3D bioprinting personalized neural tissues for drug screening

Michael Smith Foundation for Health Research/Pacific Parkinson's Research Institute Innovation to Commercialization Award

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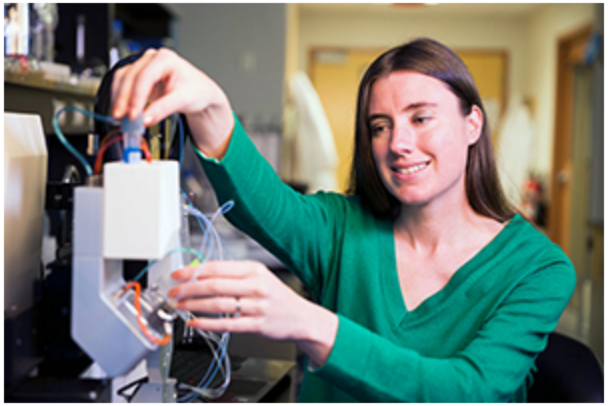
Pacific Parkinson's RESEARCH INSTITUTE

Aspect™ biosystems



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Developing a treatment for Parkinson's Disease

- Parkinson's disease affects ~100,000 Canadians with associated healthcare costs estimated at $580 million
- It costs $2.6 billion and 12 years to take a pharmaceutical drug to market
- Over 90% neurological drugs entering clinical trials fail due to the limitations of screening methods

THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

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Current drug screening methods

- Animal models serve the current gold standard for evaluating the efficacy and toxicity of drugs
  - Costly and labor intensive
  - Lack predictive capacity
- Human tissue slices cultured *in vitro*
  - Better predictive ability
  - Limited supplies

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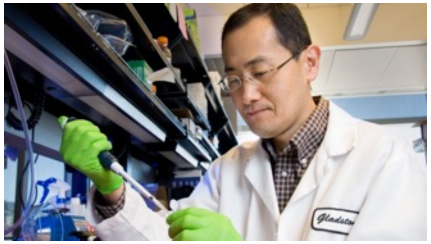
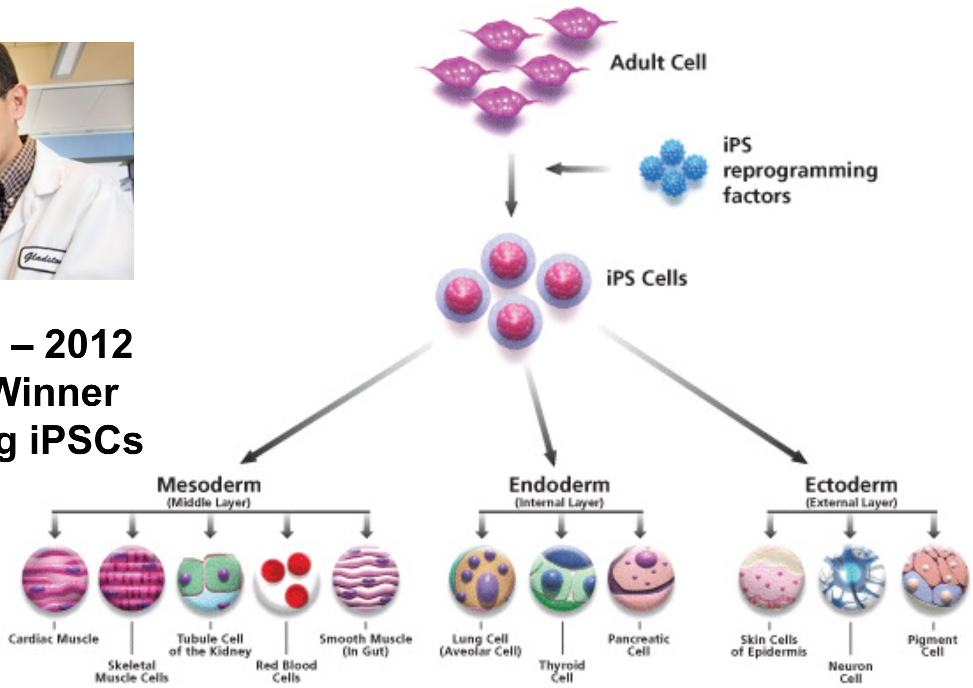
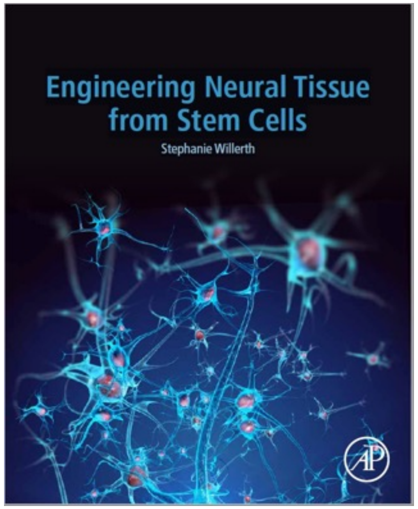
Solution: Engineer neural tissue from human induced pluripotent stem cells (hiPSCs)

Takahashi and Yamanaka discovered they could reprogram adult cells to behave like embryonic stem cells that could become any cell type in 2006



Dr. Yamanaka – 2012 Nobel Prize Winner for discovering iPSCs





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Cells found in the central nervous system to produced from hiPSCs

- **Neurons**
  - Excitable cells that transmit information using electrochemical signaling
- **Oligodendrocytes**
  - Insulate neurons by covering them with a myelin sheath, helping signals propagate
- **Astrocytes**
  - Provide nutrients to the cells of CNS and form the blood-brain barrier

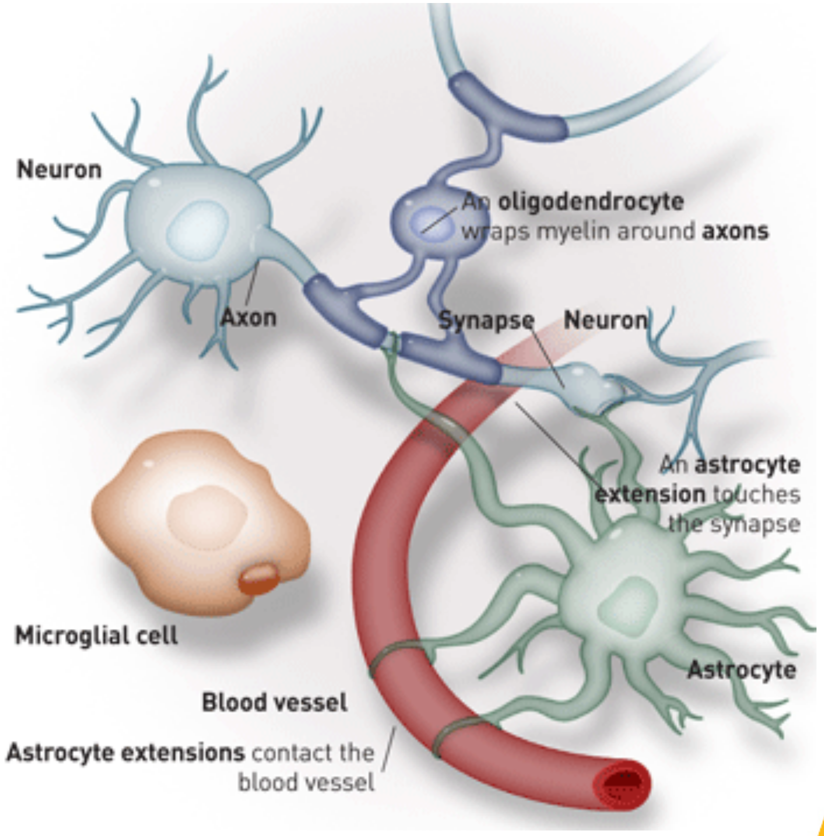

Illustration by Joe Morse – Stanford Medical School

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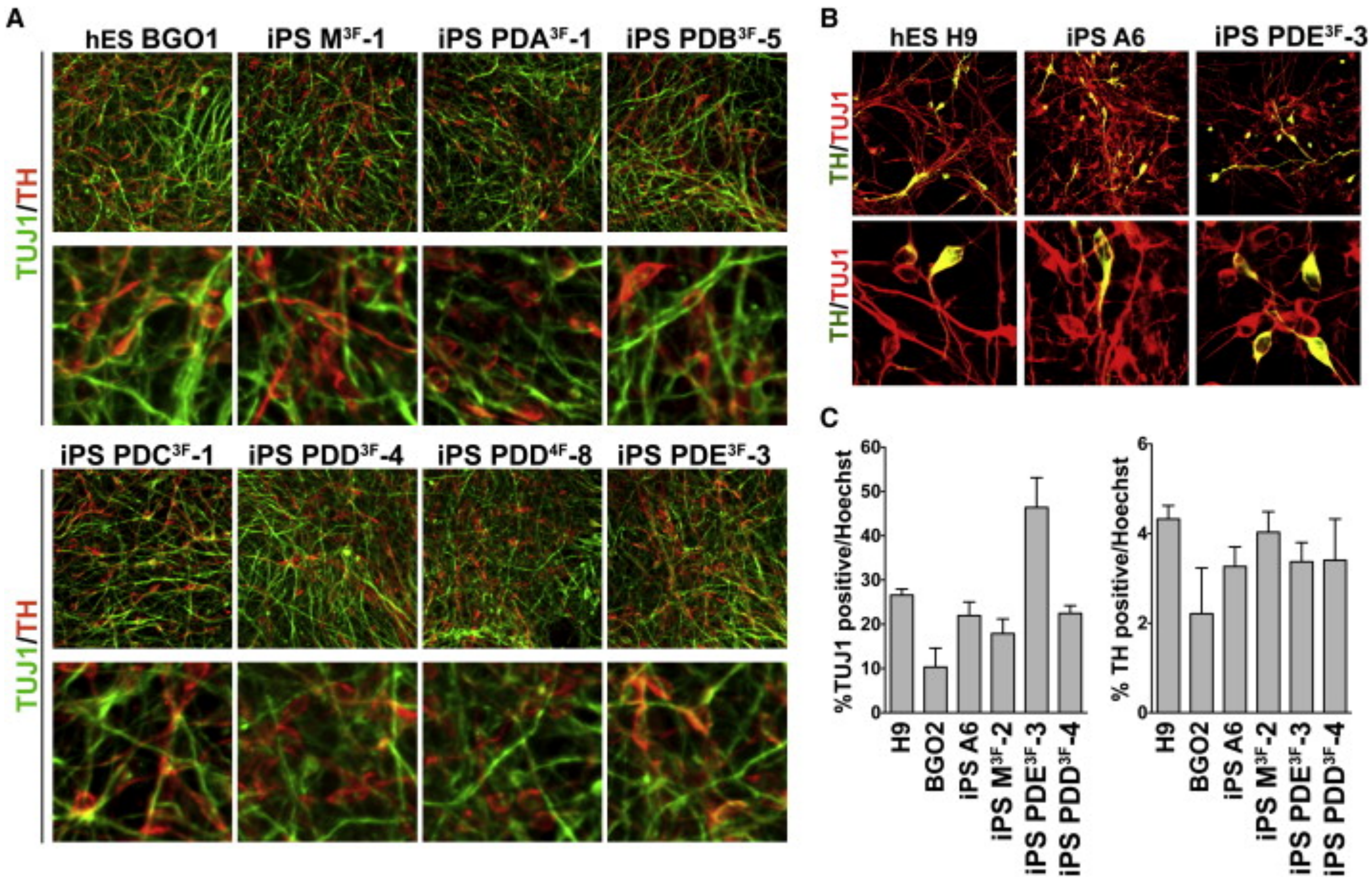
hiPSCs can differentiate into dopaminergic neurons



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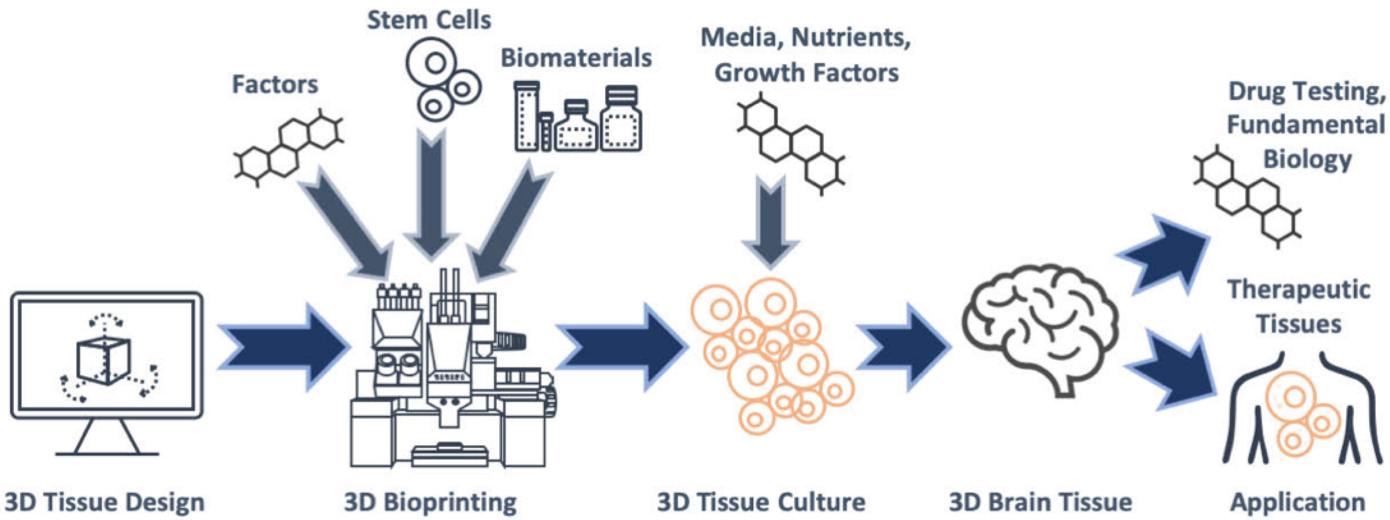
What is 3D bioprinting?

3D bioprinting produces cell patterns in defined configuration from the specifications present in a digital file where cell function and viability are preserved within the printed construct



Walus, K., Beyer, S., and Willerth, S.M. **3D bioprinting healthy and disease models of brain tissue using stem cells.** Accepted at Current Opinion in Biomedical Engineering.

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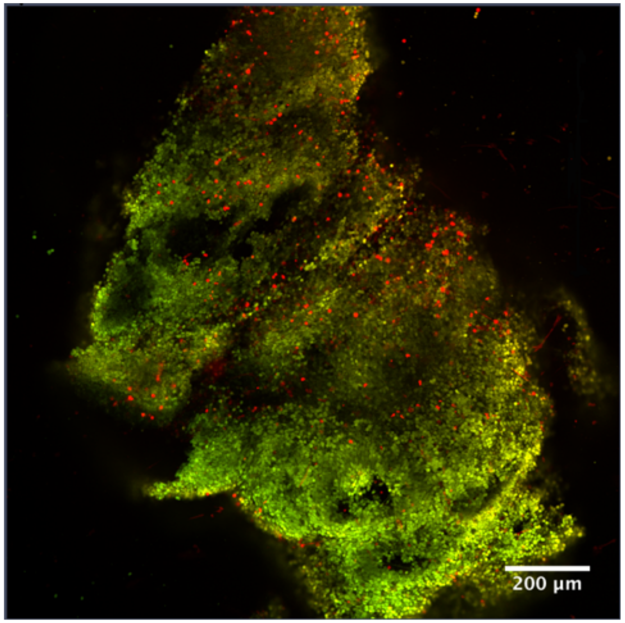
Issues with these current methods of neural tissue engineering using iPSCs

- Differentiation protocols take weeks and require significant amounts of labor
- Neural aggregate cultures extend out in all directions
  - Do not accurately replicate the structures found *in vivo*
- Organoids often experience variability from culture to culture



3D bioprinting can address these limitations!

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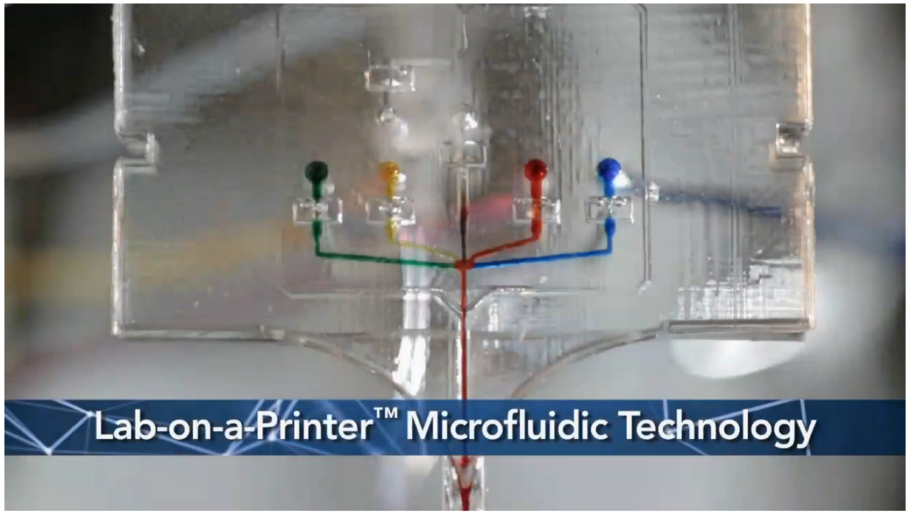
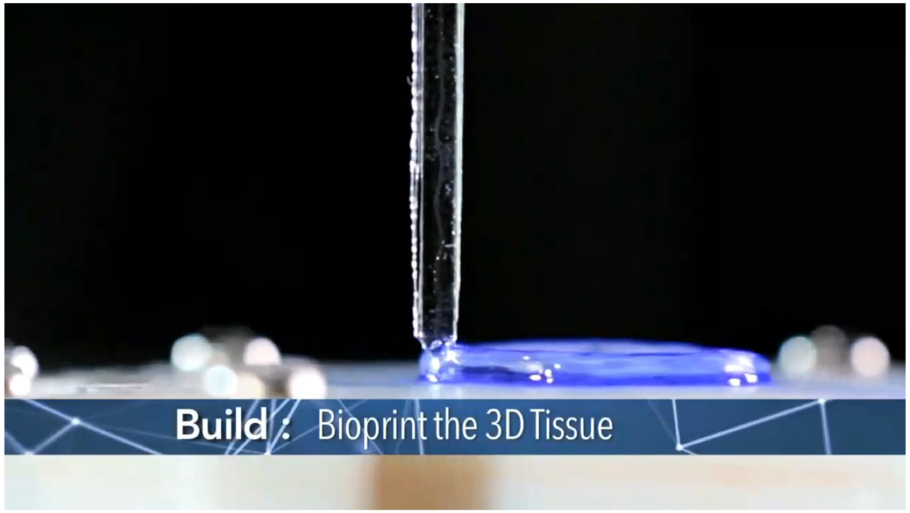
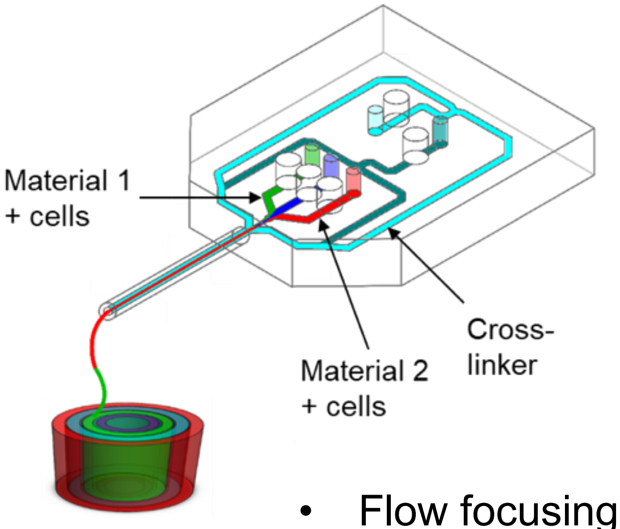
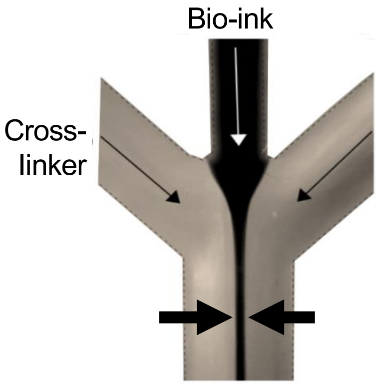
Our Method: Aspect's Lab-on-a-Printer™ Technology



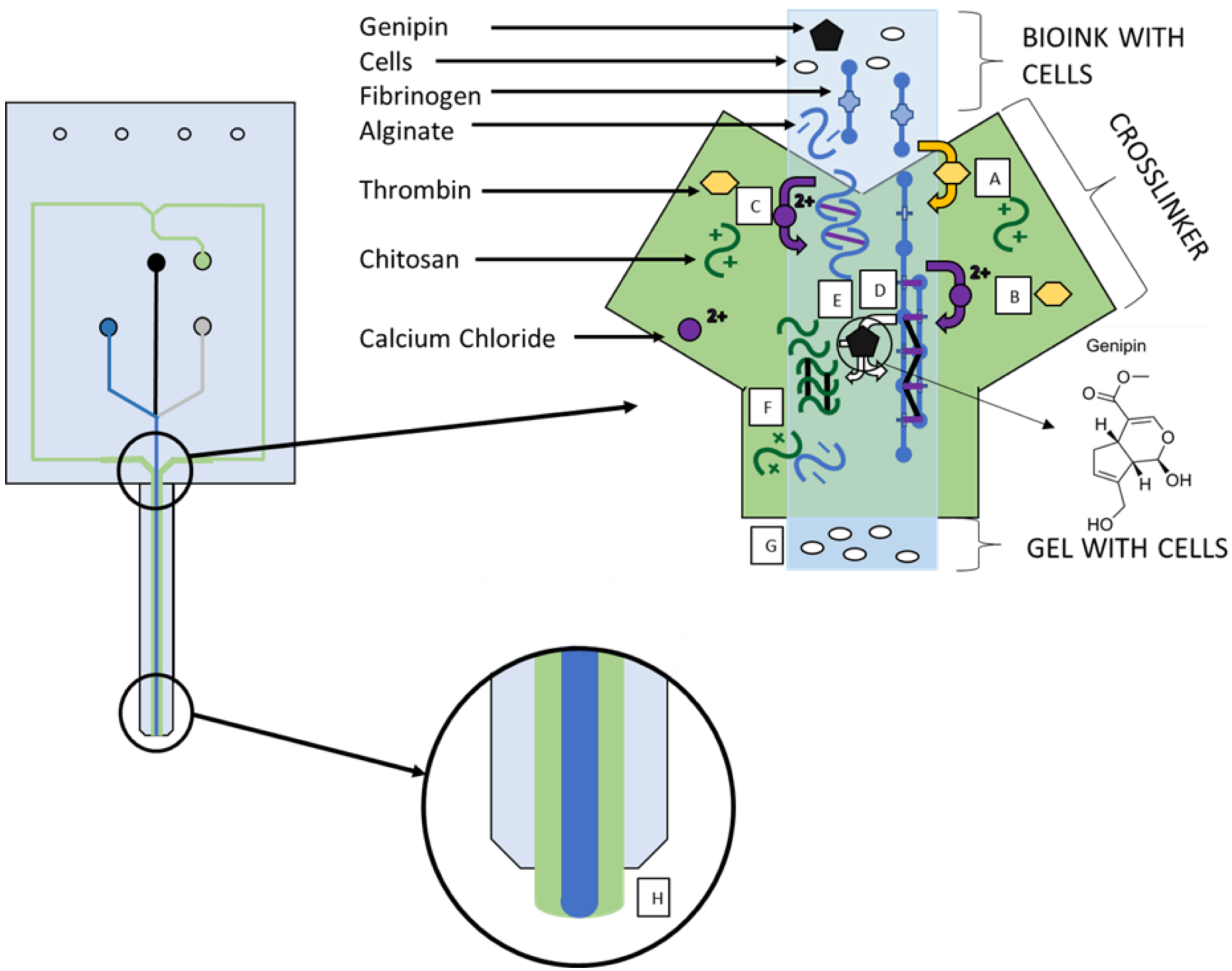






- Flow focusing minimizes shear
- Single printhead - multiple materials
- High speed, high fidelity printing
- Broad range of biomaterials with high ECM content

Our novel versatile fibrin based bioink



Abelseth, E., Abelseth, L., de la Vega, L., Beyer, S., Wadsworth, S., Willerth, S.M. **3D printing of neural tissues derived from human induced pluripotent stem cells using a fibrin-based bioink.** ACS Biomaterials Science and Engineering. 2019, (5) 234-243.

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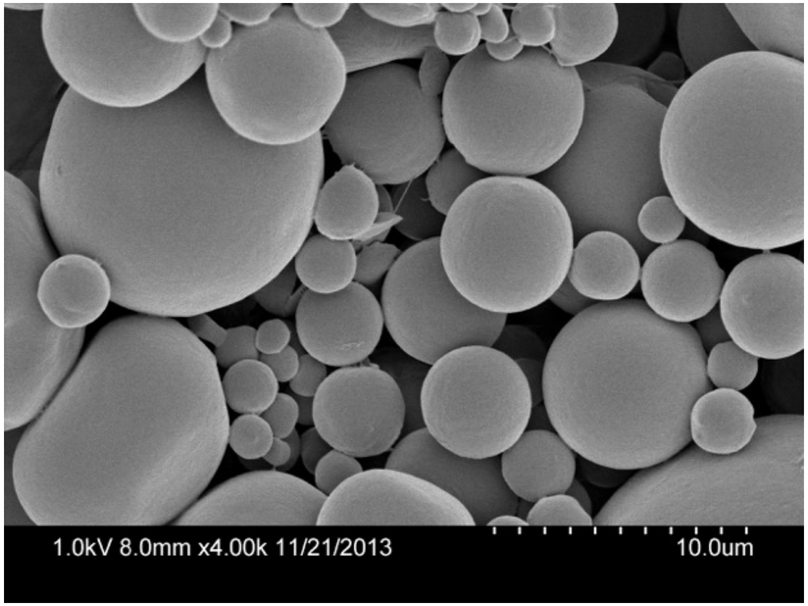
Microspheres as bioink additives

- Small spherical particles fabricated from biocompatible polymers
- Can provide tunable drug release of small molecules and growth factors
  - Can deliver retinoic acid, guggulsterone, and purmorphamine to promote neuronal differentiation of hiPSCs



Scanning electron microscopy image of drug releasing microspheres

Gomez, J.C., Edgar, J.M., Agbay, A.M., Bibault, E., Montgomery, A.L., Mohtaram, N.K., and Willerth, S.M. Cellular and Molecular Bioengineering. 2015 Sept: 8(3) 307-319.

Agbay, A., De la Vega, L., Nixon, G., and Willerth, S.M. Biomedical Materials. 2018, 13: 034104. Advanced Biosystems. 2018. 1800133. 1-11.
De la vega, L., Karminin, K., Willerth, S.M. Advanced Biosystems. 2018. 1800133. 1-11.

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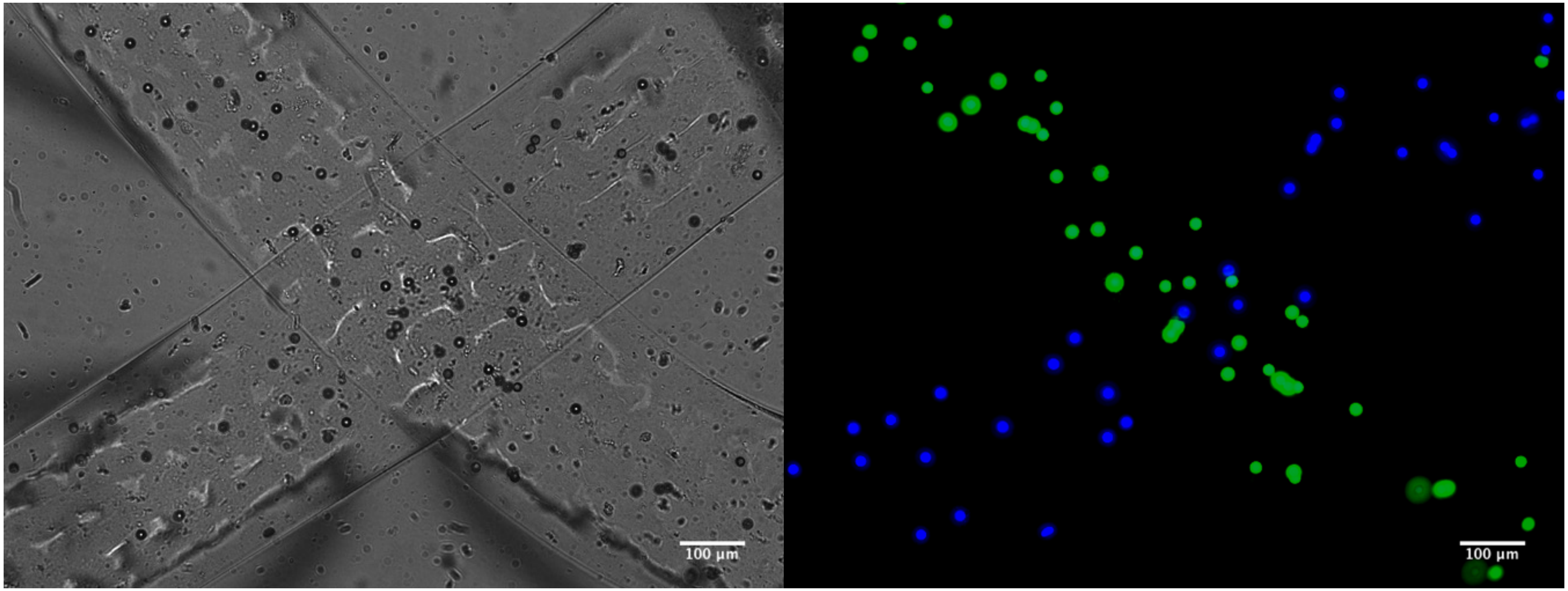
The RX1 technology can precisely place multiple types of microspheres inside our bioprinted tissues



We printed two different sets of fluorescently labeled microspheres in different layers of our tissue in a cross hatch pattern, demonstrating our ability to localize specific microspheres into structures.

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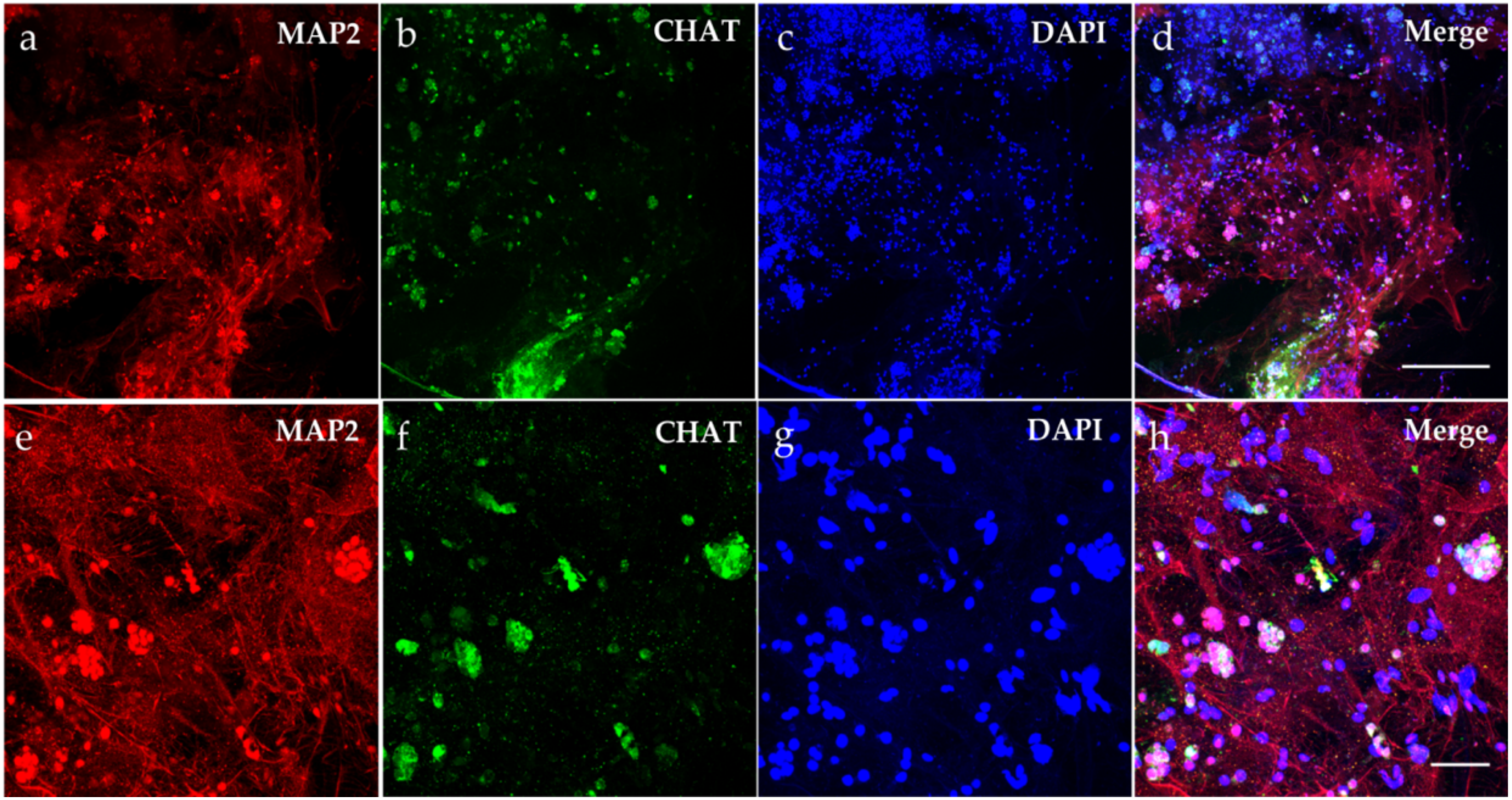
3D bioprinted neural tissues derived from stem cells using our microsphere laden bioinks



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Advantages of using our 3D bioprinted tissues for drug screening

- Can produce large numbers of tissues rapidly that contain multiple relevant cell types
- Replicate drug effects not observed in 2D cultures
- Replicate the functionality of neural tissues found *in vivo*
- Potential for personalized medicine

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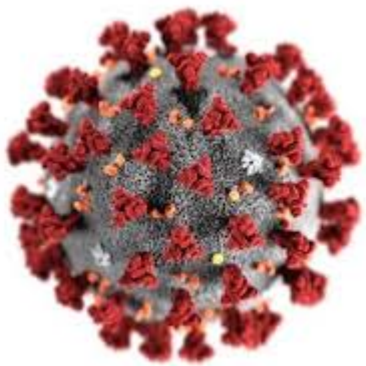
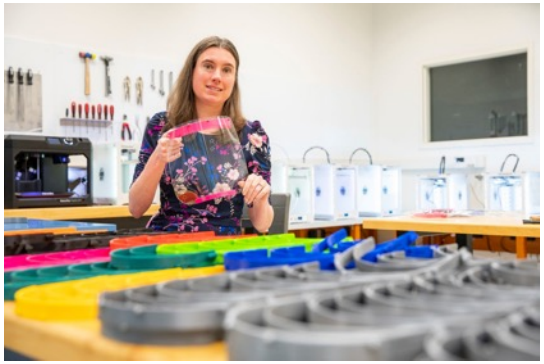
COVID19 and Neural Tissues

- Evidence of neurological effects caused by COVID19, including loss of smell, headaches, nausea, vomiting, and seizures
- The virus does infect neural tissue
- Evidence that it is transmitted through the synapses
- Submitted proposals to study its effects in our engineered tissues





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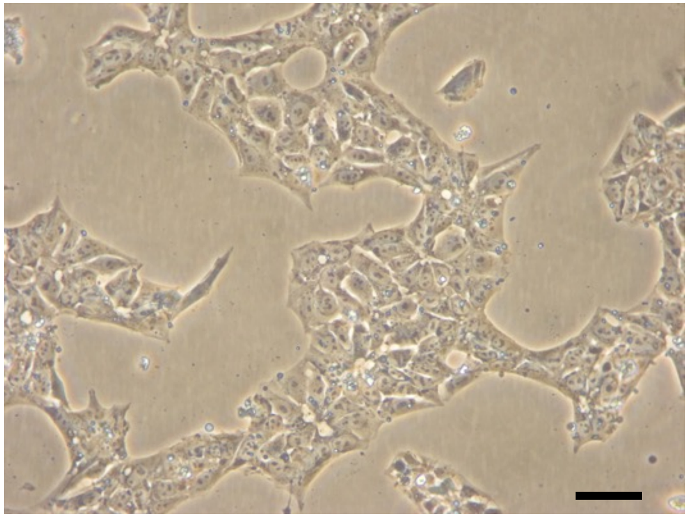
Future Work

- Bioprinting tissues using stem cell lines generated from patients suffering from Parkinson's Disease
- Commercializing our novel bioink through our start-up – Axolotl Biosciences



Axolotl Biosciences

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Follow us on twitter: @DrWillerth

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Keiran Letwin
Kali Schenk
Joshua Latimer
Alana Babcock
Dmitri Karaman

NSERC CRSNG
Mitacs
Stem Cell Network
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Alzheimer's Society United Against Dementia
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