# Peptide hydrogels as an injectable multipurpose platform for sustained HIV/AIDS-contraceptive drug delivery

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CONTROLLED RELEASE SOCIETY
CRS 2023 ANNUAL MEETING & EXPOSITION
JULY 24-28, 2023 Paris Hotel » Las Vegas, NV, USA
THE FUTURE OF DELIVERY SCIENCE

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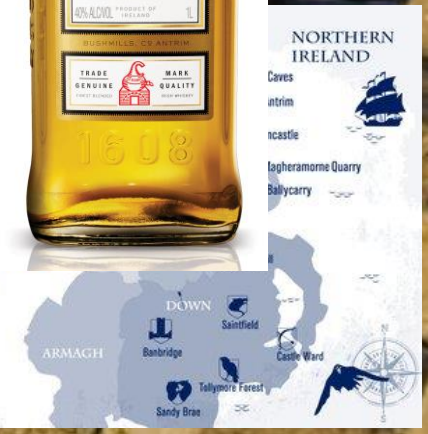
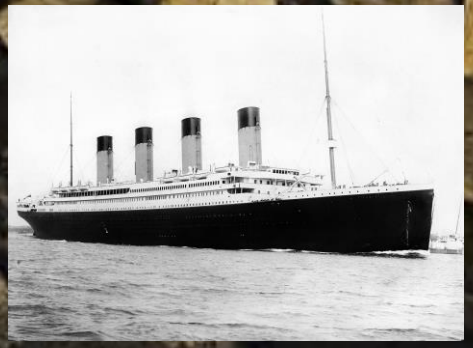
SCHOOL OF PHARMACY

# 1st in the UK for Pharmacy

(The Guardian's 2022 University Guide)



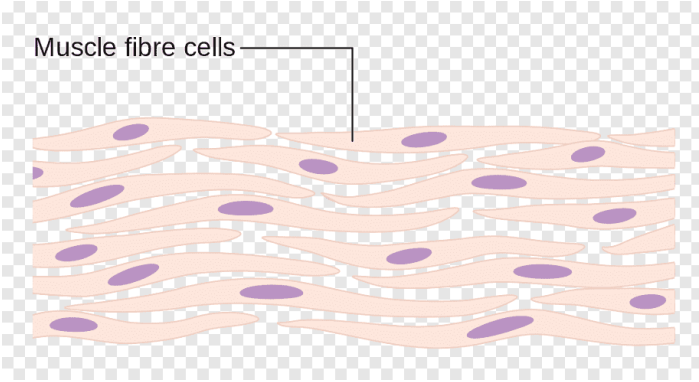



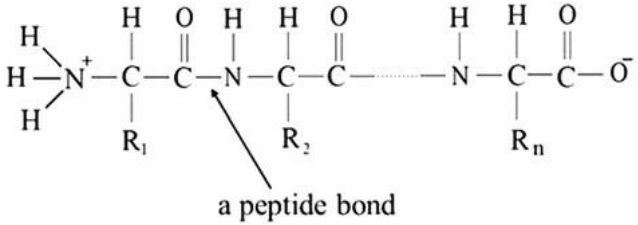



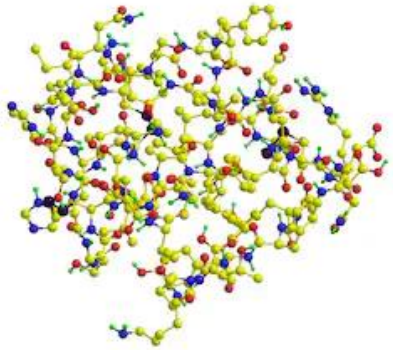
# What are Peptide Nanomaterials?


**Peptide**

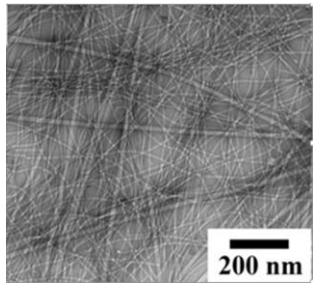
**Protein**



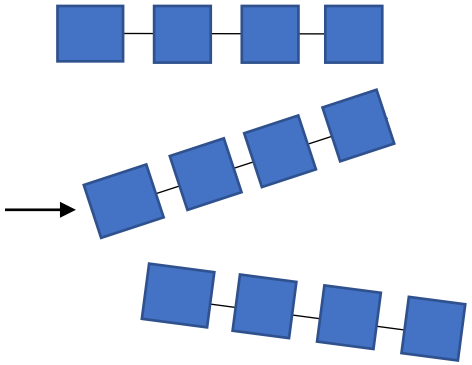



# Peptide Nanomaterials: Core Technology



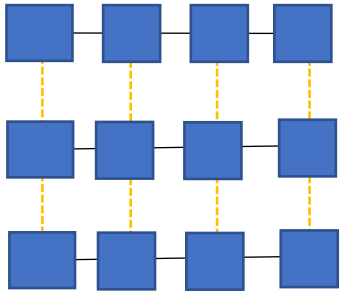

Peptide Hydrogels

Self-assembled Peptides



Stimuli

-pH
-Temperature
-Ionic Strength
-Specific enzymes



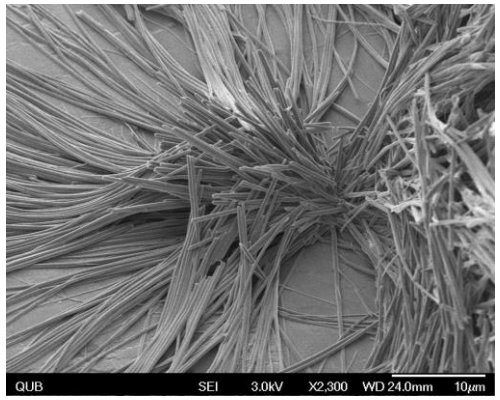
Self-assembly

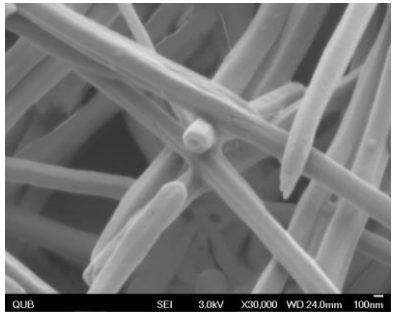
Peptide

Nanotubes

Short peptide sequences

Non assembled

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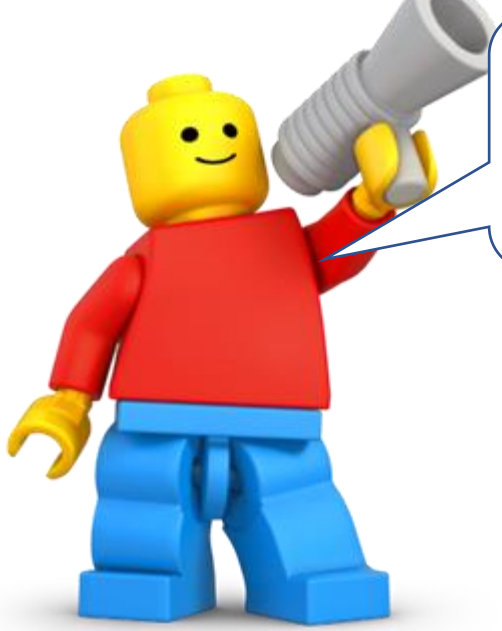
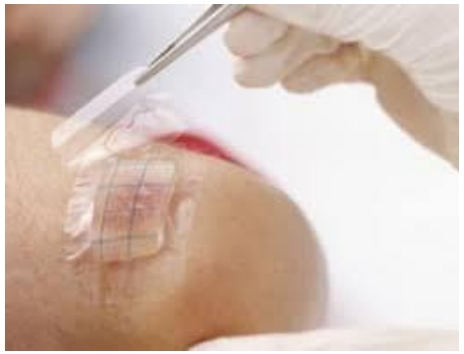


Biofunctional nanomaterials utilising the building blocks of life!

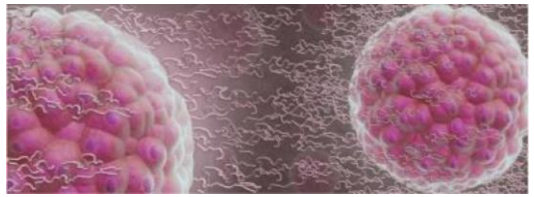
**What medical applications can we use these for?**

Infection and Medical Devices



Wound healing

Drug Delivery (*In situ* forming implants, blood brain barrier, cancer, bacteria)

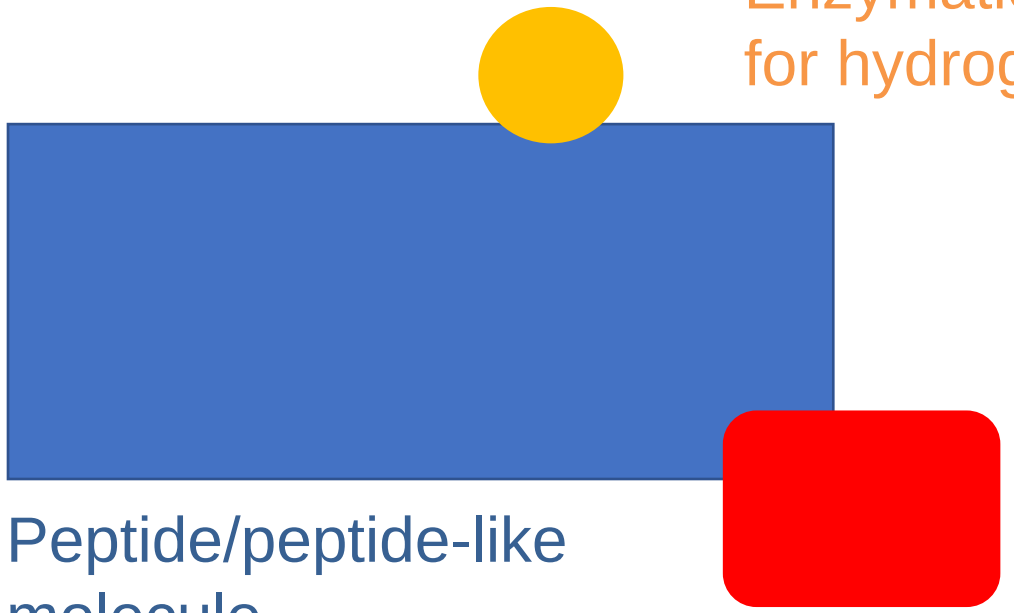


Stem Cells/Regenerative medicine

# Injectable peptide-mimetic hydrogel for sustained delivery of drugs

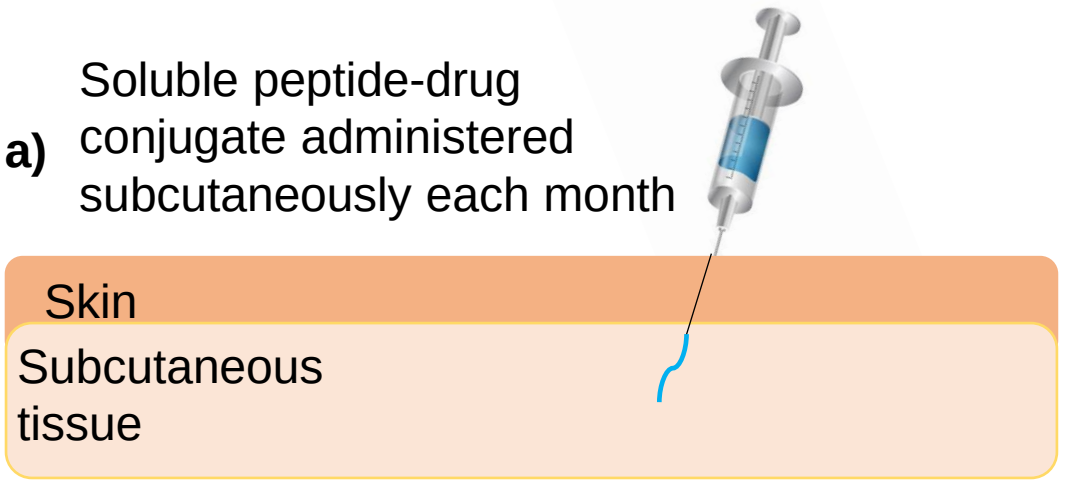
- Eradicating HIV/AIDs by 2030 remains a central goal of the World Health Organisation.
- Key to this addressing this challenge is overcoming patient medication adherence issues.
- Complicated antiretroviral regimens, including a commitment to daily intake of tablets.
- There is need for a convenient 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

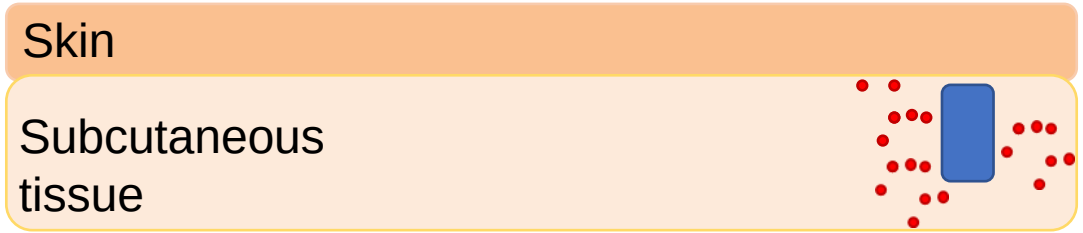
cleaves hydrophilic group

**b)**

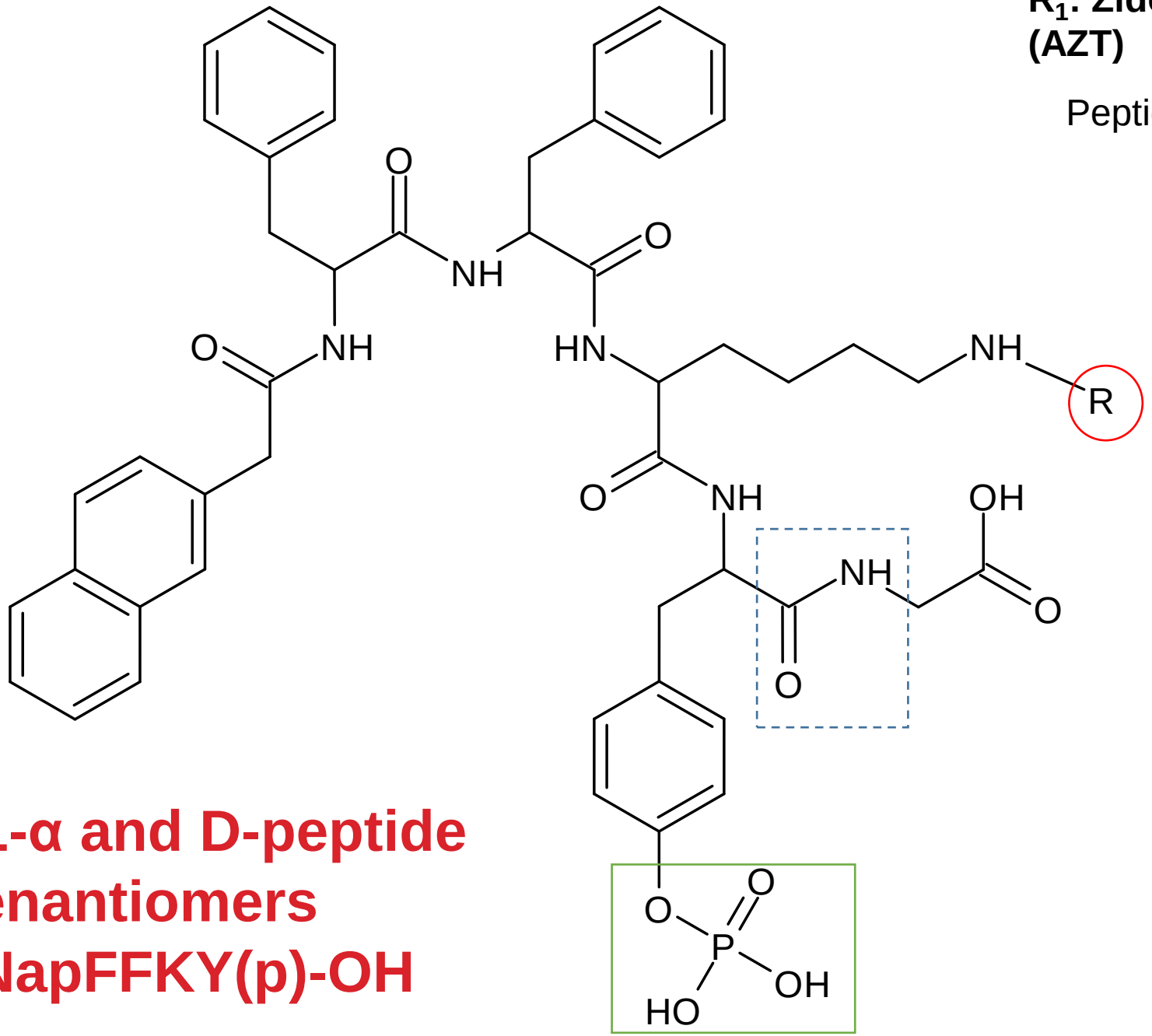

Formation of protease resistant hydrogel

**c)**

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

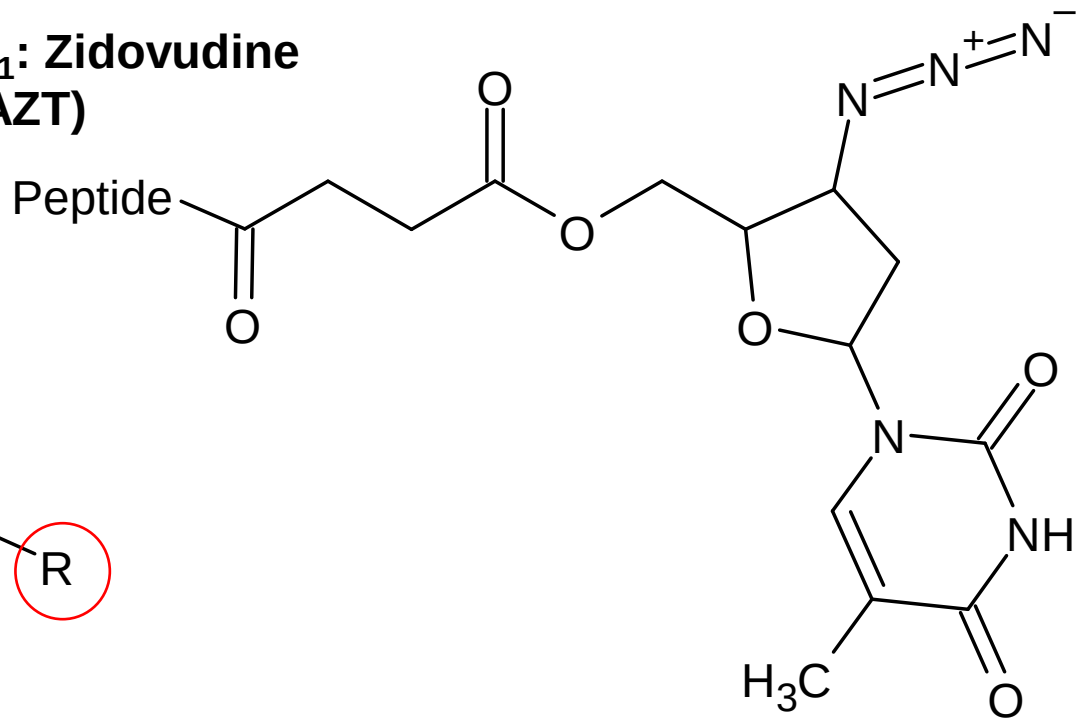



Sustained release of conjugated drugs from peptide hydrogel



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

**$R_1$: Zidovudine (AZT)**




**Key:**

Covalently attached drug

Glycine spacer

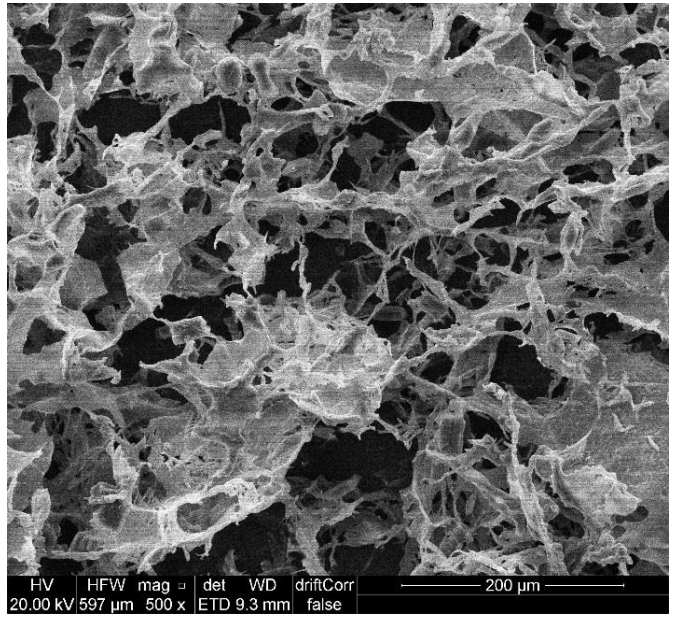
Phosphate enzyme trigger for gelation

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

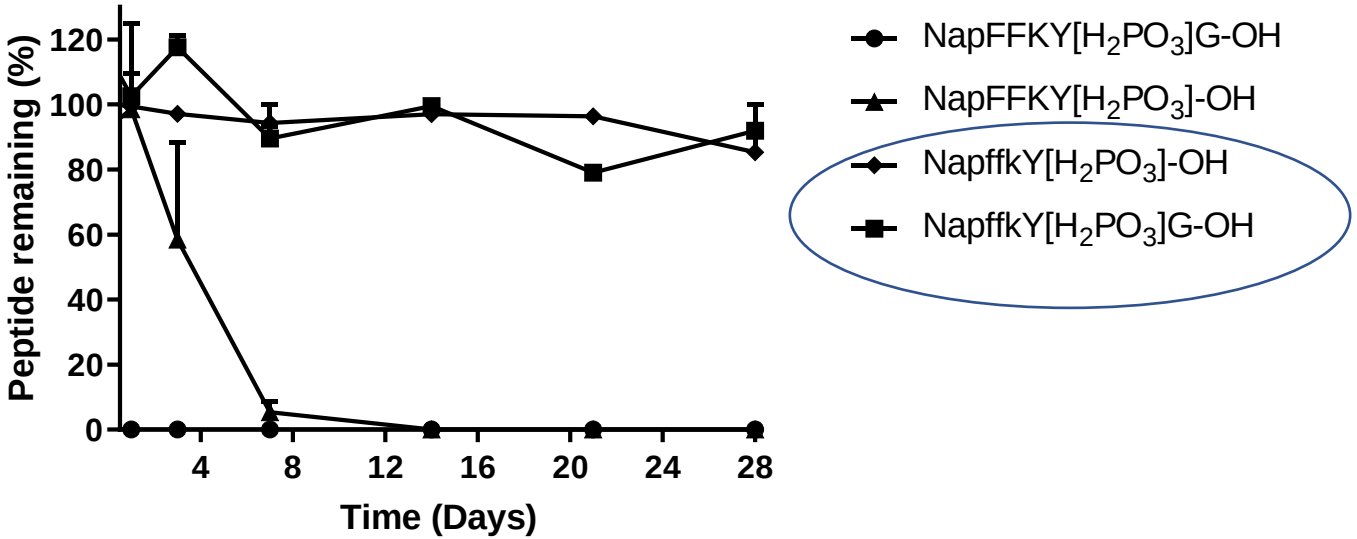
Solution
(upon injection)

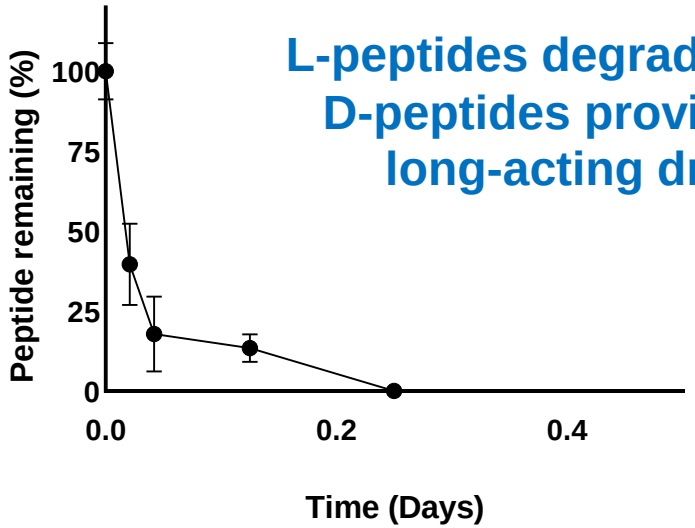
Phosphatase
enzyme

Hydrogel
(after injection)



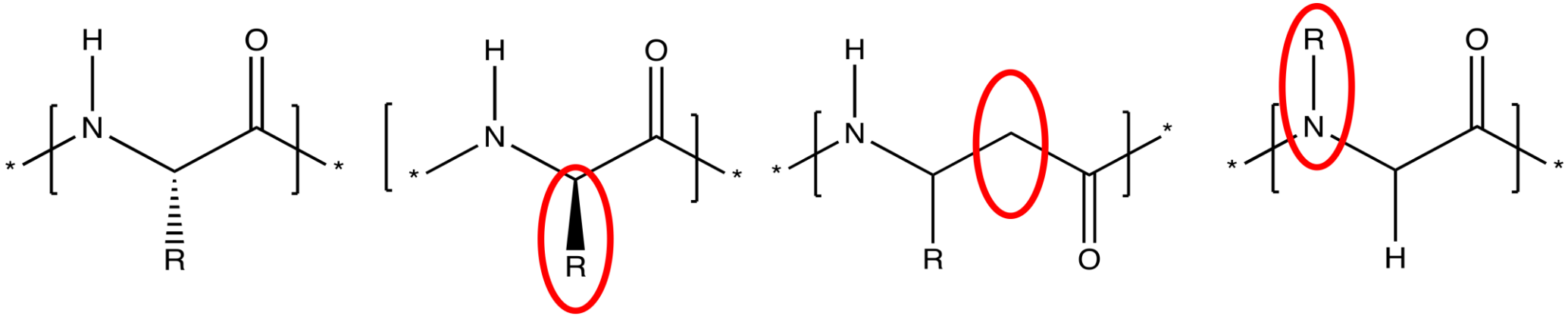

## Biostability: Proteinase K




**L-peptides degrade in hours/days.**
**D-peptides provide stability for long-acting drug delivery.**

# Peptide-mimetics versus peptides




*Structural differences (red circle) between L-α-peptides (i) and peptide-mimetics (ii-iv). ii) D-peptide is opposing stereoisomer of L-form. iii) β-homo peptides possess additional methylene (–$CH_2$) within each unit. iv) peptoid R-group on nitrogen rather than α-carbon.*

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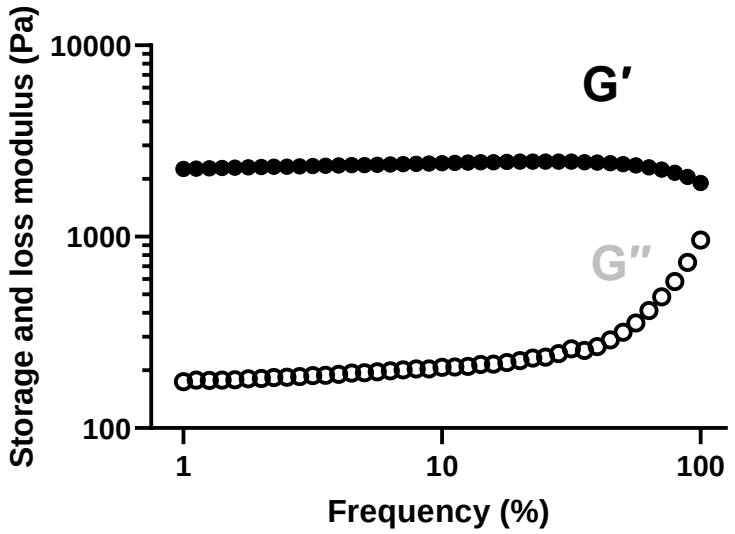
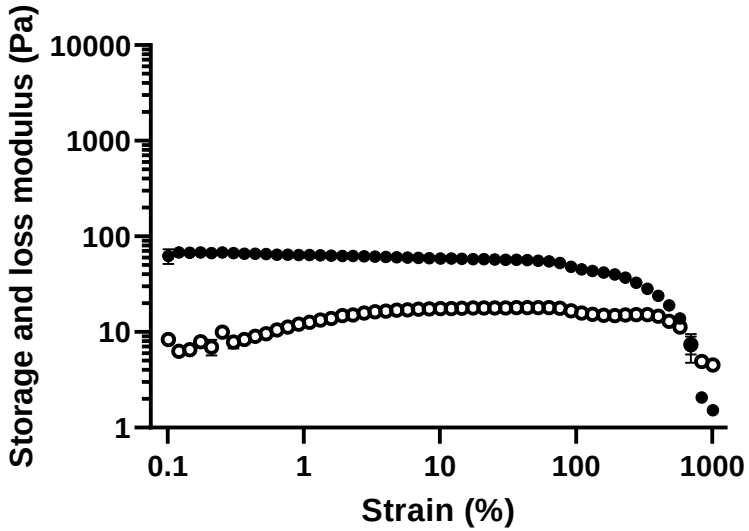
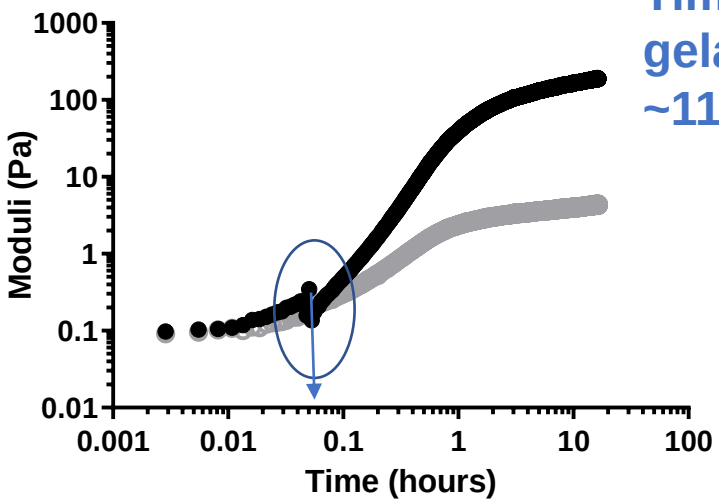
# Rheology: Hydrogel formation 2% w/v Napffk(AZT)YG-OH.

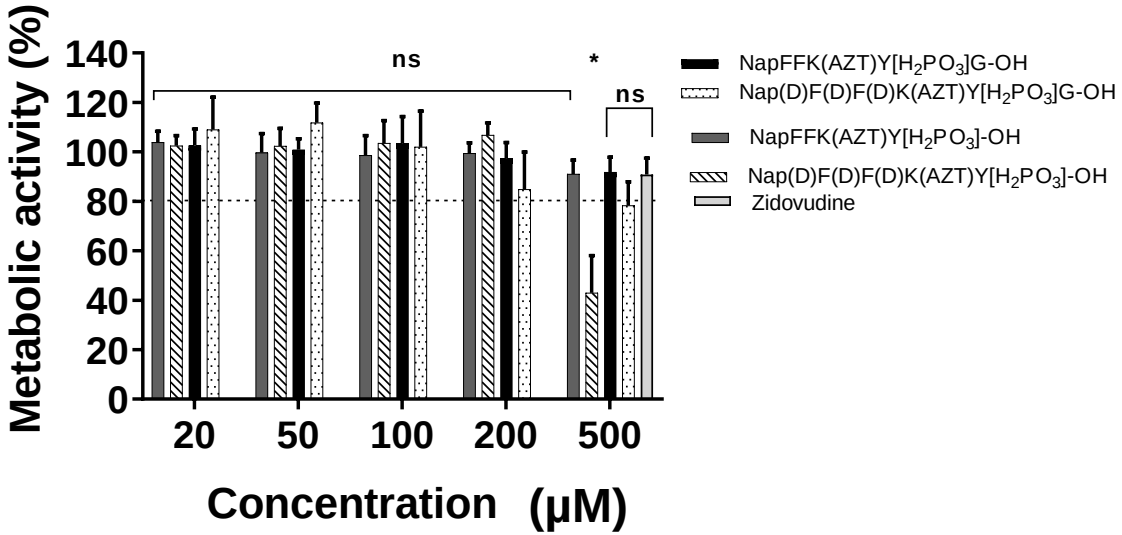


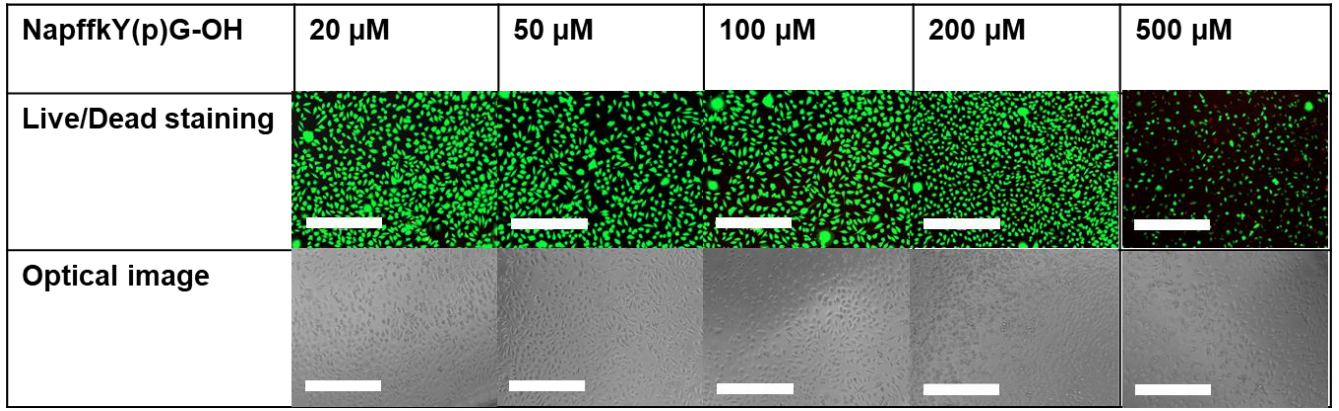




**Time for gelation: ~110 secs**

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

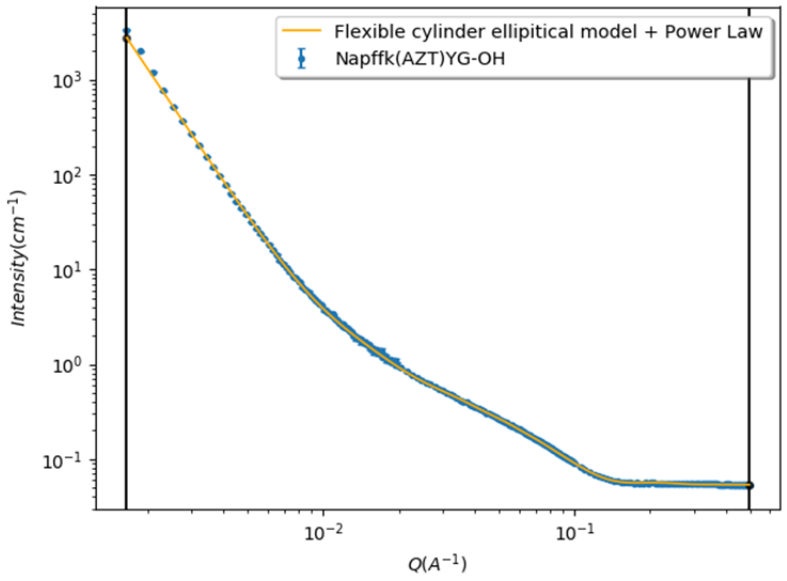



Coulter, S. M., *et al*. *Adv. Healthcare Mater*. 2023, 2203198.

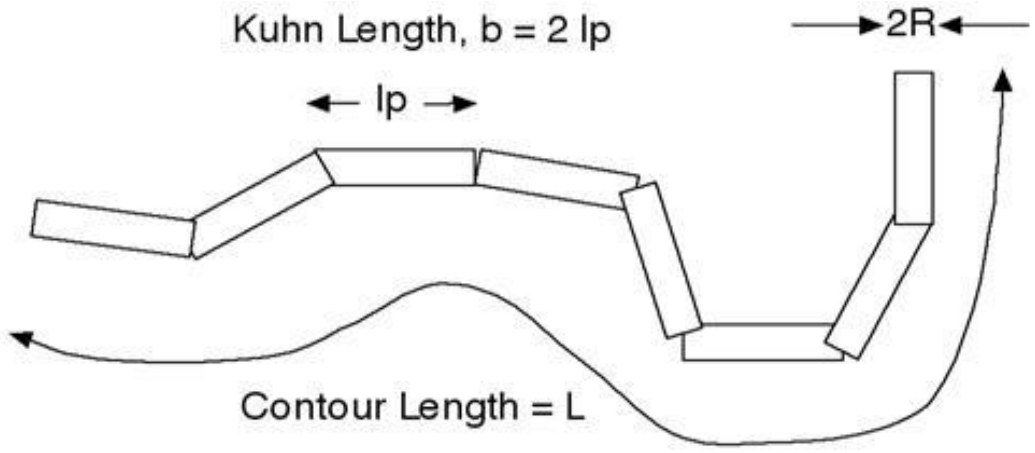
# Small Angle Neutron Scattering (SANS)

- 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 very large (>1000 nm): common of entangled gel fibres.
- Presence of entangled fibres suggests there a large component of gel stiffness/strength can be controlled by external conditions, e.g. gelation/formulation process.




## Fits flexible cylinder elliptical model

R = 2.152 nm

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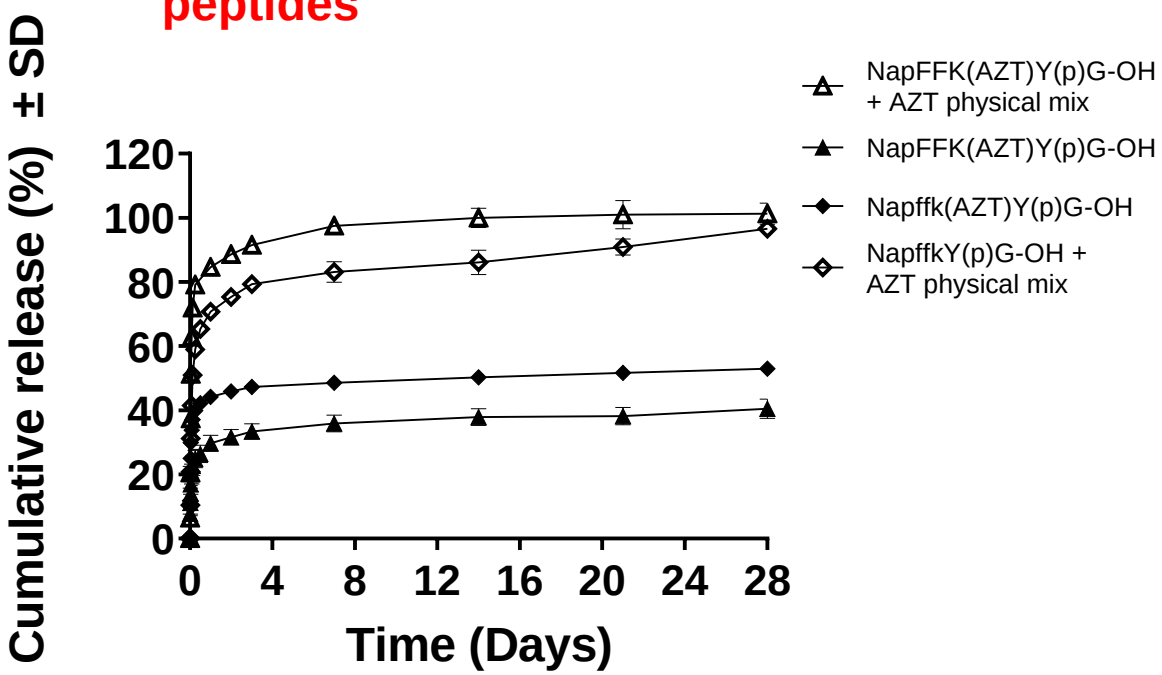
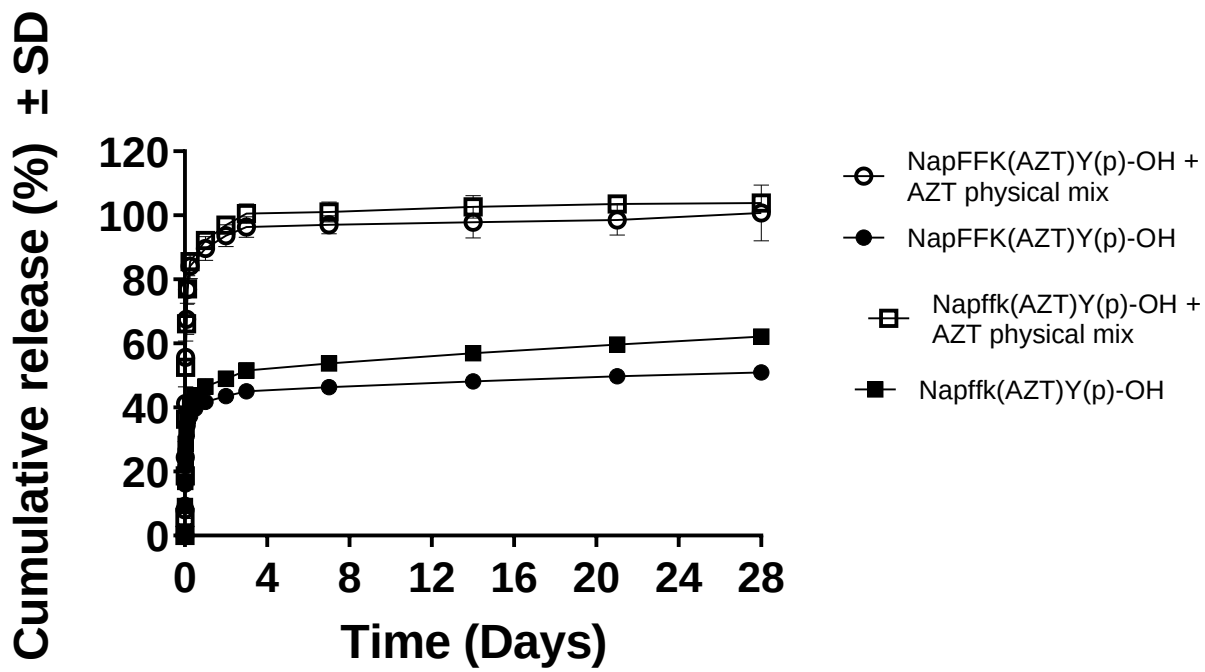
Coulter, S. M., *et al*. *Adv. Healthcare Mater*. 2023, 2203198.

# *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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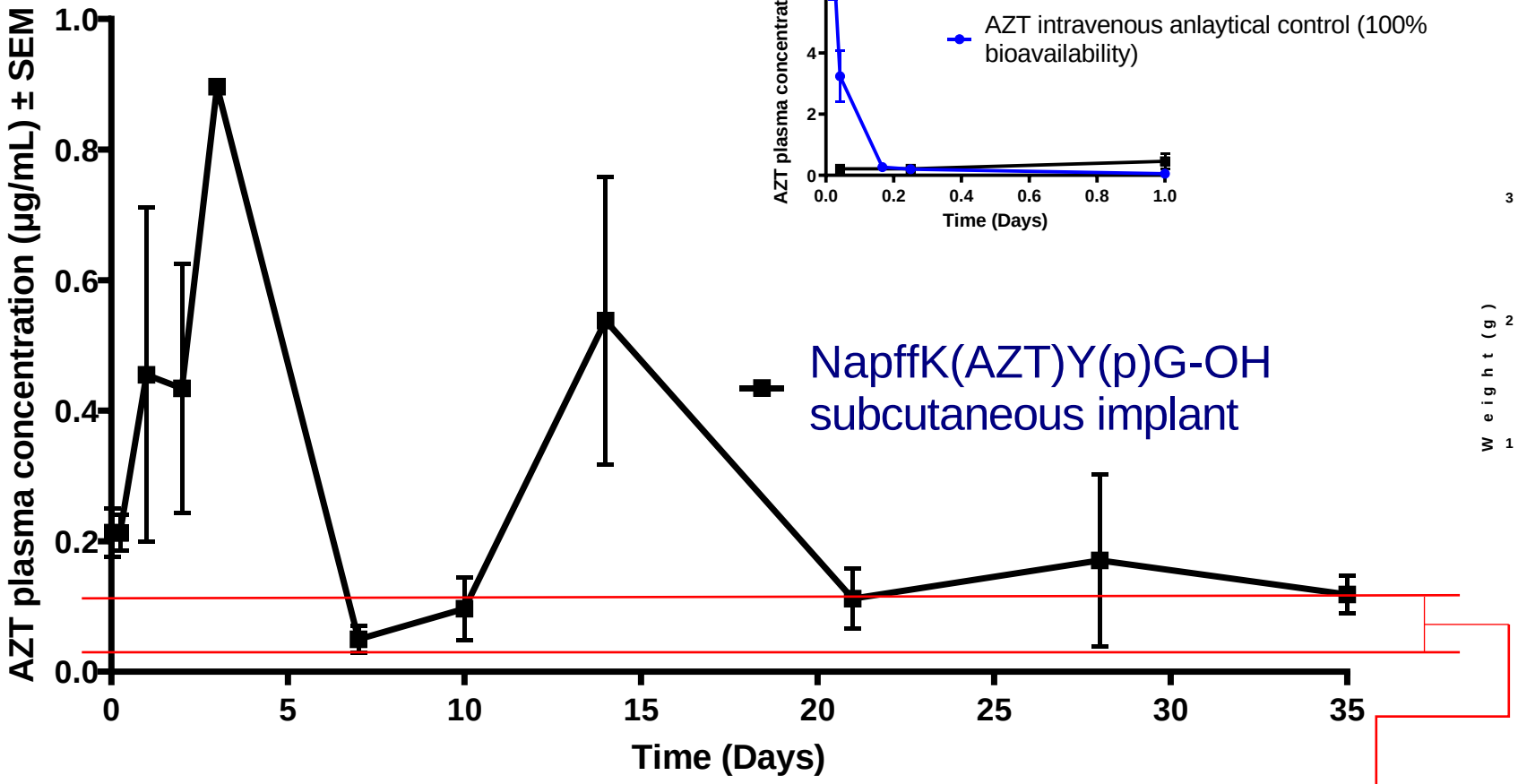
Coulter, S. M., *et al*. *Adv. Healthcare Mater*. 2023, 2203198.

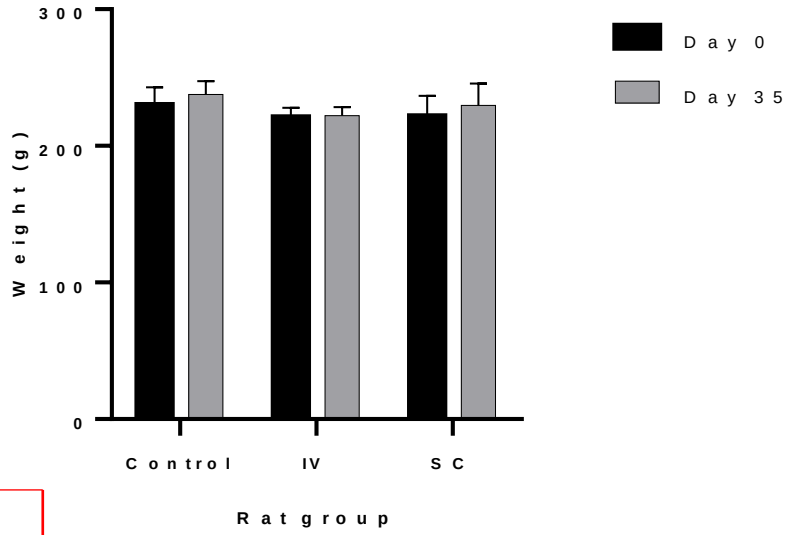
# *In vivo* drug release: Chemically conjugated zidovudine (AZT), extended to 35 days







## Preliminary *in vivo* toxicity




**Within $IC_{50}$ range for AZT = 0.03 – 0.13 µg/mL for 35 days**

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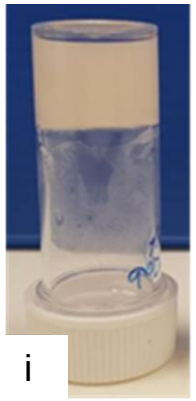
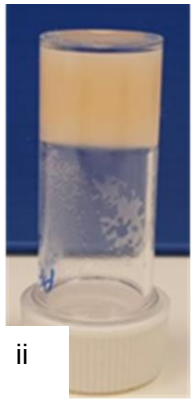
5% w/v MIV-150: HIV/AIDS

(i) 1.0 % (ii) 2.0 % w/v Cabotegravir HIV/AIDS

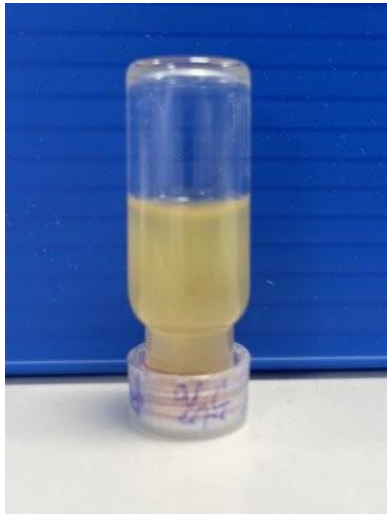


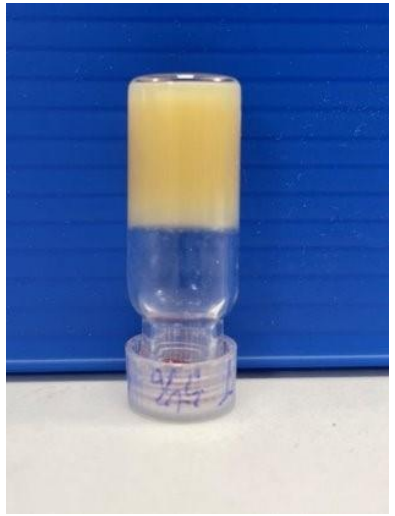
i



ii

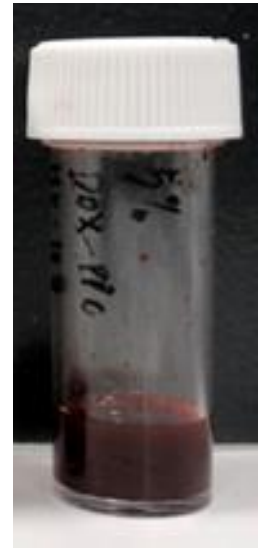
5% w/v Etonogestrel: Contraception





5% w/v Haloperidol: Antipsychotic

5% w/v Doxorubicin Anticancer



Before (left) and after (right) phosphatase enzyme addition

# Multipurpose product: Long-acting combined HIV/AIDS Prevention + Contraceptive



**Existing long-acting HIV/AIDS prevention**
**Cabenuva: Ripilvirine + Cabotegravir**

**Existing single combined HIV/AIDS + Contraception**

# Combined HIV/AIDS + Contraception: Etonogestrel + MIV-150

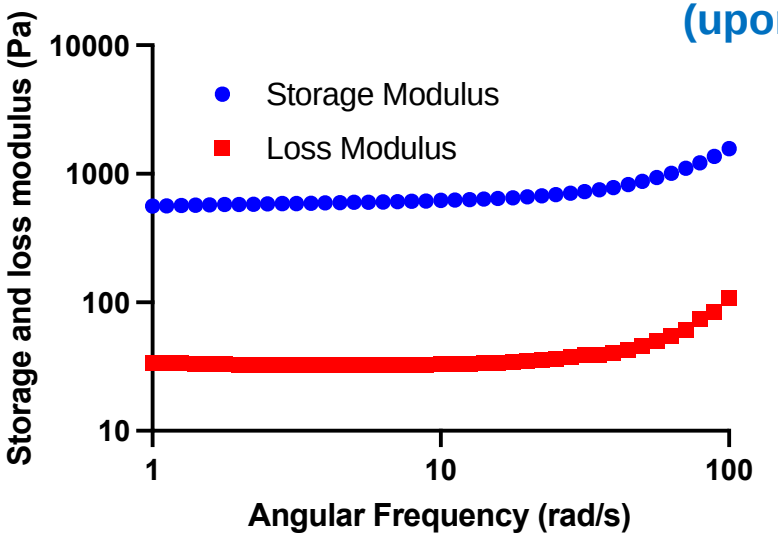
Coulter, S. M., *et al*. *In preparation.*

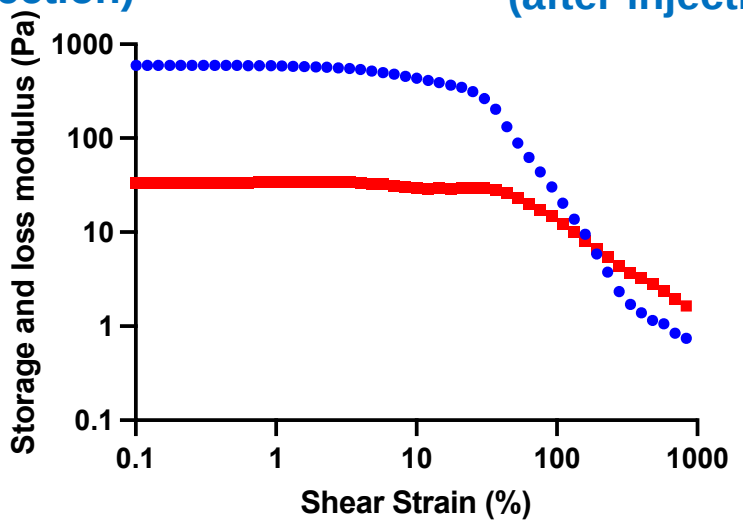
**1:9 ratio of 0.5% w/v Etonogestrel + 4.5% w/v MIV-150**

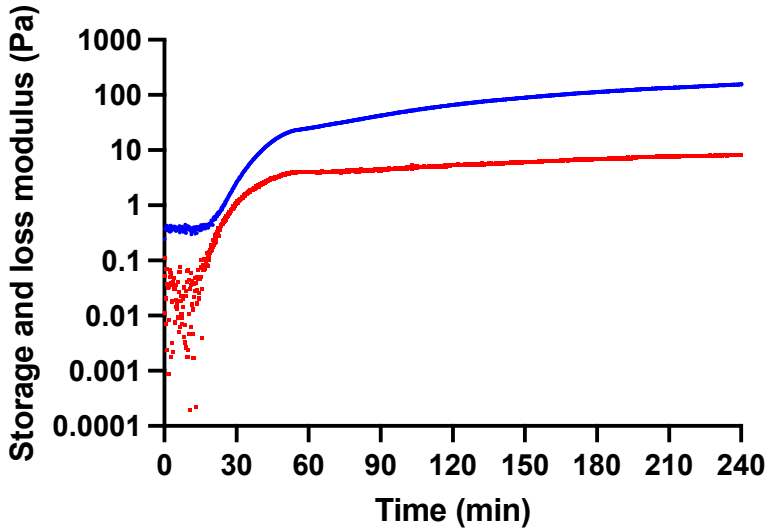
**Solution (upon injection)**

**Phosphatase enzyme**

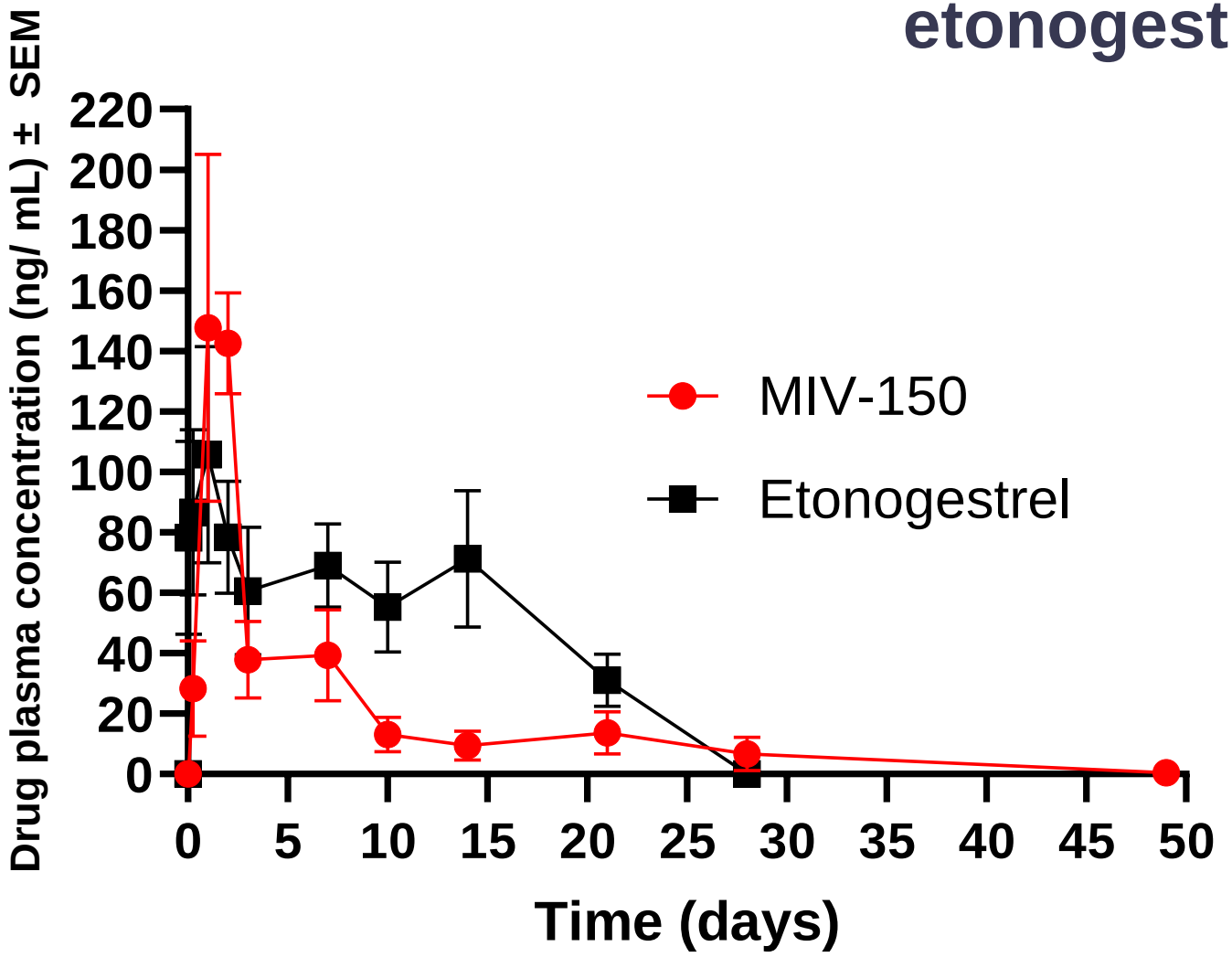
**Hydrogel (after injection)**



# Combined *in vivo* drug release: Chemically conjugated MIV-150 and etonogestrel




**MIV-150:** $IC_{50}$ = 0.37ng/mL.[1]

**Etonogestrel:** effective concentration = 90 pg/mL.[2]

Coulter, S. M., *et al*. *In preparation.*


1. Aravantinou M. AIDS Res Hum Retroviruses. 2012 Nov;28(11):1467-1475.
2. Ali M et al. Glob Health Sci Pract. 2017 Dec 28;5(4):534-539.

# 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**

4) Stability issues upon storage/transport (suspensions)

5) Limit on drug type, number and loading, e.g. suspensions only allow water-insoluble drugs

6) Persistent pain for months after injection due to hydrophobic nature (oily liquids)

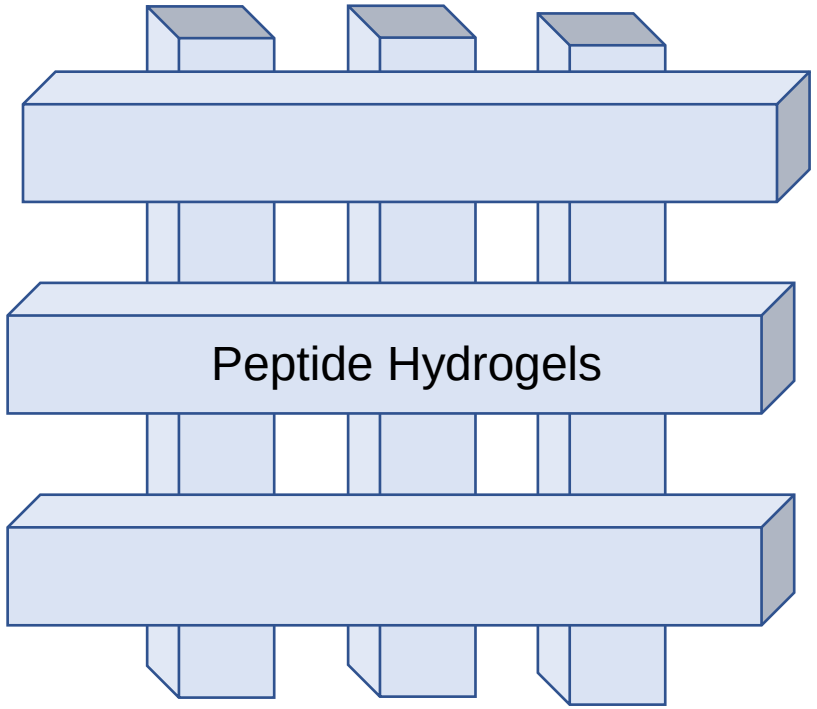
**How our approach resolves this**

4) Can be transported as freeze-dried powder for mixing with water prior to injection = increased stability

5) Drug precisely attached to peptide = increased drug loading. Vast range of multiple hydrophobic and hydrophilic drugs can be attached within one formulation

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**

# Biofunctional Nanomaterials Group

## Our Funders

1st in the UK for Pharmacy
(The Guardian's 2022 University Guide)

- Dr Garry Laverty (Principal Investigator)
- Dr Sophie Coulter (EPSRC Research Fellow)
- Dr Sreekanth Pentlavalli (EPSRC/Wellcome Trust Research Fellow)
- Dr Jessica Moore (Invest NI Research Fellow)
- Dr Emily Cross (MRC Research Fellow)
- Yuming An (PhD student)
- Han Sun (PhD student)

- The Xu Group
  Brandeis University
- The Adams Lab
  University of Glasgow
- Dr Ralf Schweins,
  Dr Mohamed Zbiri
  Institut Laue – Langevin
- Dr Mona Sarter,
- Dr Najet Mahmoudi
  STFC ISIS UK

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Group website: www.lavertylab.com