Differentiated Medicines from Polymeric Nanoparticles

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  - Woei Ping Cheng
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- Cambridge University
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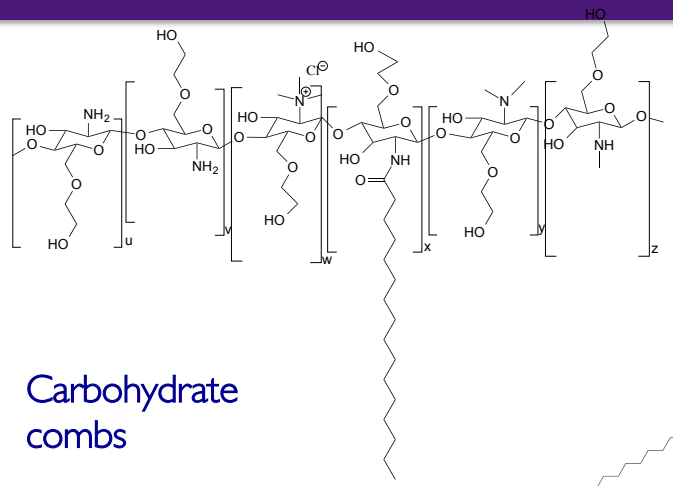
- Rutherford Laboratories
  - Pavel Matousek

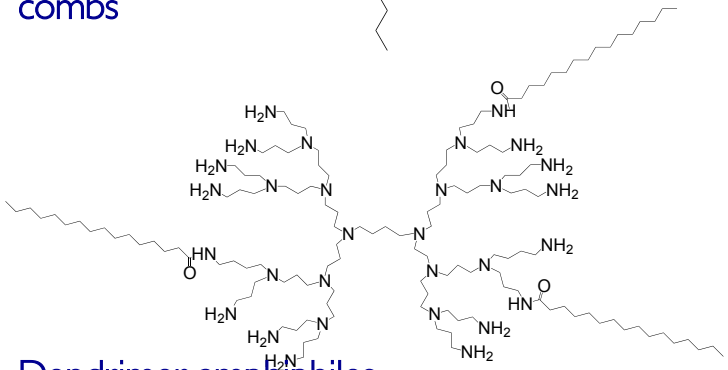
Summary

- Academic investigations
  - Nanoparticle fabrication and characterisation
- Commercialisation
  - Strategy
  - Technology
  - Licensing
    - Nasal and ocular assets
  - Oral dosage form case Studies
- Current academic focus
  - Diagnostics

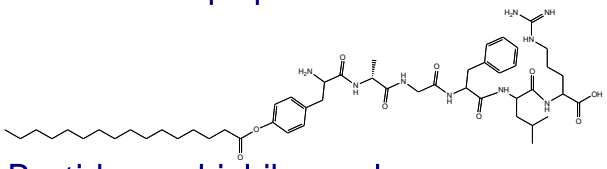
Building Blocks



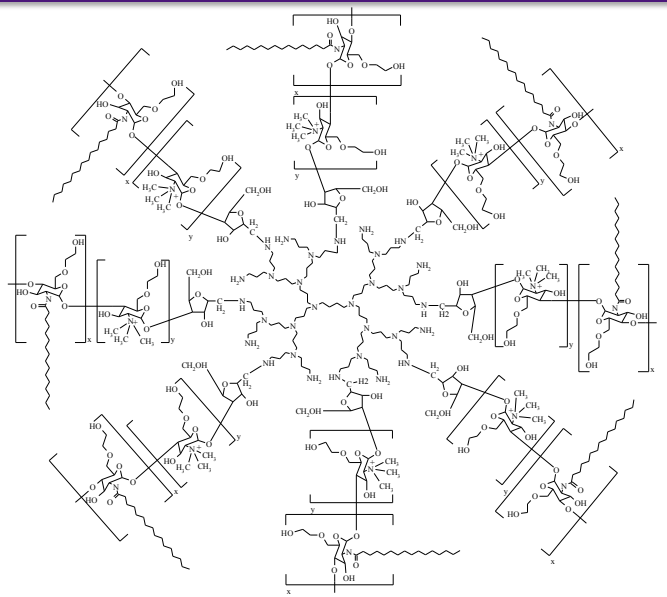
Carbohydrate combs



Dendrimer amphiphiles



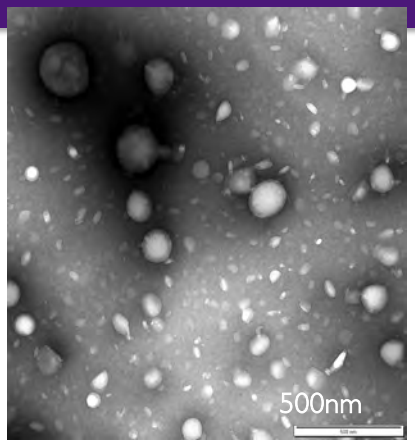
Peptide amphiphile prodrugs



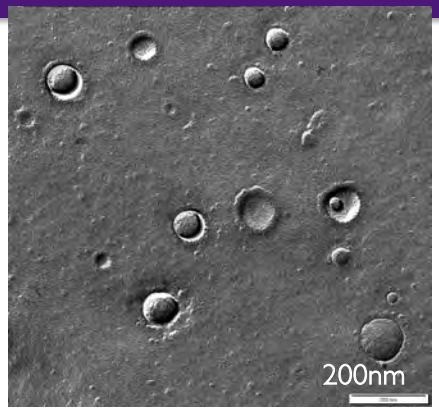
Claws

Wang et al (2004) Macromolecules, 37: 9114 - 9122.
Qu et al (2008) Langmuir, 24: 9997–10004
Chooi et al (2010) Langmuir, 26: 2301 – 2316
Ahmad et al (2010) J Royal Society Interf, 2010, 7: S423 – S433
Siew et al (2012) Mol Pharmaceutics, 9: 14 – 28.
Lalatsa et al (2012) Mol Pharmaceutics, 9: 1665-1680
Mazza et al (2013) ACS Nano, 7, 1016 – 1026
Lalatsa et al (2015) J Control Rel, 197: 87 – 96
Fisusi et al (2016) Pharm Res, 33: 1289-1303.
Godrey et al (2017) J Control Rel, 270, 135-144
Hobson et al (2019) Nanomedicine, 14, 1135-1152

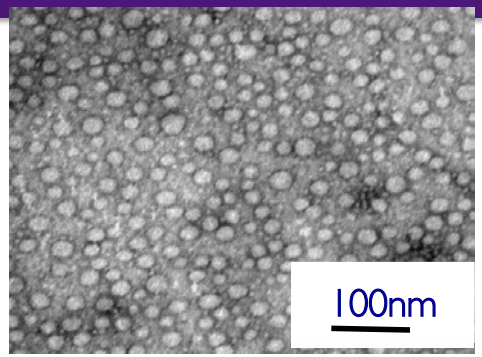
Polymeric, Dendrimer and Peptide Nanoparticles



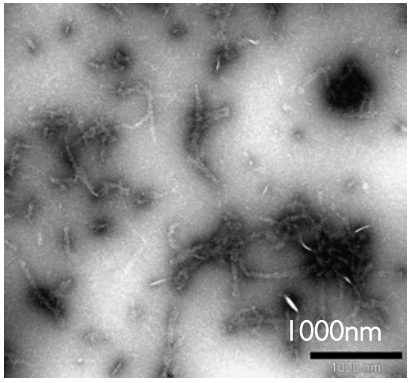
Dense Spheres



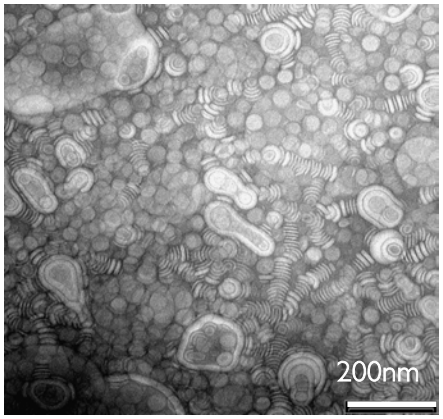
Vesicles



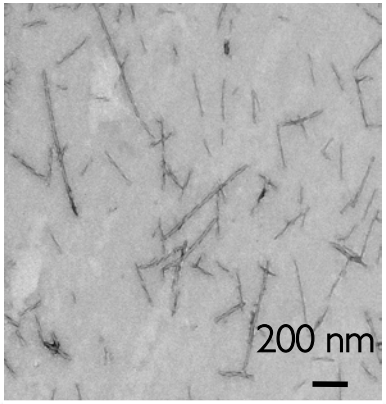
Polymeric Micelles



Worm-like



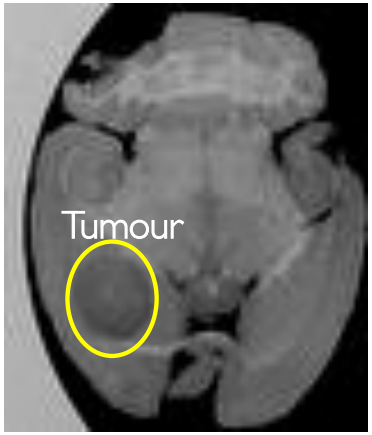
Discs

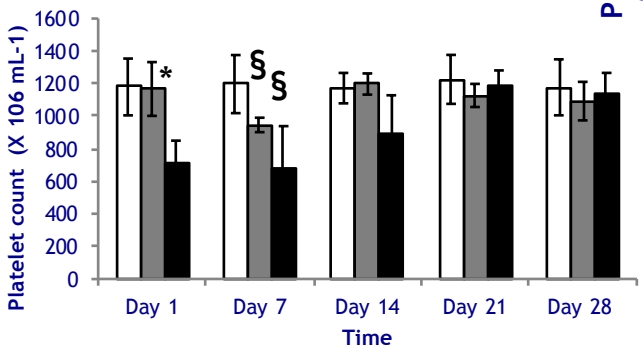


Peptide Nanofibres

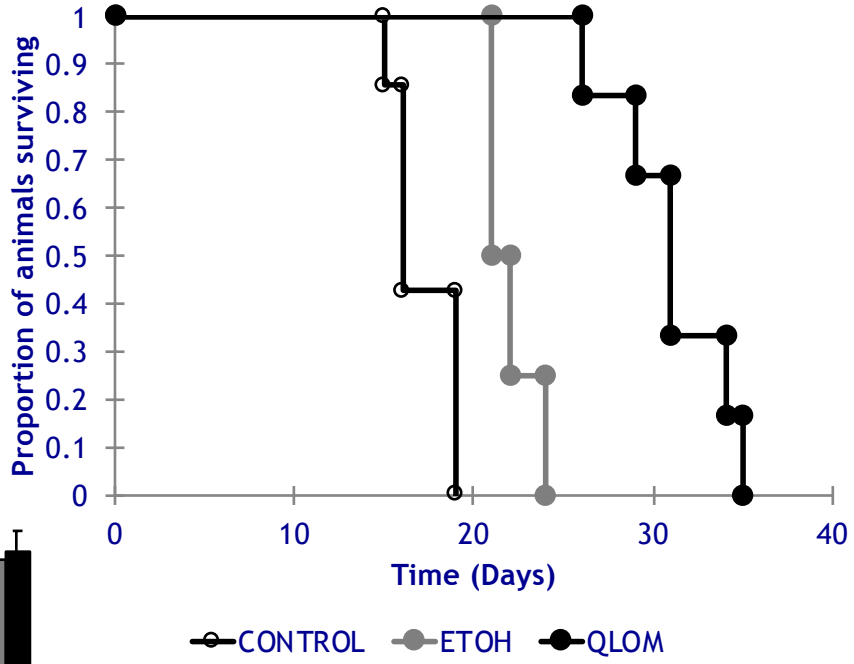
Wang et al (2004) Macromolecules, 37: 9114 - 9122.
Qu et al (2008) Langmuir, 24: 9997–10004
Lalatsa et al (2012) J Control Rel, 161: 523 – 536.
Mazza et al (2013) ACS Nano, 7: 1016-1026

Intracranial Tumours





Lomustine polymer Nanoparticles (13 mg kg-1) ■
Ethanolic lomustine (1.2 mg kg-1) ■
Untreated animals □



Nanoparticles prolong survival
No differences in femoral, white and red cell counts
Both treatments cause a change in platelets

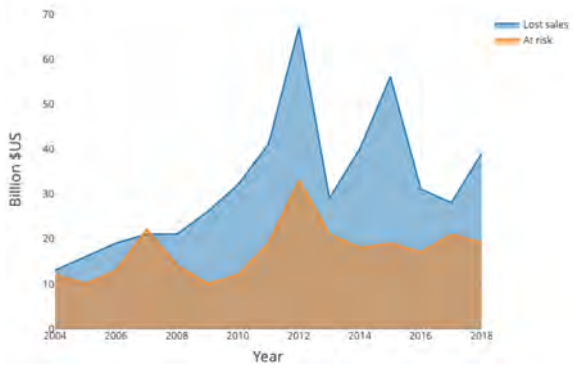
Fisusi et al, 2016, Pharm Res, 33, 1289-303.


nanomerics
...deliver more

Pharma Market Challenges as Drivers

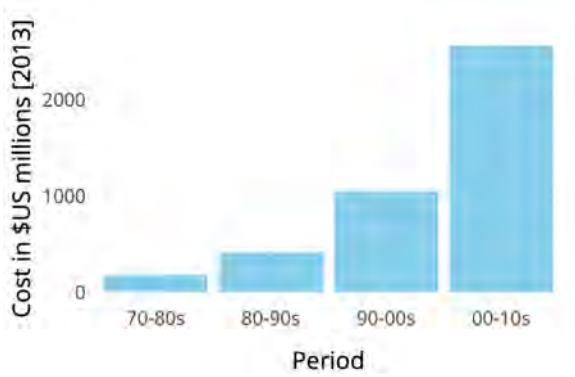
Loss of patent protection

- US$194 billion in lost sales 2017-2022
- US$31 billion in lost sales in 2018 alone



Increasing cost of NEW drugs

- Low Productivity
- Total cost increase to >US$ 2.5 billion

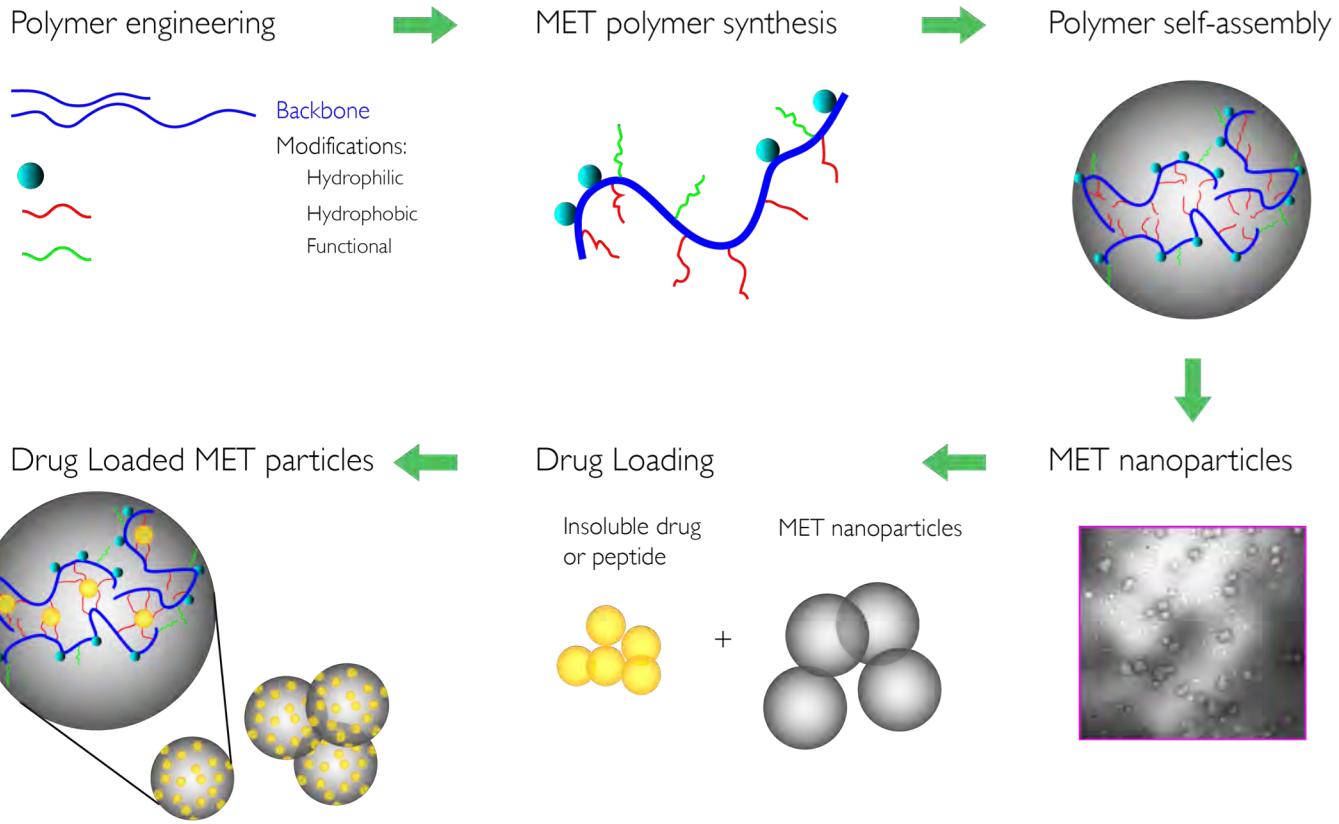


Wrapping drugs with Nanomerics' Molecular Envelope Technology (MET) creates:

- improved 'known' medicines, rescued new chemical entities
- Patent protected and premium pricing

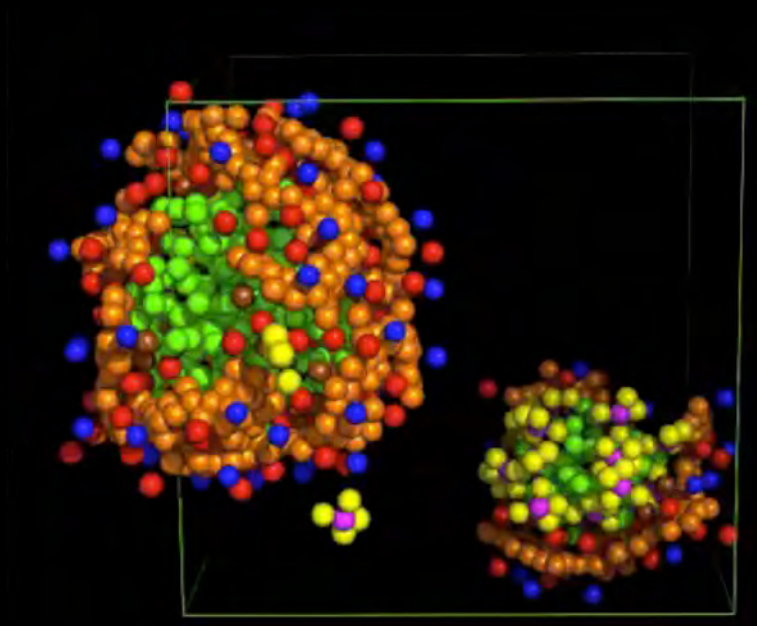
Solution: Molecular Envelope Technology (MET)

Engineered from scratch for enhanced delivery



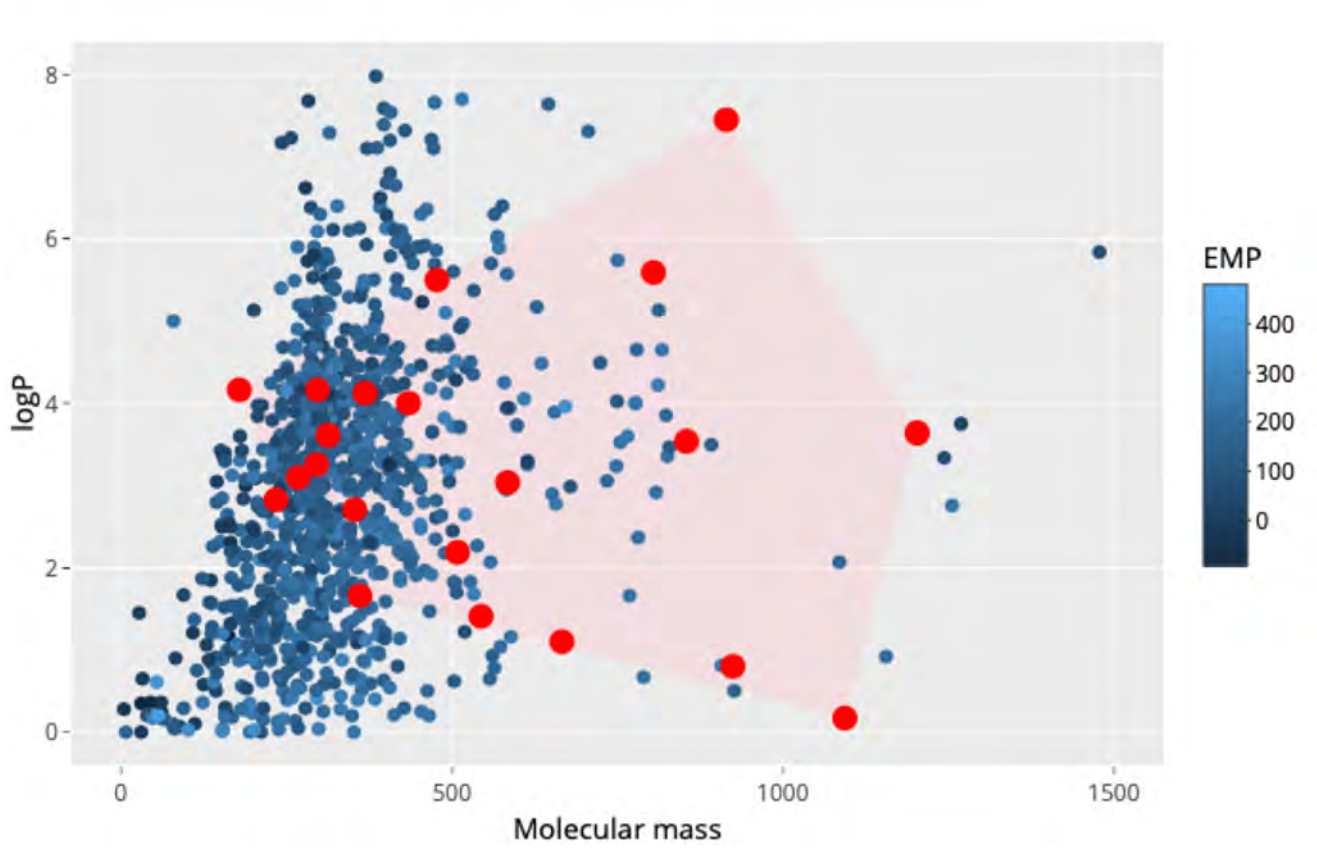
Molecular Envelope Technology

1. Non-covalent Encapsulation
2. High drug loading: 9 – 50% w/w
3. Highly stable nanoparticles: low micromolar CMC



MET Formulation Space

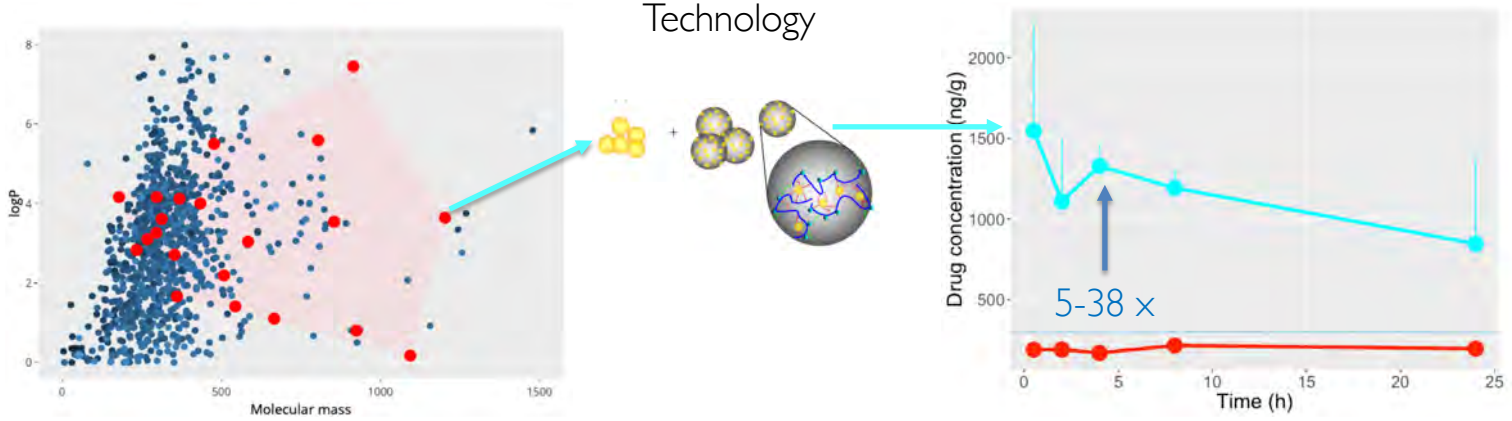
- Data mapped on www.drugbank.ca



Nanomerics Solution

- Molecular Envelope Technology (MET) wrapping of known drugs:
  - Creates better medicines for patients
  - Gives patent protection and retains/creates value

Poorly soluble drugs + Molecular Envelope Technology = Better Drugs + Patent protection



Royal Society of Chemistry Award 2017

MET Safety Demonstrated in GLP Regulatory Toxicology Studies

Test	Outcome
Single intravenous dose in the rat	Maximum tolerated dose = 150 mg kg^{-1}
7 Day repeat intravenous dose study in the rat	Maximum tolerated dose = 100 mg kg^{-1}
GLP Mutagenicity testing Ames test	Negative
GLP Mutagenicity testing Mouse Lymphoma Test	Negative
GLP Intravenous Rat Irwin Study	Nothing abnormal detected at 100 mg kg^{-1}
GLP Intravenous respiratory safety pharmacology in the rat	NOAEL = 40 mg kg^{-1}
Oral 7 day repeat dose ranging dog study	NOAEL = 300 mg kg-1 (top dose studied)
GLP oral 28 day repeat dose dog study	NOAEL = 150 mg kg^{-1} (top dose studied)
Oral 7 day repeat dose ranging rat study	NOAEL = 200 mg kg^{-1}
GLP oral 28 day repeat dose rat study	NOAEL = 200 mg kg^{-1} (top dose studied)
Intranasal 7 day repeat dose ranging rat study	NOAEL = 30 mg kg^{-1} (Reduced weight gain at 50 mg kg^{-1})
GLP 28 day intranasal dose in the rat	NOAEL = 18 mg kg^{-1}
6 day topical Ocular tolerability study in the rabbit	NOAEL = 40 mg mL^{-1} (top concentration studied)

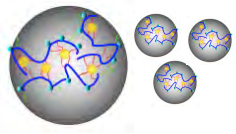
FDA 505(b)(2) FDA Pre-IND Guidance Summary

- ✓ Polymer sufficiently characterised
- ✓ Target product profile and specifications
- ✓ Preclinical PK data
- ✓ First in Human Safety and Tolerability Study Design
- ✓ Manufacturing guidance and pilot batch data for NDA stated
- ✓ Pivotal study design
  - Two clinical efficacy studies with a limited number of primary end points
- ✓ Advice on analytical qualification & later stage CMC meeting

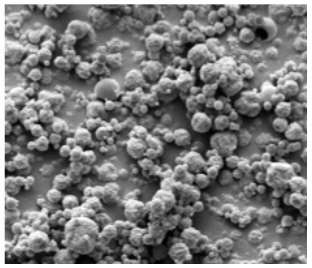
Licensed assets

Nose-to-brain delivery

① Loaded Nanoparticles



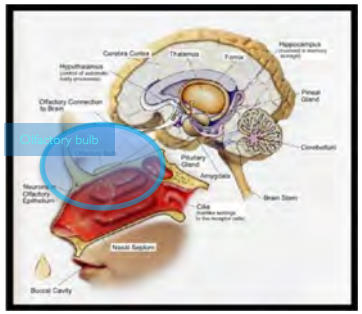
② Spray dried micro-particles



③ Naltos™ Powder Device

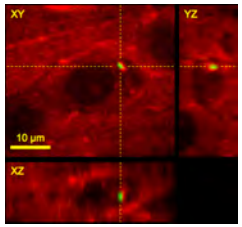
④ Cyclonic Plume

⑤ Olfactory deposition into nano-particles

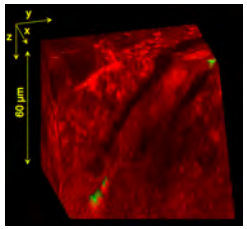


⑥ Brain transport & activity

Thalamus



Cortex

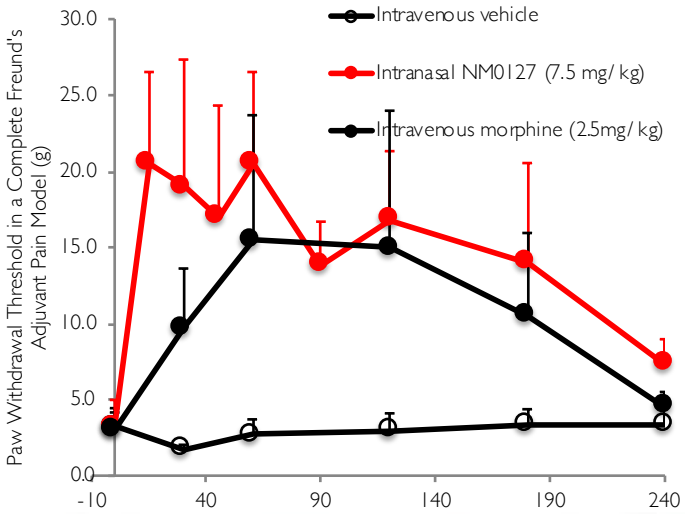


NM127 – Peptide replacement of opiates

Nose to brain 505(b)(1)

NCE - endogenous API

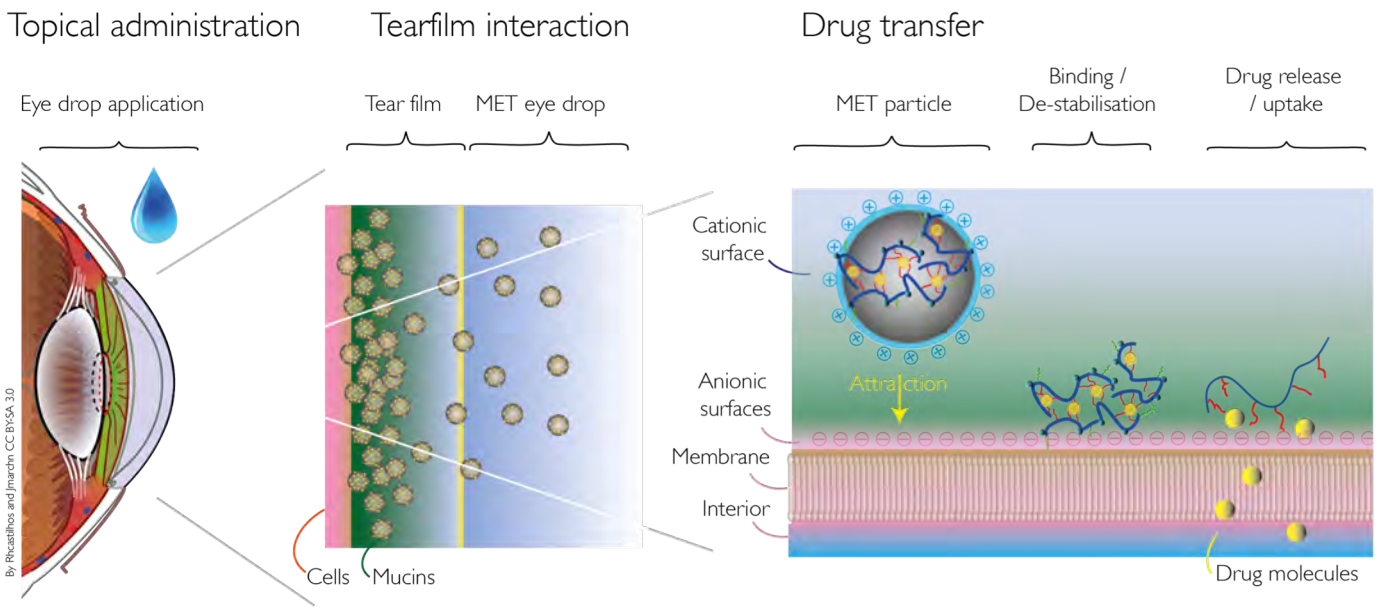
- opiate analgesic replacement
- Fast pain relief for the treatment of acute and chronic pain
- Endogenous peptide delivered non-invasively to the brain
- As potent as opiates but avoids the side effects
- No habit forming potential
- Enkephalin is active in humans



Opioid sparing pain killer

- NM127 VIRPAX PHARMACEUTICALS
  - Enkephalin based pain killer for acute and chronic pain
  - No analgesic tolerance or risk of addiction
  - Active in all preclinical pain models
  - Licensed to Virpax Pharmaceuticals

MET Application - Ocular delivery



Proposed mechanism

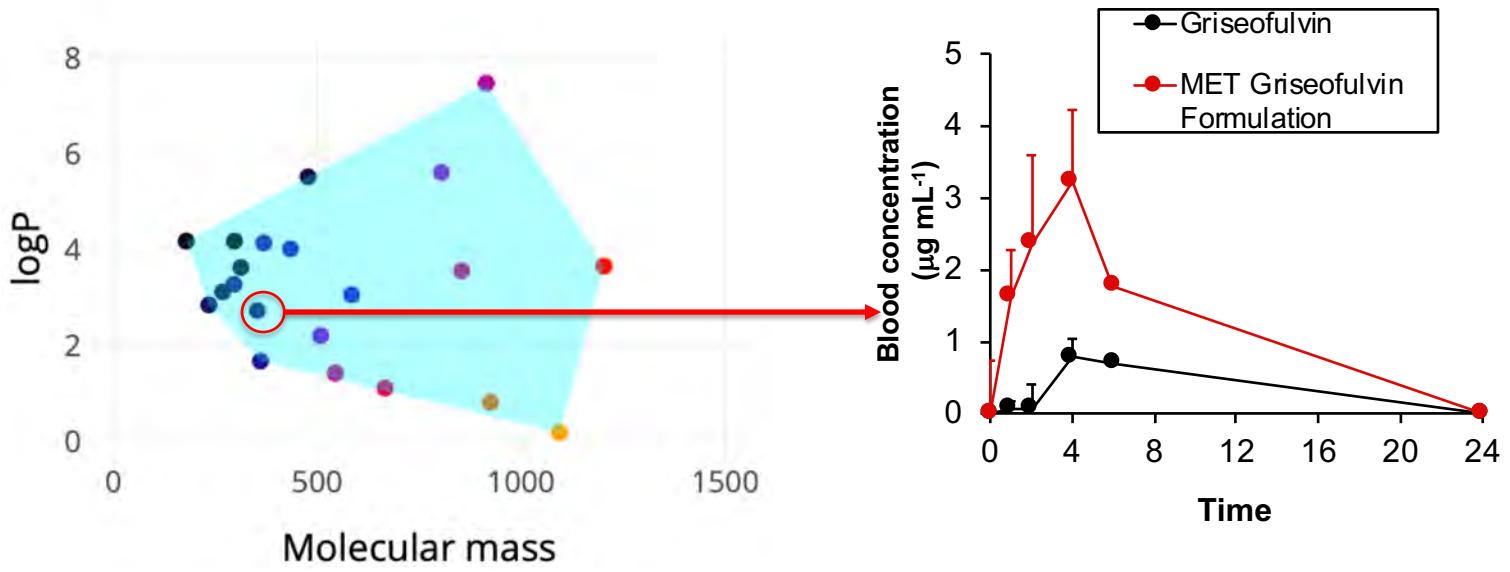
Non-irritant ocular medicine

- NM133 

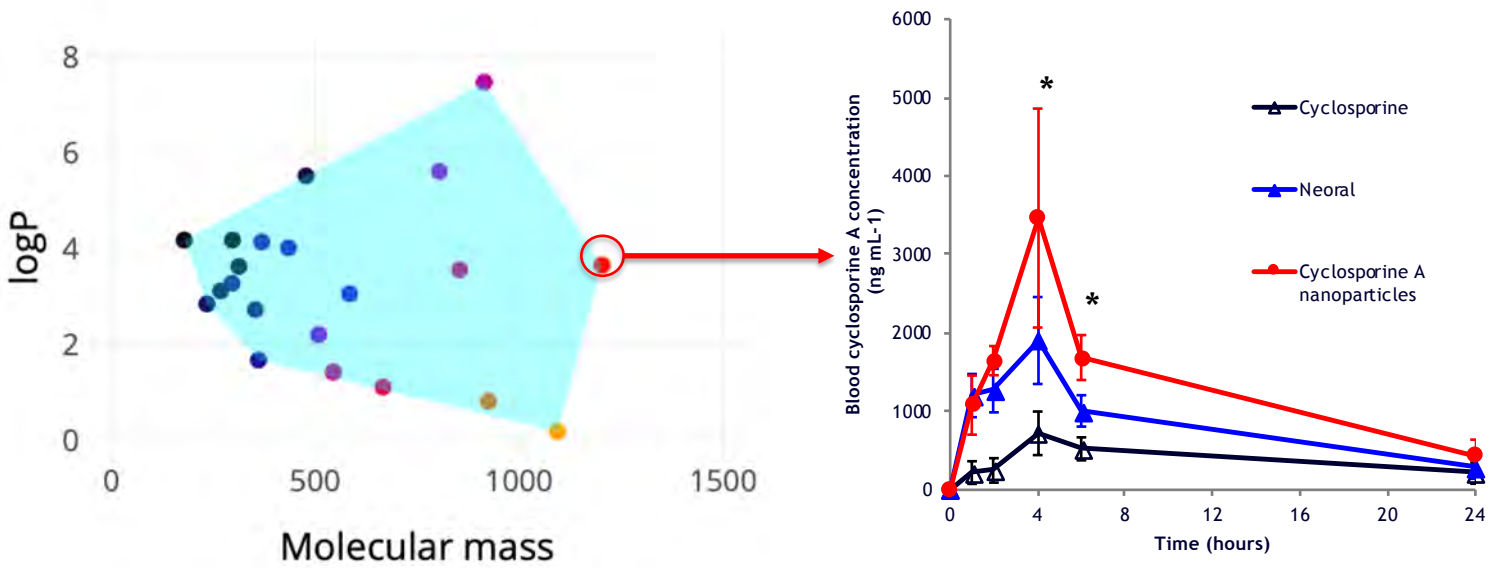
  - Cyclosporine A eye drops for dry eye disease
  - Superior to the market leader
    - Vehicle is non-irritant
    - Delivers 5 – 8 times more drug to tissues
    - Clear aqueous liquid – oil free
  - Clear regulatory pathway: FDA pre-IND guidance
  - Licensed to Iacta Pharmaceuticals

The oral route

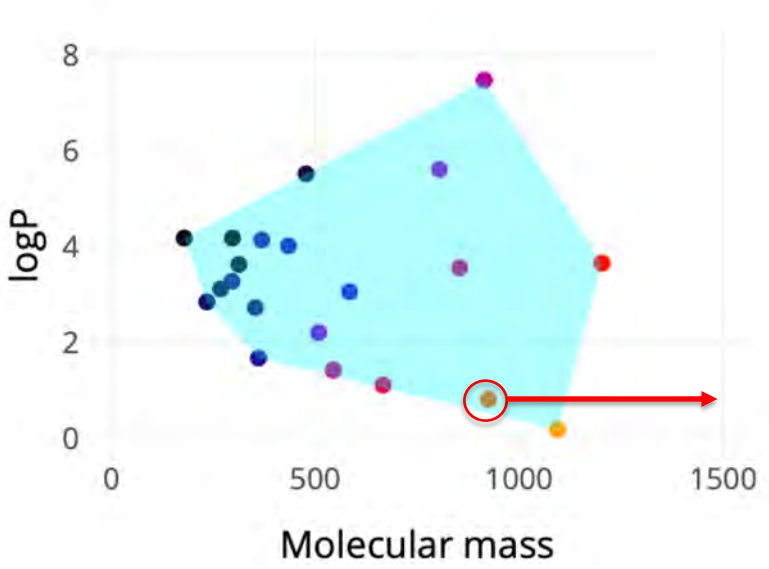
Oral Griseofulvin

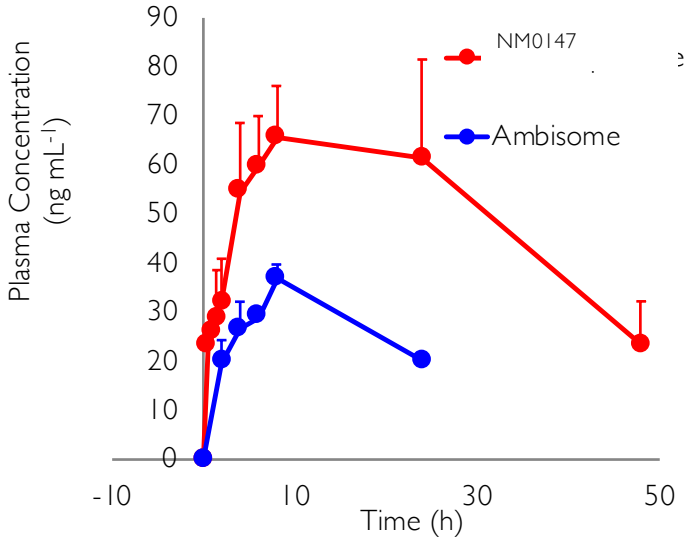


Oral Cyclosporine

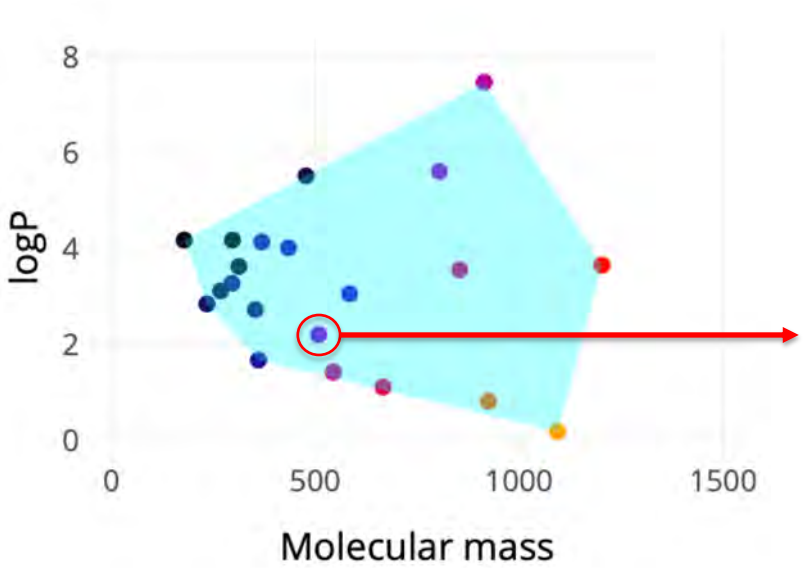


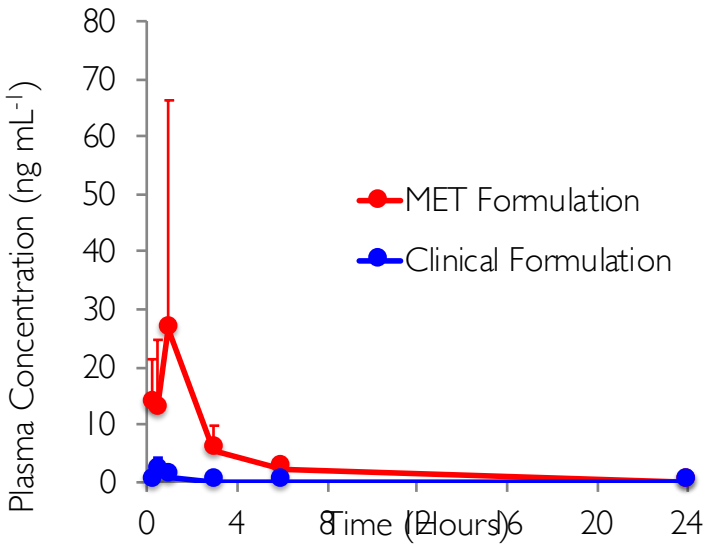
Oral Amphotericin B



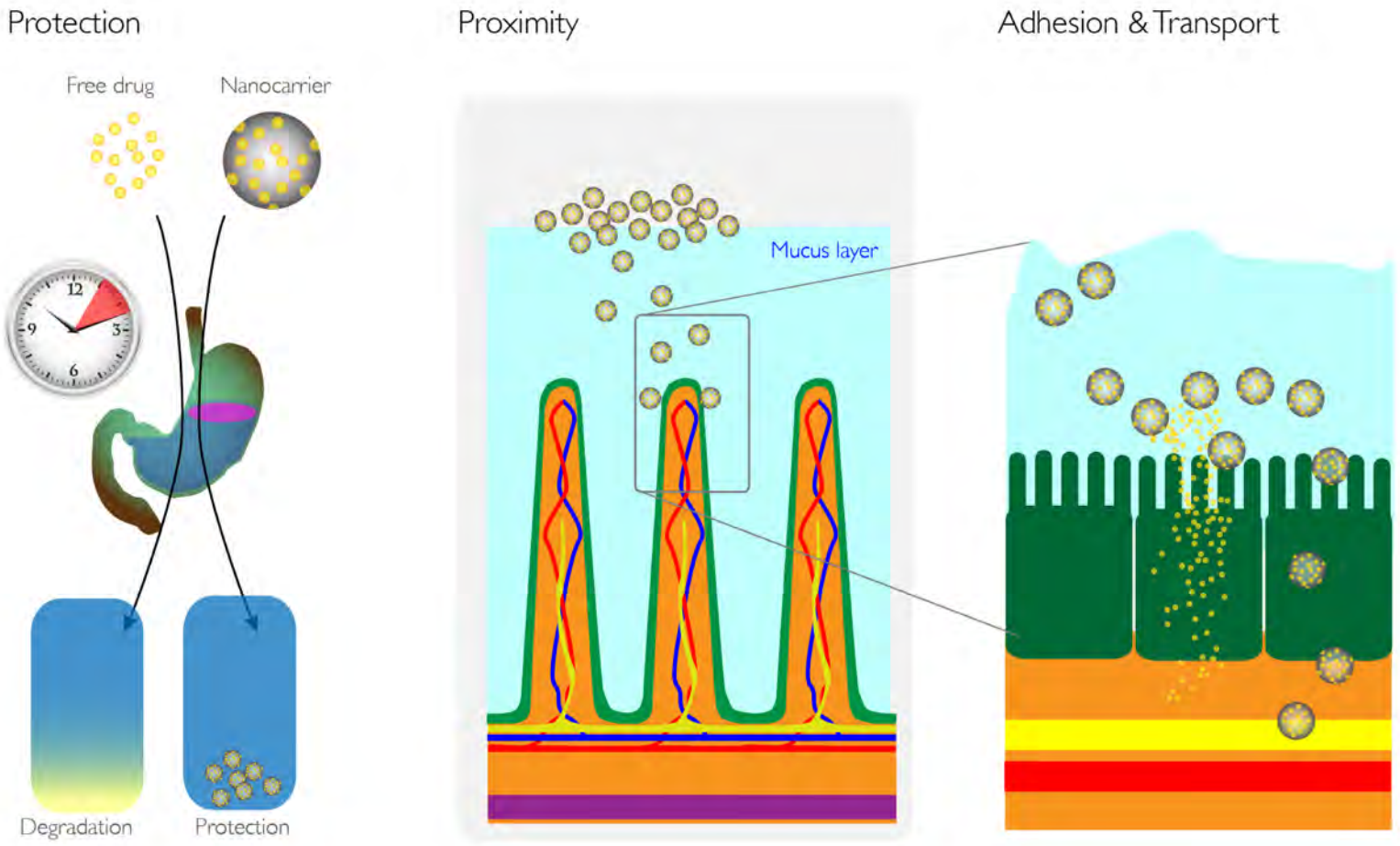


Oral formulation of Phase II anti-cancer drug

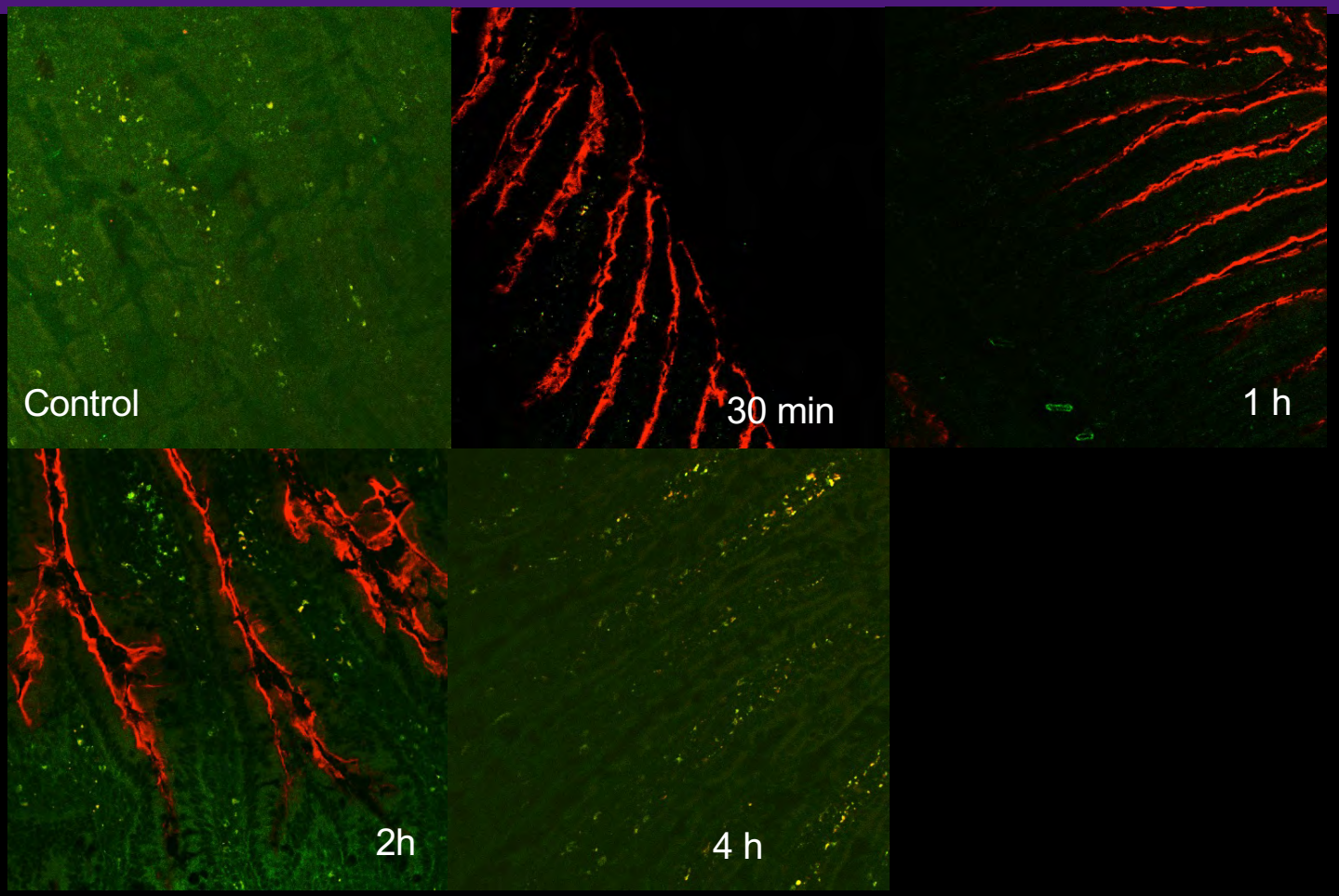




MET – Proposed Mechanism

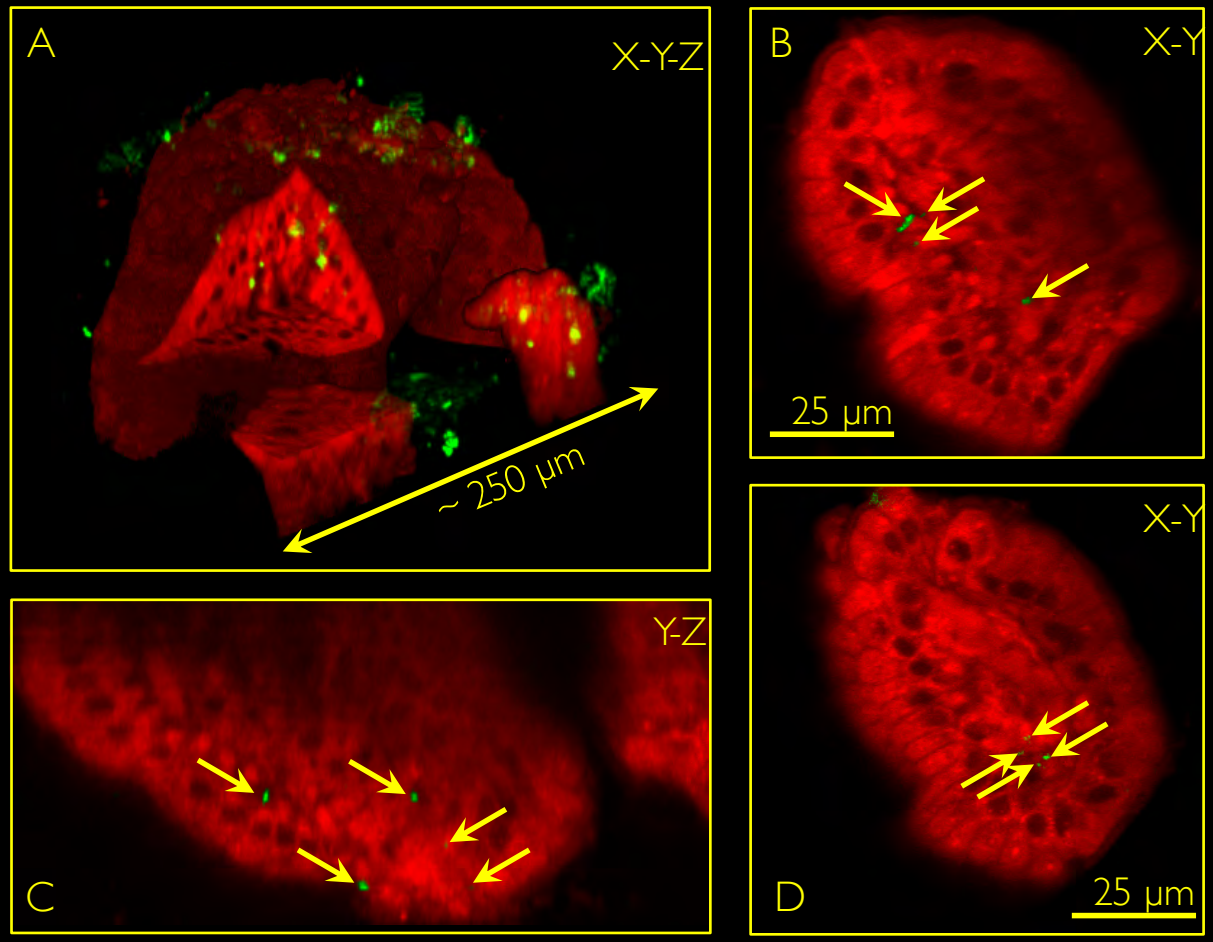


Mucus penetration

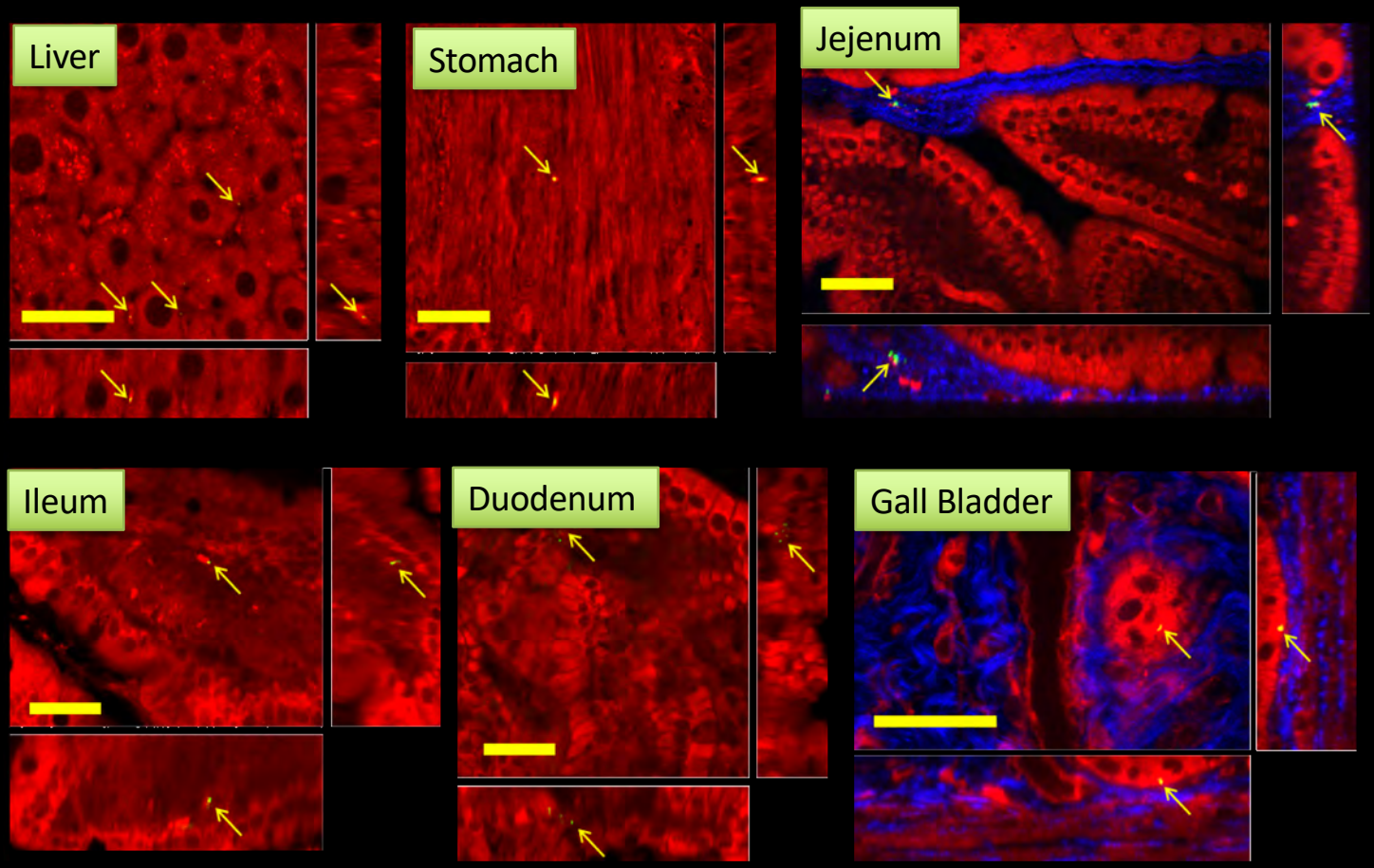


Siew et al, Mol Pharm, 9, 14-28 (2012)

MET particle uptake in intestinal villi

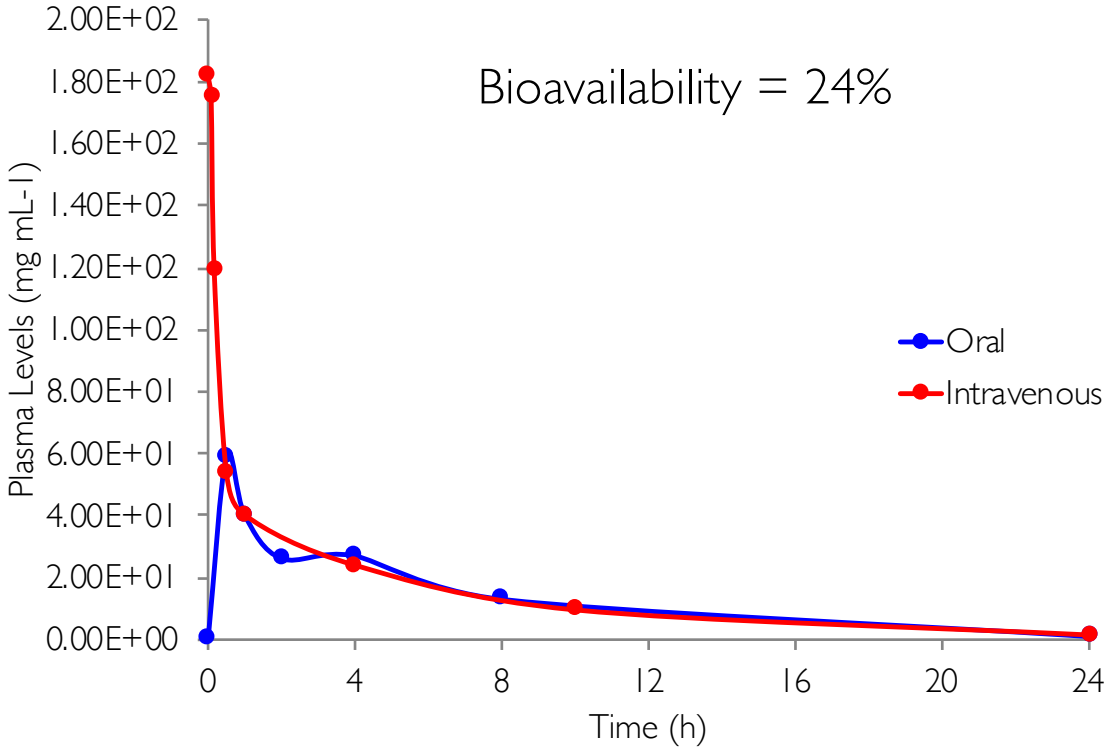


MET Particles by CARS Microscopy in the GIT



Garrett et al (2012) J Biophotonics, 5: 458-468
Garrett et al (2012) J Raman Microscopy, 43: 681-688

MET Particle Bioavailability



Lalatsa et al (2012) Mol Pharm, 9: 1764-1774.

MET Competitive Advantage – Nanoparticle Technologies

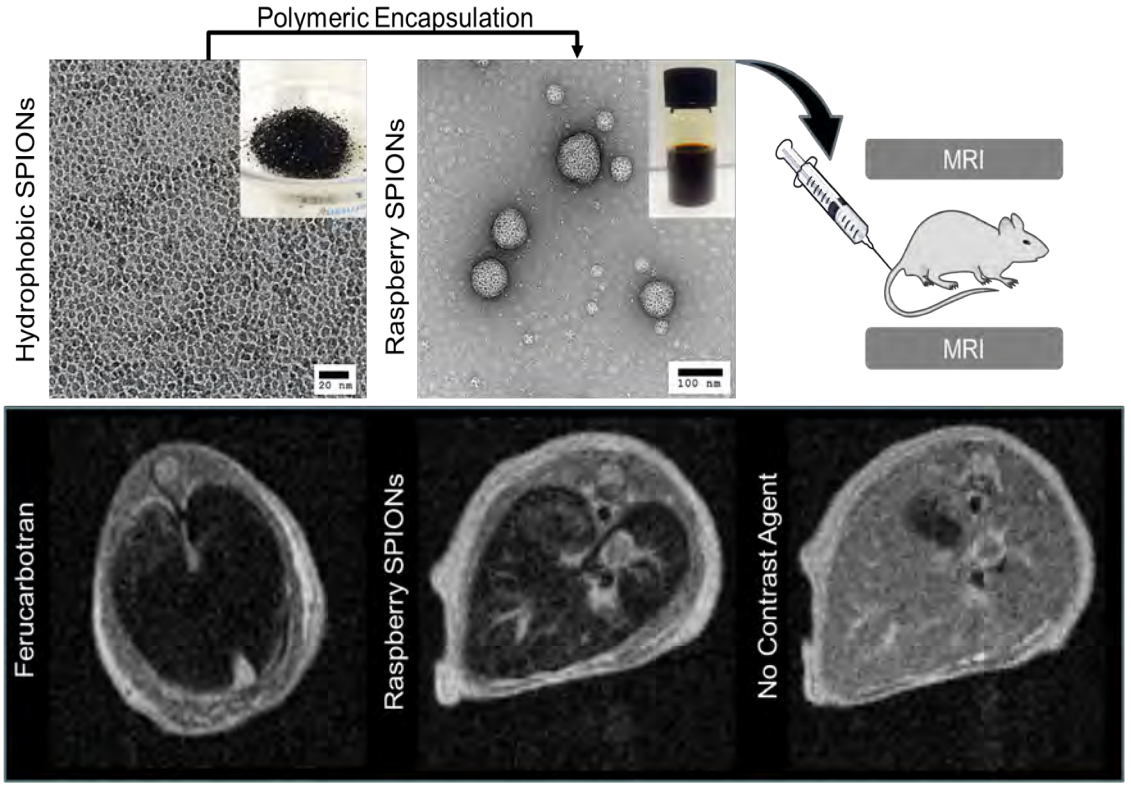
Attributes	MET	Pegylated Liposomes	Poly-(L-lactide-co-glycolide)-co-poly(ethylene glycol) nanoparticles	Albumin stabilised nanoparticles
Oral particle uptake and tablet formulations				
Nose to brain delivery				
Non-irritant ocular drug delivery and penetration enhancement				
Intravenous drug delivery				
Hydrophobic drug delivery				
Hydrophilic drug delivery				
Amphiphilic drug delivery				
Ease of manufacture			Unknown	Unknown
Marketed Products				

Summary of MET Advantages

- GLP safety studies conducted - no safety issues
- High API payload: 10 – 50% w/w
- Stable system: micromolar CMC
- Liquid and solid formulations
- Bioavailability enhancement: 5 - 38 fold higher
- Drug targeting
  - Oral to the lung and spleen
  - Nasally to the brain
- *Enable*s peptide bioavailability
  - Limits degradation of drug cargo
  - Enhanced transport across epithelial barriers
- Multiple routes of administration
  - Topical to the eye
  - Intranasal to the brain
  - Oral to the liver, lungs and spleen
- Multiple molecules
  - Hydrophobic drugs
  - Amphiphilic peptides

Qu, et al (2006) Biomacromolecules, 7, 3452-3459
Siew et al (2012) Mol Pharmaceutics, 9: 14 – 28.
Lalatsa et al (2012) Mol Pharmaceutics, 9: 1665-1680
Serrano et al (2015) Mol Pharmaceutics, 12,: 420-431,
Lalatsa et al (2015) J Control Rel, 197: 87 – 96
Fisusi et al (2016) Pharm Res, 33: 1289-1303.
Godrey et al (2017) J Control Rel, 270, 135-144

Iron Oxide Imaging



Good visualisation of the liver vasculature 1 hour after dosing

Hobson et al (2019) *Nanomedicine (Lond)*, 14, 1135-1152

RaNT Programme Grant

Nick Stone
Exeter University

Julian Moger
Exeter University

Francesca Palombo
Exeter University

Pavel Matousek
Rutherford Laboratories

Jeremy Baumberg
Cambridge University

Ijeoma Uchegbu
UCL

Andreas Schätzlein
UCL

EPSRC Raman NanoTheranostics Programme Grant
£5.7 million

EPSRC
Engineering and Physical Sciences Research Council
UK Research and Innovation

Thank you