EDI Presentation

Meeting 1
Eindhoven, 26th March 2019

Institute of Genetics & Molecular Medicine
Innovative Therapeutics Lab

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

Institution description

THE UNIVERSITY *of* EDINBURGH
Edinburgh Medical School

igmm
INSTITUTE OF GENETICS & MOLECULAR MEDICINE

Research group description

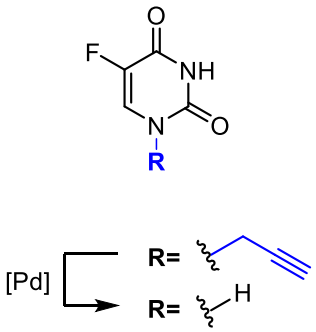
- ***The Innovative Therapeutics Lab*** *is head by Prof Asier Unciti-Broceta and based at the Cancer Research UK Edinburgh Centre, part of the Institute of Genetics & Molecular Medicine – University of Edinburgh.*

- ***It aims to develop novel chemical strategies to improve the efficacy and safety of cancer therapies***

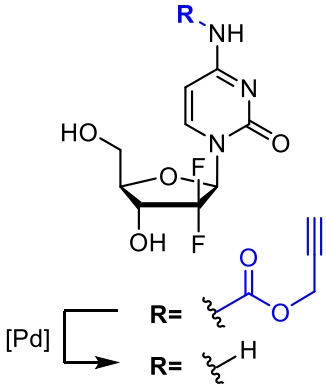
- ***Lab expertise lies in the interface of chemistry and biomedicine:*** *medicinal chemistry, organic synthesis, chemical biology, phenotypic assays, cell biology.*

- ***Main interests:*** *kinase inhibitors, prodrug development, sensors, nanomaterials, heterogeneous catalysts, target ID & target engagement, preclinical studies (outsourced)*

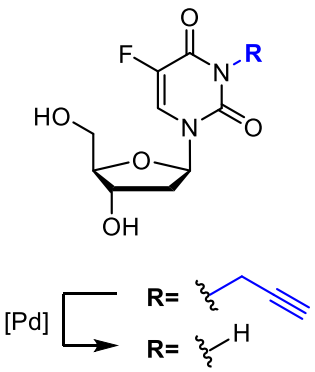
Selected Past Research Results



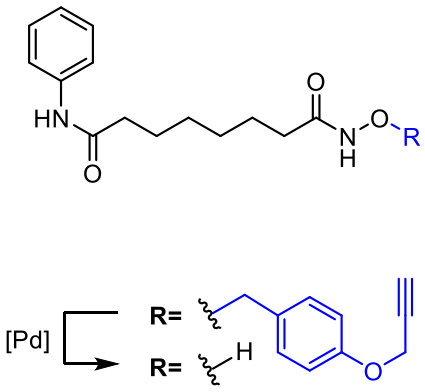
Nat. Commun. **2014**, *5*, 3277



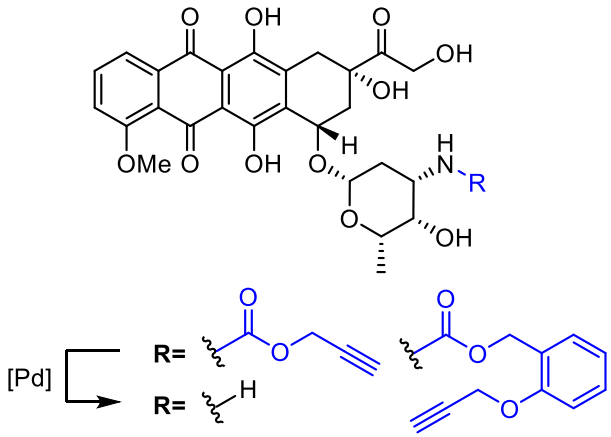
J. Med. Chem. **2014**, *57*, 5395



Sci. Rep. **2015**, *5*, 9329

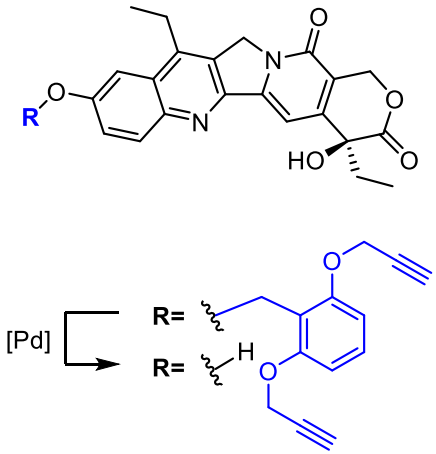


J. Med. Chem. **2016**, *59*, 9974



Angew. Chemie **2017**, *56*, 12548

Chem. Sci. **2018**, *9*, 7354-7361



Chem. Eur. J. **2018**, *24*, 16783-16790

Innovative Training Networks (ITN) – Marie Skłodowska-Curie Actions
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Recruitment

ESR5: Prodrug design and synthesis

Job position advertised on:

Euraxess: Offer ID 333581

Websites:

www.vacancies.ed.ac.uk

www.boomchemistry.com

www.findaphd.com

Number of Applicants: 18

Applicants Interviewed: 3

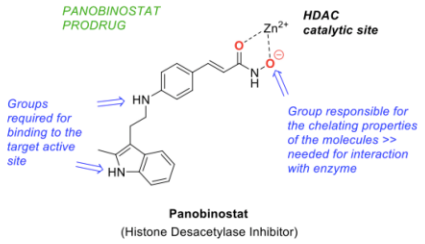
Name of selected researcher: **Stephen Croke**

Contract start date: 12/11/2018

Contract end date: 11/11/2021

ESR 5 - EDI	Prodrug design and synthesis	PhD: Yes	Deliv.: 2.1, 2.3	Start date: M6	Duration 36	WP2

Objectives: **1.**Synthesis of prodrugs; **2.**Validation of Pd-mediated drug release in vitro; **3.**Reduction of prodrugs' activity by 100-fold relative to parent drug; **4.**Demonstration of Pd-triggered release of the functional drug in cell culture.



Description: ESR5 will investigate the development of a series of biochemically-stable (= bio-orthogonal) prodrugs specifically designed to become active upon reaction with Palladium (Pd) catalysts. We will generate and test Pd-activated prodrugs using a range of Pd-labile protecting groups. Such studies will enable to expand the arsenal of chemotherapy drugs that can be exploited through this novel spatially-targeted strategy, including therapeutics that are either currently used in the clinic for melanoma and breast cancer treatment. To maximize the clinical impact of the strategy, Pd-labile prodrugs will be developed from a selection of therapeutics with different mode of actions, e.g. HDAC inhibitors (panobinostat), kinase inhibitors (dabrafenib and selumetinib) and alkylating agents (duocarmycin). Prodrugs' sensitivity to Pd will be tested using the methodology developed by ESR6. The efficacy of the deactivation strategy (= bio-orthogonality) will be determined by performing dose response studies with the prodrug and the parent drug in cancer cell lines, which will be followed by the study of the Pd-mediated release of each drug using standard phenotypic assays.

Planned secondments: TAG – Pro-imaging PET agents (M24, 4 months); **TAU** – Test micelles catalysts (M34, 3 months).	**Expected results (deliverables)**: Synthesis of 6-10 prodrugs (D2.1); Pd-mediated drug release ranked by reaction kinetics (D2.3); 2-4 prodrugs showing >100-fold reduction in activity (D2.3); Prodrug activation in cell culture (D2.3).

Supervisor: **Prof Asier Unciti-Broceta**

Recruitment completed

Recruitment

ESR11: Pd in vivo: implants and Pd-activatable tools

Job position advertised on:

Euraxess: Offer ID 332500

Websites:

www.vacancies.ed.ac.uk

www.boomchemistry.com

https://twitter.com/BOOMchemistry

www.findaphd.com

Number of Applicants: 12

Applicants Interviewed: 2

Name of selected researcher: **Melissa van de L'Isle**

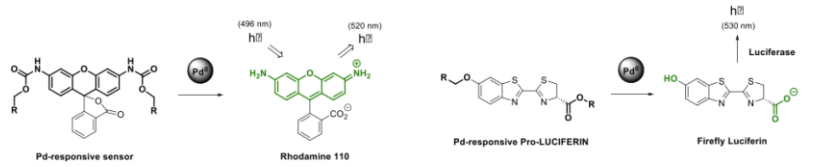
Contract start date: 01/02/2019

Contract end date: 31/01/2022

ESR 11 - EDI	Pd in vivo implants and Pd-activatable tools	PhD: Yes	Deliv.: 4.2 - 4.4	Start date: M9	Duration 36	WP4

Objectives: **1.**Synthesis of Pd-implants; **2.**Synthesis of probes; **3.**Validation of Pd-mediated activation in vitro; **4.**In vivo compatibility studies of Pd-implants; **5.**Demonstration of Pd-triggered probe activation in vivo.

Description: The student will develop novel implantable Pd-devices and a range of chemical tools that will allow us to evaluate the catalytic activity of metallic Pd *in vivo* (e.g. surgically-implanted in tumour xenografts or tissues) and expend its scope. To facilitate surgical implantations, Pd-devices of appropriate size (> 4mm) will be developed. ESR11 will investigate the manufacture of larger devices by physically merging them in an appropriate mould. To enable the localised use of naked Pd nanoparticles (NP), a novel technique will be tested in which NP are "bagged" in sealed sachets made out of dialysis tubing. The catalytic capabilities of Pd-implants will be investigated using Pd-responsive sensors prepared from well-established fluorescent, bioluminescent and chemoluminiscent reagents (see Figure) and tetrazines (for click-to-release strategies, ESR12). Masking of reagents' strategic groups will block their reporting properties, which will only be restored upon Pd catalysis (see Figure). In vitro comparative analysis of the probes will allow ranking the best probes for in vivo sensing. In collaboration with consortium partners, animal studies will be performed to determine the compatibility of the devices. After tumour mass formation, devices will be surgically implanted in the tumour and the chosen sensor/protetrazine intravenously-administered. Mice health will be monitored over time and sensor activation analysed by non-invasive in vivo optical imaging.



Planned secondments: BGX – gel-based implants (M21, 3 months); **TAU** – in vivo imaging (M36, 3 months).	**Expected results (deliverables)**: Synthesis of Pd-implants (D4.2); Synthesis of 6-8 probes (D4.2); Pd-mediated sensor activation ranked by reaction kinetics (D4.3); 2-4 implants show total biocompatibility (D4.2); In vivo activation of probes / tools (D4.4)

Supervisor: **Prof Asier Unciti-Broceta**

Recruitment completed

Update on IBEC Research Activities

WP2: Prodrugs design and synthesis

Task 2.1: Synthesis of a library of anti-cancer drugs (e.g. selumetinib and panobinostat) protected with propargyl/allyl groups (EDI). **Started**

Task 2.3: Spectroscopic (bulk) and microscopic evaluation (single molecule) study of catalysis (EDI, IBEC-ESR7).

Deliverables: D2.1. Library of anticancer prodrugs (M16). **D2.2.** Set of 2-3 fluorescent prodyes (M28). **D2.3.** Structure-activity relations description for the selected catalysts (M42).

WP4: In vivo evaluation

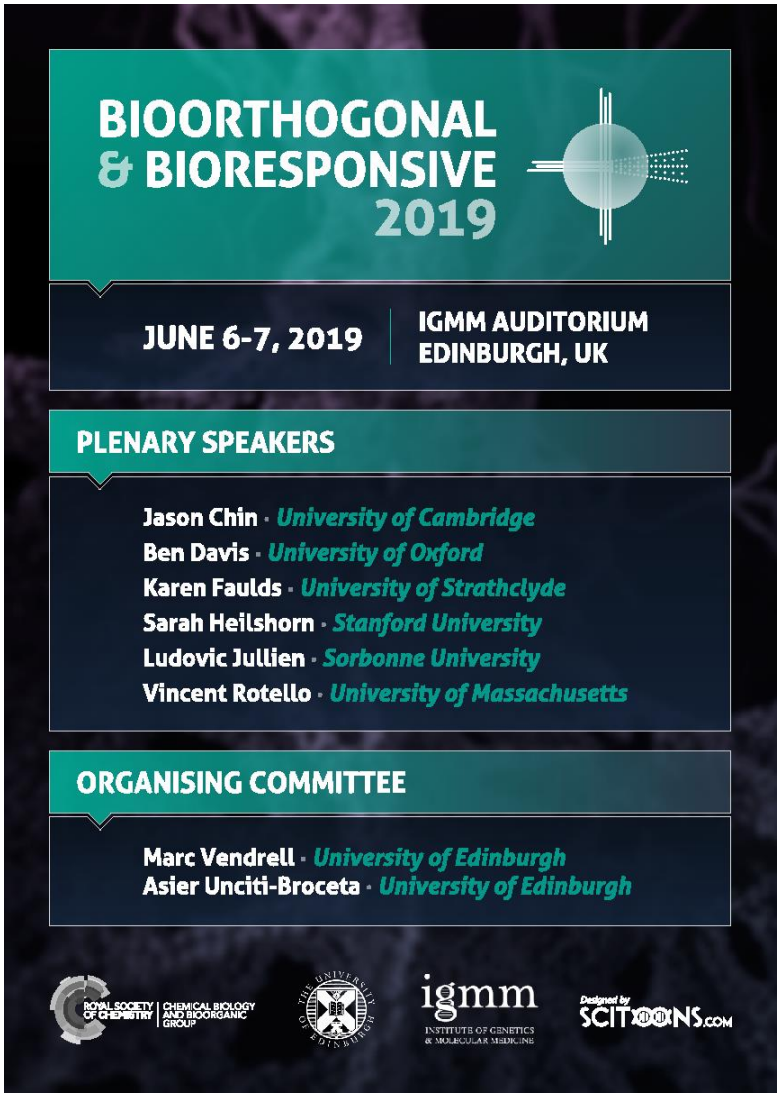
Task 4.2: In vivo administration of the catalysts and study of biocompatibility (TAU, EDI, TAG).

Deliverables: D4.2. Results of the biocompatibility tests for the catalysts (M22).

WP6: Dissemination and outreach

Task 6.1. THERACAT webpage including a private intranet for internal communication (IBEC, EDI).
Task 6.2. Open-access publications in high-impact journals and patents (EDI).
Task 6.3. **Work presented in international conferences and workshops (EDI).**
Task 6.4. THERACAT social media account creation and management (EDI, CRUK (**Sarah Thomas**)).
Task 6.5. Communication activities incl. cancer-related charity events, science festivals, European Researchers' Night, general press articles, THERACAT video (EDI, CRUK).

International Conferences



PLEASE DO NOT FORGET TO REGISTER BEFORE FRIDAY TO TAKE ADVANTAGE OF THE EARLY BIRD REGISTRATION!!!

International Conferences

Zaragoza, Spain, 16-18 October

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