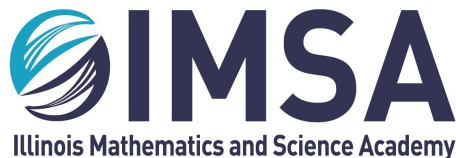


Diagnostic $A\beta$ O-targeted probes for Alzheimer's Disease

Nafay Abdul and Sophia Pribus

Advisers: Kirsten Viola, William Klein

*Collaborators: Vikas Nandwana, Rohan Chalasani, Adrian Bebenek, E. Alexandria Waters,
Nicholas Rozema, Craig Weiss*

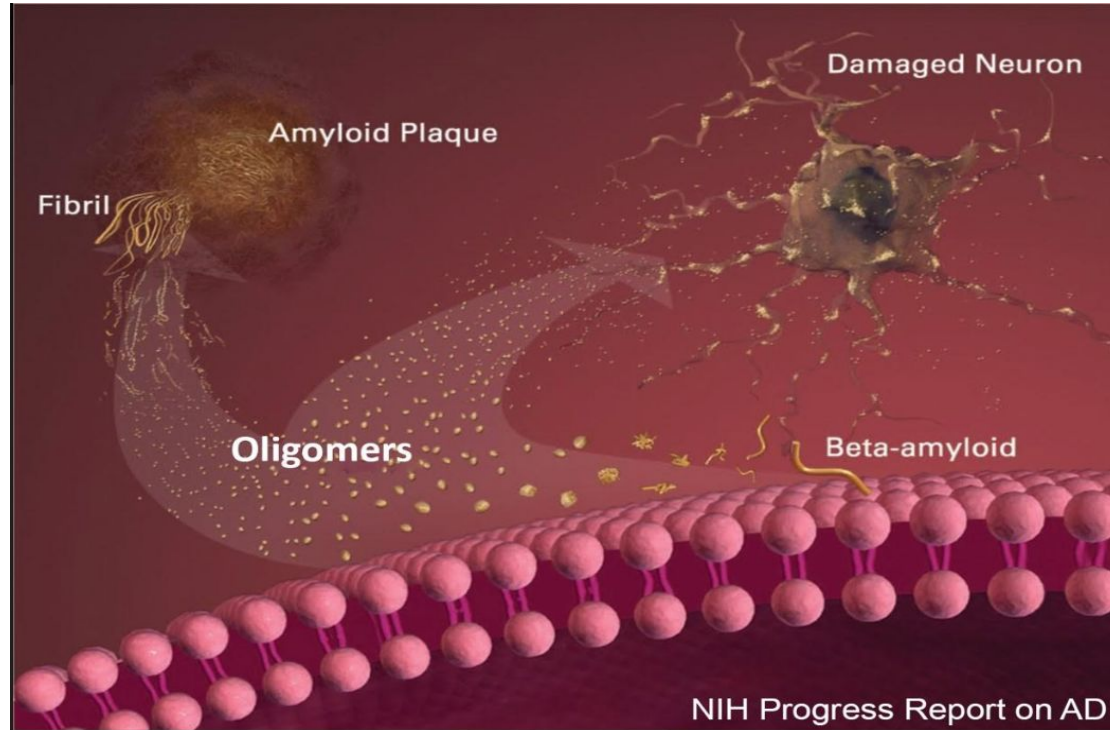


Northwestern
University

Alzheimer's Disease

- 1 person develops AD every 65 seconds
- treatment cost US \$277 billion in 2018
- plaques and tangles develop between nerves and inside cells
- symptoms: memory loss, confusion, difficulty speaking, swallowing and walking

A β oligomers vs Fibrillar Amyloids



A β Hypothesis

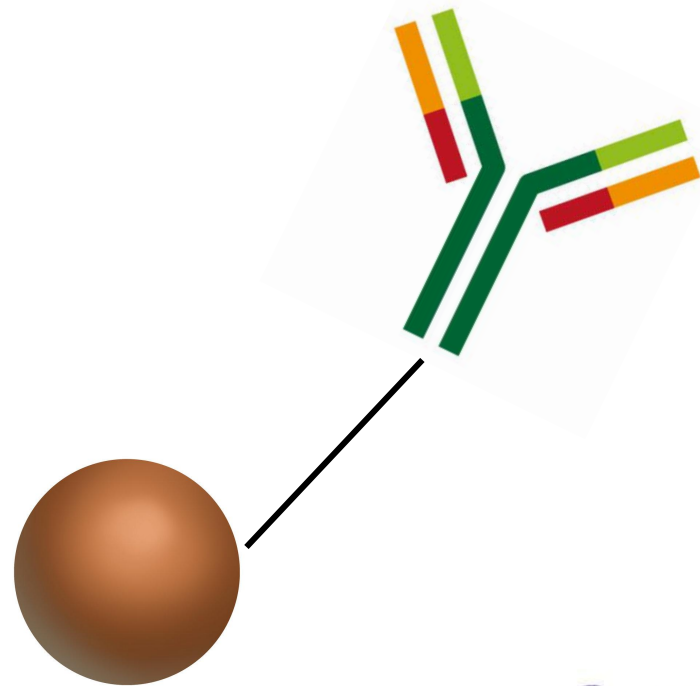
The accumulation and deposition of oligomeric or fibrillar amyloid β (A β) peptide is the primary cause of Alzheimer's disease (AD)

Current AD Diagnostics

- **MRI** → used to quantify brain volume/measure brain metabolism
- **Probes** → used to target certain structures for imaging
 - e.g. PET probes → quantify ThioS-positive amyloid plaques
 - No probe specifically for AβOs

A β O Probe

- Attach oligomer-specific antibodies onto magnetic nanostructures
- Binds to A β oligomers to give a magnetic resonance imaging signal

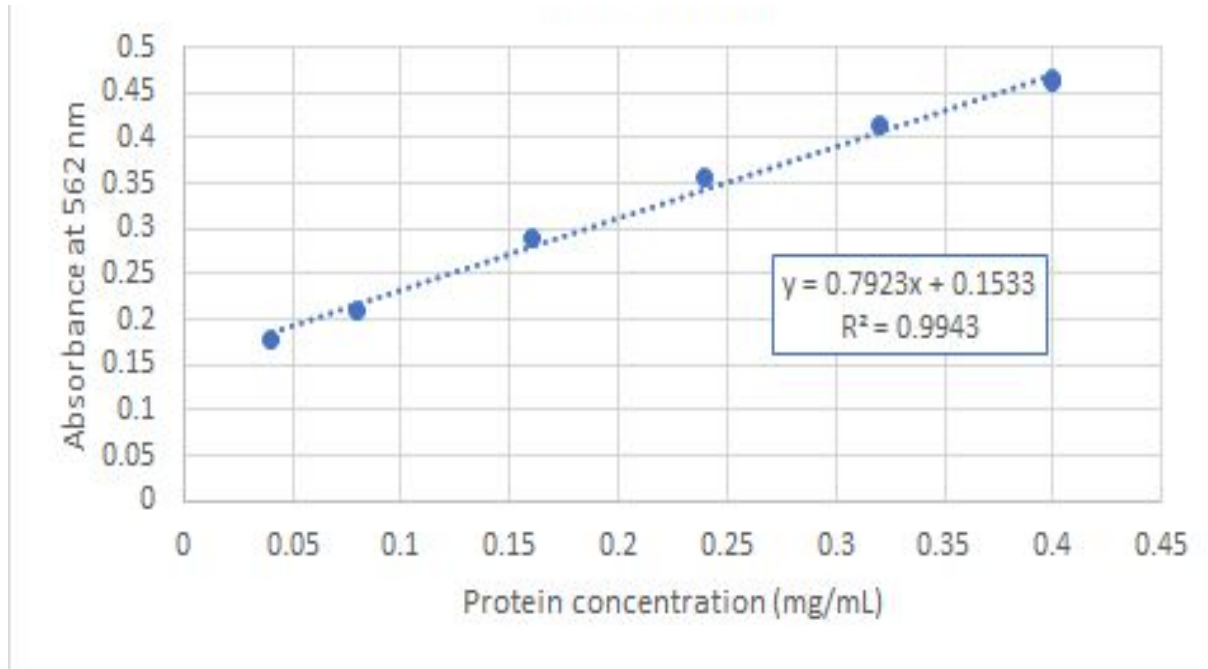


Methodology

- Protein assays
 - testing and improving conjugation efficiency of MNS to antibodies
 - optimal method - double conjugation method
- In vivo testing
 - mouse model
 - rabbit model
- Immunohistology
 - sliced brain cells
 - immunofluorescent

Probe Development Data

Absorbance of Standards



Original Probe

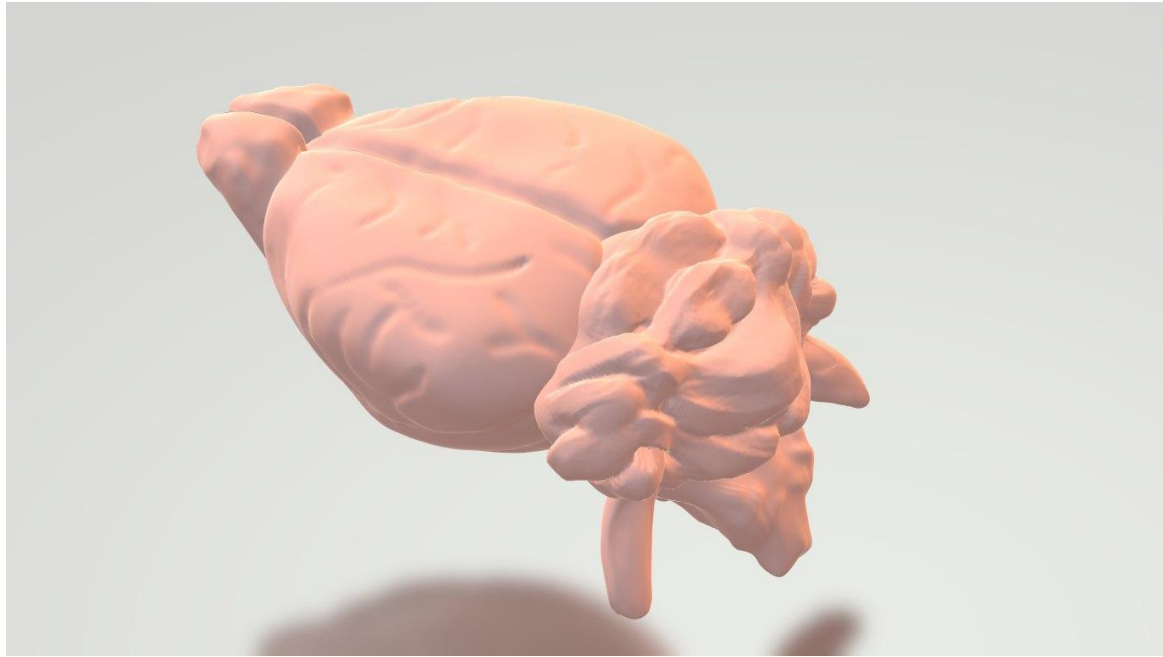
	Antibody 1	IgG antibody 1	Antibody 3	Antibody 4	IgG antibody 2	IgG antibody 3
Average Absorbance	.2545	.226	.219	.2435	.223	.222
Protein Concentration (mg/mL)	.179	.139	.129	.163	.135	.133
Percent Conjugation	35.74%	27.76%	25.80%	32.66%	26.92%	26.64%

Modified Probe

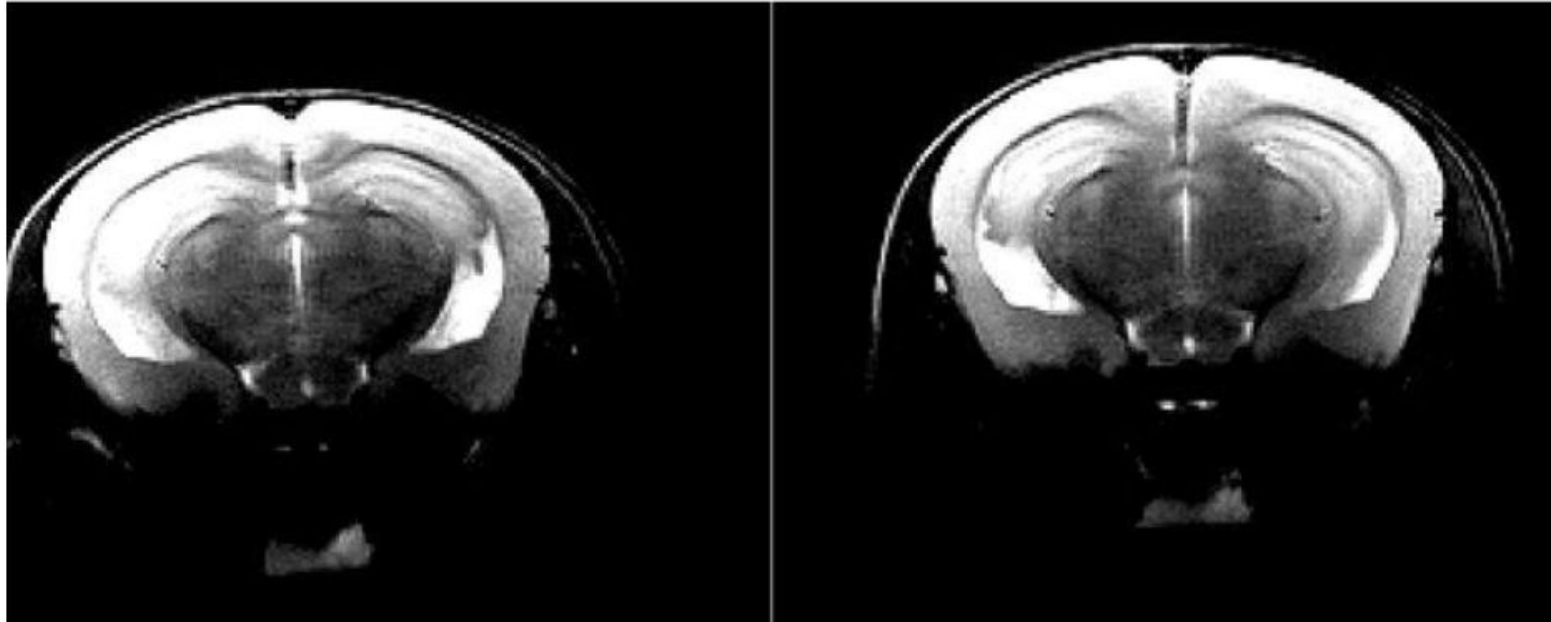
	Original ACU193 Sample	After 1 Conjugation Flow-Through	After 2 Conjugation Flow-Throughs
Average	0.109	0.1085	1.866
Protein Concentration (mg/mL)	-0.054	-0.054	2.134
Percent Conjugation	0%	0%	71.3%

Mice Data

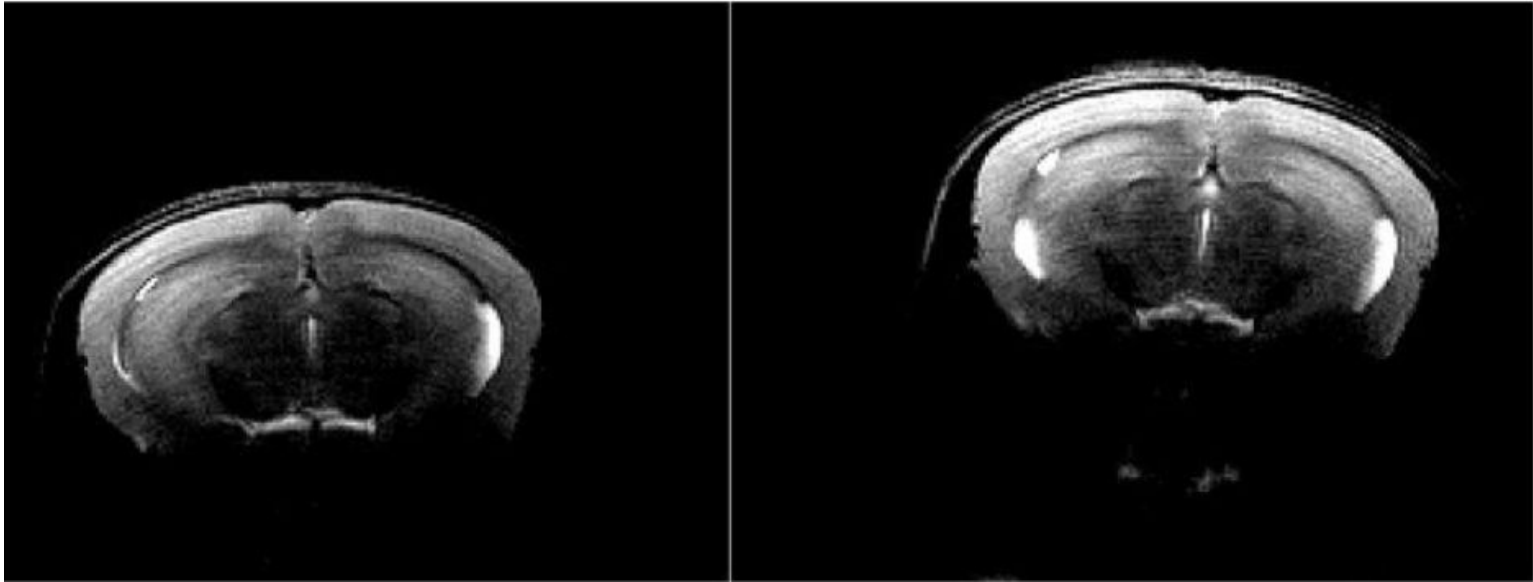
Mouse Brain Model



Wild Type Mouse with Probe

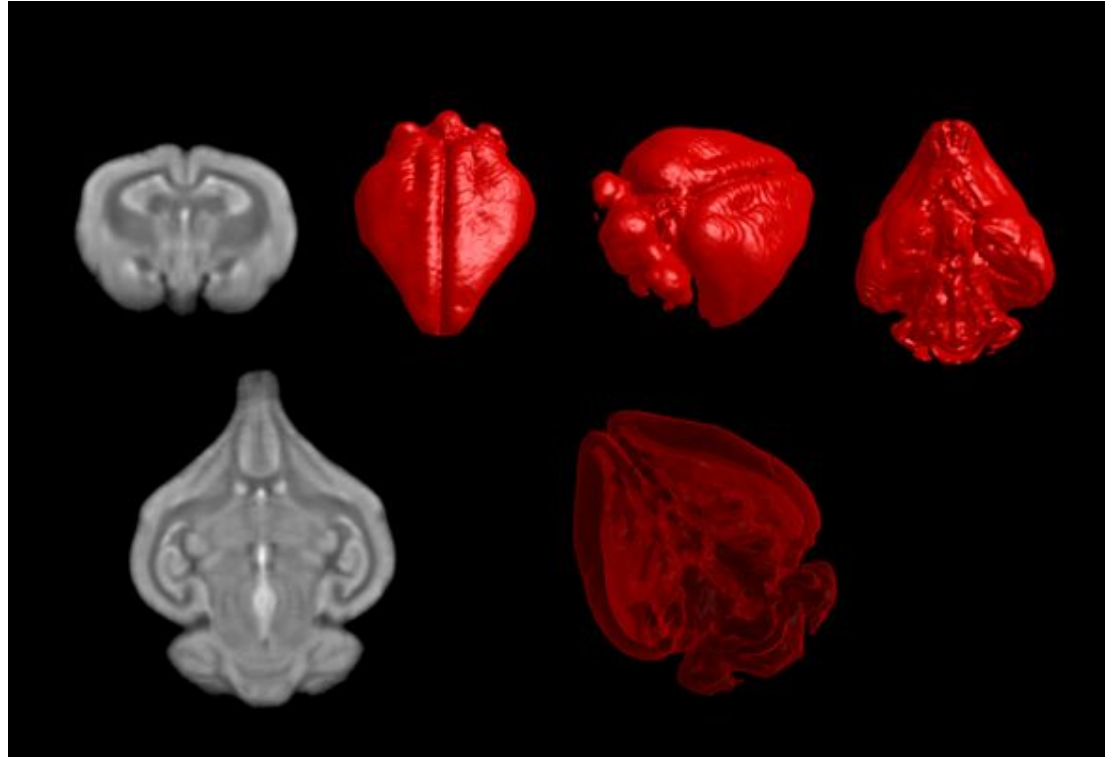


Transgenic (5XFAD) Mouse with Probe

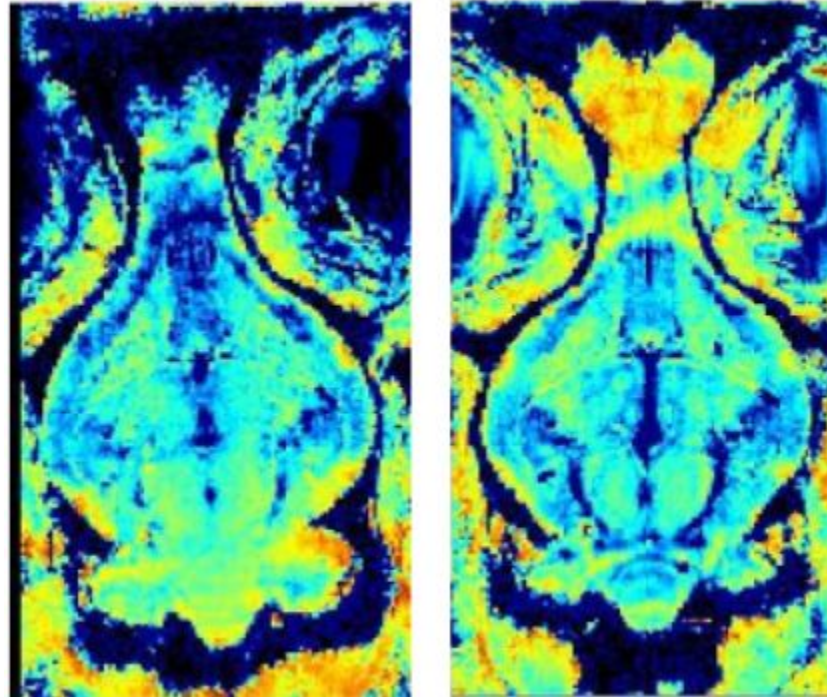


Rabbit Data

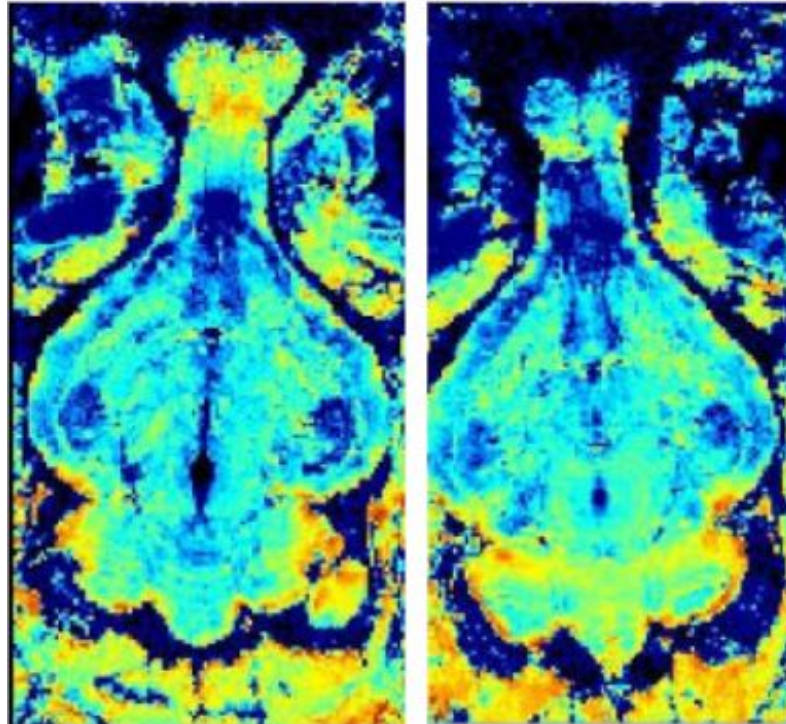
Rabbit Brain Model



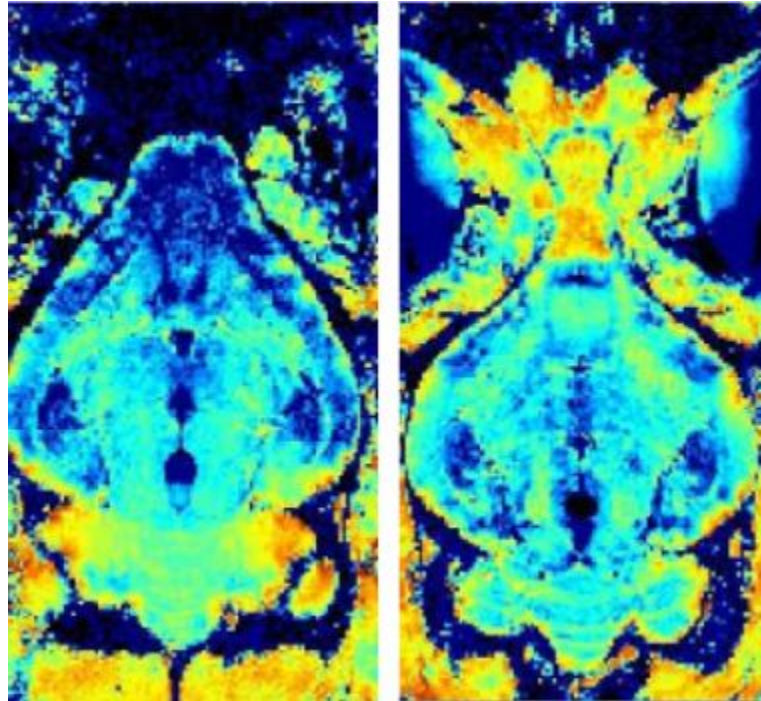
High Cholesterol Diet Rabbit with Probe



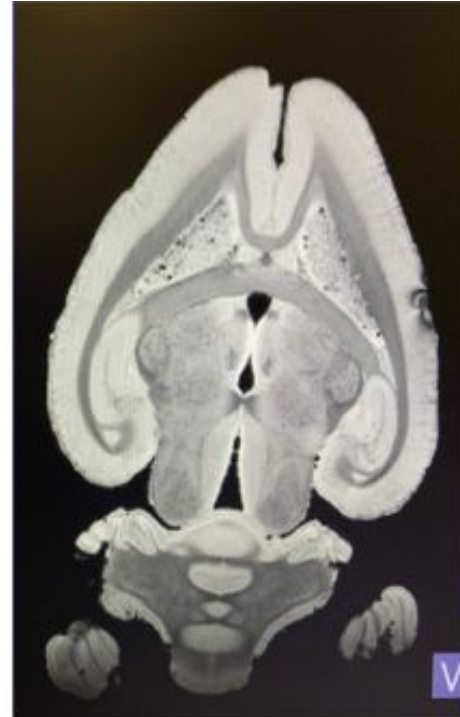
High Fructose Diet Rabbit with Probe



Control Diet Rabbit with Probe



Rabbit Ex Vivo Imaging



Conclusion and Future Research

- Double conjugation method of probe = higher percent conjugations
- Probe effective in mouse model
- Probe effective in preliminary rabbit model tests
- **Future Research:**
 - Achieve higher conjugation efficiency in probe
 - Continue testing probe in rabbit model
 - Eventually test probe in more complex animal
 - Create human-diagnostic methodology

Bibliography

- Kline E, Bicca M, Viola K, Klein W (2018) The Amyloid- β Oligomer Hypothesis: Beginning of the Third Decade. *Journal of Alzheimer's Disease* 64, 567-610.
- DiChiara et. al (2017) Alzheimer's Toxic Amyloid Beta Oligomers: Unwelcome Visitors to the Na/K ATPase alpha3 Docking Station. *Yale Journal of Biology and Medicine* 90,45-61.
- Viola et. al (2014) Towards non-invasive diagnostic imaging of early-stage Alzheimer's disease. *Nature Nanotechnology* 91-98.
- Forny-Germano et. al (2014) Alzheimer's Disease-Like Pathology Induced by Amyloid-Oligomers in Nonhuman Primates. *The Journal of Neuroscience* 34(41), 13629 -13643
- Bitel et. al (2012) Amyloid- and Tau Pathology of Alzheimer's Disease Induced by Diabetes in a Rabbit Animal Model. *Journal of Alzheimer's Disease* 32, 291-305

Acknowledgements

Special thank you to **Mrs. Kirsten Viola**, our lab advisor, and **Dr. Klein**, for giving us the opportunity to work in the Klein Lab

Thank you to our material and development collaborators: **Vikas Nandwana**, **Rohan Chalasani**, **Adrian Bebenek**, **E. Alexandria Waters**, **Nicholas Rozema**, **Craig Weiss**

Thank you to the Korea Science Academy for hosting us this week!