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COLLEGE OF ENGINEERING
The Department of Biomedical Engineering

Injectable Capsule for Tunable Extended Therapeutic Delivery

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The Ohio State University

Controlled Release Society – Ocular Delivery

Disclosures

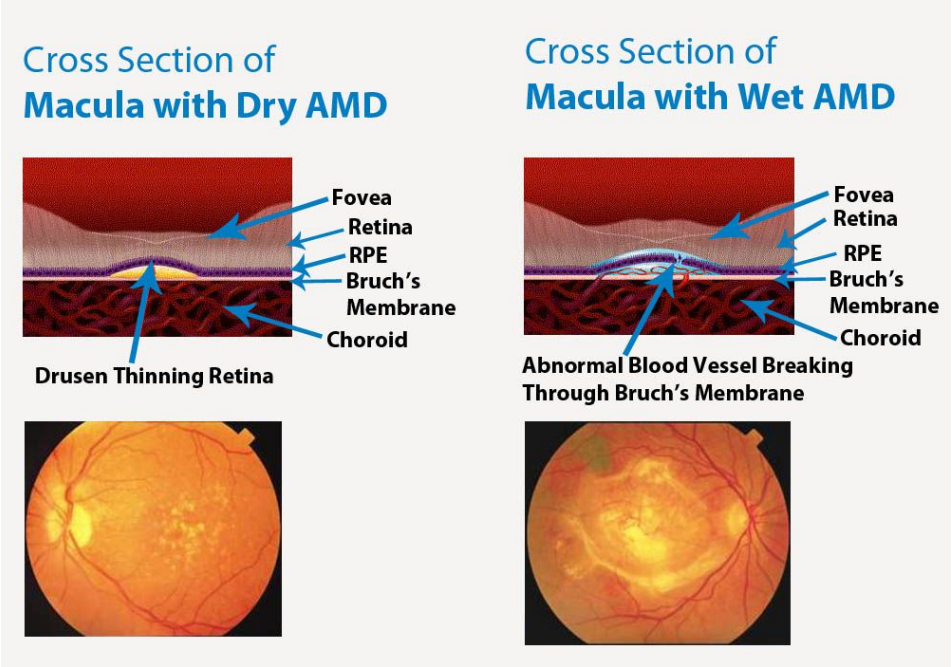
Patents and Patent Applications – KESR, PJ, AFP, JJL, MPO

Technologies licensed from Ohio State by Vitranu, Inc.

- KESR Consultant – Chief Technology Officer
- MPO Consultant – Chief Medical Officer
- Personal financial interest

Age-Related Macular Degeneration

- AMD is leading causing of blindness in the US for patients over the age of 65 and the third leading cause of blindness worldwide
  - 11M patients in US, ~200M worldwide expected to double by 2050
  - Retinal degeneration followed by yellow deposits (drusen)
  - Inflammation triggers VEGF and growth of abnormal, leaky blood vessels on the retinal pigment epithelium

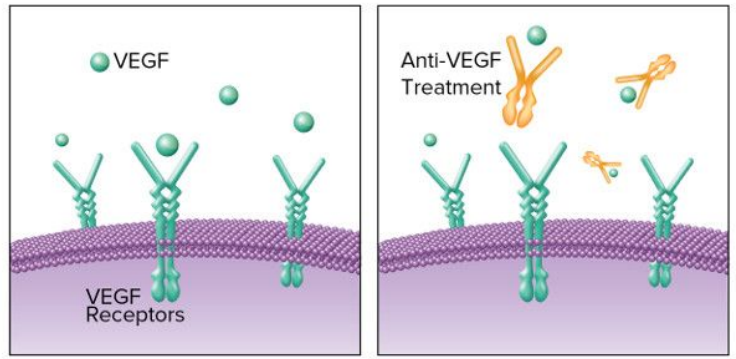


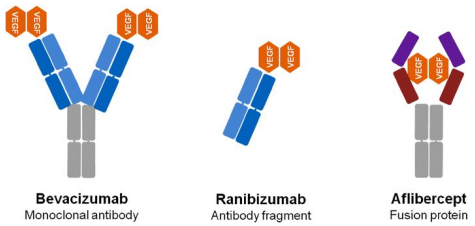
Permanent loss of vision

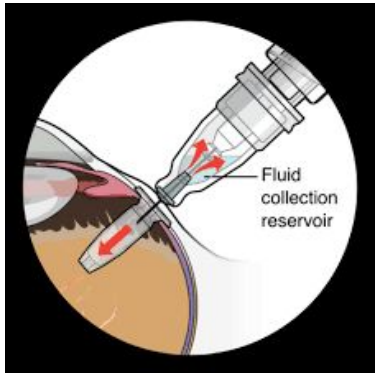
NEI

Current Treatments

- *No prevention or cure* – mitigated by intravitreal delivery of anti-VEGF
  - Bevacizumab (Avastin), Ranibizumab (Lucentis), Aflibercept (Eylea)
  - Typically injected 7-12 times per year due to short half-life of drug in vitreous
  - Recent FDA approval of SUSVIMO™ port – 6 months between refills
- Risks of frequent injections
  - Complications – pain, retinal detachment, IOP elevation, patient compliance
  - Monetary and time costs to patients, surgeons, and health care system

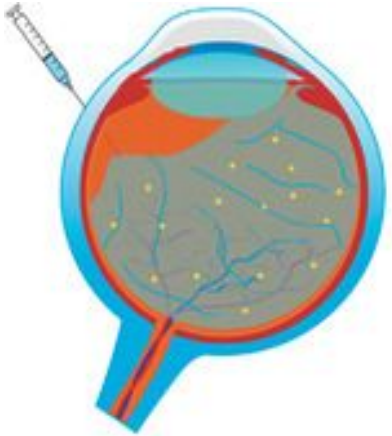






Our Approach

Can we reduce the number of injections for these patients?

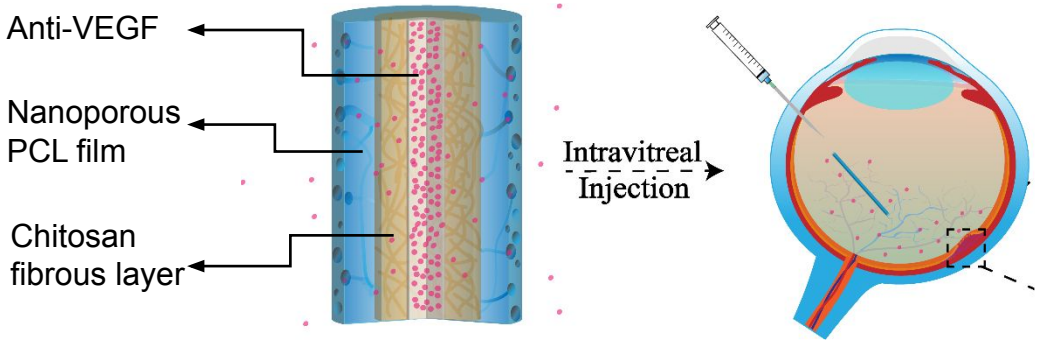


Target Design Criteria

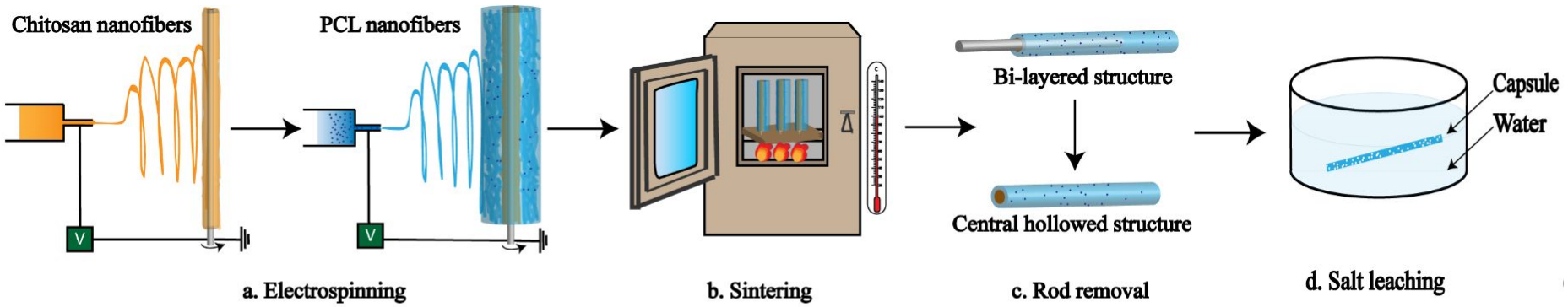
- Injectable
- Biodegradable
- Sustained release >6 months
- Preservation of therapeutic bioactivity

Injectable Capsule

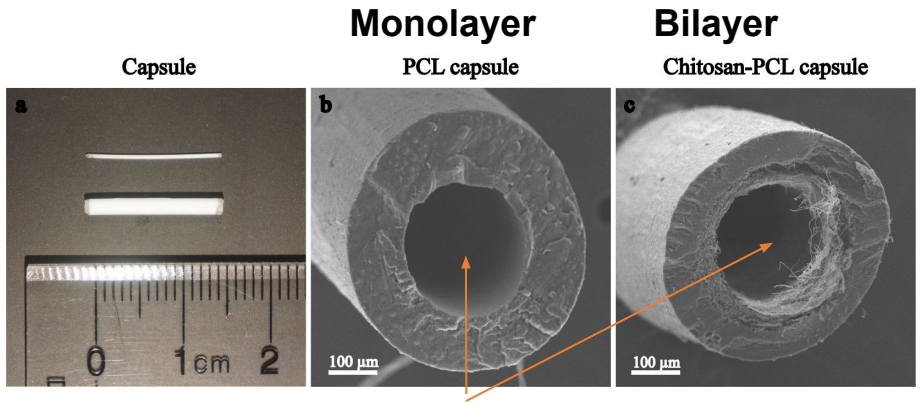
- Capsule fabrication
  - Two sizes
    - 1.646 mm diameter (proof-of-concept)
    - 260 μm diameter (injectable like Ozurdex)



- **Electrospinning** - fiber production method which uses electric force to draw charged threads of polymer solutions or melts to fiber diameters in the order of hundreds of nanometers
- **Sintering** - compacting and forming a solid mass of material by heat or pressure without melting it to the point of liquefaction
- **Salt leaching** - water soluble component to fabricate porous structure



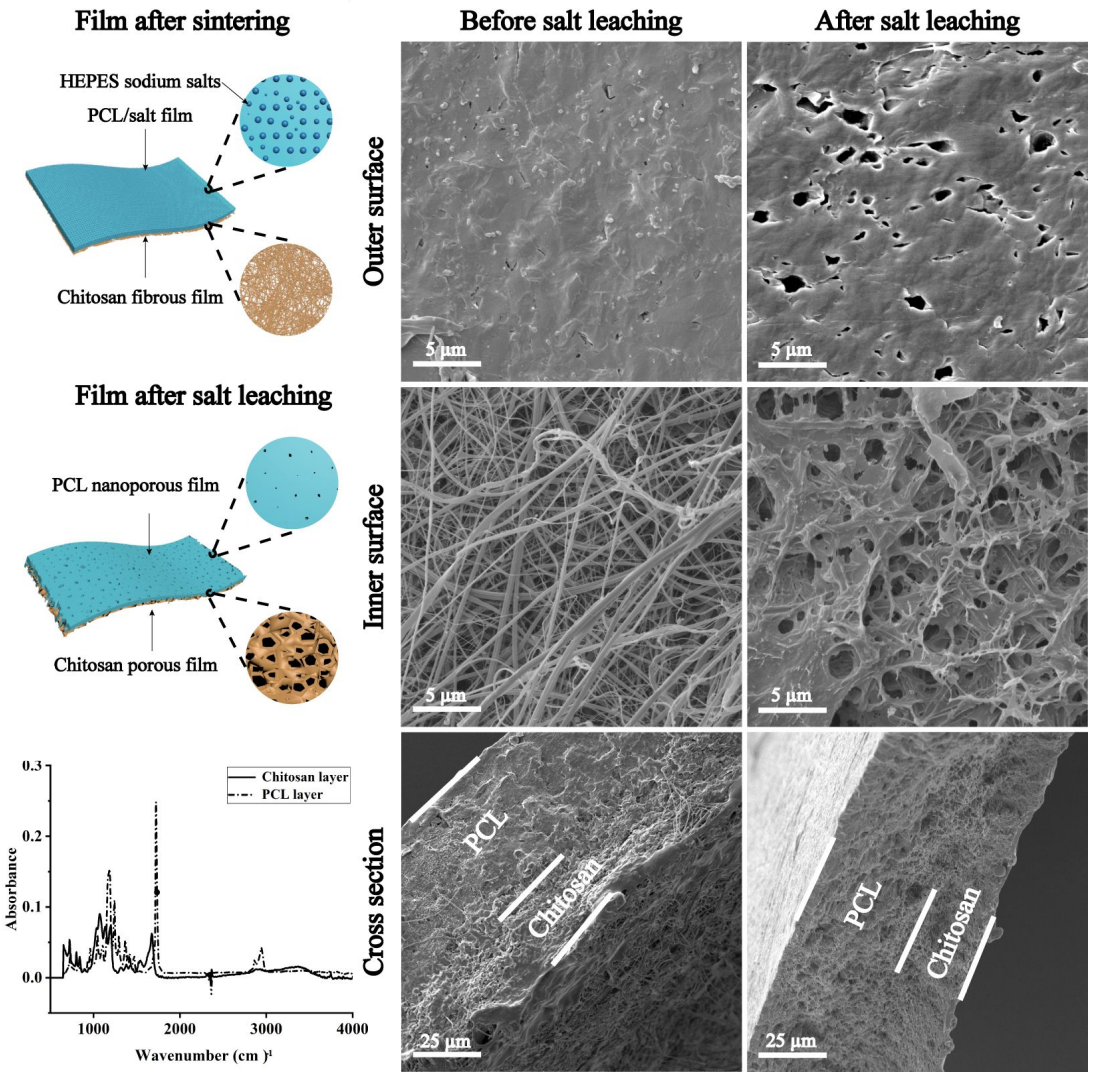
Microcapsule Characterization



Central hollow cylinder for efficient drug loading

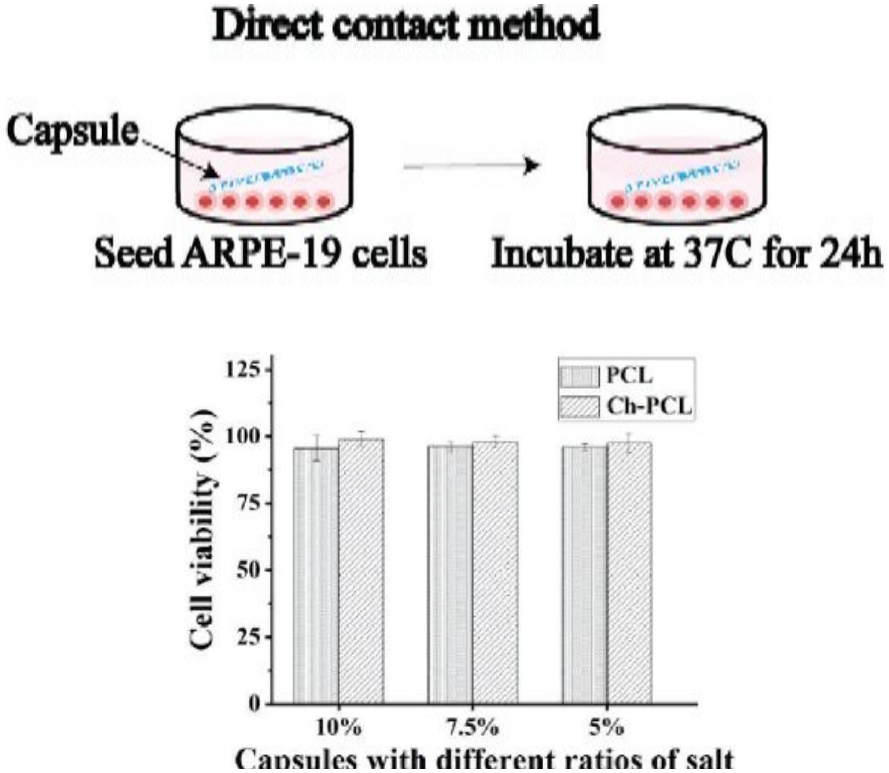
Increasing Salt Concentration Increased Porosity

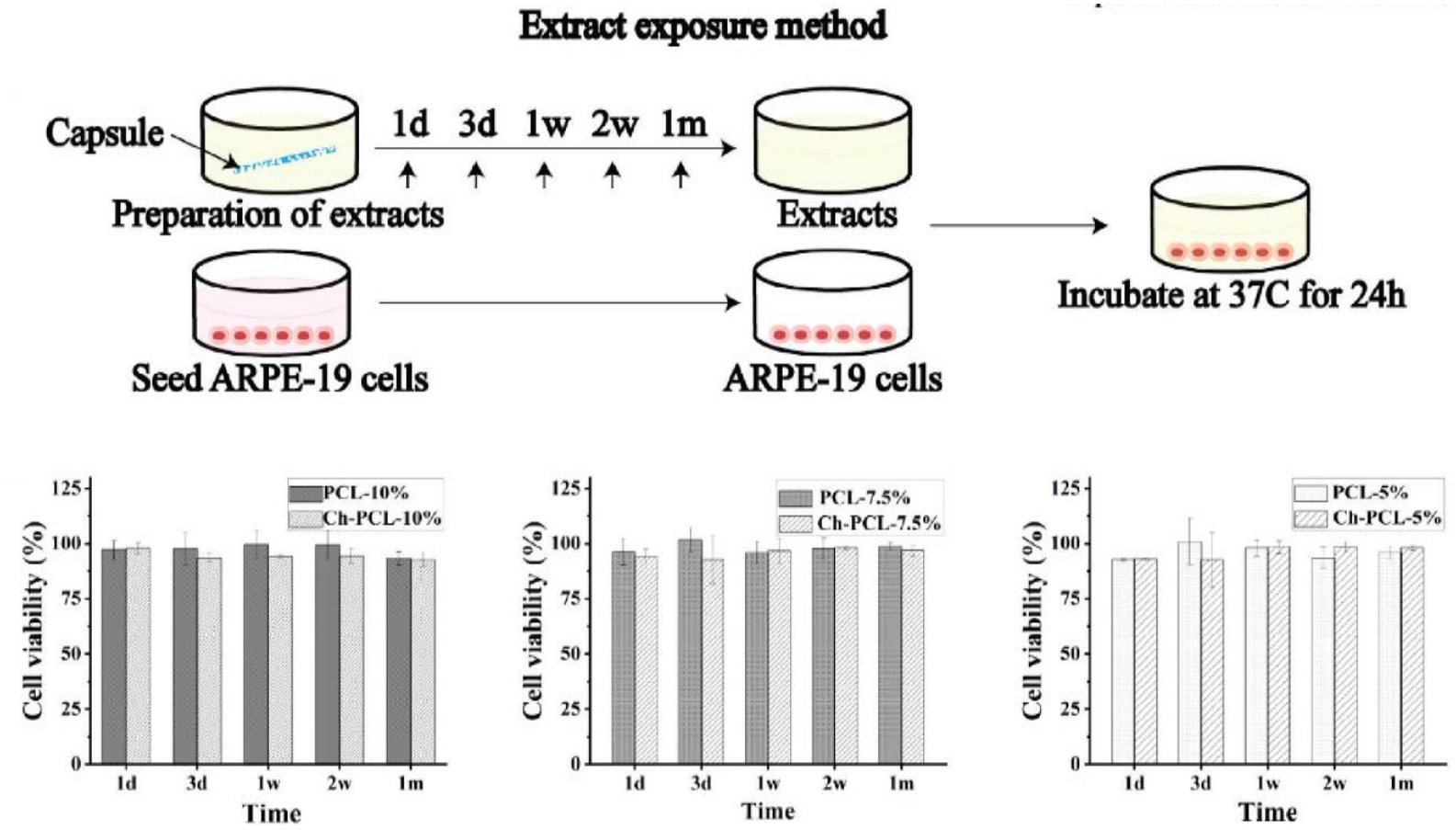
Sample name	Pore diameter (nm)	Porous channel
0.0 % HEPES salt	None	No
1.0 % HEPES salt	237.26 ± 96.93	No
5.0 % HEPES salt	371.65 ± 156.77	Yes
7.5 % HEPES salt	582.21 ± 302.17	Yes
10 % HEPES salt	608.55 ± 273.90	Yes



Microcapsule Biocompatibility

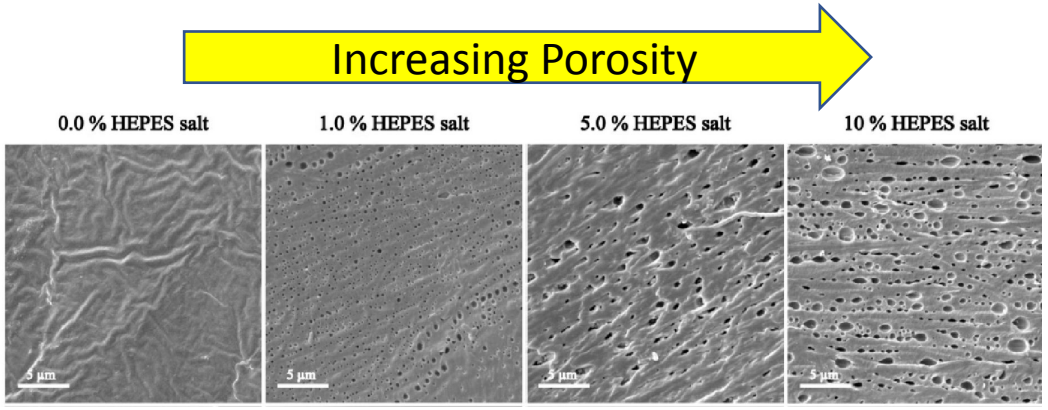
- **Biocompatibility**
  - Negligible *in vitro* cytotoxicity with human retinal cells
  - Promising biocompatibility in rabbits 3 months after injection (unpublished results)

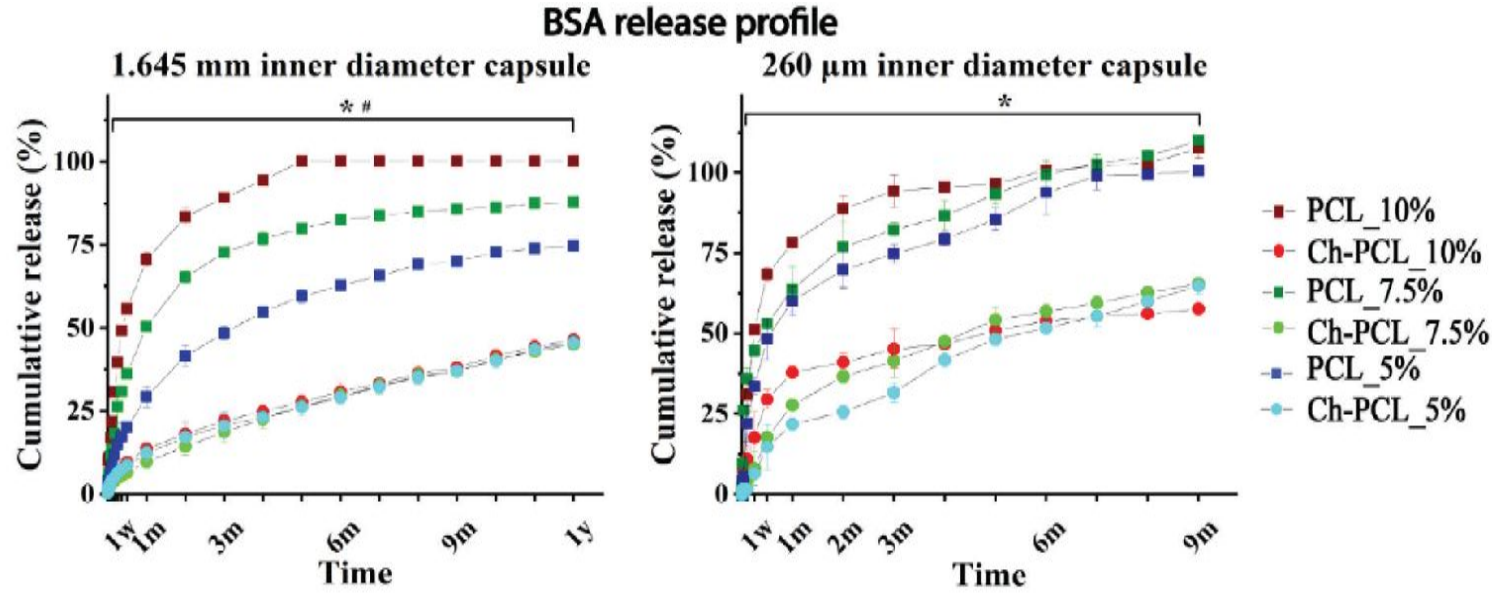


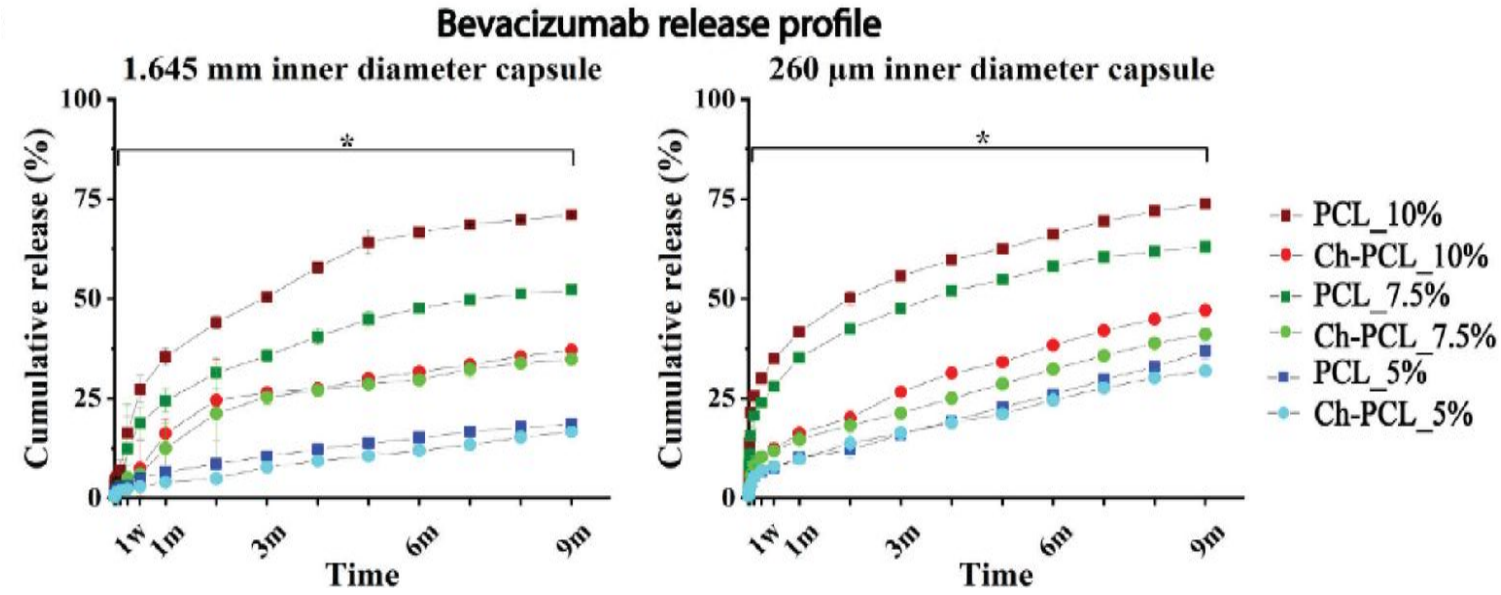


Microcapsule Drug Release

- **Drug loading**
  - 700 µg BSA (model therapeutic)
  - 500 µg Avastin (anti-VEGF)
- **Drug release rate**
  - Bi-layered capsule minimizes burst release
  - Porosity impacts release rate
  - Release stabilized at 1 µg/day
- **Release 6-12 months**

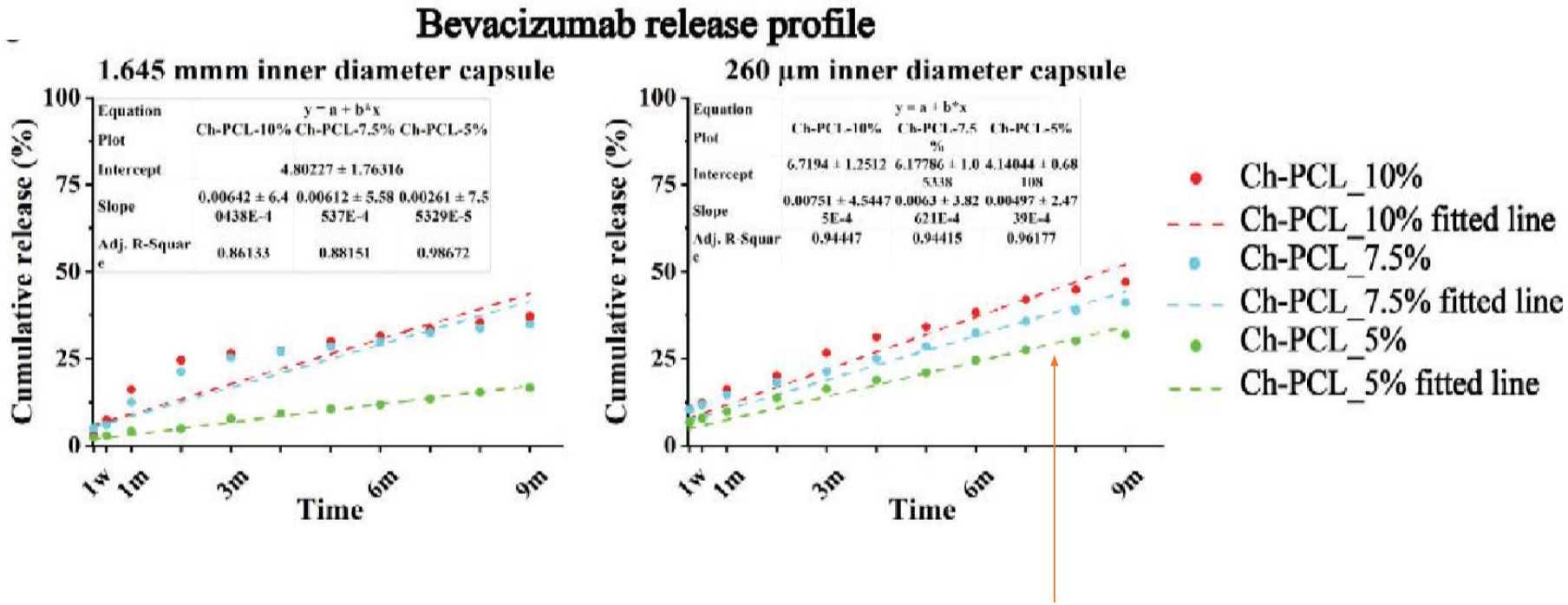






Microcapsule Drug Release

Approaches zero order release kinetics >1 month

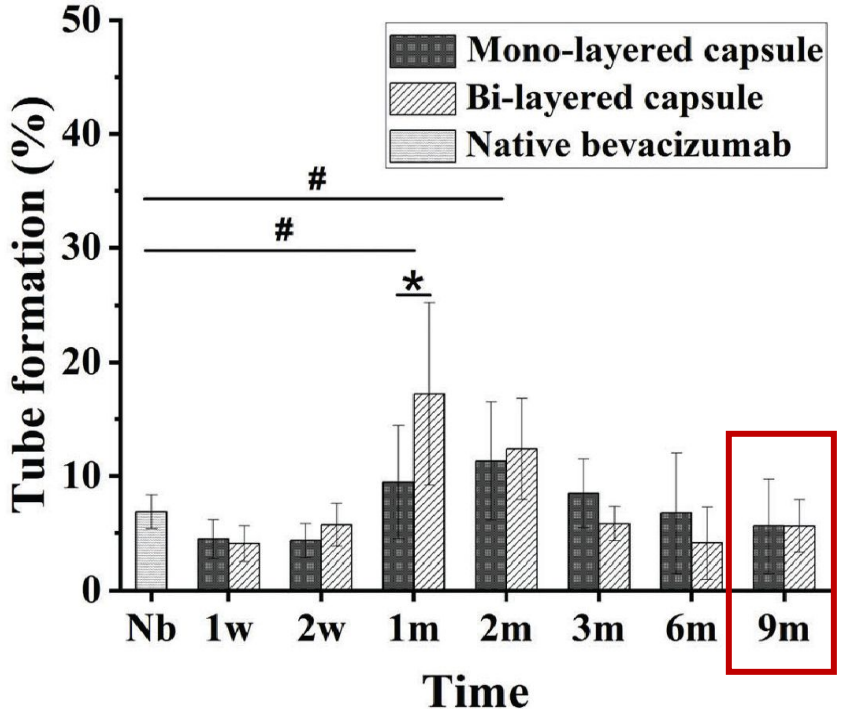


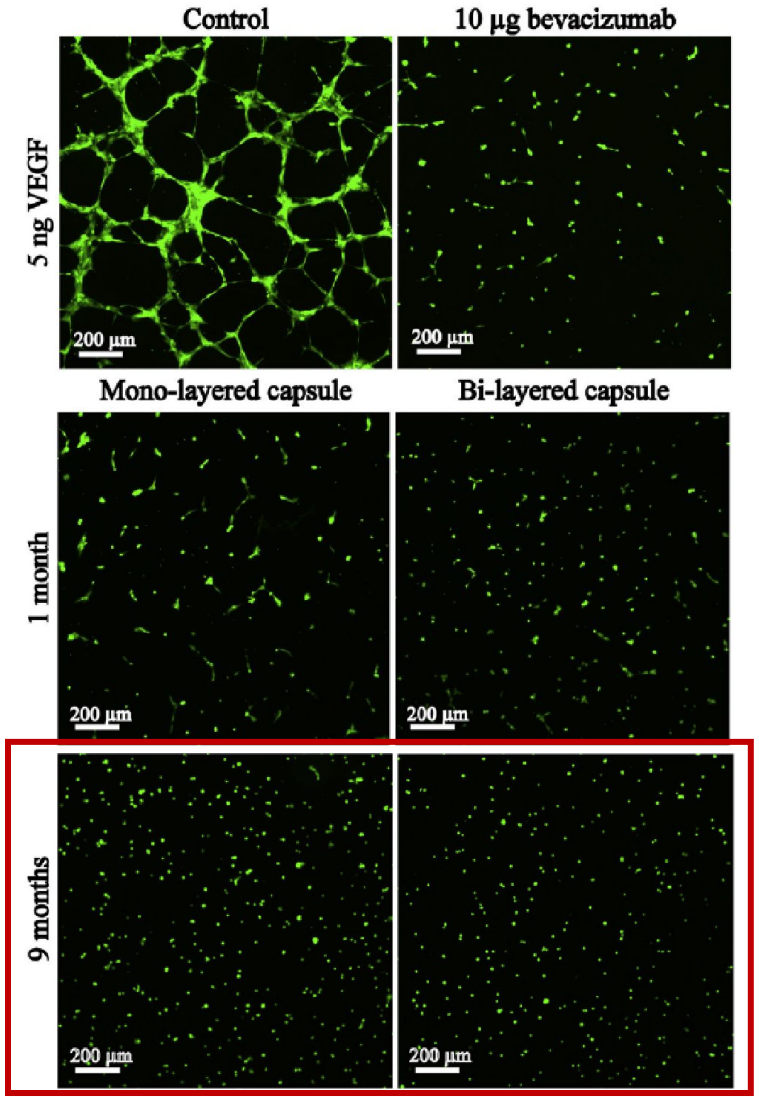
Long term constant release rates for smaller capsules and smaller pores

Therapeutic Preservation

Bioactivity

- Anti-angiogenic activity maintained at high level over nine months using HUVEC tube formation assay



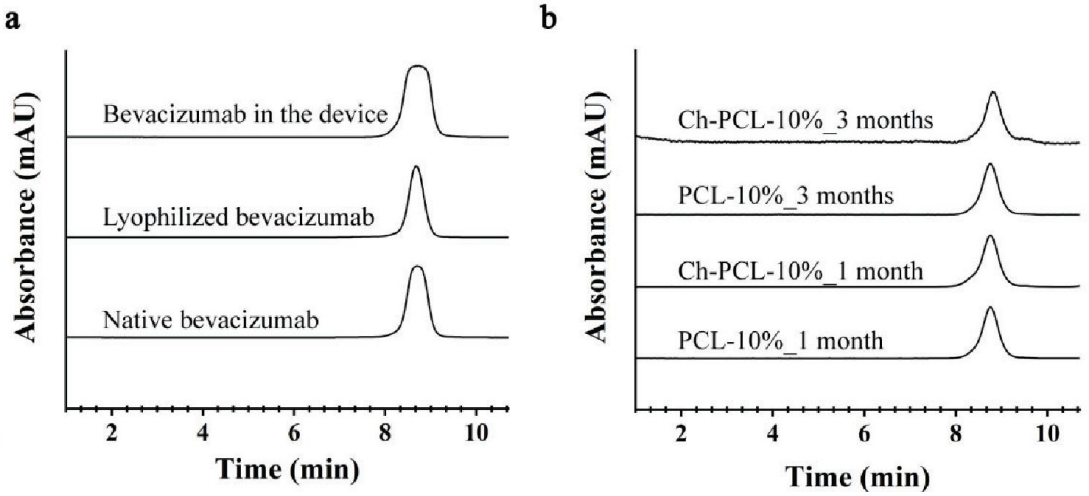


Therapeutic Analysis

SEC-HPLC Analysis

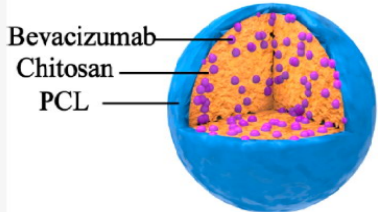
- No significant Avastin aggregation

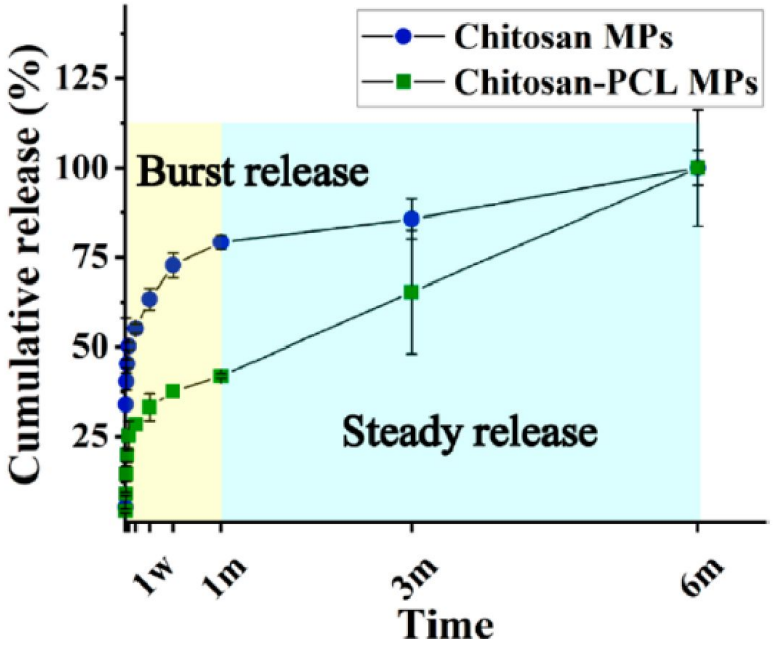
Sample name	Light Chain	Heavy Chain	Heavy +Light	Avastin -Heavy	Avastin - Light	Avastin	Aggregate	MW (kDa)
Native bevacizumab	0%	0%	0%	0%	0%	84%	16%	161
Lyophilized bevacizumab	0%	0%	0%	0%	0%	81%	19%	162
Bevacizumab in the device	0%	0%	0%	0%	0%	81%	19%	165
PCL_1 month	0%	0%	4%	0%	0%	84%	11%	155
PCL_3 month	0%	0%	5%	0%	0%	79%	16%	157
Ch-PCL_1 month	0%	3%	2%	3%	0%	82%	11%	154
Ch-PCL_3 month	0%	0%	6%	0%	0%	83%	11%	154



Microparticle Delivery System

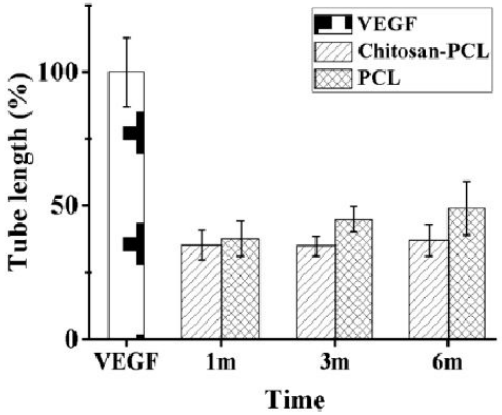
- Injectable biodegradable microparticles
  - Bi-layered chitosan-PCL structure
  - Particles injectable through 31-gauge needle

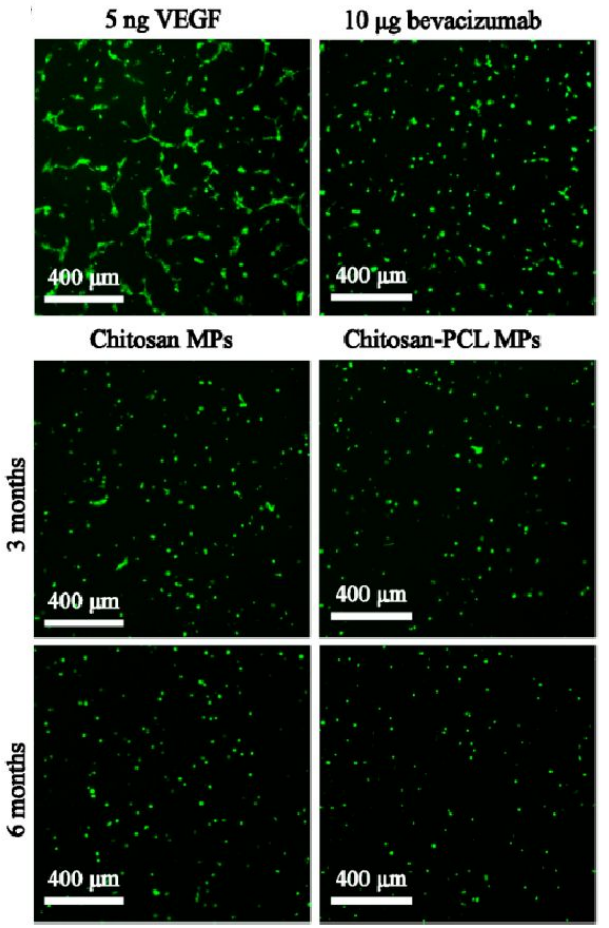




Degradation and release of anti-VEGF over 6 months

Retained anti-VEGF bioactivity



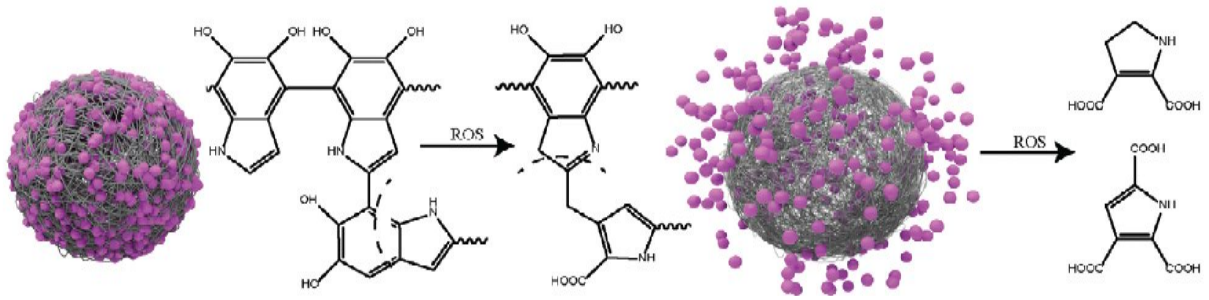


SEM images of microparticles
a) 500X, b) 5000X,
and bi-layered microparticles
e) 500X, f) 5000X

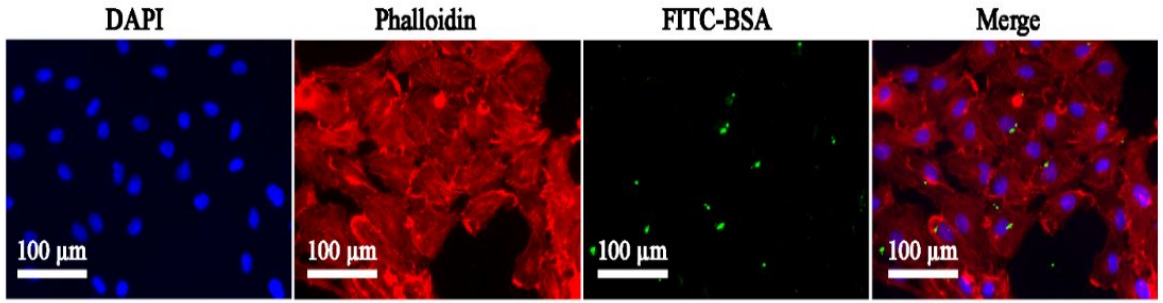
Jiang et al. Mol. Pharm. 2020

Nanoparticle Delivery System

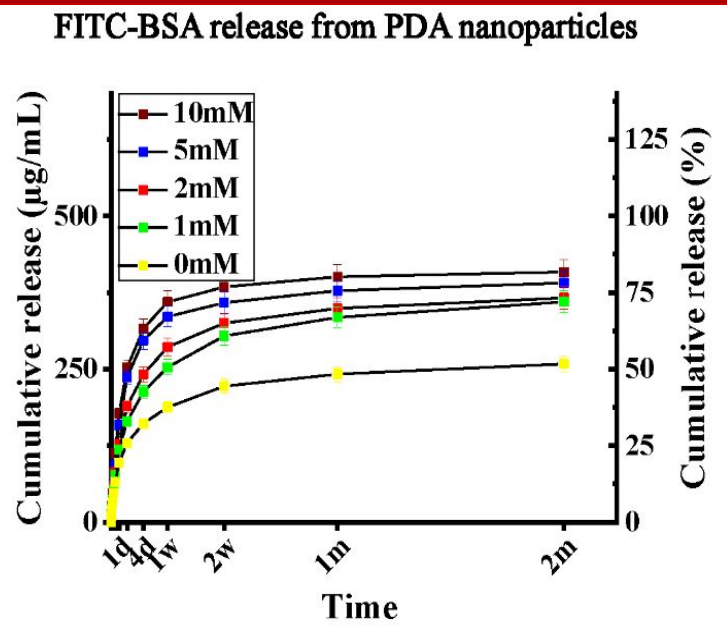
- Polydopamine (PDA) nanoparticles
  - PDA scavenges reactive oxygen species (ROS)
  - Therapeutic release rate increased with ROS

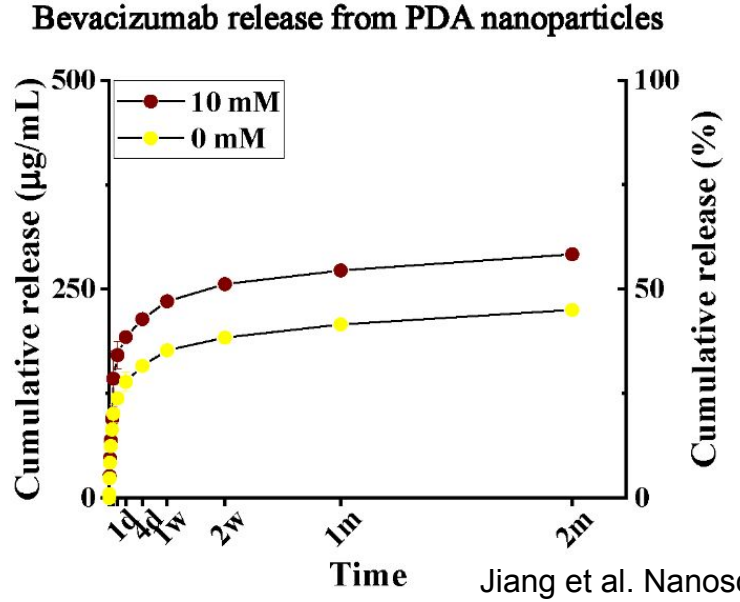


Average diameter of loaded PDA nanoparticles **152.99 ± 14.09 nm**



PDA nanoparticles entered ARPE-19 cells

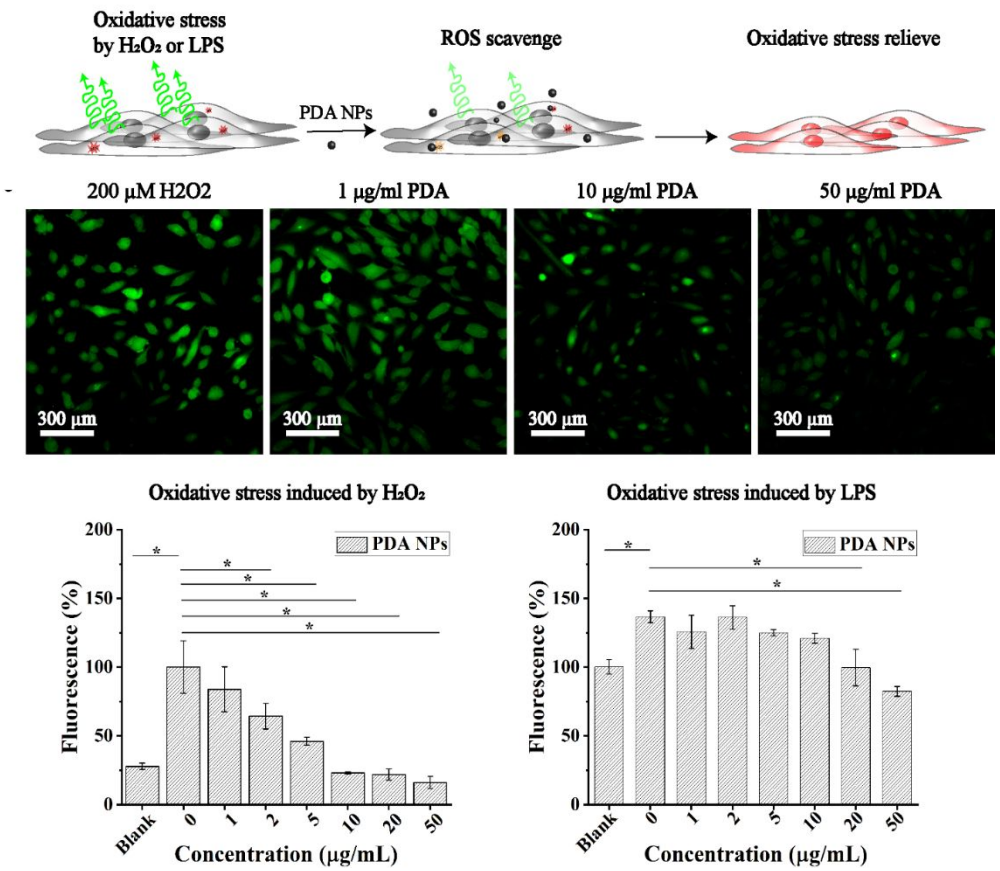




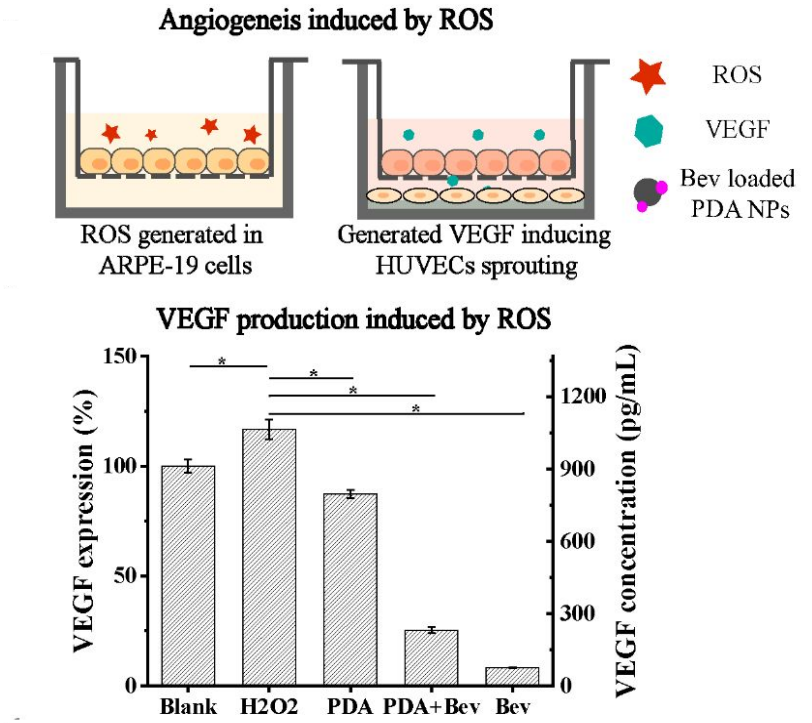
Jiang et al. Nanoscale. 2020

Nanoparticle ROS Scavenging

- DCFH-DA fluorescence used as ROS level indicator
- PDA nanoparticles reduced oxidative stress



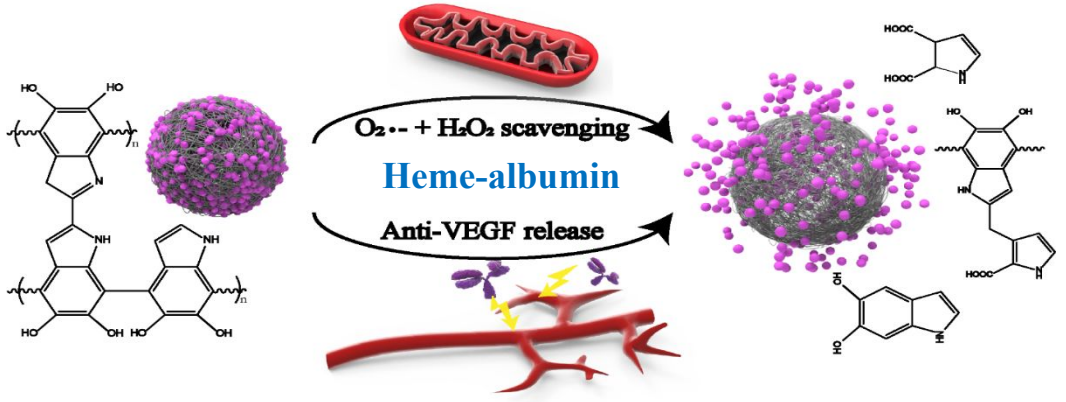
- Bevacizumab loaded PDA nanoparticles could also synergistically prevent angiogenesis *in vitro* by downregulating a **VEGF signaling pathway** and ***VEGF-independent pathway***



Summary & Future Directions

- Summary
  - Developed injectable, biodegradable capsule for extended release of proteins/antibodies >6 months
  - Delivery systems preserved therapeutic bioactivity *in vitro*
- Ongoing Ocular Delivery Projects
  - Cornea – delivery of new therapeutics to prevent scarring
  - Lens/Vitreous – antioxidant delivery for cataract prevention
  - Optic Nerve – delivery of new therapeutics for traumatic optic neuropathy
  - Retina – new therapeutic approaches for dry AMD and wet AMD

Poster – Megan Allyn
Controlled Release of Novel Protein Therapeutics for Treatment of Age-Related Macular Degeneration



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Thank You

Pengfei Jiang, PhD

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John Lannutti, PhD
1959-2022

Matthew Ohr, MD

Andre Palmer, PhD

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OHIO LIONS EYE RESEARCH FOUNDATION
RESEARCH TODAY... VISION TOMORROW

Focus Group OCULAR DELIVERY

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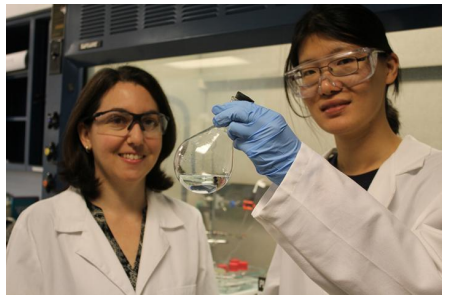

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DoD Vision Research Program

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OLERF Young Investigator Award

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Questions

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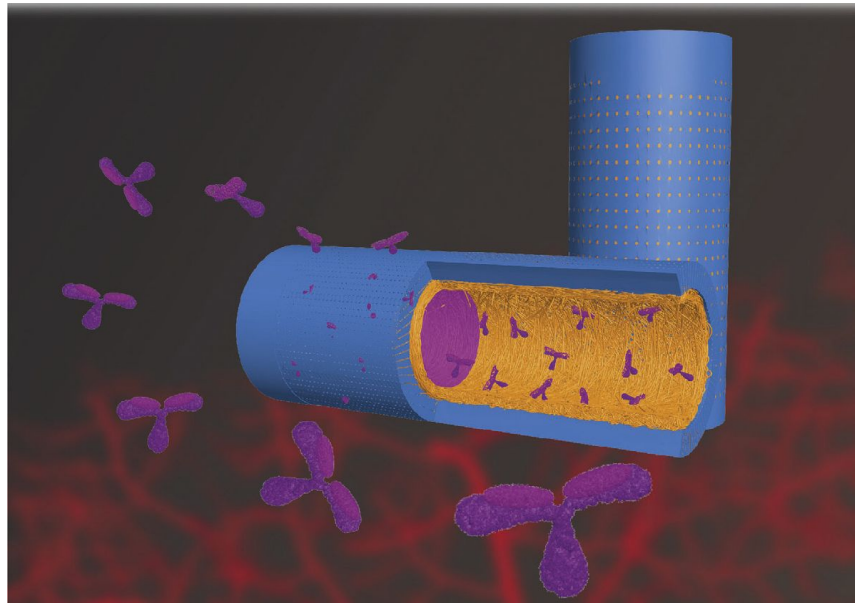

Jiang et al.
Journal of Controlled Release
320 (2020) 442-456

Additional Data

- ELISA Avastin Release