



**Chemistry at the IGMM**  
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**INNOVATING IN CANCER THERAPY**

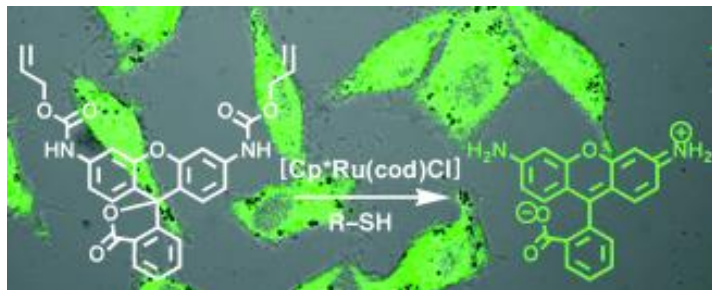
**TALK FOR THERACATS**



THE UNIVERSITY of EDINBURGH  
**Edinburgh Medical School**

**Prof Asier Unciti-Broceta FRSC**  
**Innovative Therapeutics' Lab**  
Cancer Research UK Edinburgh Centre  
Institute of Genetics and Molecular Medicine  
**University of Edinburgh**

# Non-natural metal catalysis in cells



Streu & Meggers, *Angew. Chemie* **2006**, 45, 5645

**Antecedents:** Meggers developed a water-soluble ruthenium complex that rapidly entered cells and performed an allylcarbamate cleavage, while proving to be non-toxic to cells during the short duration of the experiment (minutes).

**CHALLENGE:** Reactions mediated by non-biological transition metals in living systems. **REQUIREMENT:** Elimination / control of the inherent toxicity of the metal.

## Toxicity & Mechanism:

Metals from the platinum group trigger cell death by cross-linking of DNA >>

HIGHLY TOXIC

## Hypothesis:


Restriction of the catalyst's freedom to enter cell nuclei will suppress its toxicity mechanism >>

HETEROGENEOUS CATALYST

# Periodic Table of Elements

1 <b>H</b> Hydrogen 1.008	2 <b>He</b> Helium 4.003																	18 <b>Ar</b> Argon 39.948
3 <b>Li</b> Lithium 6.941	4 <b>Be</b> Beryllium 9.012	5 <b>B</b> Boron 10.811	6 <b>C</b> Carbon 12.011	7 <b>N</b> Nitrogen 14.007	8 <b>O</b> Oxygen 15.999	9 <b>F</b> Fluorine 18.998	10 <b>Ne</b> Neon 20.180	11 <b>Na</b> Sodium 22.990	12 <b>Mg</b> Magnesium 24.305	13 <b>Al</b> Aluminum 26.982	14 <b>Si</b> Silicon 28.086	15 <b>P</b> Phosphorus 30.974	16 <b>S</b> Sulfur 32.065	17 <b>Cl</b> Chlorine 35.453	18 <b>Ar</b> Argon 39.948			
19 <b>K</b> Potassium 39.098	20 <b>Ca</b> Calcium 40.078	21 <b>Sc</b> Scandium 44.956	22 <b>Ti</b> Titanium 47.88	23 <b>V</b> Vanadium 50.942	24 <b>Cr</b> Chromium 51.996	25 <b>Mn</b> Manganese 54.938	26 <b>Fe</b> Iron 55.845	27 <b>Co</b> Cobalt 58.933	28 <b>Ni</b> Nickel 58.693	29 <b>Cu</b> Copper 63.546	30 <b>Zn</b> Zinc 65.38	31 <b>Ga</b> Gallium 69.723	32 <b>Ge</b> Germanium 72.64	33 <b>As</b> Arsenic 74.922	34 <b>Se</b> Selenium 78.96	35 <b>Br</b> Bromine 79.904	36 <b>Kr</b> Krypton 83.798	
37 <b>Rb</b> Rubidium 85.468	38 <b>Sr</b> Strontium 87.62	39 <b>Y</b> Yttrium 88.906	40 <b>Zr</b> Zirconium 91.224	41 <b>Nb</b> Niobium 92.906	42 <b>Mo</b> Molybdenum 95.94	43 <b>Tc</b> Technetium 98.906	44 <b>Ru</b> Ruthenium 101.07	45 <b>Rh</b> Rhodium 102.91	46 <b>Pd</b> Palladium 106.42	47 <b>Ag</b> Silver 107.87	48 <b>Cd</b> Cadmium 112.41	49 <b>In</b> Indium 114.82	50 <b>Sn</b> Tin 118.71	51 <b>Sb</b> Antimony 121.76	52 <b>Te</b> Tellurium 127.6	53 <b>I</b> Iodine 126.91	54 <b>Xe</b> Xenon 131.29	
55 <b>Cs</b> Cesium 132.91	56 <b>Ba</b> Barium 137.33	57 <b>La</b> Lanthanum 138.91	58 <b>Ce</b> Cerium 140.12	59 <b>Pr</b> Praseodymium 140.91	60 <b>Nd</b> Neodymium 144.24	61 <b>Pm</b> Promethium 144.91	62 <b>Sm</b> Samarium 150.36	63 <b>Eu</b> Europium 151.96	64 <b>Gd</b> Gadolinium 157.25	65 <b>Tb</b> Terbium 158.93	66 <b>Dy</b> Dysprosium 162.50	67 <b>Ho</b> Holmium 164.93	68 <b>Er</b> Erbium 167.26	69 <b>Tm</b> Thulium 168.93	70 <b>Yb</b> Ytterbium 173.05	71 <b>Lu</b> Lutetium 174.97		
87 <b>Fr</b> Francium 223.02	88 <b>Ra</b> Radium 226.03	89 <b>Ac</b> Actinium 227.03	90 <b>Th</b> Thorium 232.04	91 <b>Pa</b> Protactinium 231.04	92 <b>U</b> Uranium 238.03	93 <b>Np</b> Neptunium 237.05	94 <b>Pu</b> Plutonium 244.06	95 <b>Am</b> Americium 243.06	96 <b>Cm</b> Curium 247.07	97 <b>Bk</b> Berkelium 247.07	98 <b>Cf</b> Californium 251.08	99 <b>Es</b> Einsteinium 252.08	100 <b>Fm</b> Fermium 257.10	101 <b>Md</b> Mendelevium 258.10	102 <b>No</b> Nobelium 259.10	103 <b>Lr</b> Lawrencium 262.11		

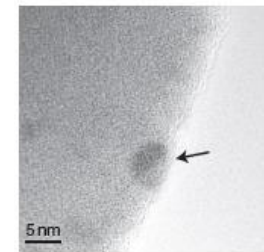
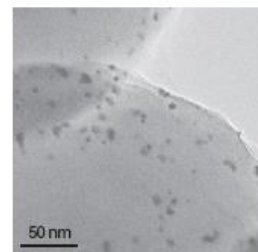
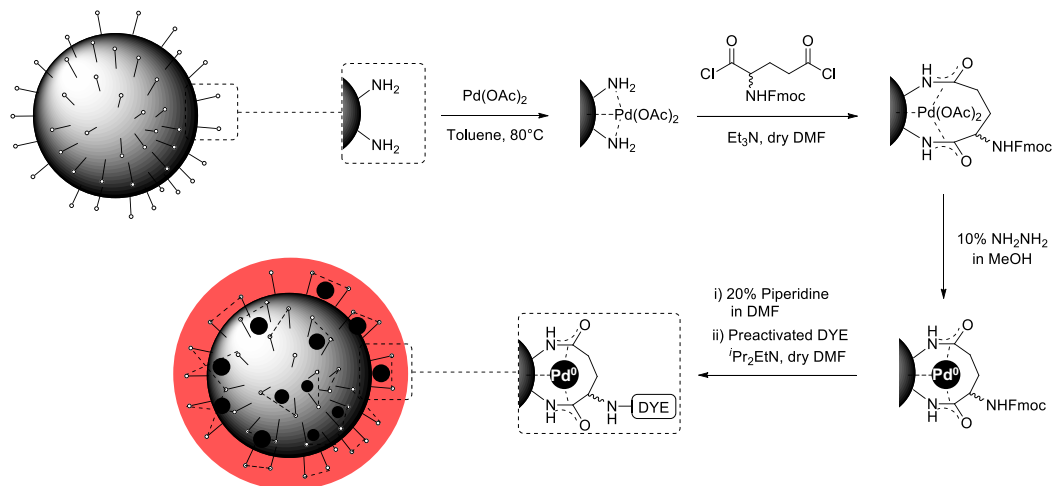
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atomic number	22
Symbol	<b>Ti</b>
name	Titanium
atomic weight	47.88


  
 University of Michigan
   
 Science and Mathematics
   
 Educational Development
   
 www.umich.edu/edu/pe

Source: Wikipedia

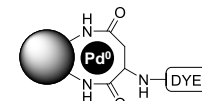
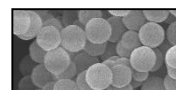
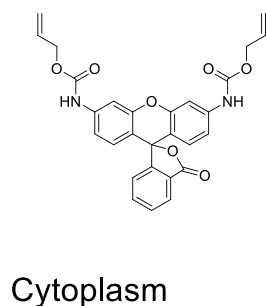
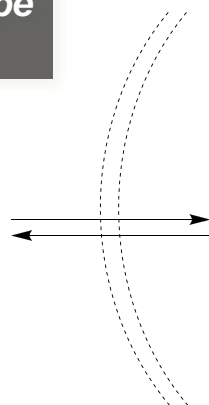
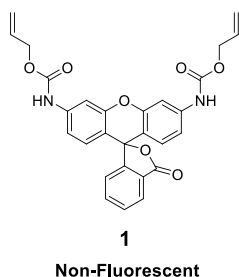


## A "bio-friendly" cell-penetrating $Pd^0$ heterogeneous catalyst

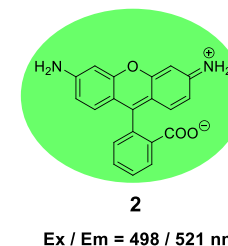


*Biocompatible microspheres that  
penetrate cells and stay in the  
cytoplasm >> exonuclear location >>  
minimal toxicity*

## $Pd^0$ Sensitive Probe (lipophilic)



## Active Dye (hydrophilic)



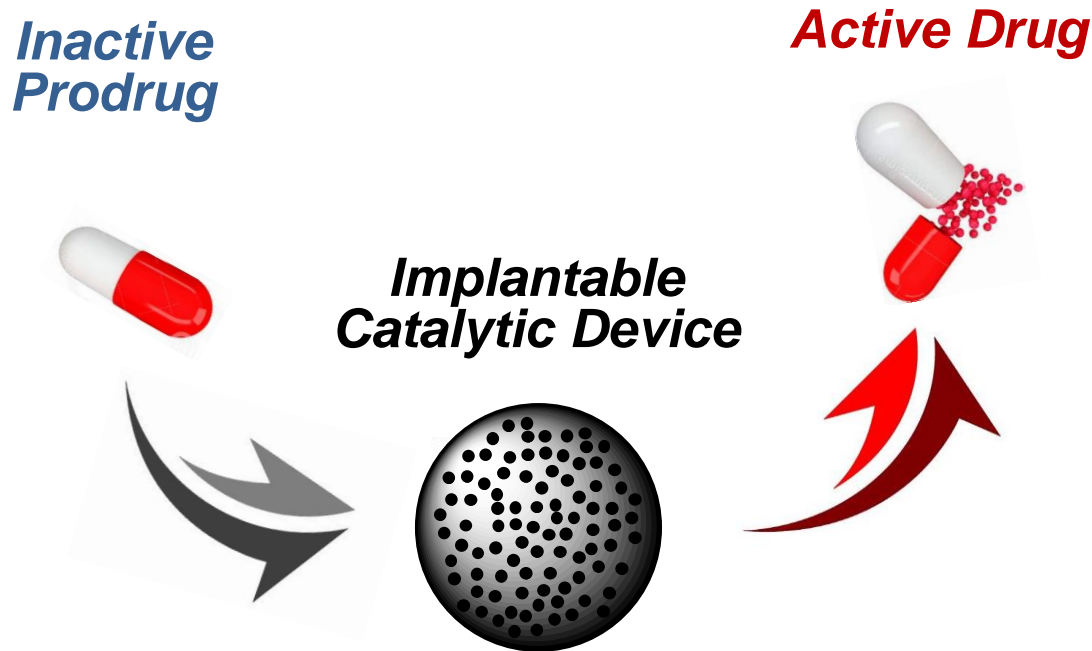
*Alloc deprotection  
& Suzuki coupling  
inside cells*

**SAFE ON THEIR OWN,**

**CYTOTOXIC TOGETHER**



# Implants that make drugs inside your body



*GLOCAL Therapy is completely benign until the **Prodrug** meets the Catalytic Device*

- *Global (systemic) dosing of orally-available **Inactive Prodrug** >>> ORAL ADMINISTRATION*
- *Prodrug stable to pH, redox potential and enzymatic metabolism >>> NO SIDE EFFECTS*
- *Activation only where the catalyst is: **Prodrug** into **Drug** >>> LOCAL TREATMENT*

# Clinical benefits



**KINDER  
TREATMENTS**

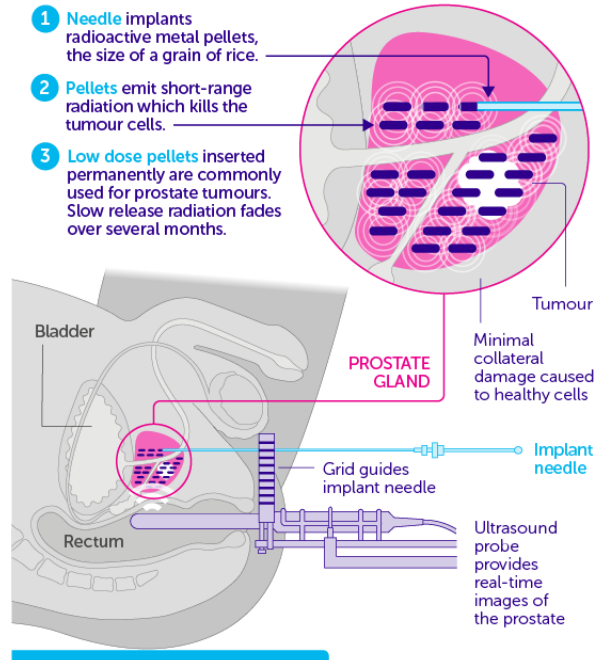
**MULTIPLE  
DRUGS**

**REPEAT  
DOSES**



***As a catalyst,  
Palladium can do the  
job of activating one  
or more drugs as  
many times as  
required, overcoming  
the useful life and  
versatility limitations of  
other local therapy  
modalities***

## **vs BRACHYTHERAPY**

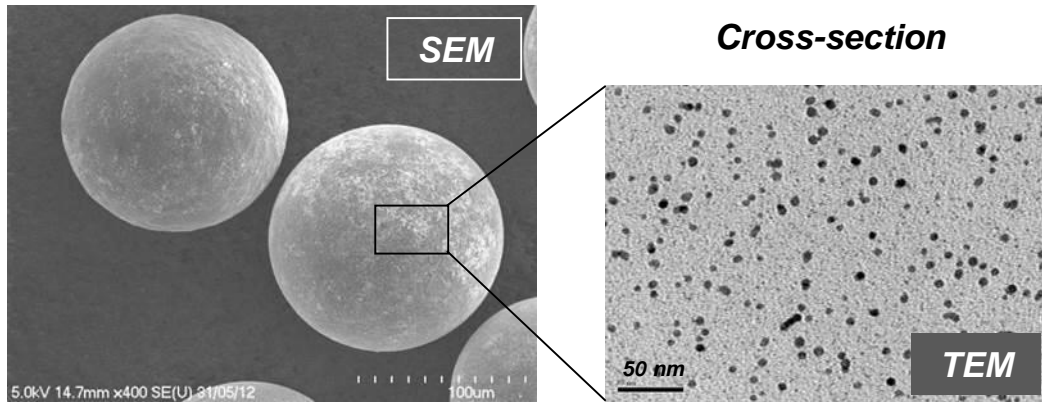


***Importantly, Pd-devices are not radioactive! Straightforward low-risk implantation procedure for clinicians***

# Development of safe Pd-devices



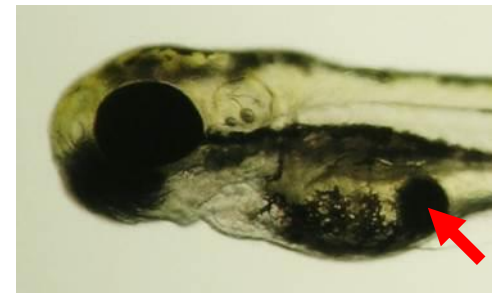
**TENTAGEL Resin:** solid support used in conventional solid-phase organic synthesis



- Zebrafish embryos (yolk or top of the head) are pierced and a Pd-resin carefully introduced (1 bead / embryo)
- Embryo development is monitored for 4 days
- Zebrafish embryos containing a **Pd-resin** (indicated with a red arrow) develop normally into their larval stage with no signs of toxicity or alteration of their morphology and behaviour



24 hpf

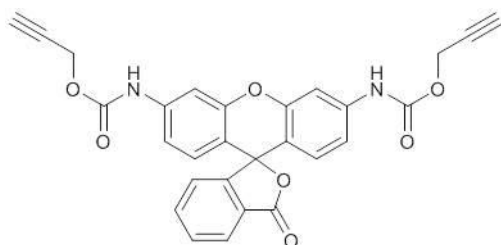


3 dpf



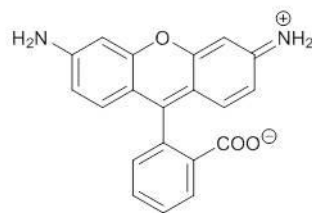
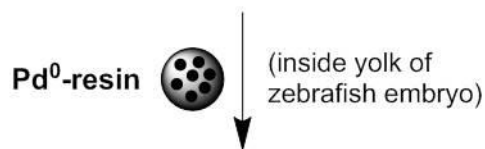
4 dpf

# *In vivo* LOCAL Activation of PROBE



**Pd-Labile PROBE**

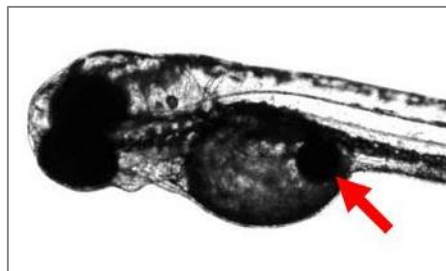
Non Fluorescent / Lipophilic



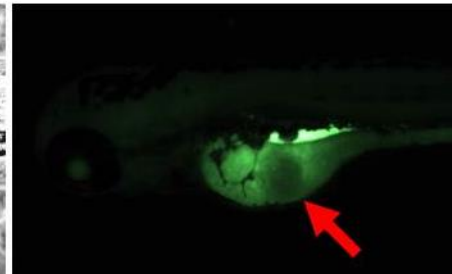
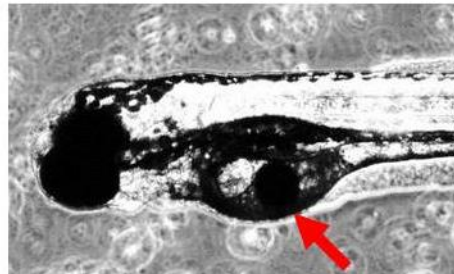
**Rhodamine 110**

Fluorescent / Hydrophilic

**Pd-resin**



**Pd<sup>0</sup>-resin  
+ PROBE**



*Strong fluorescent signal was clearly observed from the area surrounding the Pd<sup>0</sup>-resin in the yolk sac, confirming that the palladium-functionalized device is catalytically active in vivo*



## Catalyst

Palladium

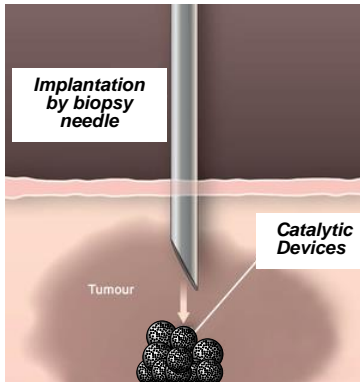
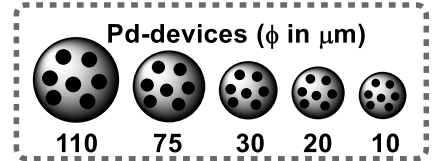
Gold

Safe\*

\*Classified as Biocompatible metals

16w in mice

84d in rats



## Chemotherapy

## Main Cancer Indication

5FU

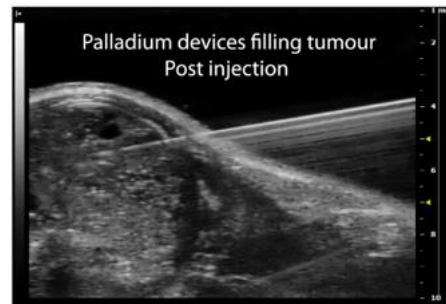
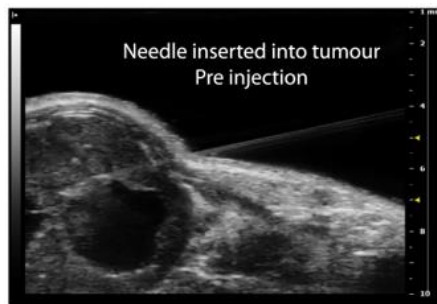
Colorectal, Breast, Pancreatic, Oesophageal, Vaginal, Cervical, Anal

Irinotecan

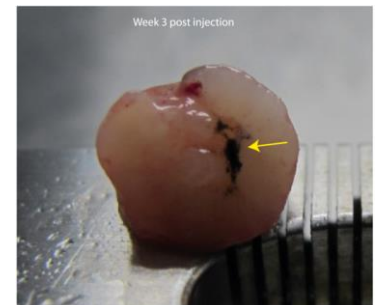
Colorectal, Lung, Pancreatic, Head & Neck

Doxorubicin

Breast, Pancreatic, GI, Bladder, kidney, Bone, CNS, Colorectal



Devices do not "move" from the point of injection



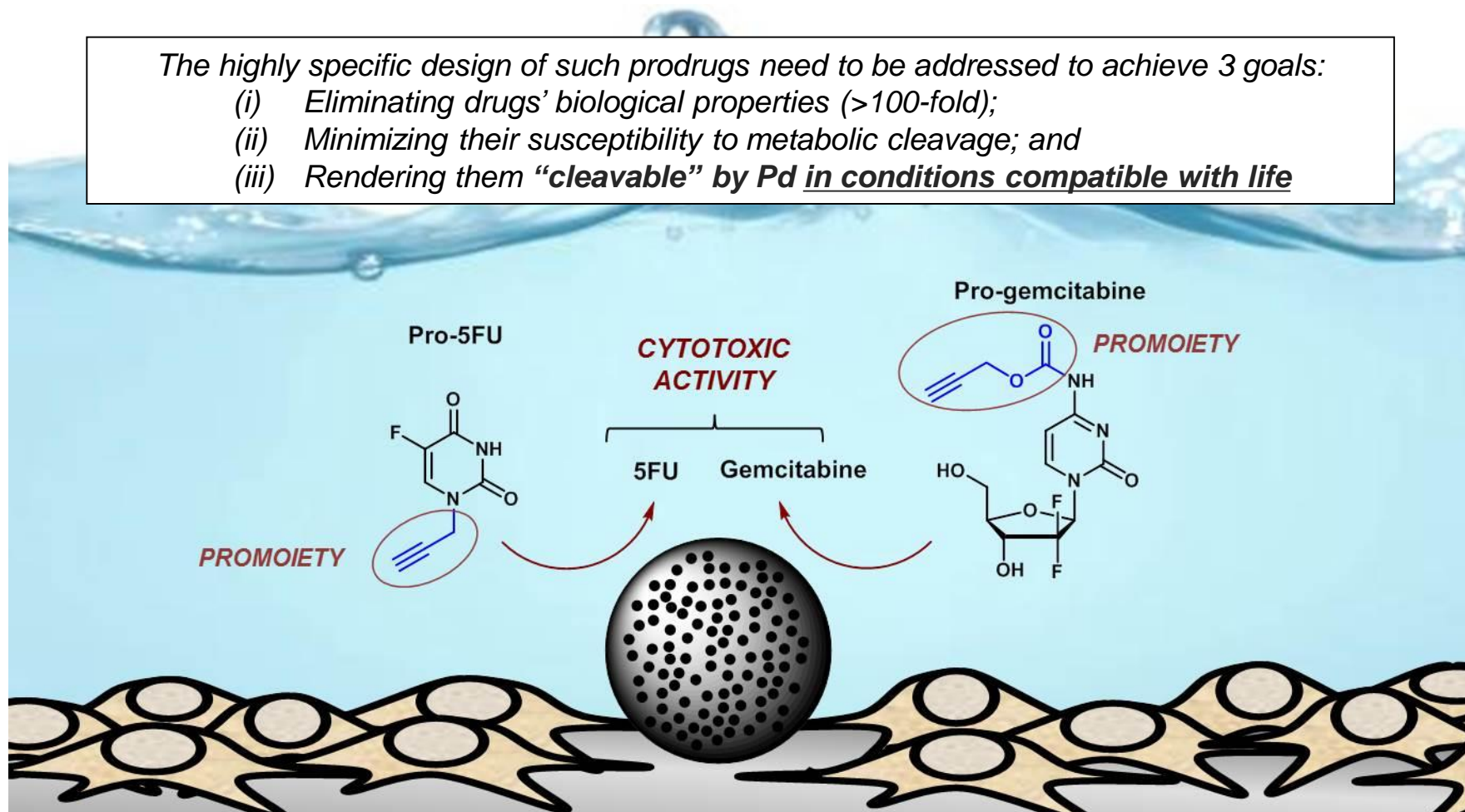
Devices are *echogenic* >> intratumoural insertion guided by ultrasound imaging

# How to make a bioorthogonal prodrug

**OBJECTIVE:** Control the activation of prodrugs **exclusively** by implant-localized palladium catalysis

The highly specific design of such prodrugs need to be addressed to achieve 3 goals:

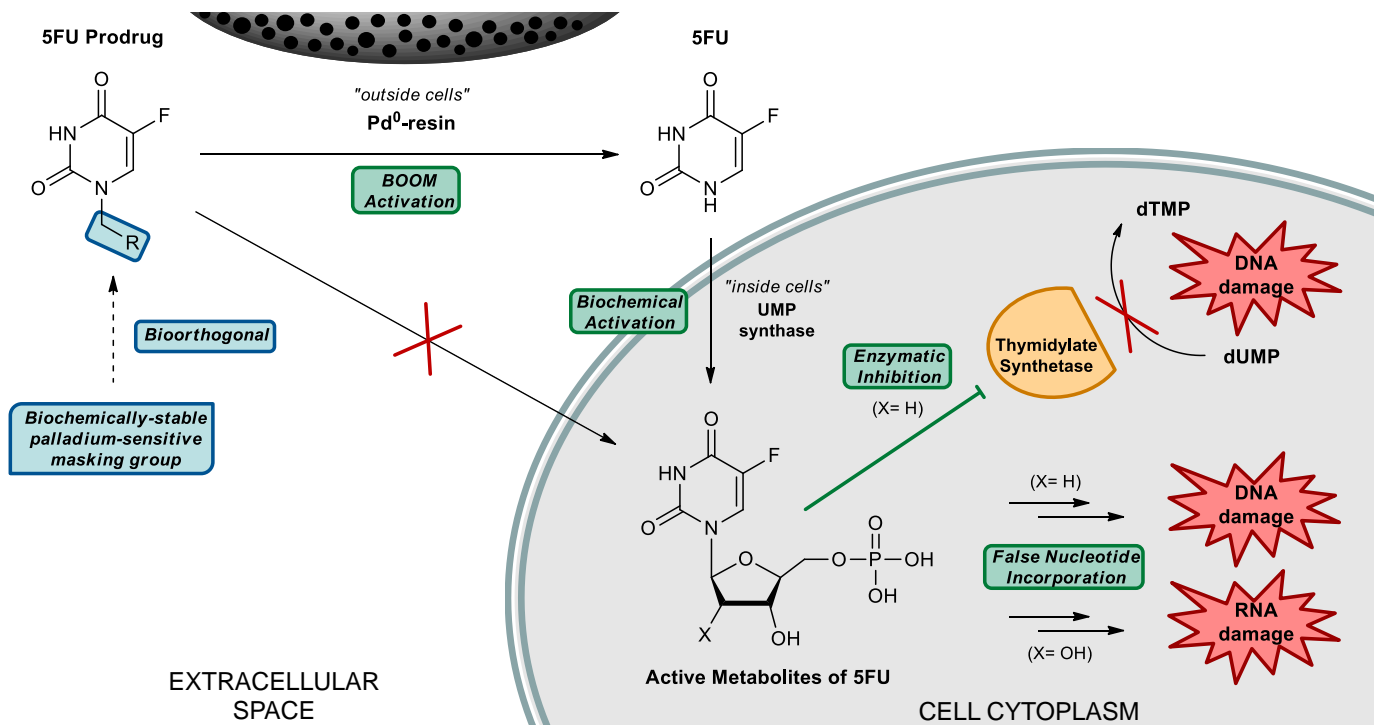
- (i) Eliminating drugs' biological properties (>100-fold);
- (ii) Minimizing their susceptibility to metabolic cleavage; and
- (iii) Rendering them “cleavable” by Pd in conditions compatible with life



# 5FU Prodrug Design



**GOAL:** To increase prodrug stability using masking groups that are not recognized by hydrolytic enzymes while being labile to Pd chemistry



## **DRUG's Mode of Action:**

5FU is converted intracellularly into cytotoxic nucleotidic metabolites, which inhibit directly thymidylate synthase or incorporates into RNA and DNA to disrupt normal cell functions

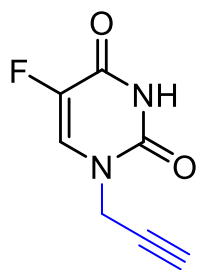
**CHALLENGE:** According to the literature, palladium-mediated N-dealkylations in water typically require temperatures incompatible with cell survival (>80 ° C) **KEY:** lactam – lactim tautomerism

# Prodrug Safety and Activation

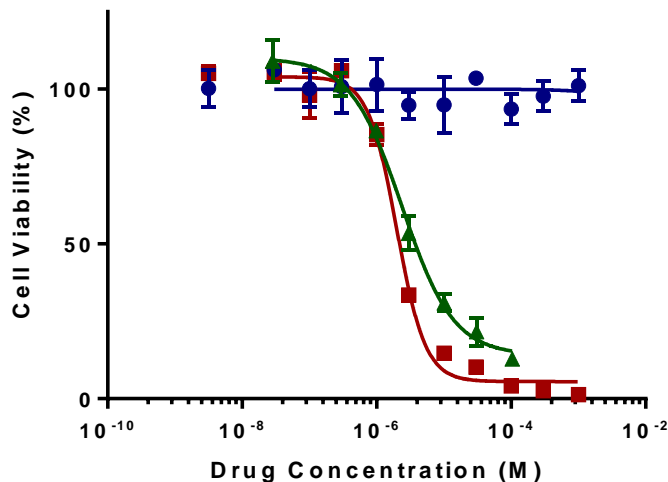
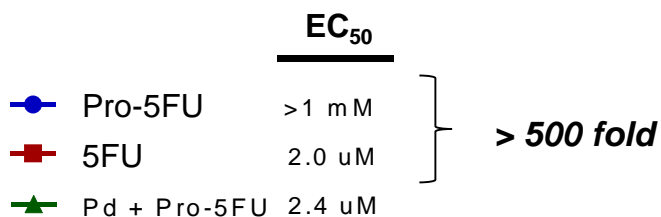


*Alkylation of the N1 position of 5FU (cytotoxic drug used to treat colorectal and pancreatic cancer) resulted in biochemically-stable inactive derivatives (reduction of cytotoxicity >500 fold).*

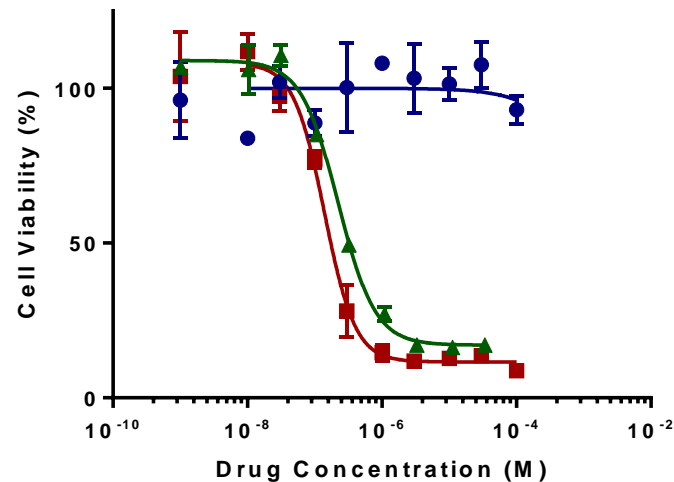
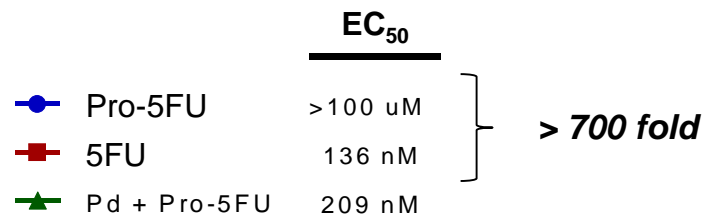
Pro-5FU



COLORECTAL  
Cancer Cells



PANCREATIC  
Cancer Cells

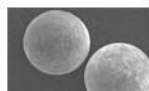


# Visualizing inactive prodrug and devices

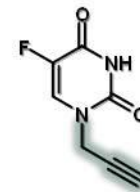
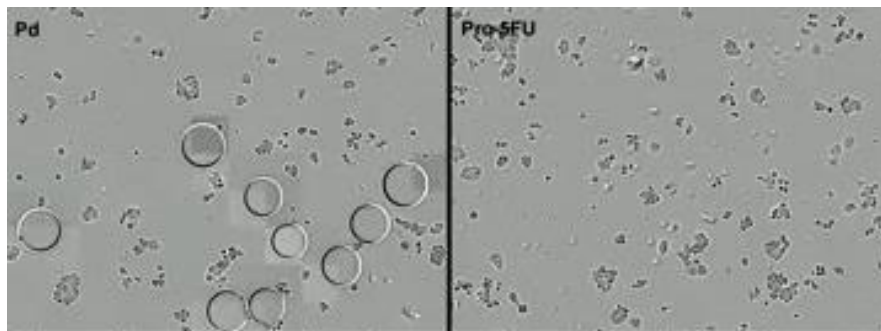
*Chemical masking of 5FU (drug used to treat colon and pancreatic cancer) results in a completely inactive derivative (reduction of cytotoxicity >500 fold).*

Palladium

SAFE



*Pd<sup>0</sup>-resins*



*Pro-5FU*

PRODRUG

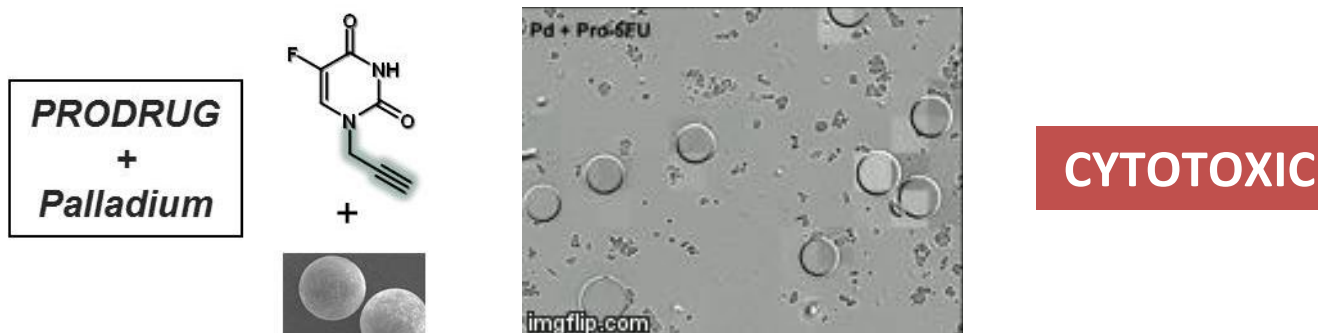
SAFE

*Real-time visualization (5 days) of cell proliferation (colorectal cancer cells)*



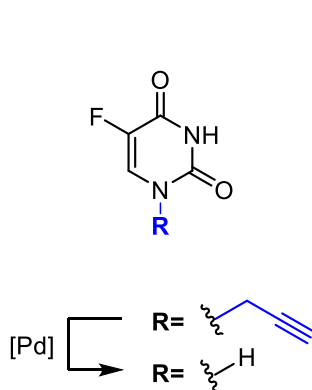
# Visualizing prodrug activation

*Combination of inactive **Pro-5FU** and **Pd-devices** mediated strong cytotoxic activity, equivalent to that of **5FU**, demonstrating the in situ manufactured of the drug*

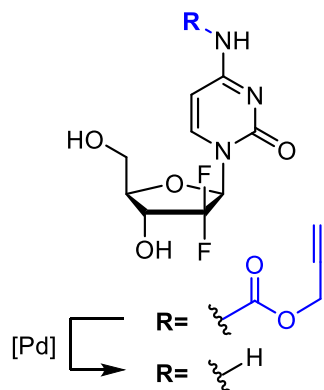


*Real-time visualization (5 days) of cell proliferation (colorectal cancer cells)*

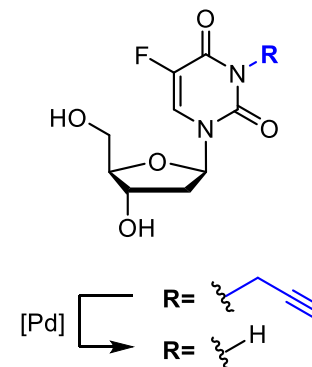
# Palladium activated prodrugs



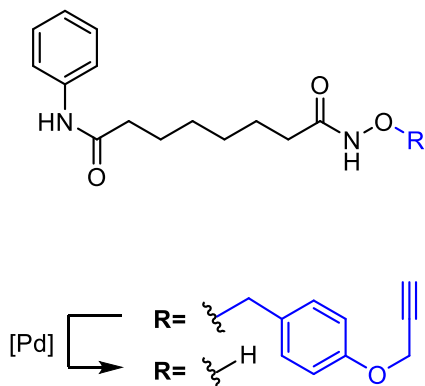
*Nat. Commun.* **2014**, 5, 3277



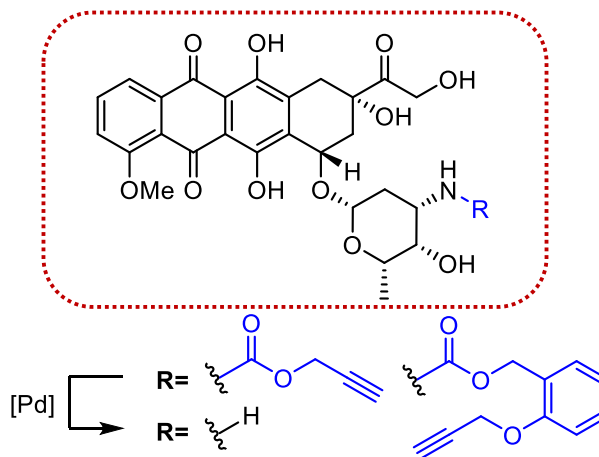
*J. Med. Chem.* **2014**, 57, 5395



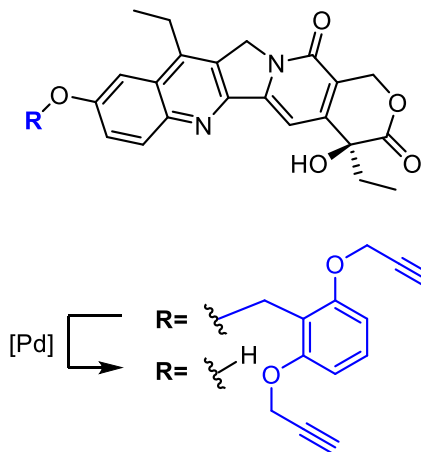
*Sci. Rep.* **2015**, 5, 9329



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

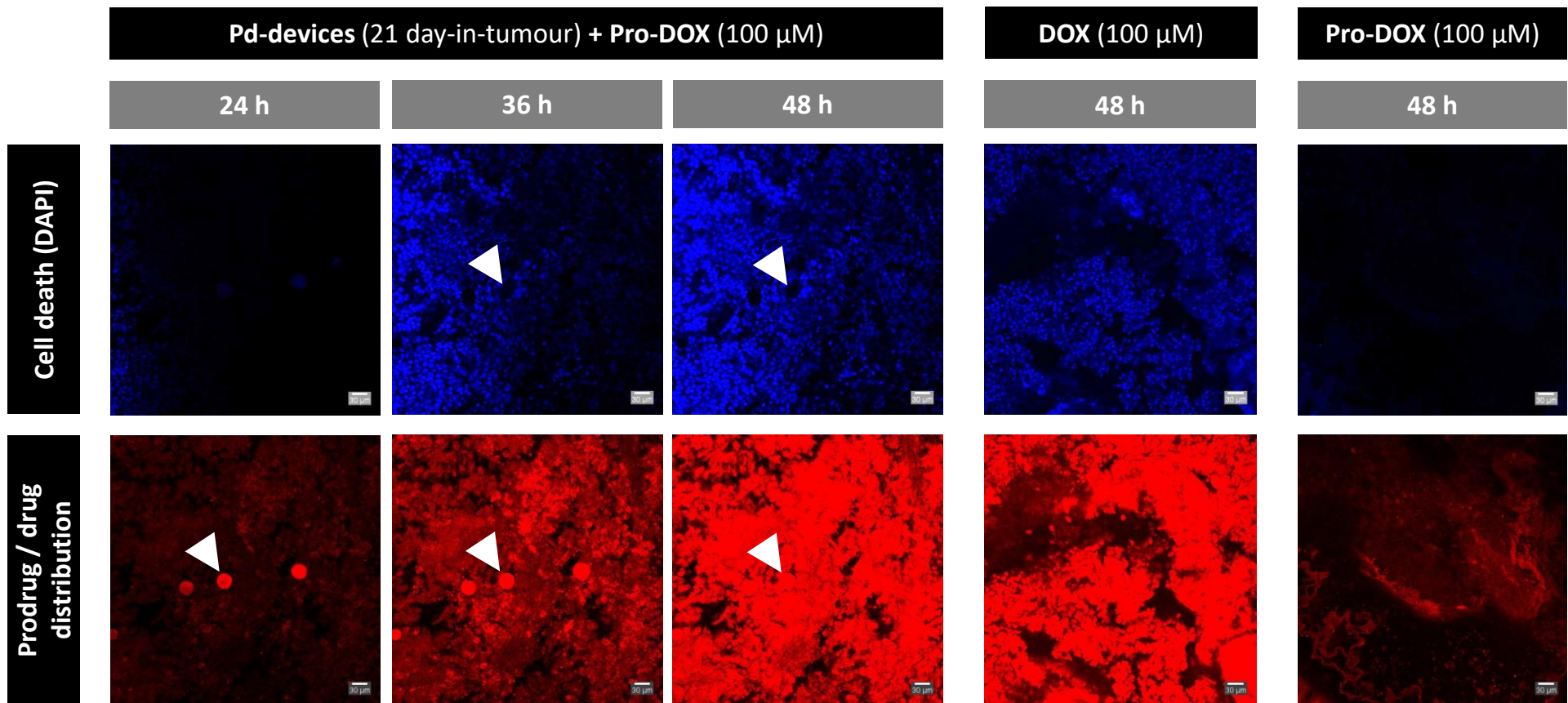


*Angew. Chemie* **2017**, 56, 12548  
*Chem. Sci.* **2018**, 9, 7354-7361



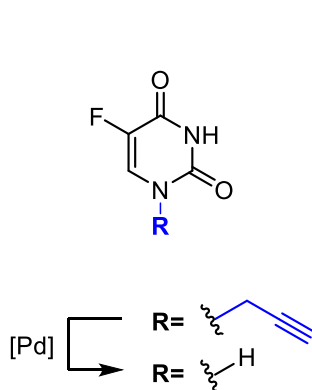
*Chem. Eur. J.* **2018**, 24, 16783-16790

# Ex vivo activation of chemotherapy

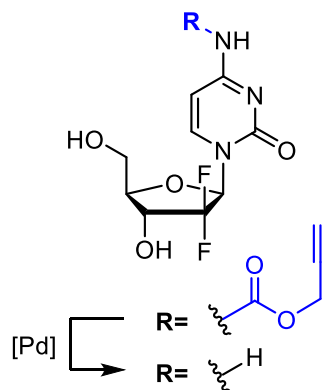


*Ex vivo Pd-mediated release of DOX from an inactive precursors in a prostate tumour explant*

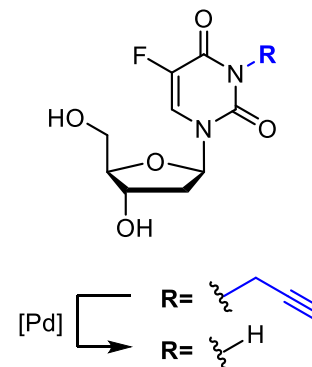
# Palladium activated prodrugs



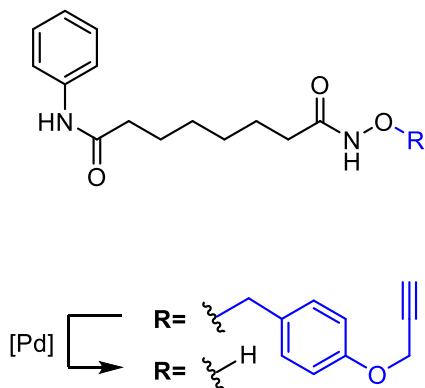
*Nat. Commun.* **2014**, 5, 3277



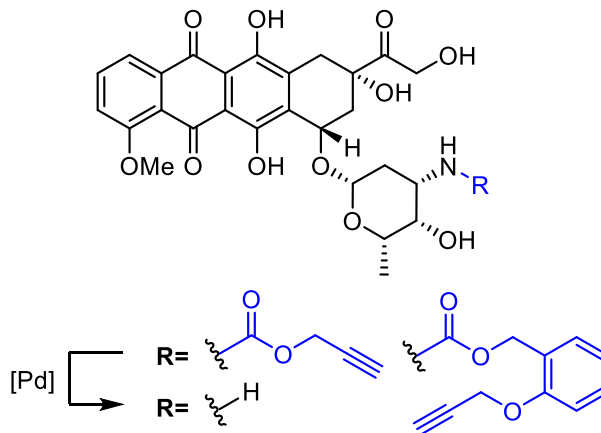
*J. Med. Chem.* **2014**, 57, 5395



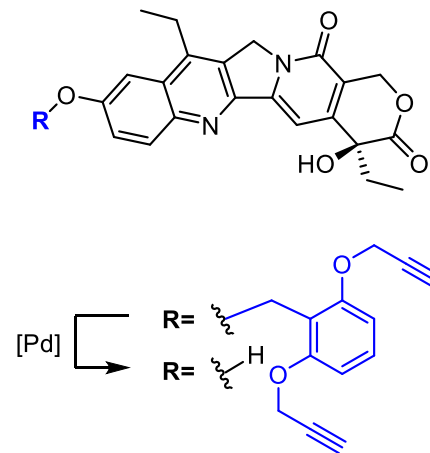
*Sci. Rep.* **2015**, 5, 9329



*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 Therapeutics Lab





**BIOORTHOGONAL  
& BIORESPONSIVE  
2019**

**JUNE 6-7, 2019**
**IGMM AUDITORIUM  
EDINBURGH, UK**

**PLENARY SPEAKERS**

**Jason Chin** · *University of Cambridge*  
**Ben Davis** · *University of Oxford*  
**Karen Faulds** · *University of Strathclyde*  
**Sarah Heilshorn** · *Stanford University*  
**Ludovic Jullien** · *Sorbonne University*  
**Vincent Rotello** · *University of Massachusetts*

**ORGANISING COMMITTEE**

**Marc Vendrell** · *University of Edinburgh*  
**Asier Unciti-Broceta** · *University of Edinburgh*

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



**Unconventional  
Catalysis,  
Reactors and  
Applications  
UCRA 2019**

**Oral Abstract  
Submission  
deadline:  
31<sup>st</sup> March 2019**

**Zaragoza, Spain, 16-18 October**

## COLLABORATORS

### FROM THE IGMM SITE

**Neil Carragher – Phenotypic 2D/3D Assays**

**Liz Patton – Zebrafish Models**

**Val Brunton & Margaret Frame – Mouse cancer models & cell biology**

### FROM THE LITTLE FRANCE AND KING'S BUILDINGS SITES

**Dirk Sieger & Catherina Becker – Zebrafish models & assays**

**Steven Pollard & Paul Brennan – Glioblastoma cells**

**Scott Webster – PK studies**

**Douglas Houston – In silico studies**

### FROM BEATSON INSTITUTE & UNIVERSIDAD DE ZARAGOZA

**Hing Leung – Prostate cancer models**

**Jesús Santamaría – Nanotechnology and hybrid bioartificial devices**

