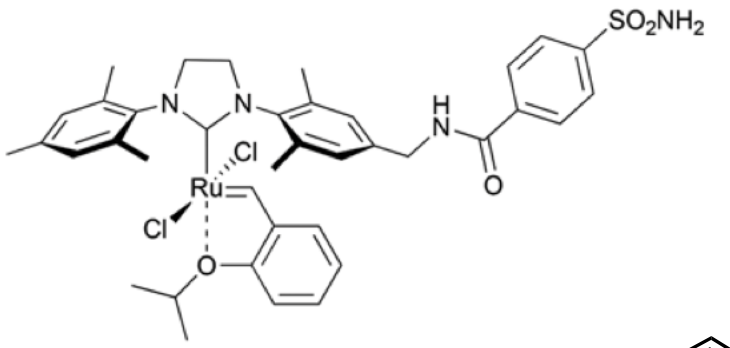
Deliverable 3.1 Synthesis of 5 metathesis catalysts (M. 18)

Deliverable 3.3 Reactivity profile of two caged fluorophores and one drug uncaged upon RCM (M 36)
Reactivity profile upon incorporation into hCA IX (M 36)

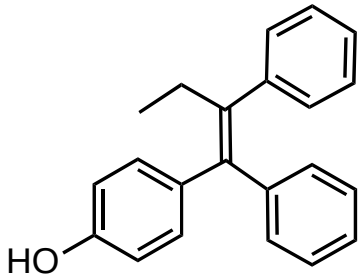
Secondments Synthesis of caged prodrugs EDI, 3 months M27-29,
Encapsulate catalyst in lipid nanoparticles TEVA 3 months M36-38

Update on UniBas Research Activities

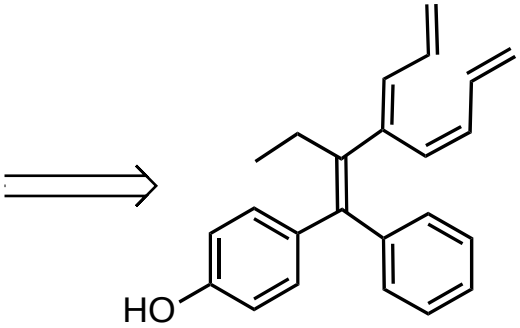




completed



tamoxifen



tamoxifen-precursor
(non-cytotoxic?)

well underway

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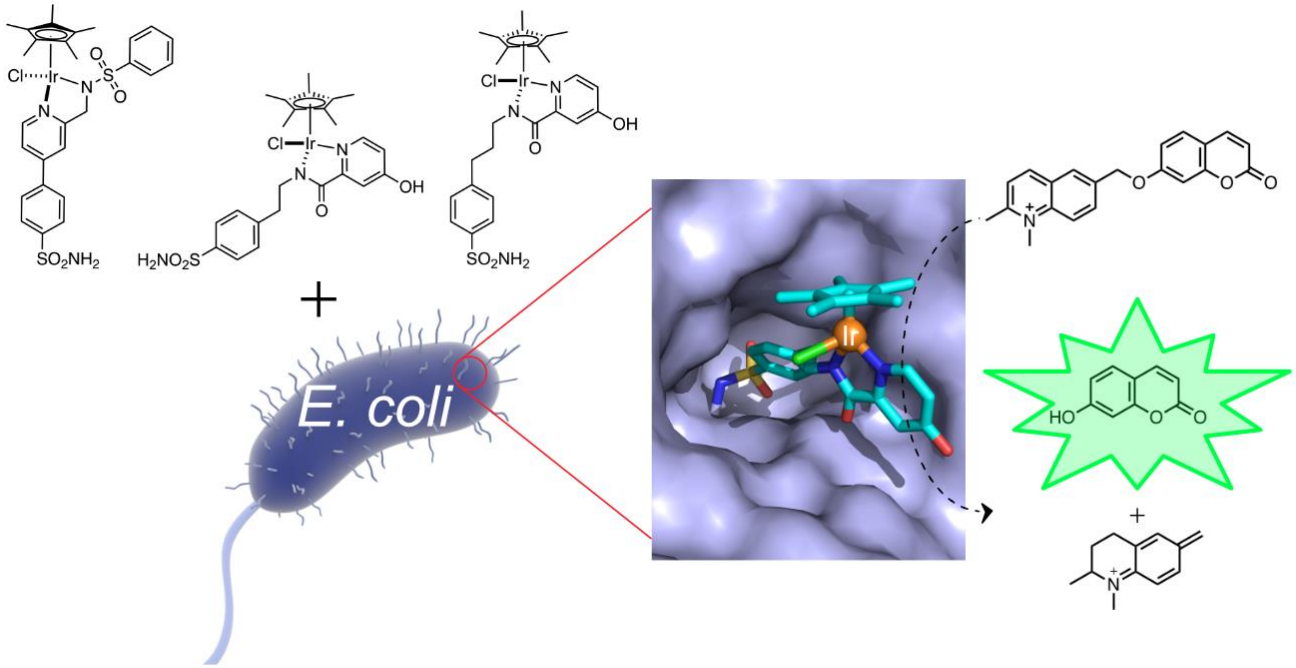
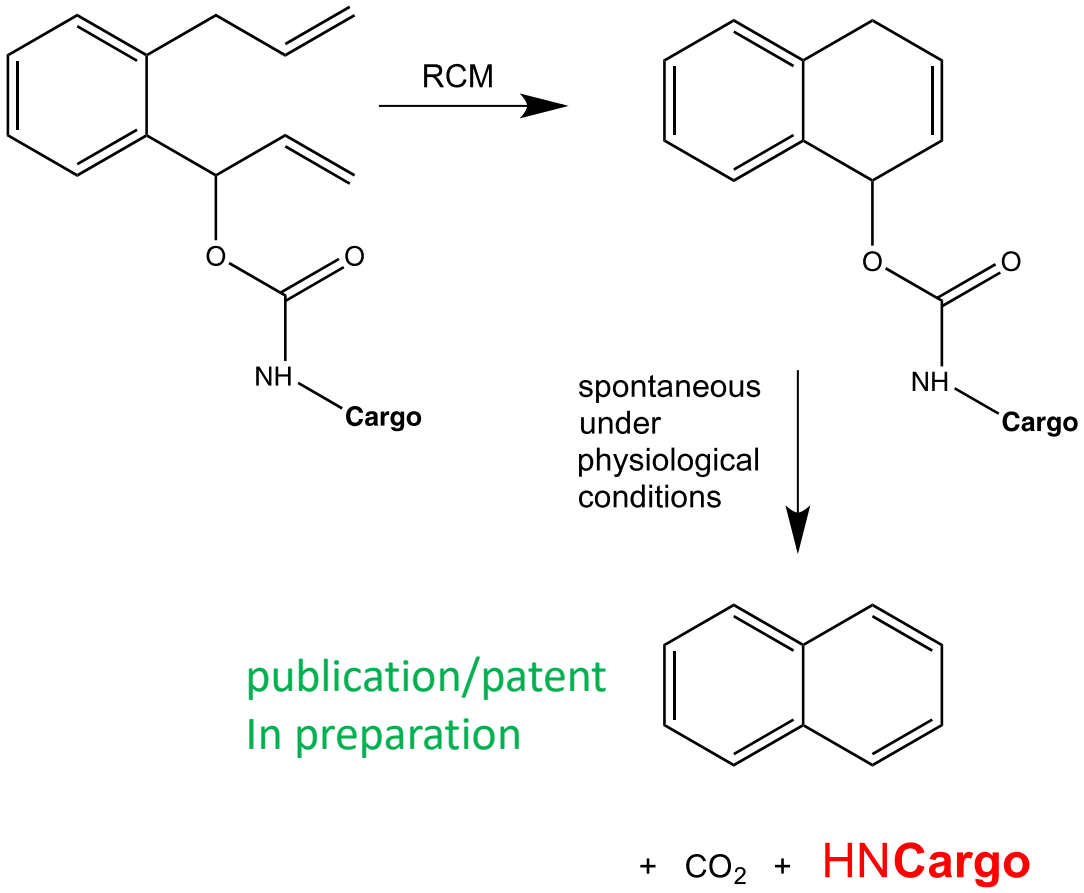
Update on UniBas Dissemination Activities



Publication submitted


RCM
O
O
NH
Cargo
spontaneous
under
physiological
conditions
publication/patent
In preparation
+ CO_2 + HNCargo

Training Courses:

1 – Chemical synthesis & catalysis. Month 18

Secondments at UniBas:

ESR4-TUE. Month 22 – 24 (3 months)
ESR12-TAG. Month 28 – 30 (3 months)

Organisation of Network Meetings & Conference:

Meeting 2. Month 18. Basel September 2019