
QUEEN'S UNIVERSITY BELFAST
EST 1845
Understanding the microscopic properties and drug diffusion kinetics in long-acting peptide hydrogel drug delivery implants for HIV/AIDs
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EPSRC Engineering and Physical Sciences Research Council
wellcome
Invest Northern Ireland
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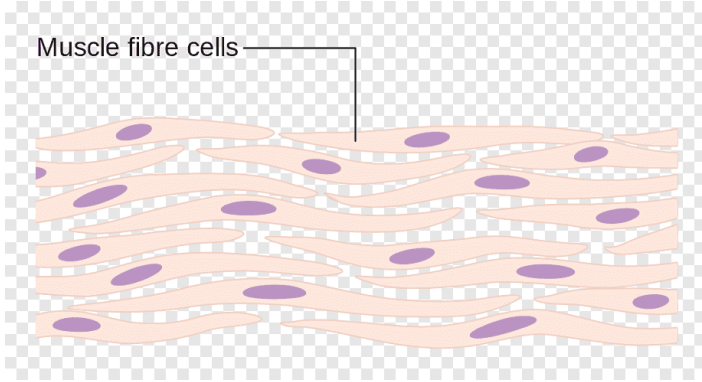
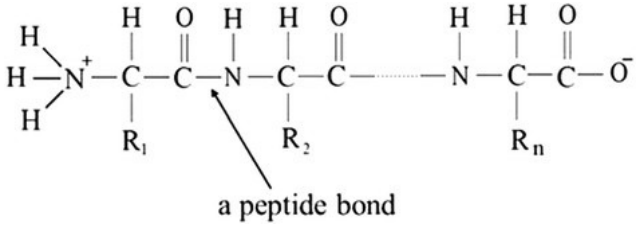
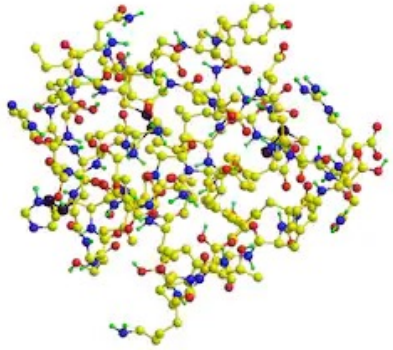
What are Peptide Nanomaterials?



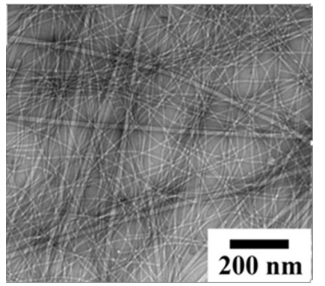
Peptide

Protein



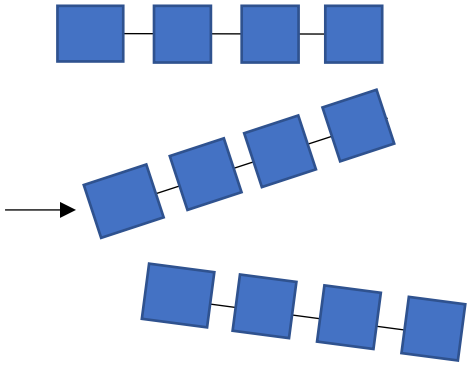


Peptide Nanomaterials: Core Technology



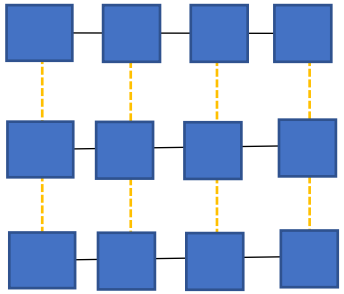
Peptide Hydrogels

Self-assembled Peptides



Stimuli

-pH
-Temperature
-Ionic Strength
-Specific enzymes



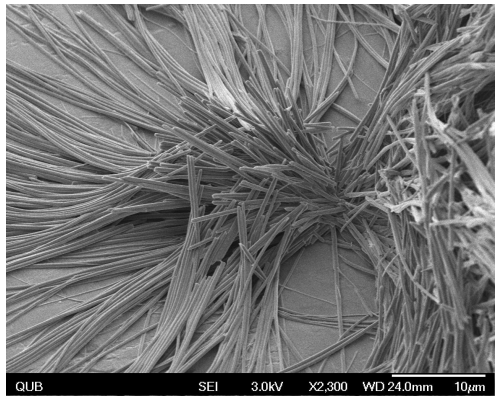
Self-assembly

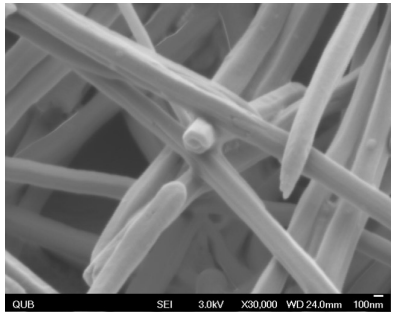
Peptide

Nanotubes

Short peptide sequences

Non assembled





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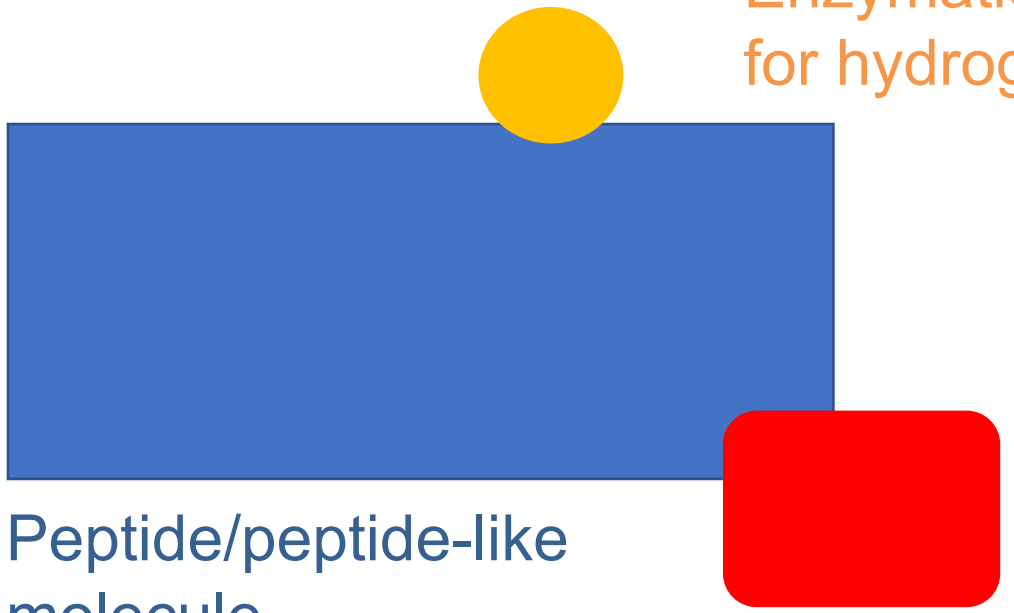
Injectable peptide-mimetic hydrogel for sustained delivery of drugs

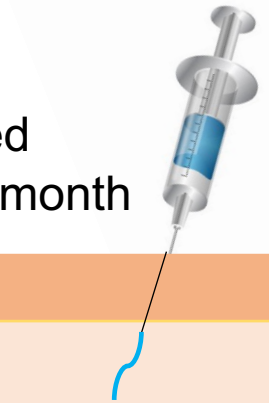
- Eradicating HIV/AIDs by 2030 remains a central goal of the World Health Organisation.
- Key to this addressing this challenge is overcoming patient medication adherence issues.
- Complicated antiretroviral regimens, including a commitment to daily intake of tablets.
- There is need for a convenient and effective long-acting formulation to deliver drugs over a sustained period e.g. 28 days.
- Multipurpose product: combined HIV + contraceptive

Structural overview of our enzyme responsive drug delivery implant



Peptide-mimetic hydrogelators for sustained delivery of drugs

a) Soluble peptide-drug conjugate administered subcutaneously each month



Specific enzyme in tissue

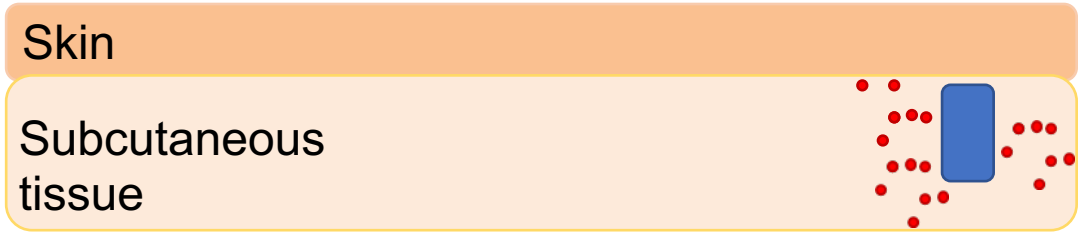
cleaves hydrophilic group

b)

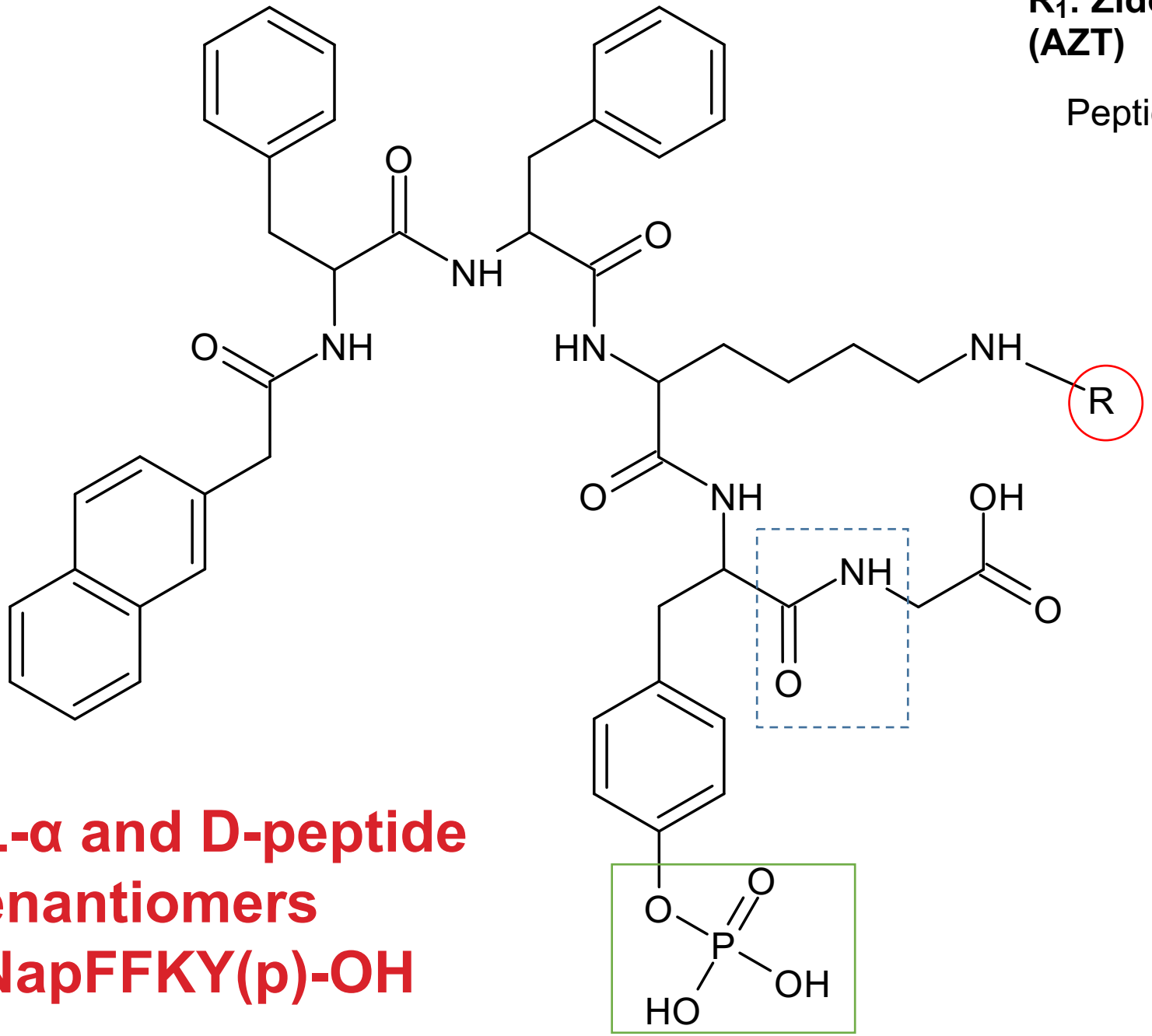
Formation of protease resistant hydrogel

c)

Tissue environment, pH 7.4, 37ºC Hydrolysis of drug-peptide linkage

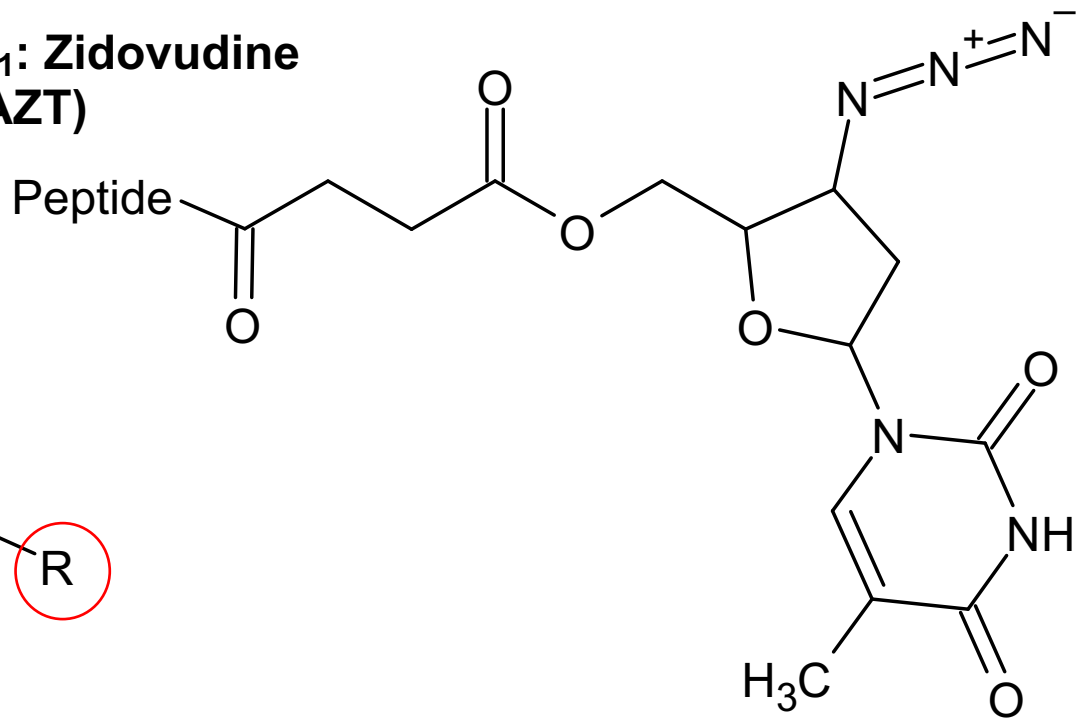


Sustained release of conjugated drugs from peptide hydrogel



L-α and D-peptide enantiomers NapFFKY(p)-OH

R_1: Zidovudine (AZT)



Key:

Covalently attached drug

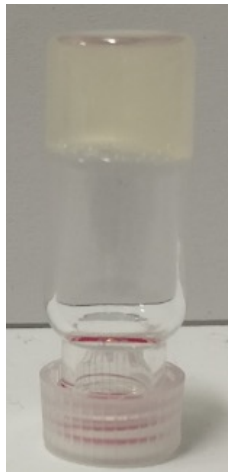
Glycine spacer

Phosphate enzyme trigger for gelation

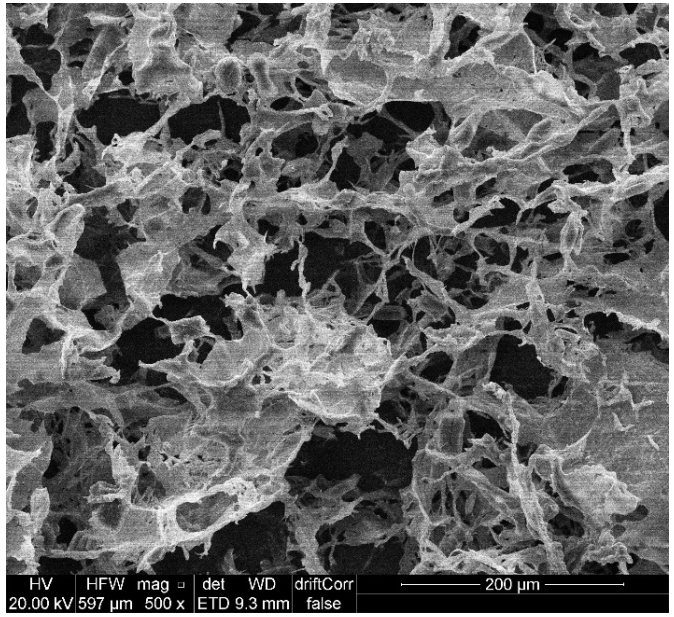
L-α and D-peptide enantiomers NapFFKY(p)-OH

Solution
(upon injection)

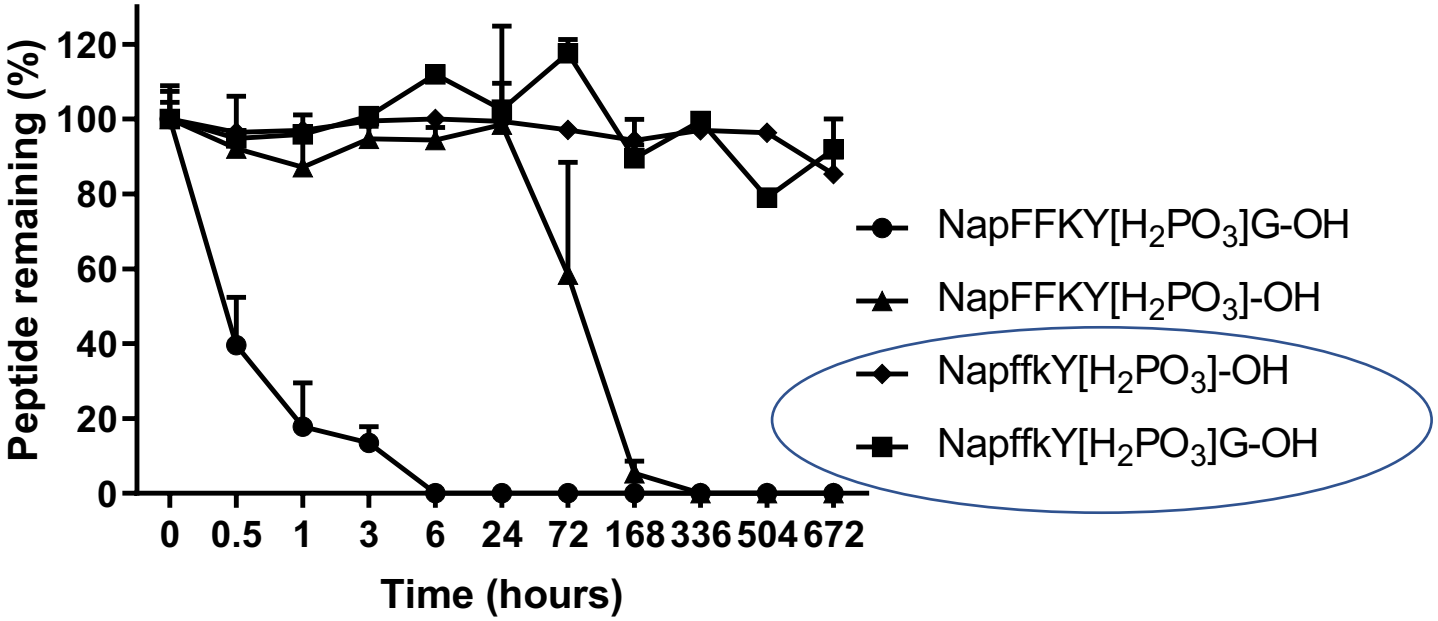
Phosphatase
enzyme



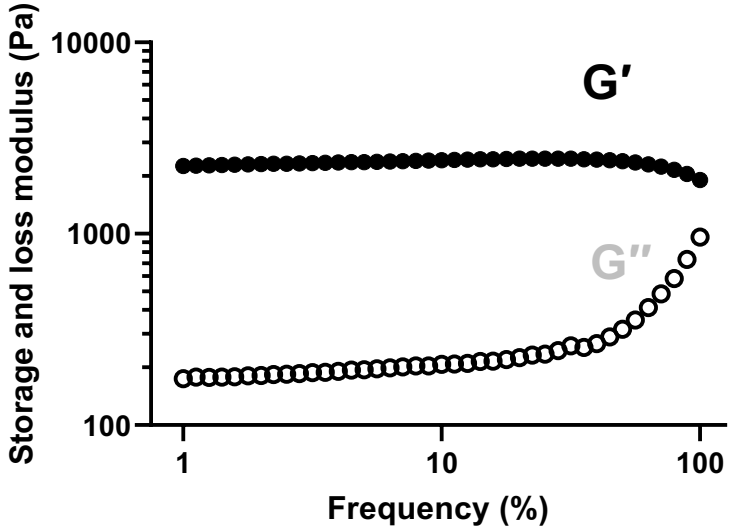
Hydrogel
(after injection)

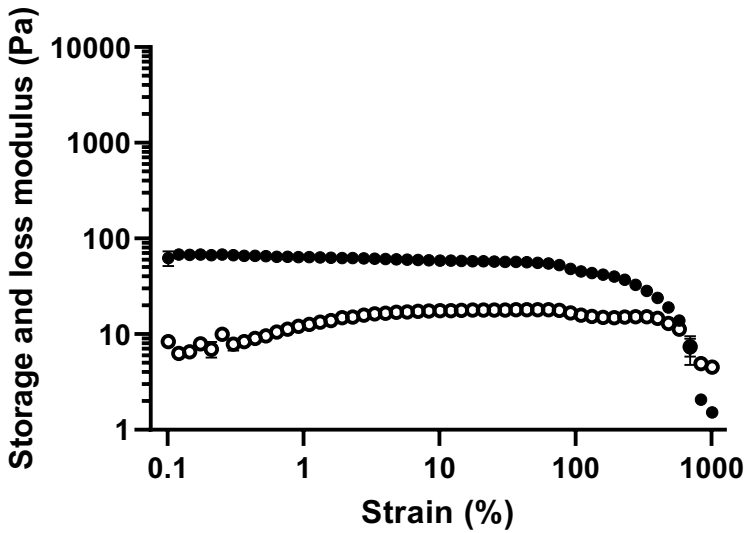


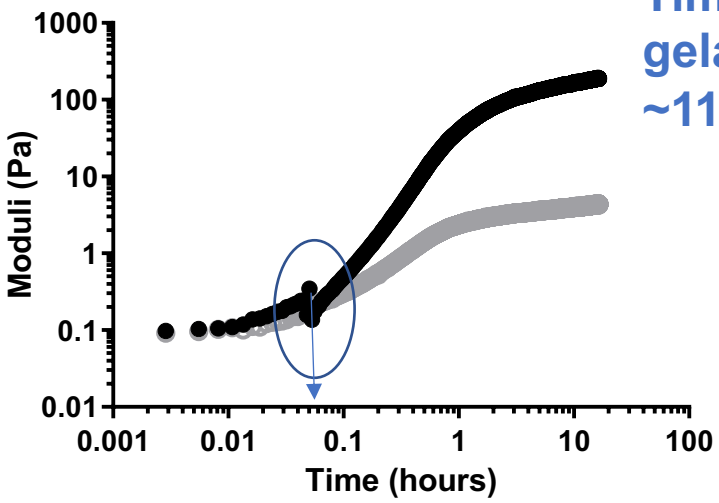
Biostability: Proteinase K



Rheology: Hydrogel formation 2% w/v Napffk(AZT)YG-OH.

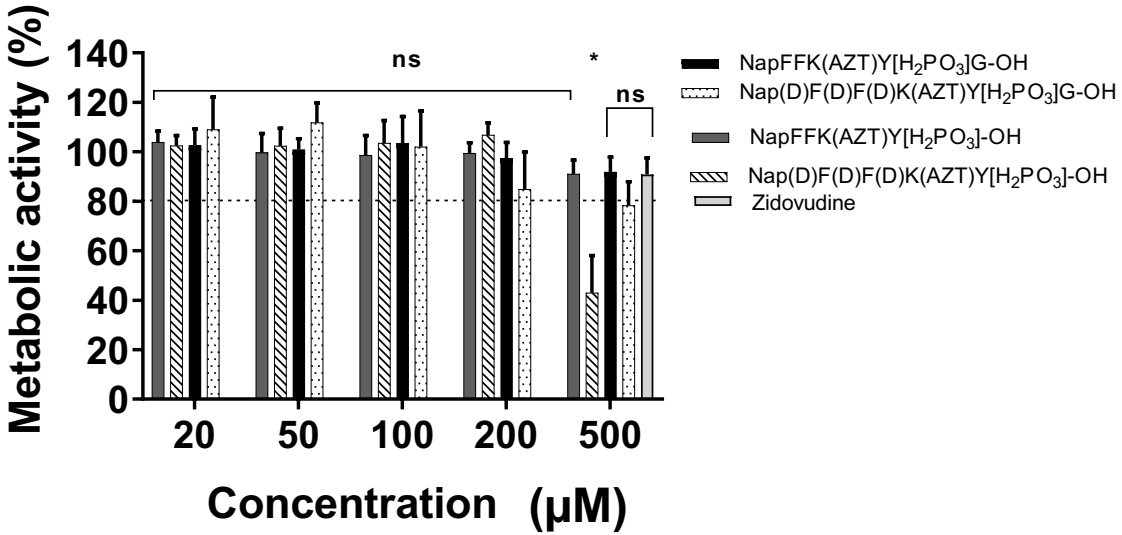


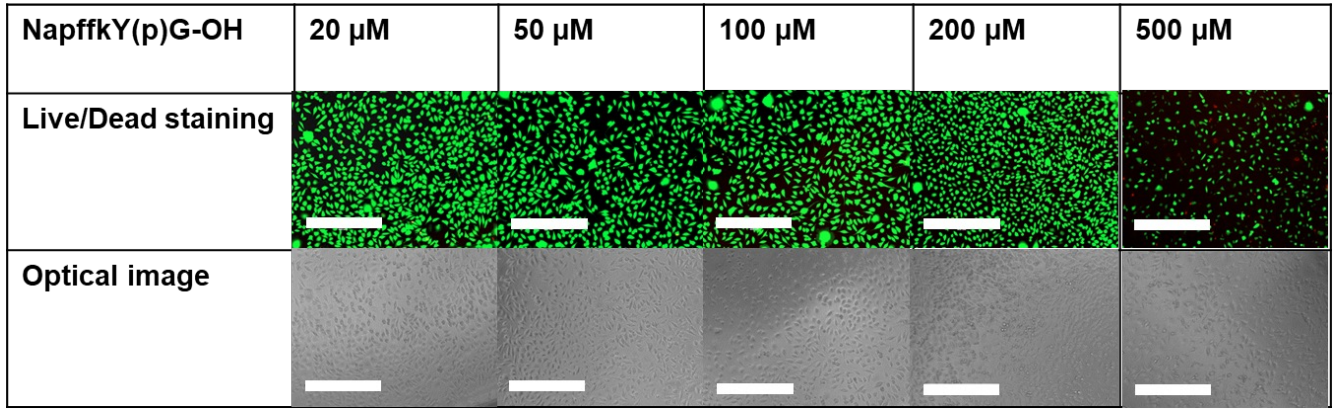




Time for gelation: ~110 secs

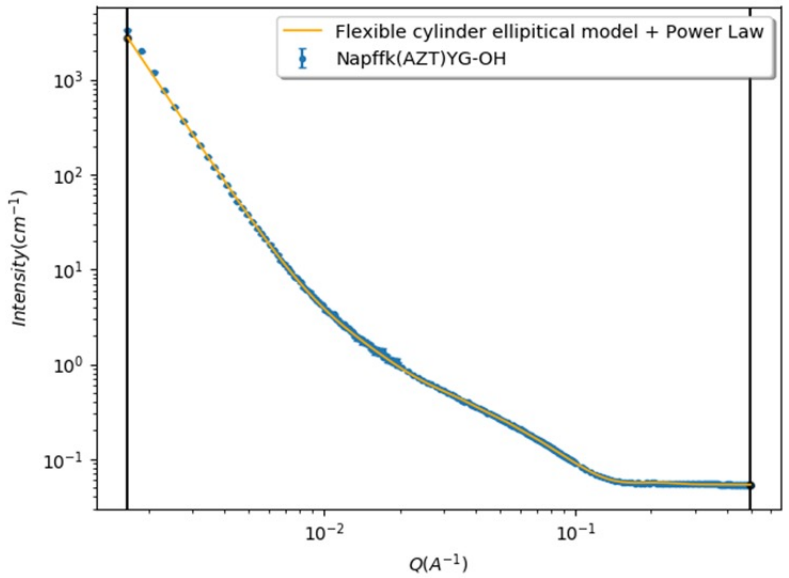
Cell toxicity 24 hours: MTS cell viability and Live/Dead assays





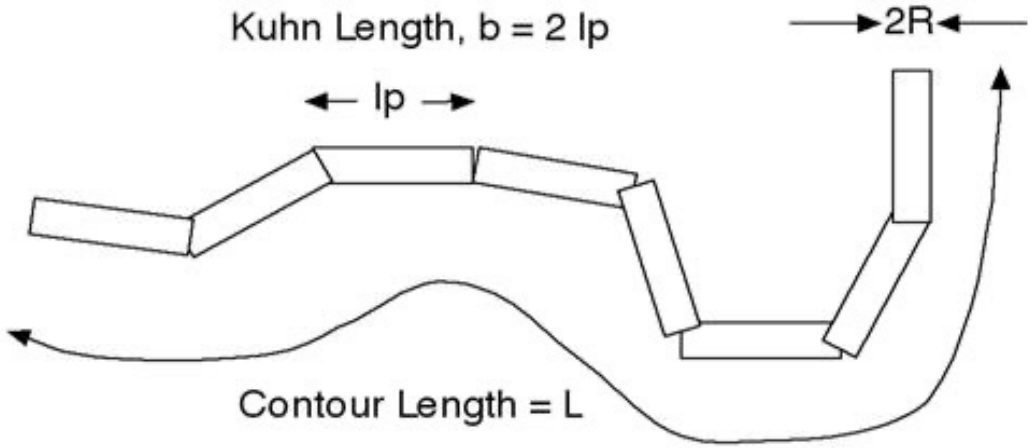
Small Angle Neutron Scattering (SANS)

- A tool for structural characterisation of materials
- Can characterise materials at macroscopic level, modify peptide sequence and see impact
- From the structural information results we can determine whether the rheology drug release kinetics are based upon the fibre structure or the entanglement of those fibres
- Length of these fibres are also very large (>1000 nm), which is also a common property of entangled gel fibres.
- The presence of entangled gel fibres also suggests there is a large component of gel stiffness/strength that can be controlled by external conditions, for example the gelation process and formulation process.



Fits flexible cylinder elliptical model

R = 2.152 nm



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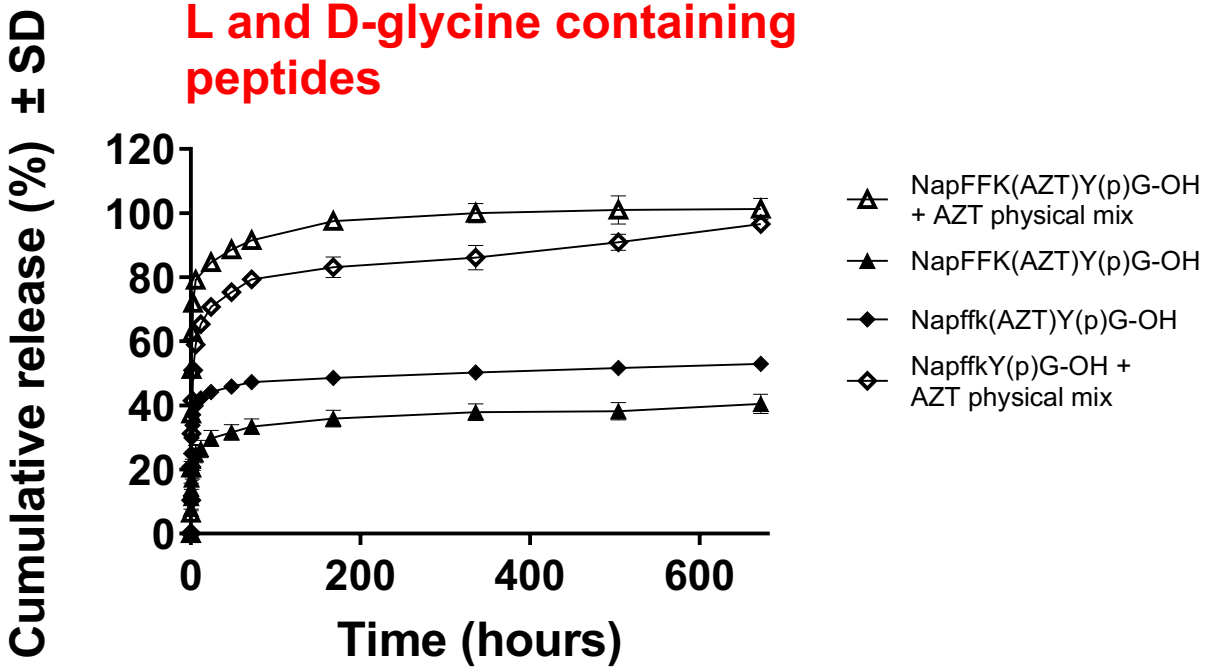
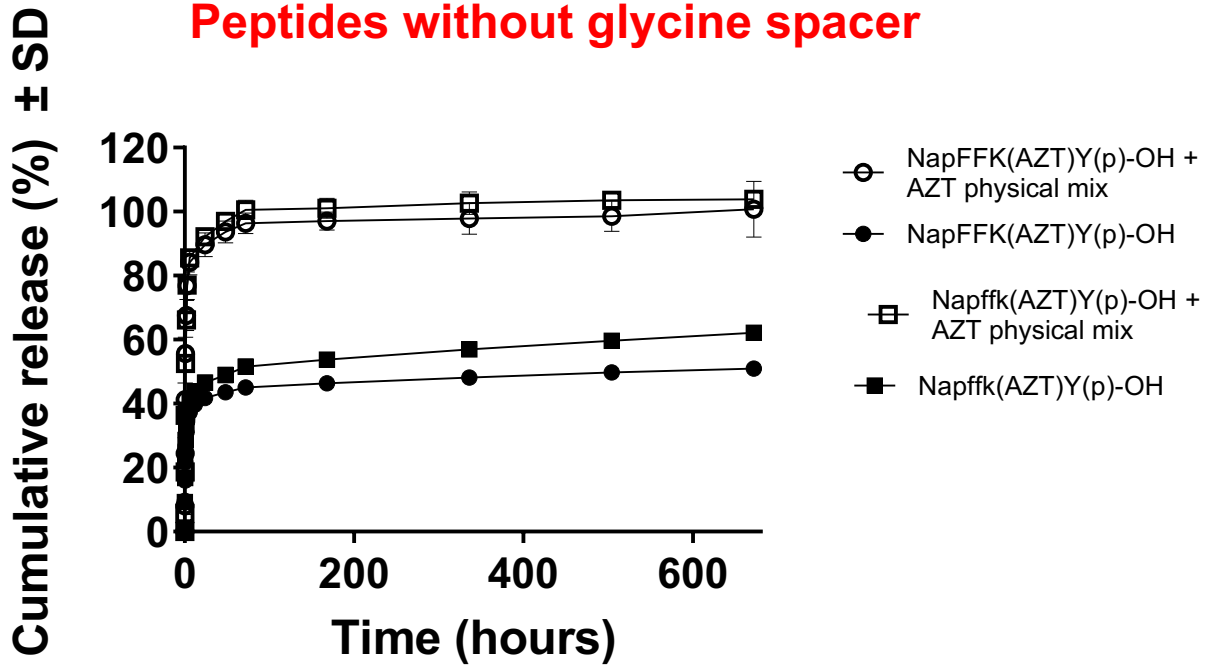
In vitro drug release 28 days: Chemically conjugated vs. physically mixed zidovudine (AZT)

L and D-glycine containing peptides



Peptides without glycine spacer



Burst release significantly reduced in chemically conjugated vs. physically mixed zidovudine (AZT): 40-50% in first 72 hours

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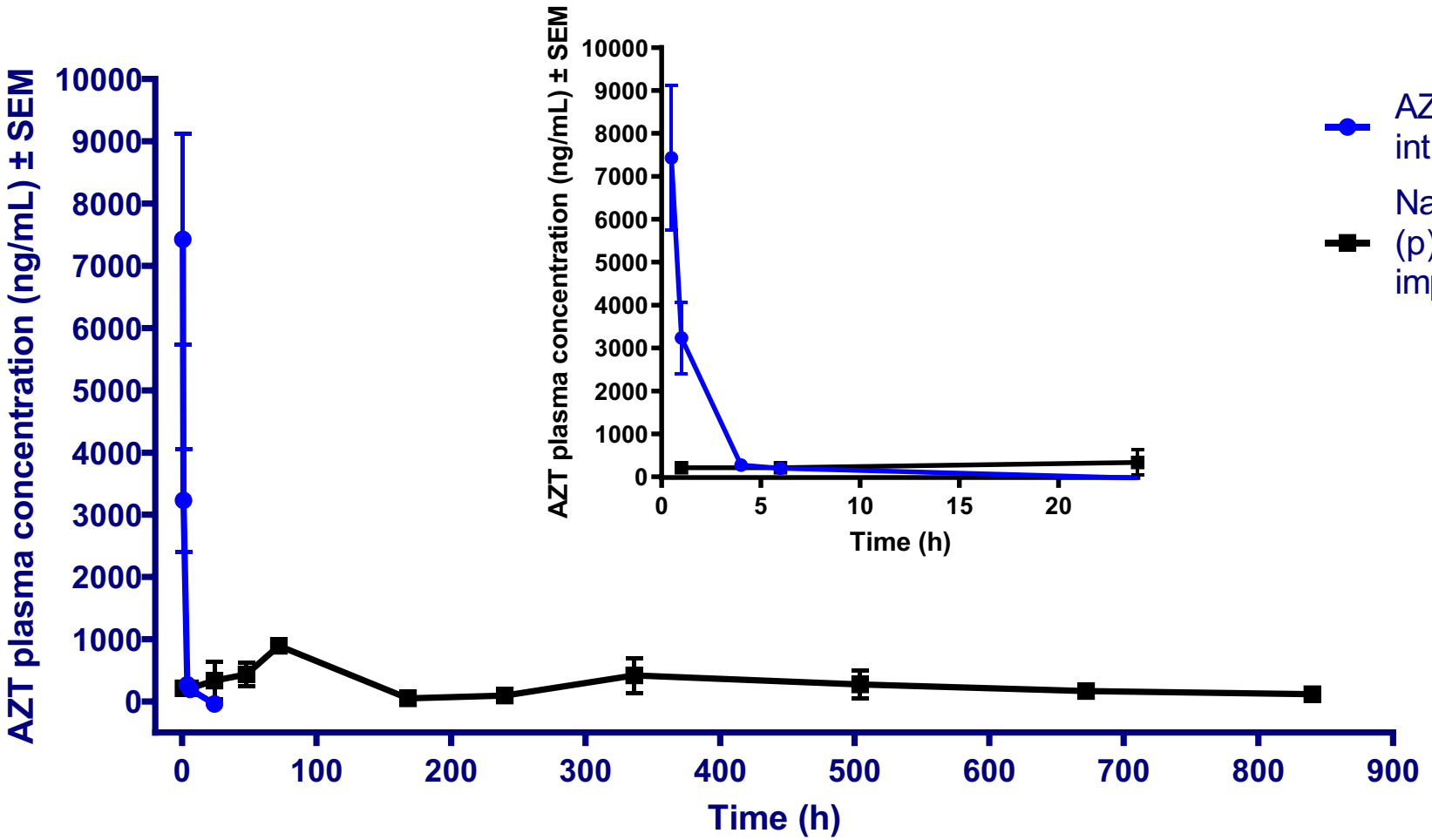
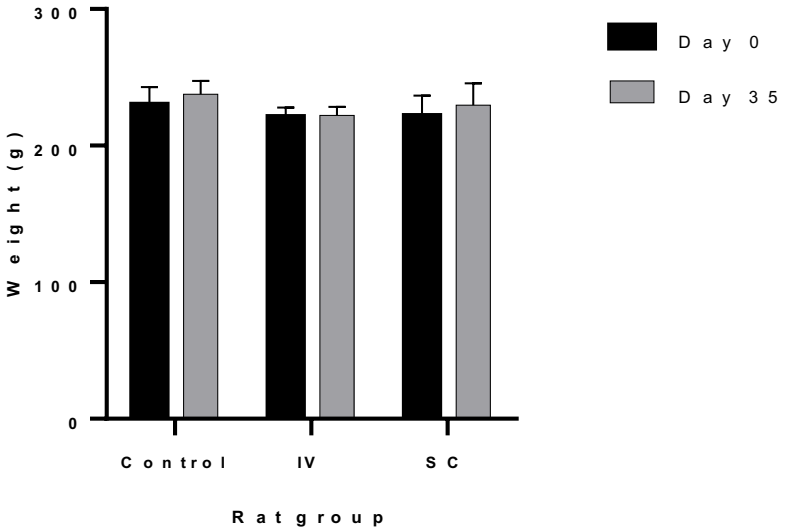
In vivo drug release: Chemically conjugated vs. physically mixed zidovudine (AZT), extended to 35 days



AZT control intravenous

Napffk(AZT)Y (p)G-OH s.c implant

Preliminary *in vivo* toxicity



With IC_{50} range for AZT = 30 – 130 ng/mL for 35 days

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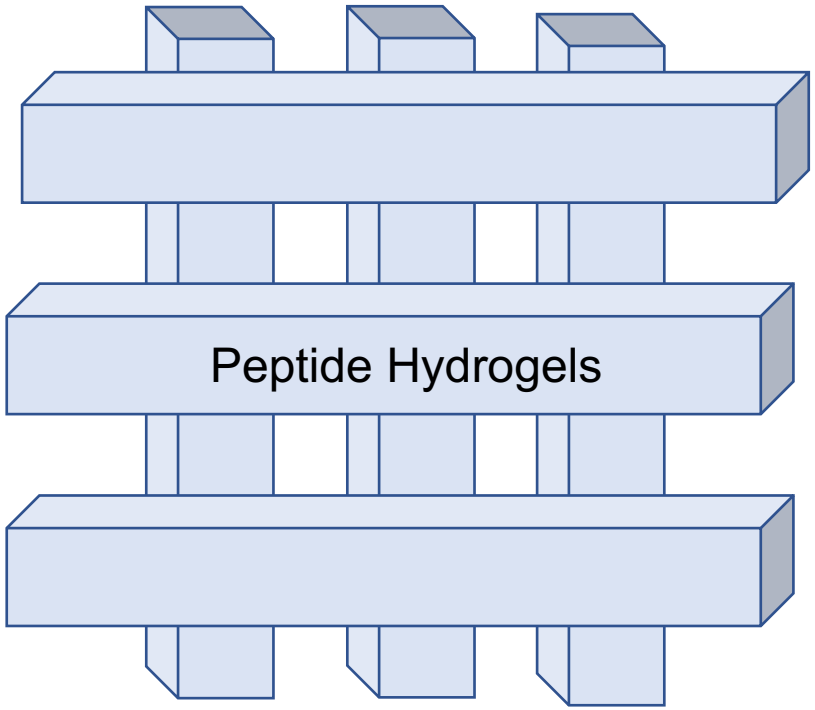
Advantages compared to current long-acting injectables

Limitations of current long-acting injectable technologies	How our approach resolves this
1) Fast ”burst” release of drug upon administration (suspensions, microspheres, polymer implants)	1) Combination of hydrogel formation and breakage of peptide-drug bond = significant reduction in “burst” release
2) Need for surgery (polymer implants)	2) Soluble injection breaks down to non-toxic products
3) Requires large needles (e.g. suspensions, microspheres)	3) Formulation is fully soluble in water enabling use of narrow bore needles

Advantages compared to current long-acting injectables

Limitations of current long-acting injectable technologies	How our approach resolves this
4) Stability issues upon storage/transport (suspensions)	4) Can be transported as freeze-dried powder for mixing with water prior to injection = increased stability
5) Limit on drug type and loading, e.g. suspensions only allow water-insoluble drugs	5) Drug precisely attached to peptide = increased drug loading. Vast range of hydrophobic and hydrophilic drugs can be attached
6) Persistent pain for months after injection due to hydrophobic nature (oily liquids)	6) Aqueous, water based solvent, improved biocompatibility

Peptide hydrogel applications



- Diseases with medication adherence issues (e.g. HIV/AIDs, schizophrenia, Substance abuse, malaria, TB)
- Cancer (intra-tumoral delivery)
- Ocular delivery
- Spinal/CNS delivery
- Vaccines: peptides as immune adjuvants, extended protection
- Infection

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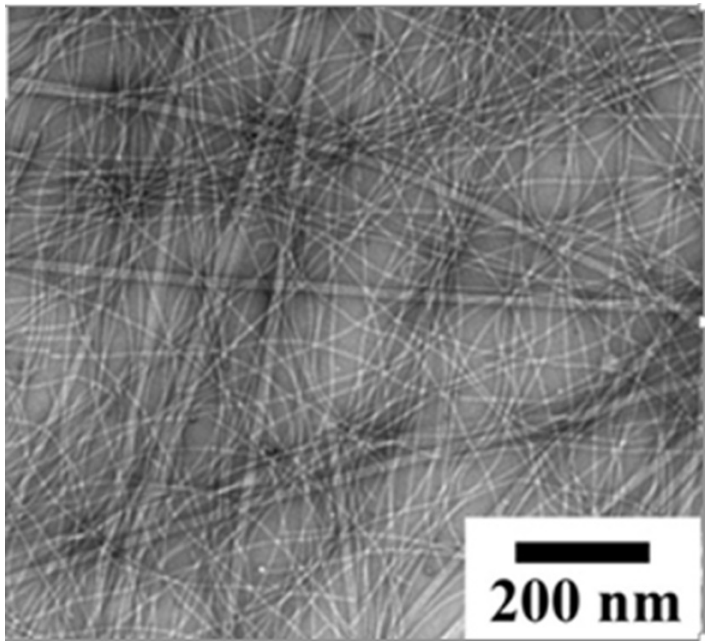
Future plans relating to neutron scattering



- Quasi electric neutron scattering (QENS): explore diffusion of water and drug (ISIS UK: 2023)
- SANS + QENS: Multiple peptide-drugs within one formulation: impact on fibre formation?
- Linking macroscopic architecture to pharmacological properties e.g. antimicrobial activity?

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- Yuming An (PhD student)

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