BMEG 3430 Biomaterials for Cartilage Tissue Repair & Regeneration

Group 3-5

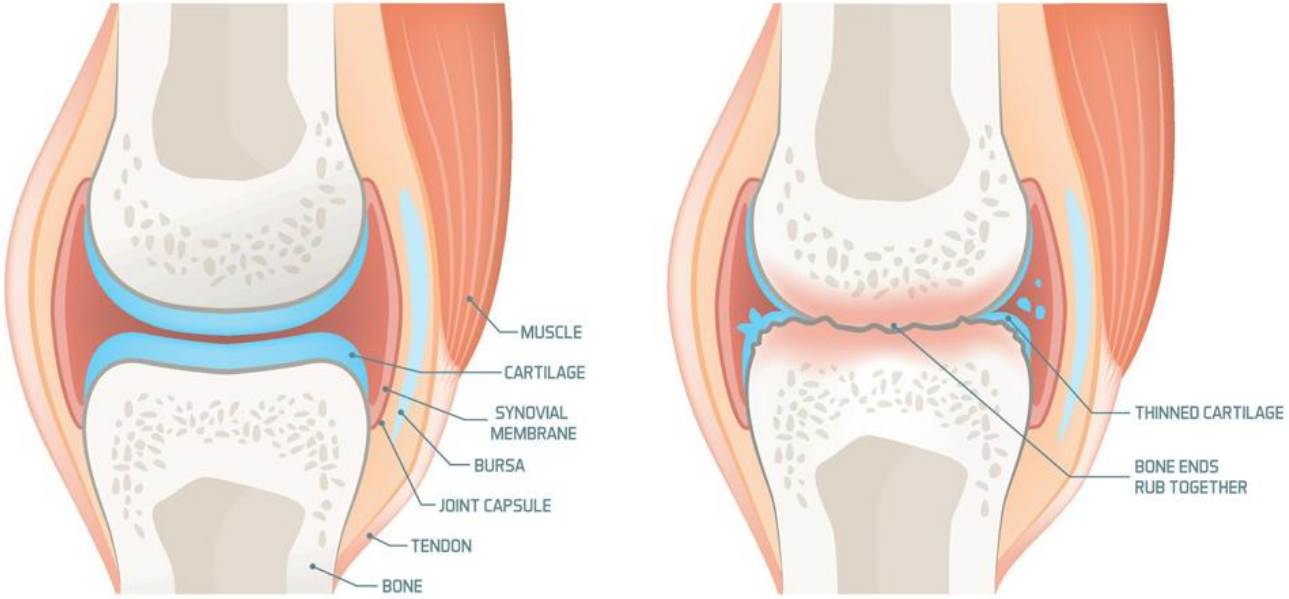
Au Wai Tak Wales	1155175068
Chan Cheuk Ka	1155174356
Ho Yu On	1155175831
Wan Chun Kit	1155175723
Lam Chi Ho	1155205935

Table of Contents

1 Background

Prevalence & Cause of OA

What is Osteoarthritis

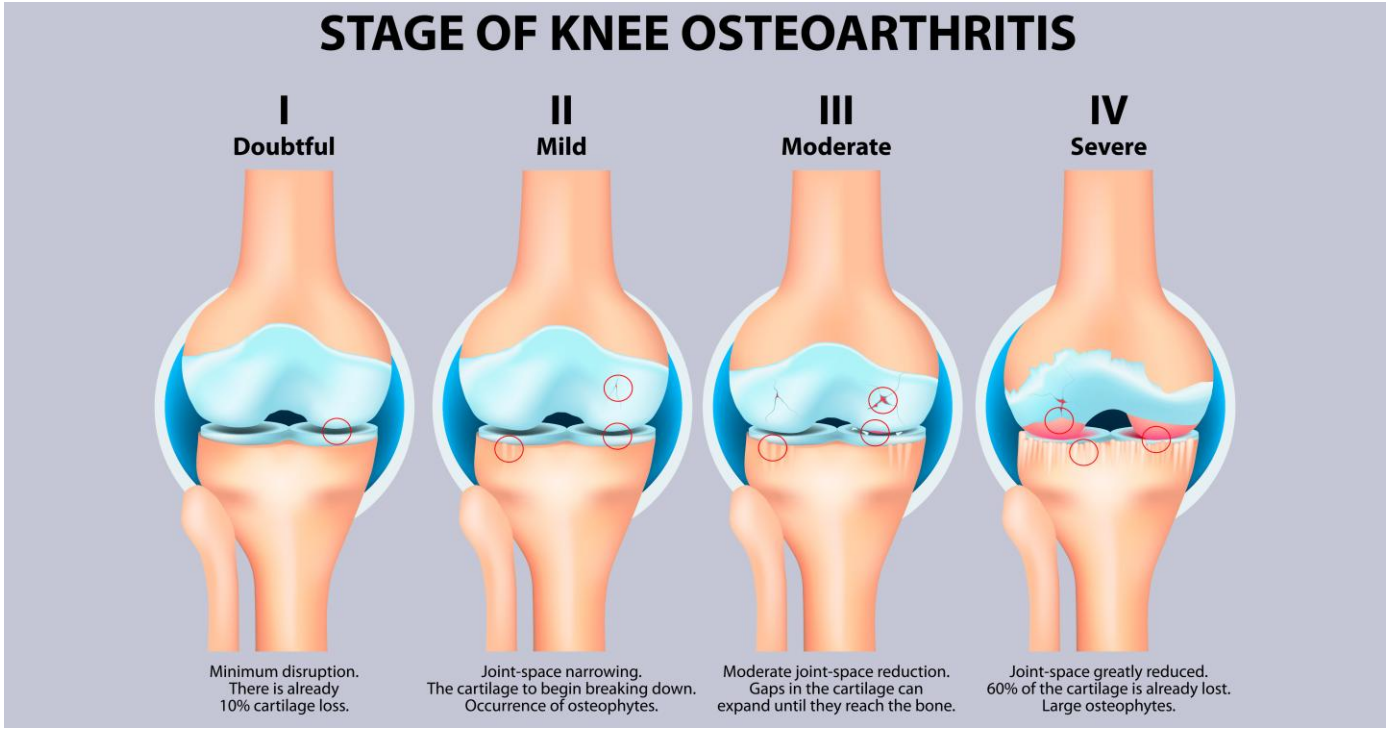


HEALTHY JOINT

OSTEOARTHRITIS

[1]

What is Osteoarthritis

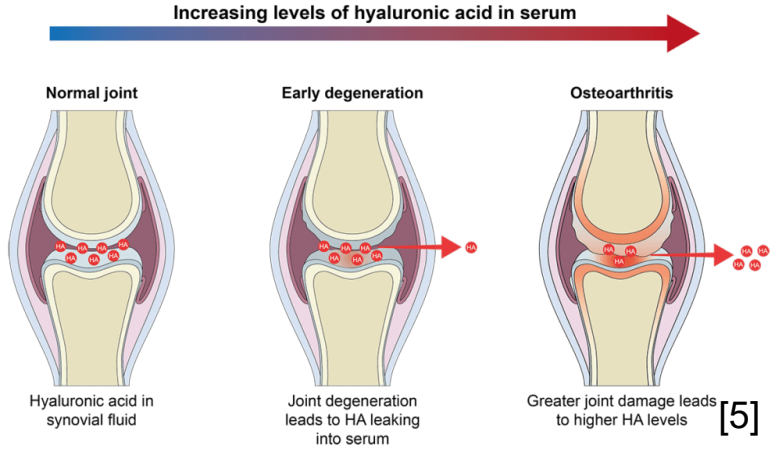


[2]

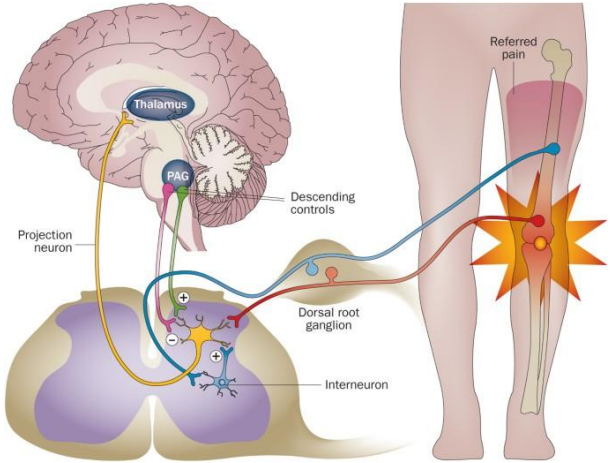
What is Osteoarthritis

Osteoarthritis occurs when the **cartilage** that cushions **the ends of bones** in your joints **gradually deteriorates**. [3, 4]

→ **Degenerative disease** that worsens over time, resulting in **chronic pain**

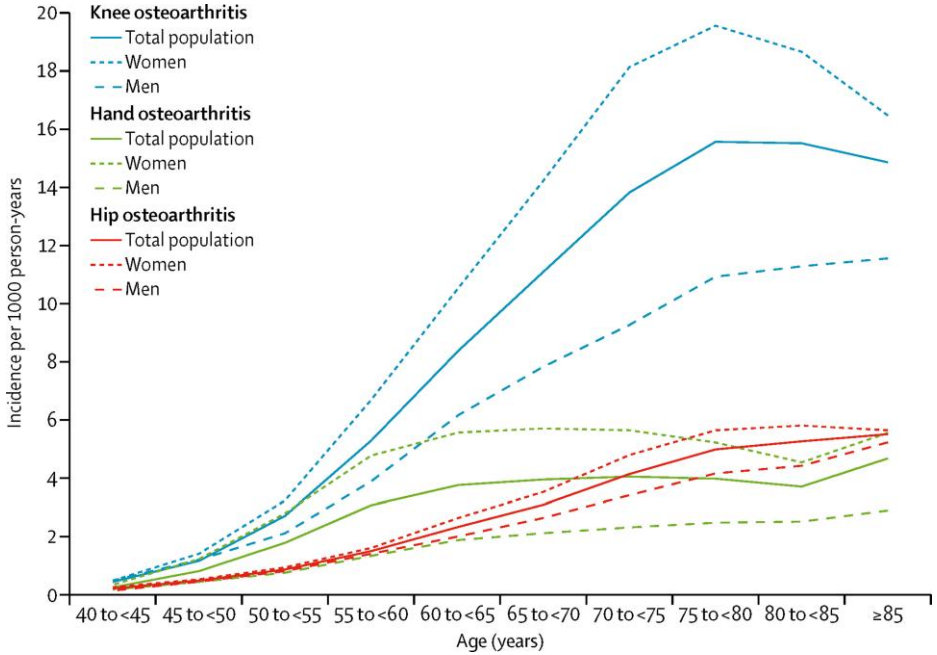


[5]



[6]

Prevalence of Osteoarthritis



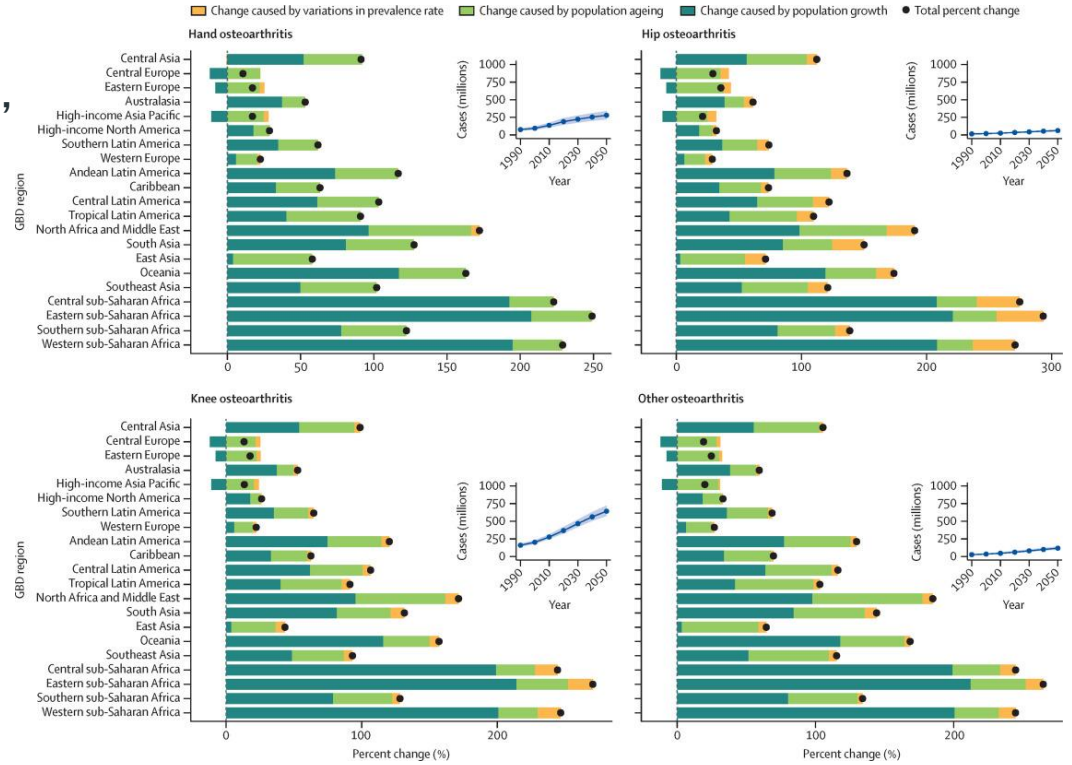
[7]

Increment of prevalence of Osteoarthritis along with ageing population

Prevalence of Osteoarthritis

According to WHO [8], **528 million** people worldwide are suffering from osteoarthritis.

An increase of **113%**, compared to 1990



[9]

Osteoarthritis Progression

- Joint articulation is facilitated by cartilage lubrication

Lubrication deteriorate because of age/wearing out/trauma → Tissue damage → Phenotypic destabilisation of chondrocytes → Hypertrophy

MMP production → ECM degradation → Cartilage thinning → Osteoarthritis

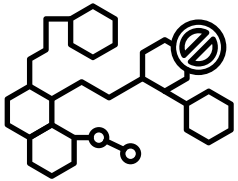
2
Motivation

Problem Focus & Gap in Current Technologies

Problem Focus

Lubrication Dysfunction

Lubricate joints to alleviate symptoms



Chondrocyte hypertrophy in OA

Stabilise phenotype to slow OA progression

Cartilage thinning in OA

Stop ECM degradation to protect against further damage

Slow cartilage regeneration

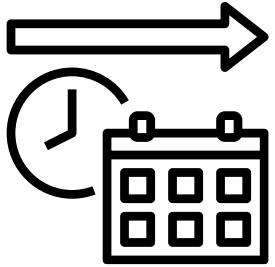
Exert long-term therapeutic effect to allow natural healing

$$\sigma = \frac{F_{\perp}}{A}$$

Requirements

$$\varepsilon = \frac{\Delta l}{l_0}$$

1. Mechanical strength: Can mimic natural cartilage
2. Bio-functionality: Able to integrate with tissue
3. Wear resistance: Able to withstand loads
4. Long term: Can provide long-term therapeutic effects



Current Technologies

APPROACH	Functionality	Strength	Wear resistance	Long-term effectiveness	Solubility
NSAIDs	Pain Relief	✗	✗	✗	✗
Hyaluronic Acid	Regeneration Enhancement	✓	✗	✓	✓
tBNPs-MTX	Targeting Synovium	✗	✗	✓	✓
Total joint replacement	Replacement Surgery	✓	✓	✓	N/A
Proposed Solution	Minimally Invasive Surgery	✓	✓	✓	✓

3

Proposed Solution

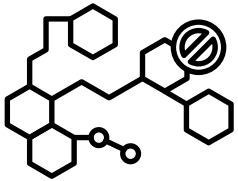
Solution Description

Proposed Solution

Joint Lubrication

↓

HPX polymer



Phenotype stabilisation

↓

HIF-1α & PHD inhibitor

ECM protection

↓

MMP inhibitor

Long-term therapeutic effects

↓

Choice of therapeutic agents

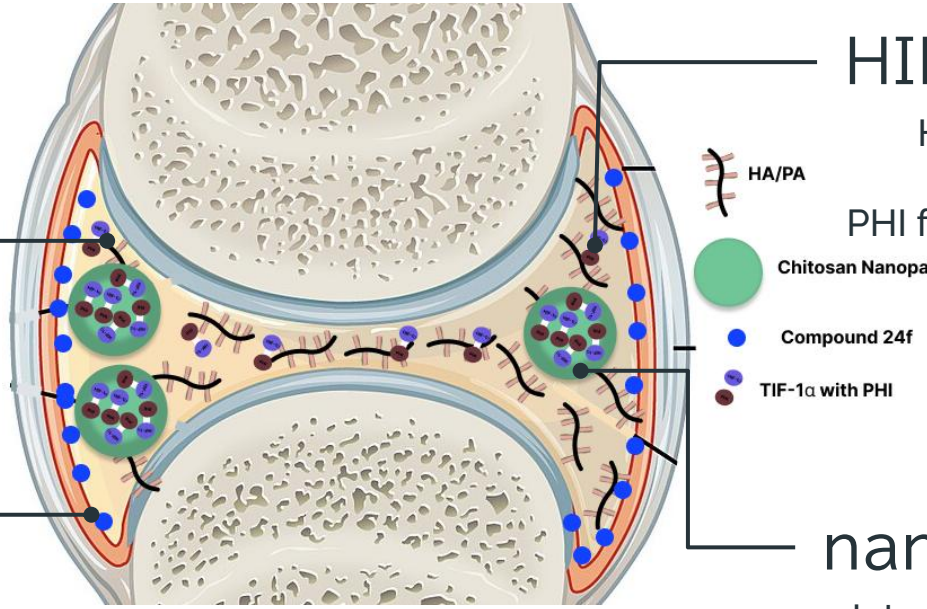
Proposed Solution

HPX/PVA hydrogel

HPX for lubrication &
PVA for biocompatibility

Compound 24f

Inhibits MMP for ECM protection against degradation [25]



HIF-1α & PHI

HIF-1α for phenotype stabilisation &
PHI for prolonging HIF-1α [18, 19]

Chitosan nanoparticles

Integrate medicine with hydrogel &
Responsive drug release

Proposed Solution

Joint Lubrication

HPX polymer

Phenotype stabilisation

HIF-1α & PHD inhibitor

ECM protection

MMP inhibitor

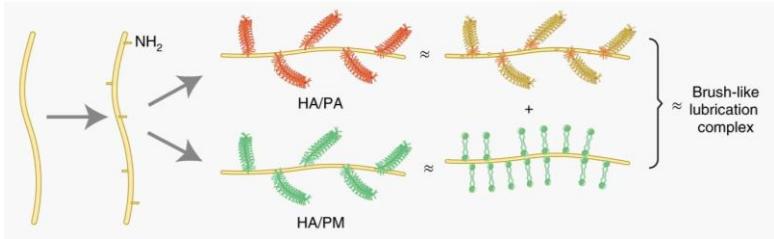
Long-term therapeutic effects

Choice of therapeutic agents

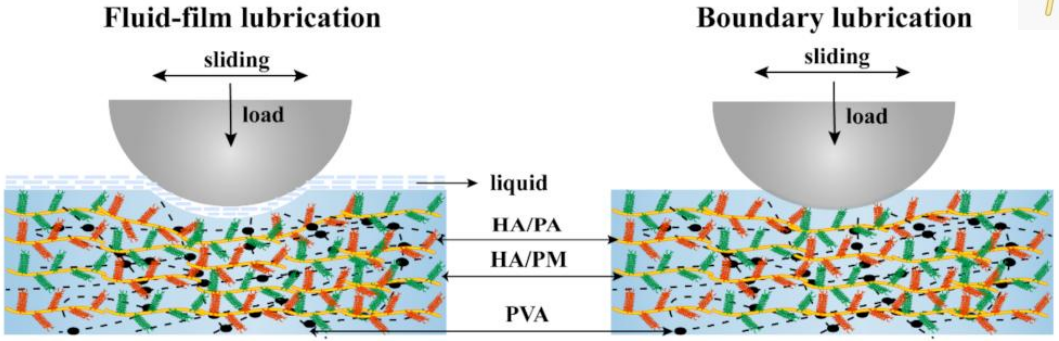
Joint Lubrication

HPX is a **combination** of **HA/PA** and **HA/PM** (hyaluronan-backbone polymer) [10]

HA/PA is **lubricin-like**
HA/PM is **lipid-like**



[10]



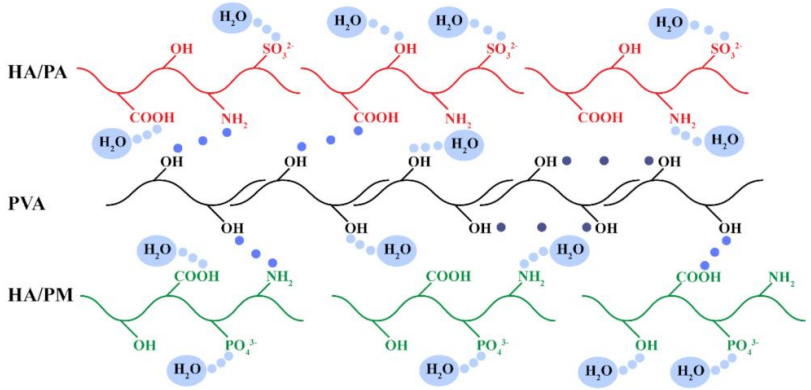
[11]

✔ Joint lubrication

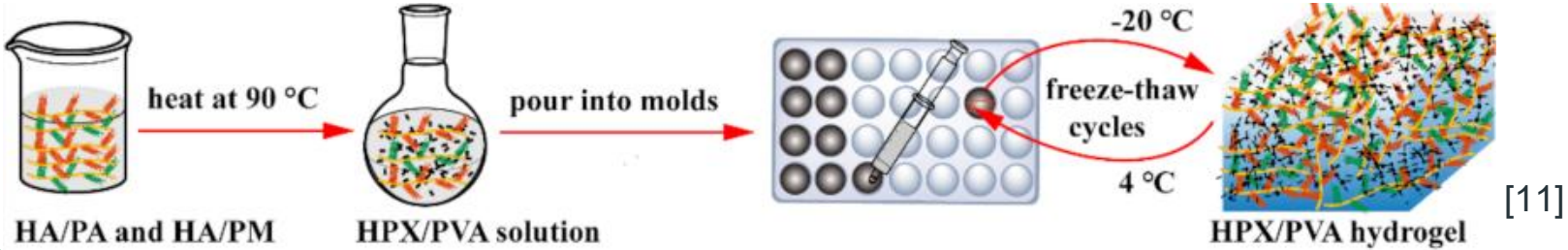
Joint Lubrication

HPX/PVA (A5M1)

- 5% HA/PA
- 1% HA/PM
- 94% PVA



[11]



[11]

✔ Joint lubrication

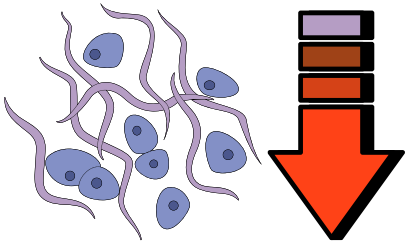
A5M1 (HPX/PVA)

A5M1 (HPX/PVA) vs PVA

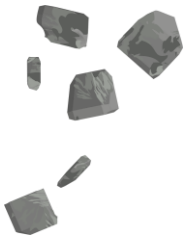
- **-30%** friction (mimic synovial fluid) [11]
- **+12%** compressive modulus (mimic cartilage)[11]
- **-70%** wear [11]
- High post-load recovery [11]
- HPX can bind with collagen for stability [12, 13]

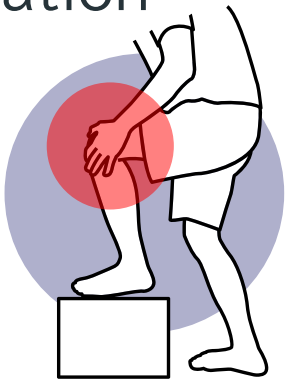
✔ Joint lubrication

Joint Lubrication



- Decrease tissue damage from rubbing
- Prevent further chondral debris formation
- Decrease pain and inflammation



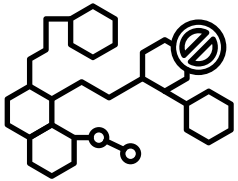


✔ Joint lubrication

Proposed Solution

Joint Lubrication

HPX polymer



Phenotype stabilisation

HIF-1α & PHD inhibitor

ECM protection

MMP inhibitor

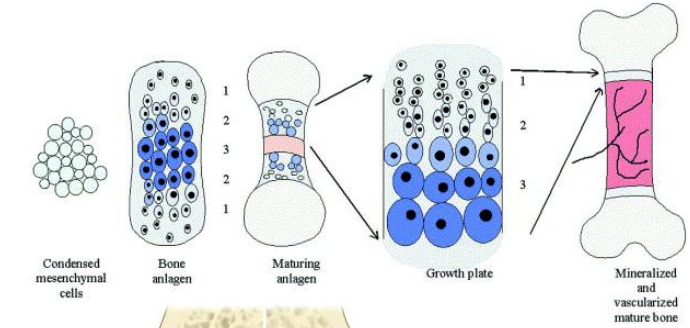
Long-term therapeutic effects

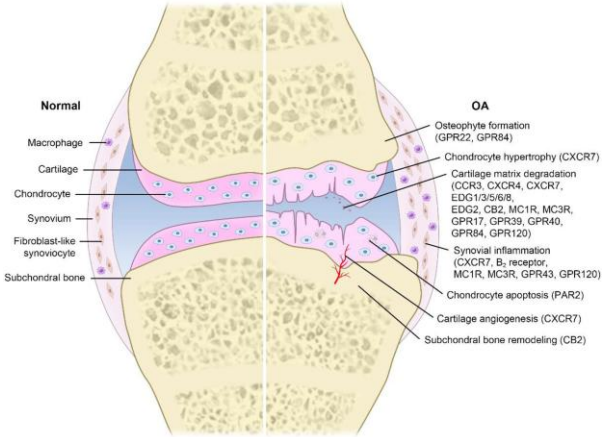
Choice of therapeutic agents

Phenotype Stabilisation

HIF-1α

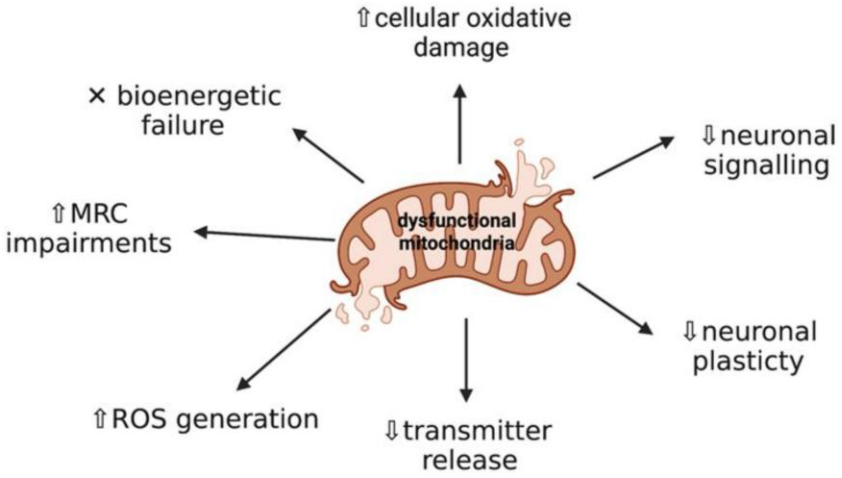
- Regulate chondrocyte growth cycle & homeostasis [14]
- Suppress chondrocyte hypertrophy [15]





✔ Phenotype stabilisation

Phenotype Stabilisation



HIF-1α underproduction

- Apoptosis [16]
- Mitochondrial dysfunction
- Chondrocyte hypertrophy [15]
- OA progression

✔ Phenotype stabilisation

Phenotype Stabilisation

HIF-1α

- Regulate chondrocyte growth cycle & homeostasis [14]
- Suppress chondrocyte hypertrophy [15]

HIF-1α underproduction

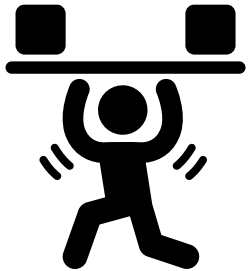
- Apoptosis [16]
- Mitochondrial dysfunction
- Chondrocyte hypertrophy [15]
- OA progression

HIF-1α

- Rapidly degraded by prolyl hydroxylase (PHD)
- 5-10 mins half-life [17]

↓

- Add 1,4-DPCA (PHD inhibitor) to stabilise HIF-1α & prolong natural HIF-1α [18, 19]
- Encapsulated in chitosan nanoparticles



✔ Phenotype stabilisation

Chitosan Nanoparticles

- Shield HIF-1α from PHD [20]
- Overcome hydrophobicity of 1,4-DPCA
- Control ratio of drugs by bundling
- Hydrolyse when OA progresses (acidic condition) [21, 22]

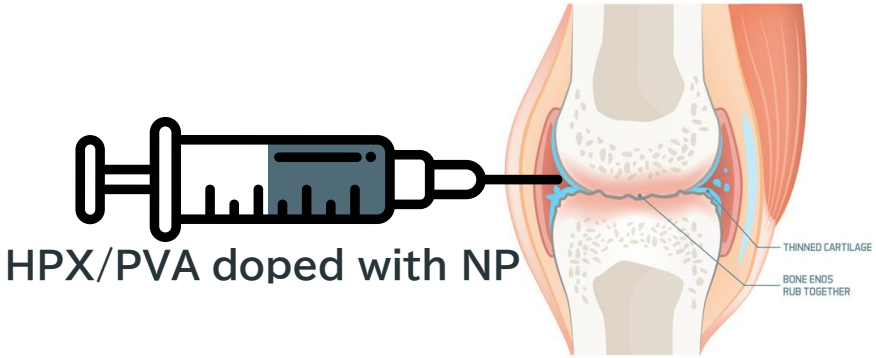
Chitosan Nanoparticles

Responsive

NP-Hydrogel Interaction

- Chitosan nanoparticles can covalently crosslink with sulphate groups in HA/PA [23]

→ **HPX/PVA doped with NP can be injected to joints**



✔ Responsive

Proposed Solution

Joint Lubrication

HPX polymer

Phenotype stabilisation

HIF-1α & PHD inhibitor

ECM protection

MMP inhibitor

Long-term therapeutic effects

Choice of therapeutic agents

Cartilage Protection

MMPs (Matrix metalloproteinases)

- MMP-13 is the major MMP in OA [24]
- Released by hypertrophic chondrocyte
- Degrade ECM & Cause cartilage thinning [24]

↓

- Add 24f (MMP inhibitor) to protect cartilage

Protection

Compound 24f

- Competitive **inhibitor of MMP-13** [25]
- **Also effective against MMP-3, -9, -14**
- Does not affect MMP-1 and TACE (TNF-α converting enzyme)

- Very **low dissociation constant** [25]

→ Pseudo-irreversible
→ Effective at lower concentrations
→ Longer duration of action

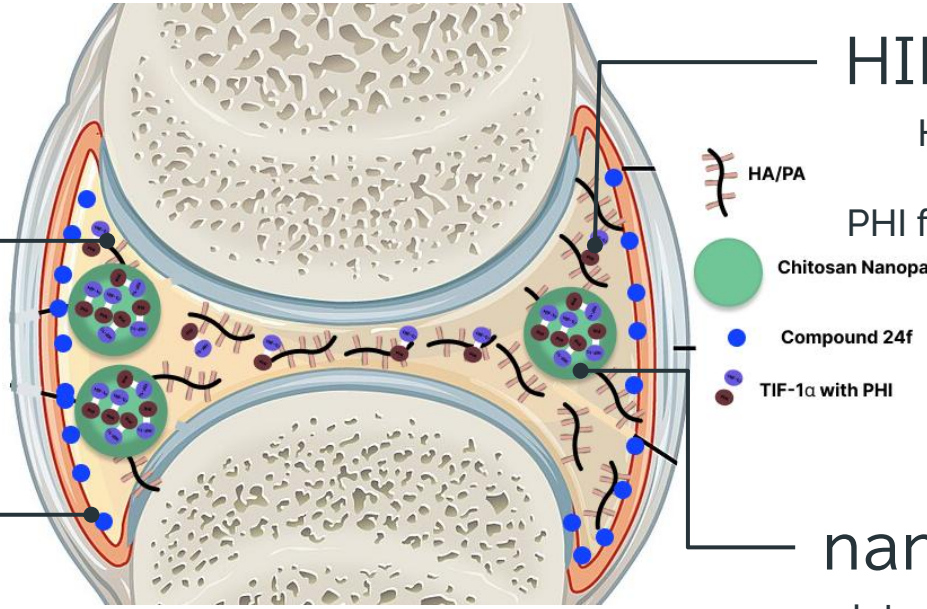
→ **Can allow slow natural regeneration**

✔ Protection

Proposed Solution Recap

HPX/PVA hydrogel

HPX for lubrication &
PVA for biocompatibility



HIF-1α & PHI

HIF-1α for phenotype stabilisation &
PHI for prolonging HIF-1α [18, 19]

Compound 24f

Inhibits MMP for ECM protection against degradation [25]

Chitosan nanoparticles

Integrate medicine with hydrogel &
Responsive drug release

Proposed Solution

Joint Lubrication

HPX polymer

Phenotype stabilisation

HIF-1α & PHD inhibitor

ECM protection

MMP inhibitor

Long-term therapeutic effects

Choice of therapeutic agents

Proposed Solution

HPX/PVA

-70% wear vs pure PVA

Mechanical strength

High post-load recovery

Stops further damage

Chitosan NPs

Hydrolyse more in low pH [21]
→ Responsive to OA severity

Long term

- OA is chronic
- Cartilage healing is slow
- Improve QoL

Regeneration

HIF-1α & 24f facilitate and encourage natural healing [14]

24f

Stop further cartilage damage [25]

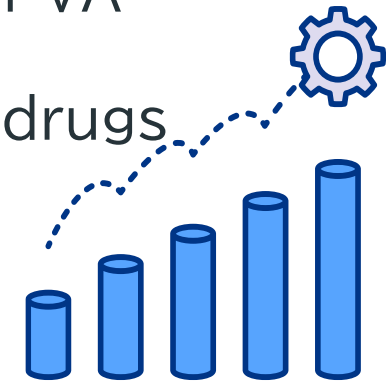
Long duration of action
→ Allow natural healing

4.1 Innovation

Novelty

Novelty

- Incorporation of chitosan NPs into HPX/PVA
- Gradual hydrolysis of NP and release of drugs



- Combination of methods into a feasible system to maximise the therapeutic effectiveness

4.2 Significance

Advantages over Current Technologies

Current Tech vs Proposed Solution

	Mechanical Properties	Long-term Effectiveness	Bundling
Current Technology	PVA hydrogels • Poor mechanical strength & friction coefficient [11] • Low wear resistance [11]	HIF-1α (hypoxia-inducible factor 1-α) • 5-10 mins half-life [17] • Not suitable for long-term therapy	1,4-DPCA • PHD inhibitor [19] • Hydrophobic; cannot easily integrate into hydrogel
Proposed Solution	A5M1 (5% HA/PA, 1% HA/PM) • -70% wear [11] • -30% friction [11] • +12% compressive modulus [11]	Chitosan NP encapsulation • Extended half-life [20] • Responsive to OA progression by acidic hydrolysis [21]	Chitosan NP encapsulation • Overcome hydrophobicity • Controllable ratio between 1,4-DPCA & HIF-1α

4.3 Drawbacks

Work to be Done

Drawbacks

- HIF-1α is not only an inhibitor for OA, but also foster OA development if it is high concentration

→ The dose need to be controlled delicately [26, 27]

- NPs may cause cytotoxicity and side effects to unintended tissues and organs [28]

→ The particle size need to be controlled delicately

5
Conclusion

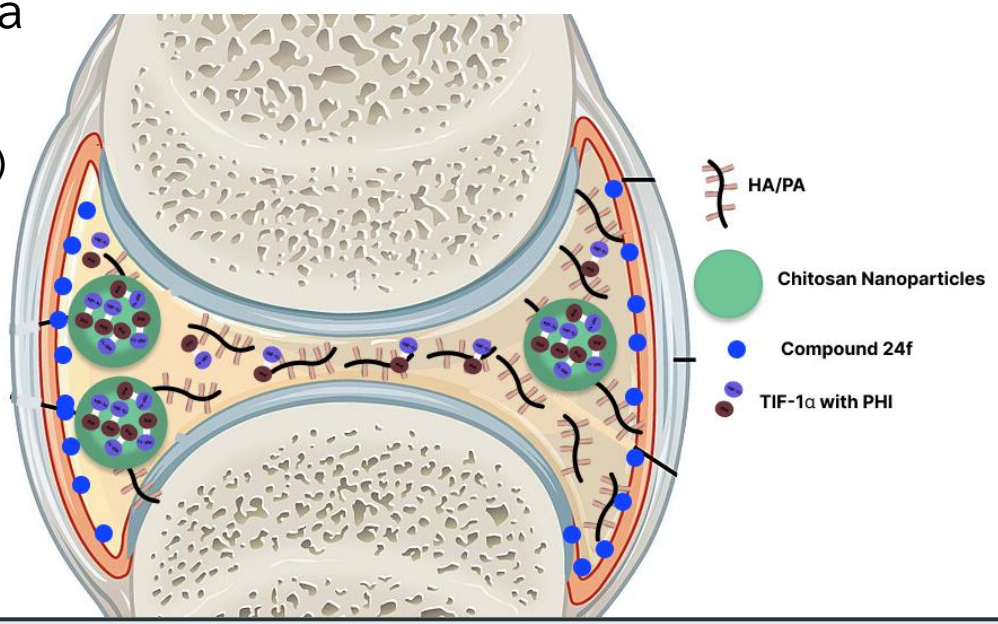
Overall Recap

Conclusion

To tackle the the widely prevalent osteoarthritis, we incorporated chitosan NPs into HPX/PVA

To provide patients with OA a new type of material able to:

- Administer drugs (HIF-1α) gradually
- Maximise the therapeutic effects of the drug
- Resist wear better than PVA hydrogels



Reference

[1] Healthdirect Australia, “Osteoarthritis,” April 2024.

[2] Comprehensive Orthopaedics, “How to manage your osteoarthritis,” 2 January 2020.

[3] D. J. Hunter, L. March and M. Chew, “Osteoarthritis in 2020 and Beyond: a Lancet Commission,” *The Lancet,* vol. 396, no. 10264, pp. 1711-1712, 28 November 2020.

[4]. A. E. Peters, R. Akhtar, E. J. Comerford and K. T. Bates, “The Effect of Ageing and Osteoarthritis on the Mechanical Properties of Cartilage and Bone in the Human Knee Joint,” *Scientific Reports,* vol. 8, p. 5931, 12 April 2018.

[5] VDI Laboratory, “Testing Joint Health with Hyaluronic Acid,” 17 April 2020.

[6] S. Liu *et al.*, “Nerves within bone and their application in tissue engineering of bone regeneration,” *Frontiers in Neurology*, vol. 13, February 2023.

[7] D. J. Hunter and S. Bierma-Zeinstra, “Osteoarthritis,” *The Lancet*, vol. 393, no. 10182, 27 April 2019.

[8] World Health Organization, “Osteoarthritis,” 14 July 2023.

[9] J. D. Steinmetz *et al.*, “Global, regional, and national burden of osteoarthritis, 1990–2020 and projections to 2050: a systematic analysis for the Global Burden of Disease Study 2021,” *The Lancet Rheumatology*, vol. 5, no. 9, August 2023.

[10] R. Xie, H. Yao, A. S. Mao, Y. Zhu, D. Qi, Y. Jia, M. Gao, Y. Chen, L. Wang, D.-A. Wang, K. Wang, S. Liu, L. Ren and C. Mao, “Biomimetic Cartilage-lubricating Polymers Regenerate Cartilage in Rats with Early Osteoarthritis,” *Nature Biomedical Engineering,* vol. 5, pp. 1189-1201, 4 October 2021.

[11] Q. Chen, Liu Sa, Z. Yuan, H. Yang, R. Xie and L. Ren, “Construction and Tribological Properties of Biomimetic Cartilage-Lubricating Hydrogels,” *Gels,* vol. 8, no. 7, p. 415, 3 June 2022.

Reference

[12] J. Laterra, J. E. Silbert and L. A. Culp, “Cell Surface Heparan Sulfate Mediates Some Adhesive Responses to Glycosaminoglycan-binding Matrices, Including Fibronectin,” *Journal of Cell Biology,* vol. 96, no. 1, pp. 112-123, 1 January 1983.

[13] A. Heremans, B. De Cock, J.-J. Cassiman, H. Van den Berghe and G. David, “The Core Protein of the Matrix-associated Heparan Sulfate Proteoglycan Binds to Fibronectin,” *Journal of Biological Chemistry,* vol. 265, no. 15, pp. 8716-8724, 23 January 1990.

[14] D. Pfander, B. Swoboda and T. Cramer, “The Role of HIF-1α in Maintaining Cartilage Homeostasis and During the Pathogenesis of Osteoarthritis,” *Arthritis Research & Therapy,* vol. 8, p. 104, 18 January 2006.

[15] D. K. Taheem, G. Jell and E. Gentleman, “Hypoxia Inducible Factor-1α in Osteochondral Tissue Engineering,” *Tissue Engineering Part B: Reviews,* vol. 26, no. 2, 16 April 2020.

[16] S. Hu *et al.*, “Stabilization of HIF-1α Alleviates Osteoarthritis via Enhancing Mitophagy,” *Cell Death & Disease,* vol. 11, no. 6, p. 481, 25 June 2020.

[17] G. L. Wang, B. H. Jiang, E. A. Rue and G. L. Semenza, “Hypoxia-inducible Factor 1 is a Basic-helix-loop-helix-PAS Heterodimer Regulated by Cellular O2 Tension,” *Proceedings of the National Academy of Sciences,* vol. 92, no. 12, pp. 5510-5514, 6 June 1995.

[18] K. Nagai *et al.*, “An Injectable Hydrogel-formulated Inhibitor of Prolyl-4-hydroxylase Promotes T Regulatory Cell Recruitment and Enhances Alveolar Bone Regeneration During Resolution of Experimental Periodontitis,” *The FASEV Journal,* vol. 34, no. 10, pp. 13726-13740, October 2020.

[19] Y. Zhang, I. Strehin, K. Bedelbaeva, D. Gourevitch, L. Clark, J. Leferovich, P. B. Messersmith and E. Heber-Katz, “Drug-induced Regeneration in Adult Mice,” *Science Translational Medicine,* vol. 7, no. 290, 3 June 2015.

Reference

[20] M. M. Gonçalves, D. F. Maluf, E. Almouazen and Y. Chevalier, “Negatively Charged Chitosan Nanoparticles Prepared by Ionotropic Gelatino for Encapsulation of Positively Charged Proteins,” *Internation Journal of Pharmaceutics,* vol. 642, p. 123164, 23 July 2023.

[21] Z. Yaneva, D. Ivanova, N. Nikolova and M. Tzanova, “The 21st Century Revival of Chitosan in Service to Bio-organic Chemistry,” *Biotechnology & Biotechnological Equipment,* vol. 34, no. 1, pp. 221-237, January 2020.

[22] S. Liao, S. Jia, Y. Yue, H. Zeng, J. Lin and P. Liu, “Advancements in pH-Responsive Nanoparticles for Osteoarthritis Treatment: Opportunities and Challenges,” *Frontiers in Bioengineering and Biotechnology,* vol. 12, 1 July 2024.

[23] S. Murali, V. Aparna, M. K. Suresh, R. Biswas, R. Jayakumar and S. Sathianarayanan, “Amphotericin B Loaded Sulfonated Chitosan Nanoparticles for Targeting Macrophages to Treat Intracellular Candida Glabrata Infections,” *International Journal of Biological Macromolecules,* vol. 110, pp. 113-139, 15 April 2018.

[24] P. Singh, K. B. Marcu, M. B. Goldring and M. Otero, “Phenotypic Instability of Chondrocytes in Osteoarthritis: On a Path to Hypertrophy,” *Annals of the New York Academy of Sciences,* vol. 1442, no. 1, pp. 17-34, April 2019.

[25] L. G. Monovich *et al.*,“Discovery of Potent, Selective, and Orally Active Carboxylic Acid Based Inhibitors of Matrix Metalloproteinase-13,” *Journal of Medicinal Chemistry,* vol. 52, pp. 3523-3538, 11 June 2009.

[26] C.-Y. Zeng, X.-F. Wang and F.-Z. Hua, “HIF-1α in Osteoarthritis: From Pathogenesis to Therapeutic Implications,” *Frontiers in Pharmacology,* vol. 13, 5 July 2022.

[27] P. Wang, P. Zhu, R. Liu, Q. Meng and S. Li, “Baicalin Promotes Extracellular Matrix Synthesis in Chondrocytes via the Activation of Hypoxia-inducible Factor-1α,” *Experimental and Therapeutic Medicine,* vol. 20, no. 6, p. 226, 15 October 2022.

[28] L. H. Zoe, S. R. David and R. Rajabalaya, “Chitosan Nanoparticle Toxicity: A Comprehensive Literature Review of In Vivo and In Vitro Assessments for Medical Applications,” *Toxicology Reports,* vol. 11, pp. 83-106, December 2023.

THE END