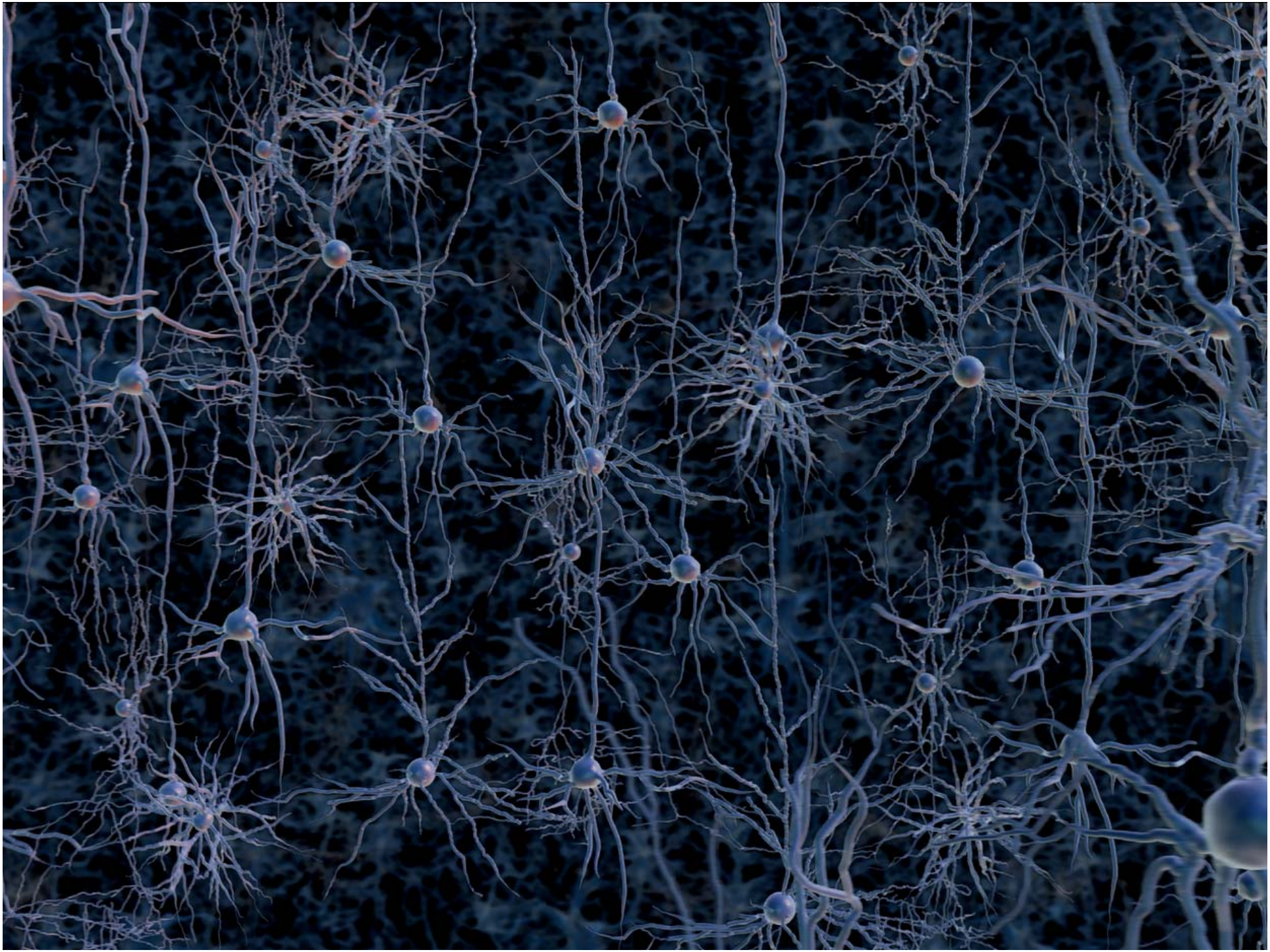


Technologies for Understanding and Repairing the Brain

Ed Boyden

MIT Media Lab &
McGovern Institute,
Departments of Biological Engineering and
Brain and Cognitive Sciences,
MIT

synthetic neurobiology

http://synthneuro.org

Massachusetts Institute of Technology

mit media lab

McGOVERN INSTITUTE FOR BRAIN RESEARCH AT MIT

MIT BE BIOLOGICAL ENGINEERING

brain+cognitive sciences

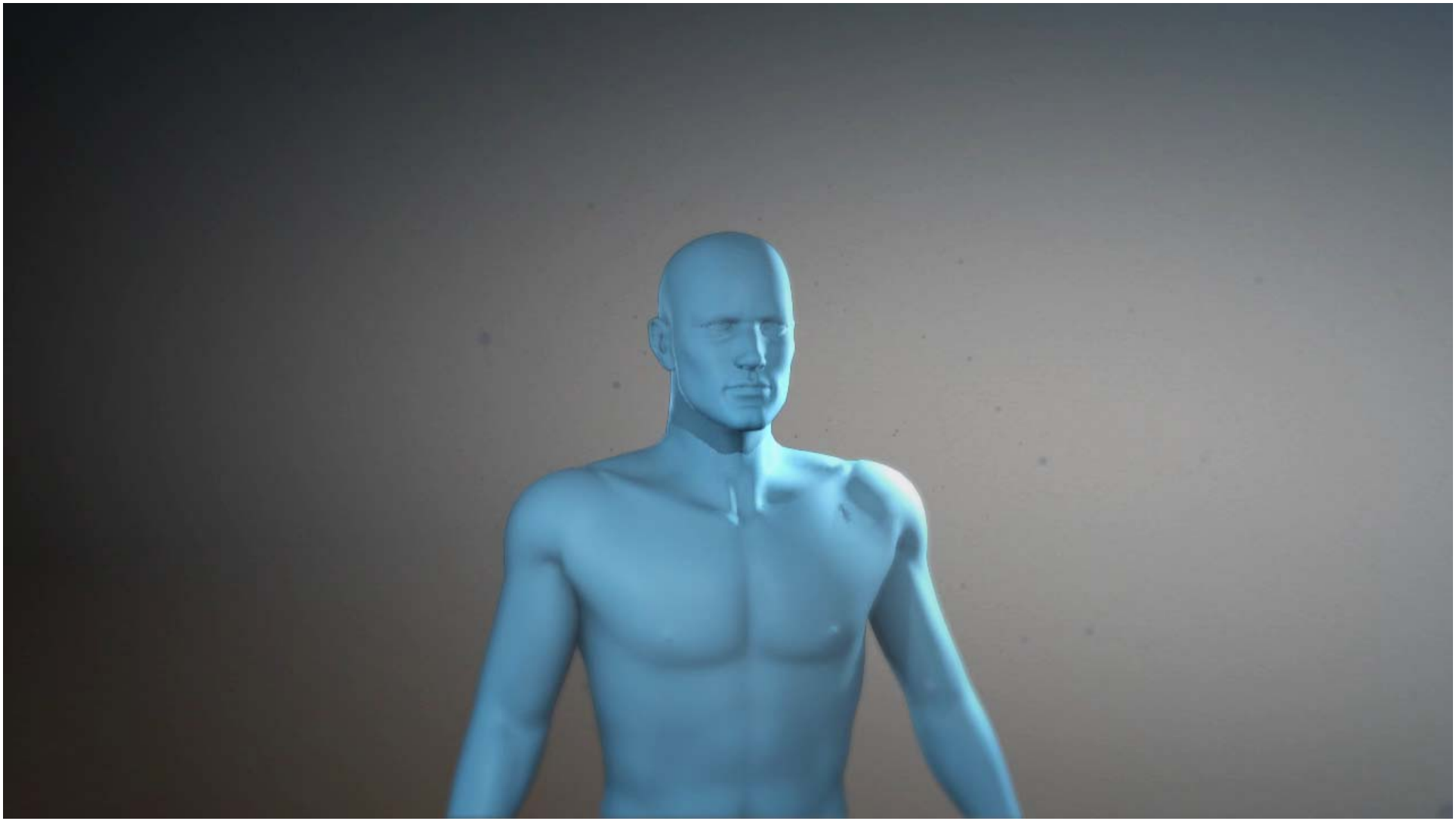
CNBE MIT CENTER FOR NEUROBIOLOGICAL ENGINEERING

KOCH INSTITUTE FOR INTEGRATIVE CANCER RESEARCH AT MIT

CSBi

MIT CEHS

Understanding the brain: one of the great quests of our time



1 billion people

Alzheimer's disease

obesity

sleep disorders

schizophrenia

depression

attention deficit disorder

stroke

ALS

anxiety

addiction

epilepsy

tinnitus

multiple sclerosis

spinal cord injury

autism

vision loss

migraine

traumatic brain injury

hearing loss

Parkinson's disease

chronic pain

Science 30 July 2010:
Vol. 329 no. 5991 pp. 502-504
DOI: 10.1126/science.329.5991.502

Is Pharma Running Out of Brainy Ideas?

Brain drugs:

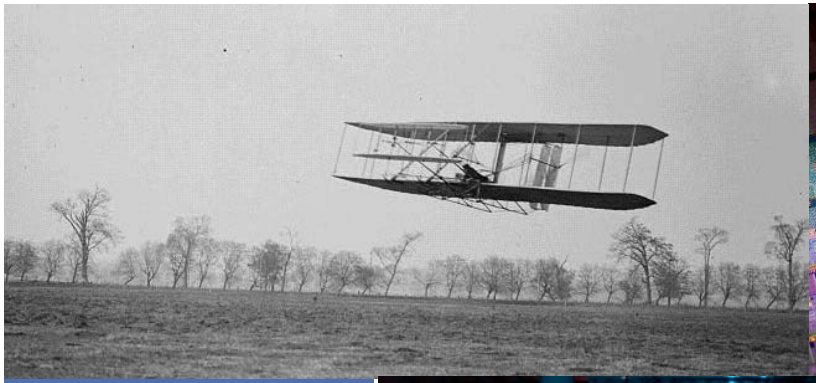
Take **9 years**

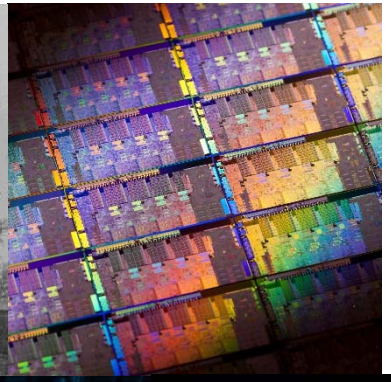
Fail 92% of the time

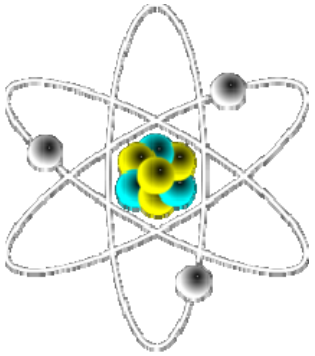
Cost $1 billion each

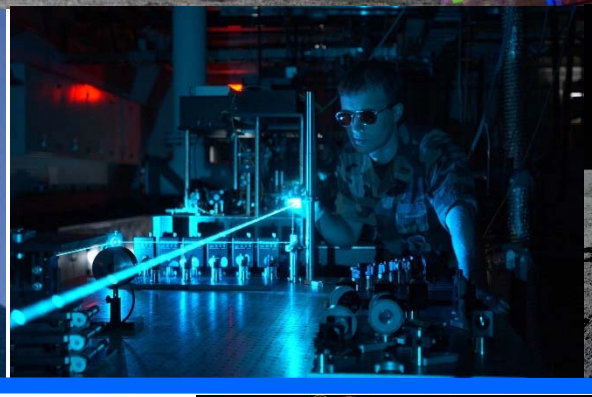
Partial success

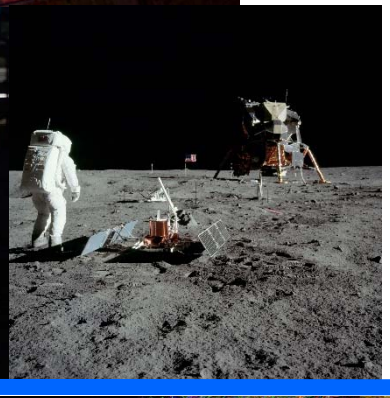
Why is the brain so hard to understand and repair?



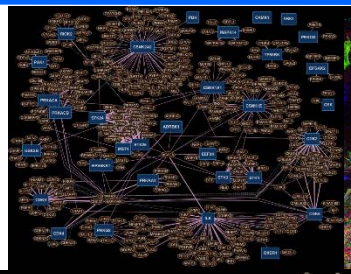


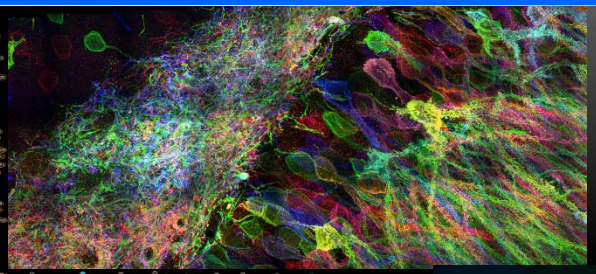


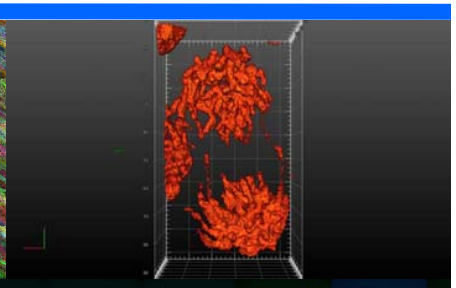


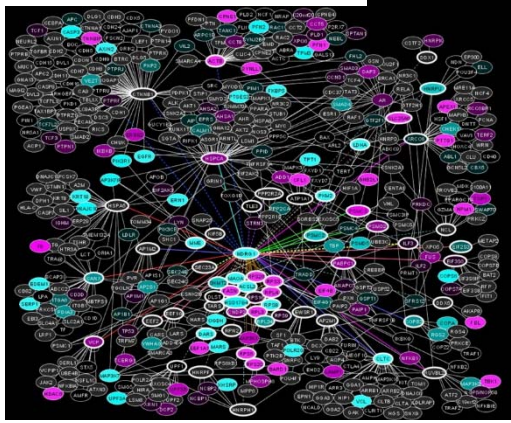


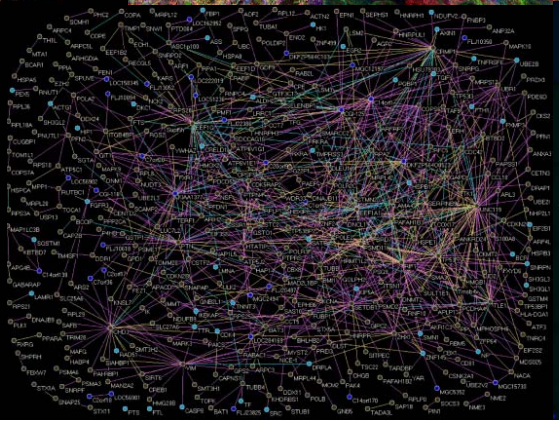
VS

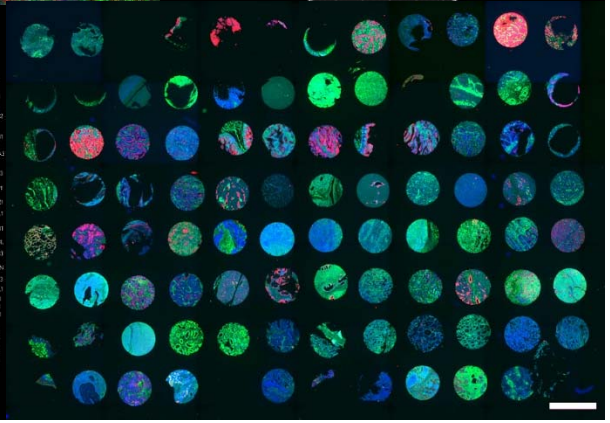




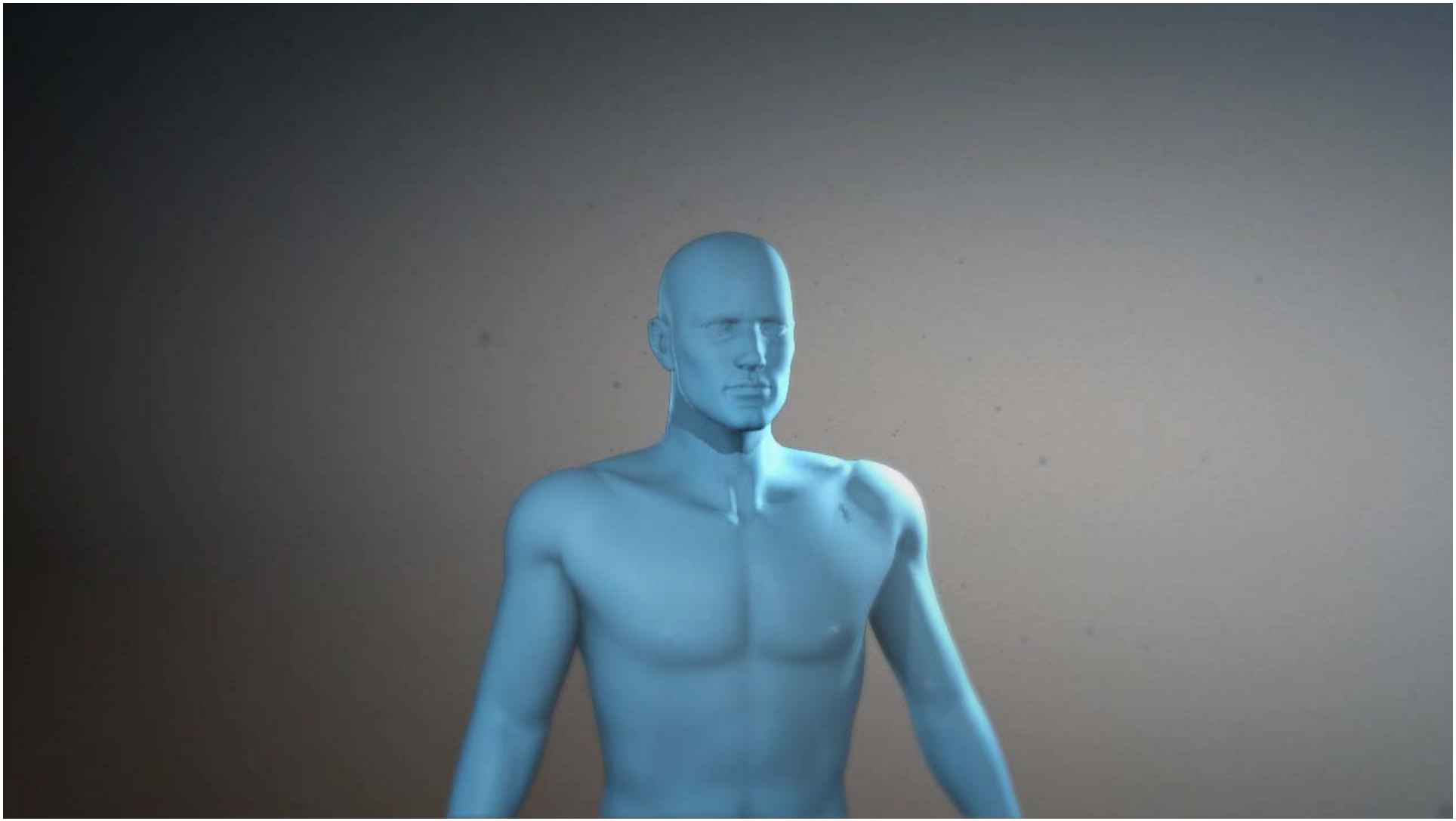




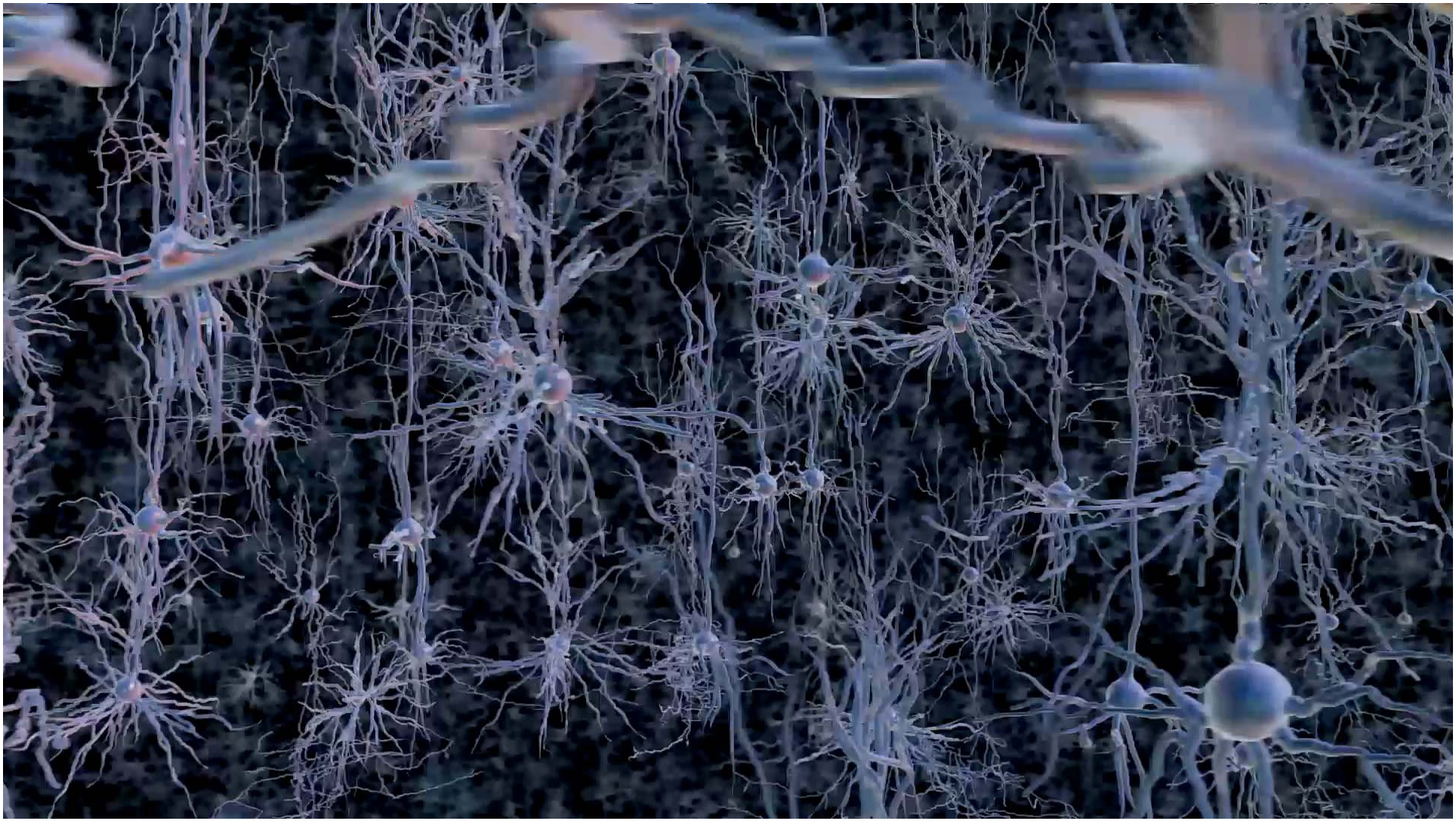




Space: Nanoscale building blocks, spanning centimeters



Time: Millisecond timescale electrical and chemical events



Can we understand the brain, to the point of making biologically realistic, comprehensible models of neural circuit function?

Map the molecules, wiring, and connections

Control the high-speed dynamics

Observe the high-speed dynamics

Technologies for understanding the brain

Map the molecules, wiring, and connections

Expansion microscopy

Control the high-speed dynamics

Optogenetics

Observe the high-speed dynamics

Tools for fluorescent imaging of dynamics

Technologies for understanding the brain

Map the molecules, wiring, and connections

Expansion microscopy

Control the high-speed dynamics

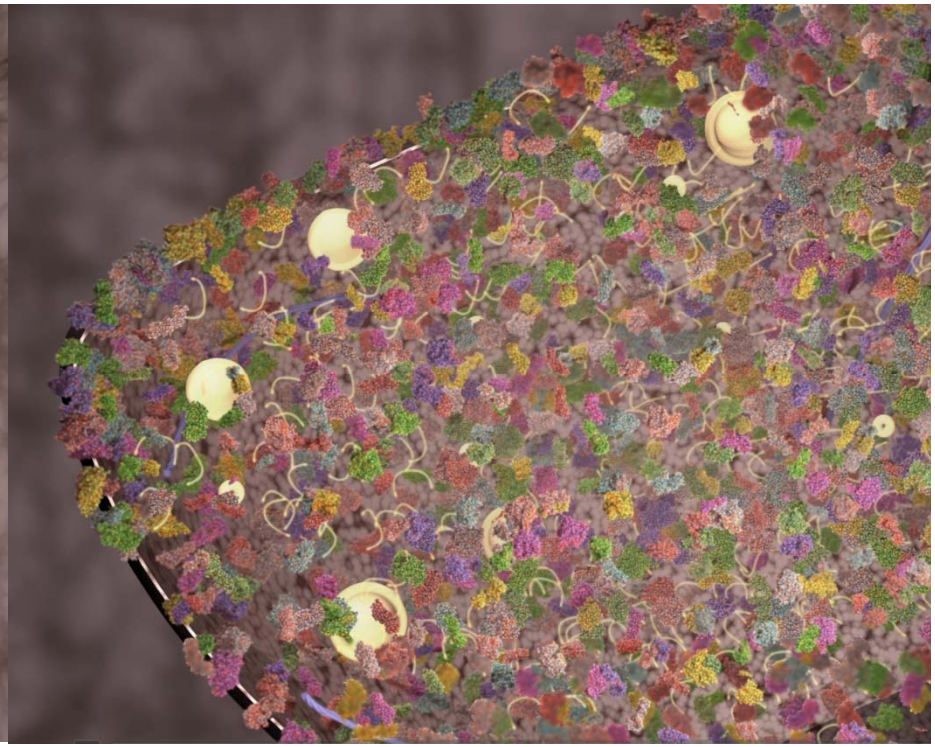
Optogenetics

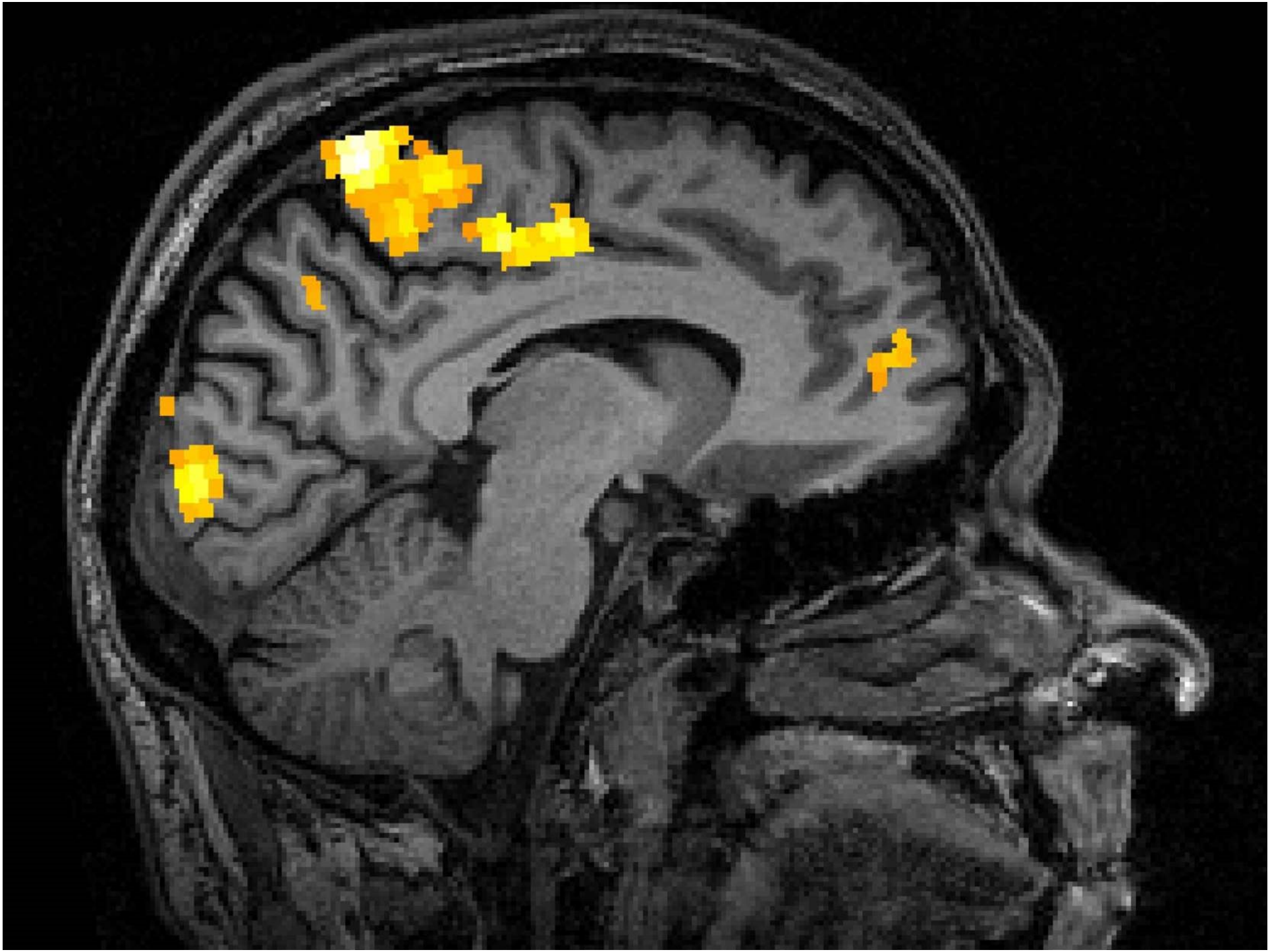
Observe the high-speed dynamics

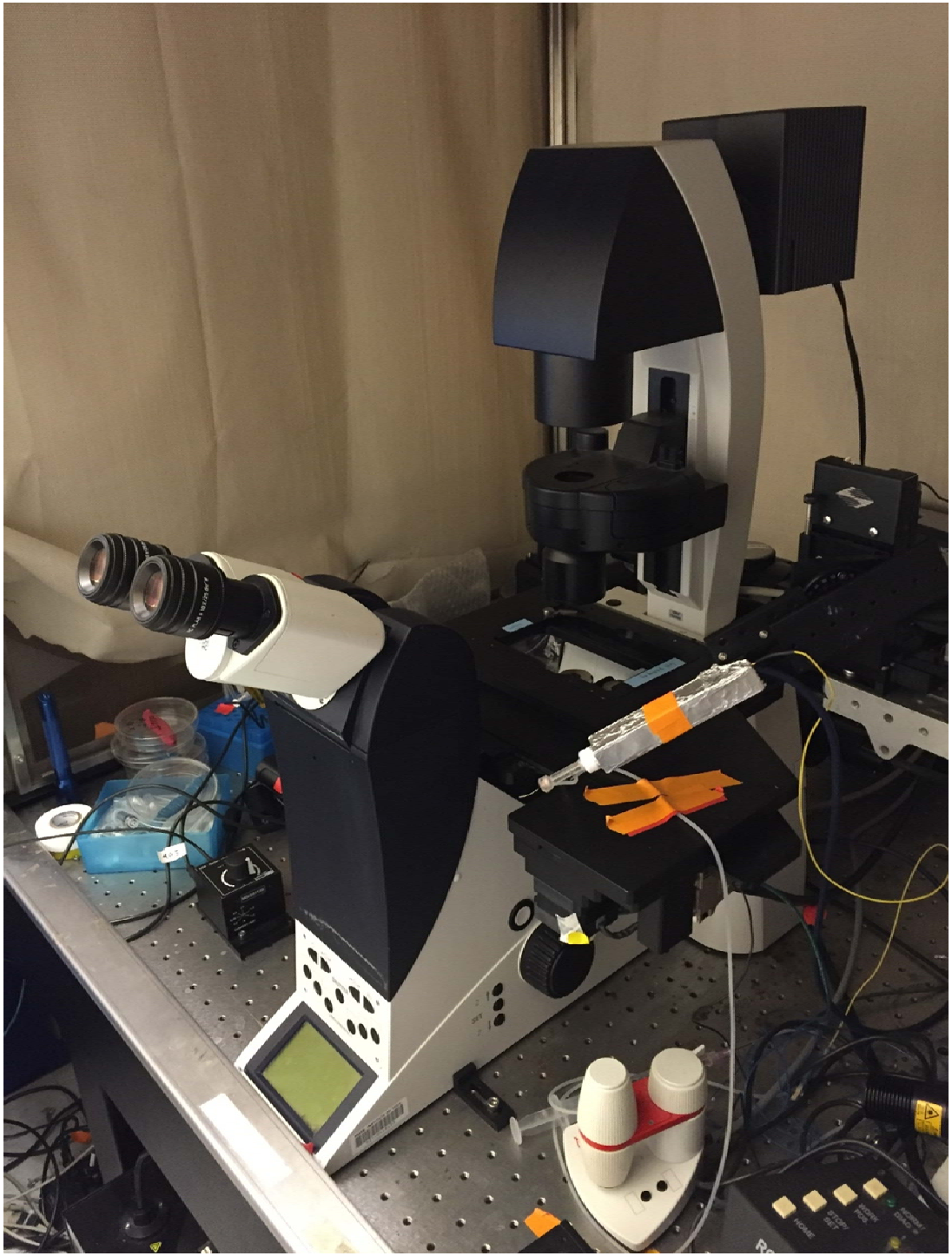
Tools for fluorescent imaging of dynamics

How are neurons organized into networks?

How are biomolecules organized within neurons?



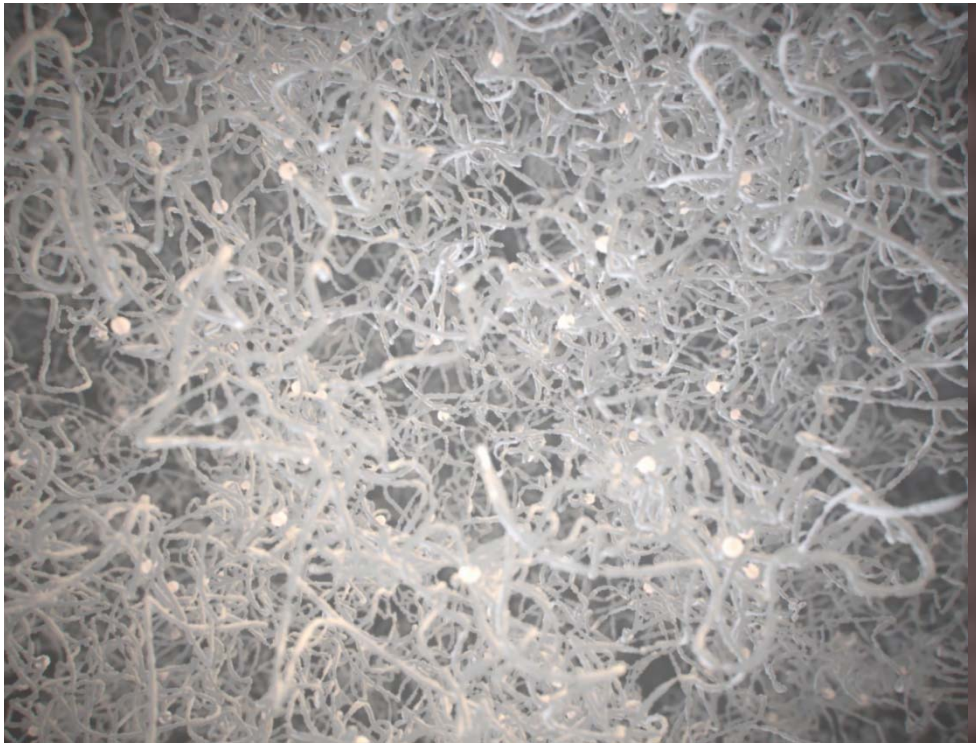


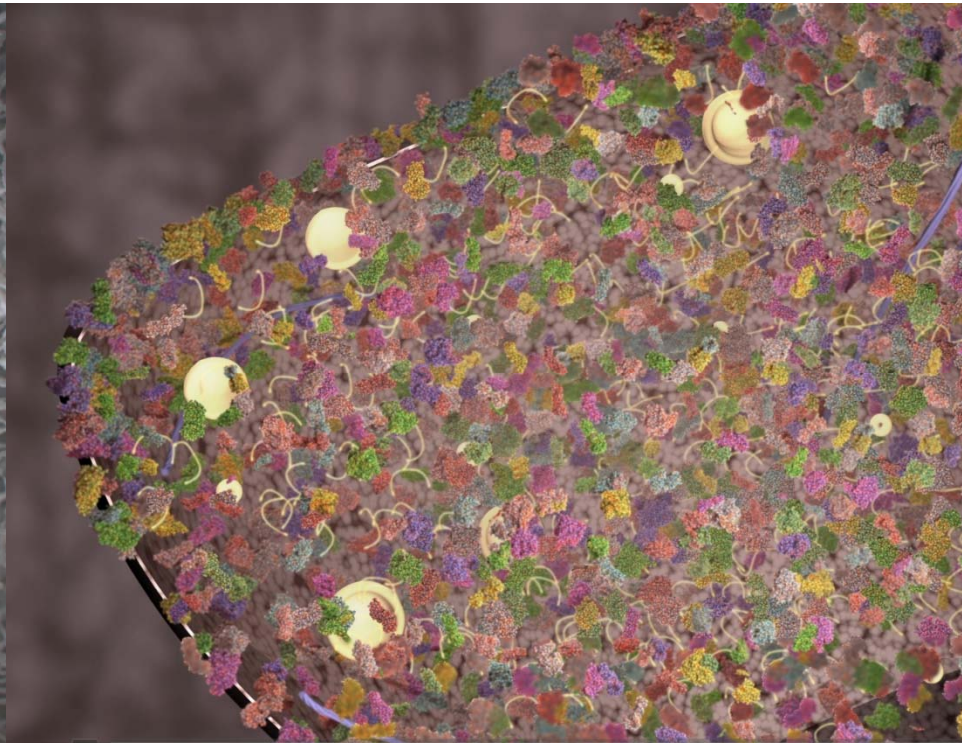


Expansion Microscopy

Can we install polymer chains of a swellable material…

…throughout cells, winding their way around biomolecules, so that we can pull the biomolecules apart?





Chen*, Tillberg*, Boyden (2015) *Science* 347(6221):543-548.

Tillberg*, Chen*, et al. (2016) *Nature Biotechnology* 34:987–992.

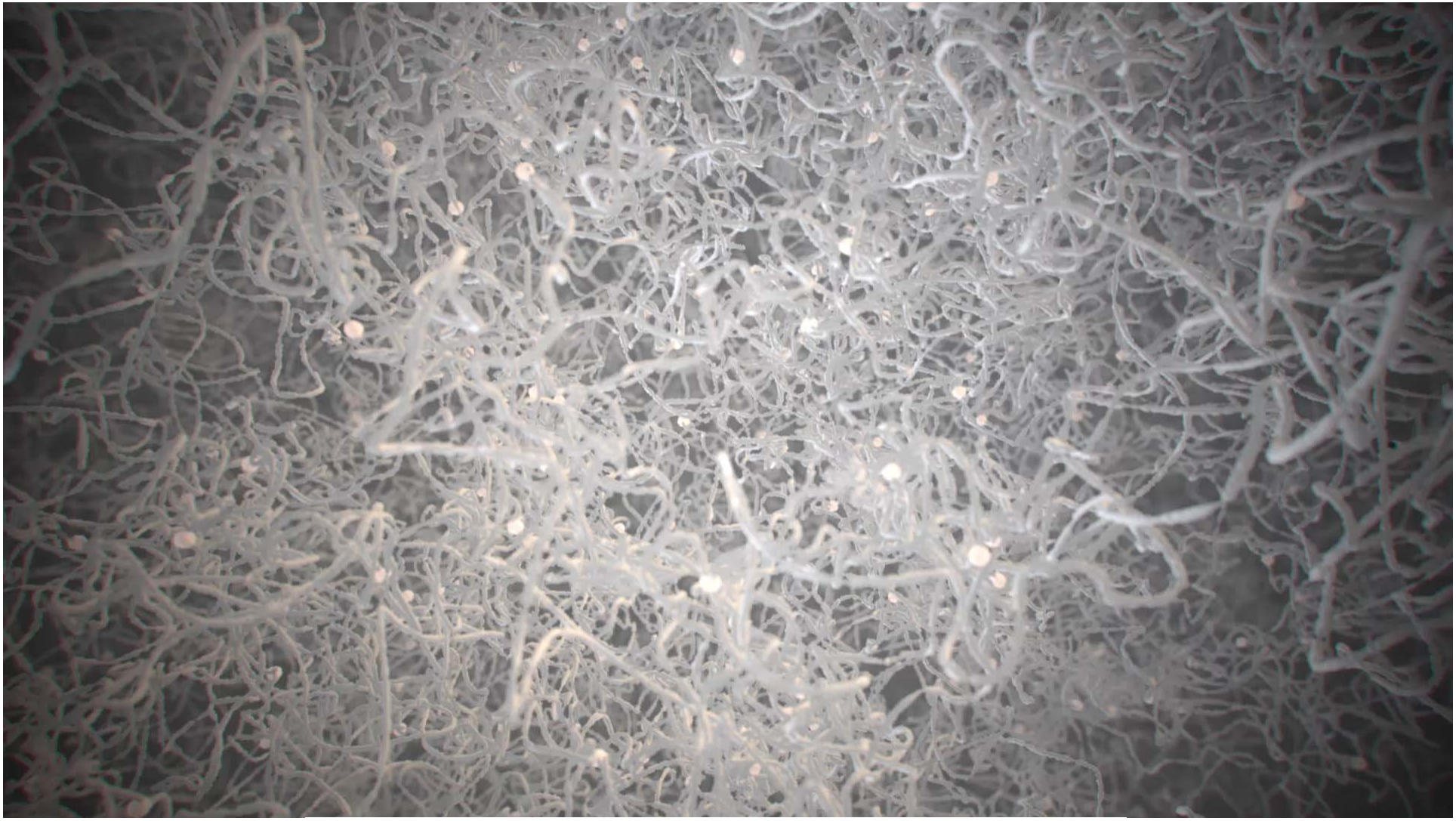
Chen*, Wassie*, et al. (2016) *Nature Methods* 13(8):679-84.

Chang et al. (2017) *Nature Methods* 14(6):593-599.

Zhao*, Bucur*, et al. (2017) *Nature Biotechnology* 35(8):757-764.

http://expansionmicroscopy.org

Commercialized by Expansion Technologies, Inc. (http://extbio.com); ESB is co-founder.



VOLUME 45, NUMBER 20 PHYSICAL REVIEW LETTERS 17 NOVEMBER 1980

1980

Phase Transitions in Ionic Gels

Toyoichi Tanaka, David Fillmore, Shao-Tang Sun, Izumi Nishio,
Gerald Swislow, and Arati Shah
Department of Physics and Center for Materials Science and Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139
(Received 13 June 1980)

The polymer network of a gel, under certain conditions, undergoes a discrete transition in equilibrium volume with changes in solvent composition or temperature. This Letter demonstrates that ionization of the gel network plays an essential role in the phase transition. The volume collapse is also observed when the *p*H within the gel is varied.

Journal
Stain Technology ›
Volume 56, 1981 - Issue 5

Original Article

The Use of Polyacrylamide as an Embedding Medium for Immunohistochemical Studies of Embryonic Tissues

Peter Hausen & Christine Dreyer

Pages 287-293 | Published online: 12 Jul 2009

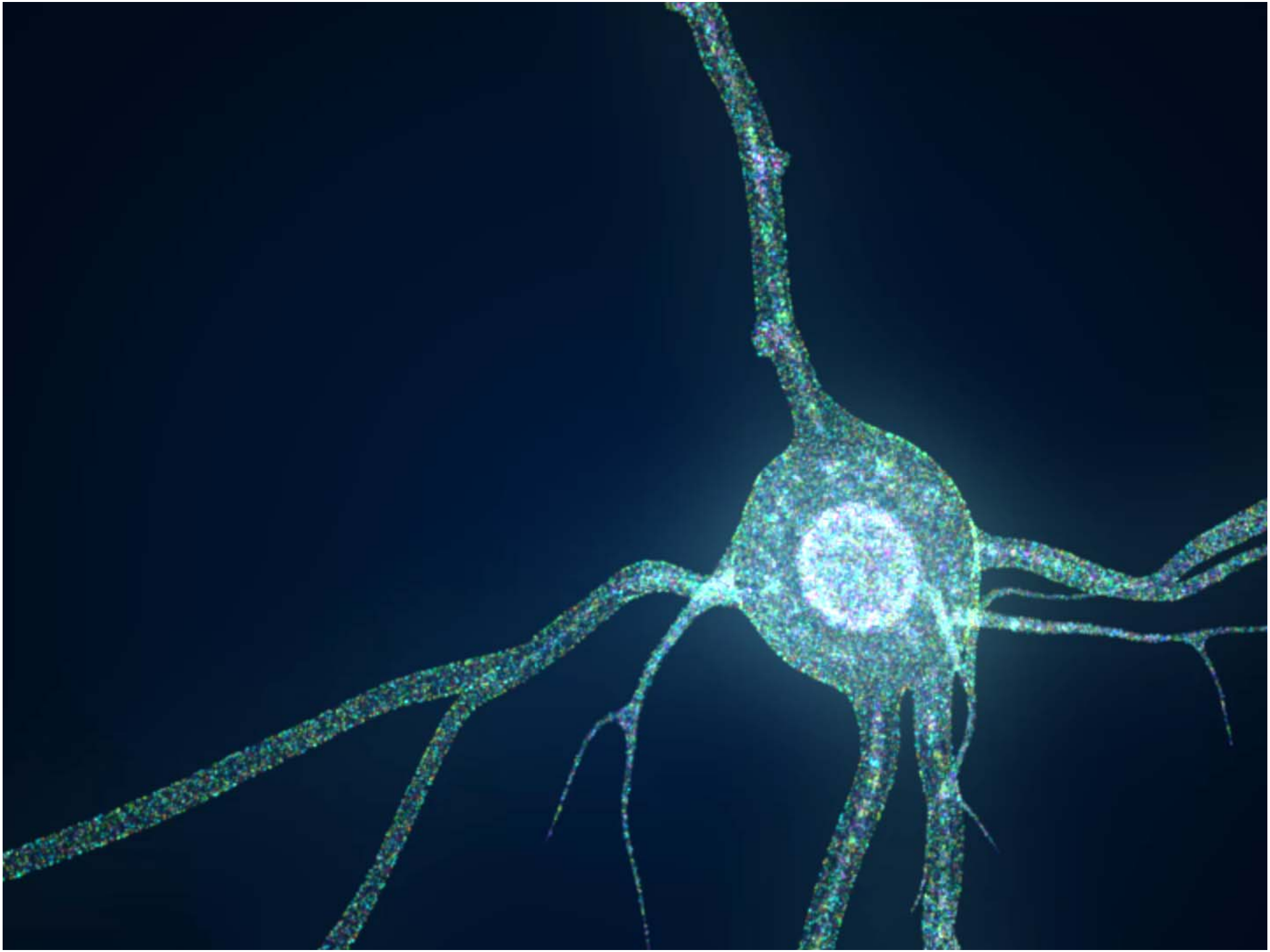
Download citation http://dx.doi.org/10.3109/10520298109067329

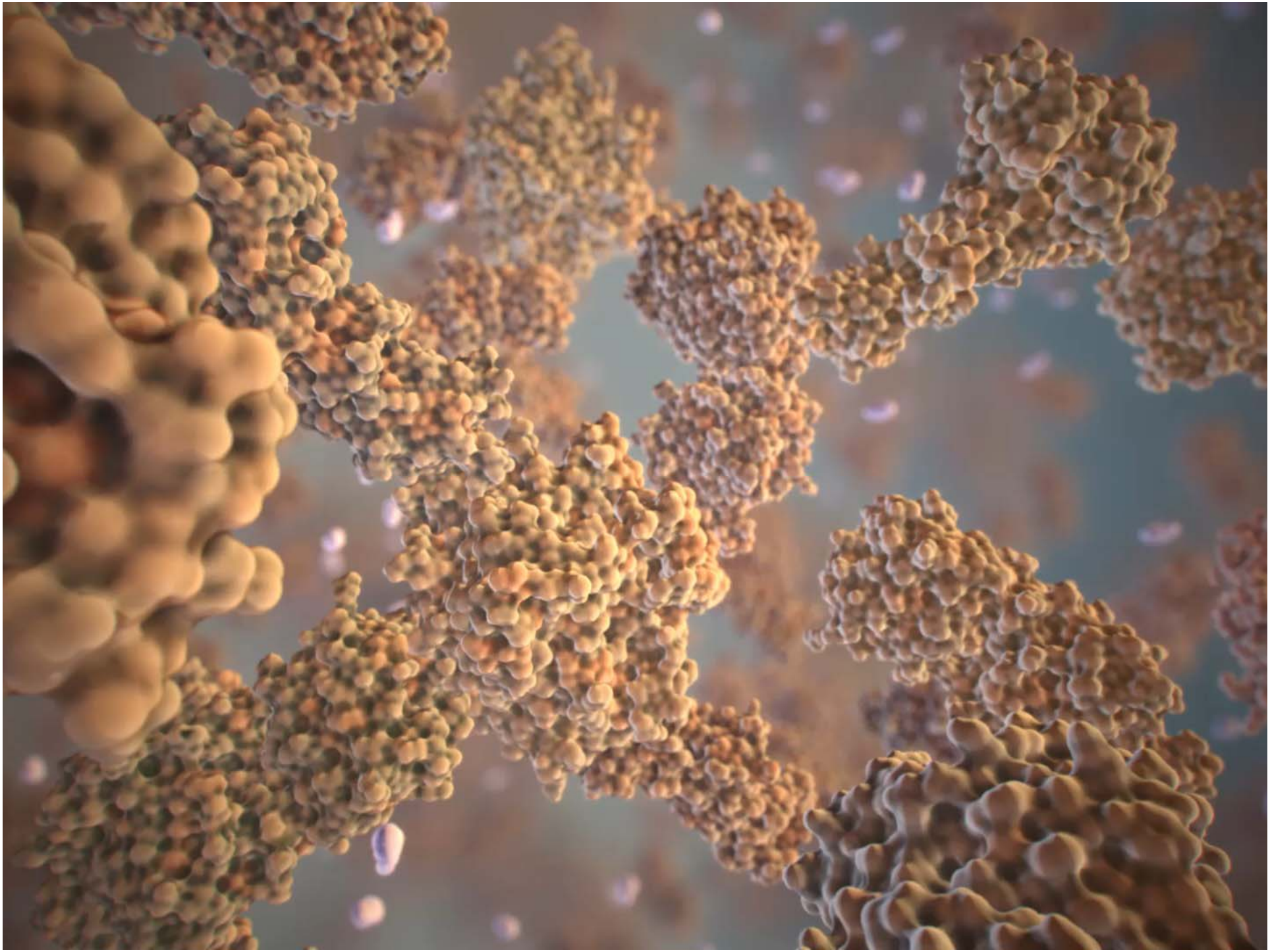
Abstract

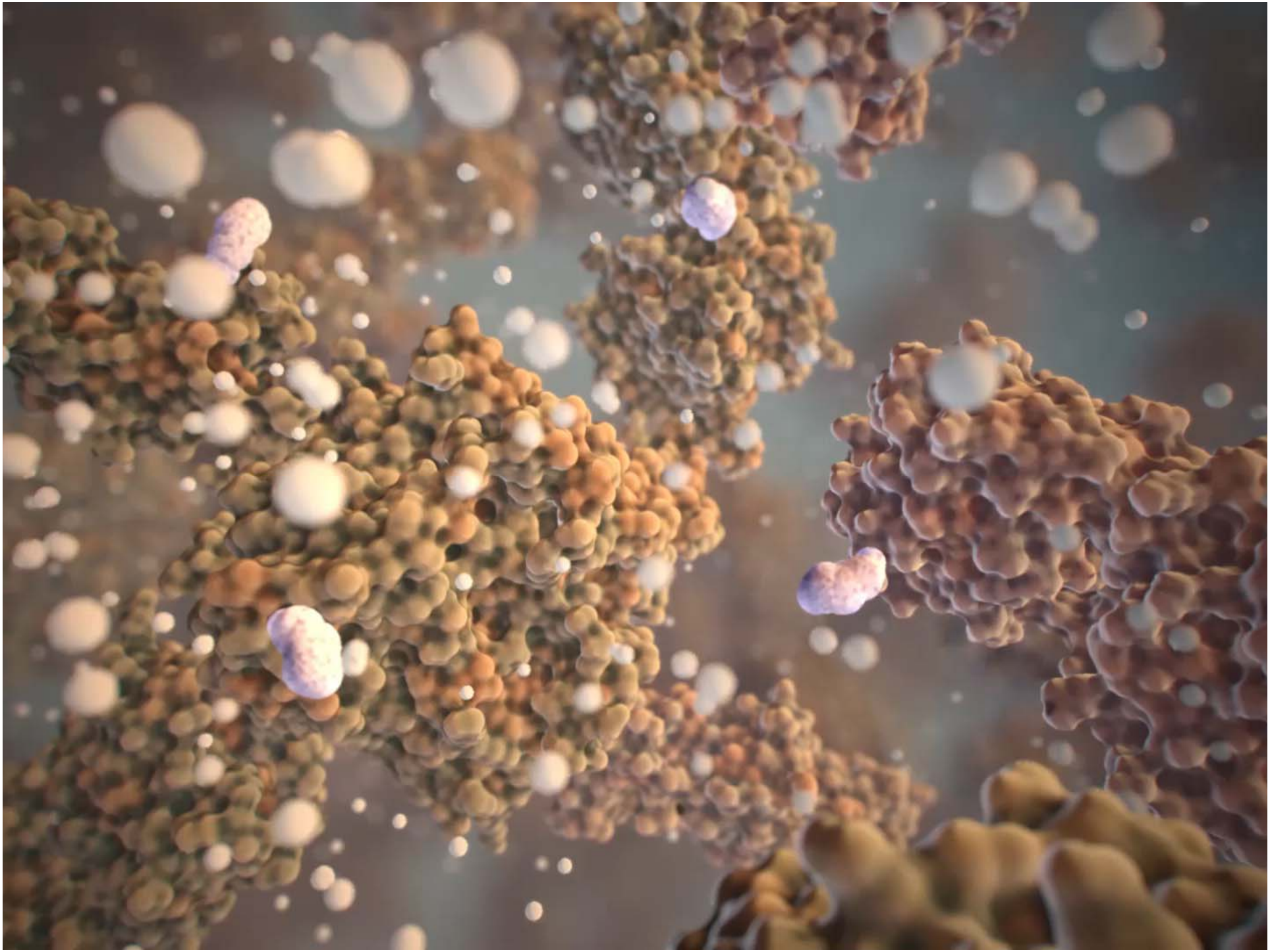
Fixed amphibian embryos and tadpoles were impregnated with acrylamide. After polymerization the gels were frozen and sectioned on a cryostat. The preservation of gross and fine morphological features in these sections is comparable to conventional paraffin sections and they can be stained by immunohistochemical methods without affecting the quality of the preparations.

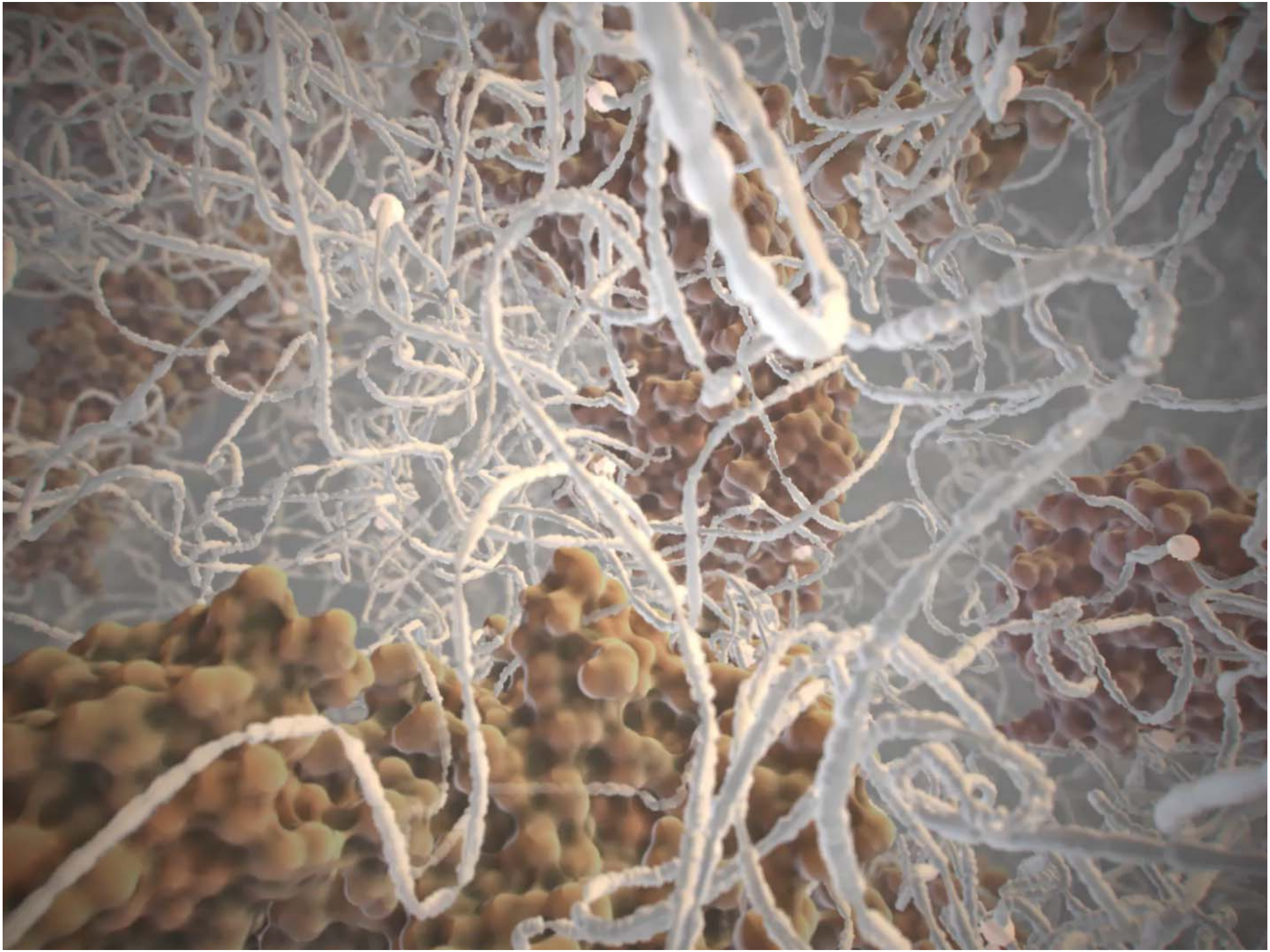
1981

Ideas hiding in plain sight

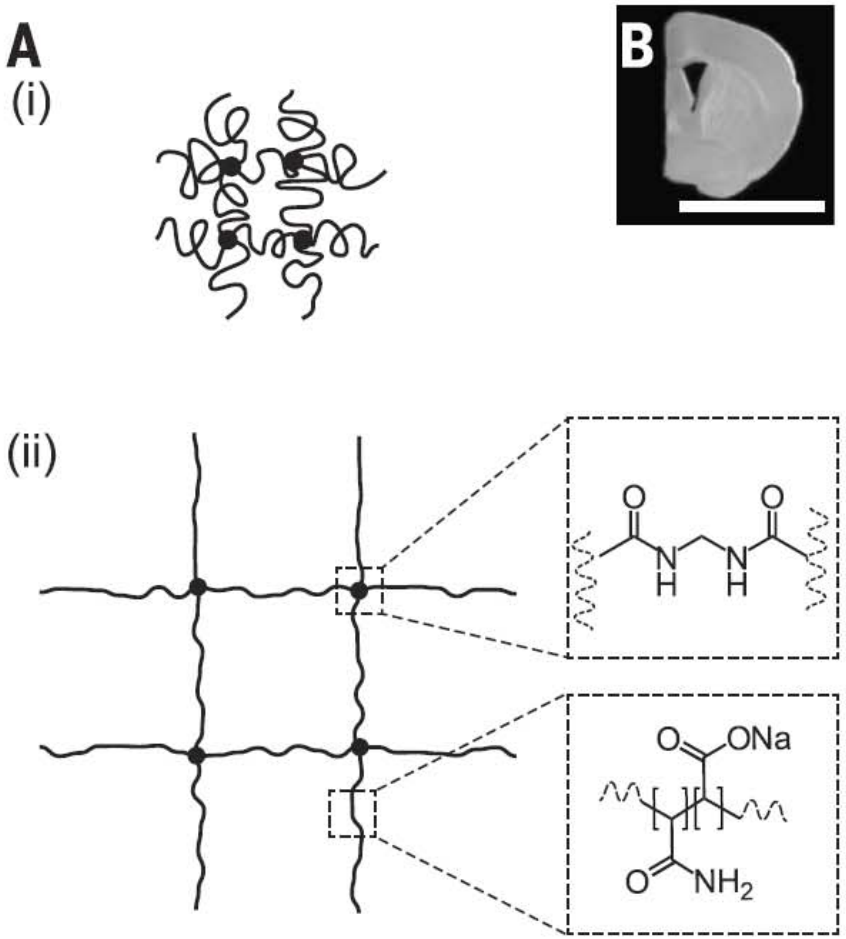


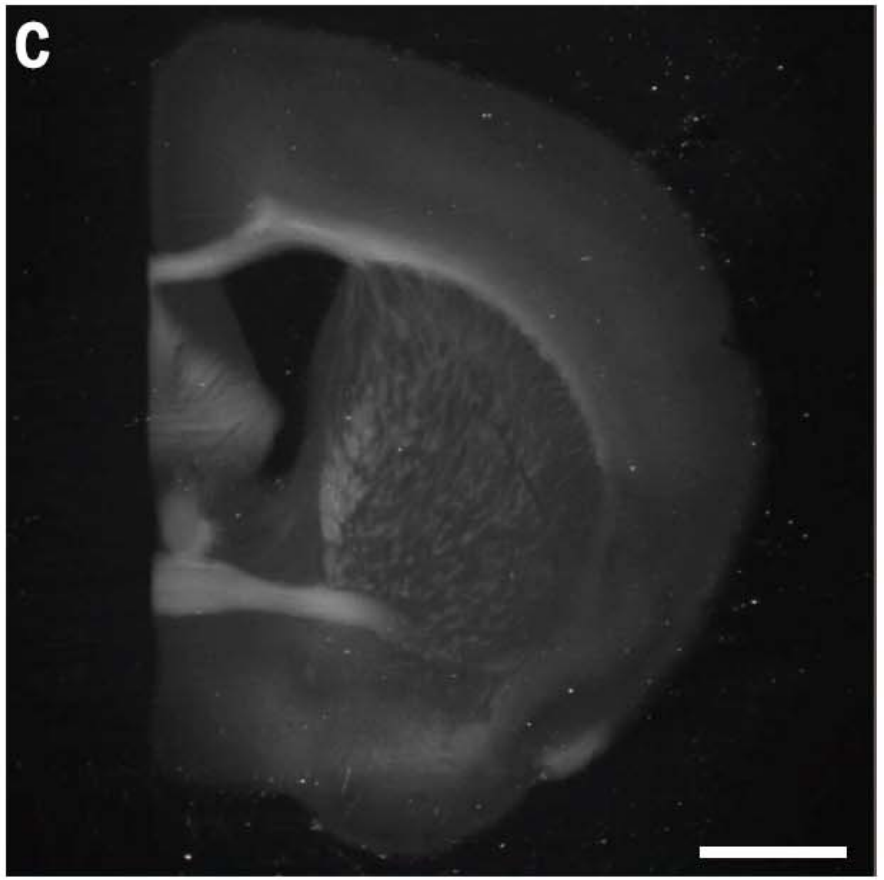




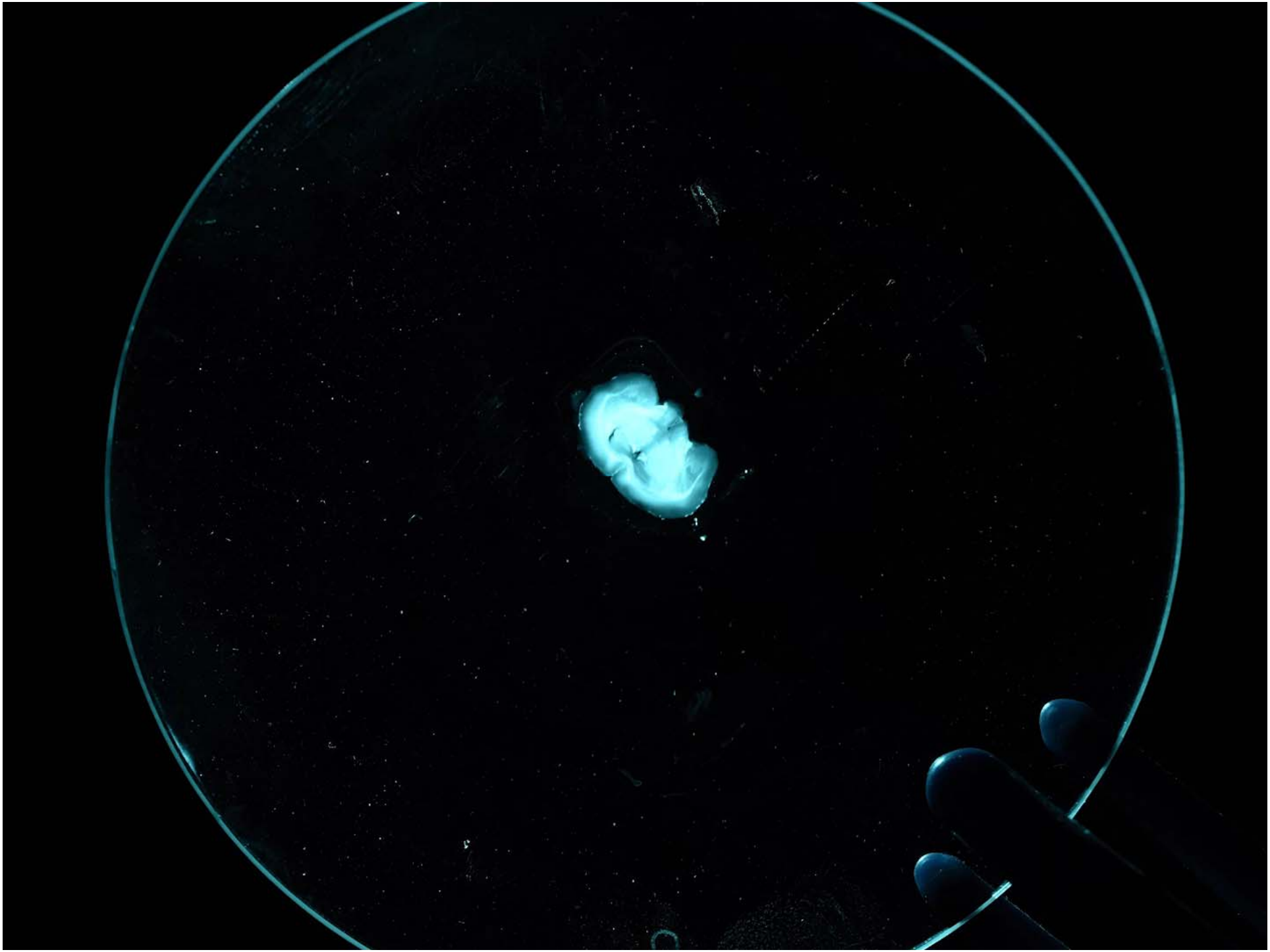


Expansion Microscopy (ExM) Version 1.0

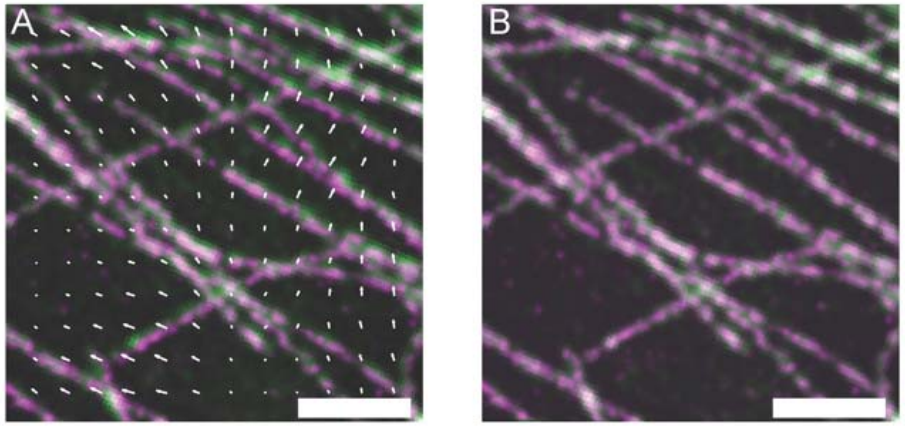




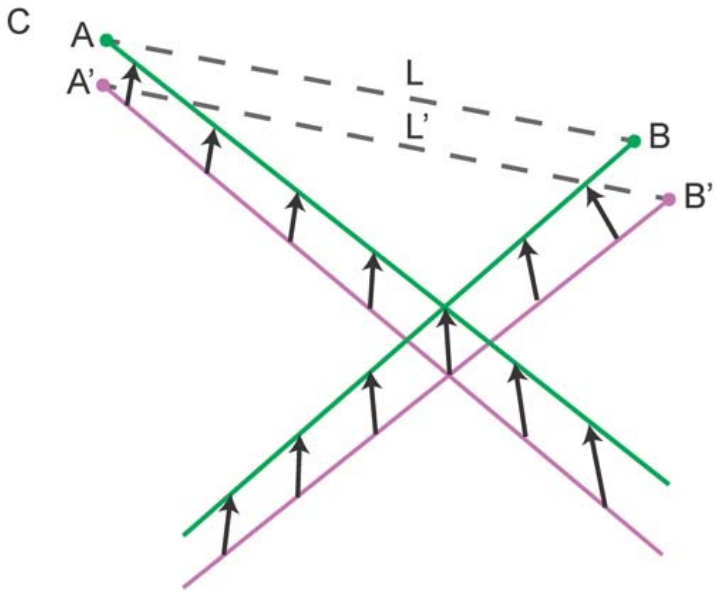
Chen*, Tillberg*, Boyden (2015) *Science* 347(6221):543-548.



Quantification of expansion error using non-rigid registration and distortion vector field calculation



Anti-tubulin, HEK cells



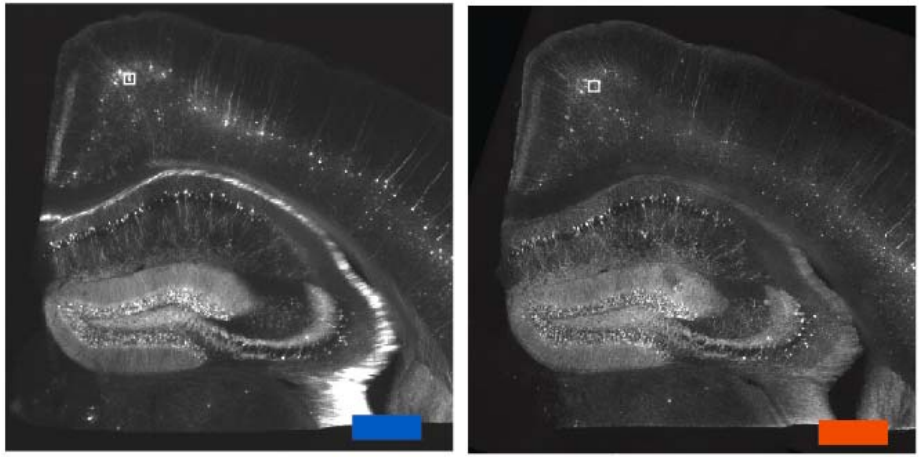
Chen*, Tillberg*, Boyden (2015) *Science* 347(6221):543-548.

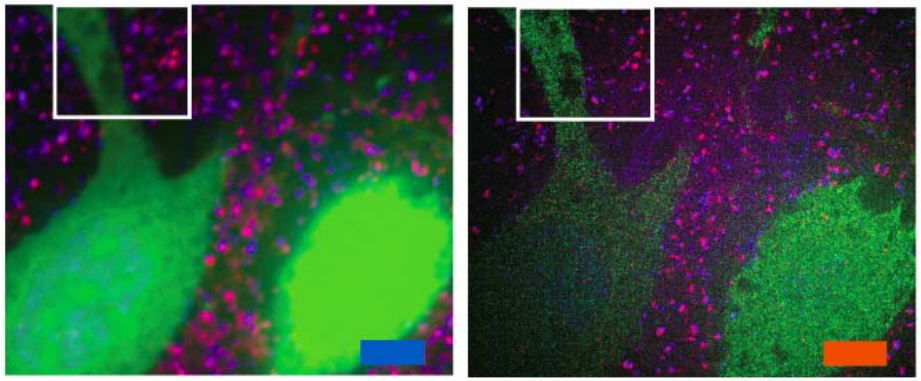
Before expansion: confocal microscopy

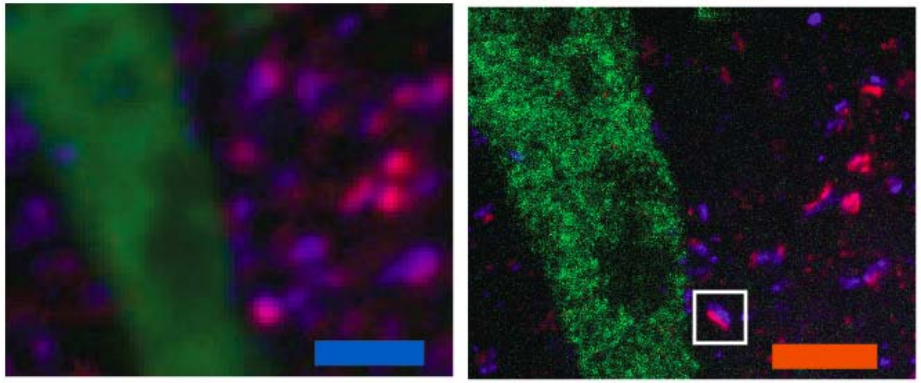
After expansion (~4.5x): confocal microscopy

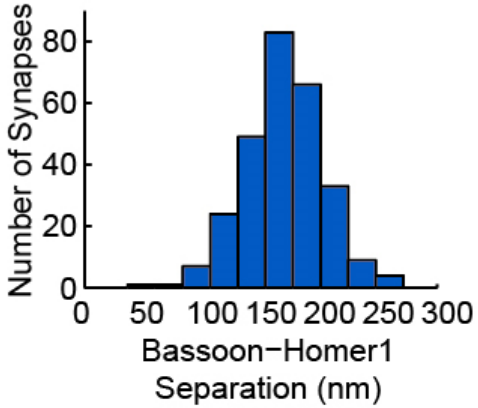
Anti-YFP, Thy1-YFP mice

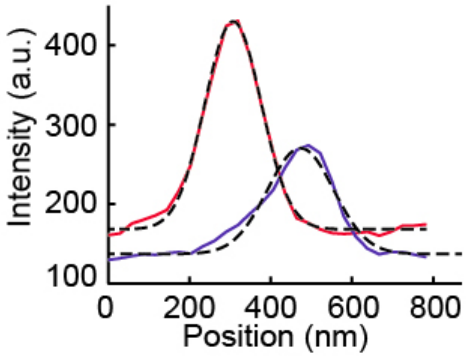
Anti-YFP (green), anti-bassoon (blue), anti-Homer1a (magenta), Thy1-YFP mouse cortex

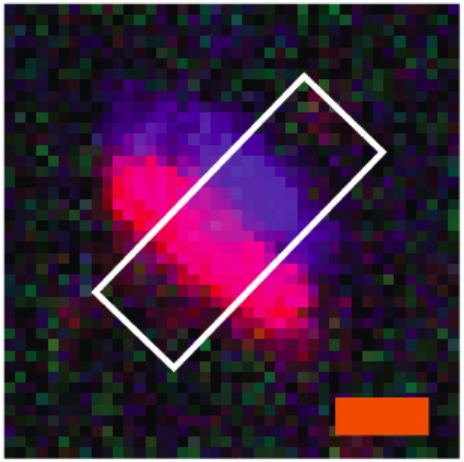






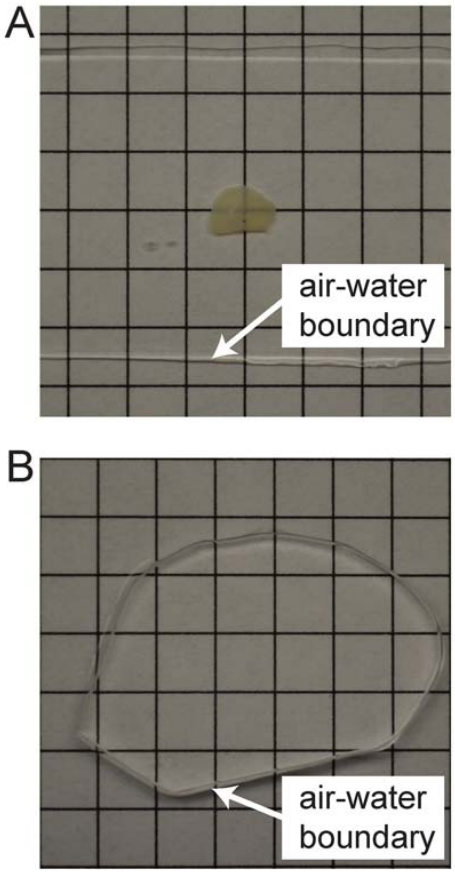




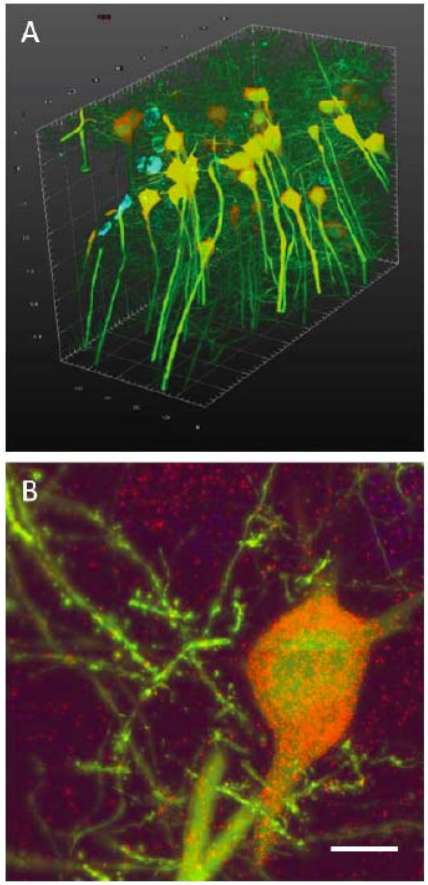


Chen*, Tillberg*, Boyden (2015) *Science* 347(6221):543-548.

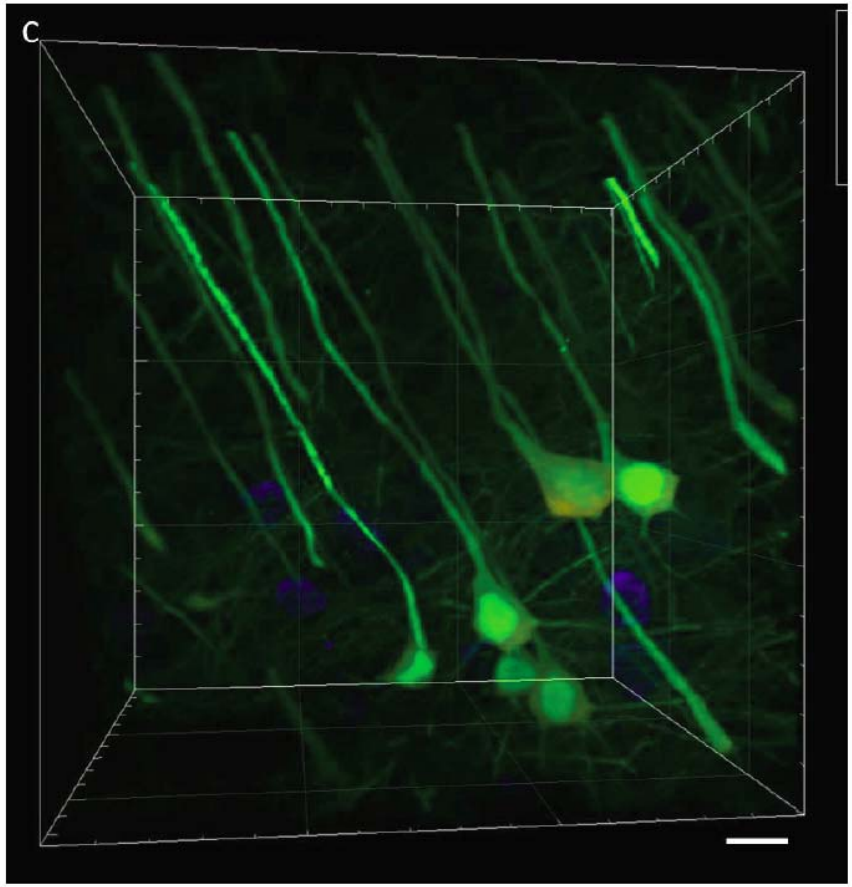
Expanded samples are transparent, and furthermore, of homogeneous refractive index since ~99% water



Chen*, Tillberg*, Boyden (2015) *Science* 347(6221):543-548.

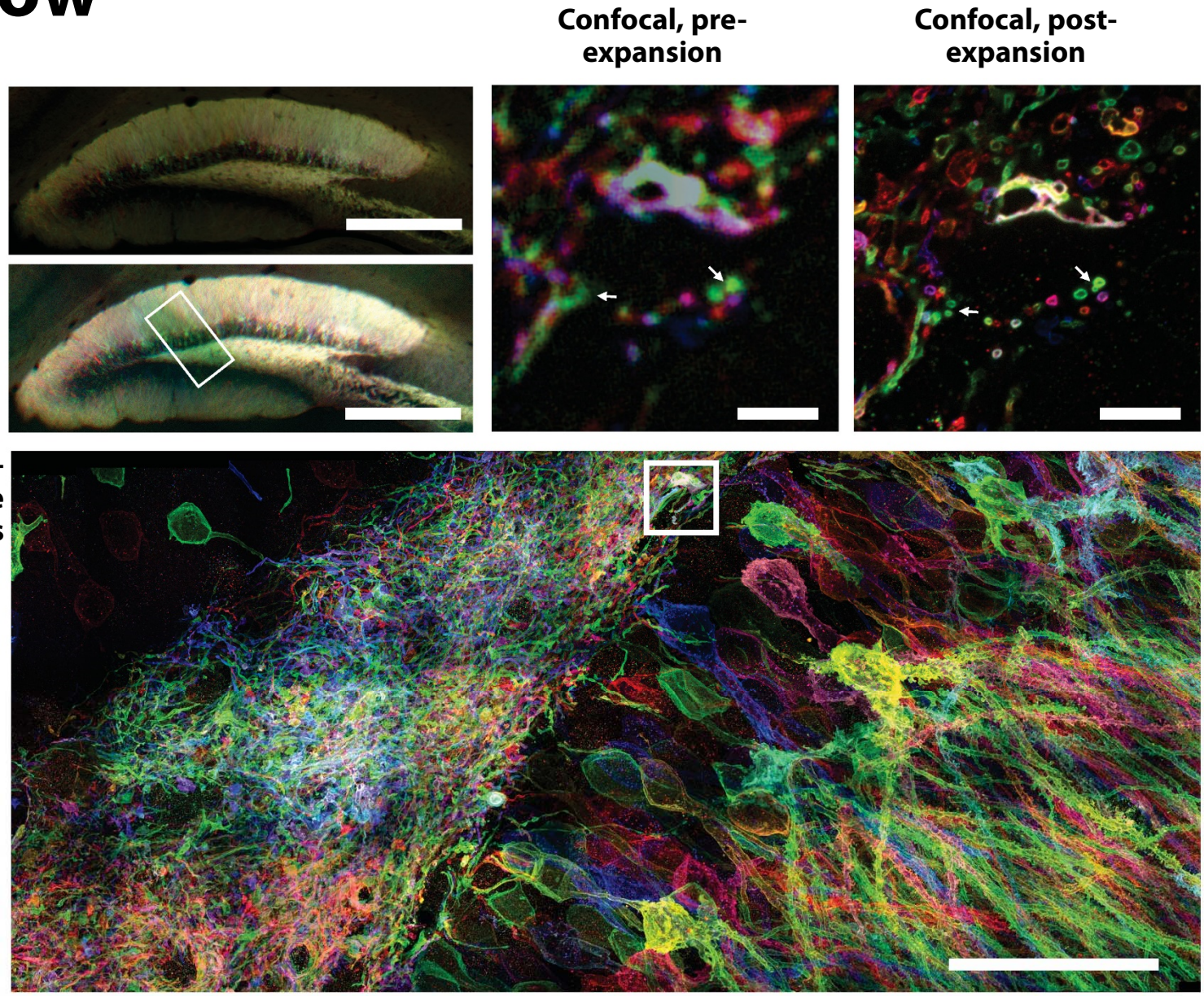


HCR-FISH, YFP (red), HCR-FISH, Gad1 (blue), Thy1-YFP (green) mouse hippocampus



Chen*, Wassie*, Cote, Sinha, Alon et al. (2016) *Nature Methods* 13(8):679-84.

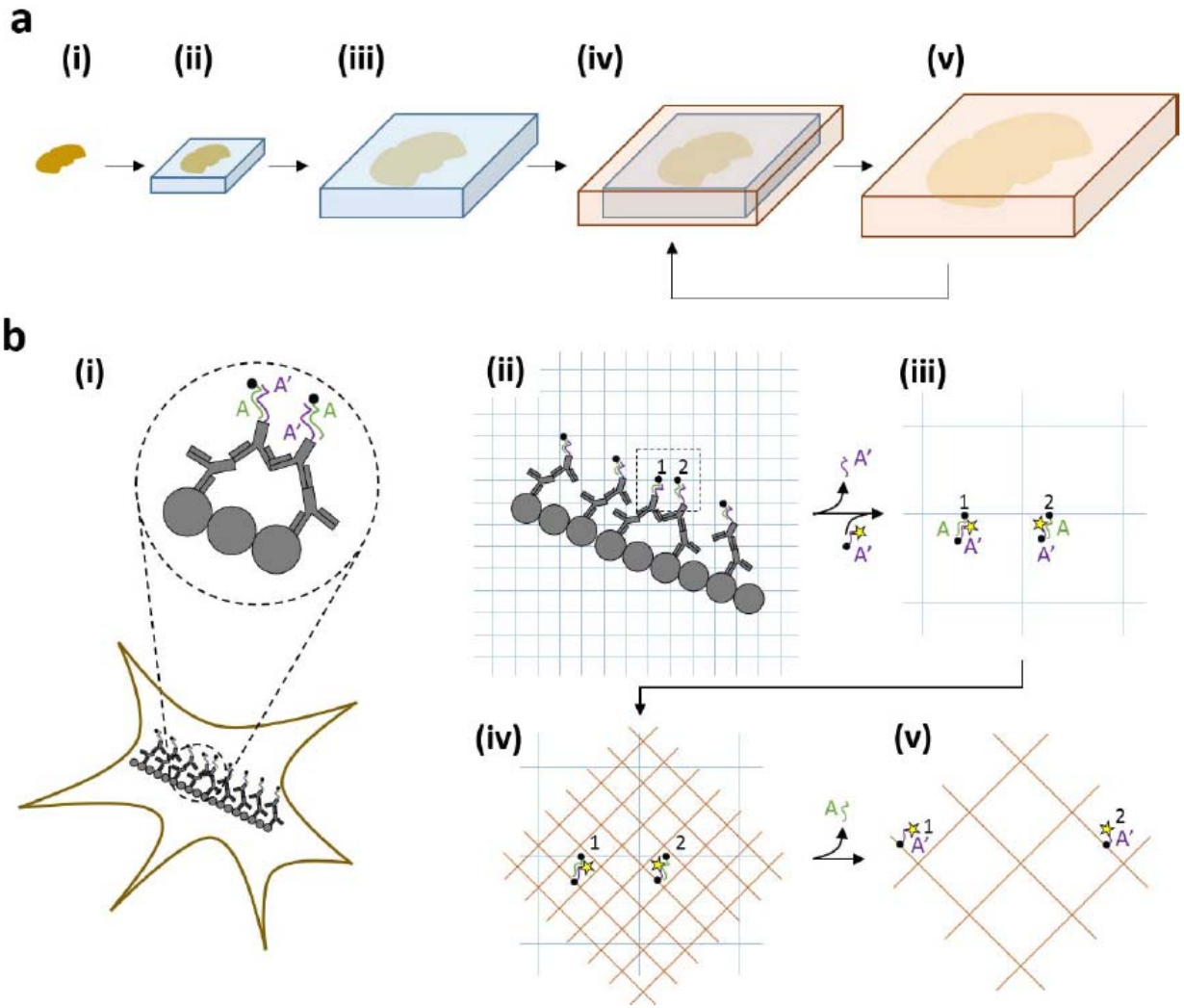
Brainbow



Tillberg*, Chen*, Piatkevich, Zhao, Yu et al. (2016) *Nature Biotechnology* 34:987–992.

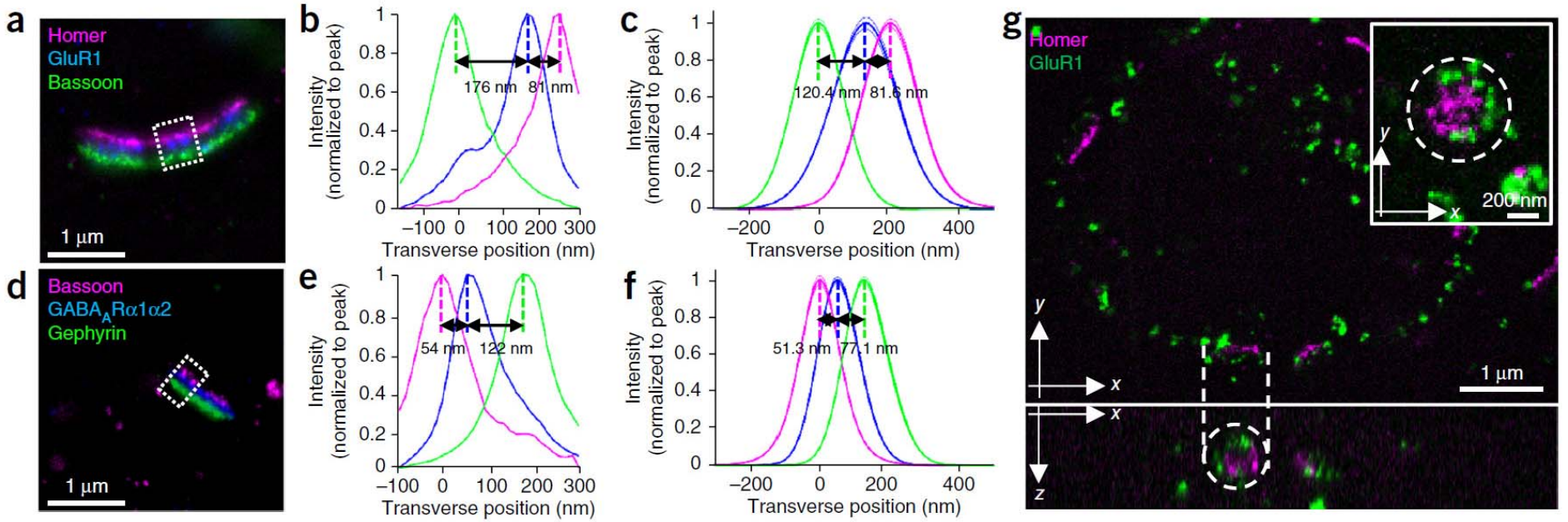
Collaborators: Steven R Tannenbaum, Robert Desimone, Dawen Cai

Iterative expansion microscopy: can we approach electron microscopy resolution?



Chang et al. (2017) *Nature Methods* 14(6):593-599.

Collaborators: Dawen Cai

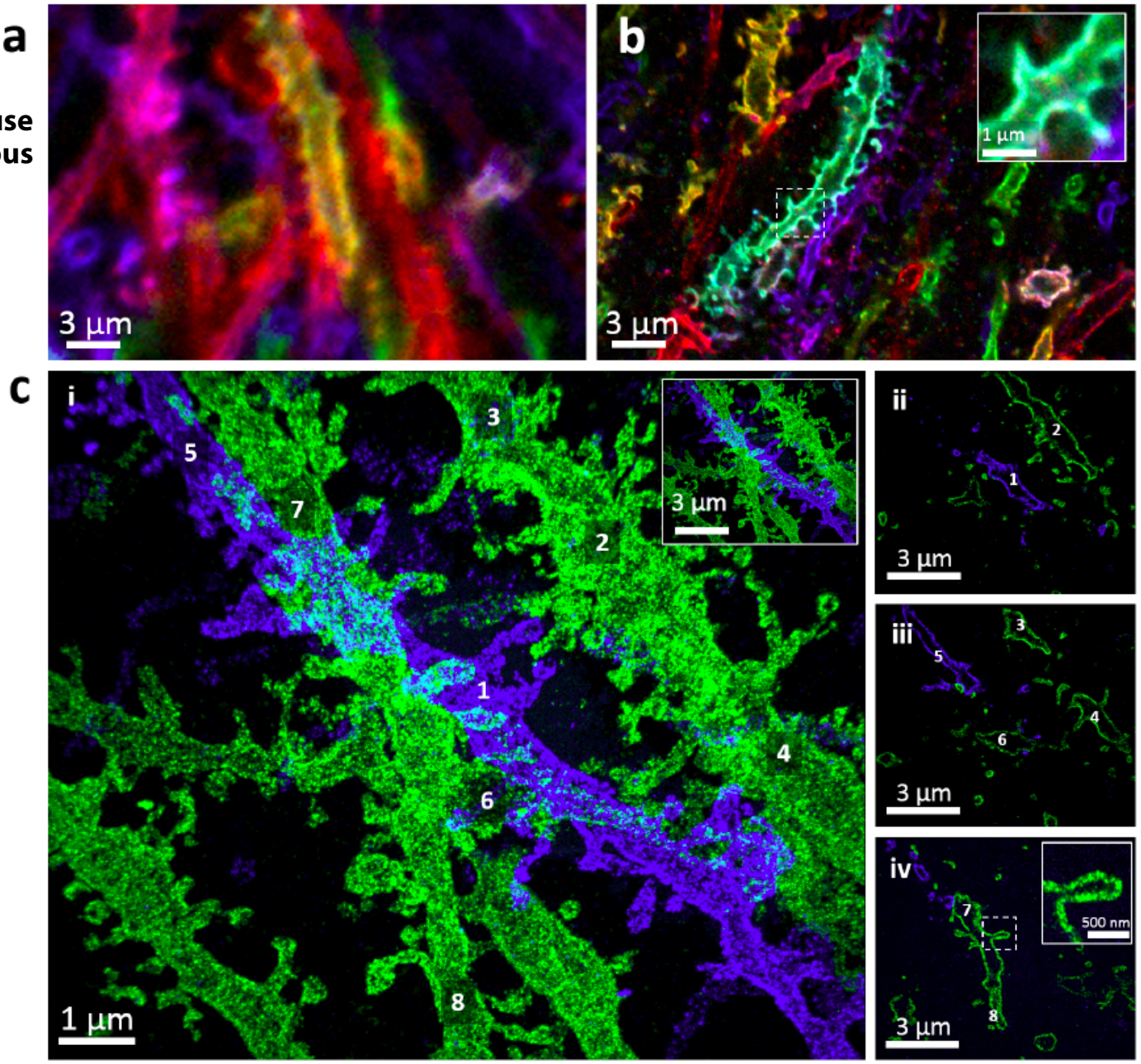


Primary mouse hippocampal cultures

Chang et al. (2017) *Nature Methods* 14(6):593-599.

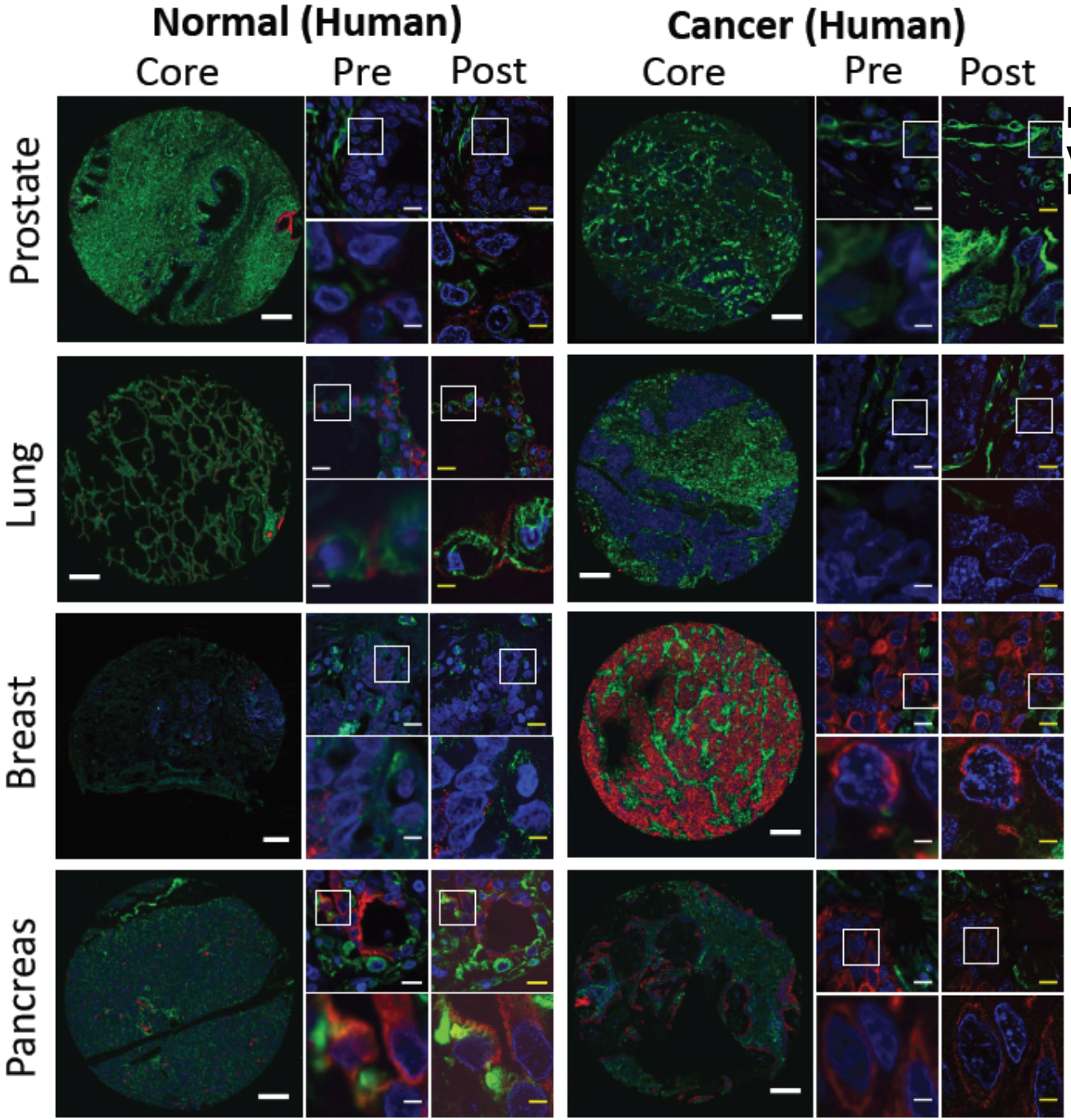
Collaborators: Dawen Cai

Brainbow mouse hippocampus



Chang et al. (2017) *Nature Methods* 14(6):593-599.

Collaborators: Dawen Cai

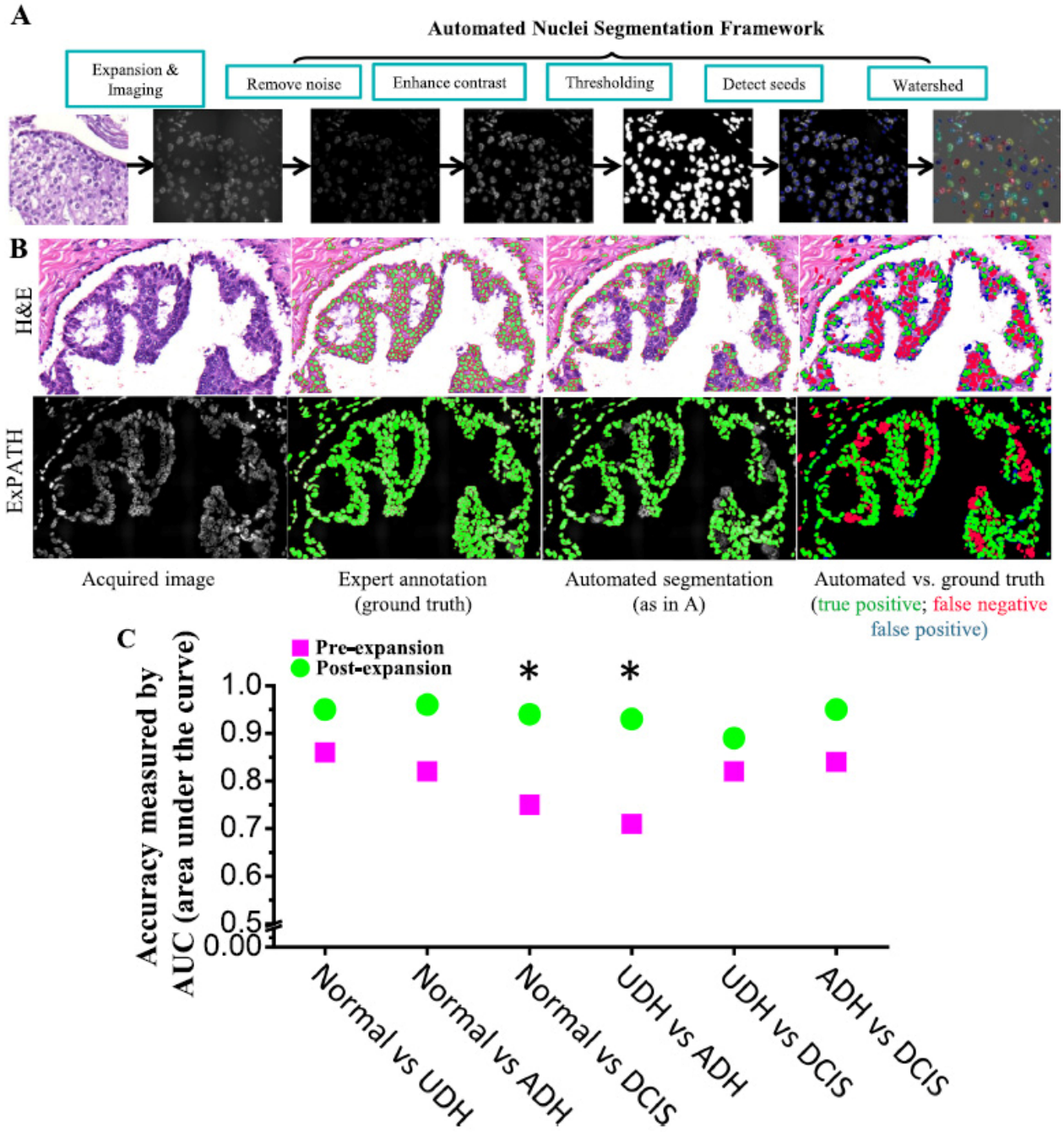


DAPI (blue), vimentin (green), KRT19 (red)

Skin,
Ovary,
Liver,
Kidney,
Colon,
…

Zhao*, Bucur*, Irshad, et al. (2017) *Nature Biotechnology*, 35(8):757-764.

Collaborators: Astrid Weins, Stuart Schnitt, Andrew Beck

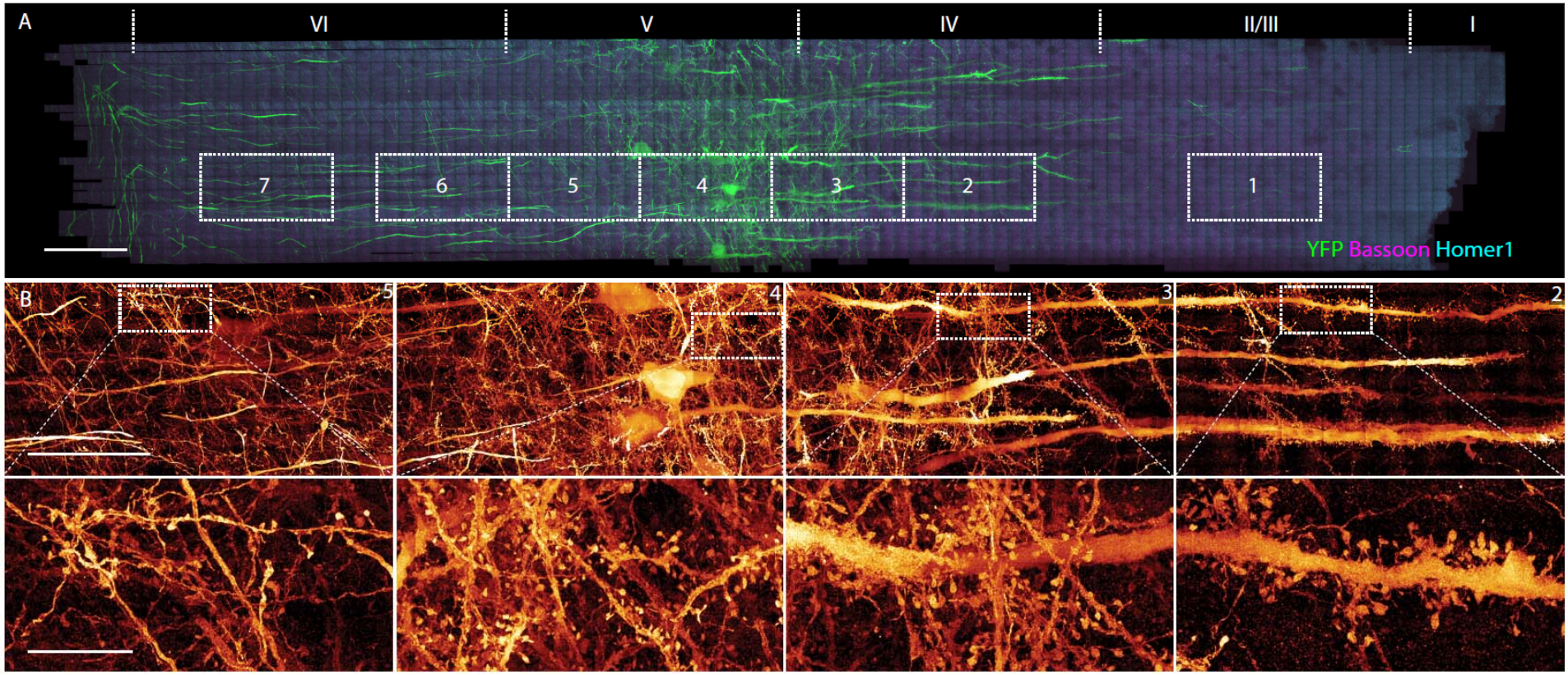


DAPI (gray)

Zhao*, Bucur*, Irshad, et al. (2017) *Nature Biotechnology*, 35(8):757-764.

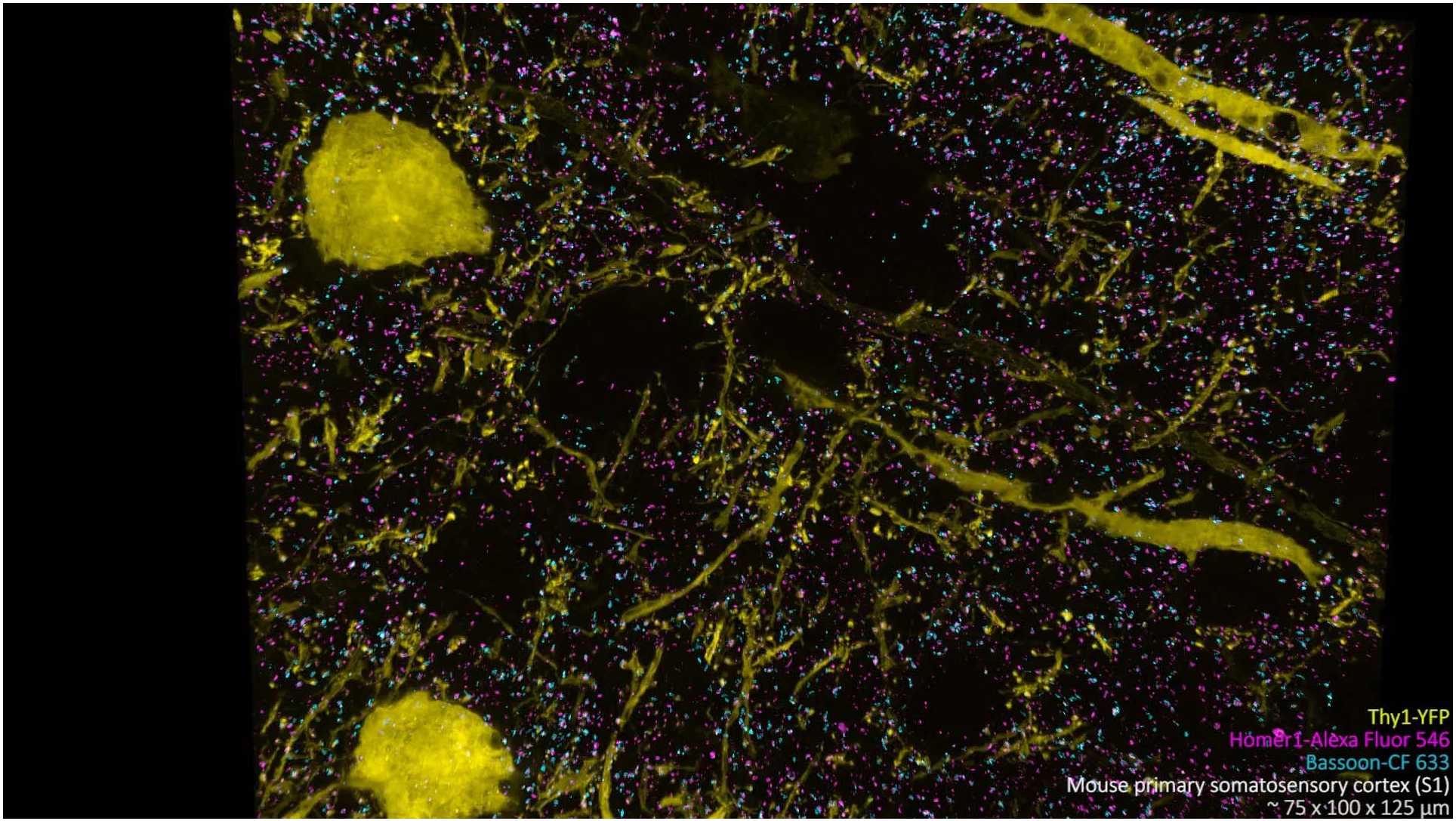
Collaborators: Astrid Weins, Stuart Schnitt, Andrew Beck

With lattice light sheet microscopy + expansion, can image 700x faster than classical super-resolution microscopy



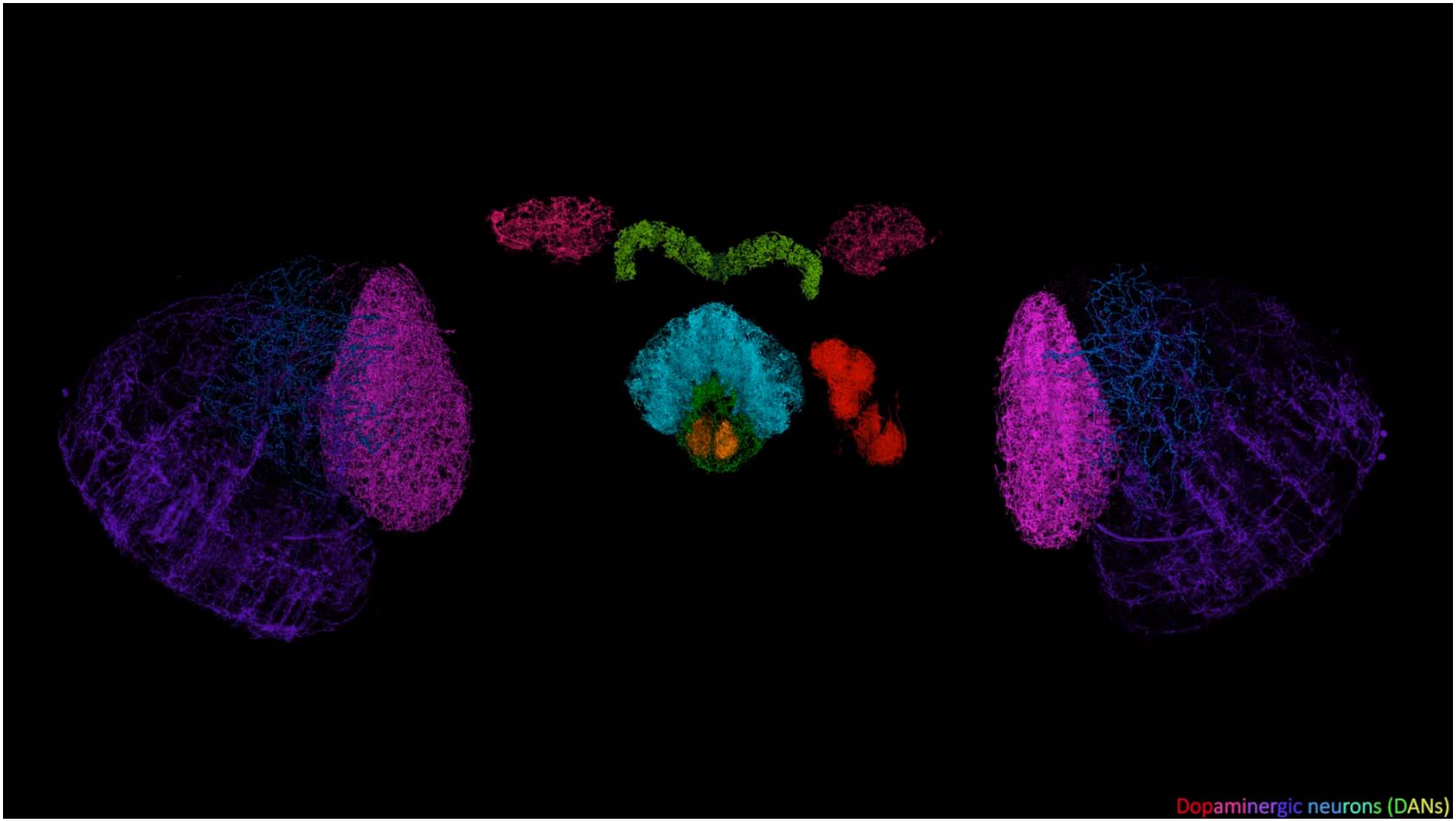
Rui Gao, Shoh Asano, Srigokul Upadhyayula

Collaborators: Eric Betzig, Jennifer Lippincott-Schwartz, Adam Hantman, Gerald M. Rubin, Tom Kirchhausen, Stephan Saalfeld, Sean Megason



Rui Gao, Shoh Asano, Srigokul Upadhyayula

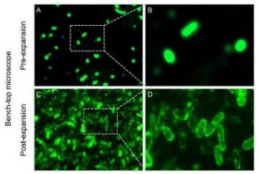
Collaborators: Eric Betzig, Jennifer Lippincott-Schwartz, Adam Hantman, Gerald M. Rubin, Tom Kirchhausen, Stephan Saalfeld, Sean Megason



Rui Gao, Shoh Asano, Srigokul Upadhyayula

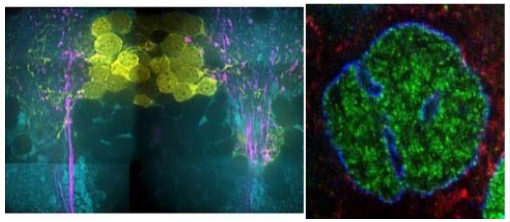
Collaborators: Eric Betzig, Jennifer Lippincott-Schwartz, Adam Hantman, Gerald M. Rubin, Tom Kirchhausen, Stephan Saalfeld, Sean Megason

E. coli



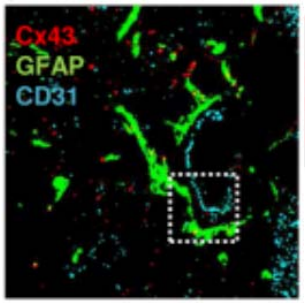
Zhang*, Chang* et al. (2016) Scientific Reports 6:22691.

Larval zebrafish



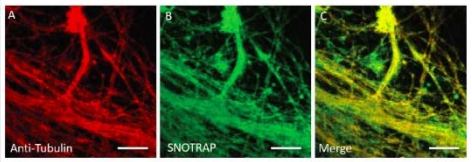
Freifeld et al. (2017) PNAS doi:10.1073/pnas.1706281114.

Human brain



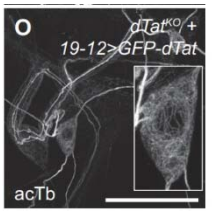
Deshpande et al. (2017) Glia 65(11):1809-1820.

Post-translational modifications



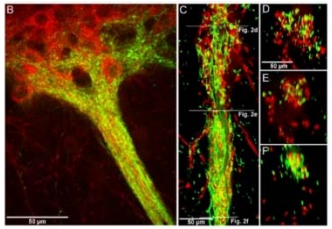
Tillberg*, Chen*, Piatkevich, Zhao, Yu et al. (2016) Nature Biotechnology 34:987–992.

Actin in peripheral nerves



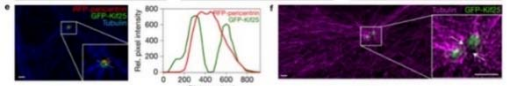
Yan et al. http://dx.doi.org/10.1101/252601

Mouse striatal circuits



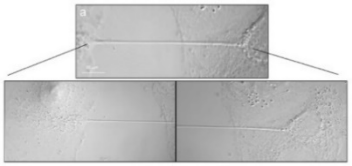
Crittenden et al. (2016) PNAS, 113(40):11318–11323.

Kinesins/cytoskeleton in cells



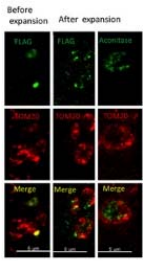
Decarreau et al. (2017) Nature Cell Biology 19:384–390.

Cellular nanotubes



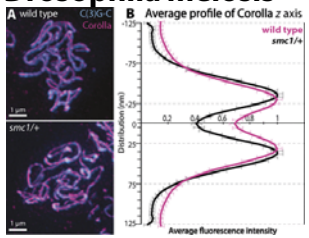
Kumar et al. (2017) Scientific Reports 7:40360.

Mitochondria



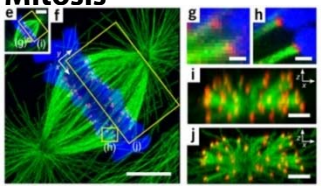
Suofu et al. (2017) PNAS 114(38):E7997-E8006.

Drosophila meiosis



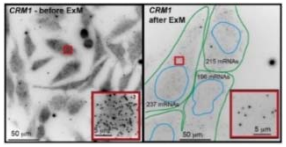
Cahoon et al. (2017) PNAS 114(33):E6857–E6866

Mitosis



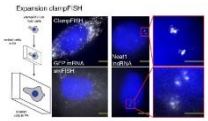
Chozinski et al. (2016) Nature Methods 13:485-8.

FISH



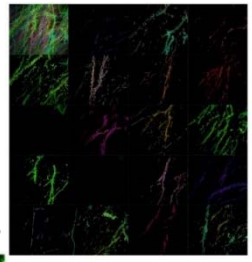
Tsanov et al. (2016) Nucleic Acids Research 44(22):e165.

Click-amplified FISH



https://www.biorxiv.org/content/early/2017/11/21/222794

Brainbow tracing

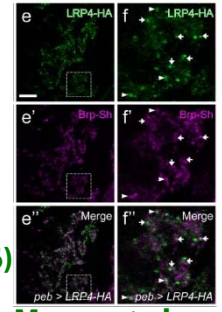


Sümbül et al. (2016) Advances in Neural Information Processing Systems, p. 1912-1920.

Mouse brain

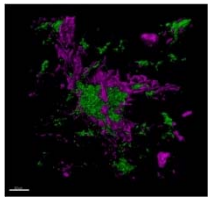
Ku et al. (2016) Nature Biotechnology 34:973-981.

Drosophila brain



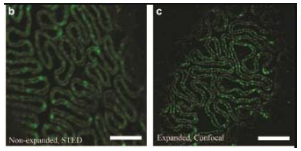
Mosca et al. (2017) eLife 6:e27347.

Planaria



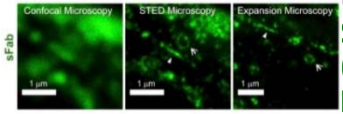
Wang et al. (2016) Elife 5:e16996.

Kidney stained with anti-podocin



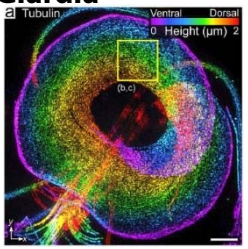
Unnersjö-Jess et al. (2017) Kidney International http://dx.doi.org/10.1016/j.kint.2017.09.019

Tubules mediating transcytosis across BBB



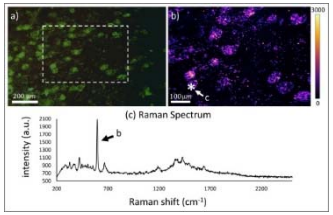
Villasenor et al. (2017) Cell Reports 21(11):3256-3270.

Giardia



Halpern et al. (2017) ACS Nano, DOI:10.1021/acsnano.7b07200

Surface-enhanced Raman imaging of expanded samples



Artur et al. (2018) Biomedical Optics Express 9(2):603-15.

Technologies for understanding the brain

Map the molecules, wiring, and connections

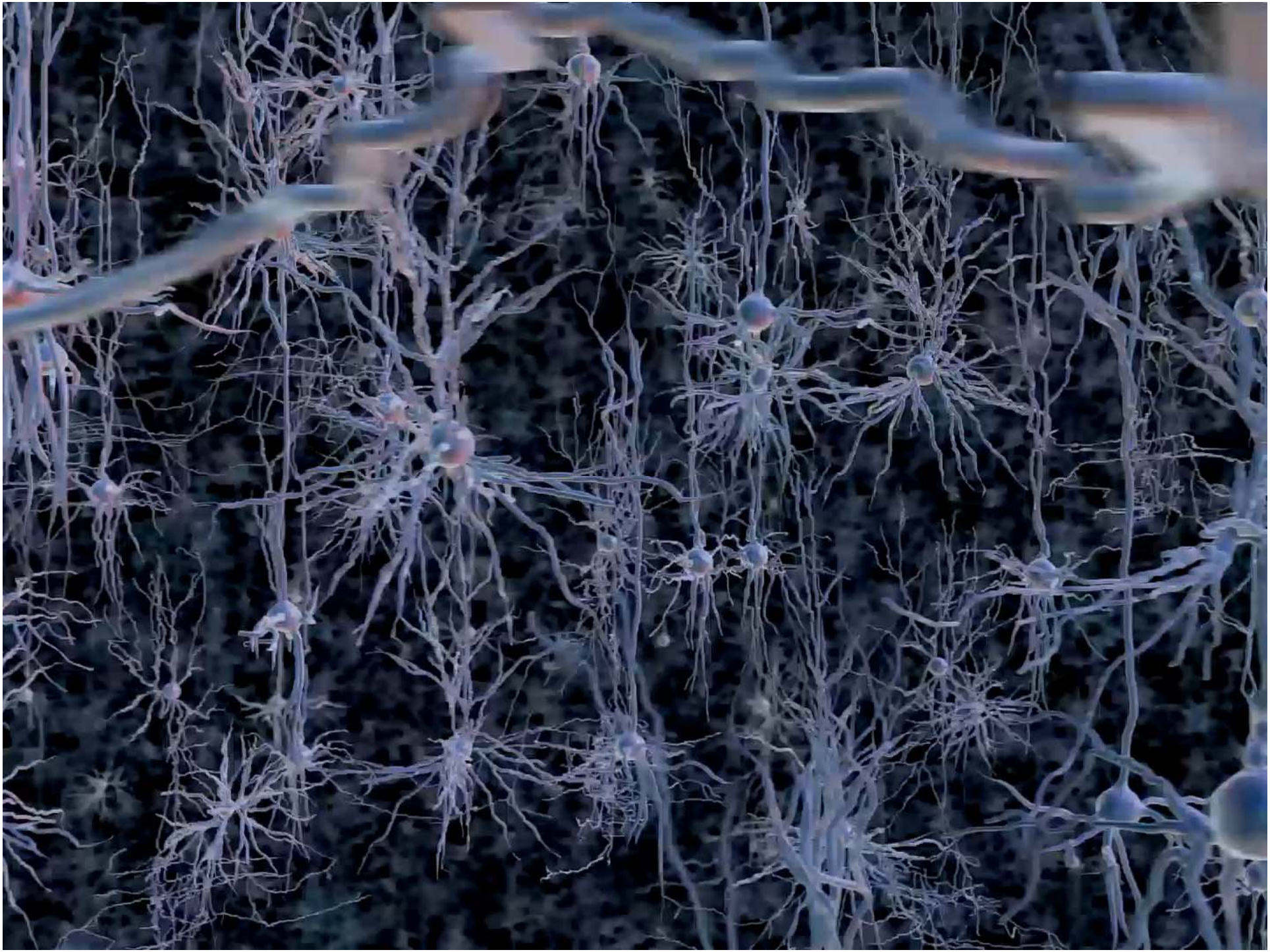
Expansion microscopy

Control the high-speed dynamics

Optogenetics

Observe the high-speed dynamics

Tools for fluorescent imaging of dynamics



Technologies for understanding the brain

Map the molecules, wiring, and connections

Expansion microscopy

Control the high-speed dynamics

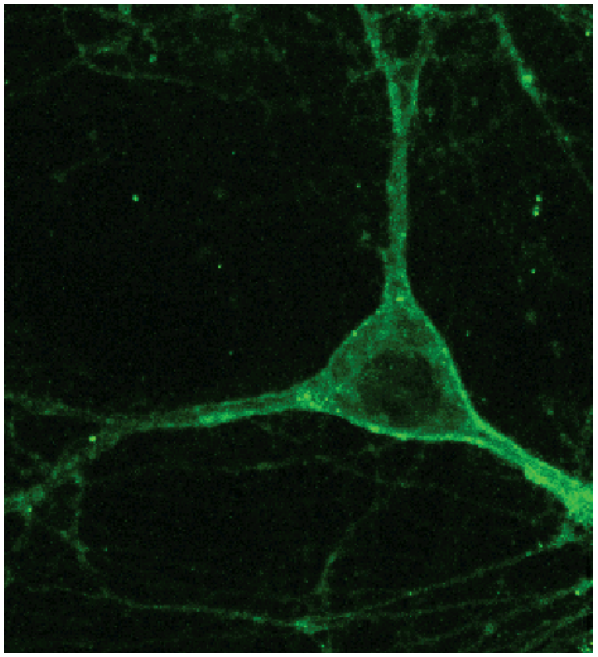
Optogenetics

Observe the high-speed dynamics

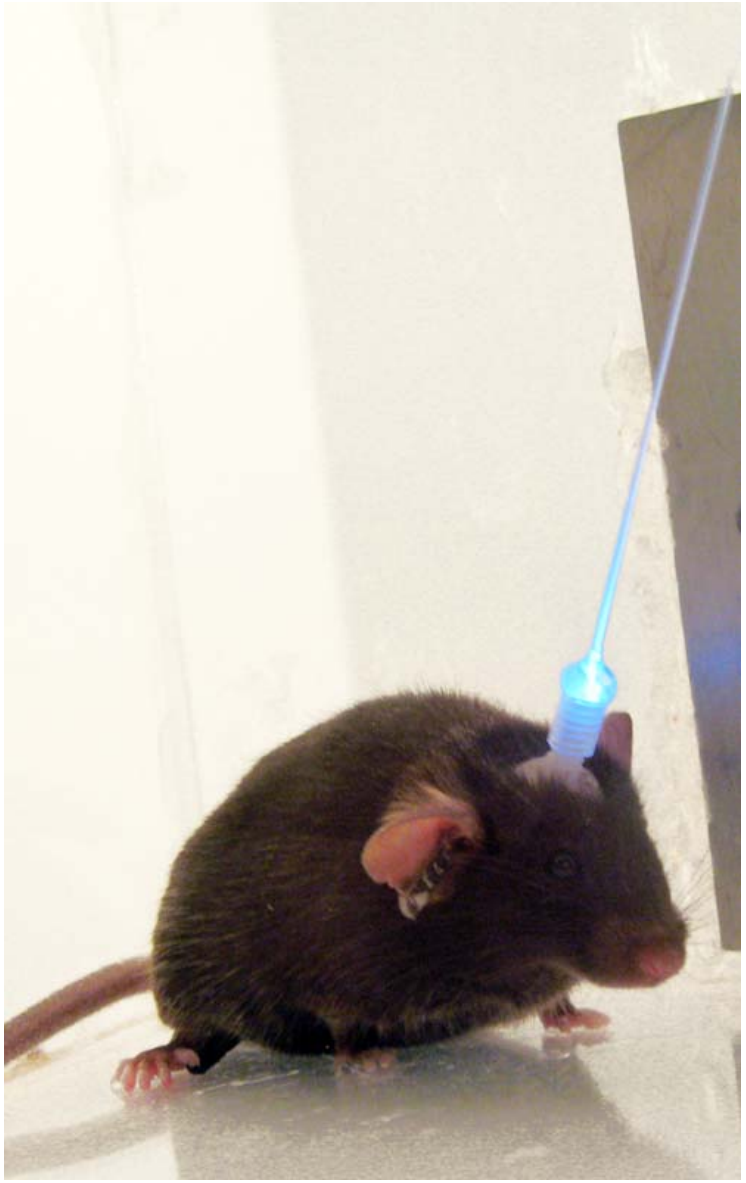
Tools for fluorescent imaging of dynamics

install

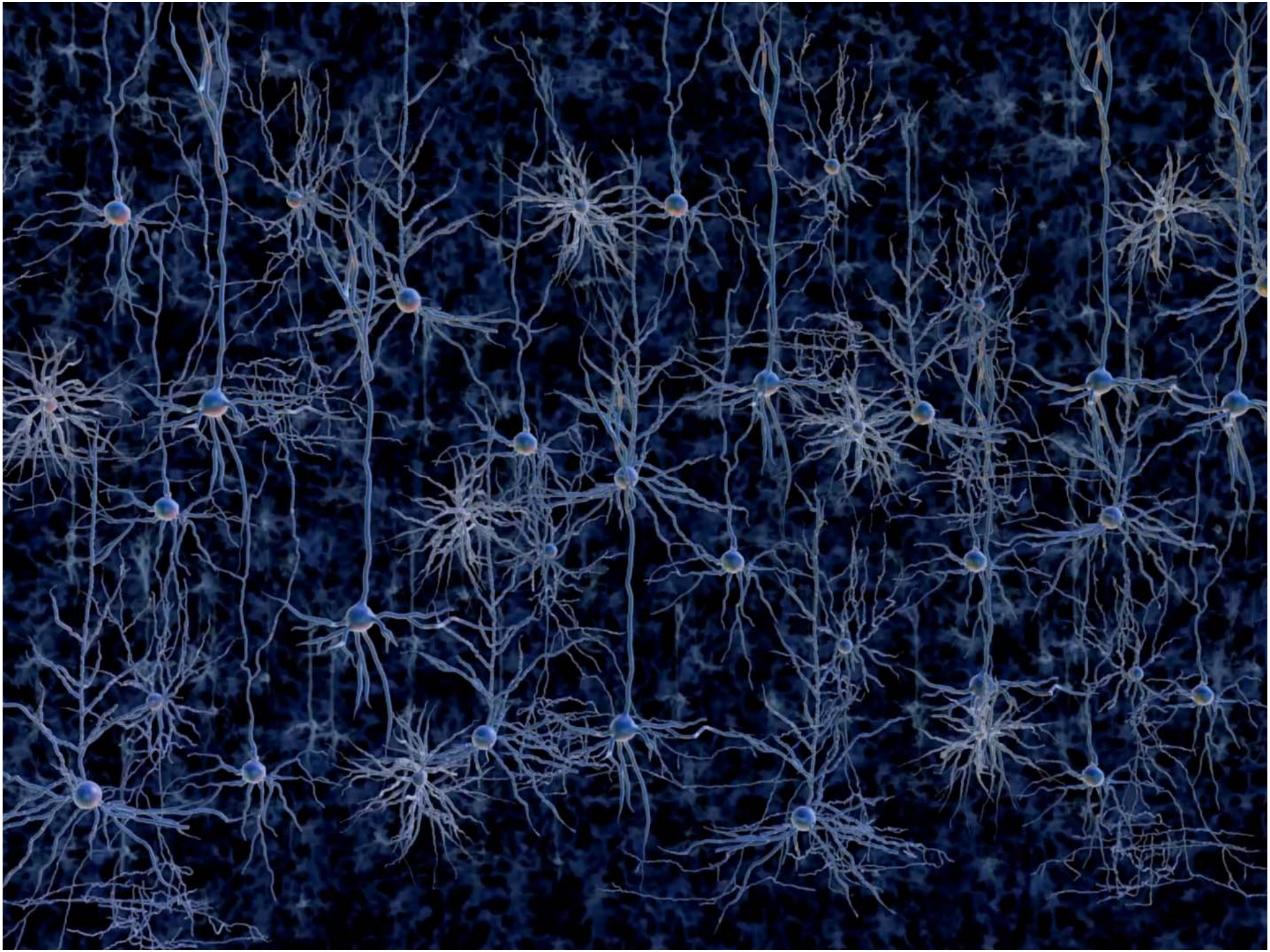
in

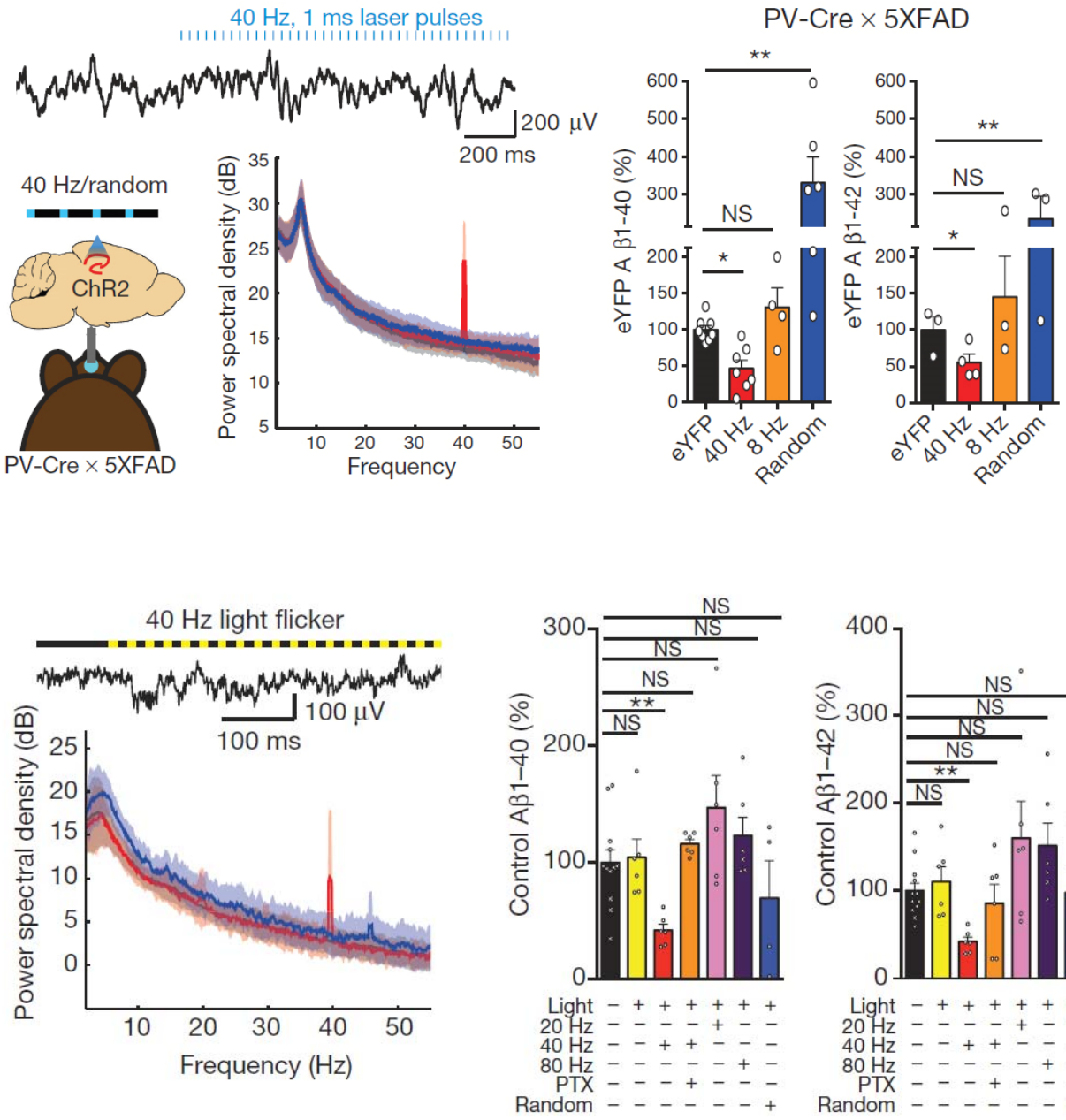


deliver light
via



Boyden (2011) *Faculty of 1000 Biology Reports* 3:11.
Resources at: http://syntheticneurobiology.org/protocols
ESB is inventor on related patents.



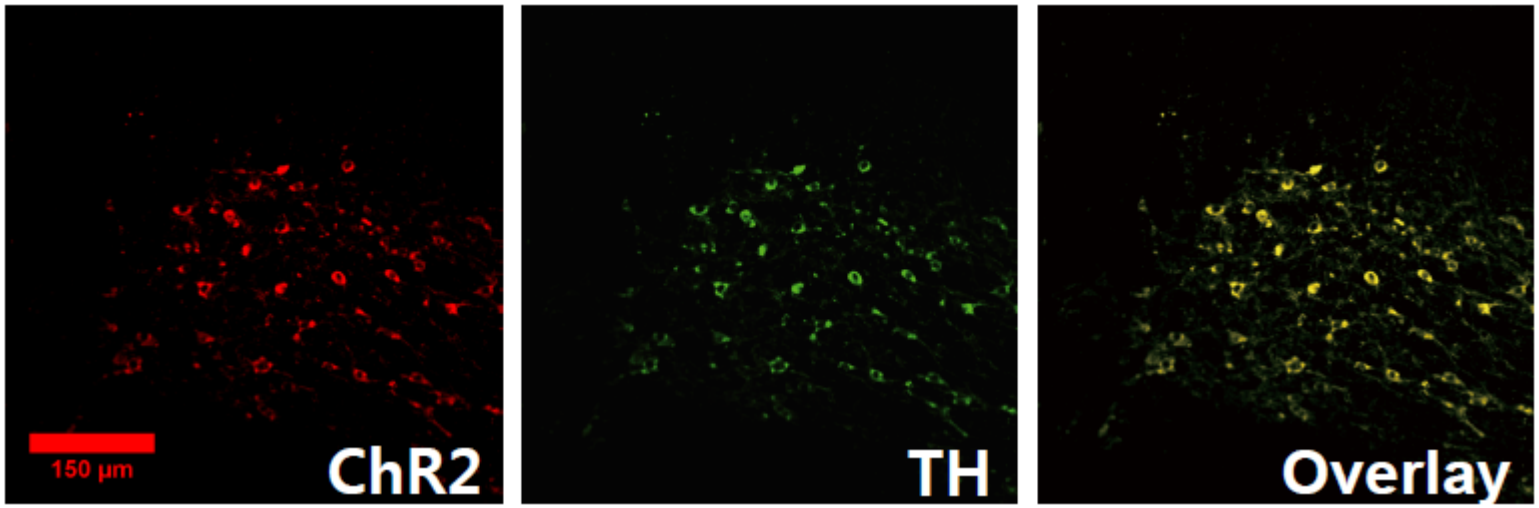


Iaccarino*, Singer*, et al. (2016) *Nature* 540(7632):230-235.

Commercialized by Cognito Therapeutics, Inc. (http://cognitotx.com); ESB is co-founder.

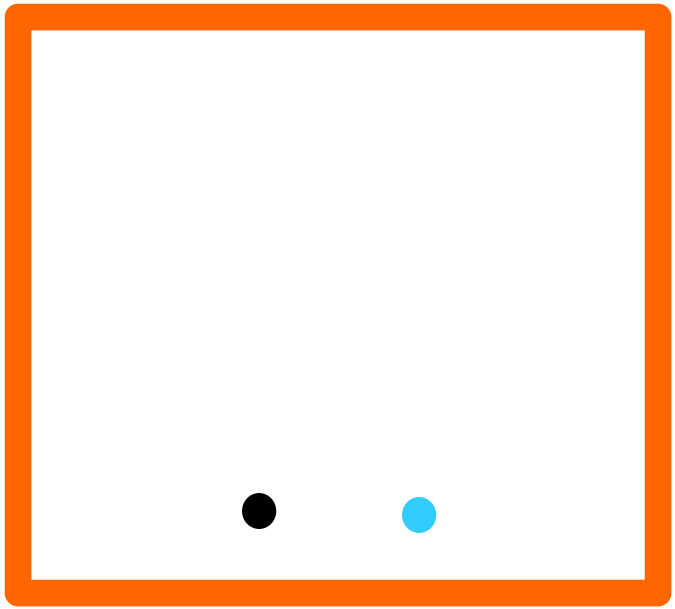
Lab of Li-Huei Tsai

Making dopamine neurons sensitive to light



Kim et al. (2012) *PLoS One* 7(4):e33612

What do dopamine neurons do?

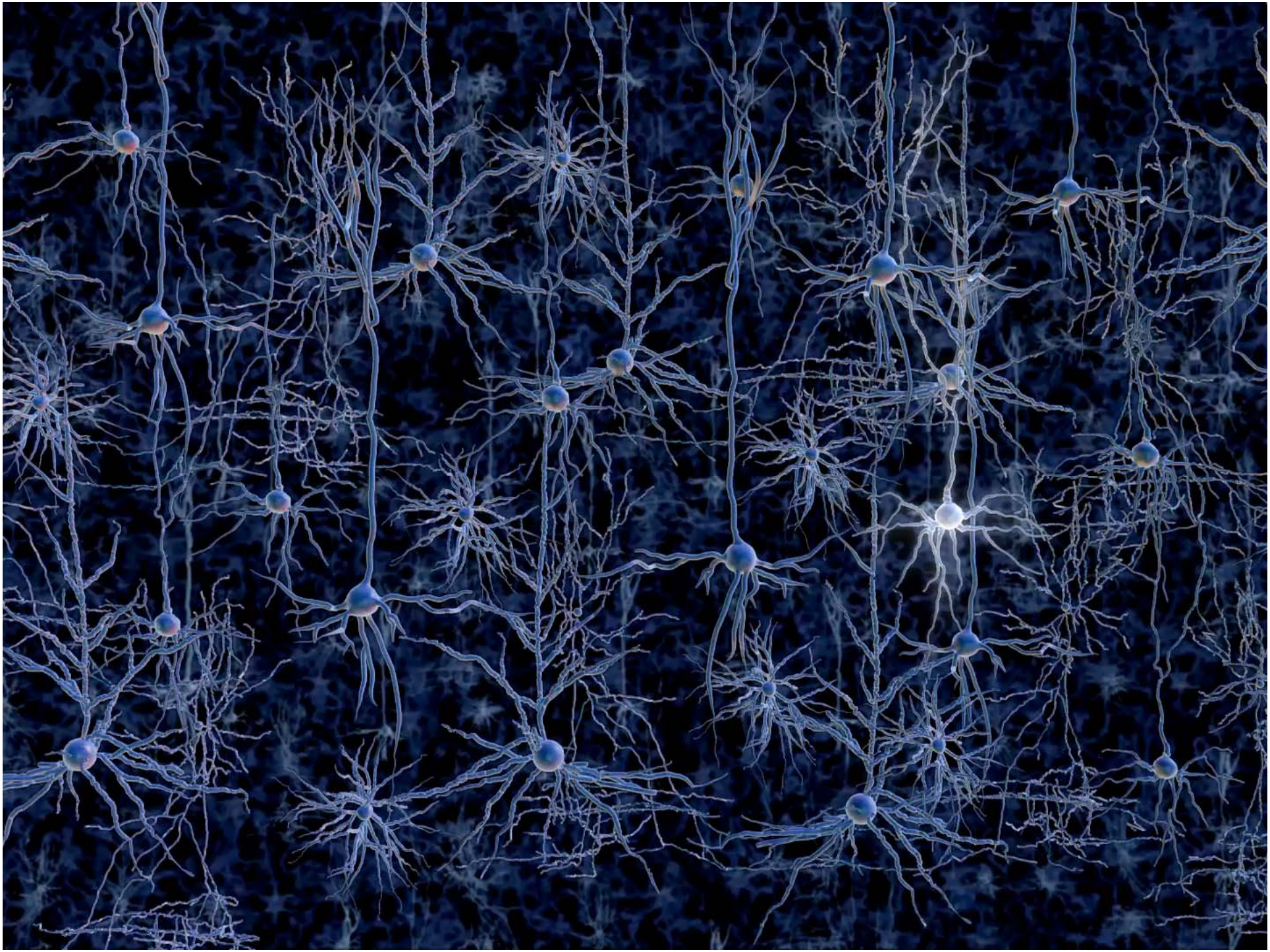


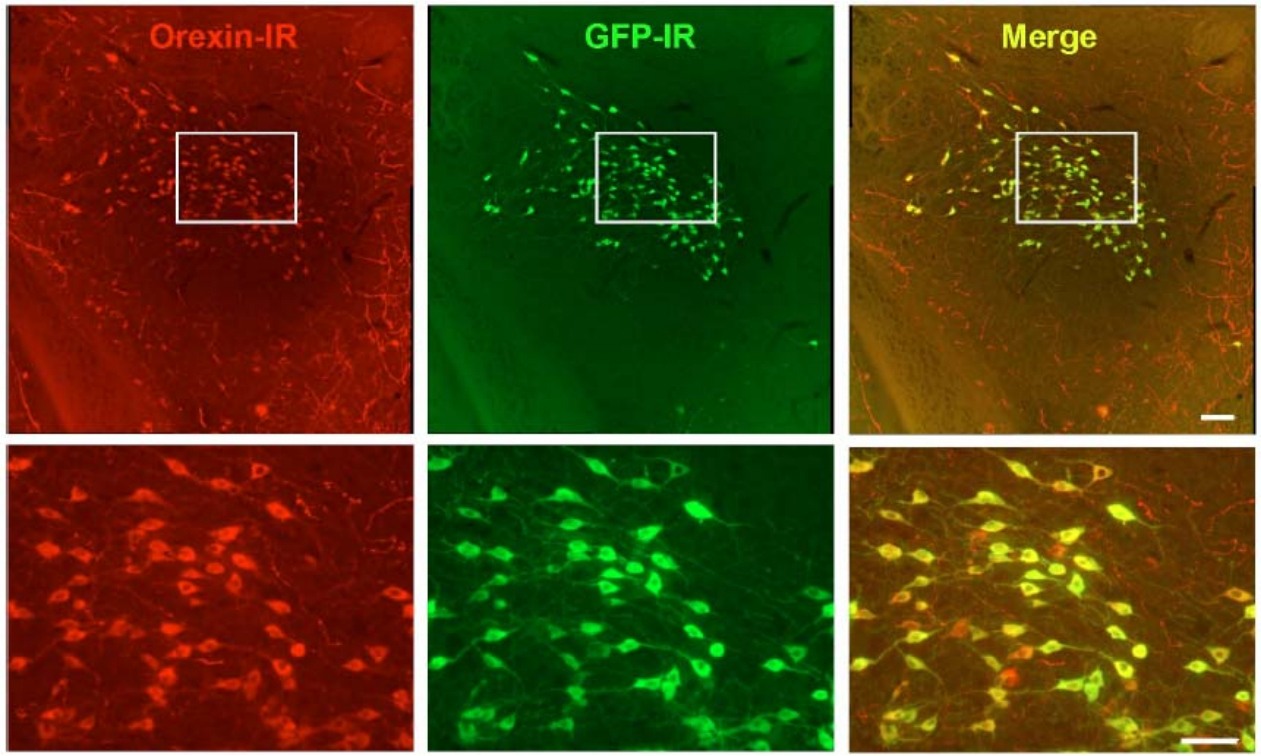
no light stimulation

light stimulation

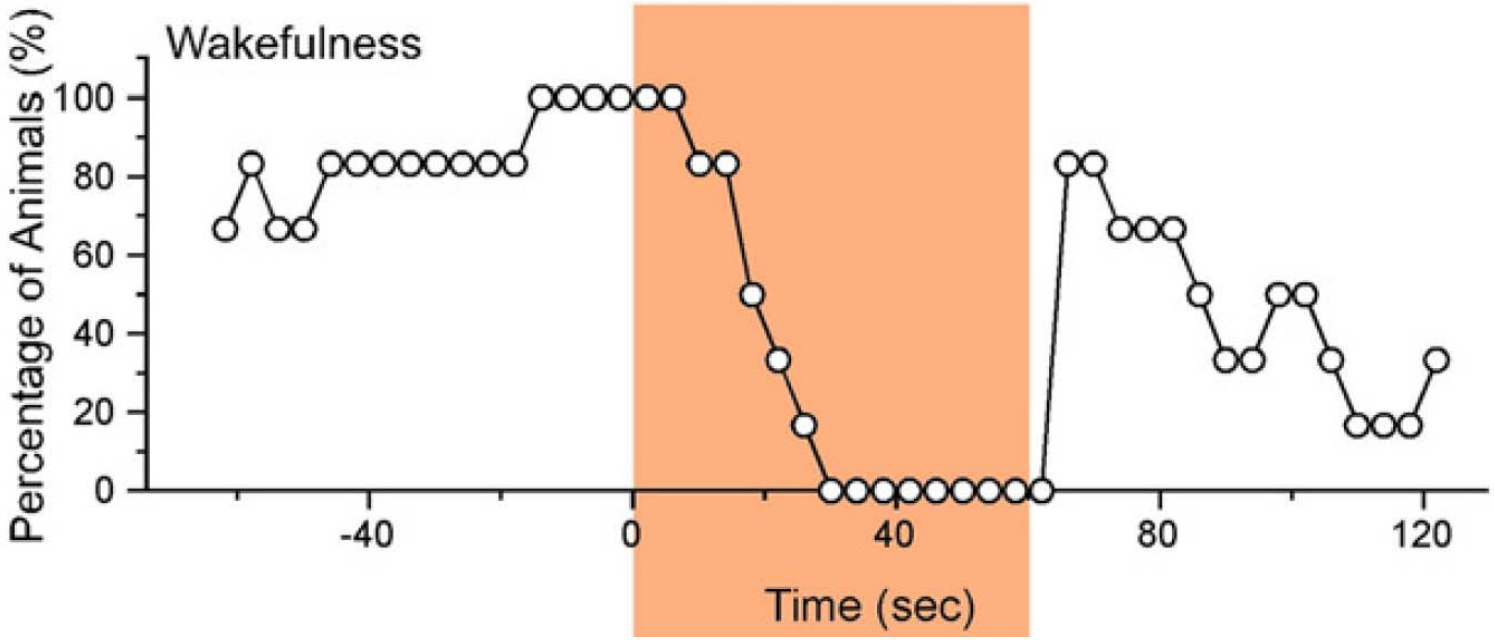
Kim et al. (2012) *PLoS One* 7(4):e33612

Kim et al. (2012) *PLoS One* 7(4):e33612





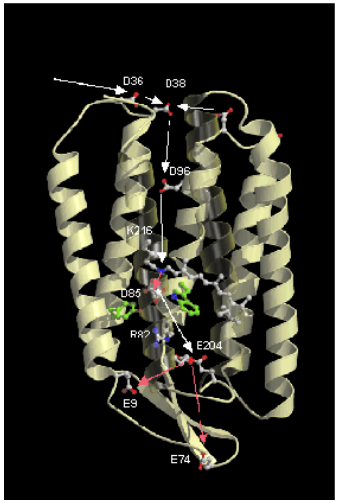
Tsunematsu et al. (2011) *Journal of Neuroscience* 31(29): 10529-10539.



Tsunematsu et al. (2011) *Journal of Neuroscience* 31(29): 10529-10539.

Bacteriorhodopsins: Light-driven proton pumps

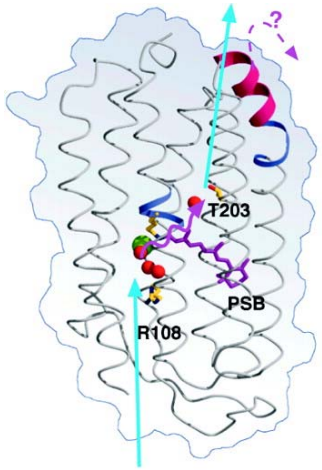
http://www.genome.duke.edu/genomelife/2011/03/systems-under-stress/



http://www.biochem.mpg.de/523002/Protein_BR

D. Oesterhelt and W. Stoeckenius (1971) Rhodopsin-like Protein from the Purple Membrane of Halobacterium halobium. Nature New Biology 233:149-152.

Halorhodopsins: Light-driven chloride pumps



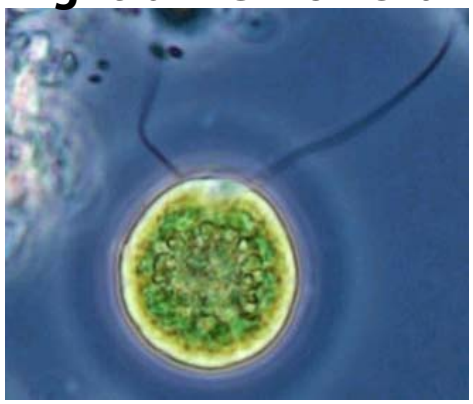
http://www.sciencemag.org/content/288/5470/1390.full

Matsuno-Yagi A, Mukohata Y (1977) Two possible roles of bacteriorhodopsin; a comparative study of strains of Halobacterium halobium differing in pigmentation. Biochem Biophys Res Commun 78:237-43.

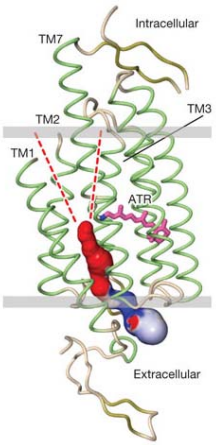
Matsuno-Yagi A, Mukohata Y (1980) ATP synthesis linked to lightdependent proton uptake in a rad mutant strain of Halobacterium lacking bacteriorhodopsin. Arch Biochem Biophys, 199:297-303.

Schobert B, Lanyi JK (1982) Halorhodopsin is a light-driven chloride pump. J Biol Chem, 257:10306-13.

Channelrhodopsins: Light-driven ion channels



http://starcentral.mbl.edu/microscope/portal.php?pagetitle=assetfactsheet&imageid=3245

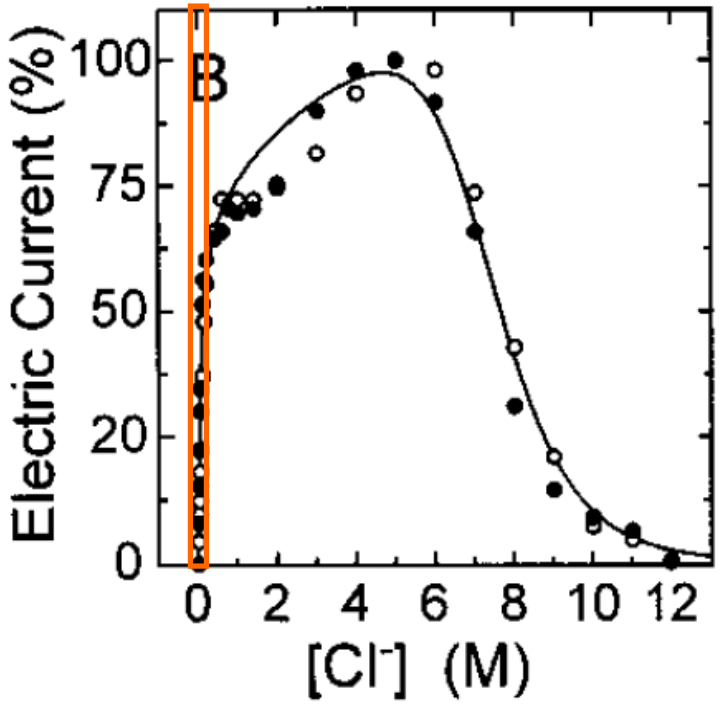


http://www.nature.com/nature/journal/v482/n7385/full/nature10870.html

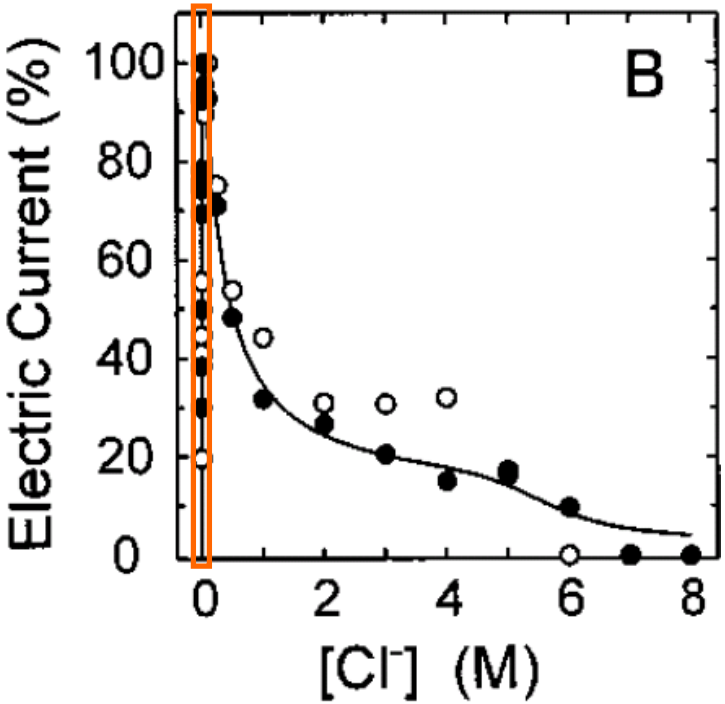
Nagel G, Ollig D, Fuhrmann M, Kateriya S, Musti AM, Bamberg E, Hegemann P (2002) Channelrhodopsin-1: a light-gated proton channel in green algae. Science, 296:2395-8.

Nagel G, Szellas T, Huhn W, Kateriya S, Adeishvili N, Berthold P, Ollig D, Hegemann P, Bamberg E (2003) Channelrhodopsin-2, a directly light-gated cation-selective membrane channel. Proc Natl Acad Sci U S A, 100:13940-5.

Opsins: found in halophiles, but sometimes work at neuronal salt levels



Halorhodopsin from *H. salinarum*

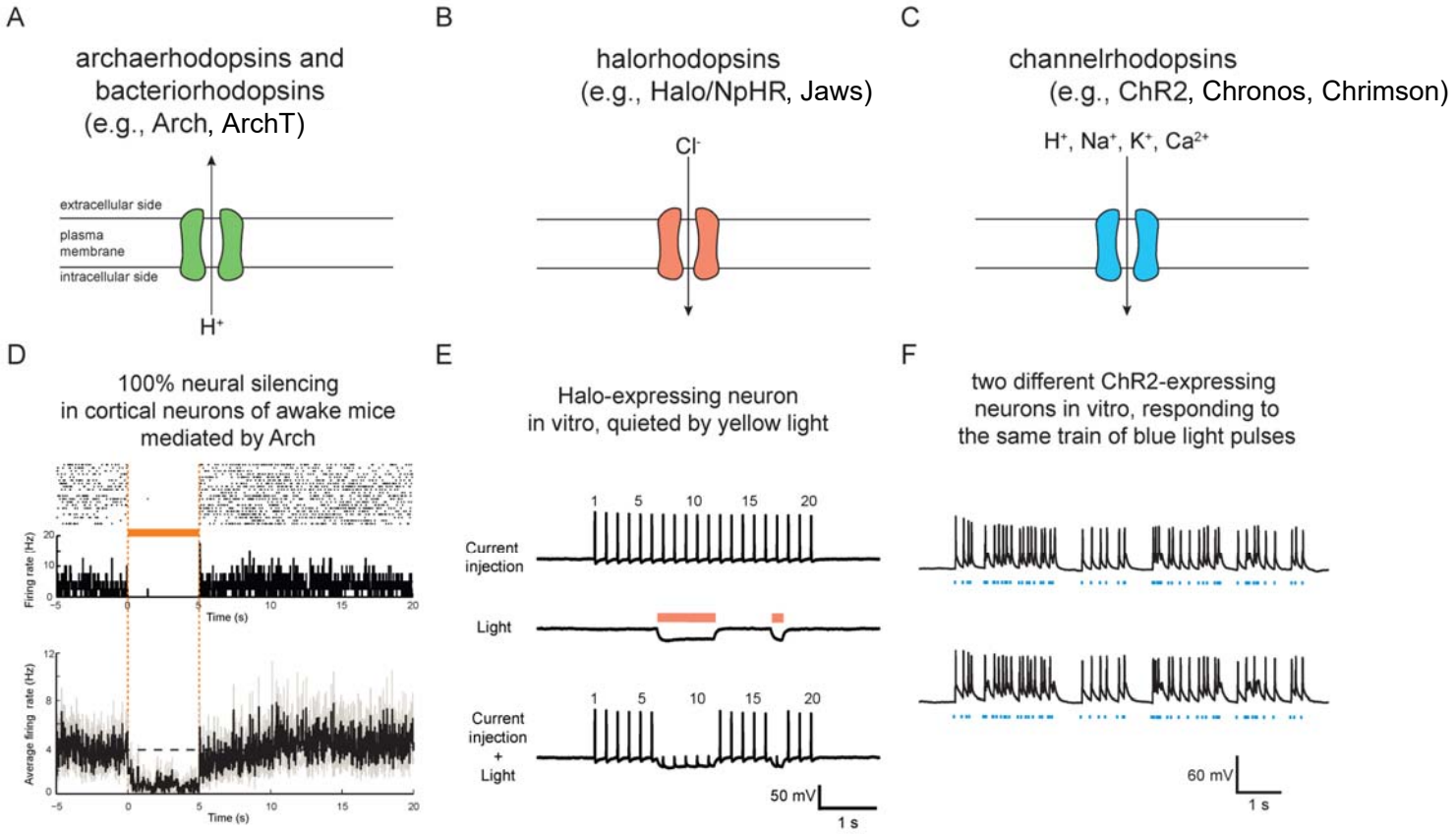


Halorhodopsin from *N. pharaonis*

Okuno D, Asaumi M, Muneyuki E (1999) Chloride concentration dependency of the electrogenic activity of halorhodopsin. Biochemistry 38:5422-29.

Boyden (2011) *Faculty of 1000 Biology Reports* 3:11.

Optogenetics: microbial opsins, seven-transmembrane proteins, binding endogenous all-trans-retinal



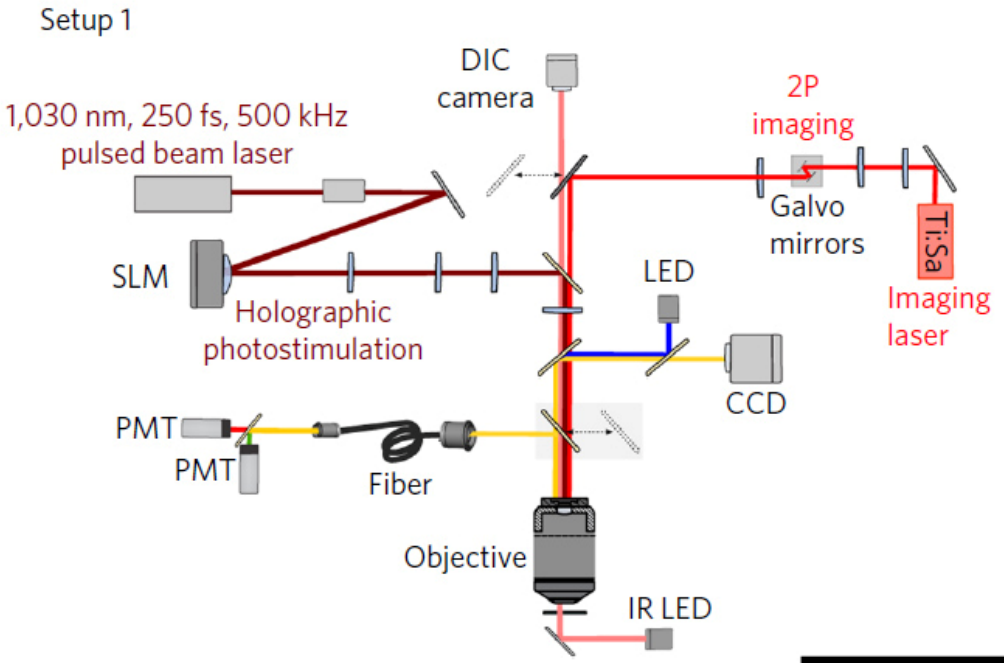
Chow*, Han* et al. (2010) *Nature* 463:98-102; Han*, Chow* et al. (2011) *Frontiers in Systems Neuroscience* 5:18.

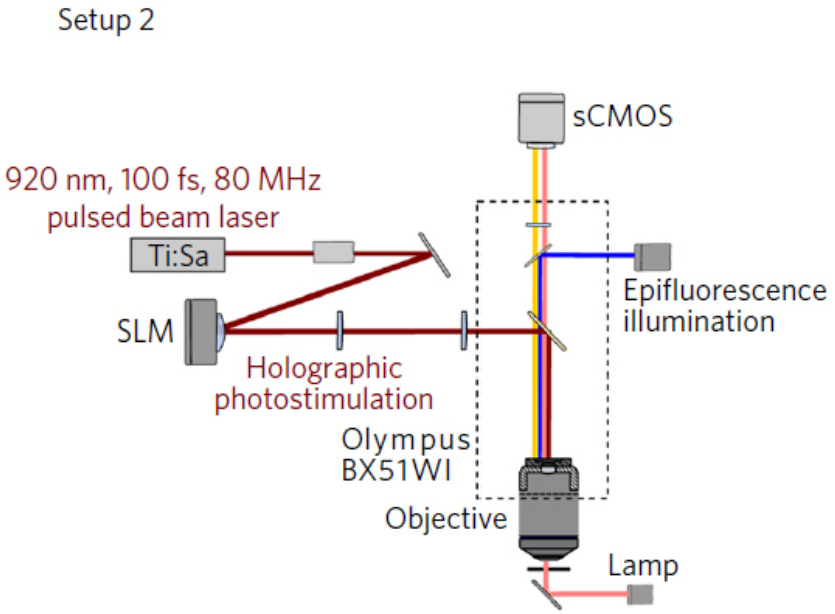
Han and Boyden (2007) *PLoS ONE* 2(3): p. e299; Chuong et al. (2014) *Nature Neuroscience* 17:1123-1129.

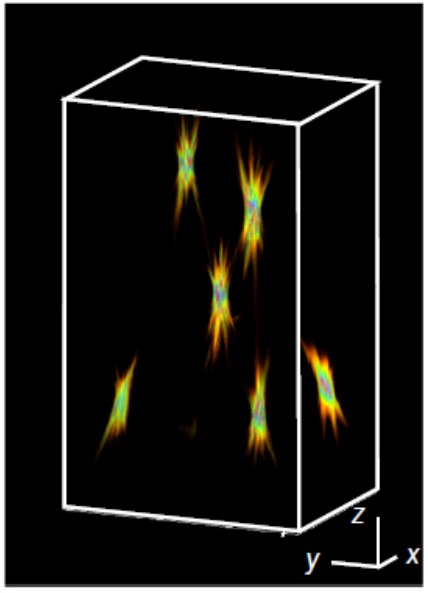
Boyden et al. (2005) *Nature Neuroscience* 8(9):1263-1268; Klapoetke et al. (2014) *Nature Methods* 11:338–346.

Boyden (2011) *Faculty of 1000 Biology Reports* 3:11.

Sequences, plasmids, links to DNA/virus providers, at http://syntheticneurobiology.org/protocols



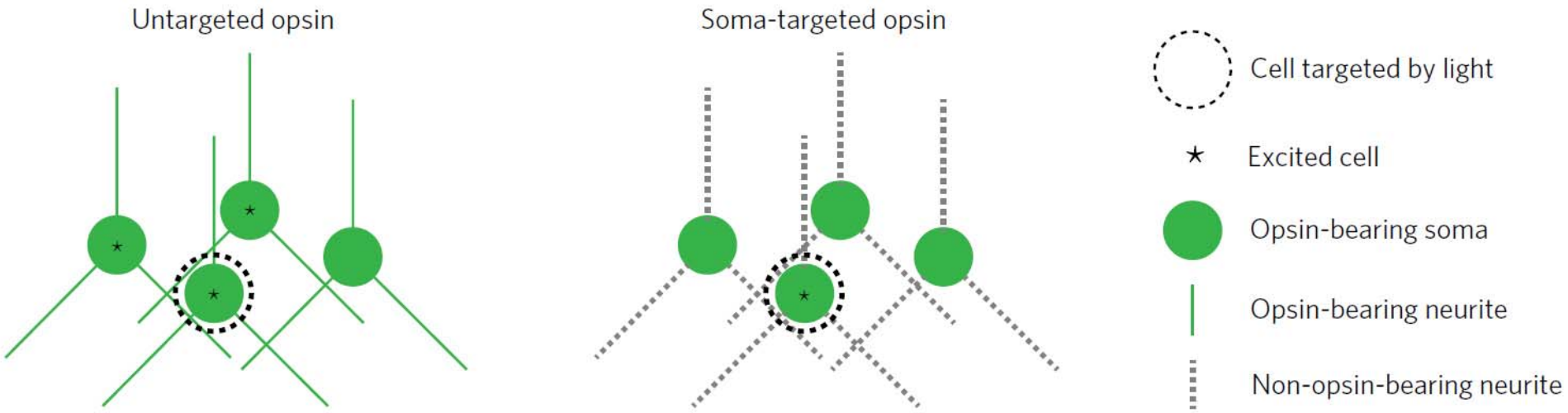




Or A. Shemesh*, Dimitrii Tanese*, Valeria Zampini*, et al., *Nature Neuroscience* 20:1796–1806.

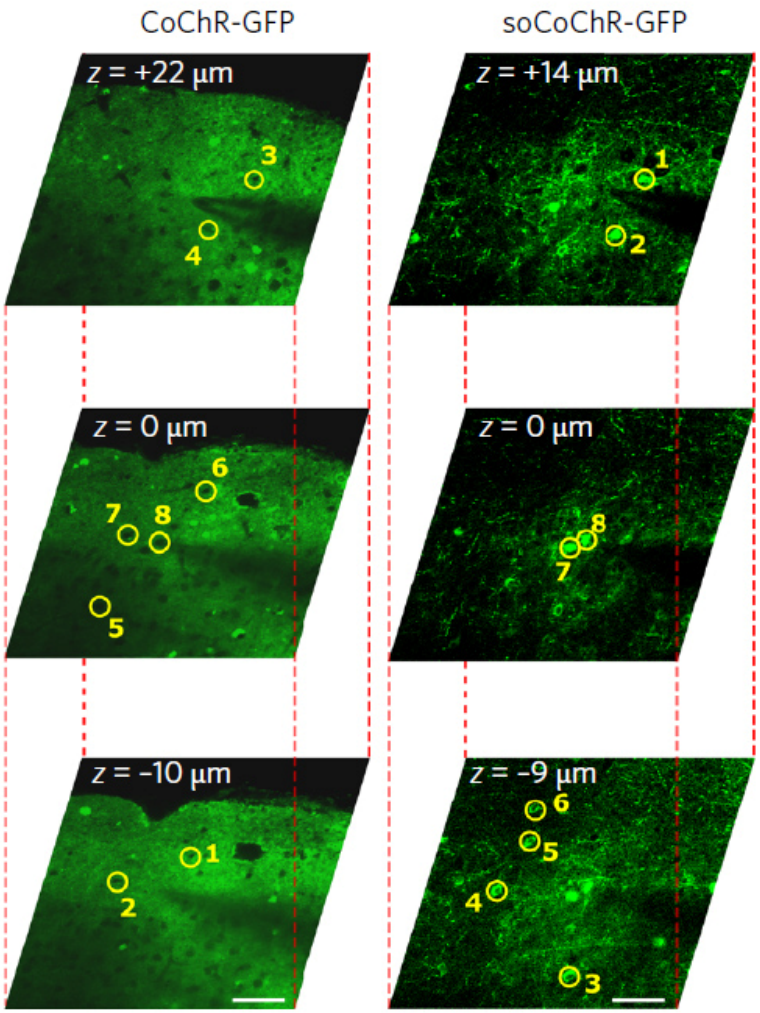
Collaboration with Valentina Emiliani

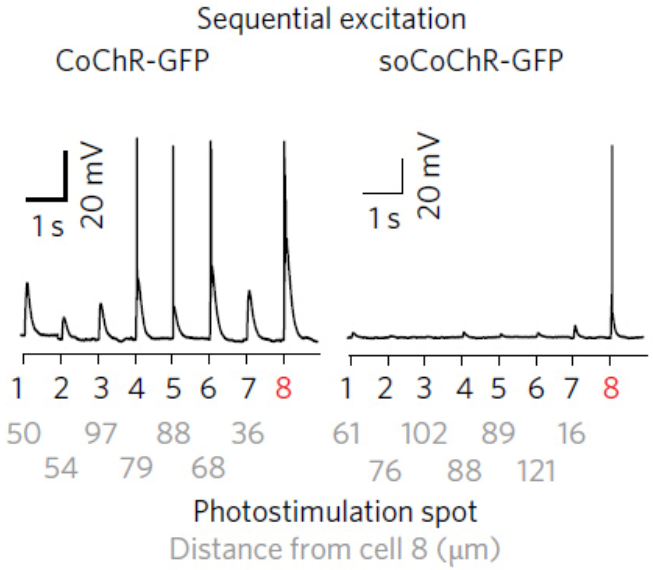
Soma-targeting of opsins

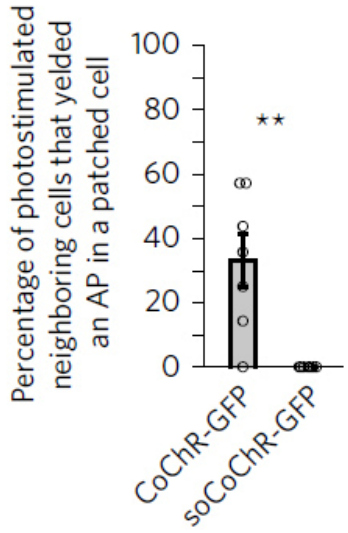


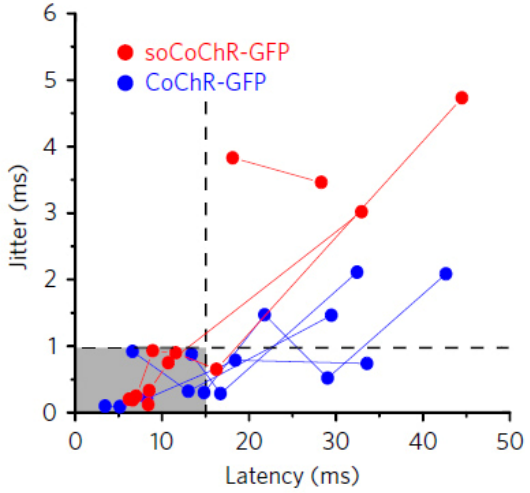
Or A. Shemesh*, Dimitrii Tanese*, Valeria Zampini*, et al., *Nature Neuroscience* 20:1796–1806.

Collaboration with Valentina Emiliani









Or A. Shemesh*, Dimitrii Tanese*, Valeria Zampini*, et al., *Nature Neuroscience* 20:1796–1806.

Collaboration with Valentina Emiliani

Technologies for understanding the brain

Map the molecules, wiring, and connections

Expansion microscopy

Control the high-speed dynamics

Optogenetics

Observe the high-speed dynamics

Tools for fluorescent imaging of dynamics

Technologies for understanding the brain

Map the molecules, wiring, and connections

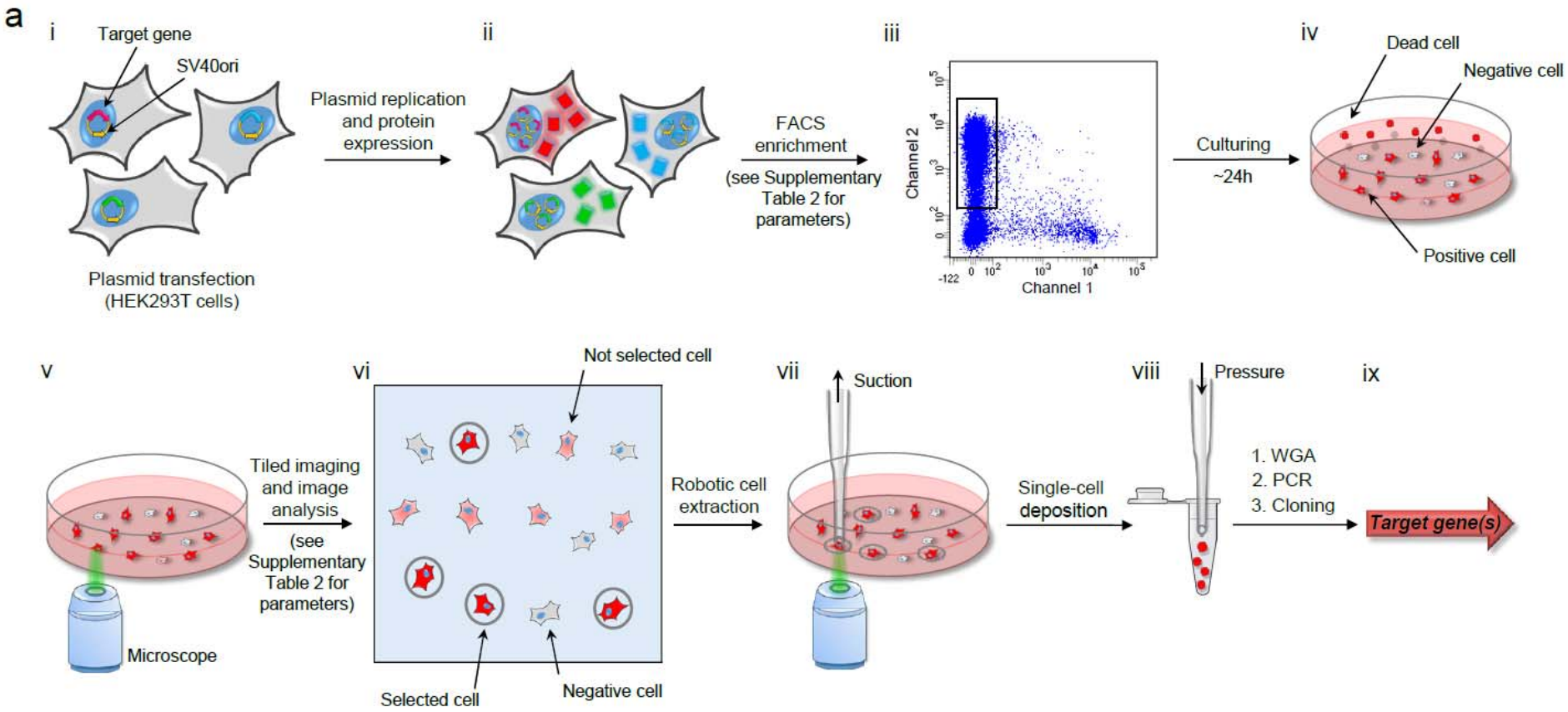
Expansion microscopy

Control the high-speed dynamics

Optogenetics

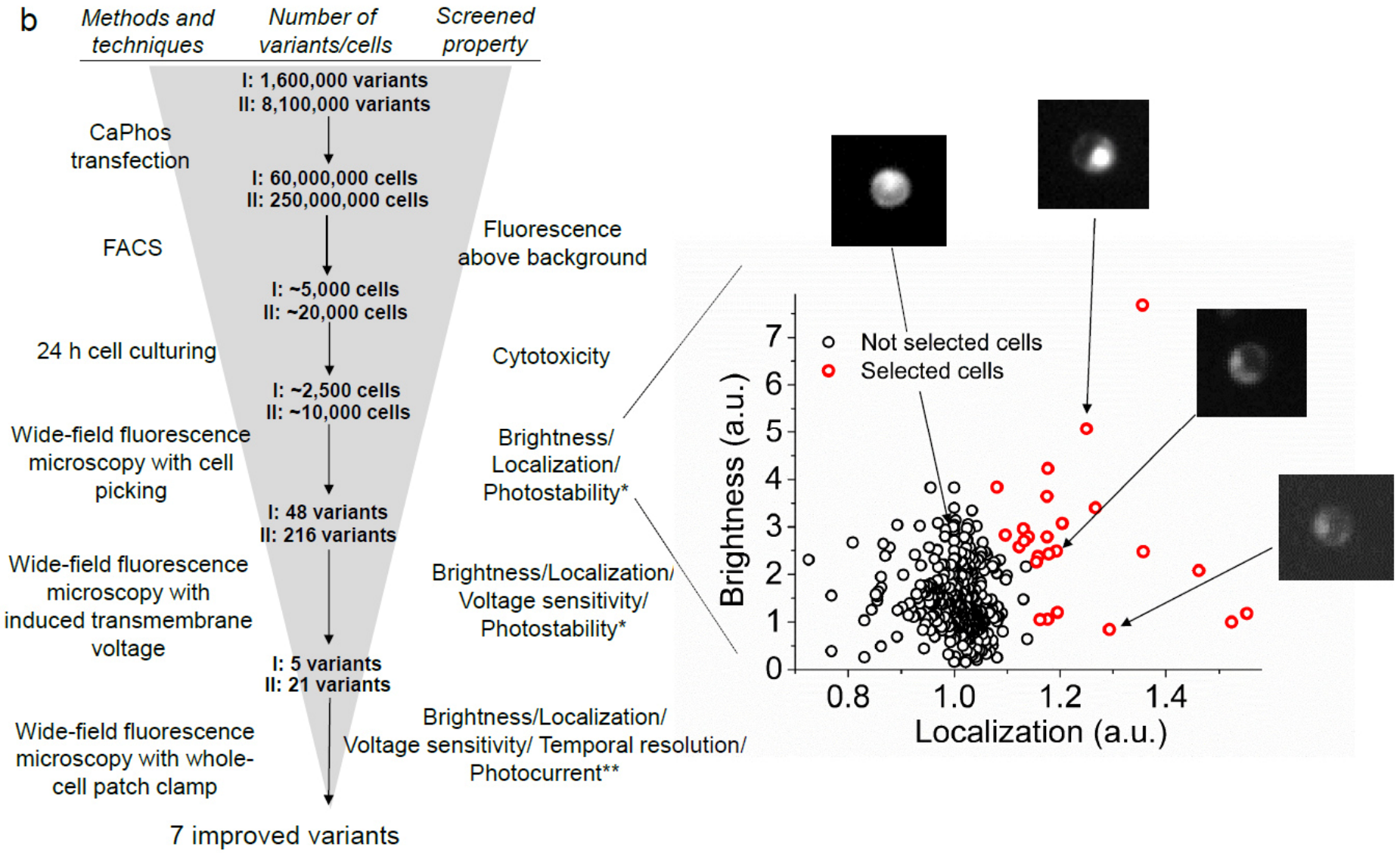
Observe the high-speed dynamics

Tools for fluorescent imaging of dynamics



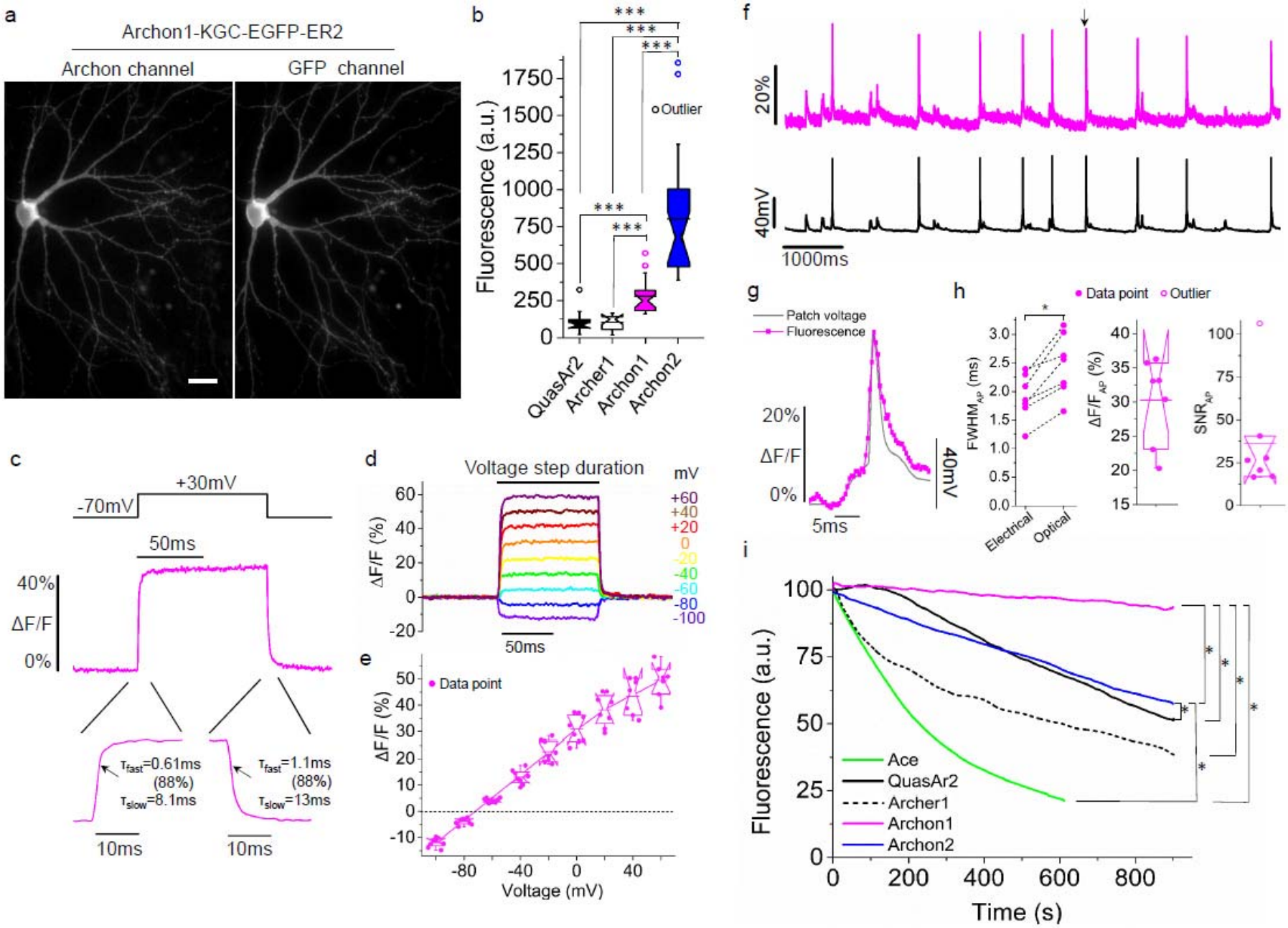
Piatkevich*, Jung*, et al. (2018) *Nature Chemical Biology*, doi:10.1038/s41589-018-0004-9.

Collaborators: Florian Engert, Thom Hughes, Mikhail Drobizhev, Balint Szabo, Misha Ahrens, Steven Flavell, Bernardo Sabatini



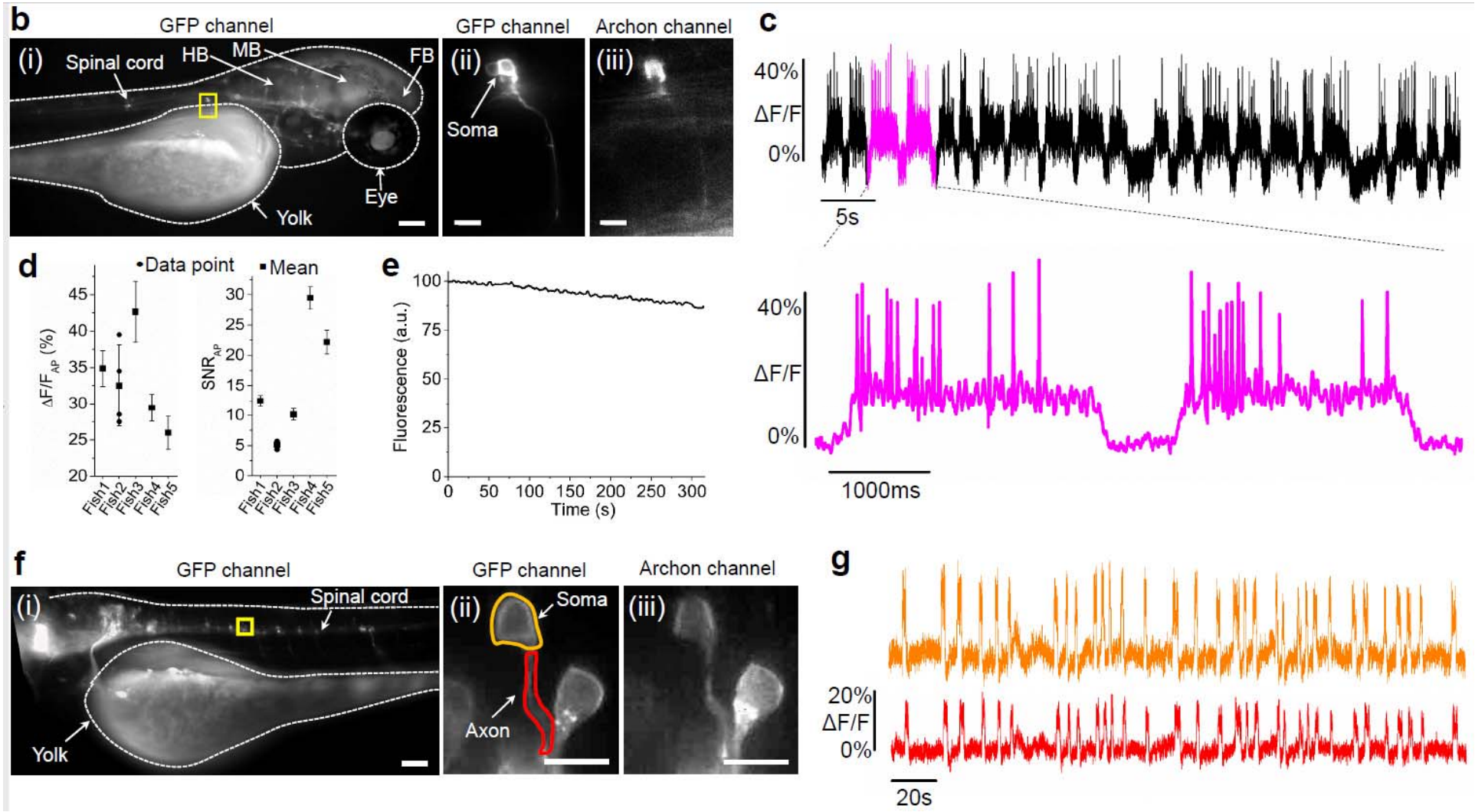
Piatkevich*, Jung*, et al. (2018) *Nature Chemical Biology*, doi:10.1038/s41589-018-0004-9.

Collaborators: Florian Engert, Thom Hughes, Mikhail Drobizhev, Balint Szabo, Misha Ahrens, Steven Flavell, Bernardo Sabatini



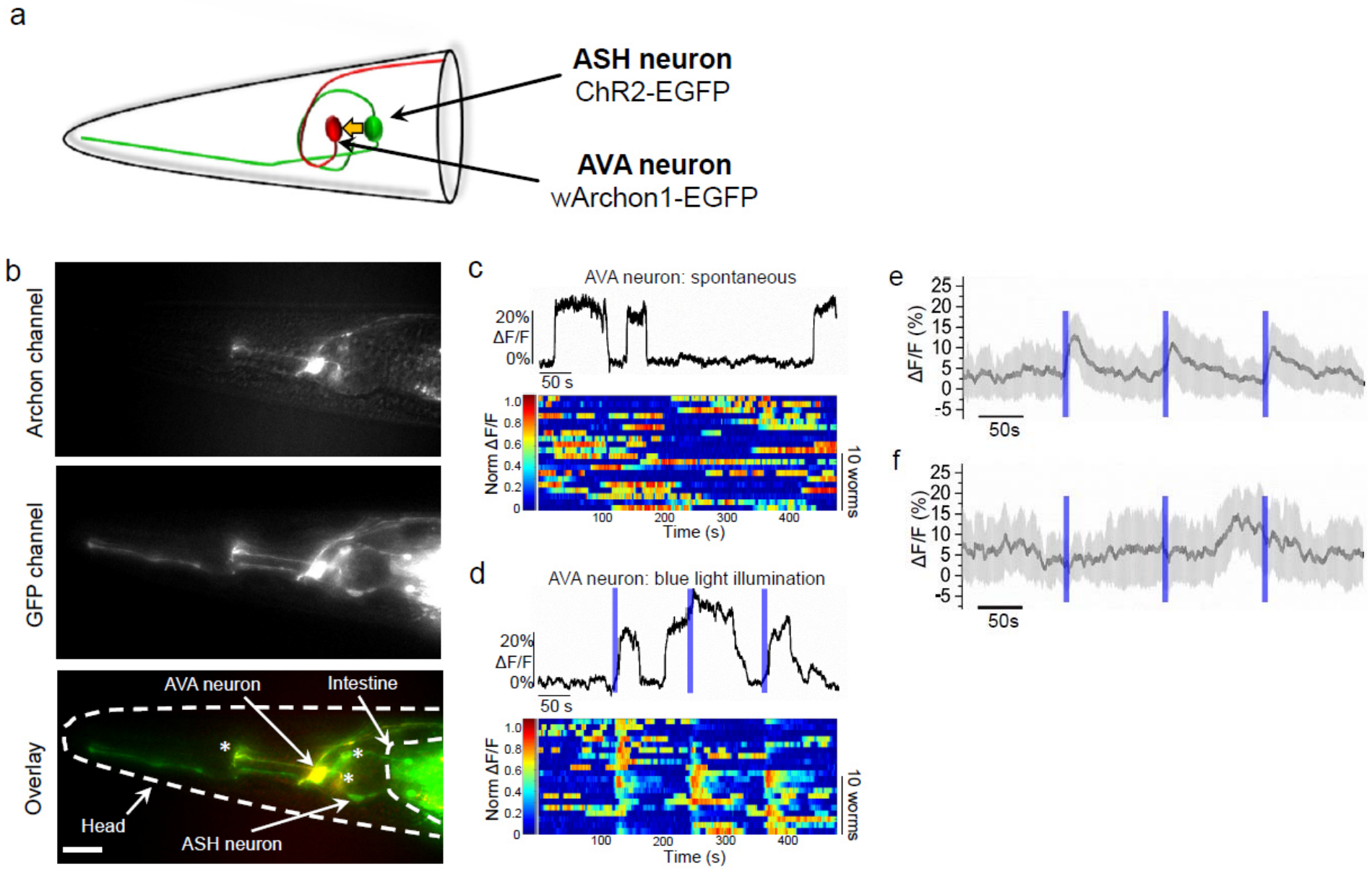
Piatkevich*, Jung*, et al. (2018) *Nature Chemical Biology*, doi:10.1038/s41589-018-0004-9.

Collaborators: Florian Engert, Thom Hughes, Mikhail Drobizhev, Balint Szabo, Misha Ahrens, Steven Flavell, Bernardo Sabatini



Piatkevich*, Jung*, et al. (2018) *Nature Chemical Biology*, doi:10.1038/s41589-018-0004-9.

Collaborators: Florian Engert, Thom Hughes, Mikhail Drobizhev, Balint Szabo, Misha Ahrens, Steven Flavell, Bernardo Sabatini



Piatkevich*, Jung*, et al. (2018) *Nature Chemical Biology*, doi:10.1038/s41589-018-0004-9.

Collaborators: Florian Engert, Thom Hughes, Mikhail Drobizhev, Balint Szabo, Misha Ahrens, Steven Flavell, Bernardo Sabatini

Technologies for understanding the brain

Map the molecules, wiring, and connections

Expansion microscopy

Control the high-speed dynamics

Optogenetics

Observe the high-speed dynamics

Tools for fluorescent imaging of dynamics

Synthesis: towards computational models of neural circuit function

Map the molecules, wiring, and connections

Expansion microscopy

Control the high-speed dynamics

Optogenetics

Observe the high-speed dynamics

Tools for fluorescent imaging of dynamics

Ed Boyden Synthetic Neurobiology Group http://synthneuro.org/

Research Scientists, Postdocs, Graduate Students, and Undergraduate Researchers (On Work Discussed)

Leah Acker, Kate Adamala, Brian Allen, Shahar Alon, Shoh Asano, Rachel Bandler, Mike Baratta, Jake Bernstein, Orhan Celiker, Jae-Byum Chang, Fei Chen, Linlin Chen, Yongku Cho, Brian Chow, Amy Chuong, Emma Costa, Joel Dapello, Cortni Dick, Allison Dobry, Limor Freifeld, Linyi Gao, Rui Gao, Dan Goodwin, Nir Grossman, Alex Guerra, Katriona Guthrie-Honea, Xue Han, Mike Henninger, Erica Jung, Louis Kang, Justin Kinney, Nathan Klapoetke, Suhasa Kodandaramaiah, Mingjie Li, Changyang Linghu, Adam Marblestone, Daniel Martin-Alarcon, Patrick Monahan, Caroline Moore-Kochlacs, Tania Morimoto, Masaaki Ogawa, Nikita Pak, Demian Park, Kiryl Piatkevich, Xiaofeng Qian, Paul Reginato, Alex Rodriguez, Sam Rodriques, Deblina Sarkar, Daniel Schmidt, Jorg Scholvin, Or Shemesh, Annabelle Singer, Anu Sinha, Harbi Sohal, Ho-Jun Suk, Giovanni Talei Franzesi, Paul Tillberg, Ingrid van Welie, Oz Wassie, Christian Wentz, Aimei Yang, Young-Gyu Yoon, Fumi Yoshida, Jay Yu, Yongxin Zhao, Anthony Zorzos

Collaborating Groups (On Work Discussed)

Misha Ahrens, Paola Arlotta, Herwig Baier, Ernst Bamberg, Laszlo Barabasi, Mark Bathe, Mark Bear, Andy Beck, Shaun Berry, Eric Betzig, Tim Blanche, David Bono, Christoph Borgers, Chad Bouton, M. Christian Brown, Emery Brown, Randy Buckner, Jason Buonrostro, Dawen Cai, Jess Cardin, Alex Chubykin, Martha Constantine-Paton, George Church, Utkan Demirci, Bob Desimone, Jim DiCarlo, Mikhail Drobizhev, Elazer Edelman, Howard Eichenbaum, Valentina Emiliani, Florian Engert, Dirk Englund, Chris Fiorillo, Steve Flavell, Clif Fonstad, Craig Forest, Ki Goosens, Ann Graybiel, Reid Harrison, Alan Horsager, Thom Hughes, Joe Jacobson, Vivek Jayaraman, Ali Khademhosseini, Nancy Kopell, Konrad Kording, Niels Kuster, Leaflabs, Joe LeDoux, Albert Lee, Daniel Lee, Eric Leuthardt, Yingxi Lin, Michael Melkonian, Mario Moises Alvarez, Chris Moore, Peder Olofsson, Alvaro Pascual-Leone, Brad Pentelute, Daniel Polley, Arjun Raj, Ramesh Raskar, Aviv Regev, Botond Roska, Mordechai Rothschild, Bernardo Sabatini, Andreas Schaefer, Steven Schiff, Stuart Schnitt, Wolfram Schultz, Nir Shavit, Ken Shepard, Peter So, Michael Strano, Mriganka Sur, Balint Szabo, Steve Tannenbaum, Max Tegmark, Todd Thorsen, Kevin Tracey, Li-Huei Tsai, Kay Tye, Keith Tyo, Wim Vanduffel, Alipasha Vaziri, Vlad Verkhushka, Astrid Weins, Gane Wong, Lowell Wood, Ting Wu, Robert Wurtz, Akihiro Yamanaka, Peng Yin, Hongkui Zeng, Xiaowei Zhuang, Manuel Zimmer

Current Funders

Cancer Research UK, DARPA, DOD MURI, Google, HFSP, HHMI, IARPA, John Doerr, Kavli Foundation, Ludwig Family Foundation, McGovern Institute, Media Lab, MIT Aging Brain Initiative, NIH, NSF, Open Philanthropy Project, Paul Allen Frontiers Group, Ted Poitras, US-Israel Binational Science Foundation

Past Funders

Allen Institute, Bahaa Hariri, DOD CDMRP, Harvard/MIT Research Grants Program in Basic Neuroscience, IET Harvey Prize, Jeremy and Joyce Wertheimer, Jerry and Marge Burnett, Lincoln Lab, MIT Intelligence Initiative, NARSAD, New York Stem Cell Foundation, Picower Institute, Simons Foundation, Sloan Foundation, Skolkovo-MIT Project, Templeton Foundation, Wallace H. Coulter Foundation

Conflict of Interest Statement

ESB is a co-founder of Eos Neuroscience, Cognito Therapeutics, Expansion Technologies, and SynLife, on the advisory boards of Inner Cosmos, Kernel, OccamzRazor, and PureTech Ventures, and compensated by or an equity holder in Constellation Diagnostics and Intellectual Ventures