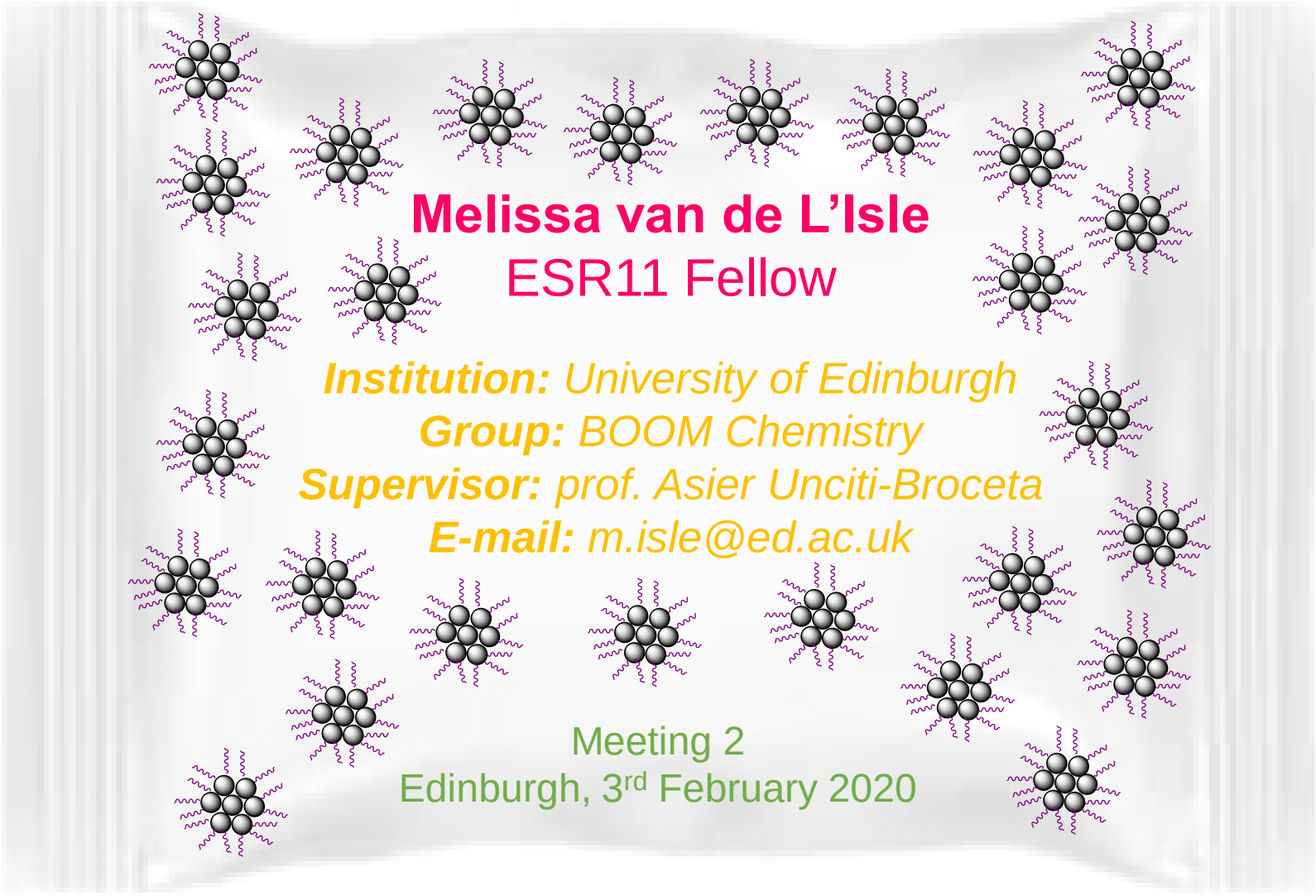


Melissa van de L'Isle

ESR11 Fellow

Institution: *University of Edinburgh*

Group: *BOOM Chemistry*

Supervisor: *prof. Asier Unciti-Broceta*

E-mail: *m.isle@ed.ac.uk*

Meeting 2

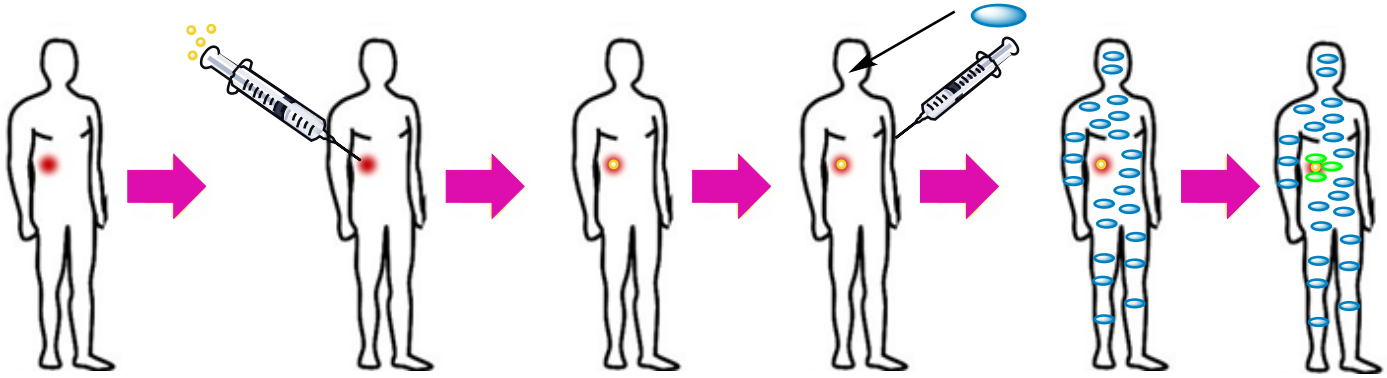
Edinburgh, 3rd February 2020

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

Thesis dissertation:

Explore novel methods to enable transition-metal nanoparticle catalysed bio-orthogonal reactions *in vitro* and *in vivo*

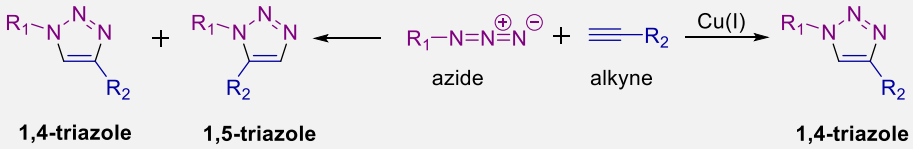
- Au, Cu and Pd nanoparticles & improve their biocompatibility/stability
- Demonstrate the reactivity of the nanoparticles in bio-orthogonal reactions by the use of pro-dyes and pro-drugs



A Stepwise Huisgen Cycloaddition Process: Copper(I)-Catalyzed Regioselective "Ligation" of Azides and Terminal Alkynes**

Vsevolod V. Rostovtsev, Luke G. Green, Valery V. Fokin,* and K. Barry Sharpless*

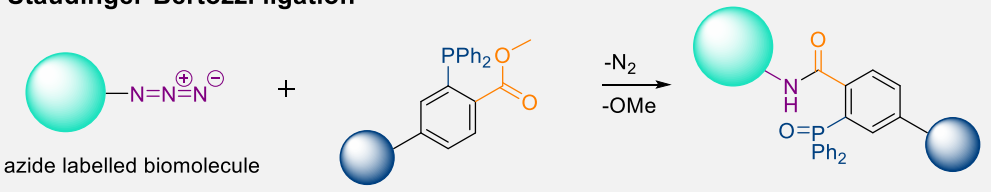
Huisgen 1,3-dipolar click reaction **CuAAC**



Cell Surface Engineering by a Modified Staudinger Reaction

Eliana Saxon and Carolyn R. Bertozzi*

Staudinger-Bertozzi ligation



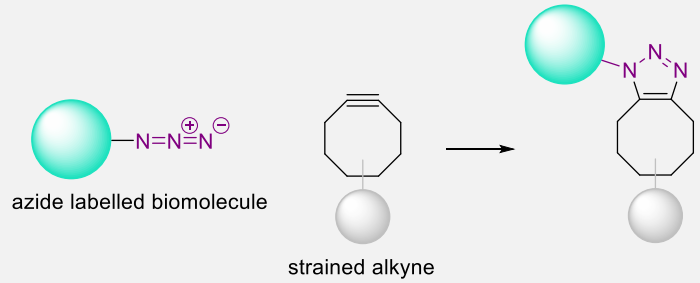
JACS COMMUNICATIONS

Published on Web 11/02/2004

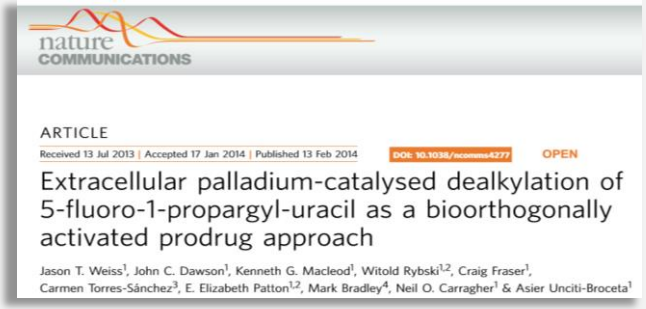
A Strain-Promoted [3 + 2] Azide–Alkyne Cycloaddition for Covalent Modification of Biomolecules in Living Systems

Nicholas J. Agard, Jennifer A. Prescher, and Carolyn R. Bertozzi*

Strain-promoted azide-alkyne click reaction (SPAAC)



Research Project: Bio-orthogonal reactions UAB

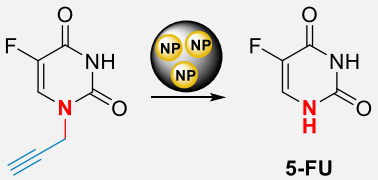

nature COMMUNICATIONS

ARTICLE

Received 13 Jul 2013 | Accepted 17 Jan 2014 | Published 13 Feb 2014 DOI: 10.1038/ncomms4277 OPEN

Extracellular palladium-catalysed dealkylation of 5-fluoro-1-propargyl-uracil as a bioorthogonally activated prodrug approach

Jason T. Weiss[1], John C. Dawson[1], Kenneth G. Macleod[1], Witold Rybski[1,2], Craig Fraser[1], Carmen Torres-Sánchez[3], E. Elizabeth Patton[1,2], Mark Bradley[4], Neil O. Carragher[1] & Asier Unciti-Broceta[1]




Chemical Science

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Cite this: Chem. Sci., 2018, 9, 7354

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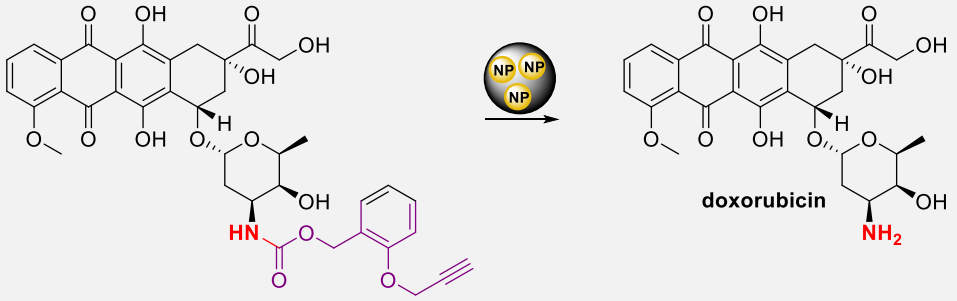
Bright insights into palladium-triggered local chemotherapy†

Thomas L. Bray,[a] Mark Salji,[bc] Alessandro Brombin,[ad] Ana M. Pérez-López,[a] Belén Rubio-Ruiz,[a] Laura C. A. Galbraith,[bc] E. Elizabeth Patton,[ad] Hing Y. Leung[bc] and Asier Unciti-Broceta[a]

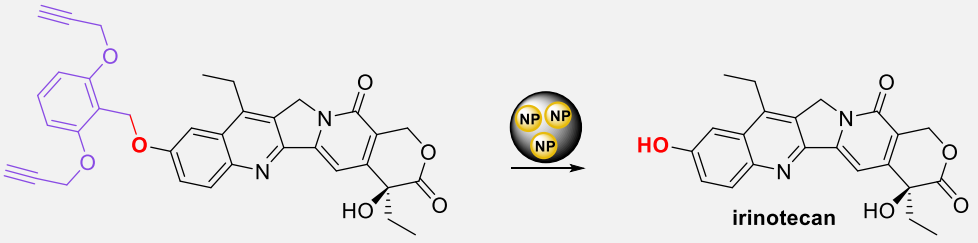



ChemPubSoc Europe DOI: 10.1002/chem.201803725 CHEMISTRY A European Journal Full Paper

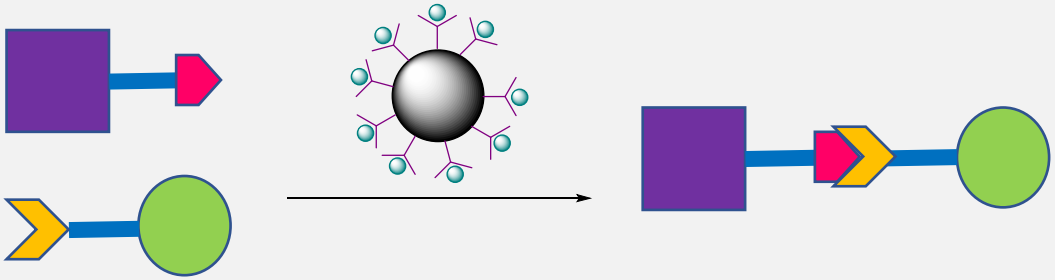
Nanomedicine |Hot Paper|

Bioorthogonal Uncaging of the Active Metabolite of Irinotecan by Palladium-Functionalized Microdevices

Catherine Adam,[a] Ana M. Pérez-López,[a] Lloyd Hamilton,[b] Belén Rubio-Ruiz,[a] Thomas L. Bray,[a] Dirk Sieger,[a, b] Paul M. Brennan,*[a, c] and Asier Unciti-Broceta*[a]

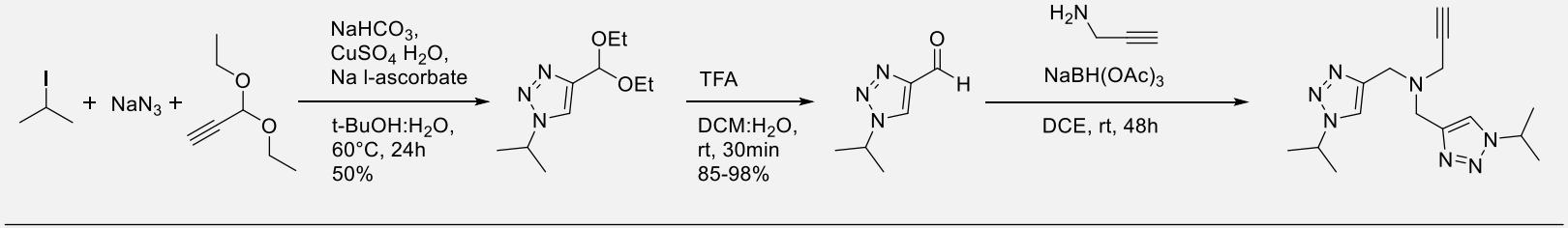


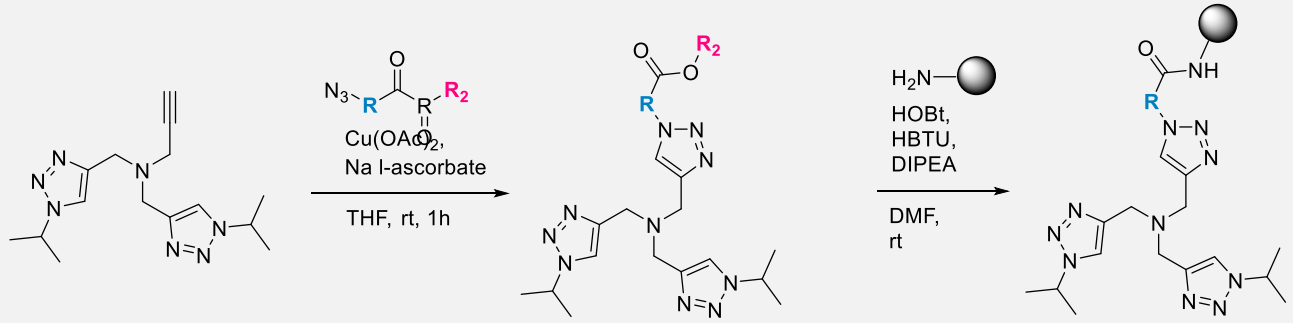
Research Project 1: Catalytic beads



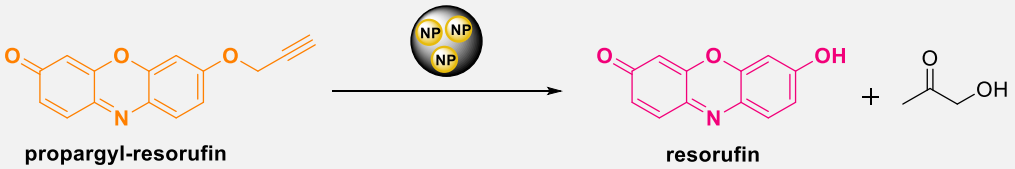
Catalyst functionalised beads

- **Tentagel resins (polystyrene)**
- **Triazole amine ligands**
- **Cu(I) ions**
- **CuAAC reactions *in vitro***



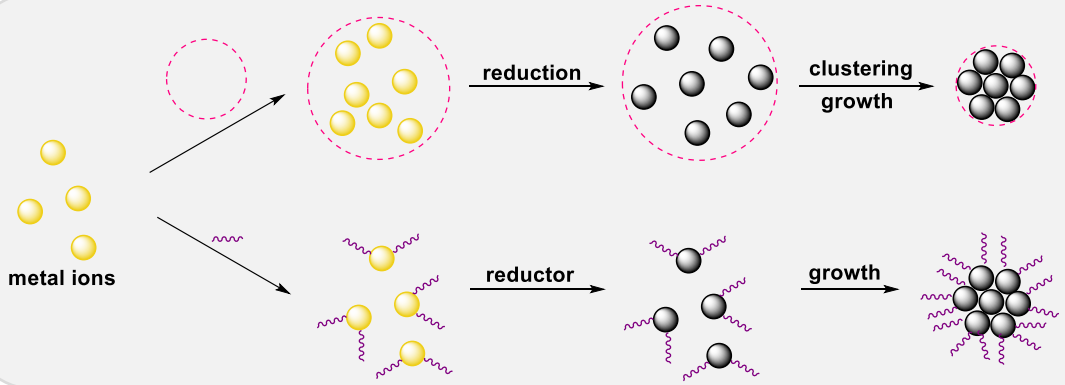


Research Project 2: background nanoparticles



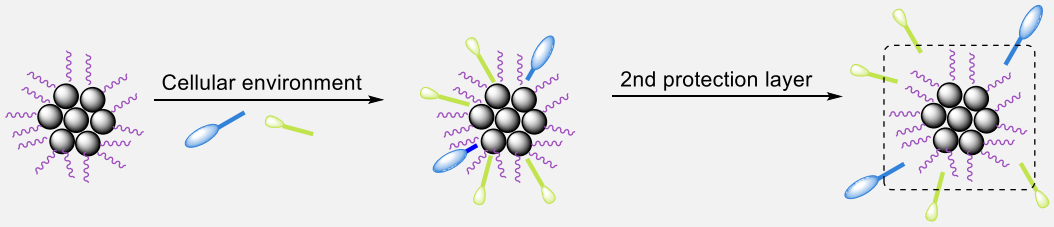
Pro-dye:

- propargyl-Resorufin
- Cleavage 1-hydroxyacetone
- Au and Pd nanoparticles



Methods to prepare mono-layered nanoparticles

- Solubility & biocompatibility
- Capping agents & reductors
- "Green" synthesis
- Brust-Schiffrin method



Deactivation of nanoparticles (NPs)

- 2nd protection barrier
- Semi-permeable material
- Biocompatible protection

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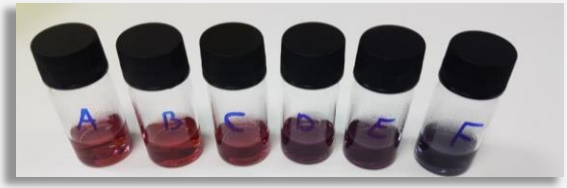
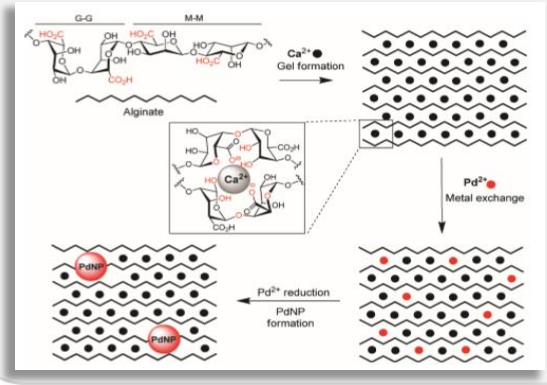
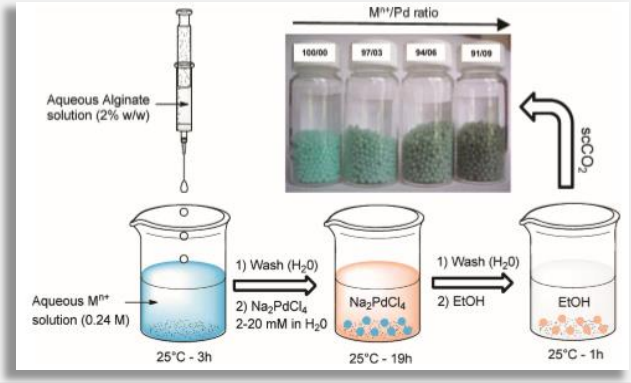


Table 1 Experimental Data on the Preparation of Mono-disperse Gold Sols

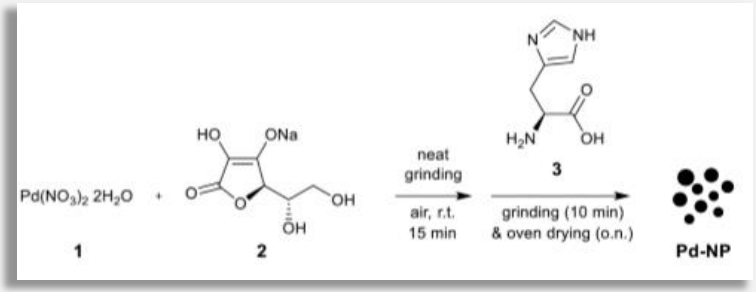
Sol	Amount of Solution II (ml.)	Diameter (Å)	Colour	t_{blue} (s)	t_{red}(s)
A	1.00	160	Orange	25	145
B	0.75	245	Red	25	120
C	0.50	410	Red	25	70
D	0.30	715	dark red *	40	140
E	0.21	975	violet *	60	435
F	0.16	1470	violet *	80	850

Au NPs
- **Reductor & capping agent**
- **L-ascorbic acid**
- **80°C in H_2O**
- **NPs = 16 to 98 nm**



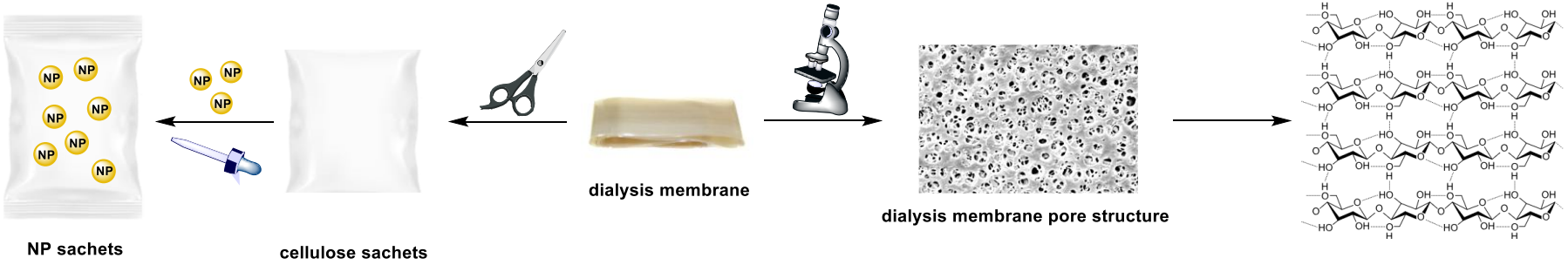


Pd NPs in alginate matrix
- **Calcium ions chelators**
- **Metal exchange Ca and Pd**
- **Reduction with EtOH**
- **Black dots after air drying**
- **NPs = 3nm**



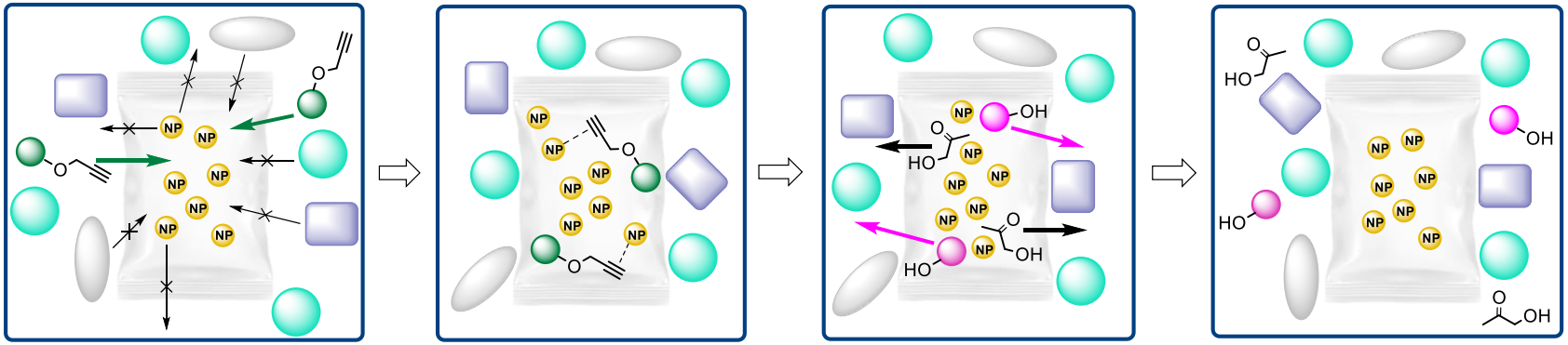
Pd NPs by grinding
- **L-ascorbic acid = reductor**
- **Histidine = capping agent**
- **30 min total grinding**
- **NPs = 6.5nm**

Research Project 2: dialysis membrane sachets



Dialysis membrane → Cellulose → 1,4-beta-glucose

- Humans lack enzymes to hydrolyse this glycosidic bond
- Pore size = molecular weight cut-off
- The sachets are closed with nail polish glue → ethyl cyanoacrylate & methyl methacrylate
- For *in-vitro* & *in-vivo* surgical glue could be used → 2-octanoyl cyanoacrylate



NP cellulose sachets in solution containing small molecules and cellular components

Discrimination between small molecules and larger cellular components entry and interaction with NPs

Cleavage of *O*-propagyl from small molecules resulting into fluorescence and conversion into 1-hydroxyacetone

The fluorescent small molecules and 1-hydroxyacetone diffused into surrounding solution and NPs reside inside sachet

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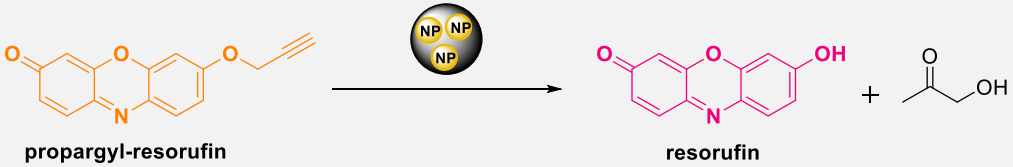
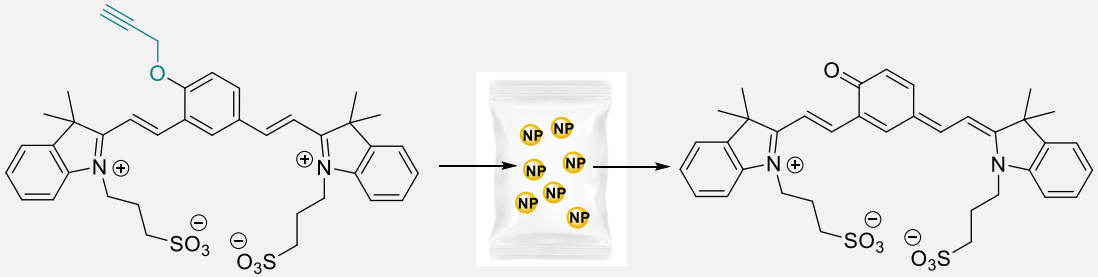
Research Project 2: pro-dyes



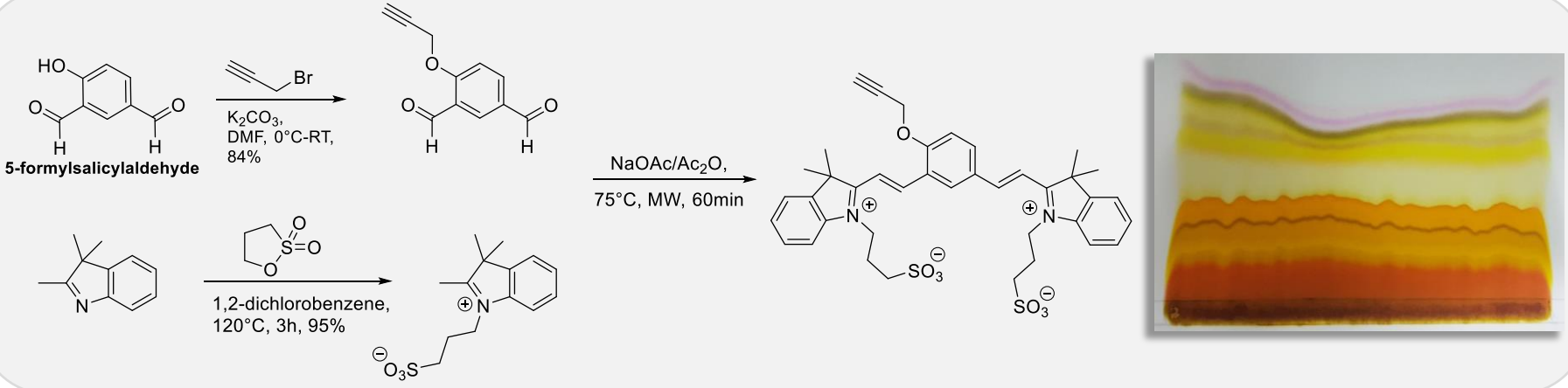
Pro-dye (UV-VIS window)

- propargyl-Resorufin
- Cleavage 1-hydroxyacetone
- Au and Pd nanoparticles



Pro-dye (NIR-I window)

- Tel Aviv University
- QCy7 derivative
- Ex: 570nm, Em: 720nm



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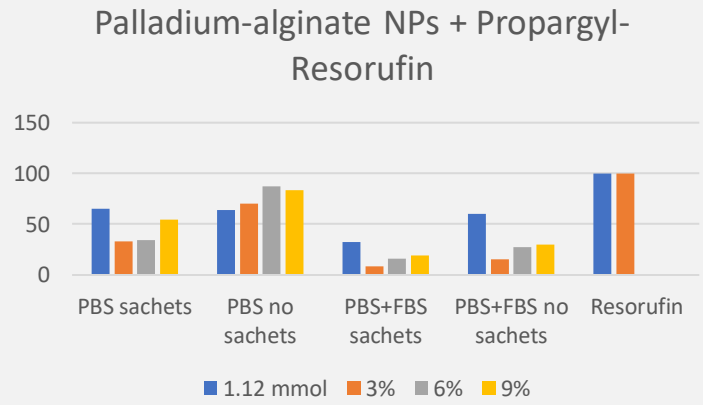
Results: testing dialysis membrane NP sachets

Au beads

- **Sodium alginate gel**
- **PBS vs PBS+FBS**
- **Less catalytic active with propargyl-Resorufin cleavage**



Fluorescence assay

- **Pd-alginate NPs**
- **PBS or PBS+FBS**
- **+ or – sachets**
- **Resorufin control (5ul)**

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H2020-MSCA-ITN-2017 (THERACAT-765497)

Hands-on training in preparing Au nanoparticles on Tentagel beads

- Demonstrated the catalytic activity of the Au nanoparticle beads with propargyl-Resorufin
- Analysis via fluorescence assay → will receive training how to use the machine for NIR assays
- Will receive training for TEM and ICP-MS analysis of the nanoparticles

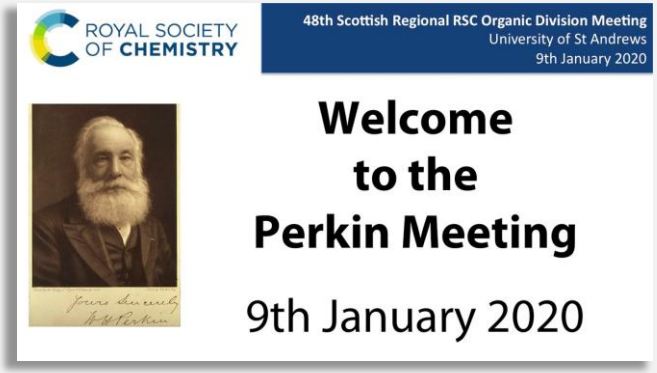
Every other week meetings, weekly ECRC WIP talks and drug discovery club
Online/Blackboard courses (start PhD, bullet journal club, academic writing and others)
Participated in the organisation of the Bio-orthogonal and bioresponsive symposium 2019

First secondment

Biogelx (24th February – 24th May 2020)

- **Institution and sector**: Biogelx, non-academic sector
- **Duration:** 3 months
- **Main research objectives:** design hydrogel-based implants
- **New knowledge and competences expected to be acquired:**
  - Prepare hydrogels and use for applications; "model *in vivo* conditions *in vitro*"
  - Demonstrate & evaluate the activity and biocompatibility of the hydrogel-based implants
  - Gain knowledge about 3D bioprinter techniques & 2D vs 3D cell culturing

Communication and dissemination




THANK YOU!!