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Challenges in the development of long-acting therapeutics

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Coordinator Nanotherapeutics Hub
Biocompatibility lead CELT

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Team background

- Extensive experience in the determination of interactions between advanced materials, and complex medicines, with the **immune and haematological systems**
- Pharmacological, Pharmacokinetic and PBPK modelling of nanoformulated therapeutics
- (Basic) Physical and Chemical characterisation of nanotherapeutic delivery systems.
- Leading similar programmes both nationally and internationally - leveraging our expertise to accelerate the translation of nanotherapeutics

CELT

EUNCL Nanomedicine Characterisation Laboratory

safe nmt

REFINE
Regulatory Science Framework for Nano(bio)material-based Medical Products and Devices

ASTM INTERNATIONAL

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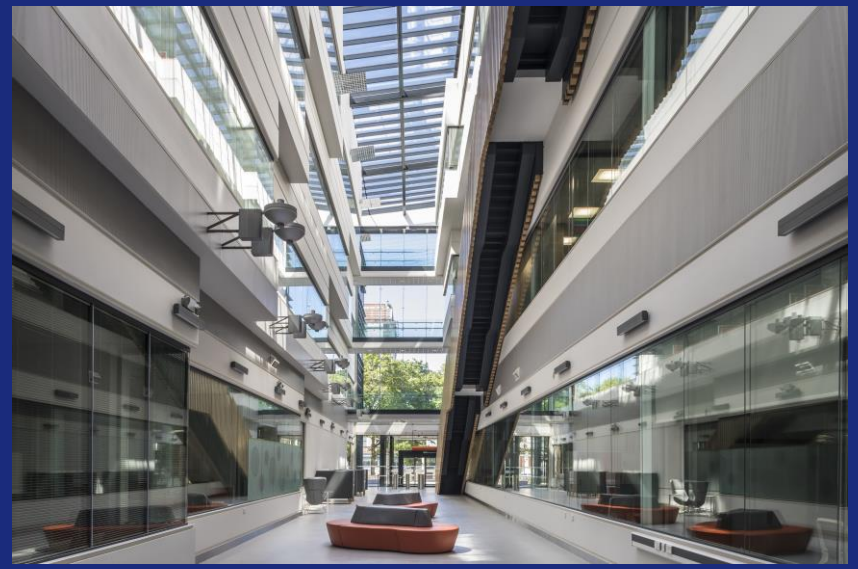
Nanotherapeutics Hub

- Currently based in the Materials Innovation Factory.
- Established in 2019, in partnership with the National Measurement Laboratory (UK)
- Working with academic groups, SMEs and Pharma to support lead candidate optimisation translation.
- Platform within iiCON (£160 million consortium for the development of therapeutics for infectious disease)



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Overview of current priorities/needs

1. Impact of biotransformation/weathering on nanoparticle-biological interactions

2. Intracellular fate of nanoparticles

3. Characterisation of depot “surfaces” and the impact on biocompatibility and PK

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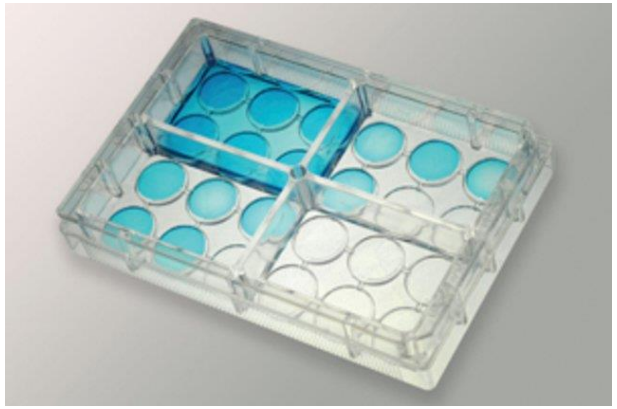
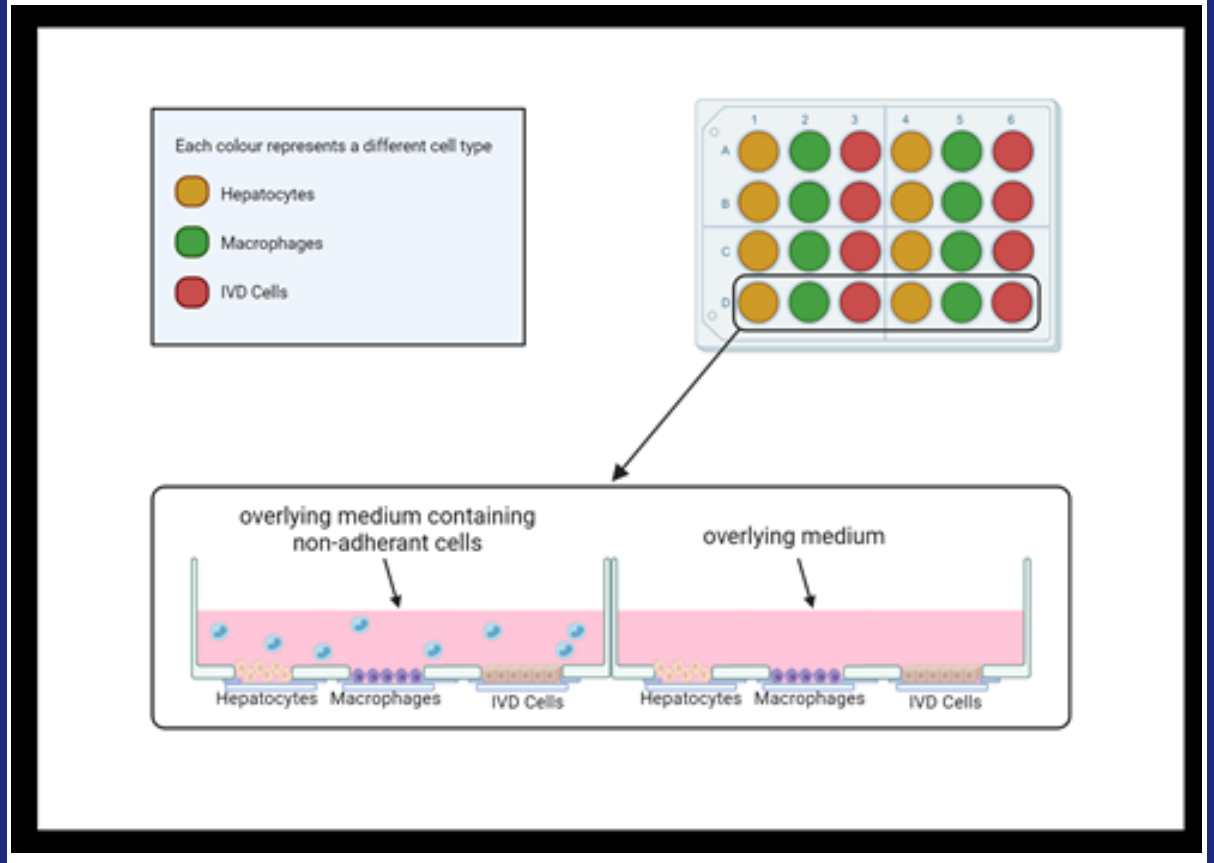
1. Biotransformation

- Nanoparticle characteristics will change when entering, and remaining, in a complex biological environment e.g., protein corona
- Interaction with intra-, or extracellular, processes may affect nanoparticle chemical characteristics e.g., lipid peroxidation in liposomes – in turn affecting biocompatibility.

idMOC

Integrated, discrete, multi-organ culture





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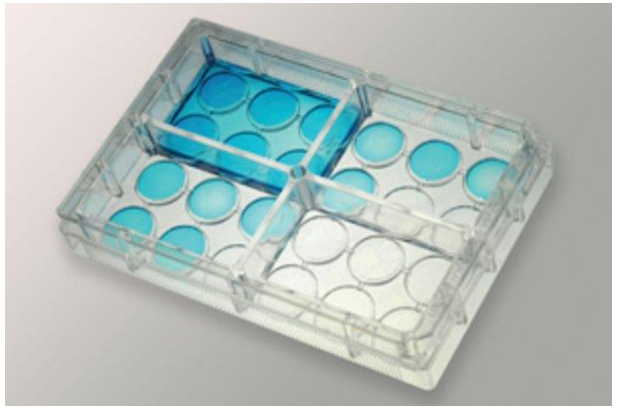
1. Biotransformation

- Nanoparticle characteristics will change when entering, and remaining, in a complex biological environment e.g., protein corona
- Interaction with intra-, or extracellular, processes may affect nanoparticle chemical characteristics e.g., lipid peroxidation in liposomes – in turn affecting biocompatibility.
- Need for robust methodologies to be able to detect these changes in multiple complex matrices; not just plasma/blood

idMOC

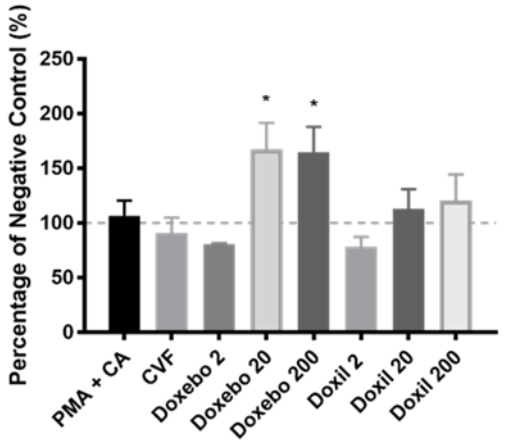
Integrated, discrete, multi-organ culture



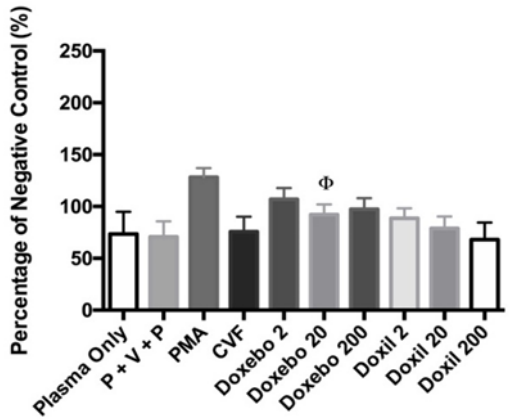
Incubate cells with liposomes directly (no other cells) or indirectly (with hepatocytes, endothelial cells, and macrophages.

Basophil activation (CD164), in response to liposomes:

Direct



Indirect



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2. Intracellular fate of nanoparticles

- Most small molecule drugs accumulate in cells via membrane transporters
- Nanoparticles tend to accumulate via active uptake mechanisms for macromolecules such as endocytosis and phagocytosis.

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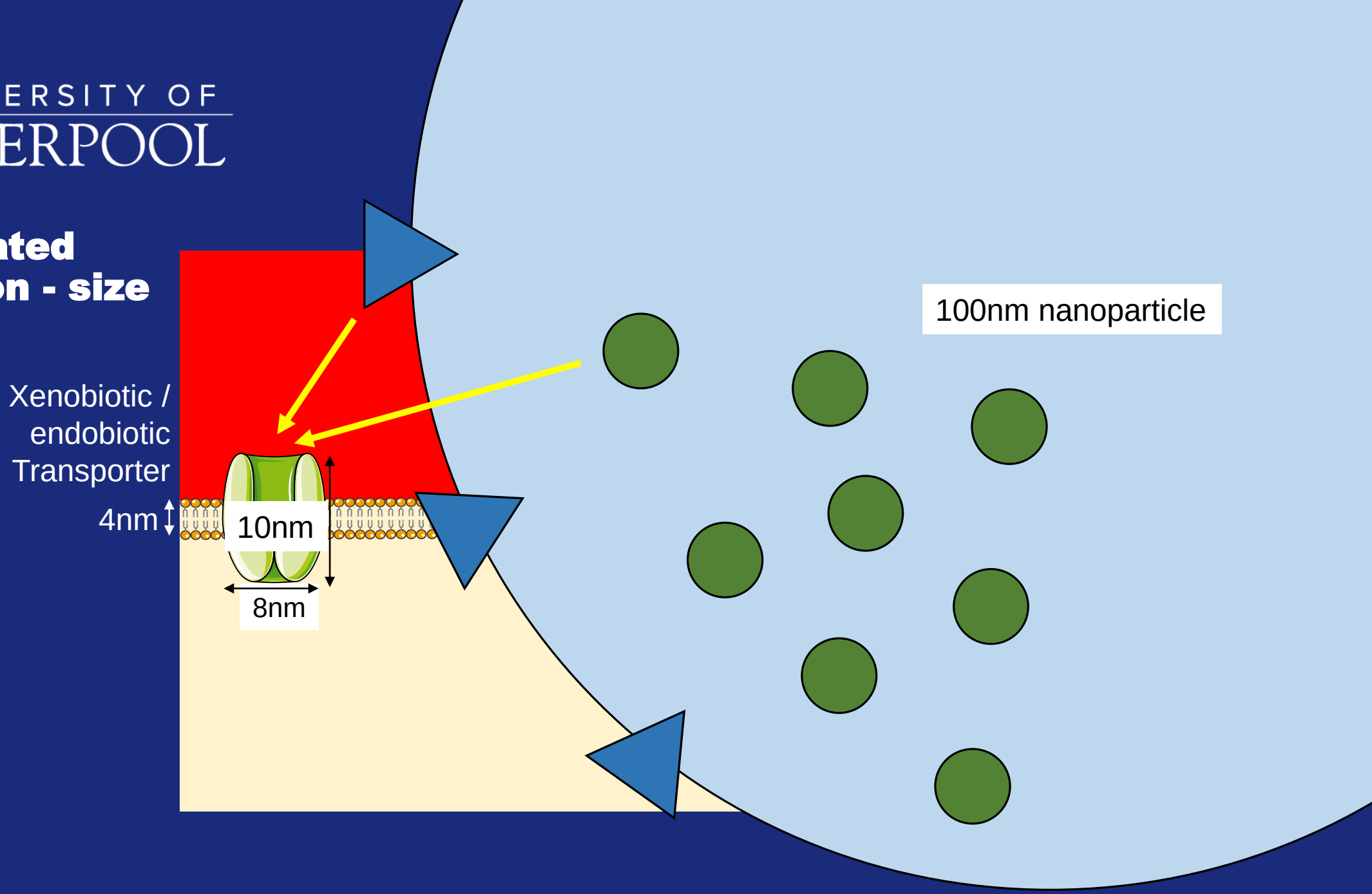
Free vs. nanoformulated accumulation - size



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2. Intracellular fate of nanoparticles

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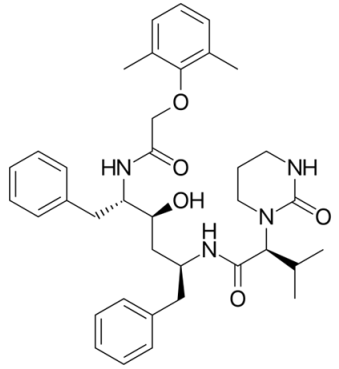
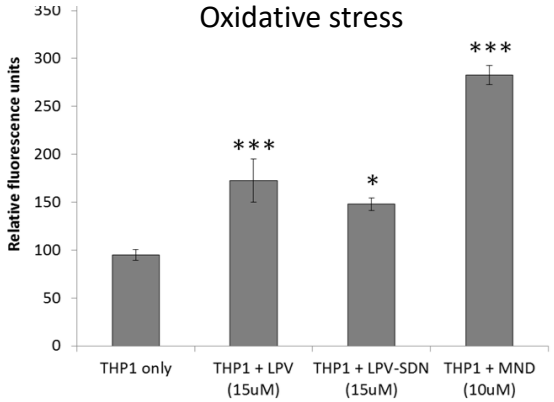
- Our antiretroviral based, solid-drug, nanoparticles have been shown to have superior PK parameters, compared to free drug.

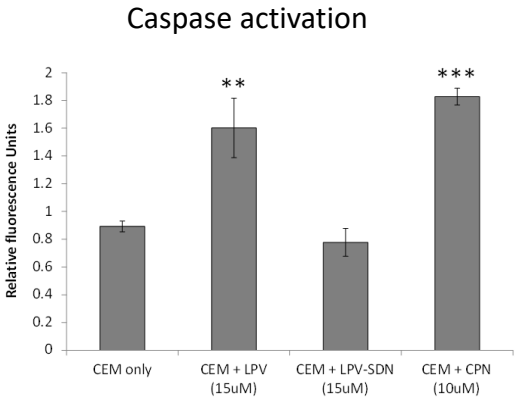
- Biocompatibility assessment also revealed unanticipated benefits

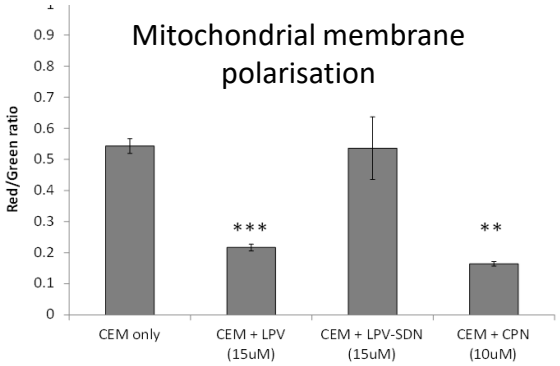
HIV protease inhibitors;

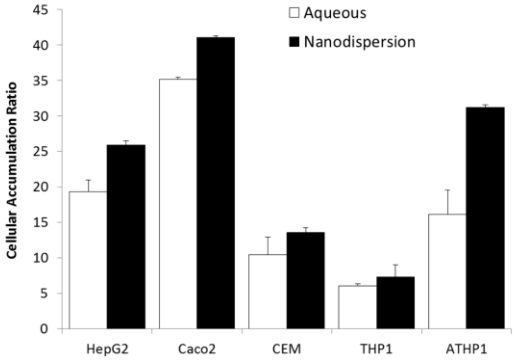
- significantly reduced HIV-induced morbidity and mortality and the lifespan of HIV patients prolonged.
- Compromised by serious side effects such as lipodystrophy and hepatotoxicity (ER stress, UPR effect)











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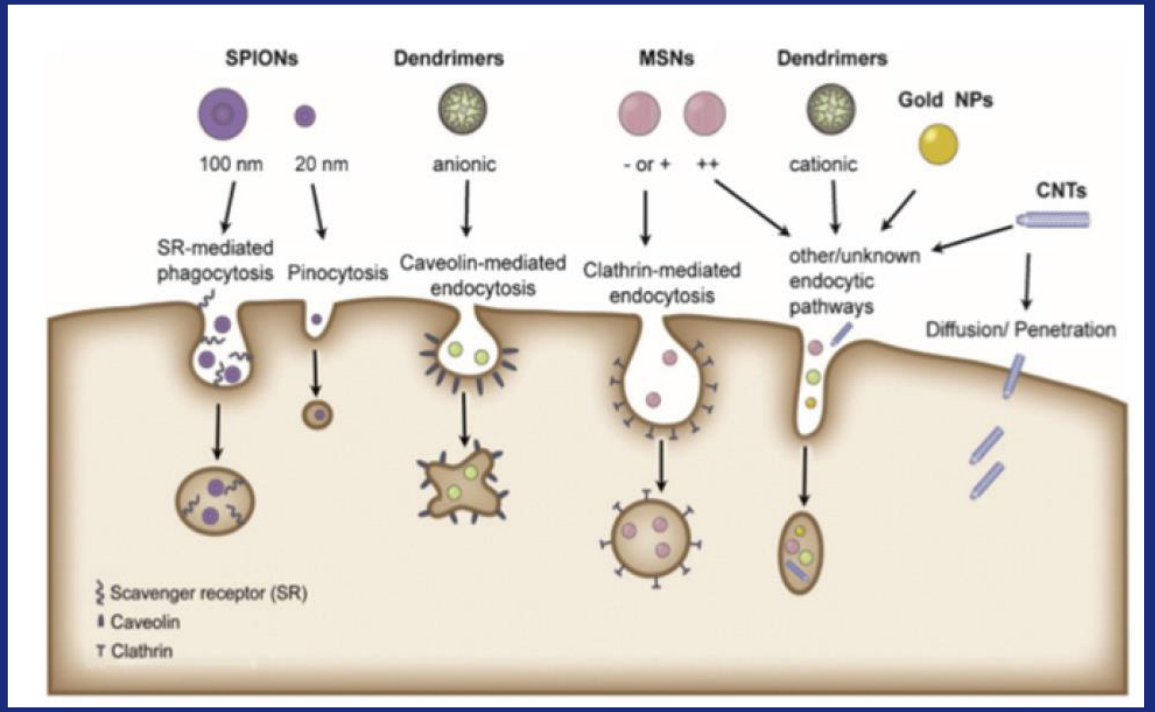
2. Intracellular fate of nanoparticles

- Most small molecule drugs accumulate in cells via membrane transporters
- Nanoparticles tend to accumulate via active uptake mechanisms for macromolecules such as endocytosis and phagocytosis.
- Differential routes of uptake, for drug-loaded nanoparticles appears to have beneficial effects on cellular health
- Does intra-vesicle accumulation affect NP properties and in turn affect drug release?
- Requirement for intra-vesicle characterisation.



Iversen et al, 2011

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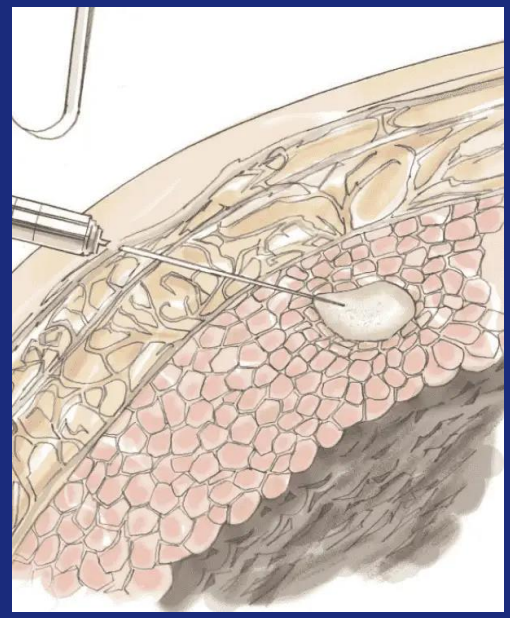
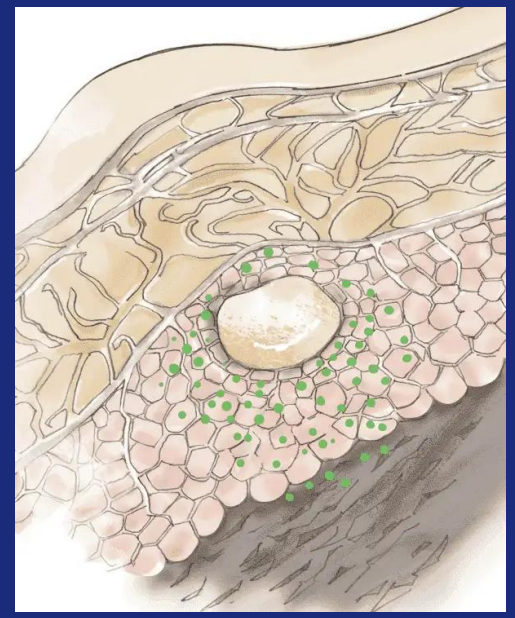
3. Long-acting depots





- Long-acting formulations offer a number of advantages for various therapies, particularly in chronic conditions such as HIV, or in complex patient groups such as mental health.

- Most long-acting formulations are administered subcutaneously and upon administration, form a depot that eventually releases drug into surrounding tissues and vasculature.

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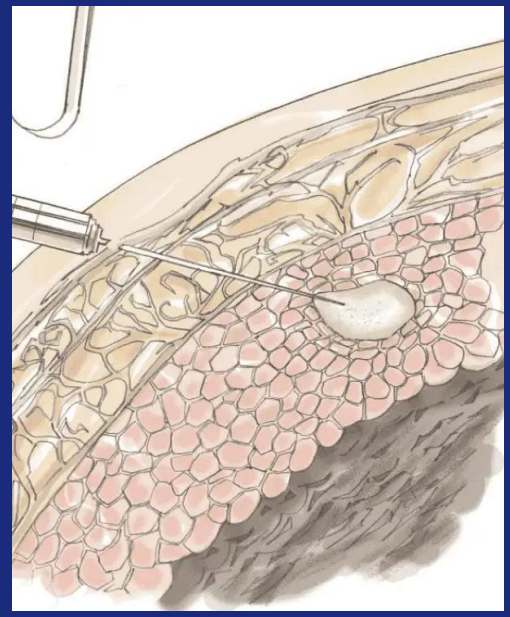
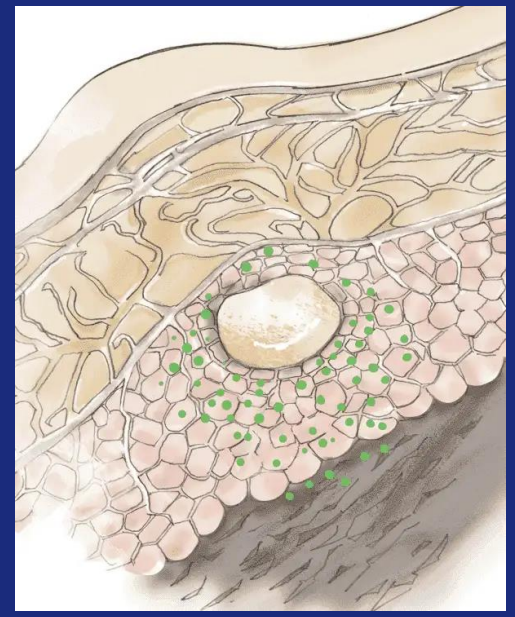
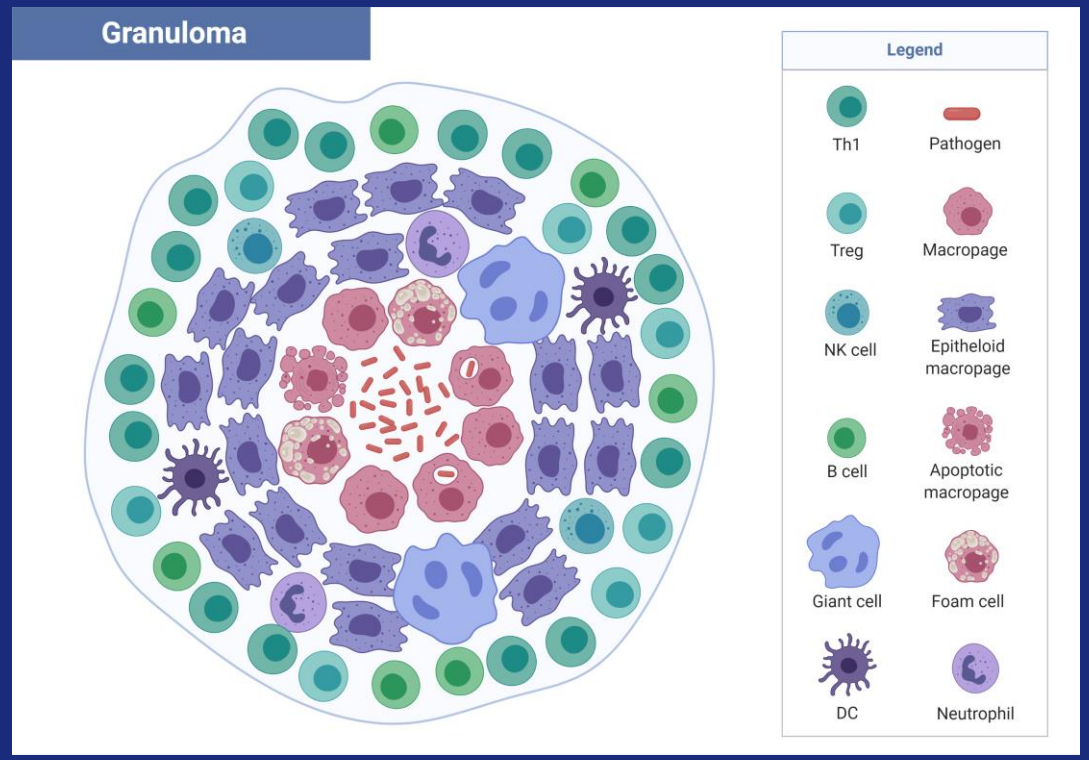
- Some depots, have been shown to trigger a “foreign body” reaction and subsequent granuloma formation.







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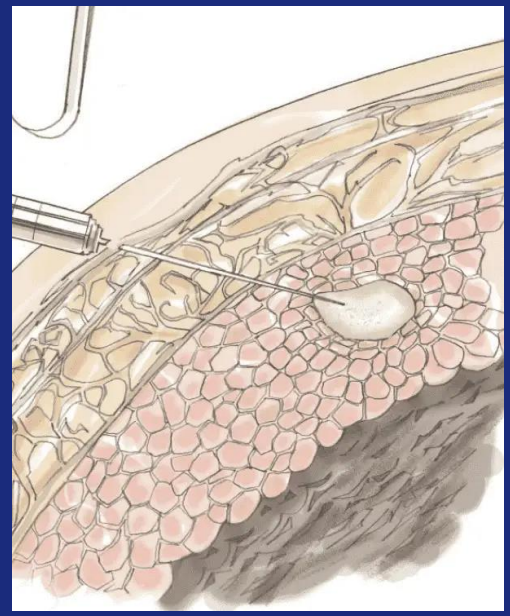

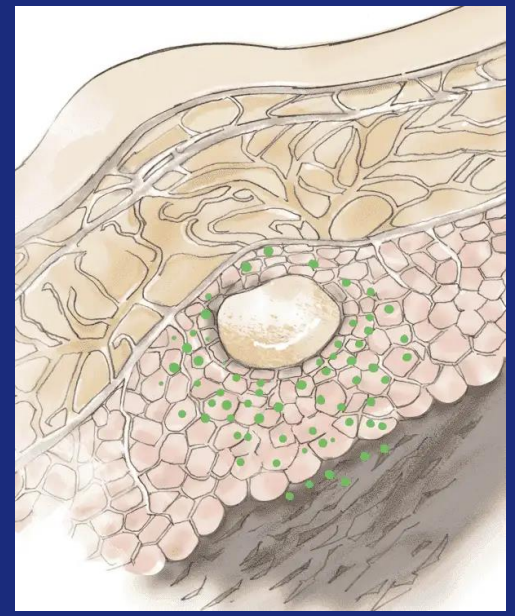

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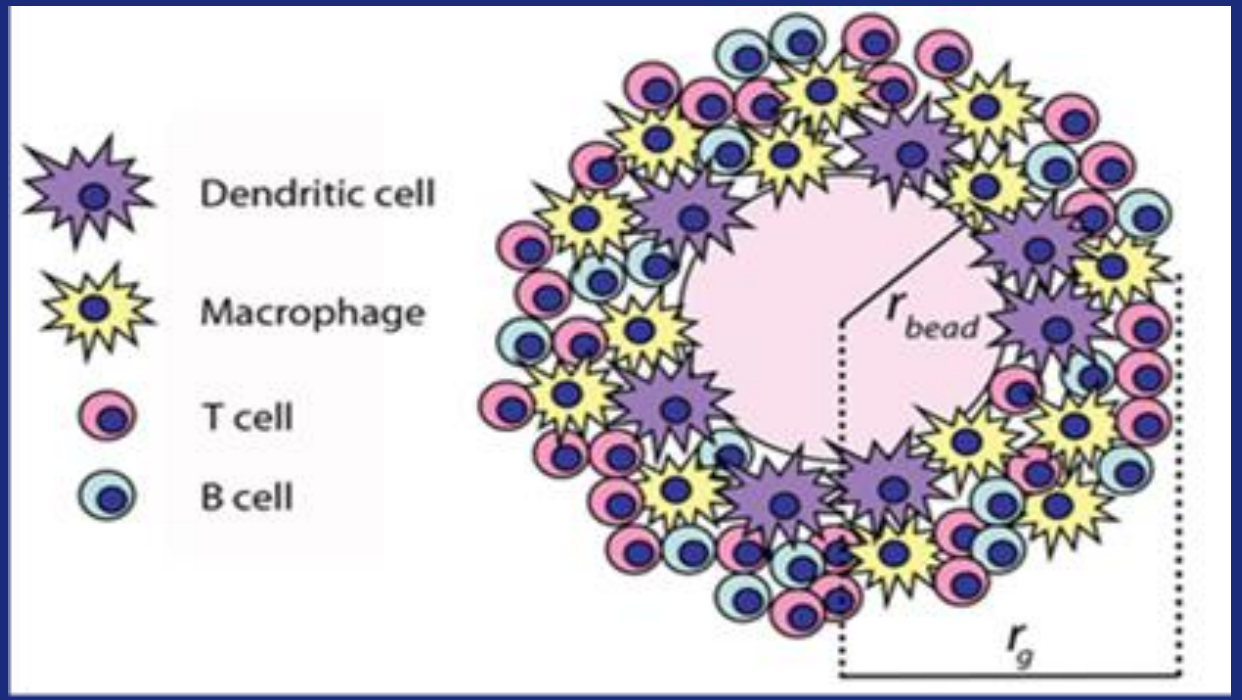
- Most long-acting formulations are administered subcutaneously and upon administration, form a depot that eventually releases drug into surrounding tissues and vasculature.

- Some depots, have been shown to trigger a “foreign body” reaction and subsequent granuloma formation.
- The composition of the granuloma, has been shown to affect the release of drugs from the depot
- Unclear how this new “interface” affects this



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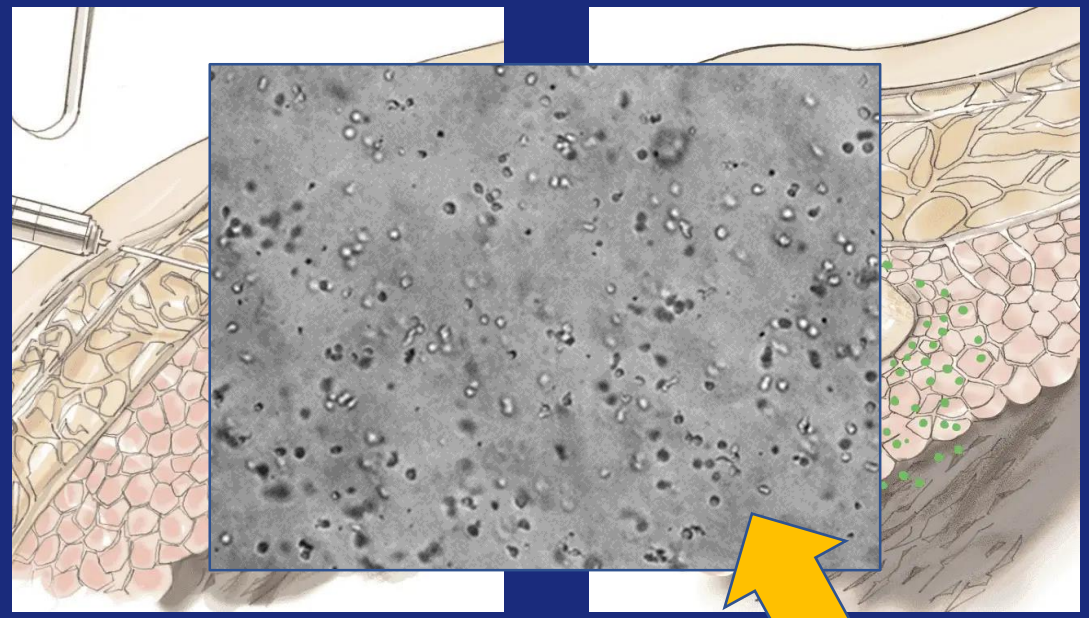

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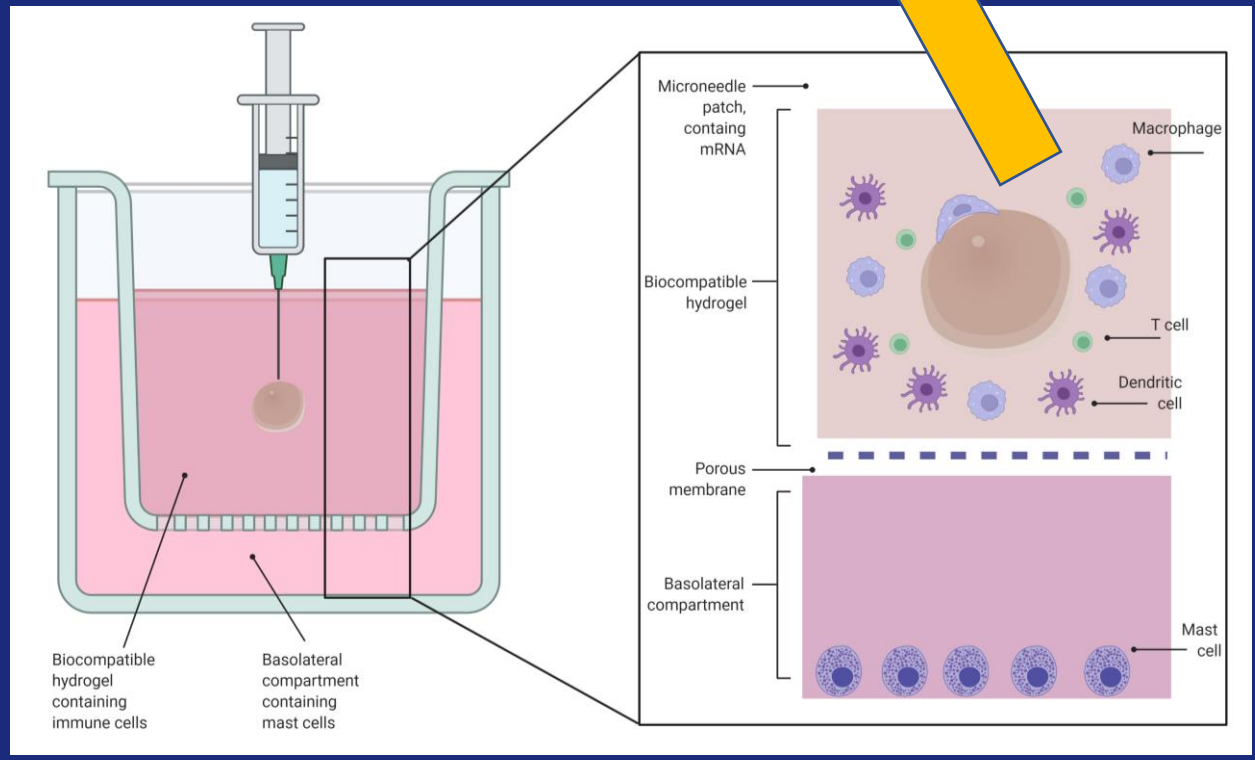

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Overview of current priorities/needs

1. Impact of biotransformation/weathering on nanoparticle-biological interactions
   - Physico-chemical characteristics in complex matrices
   - Impact of matrices on biotransformation and response

2. Intracellular fate of nanoparticles
   - PCC linked to route of uptake
   - Altered PCC in intracellular vesicles, which may affect cellular health and drug release.

3. Characterisation of depot “surfaces” and the impact on biocompatibility and PK
   1. PCC at interface of depots


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