TAIPEI MEDICAL UNIVERSITY HOSPITAL

Injectable ChitHCl-DDA Tissue Adhesive with High Adhesive Strength and Biocompatibility for Torn Meniscus Repair and Regeneration

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Trust, Moral, Universal, Hand in Hand

FACULTY DISCLOSURE

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- The author has no relevant financial relationships or conflicts of interest to disclose.

Development of Tissue Adhesives

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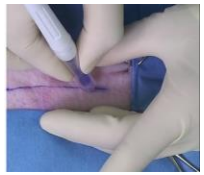
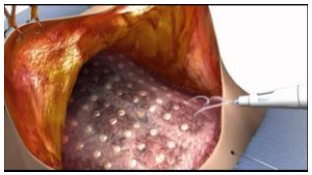
Suture pull-through is a clinical problem in meniscus repair surgery due to the sharp leading edge of sutures.

Various tissue adhesives

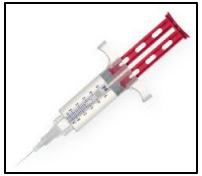
- **Tissue adhesives aim to overcome limitations of sutures. Examples include:**
  - **Dermabond® (topical skin adhesive), fibrin glue (pulmonary leaks), TissuGlu® (abdominoplasty).**
- **Limitations of current adhesives:**
  - **Cytotoxicity, low tensile strength, foreign body reactions, and long setting times.**
- ***No adhesive has been specifically for meniscal repair in clinical practice.***



Dermabond®

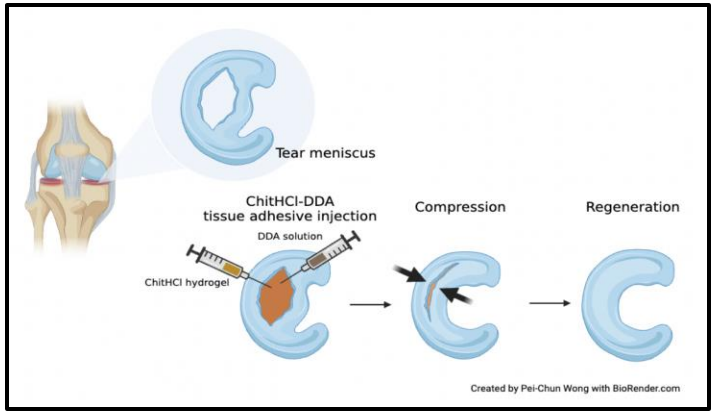


TissuGlu®



Fibrin glue

Novel Tissue Adhesive Development



- **We synthesized a new adhesive using chitosan hydrochloride (ChitHCl) and oxidized dextran (DDA), forming a hydrogel via Schiff's base reaction.**
- **Key properties and testing:**
  - **Optimization of DDA to ChitHCl ratios for adhesion.**
  - **Evaluated mechanical strength, swelling ratio, degradation behavior, cytotoxicity, and protein expression.**
  - **Tested in ex vivo porcine meniscus and in vivo rabbit models to assess effectiveness.**

Study Design

- Study design
- Synthesis of the ChitHCl-DDA tissue adhesive
- Adhesive properties of the ChitHCl-DDA tissue adhesives
- Characterization of the ChitHCl-DDA tissue adhesives
- Viscoelastic and viscosity behaviors of the ChitHCl-DDA tissue adhesives
- Swelling ratios of the ChitHCl-DDA tissue adhesives
- Degradation behavior of the ChitHCl-DDA tissue adhesives
- Precipitate medium preparation
- Cell viability of SW1353 chondrocytes
- Migratory capacity of SW1353 chondrocytes through a scratch analysis
- Chemotactic effect of the ChitHCl-DDA tissue adhesive on SW1353 chondrocytes through a channel test
- GAG synthesis of SW1353 chondrocytes
- Torn meniscus repair and regeneration of a porcine model by an ex vivo test
- In vivo test
- Statistical analysis

Table 1
Experimental design.

Type of DDA concentration	DDA 1	DDA 2	DDA 3	DDA 4
1 (10 mg/ml)	1–1	2–1	3–1	4–1
2 (20 mg/ml)	1–2	2–2	3–2	4–2
5 (50 mg/ml)	1–5	2–5	3–5	4–5
10 (100 mg/ml)	1–10	2–10	3–10	4–10
15 (150 mg/ml)	1–15	2–15	3–15	4–15

DDA, oxidative periodate-oxidized dextran.

Gelation Time

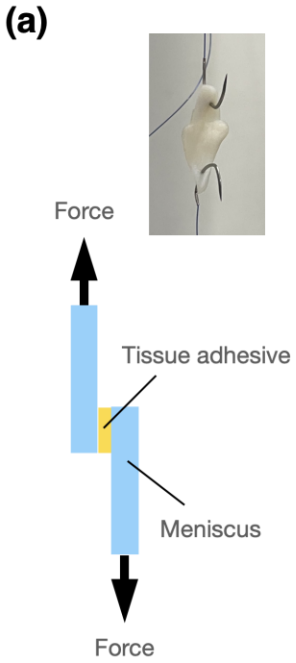
Type of DDA / Concentration	DDA 1	DDA 2	DDA 3	DDA 4
1 (10 mg/ml)	Failed	Failed	Failed	Failed
2 (20 mg/ml)	Failed	Failed	33 ± 1	33 ± 2
5 (50 mg/ml)	Failed	**280 ± 4**	**201 ± 2**	35 ± 1
10 (100 mg/ml)	Failed	76 ± 1	**155 ± 8**	95 ± 6
15 (150 mg/ml)	Failed	**185 ± 6**	**262 ± 6**	107 ± 1

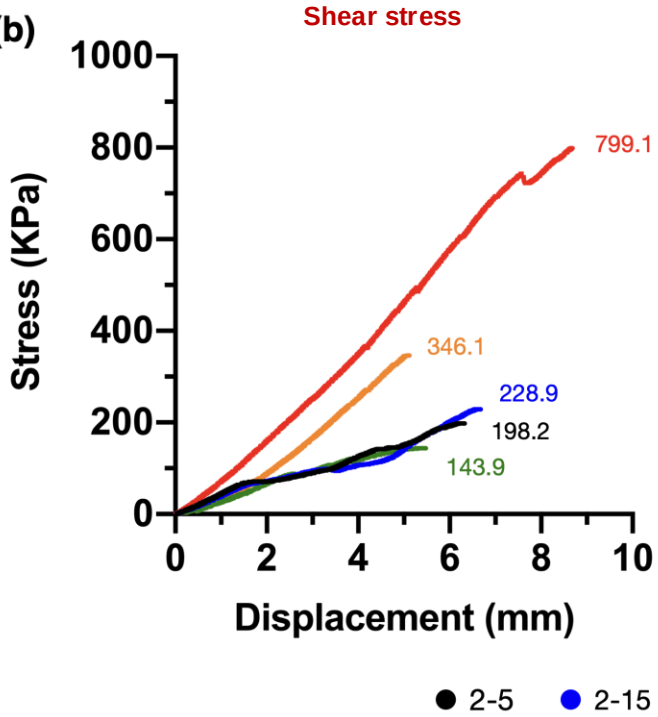
- **No successful cross-linking**
- **Too fast**

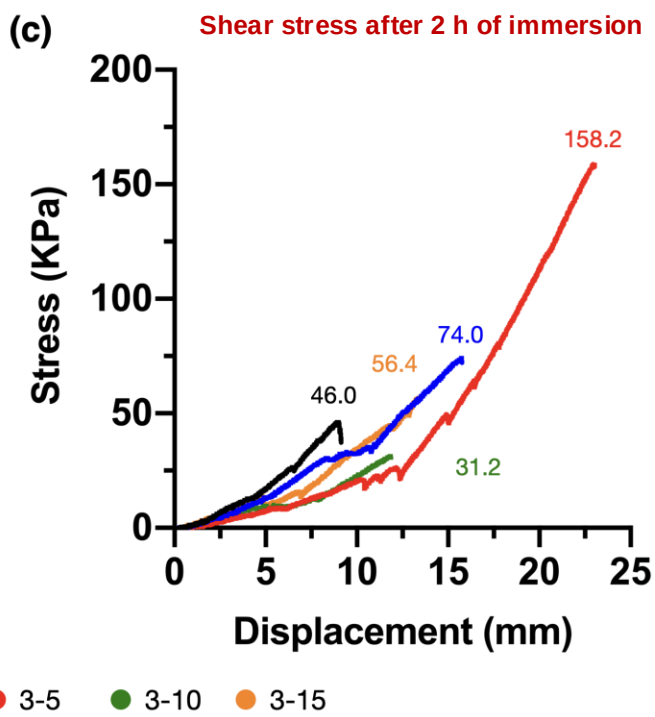
- The ChitHCl-DDA hydrogel with a gelation time of **2–5 min** was selected as a candidate for further experiments to prevent the formation of inappropriate hydrogels due to either a too-slow or too-fast gelation rate .

- Y.R. Ji, et al., ACS Biomater Sci. Eng. 7 (2021) 637–4644.

Adhesion Strength







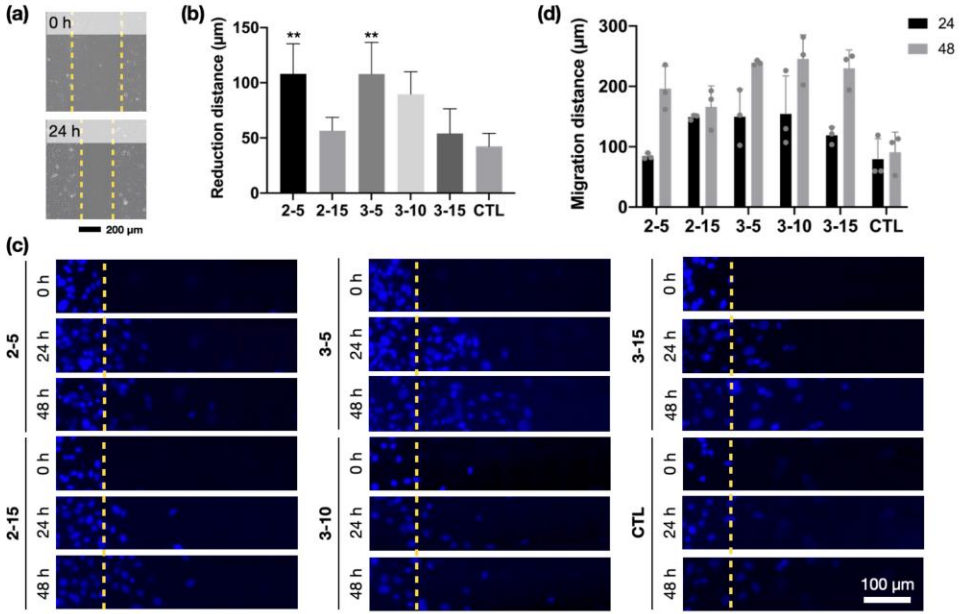
2-5 2-15 3-5 3-10 3-15

- **Sample test setup**

- **The tissue adhesive that provides stresses of 50–100 KPa to hold a torn meniscus together is able to meet the requirements of a meniscus tissue adhesive .**
  - A.I.H.G. et al., J. Mater. Sci. Mater. Med. 27 (2016) 85.

Cell Migration Ability

The cell migration speed and capacity induced by materials may play a role in reducing healing time



- **Cells in all groups migrated, and migration was much higher than in the control group after 24 and 48 h of incubation for different levels.**

- **Interestingly, the trend of migration distances in each group in the microchannel test for the chemotactic effect test was similar to the wound-healing test for the migration capacity.**
- **These findings are consistent with other studies which reported that the cell migratory capacity can be enhanced by chitosan and dextran.**

- C.J. Park,et al.,Biomaterials 30 (2009) 436–444; A.E. Erickson, et al., Biomed. Microdevices 21 (2019) 34; X. Yin,et al., Adv. Mater. Interfaces 8 (2021) 2100494.

Glycosaminoglycans (GAG) Expression

The GAG content reflects the degree of healing

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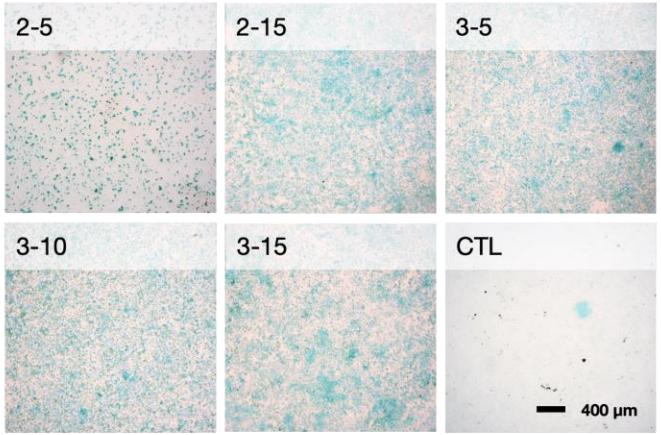
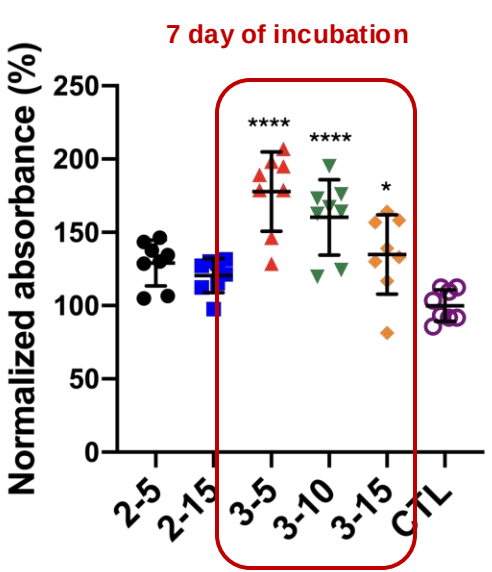
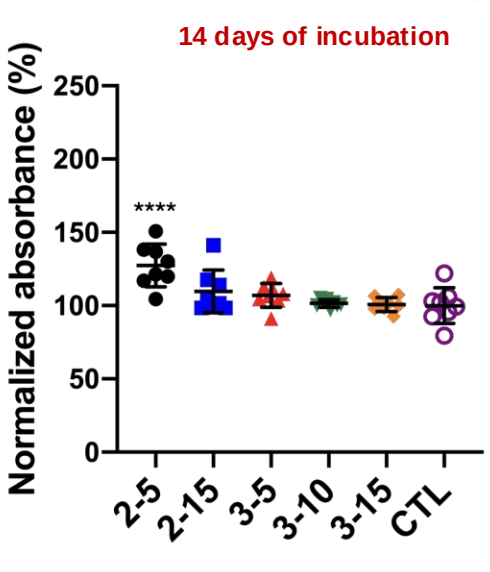
(a)



(b)



(c)



- The meniscus tissue mainly contained 72 % water, 22 % collagens, and 0.8 % GAG.
  - P.C. Verdonk, et al., Cartil. 13 (2005) 548–560.
- **In the primary weight-bearing area of meniscal horns and the inner half of menisci, the highest GAG concentrations support bulk compression.**
  - P. Ghosh,et al., Clin. Orthop. Relat. Res. 224 (1987) 52–63; J. Herwig, et al., Ann. Rheum. Dis. 43 (1984) 635–640; J.T. Moyer, et al., Acta Biomater. 9 (2013) 6624–6629.

Histological Analysis of Adhesive Menisci in the ex vivo test _Mechanical Strength

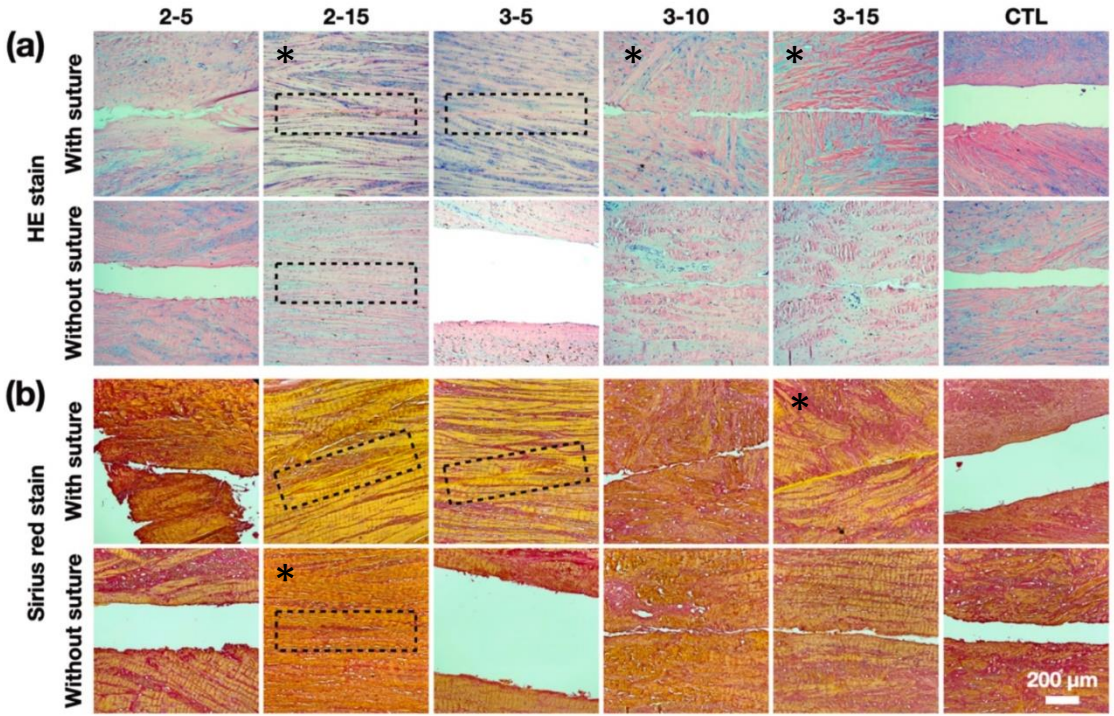


Fig. 11. Tissue profile images of adhesive menisci with different compositions of chitosan hydrochloride reacted with oxidative periodate-oxidized dextran (ChitHCl-DDA) tissue adhesives. (a) H&E stain and (b) Sirius red stain.

Meniscus Extrusion Test

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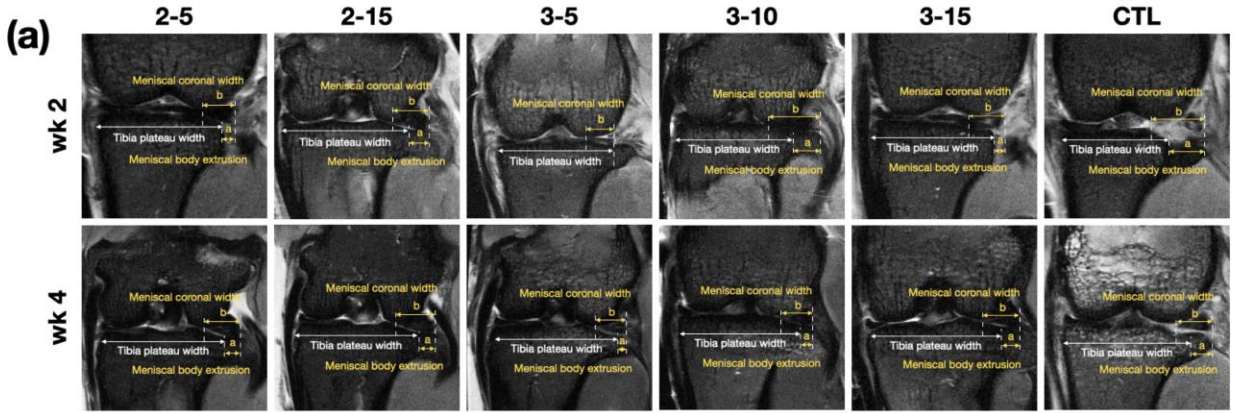
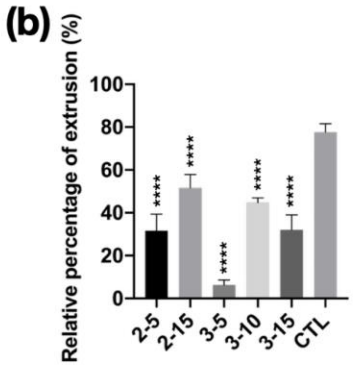
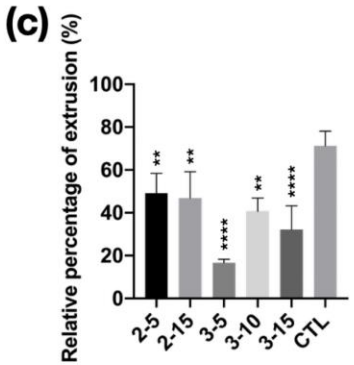
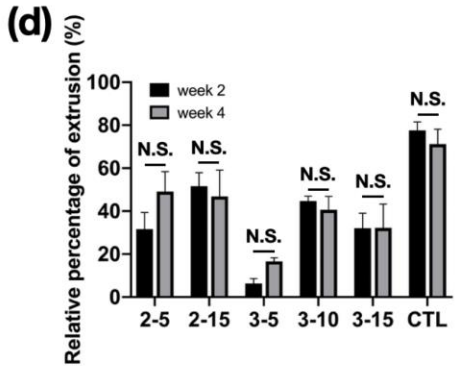
- **MR images of a repaired meniscus from New Zealand rabbits at 2 and 4 weeks postoperatively.**



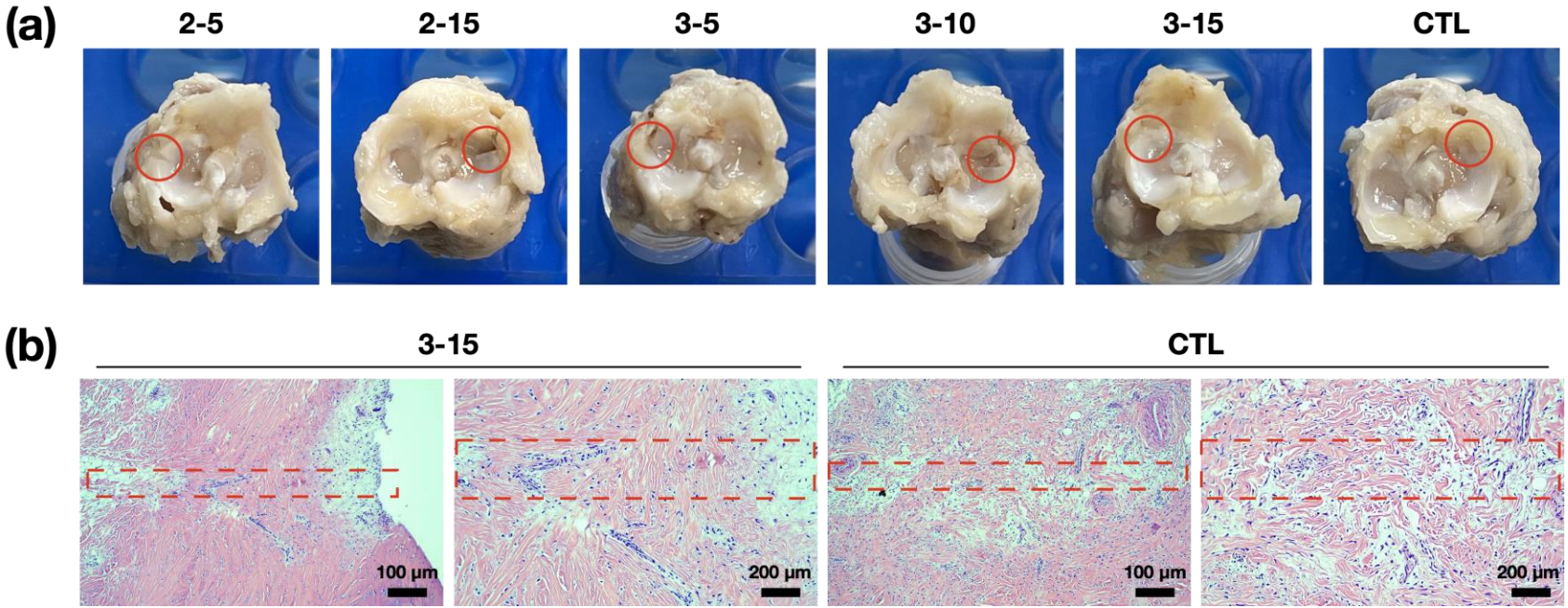






- All of the tissue adhesive groups exhibited less meniscus extrusion at 2 and 4 weeks postoperatively
- Group 3–5 displayed relatively less extrusion compared to the other tissue adhesive groups.
- In addition, the level of meniscus extrusion between 2 and 4 weeks was not significant in any groups including the control (untreated) and experimental groups.
- These results indicated that meniscus extrusion was not affected by time progression, but also that tissue adhesion had effectively decreased the degree of meniscus extrusion.
- ***The tissue adhesive can provide good adhesion onto a torn meniscus.***

Meniscus Healing Situation



- Group 3–15 showed dense newly formed tissue at the defect site.
- Cells had been induced to the repair site and showed a specific regular arrangement.

Conclusion

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Injectable ChitHCl-DDA tissue adhesive with high adhesive strength and biocompatibility for torn meniscus repair and regeneration

Pei-Chun Wong [a], Kuan-Hao Chen [b,c], Wei-Ru Wang [a], Chieh-Ying Chen [d], Yu-Tzu Wang [e], Yu-Bin Lee [f], Jia-Lin Wu [g,h,i,j,*]

- **Strong tissue adhesives for weight-bearing tissues remain scarce.**
- **To address this, we developed a chitosan-dextran adhesive with high biocompatibility and adhesion strength.**
- **Our adhesive promotes cell migration, chemotaxis, and chondrogenesis, showing great potential for meniscus repair and regeneration, as well as other applications.**

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