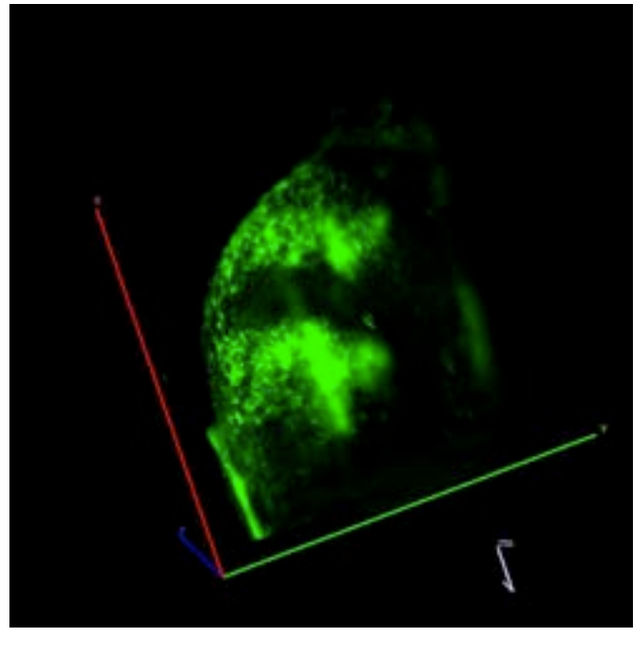
Optically transparent organs: seeing is believing



Dr. Douglas Shepherd
Department of Physics, College of Liberal Arts and Sciences
Pediatric Heart Lung Center, School of Medicine
University of Colorado Denver | Anschutz Medical Campus
http://clasfaculty.ucdenver.edu/dshepherd

University of Colorado
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Pediatric Heart Lung Center

Colorado State University

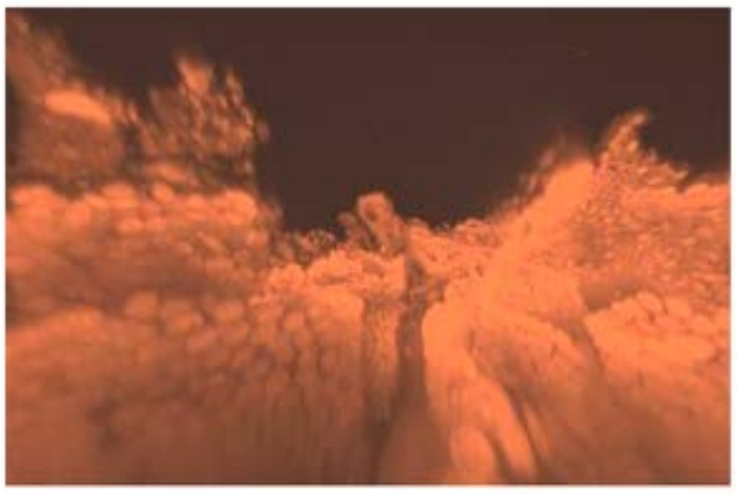
MINI-STEM SCHOOL

Recent advancements have made rendering entire animal transparent possible!

SCIENCE/TECH

3D Transparent Organs Will Help Doctors Make Better Diagnoses, Biomedical Discoveries

Jul 31, 2014 02:34 PM By Lecia Bushak



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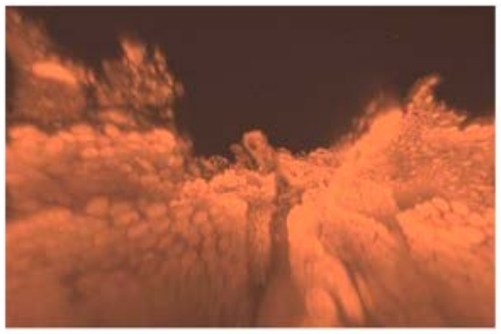

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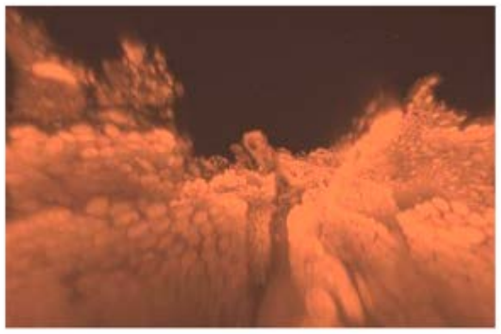

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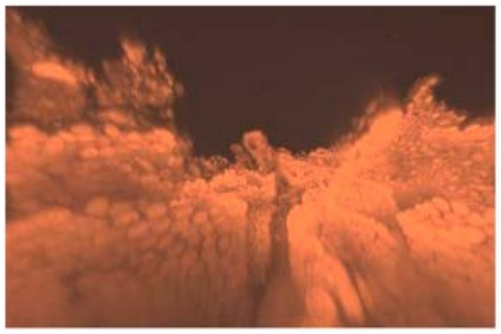

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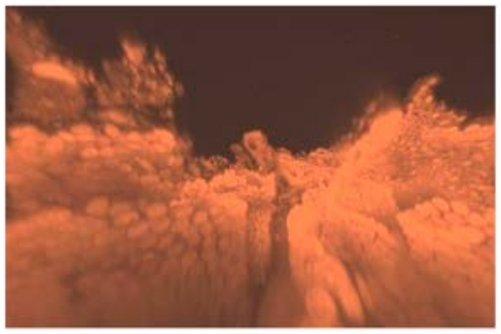

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Speaking of Science

Why a see-through mouse is a big deal for scientists

This could revolutionize how we measure pathology samples and understand structural/developmental biology

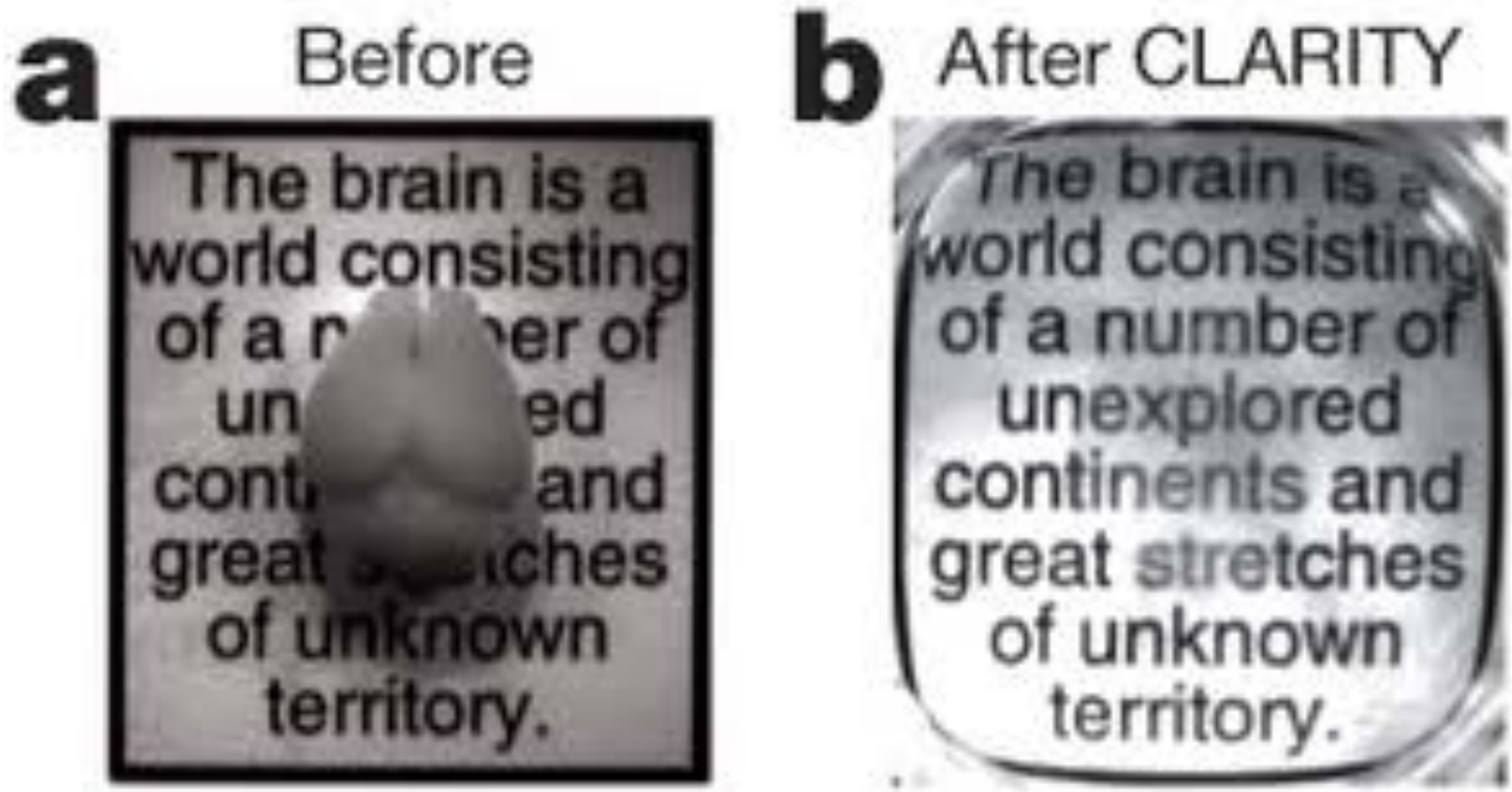
While scientists have attempted to create see-through organ and tissue samples since the 1800s, researchers have relied primarily on the sectioning of samples - slicing organs into extremely thin cross sections and examining these pieces in succession.

"That's been useful but it's also been slow and tedious," said senior study author Viviana Gradinaru, an assistant professor of biology and biological engineering at Caltech.

Recent advancements in tissue clearing have enabled researchers to study nerve connections and organ structures without having to slice them up, providing scientists with new insights into previously hidden anatomical structures.

Moving from physically cutting up a brain

To making it see-through!



Learning Objectives

1. Explain why tissue scatters light and how one can alter the light scattering properties of tissue.
2. Describe laser-induced fluorescence and light-sheet fluorescence microscopy.
3. Summarize how combining these two methods allows one to measure structures within intact tissue and organs.
4. Theorize how these advancements may help with pressing public health issues.

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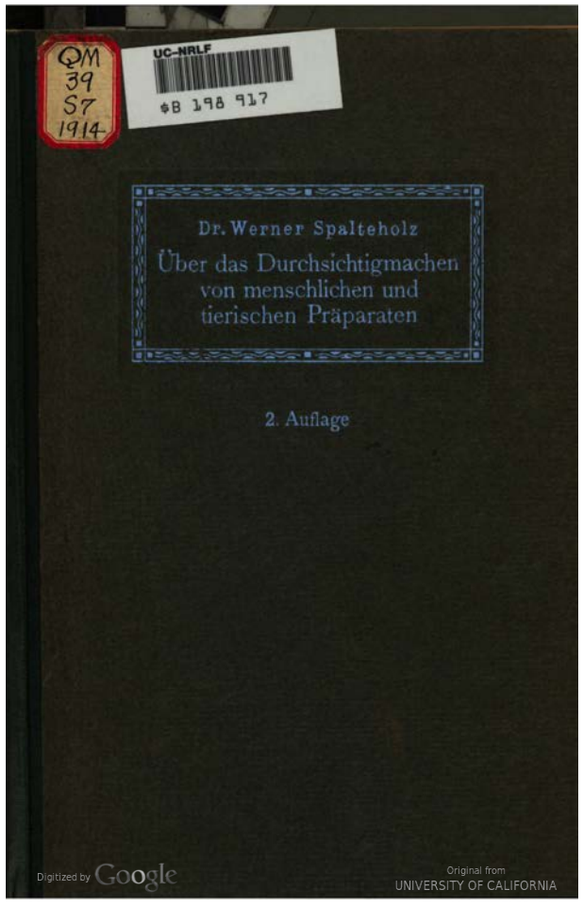
Natural curiosity about our (and animal) insides



"About the transparentizing of human and animal preparations"
Published in 1914 by Werner Spalteholz

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$$p\frac{n-1}{d}=p_1\frac{n_1-1}{d_1}+p_2\frac{n_2-1}{d_2}+\cdots,$$

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Leider gibt auch diese Formel, die als die zuverlässigste gilt, nicht immer ganz genaue Resultate.

Für die von mir hauptsächlich benutzten Flüssigkeiten habe ich nach wiederholten eigenen Messungen folgende Zahlen zugrunde gelegt:

Wintergrünöl, künstlich	$n_D = 1{,}538$,	spez. Gew. = 1,188
Safrol	$n_D = 1{,}542$,	„ „ = 1,102
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Isosafrol, farblos	$n_D = 1{,}577$,	„ „ = 1,115.

Die Neuheit des Problems und der Wunsch, über verschiedene scheinbare Unstimmigkeiten Klarheit zu erhalten,

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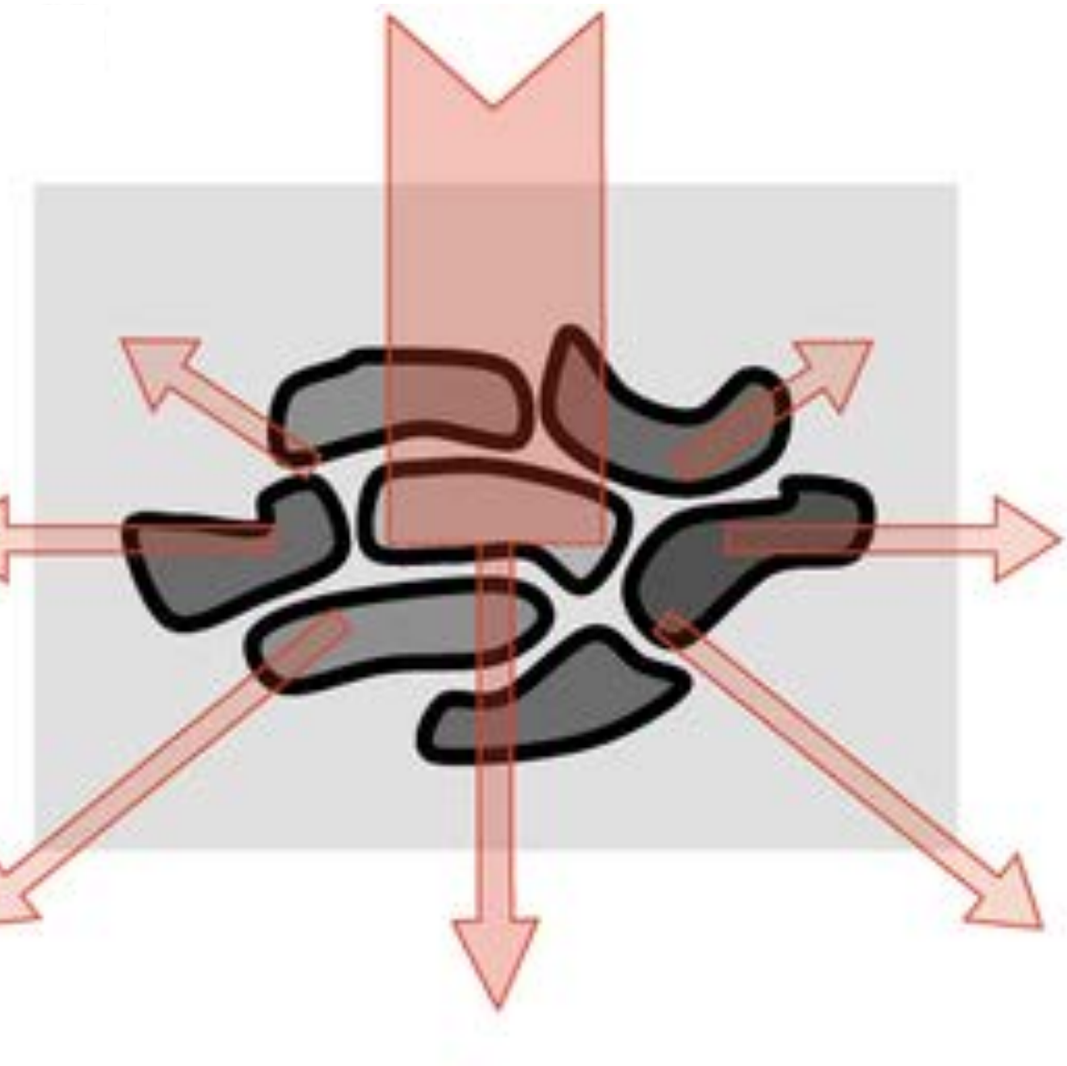

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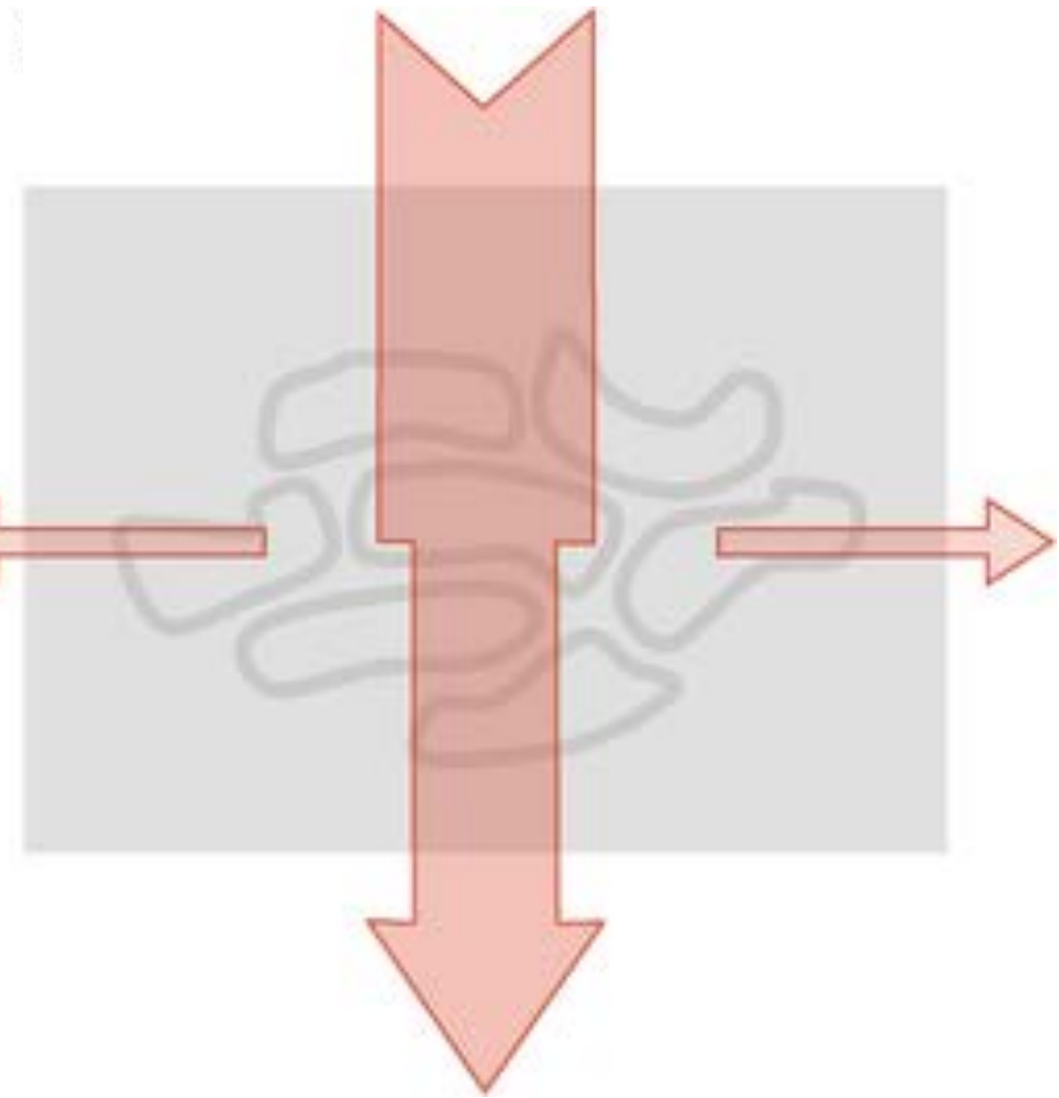

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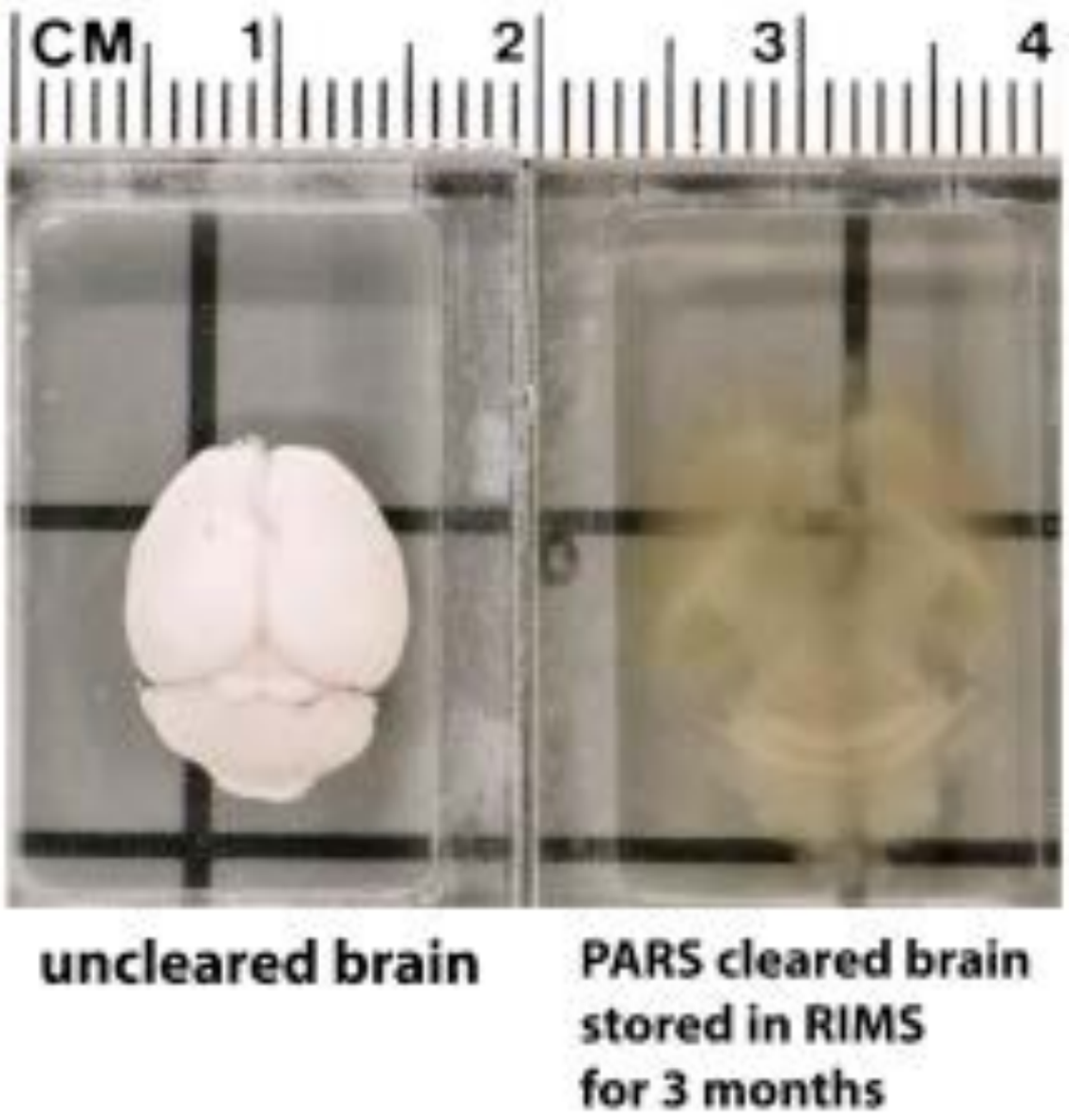

Yang et al Cell 2015

The search for the magic bullet…or…an excuse to make up a lot of acronyms

Technique	Clearing time for whole-brain	Complete transparency	Fluorescent quenching	Tissues validated	Significant contribution to field	Drawback
***BABB, THF, DBE*(Becker et al., 2012; Dodt et al., 2007)**	hours-days	Yes, but tissue shrinkage	Yes (Ertürk et al., 2012a; Ke et al., 2013)	Rodent brain, spinal cord, peripheral tissues	Among first clearing reagents	Harsh reagents (Ke et al., 2013)
***ClearT2*(Kuwajima et al., 2013)**	days	No	No-partial (Ke et al., 2013)	Rodent brain and embryo	Less quenching than BABB; novel reagents	Immunlabeling only through 120 μm
***Scale (A2, U2)* (Hama et al., 2011)**	weeks-months (slowest)	Yes, but tissue swelling (Chung et al., 2013; Ke et al., 2013; Kuwajima et al., 2013)	No-minimal (Ke et al., 2013; Kuwajima et al., 2013)	Mouse brain, embryo (Hama et al., 2011)	Transparency without quenching; IHC/F	Slow; tissue deformation; potential protein loss with clearing (Ke et al., 2013)
***3DISCO* (Ertürk et al., 2012a; Ertürk and Bradke, 2013)**	< week	Yes	No, but signal decay w/in days (Ertürk et al., 2012a; Ertürk and Bradke, 2013)	Peripheral/central organs, embryos, tumors (Ertürk and Bradke, 2013); Central (Erturk et al., 2012b) and peripheral (Jung et al., 2014) nerves	Balance between rapidity and quality of cleared tissue; imaging protocol	Requires immediate sample imaging; IHC-very limited
***CLARITY* (Chung and Deisseroth, 2013; Chung et al., 2013; Kim et al., 2013)**	10 days	Yes	No	Rodent, human and non-human primate brains, spinal cord, zebrafish (Zhang et al., 2014)	Hydrogel-embedding; best tissue quality when performed correctly; IHC/F	ETC difficult, customized equipment, expensive (Chung et al., 2013)
***Advanced CLARITY* (Tomer et al., 2014; Zhang et al., 2014)**	3 weeks	Yes	No	Whole mouse brain	No ETC – passive thermal CLARITY, COLM, CLARITY objectives, rapid imaging protocol	Requires COLM set-up
***SeeDB* (Ke et al., 2013; Ke and Imai, 2014)**	days (fastest)	No	No	Young rodent brains (Ke et al., 2013)	No tissue deformation, fast	Tissue browning, incomplete clearing,
***CUBIC* (Susaki et al., 2014)**	2 weeks	Mostly-Yes	No	Rodent and non-human primate brain	CUBIC informatics, optimized Scale (Susaki et al., 2014)	Brain only; potential protein loss during clearing
PACT, PARS	days-weeks	Yes	No	All major rodent organs; whole-body clearing	optimized/simplified CLARITY; permits long-term tissue storage; IHC/F	Slower than 3DISCO

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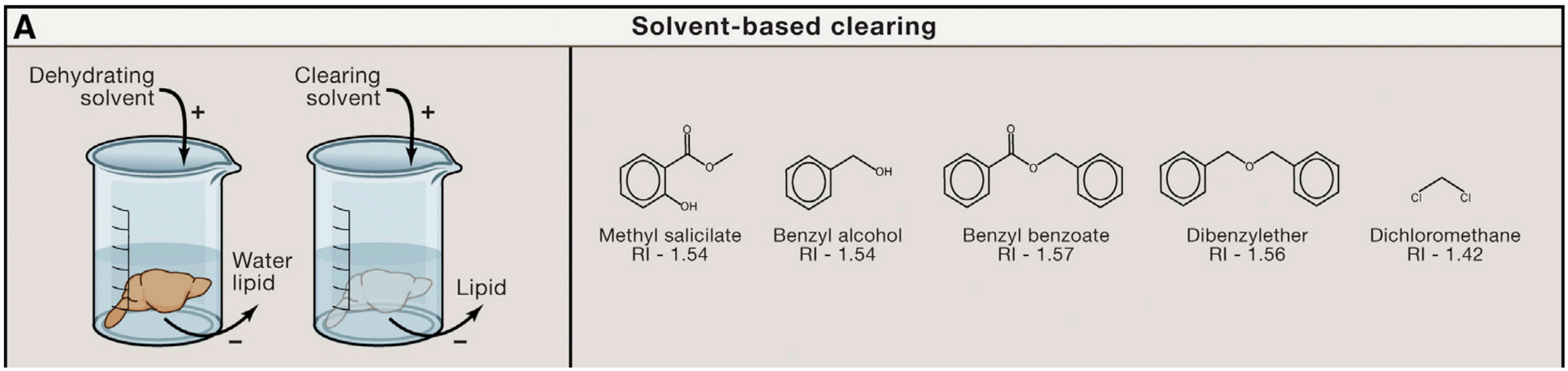
So many techniques!!
What is different about all of them?

Yang et al Cell 2015

The search for the magic method…

Four general categories:

1. Solvent-based



Richardson and Lichtman Cell 2015

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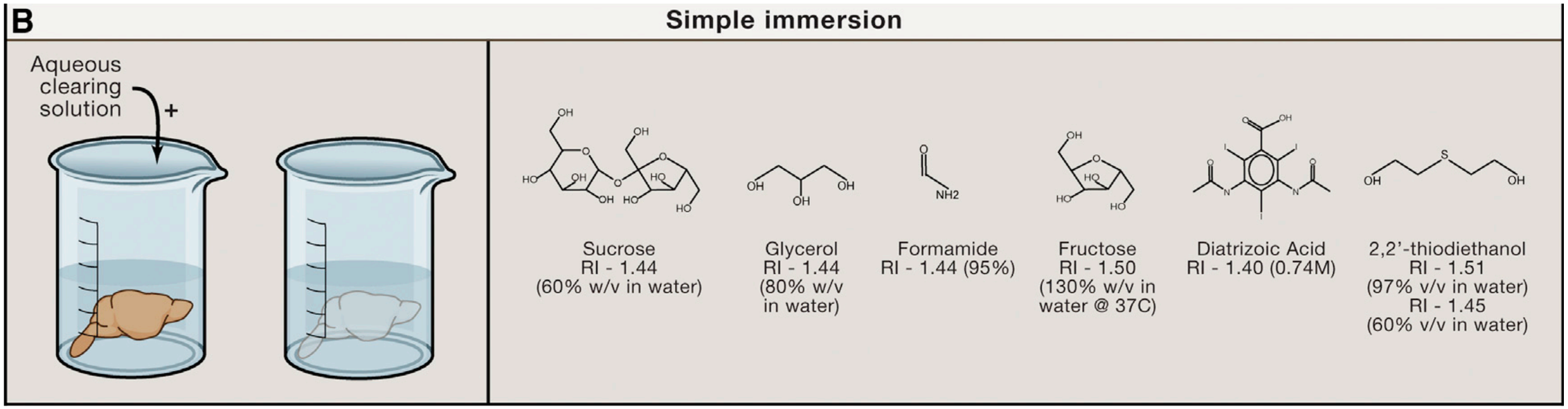

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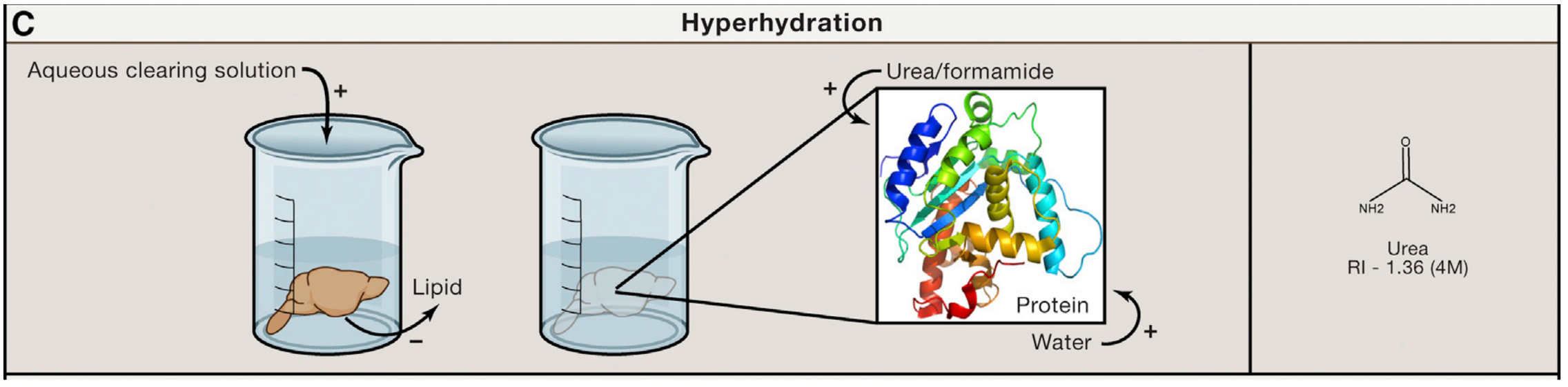

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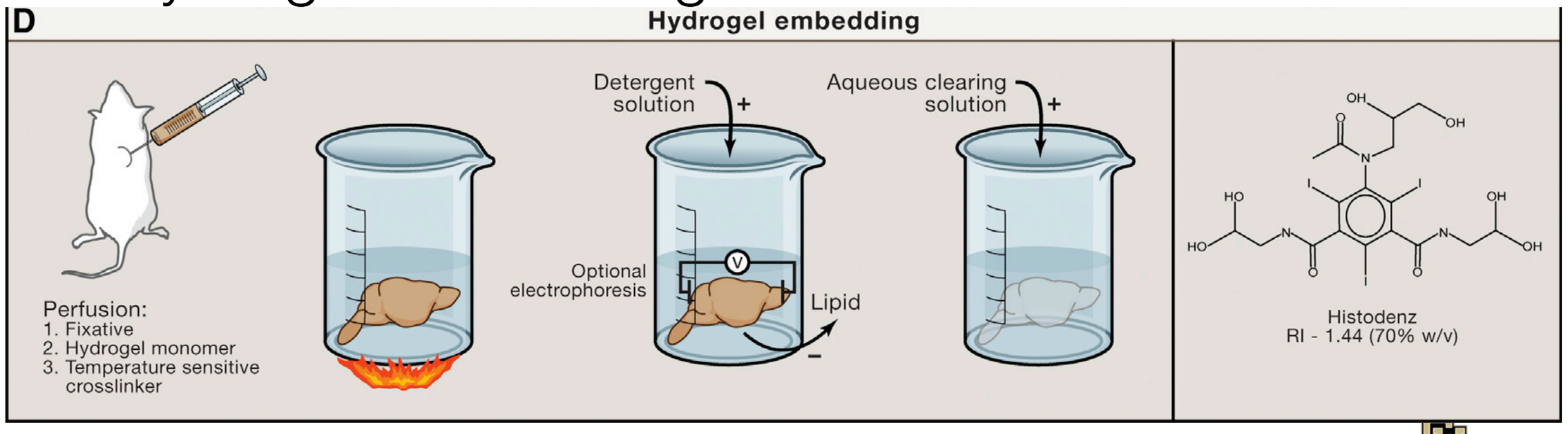

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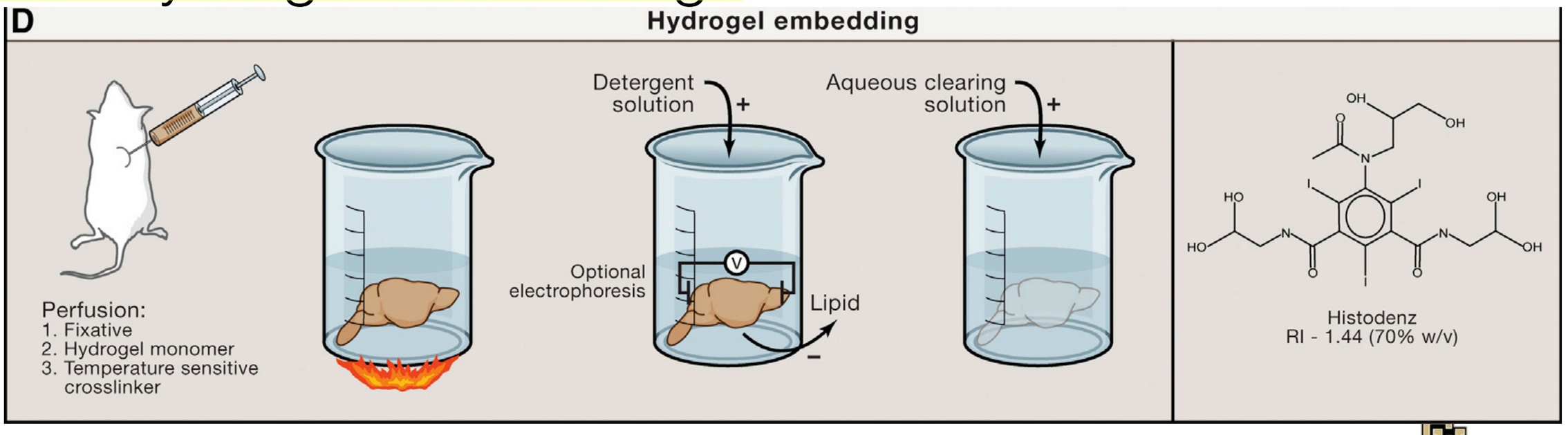

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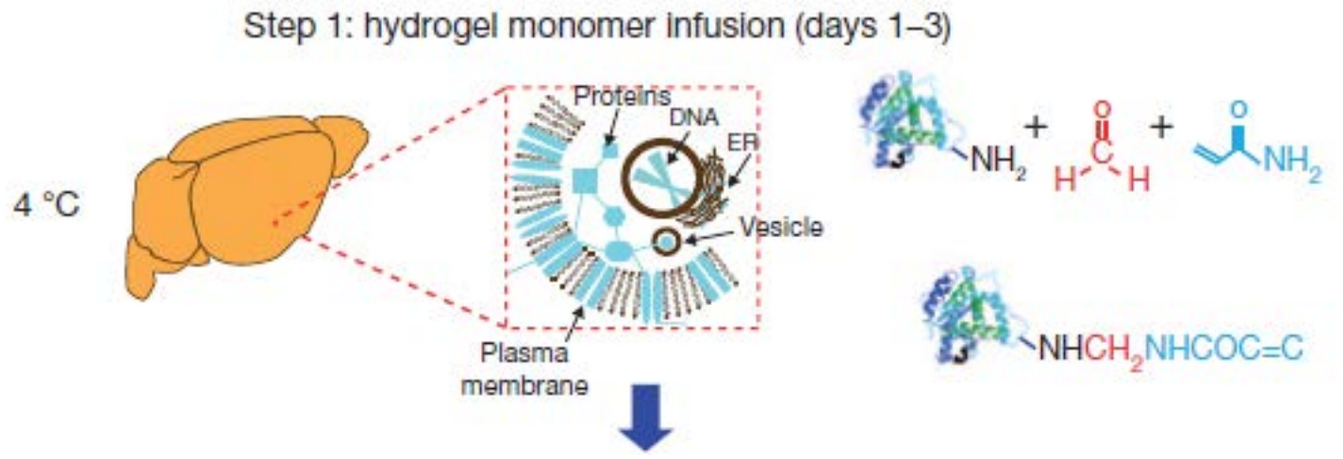
Hydrogel embedding



Chung et al Nature 2013

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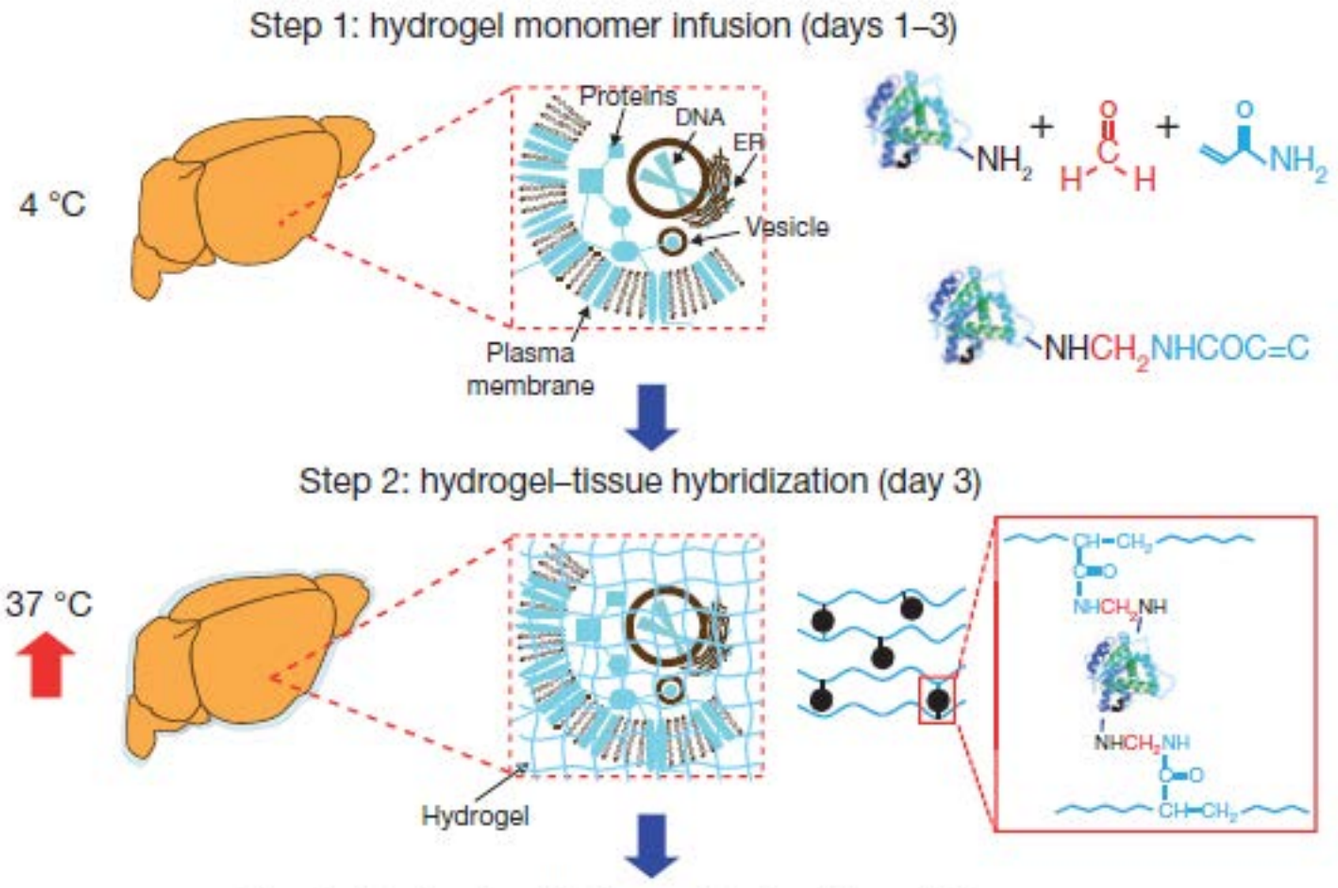

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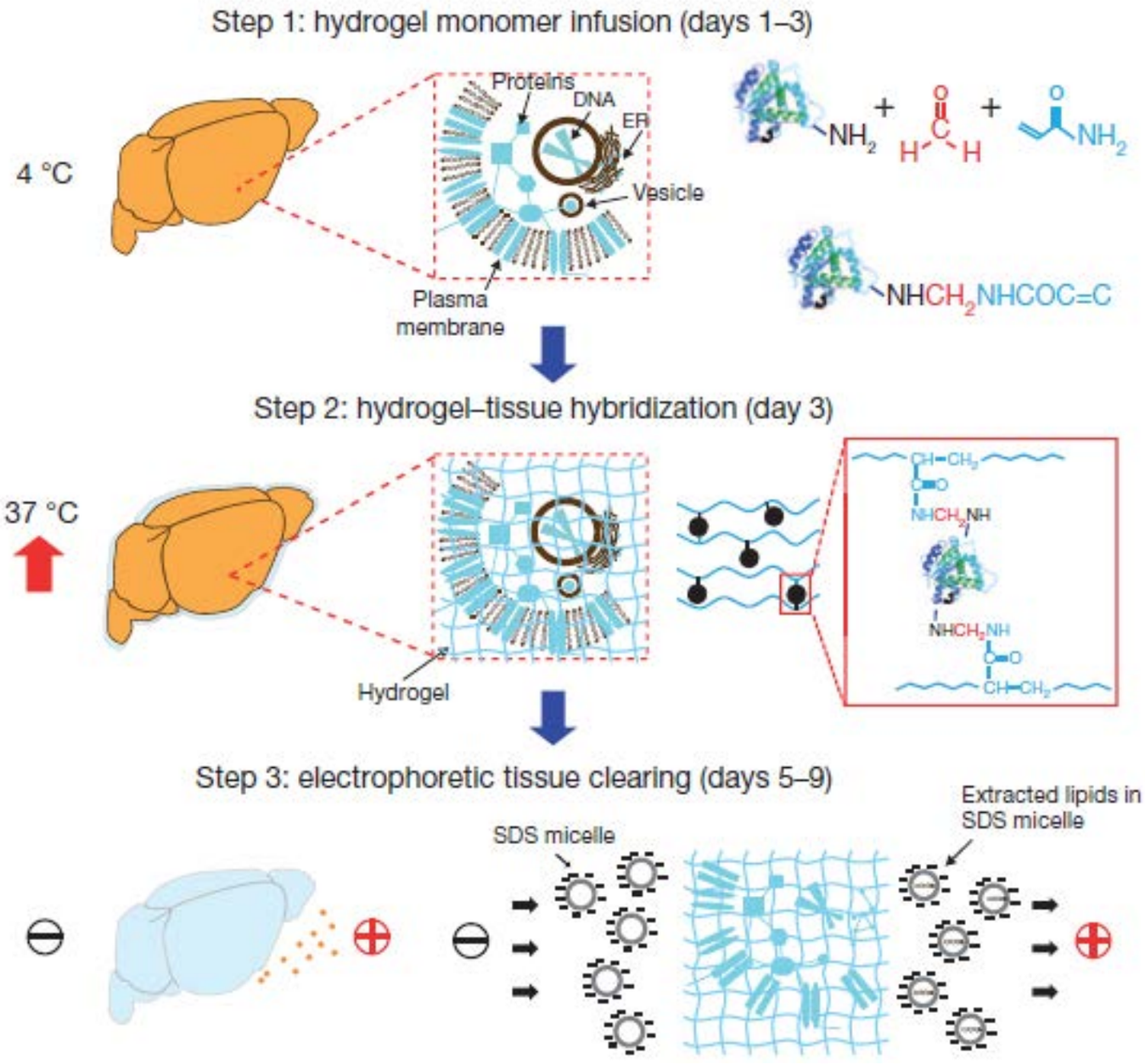

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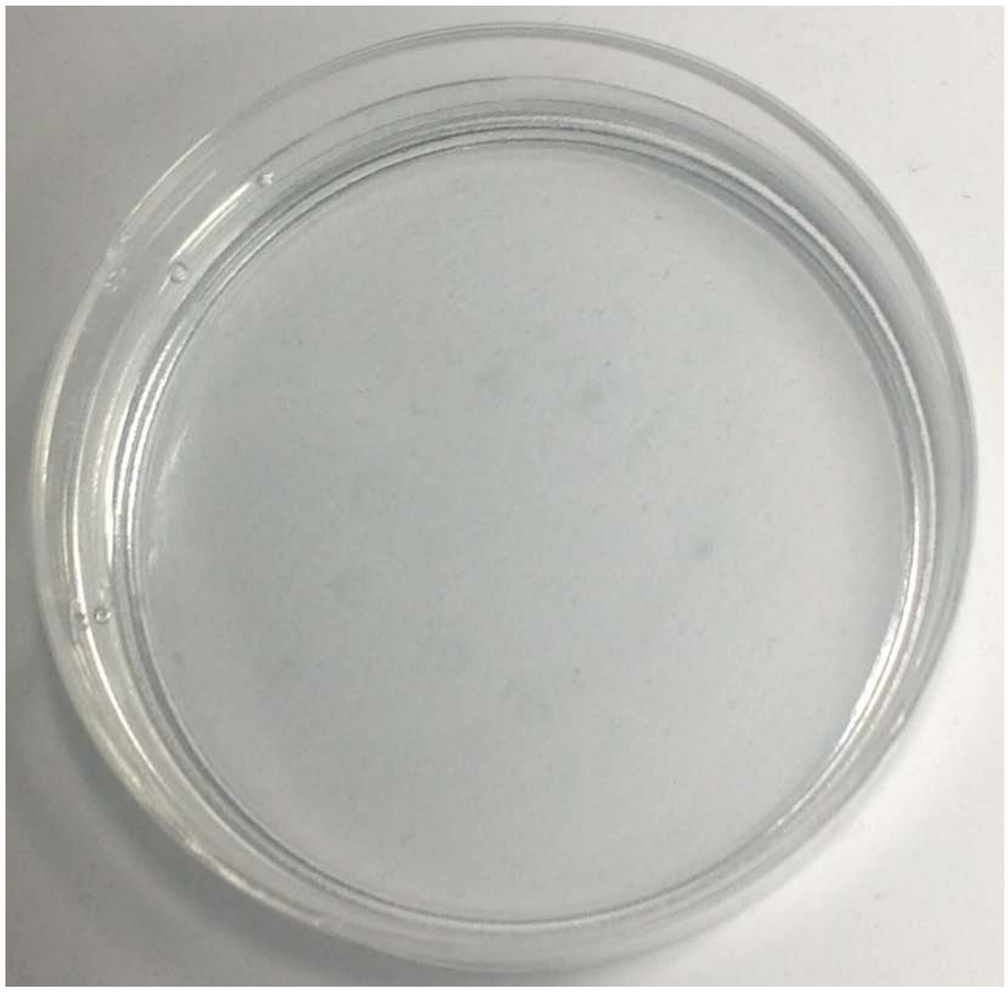

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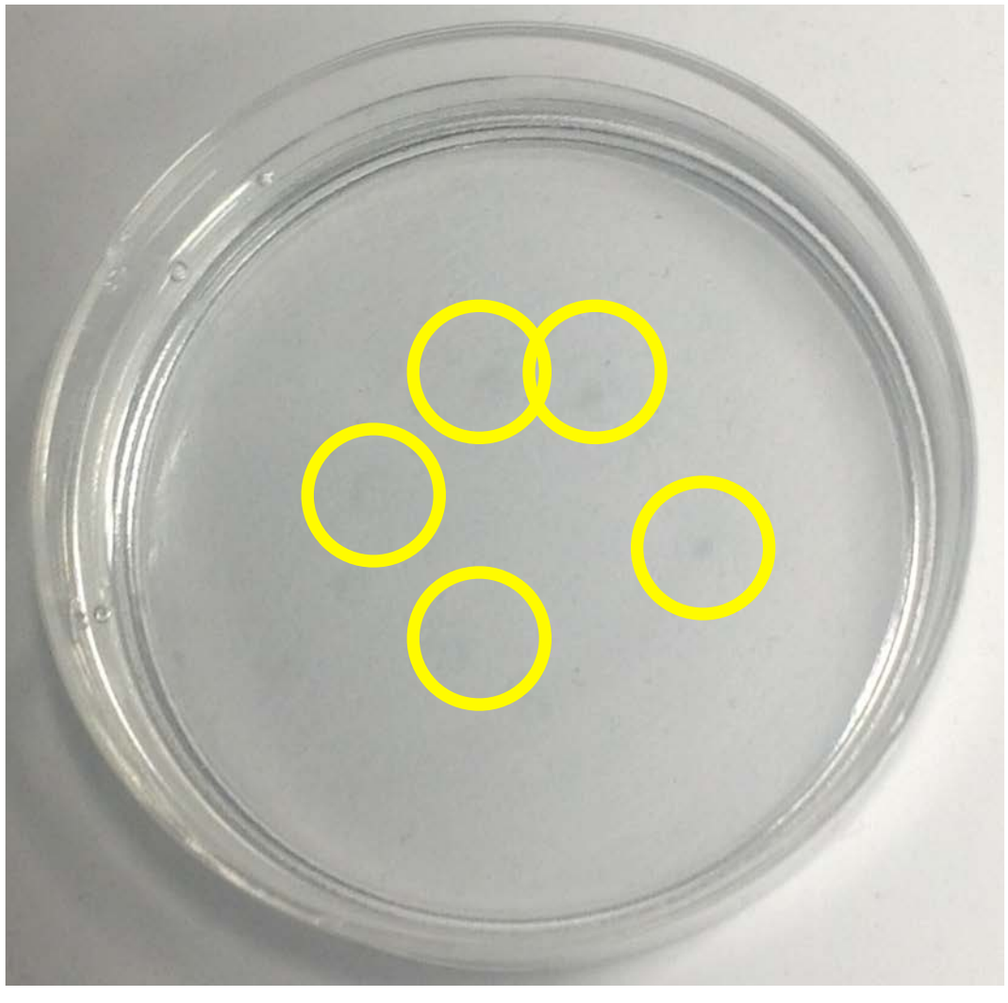
Hydrogel embedding



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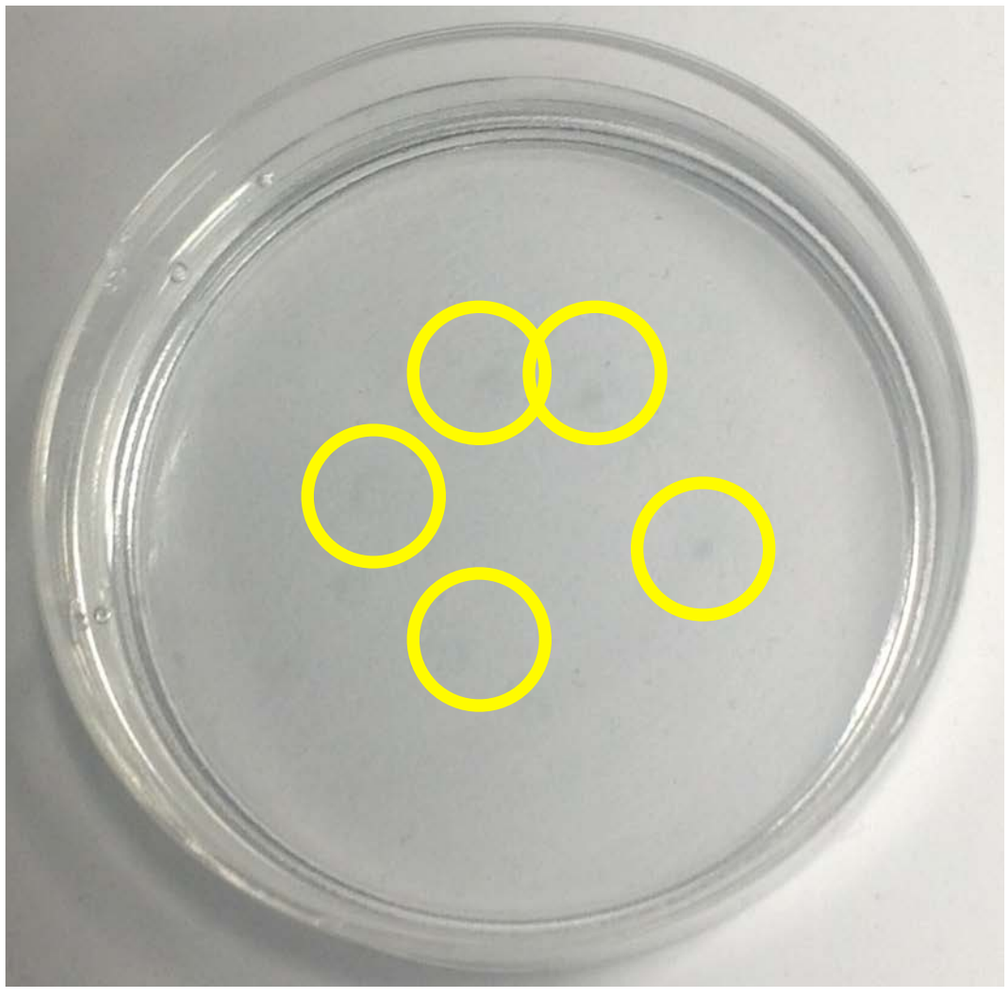
Hydrogel embedding



Now what? We can't the eye(s) anymore!

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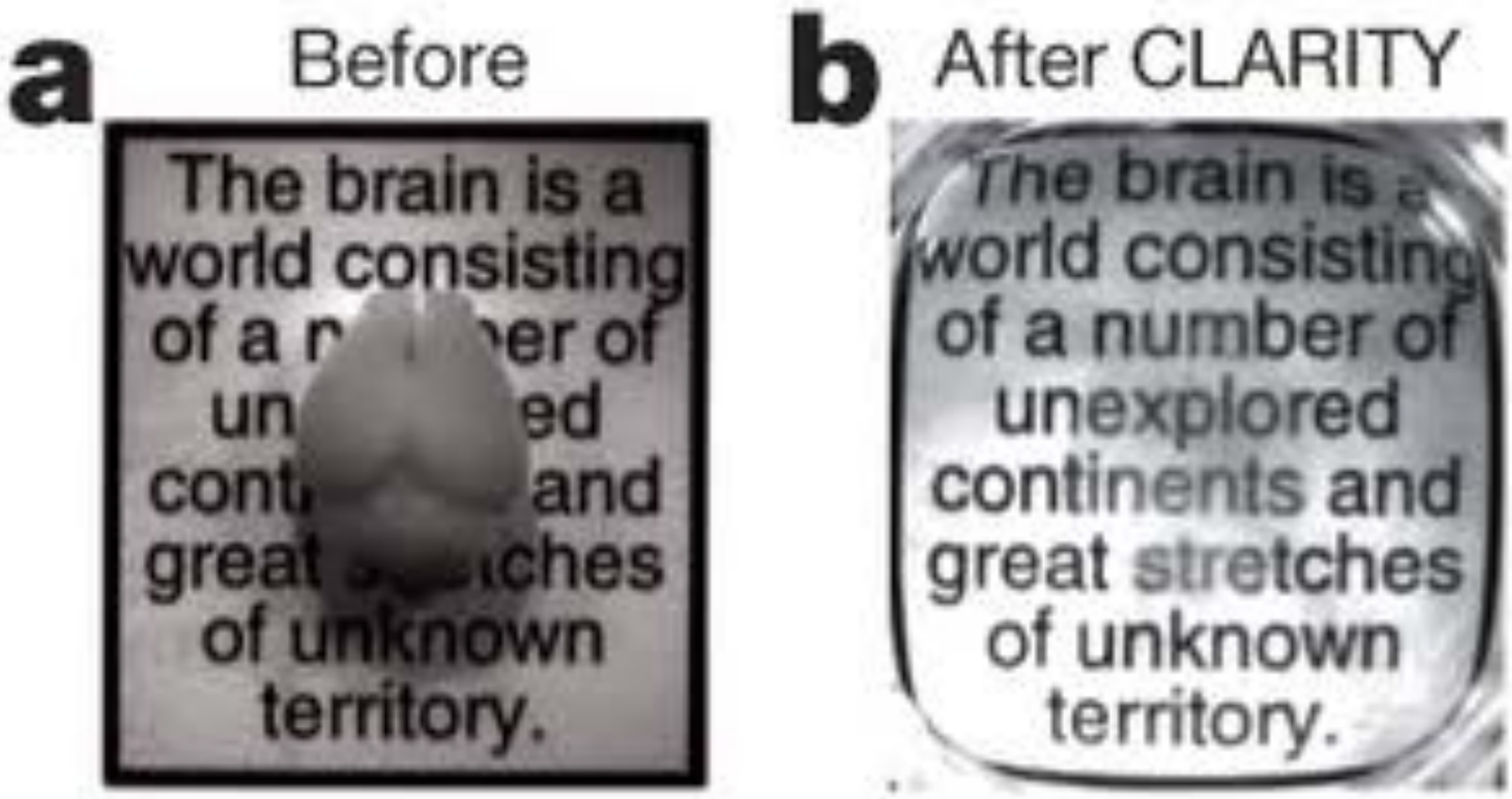
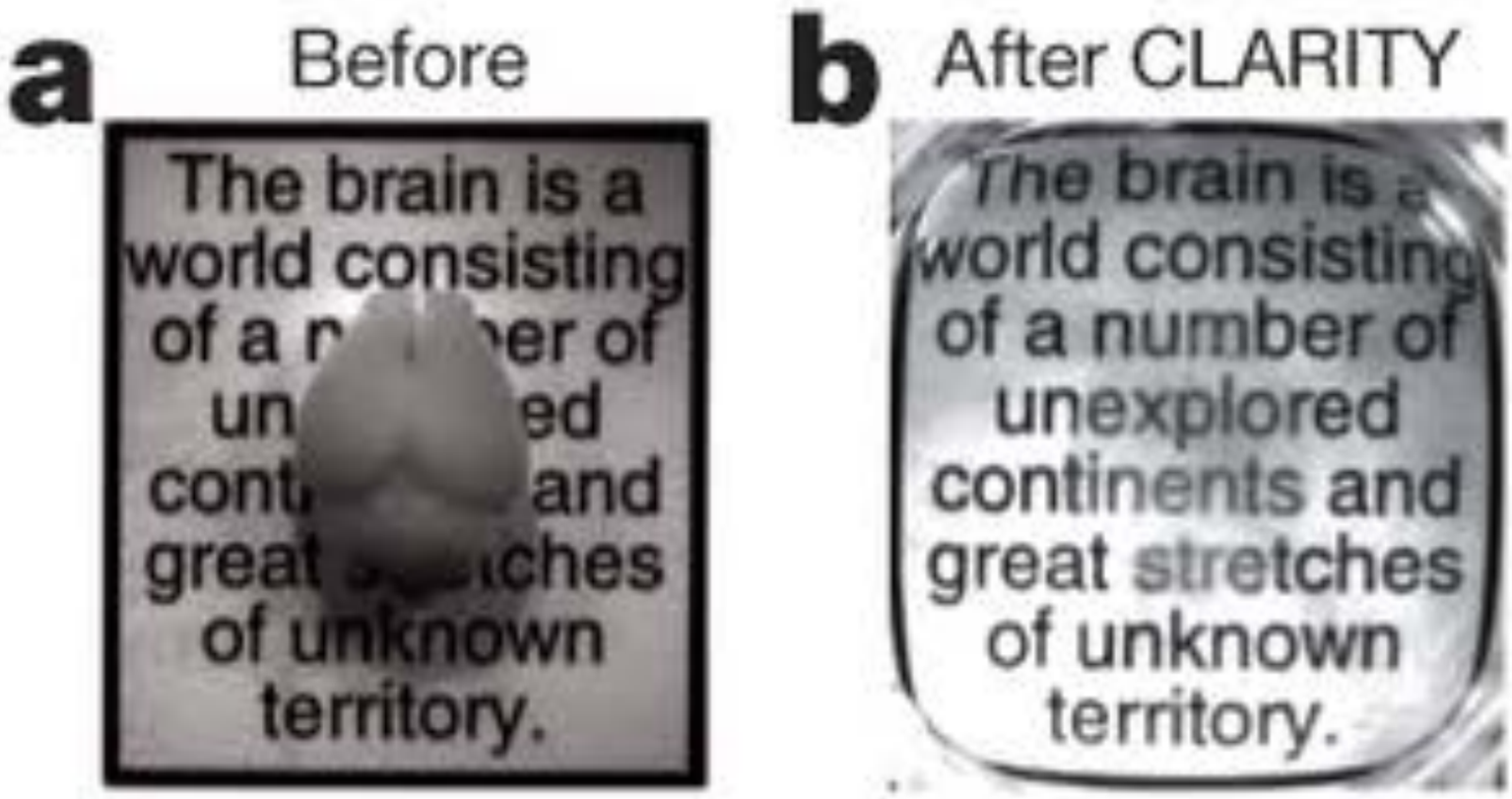
Hydrogel embedding



Chung et al Nature 2013

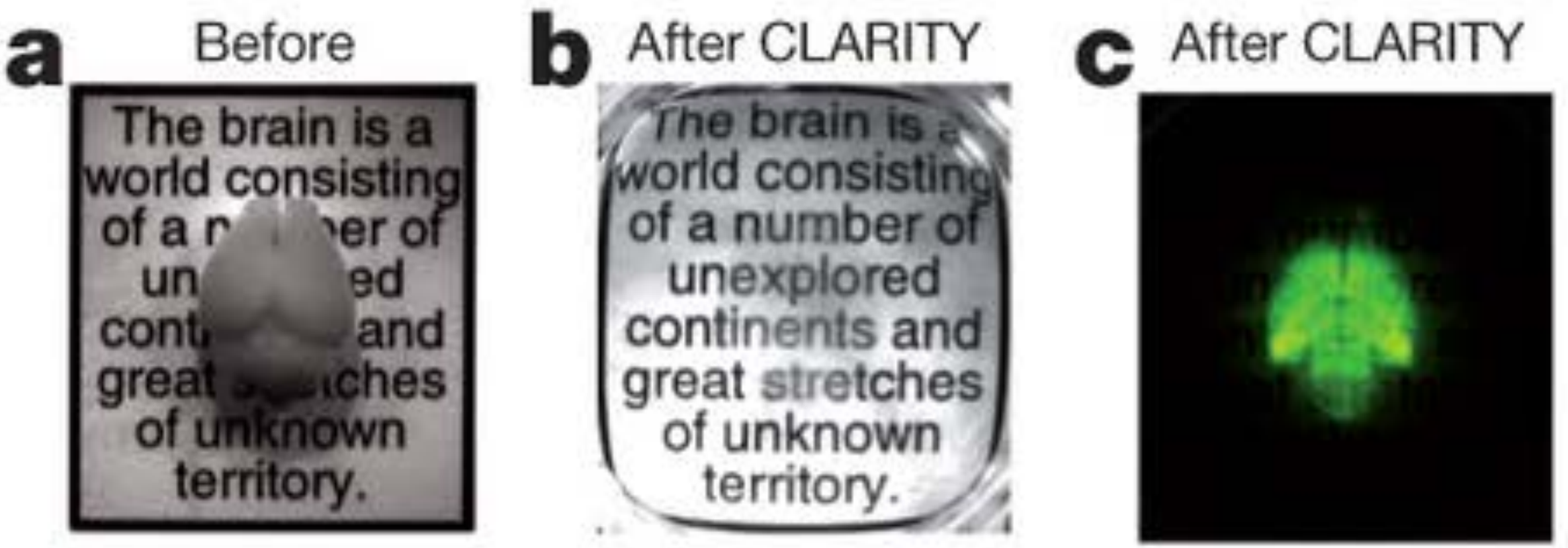
Hydrogel embedding



Can’t see anything in the brain either!

Chung et al Nature 2013

Hydrogel embedding



Need another way to “see” inside the tissue

Chung et al Nature 2013

Learning Objectives

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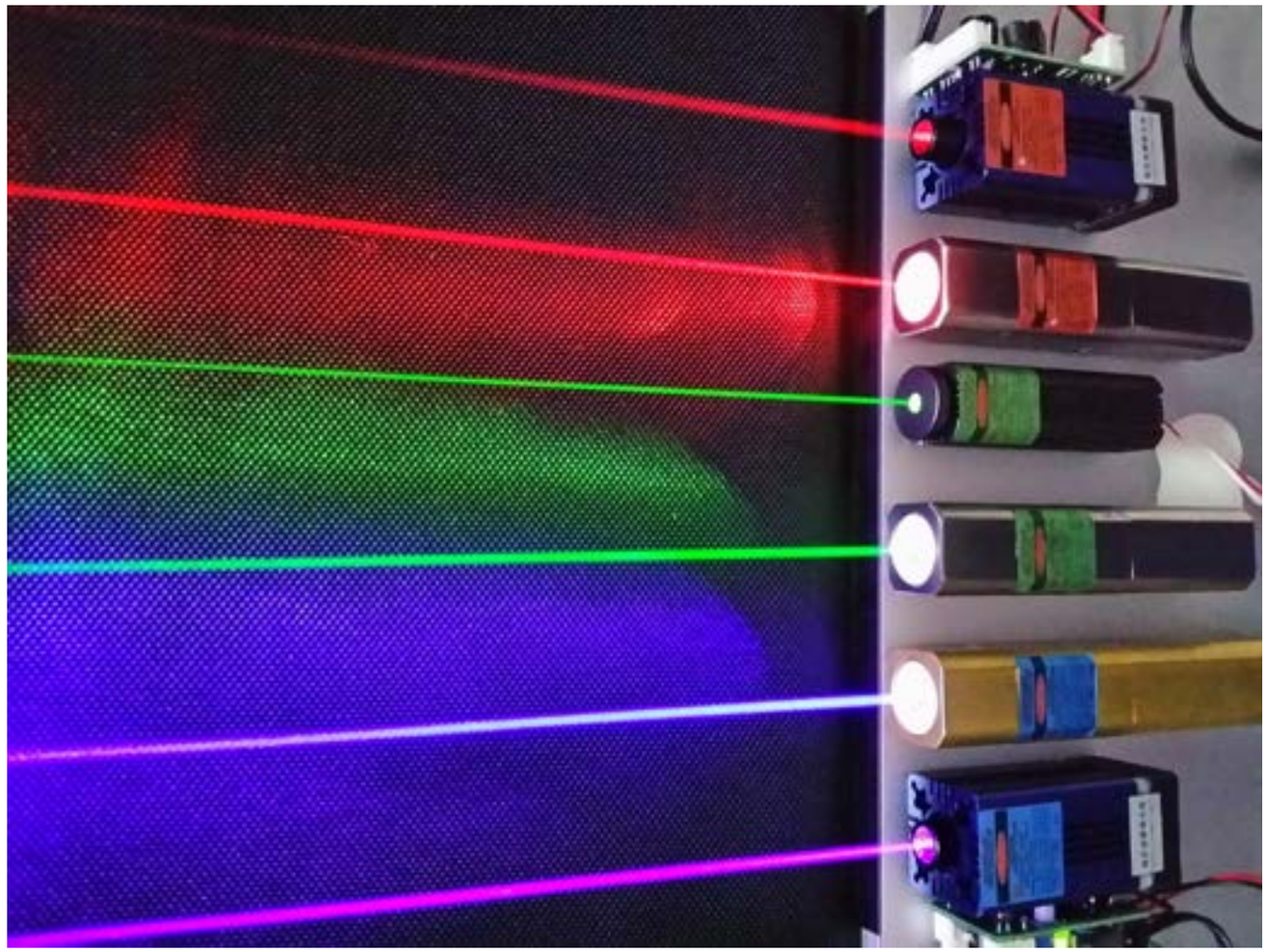
What is a laser?



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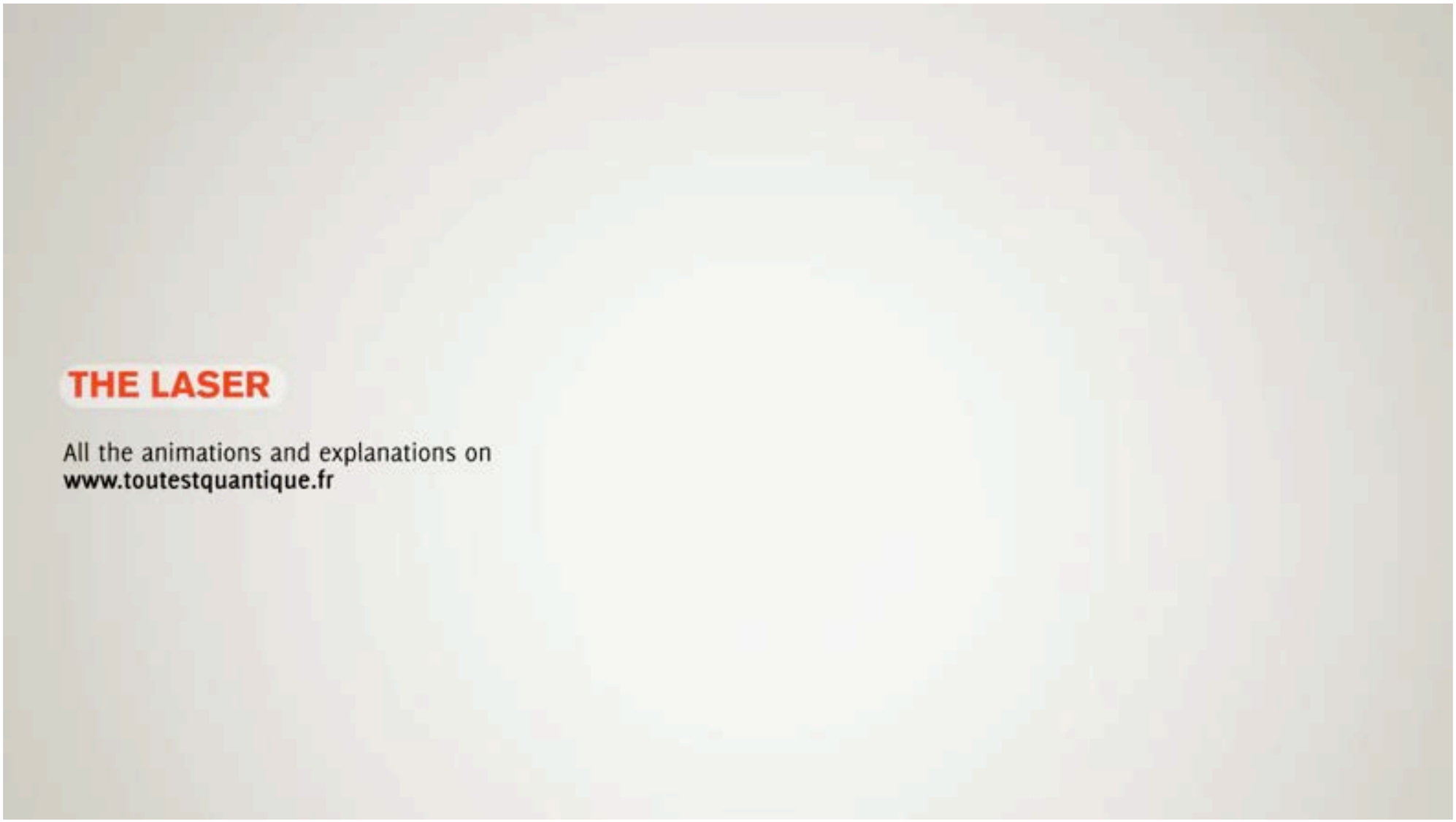

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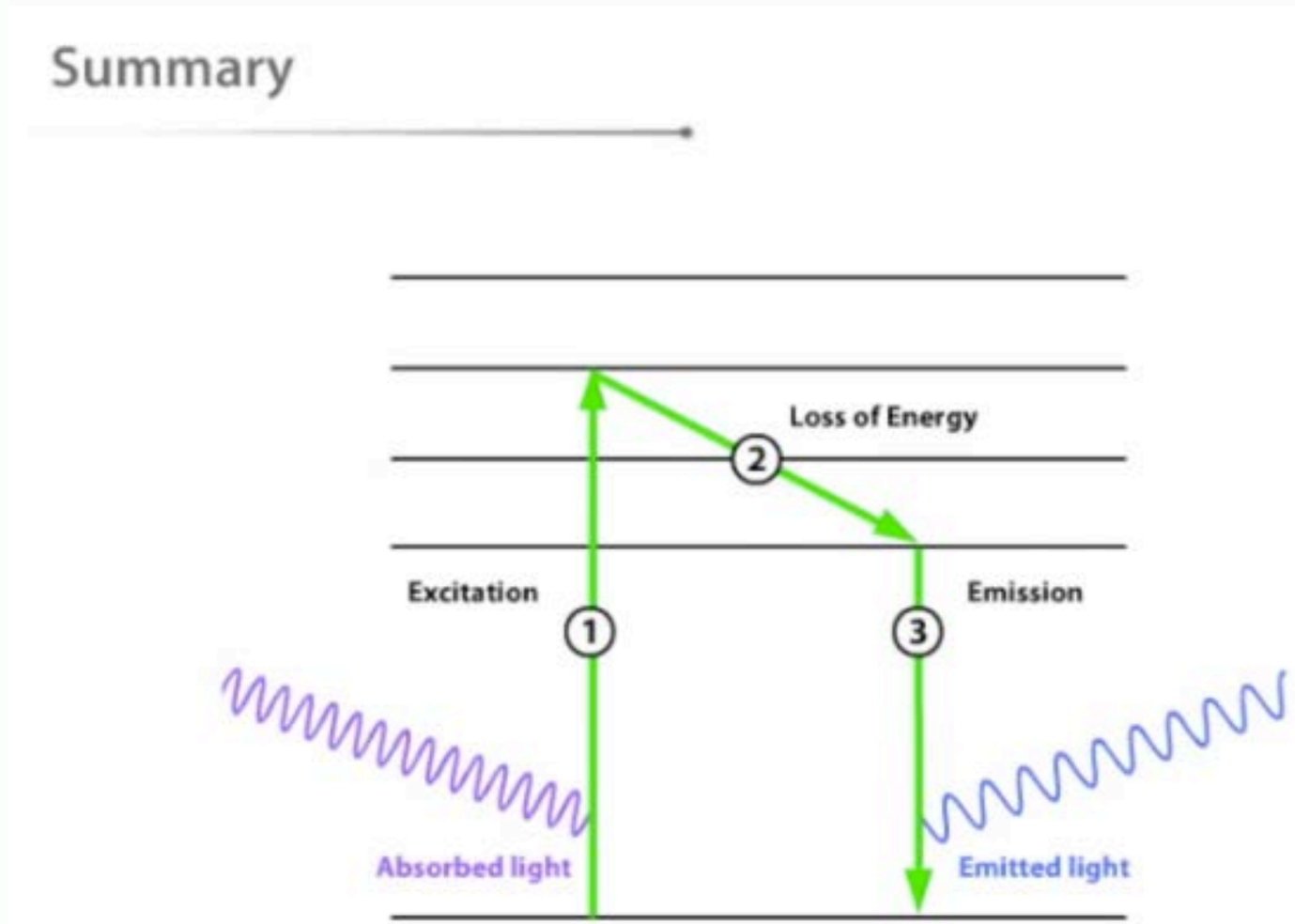
What is laser-induced fluorescence?



molecular probes

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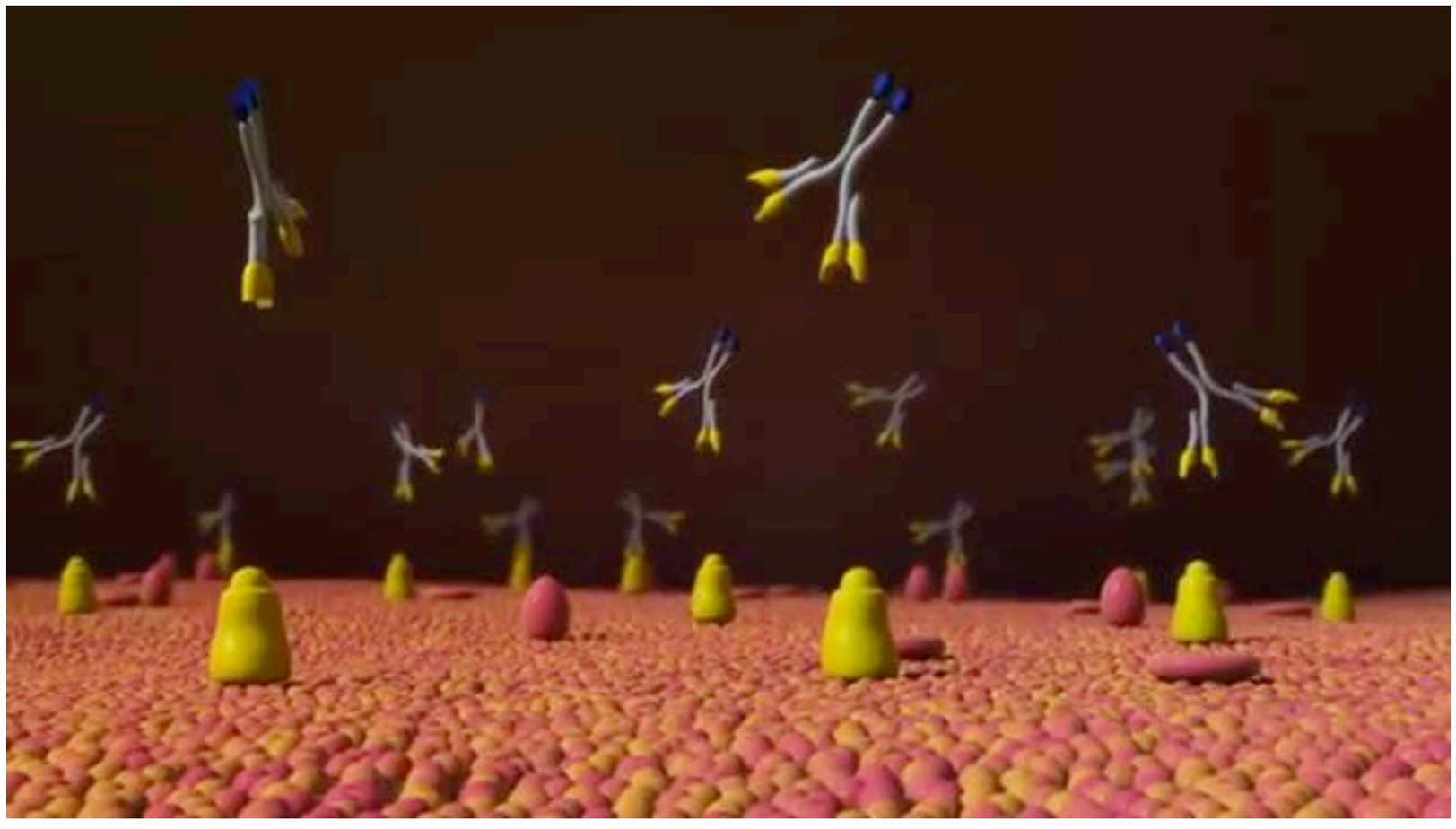
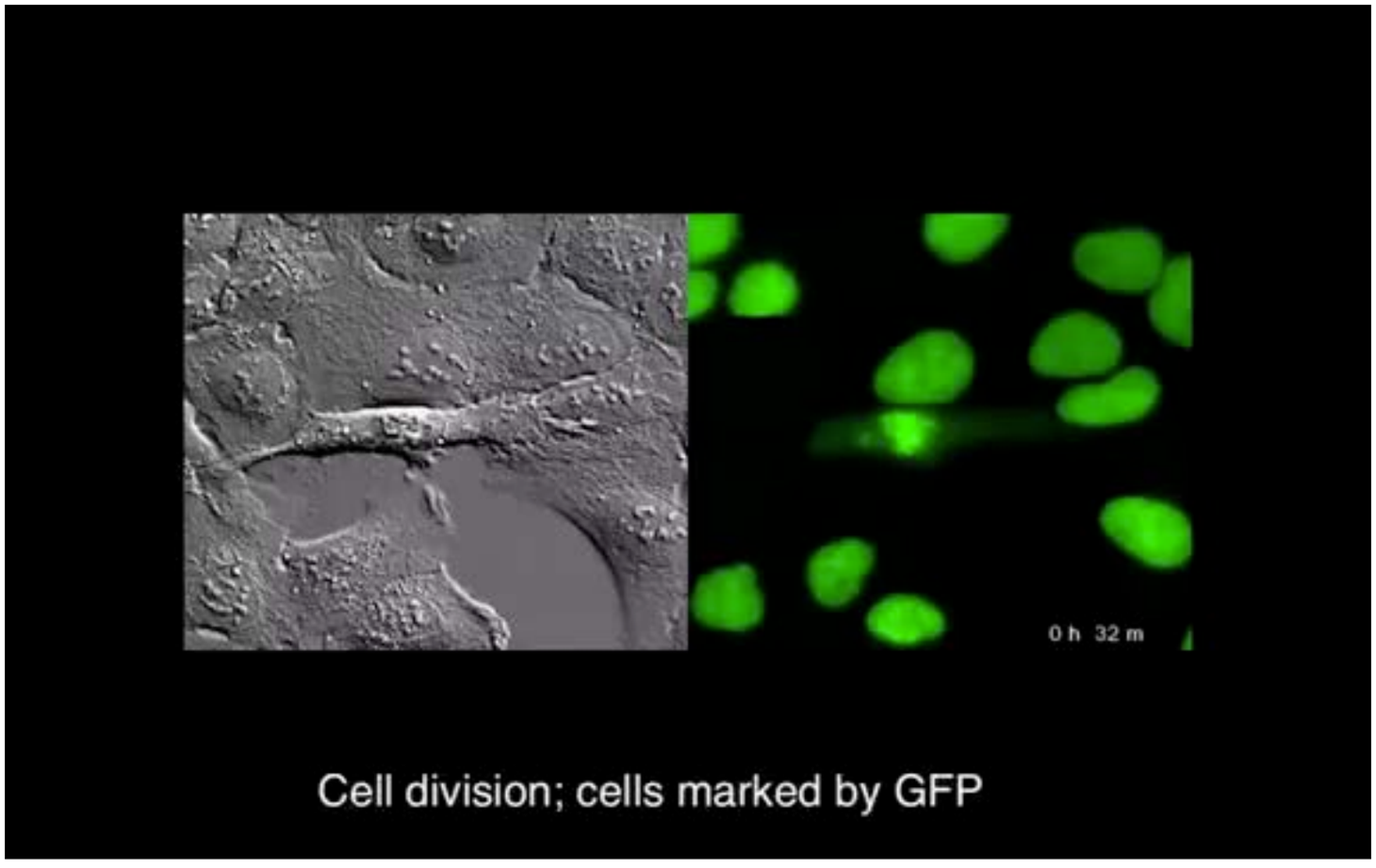
How can we attach flourophores to a biological target?

1. Antibody labels



How can we attach flourophores to a biological target?

1. Antibody labels
2. Fluorescent proteins



Multiples types of fluorescent microscopy

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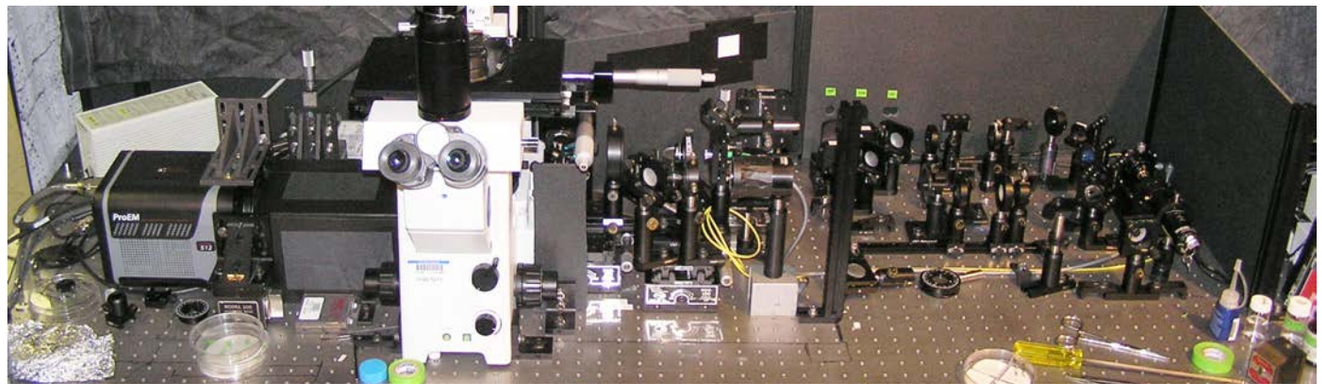
Multiples types of fluorescent microscopy



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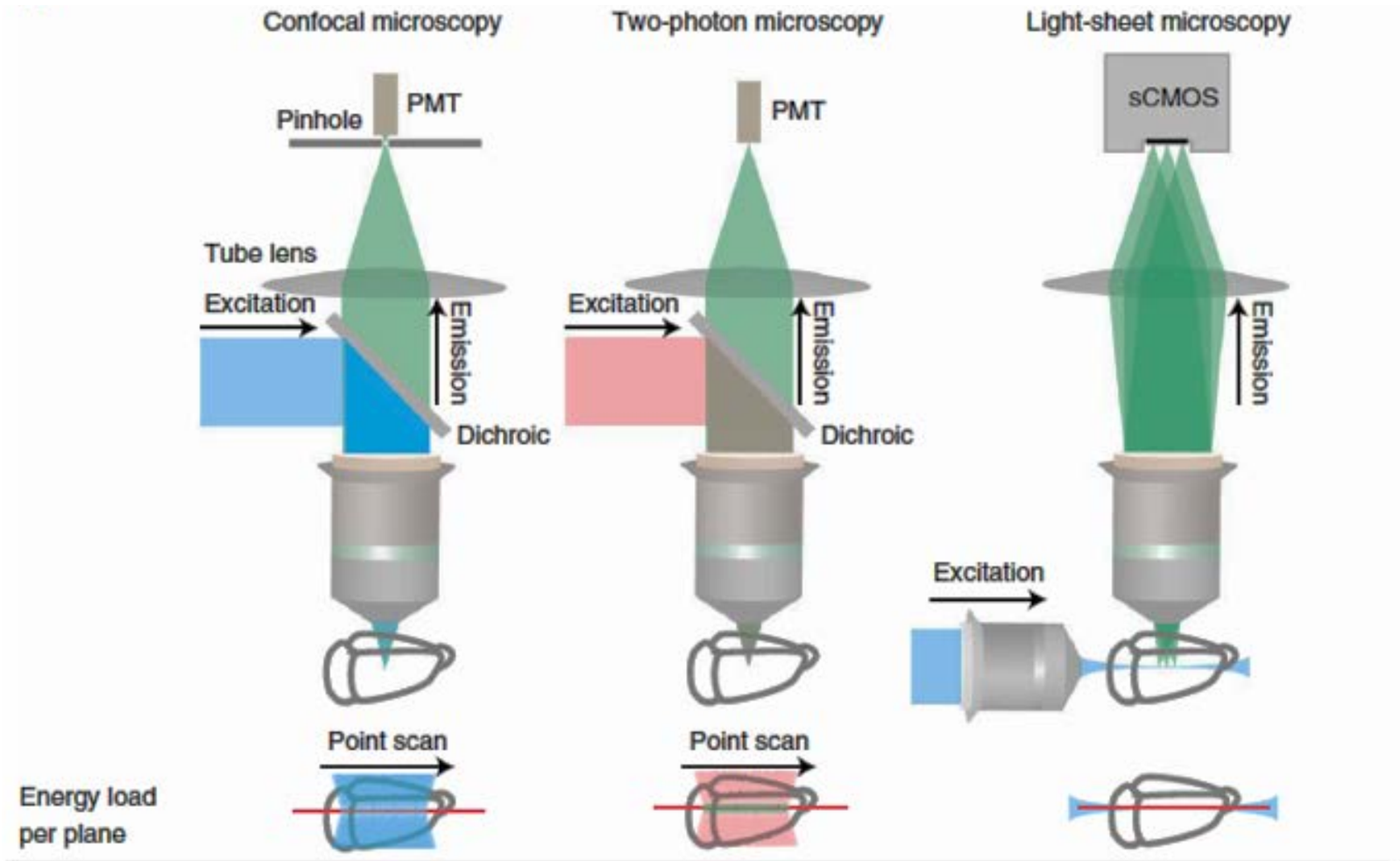
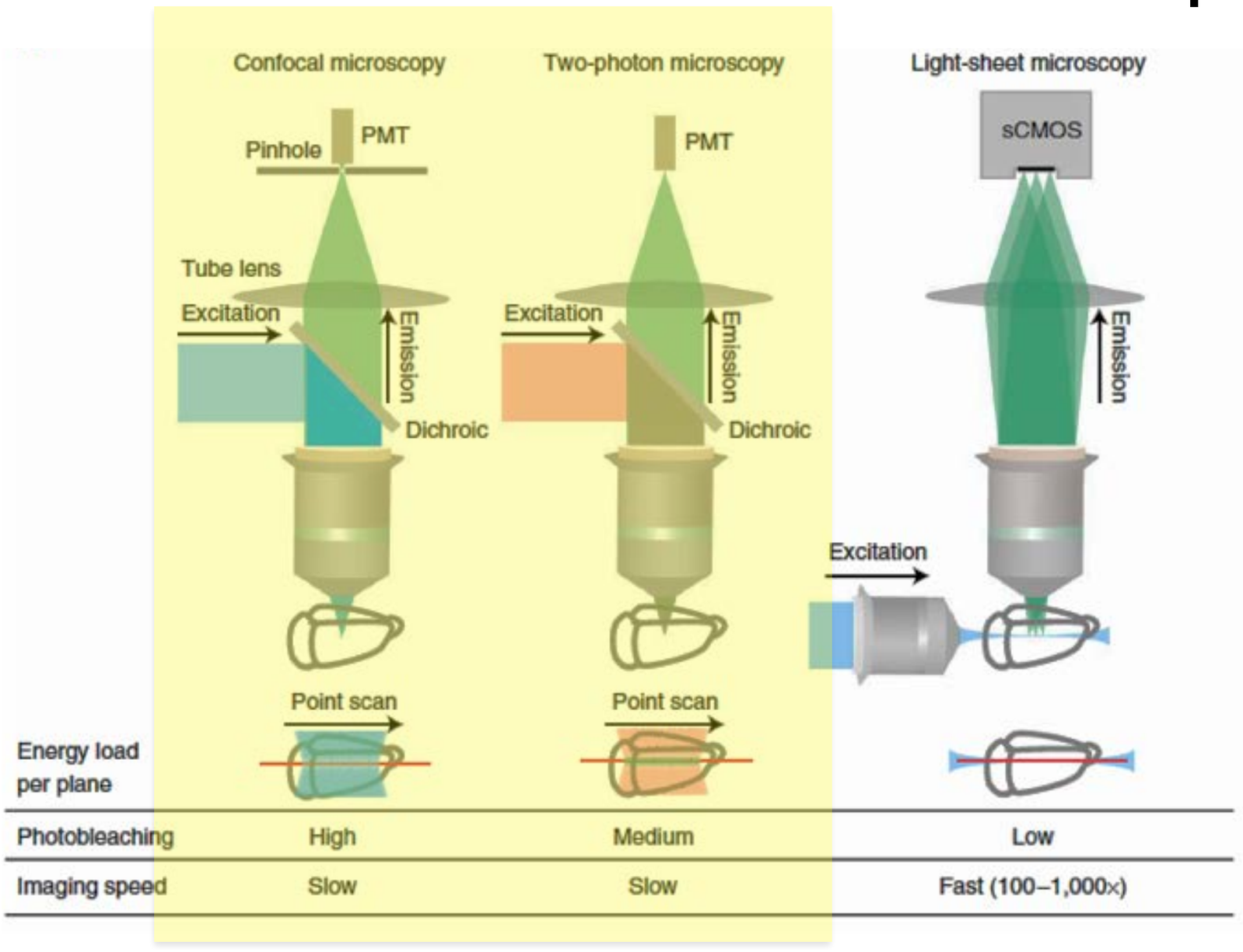
Multiples types of fluorescent microscopy



Photobleaching	High	Medium	Low
Imaging speed	Slow	Slow	Fast (100–1,000×)

Tomer et al Nature Protocols 2014

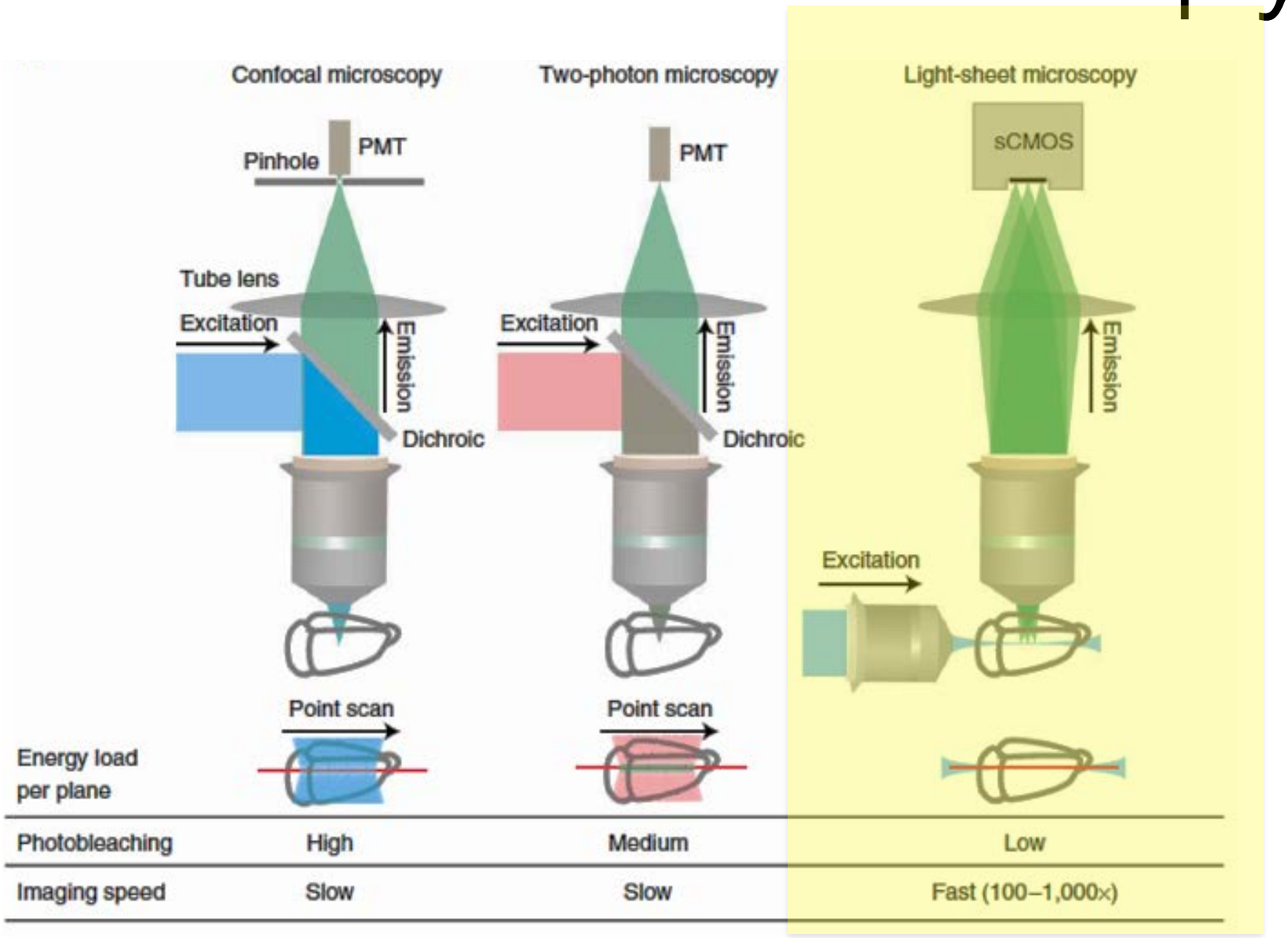
Multiples types of fluorescent microscopy



Tomer et al Nature Protocols 2014

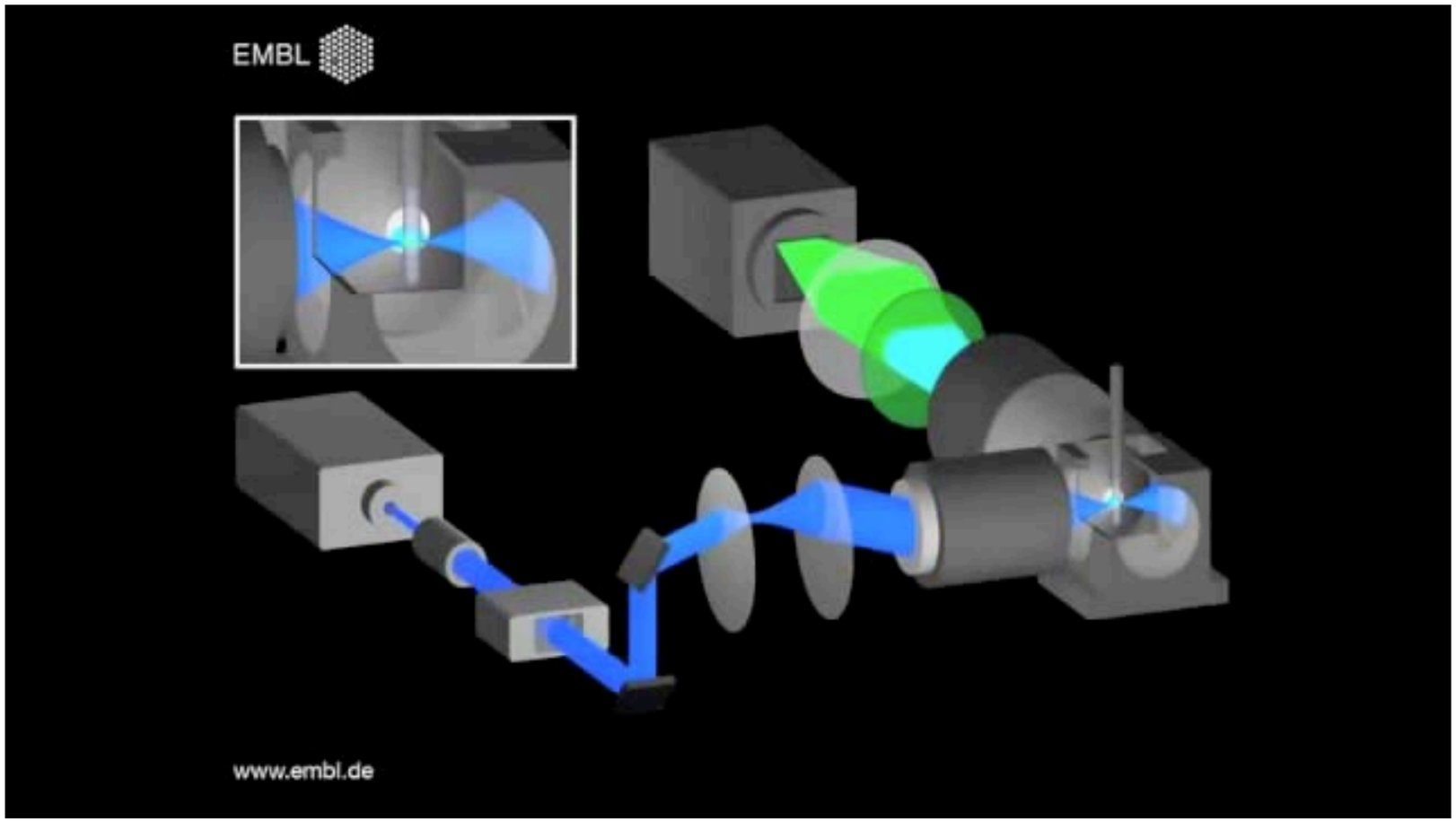
Microscope restrictions mean back to the guillotine!

Multiples types of fluorescent microscopy

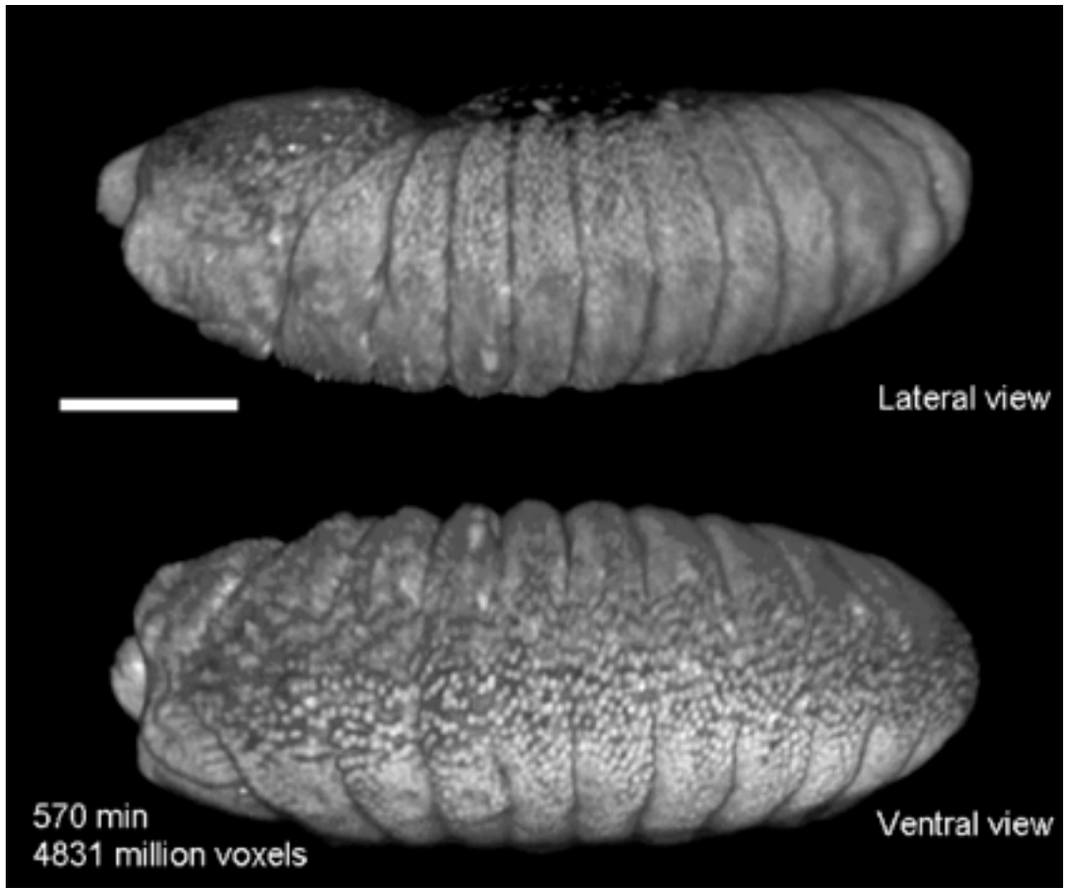


Tomer et al Nature Protocols 2014

How does LSFM work?



LSFM has mainly been used to image small model animals



Truong et al Nature Methods 2011

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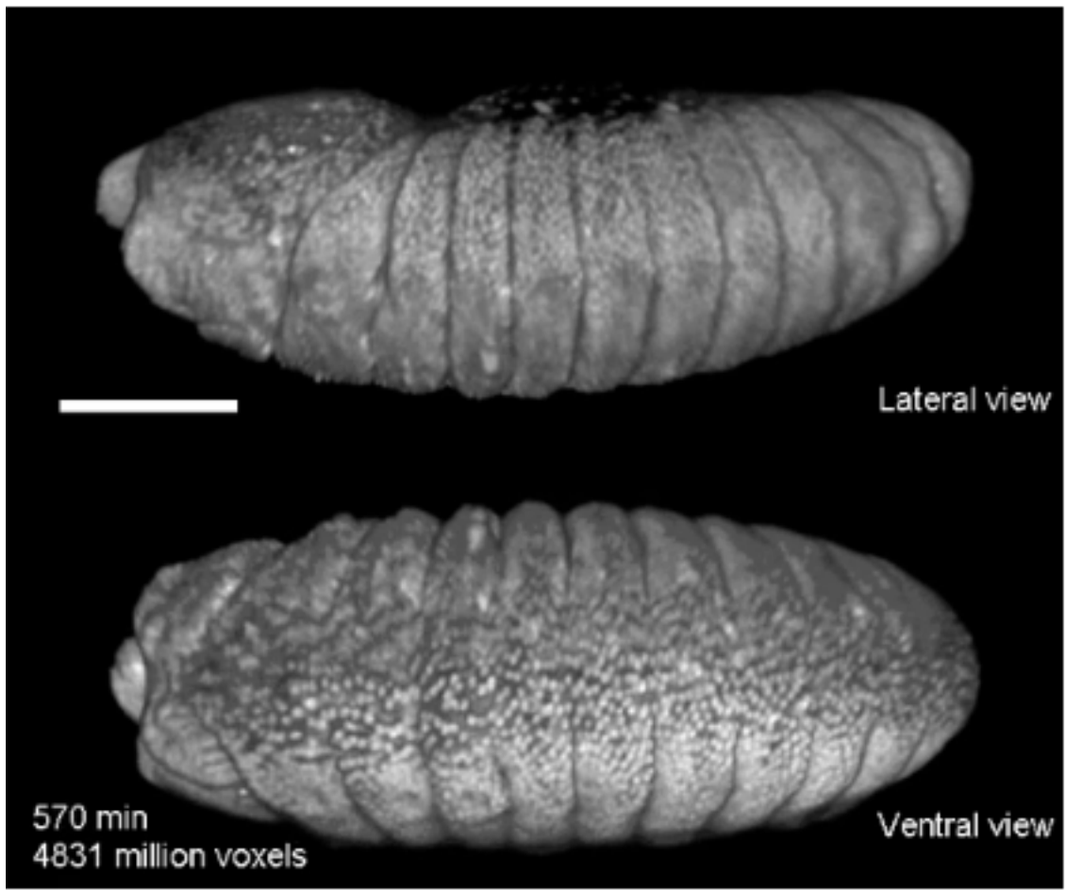

Truong et al Nature Methods 2011

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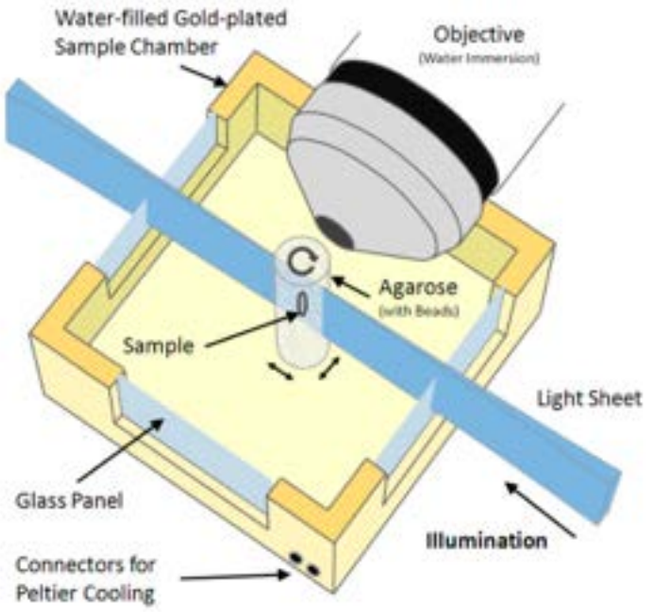
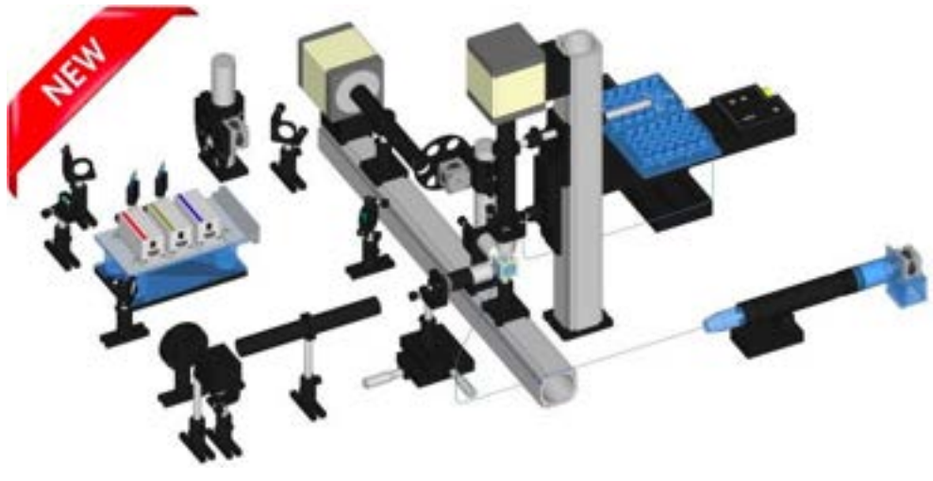
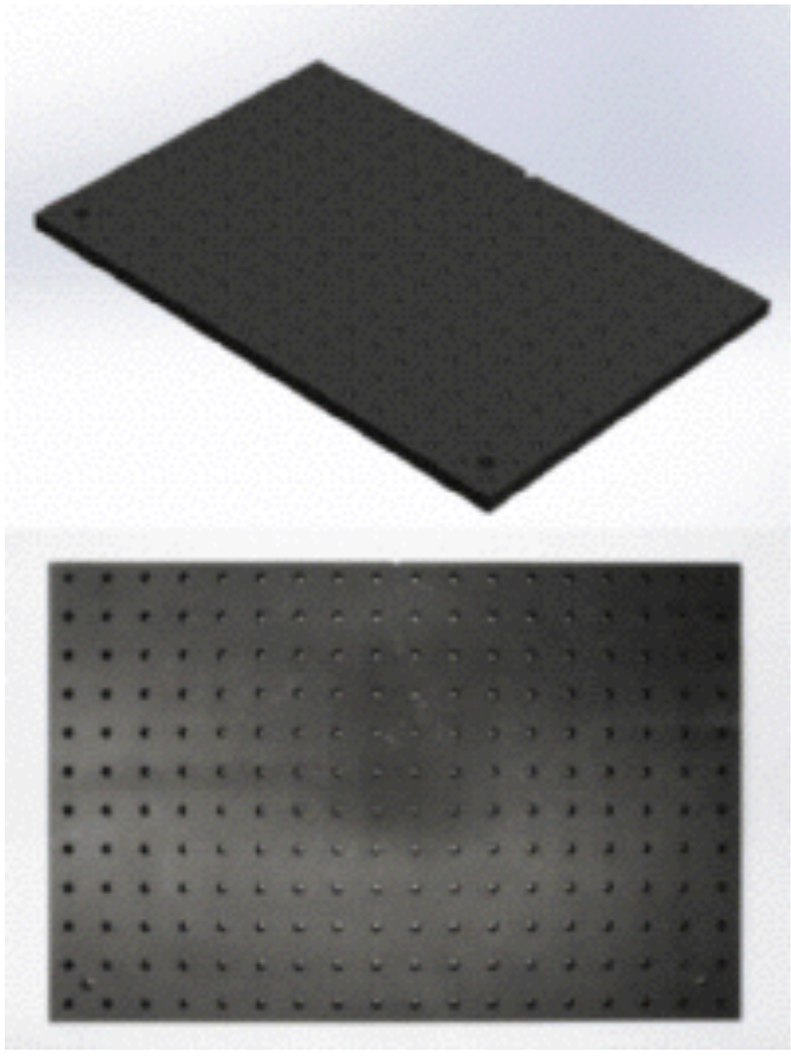
You can build an LSFM almost like LEGOs now!

OpenSPIM



OpenSPIN





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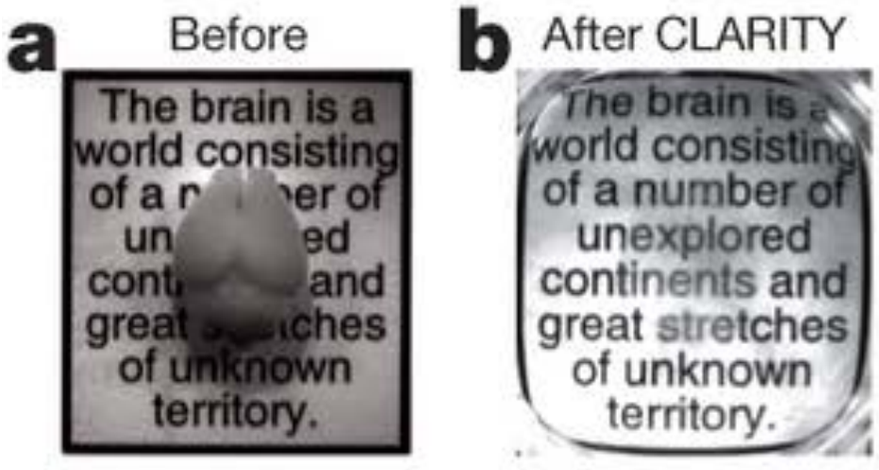
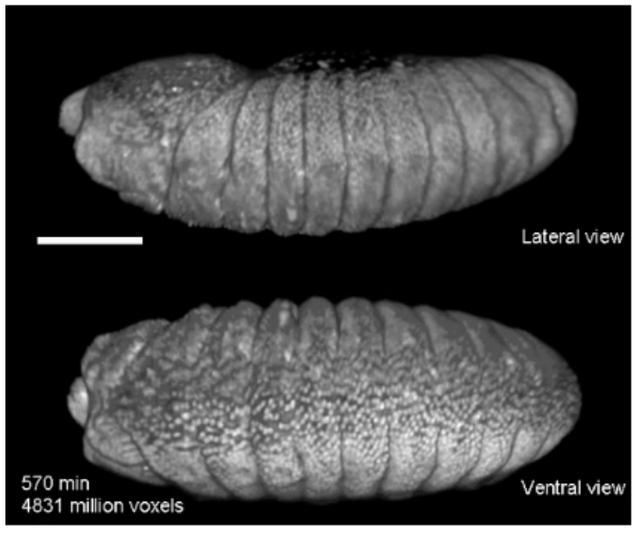
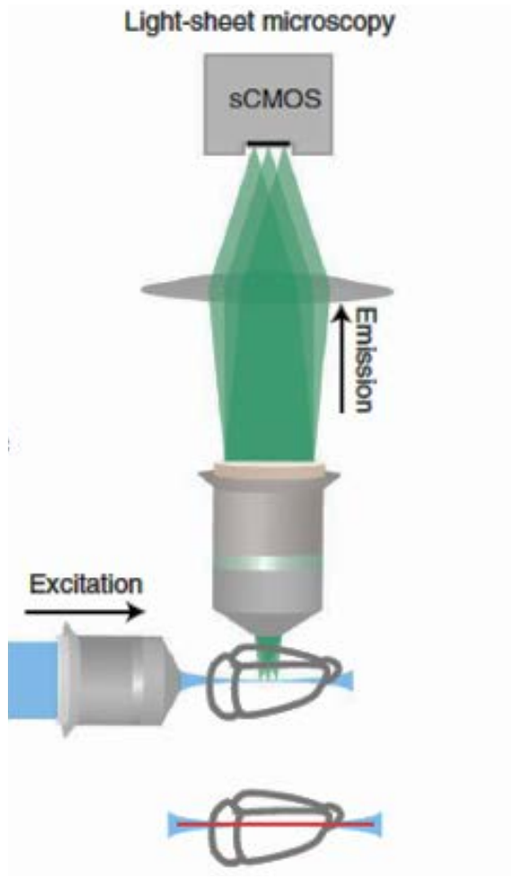
We have cleared tissue, fluorescent labels, and an appropriate fluorescent microscope







Truong et al Nature Methods 2011
Chung et al Nature 2013
Tomer et al Nature Protocols 2014

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Combining LSFM and optically cleared tissue

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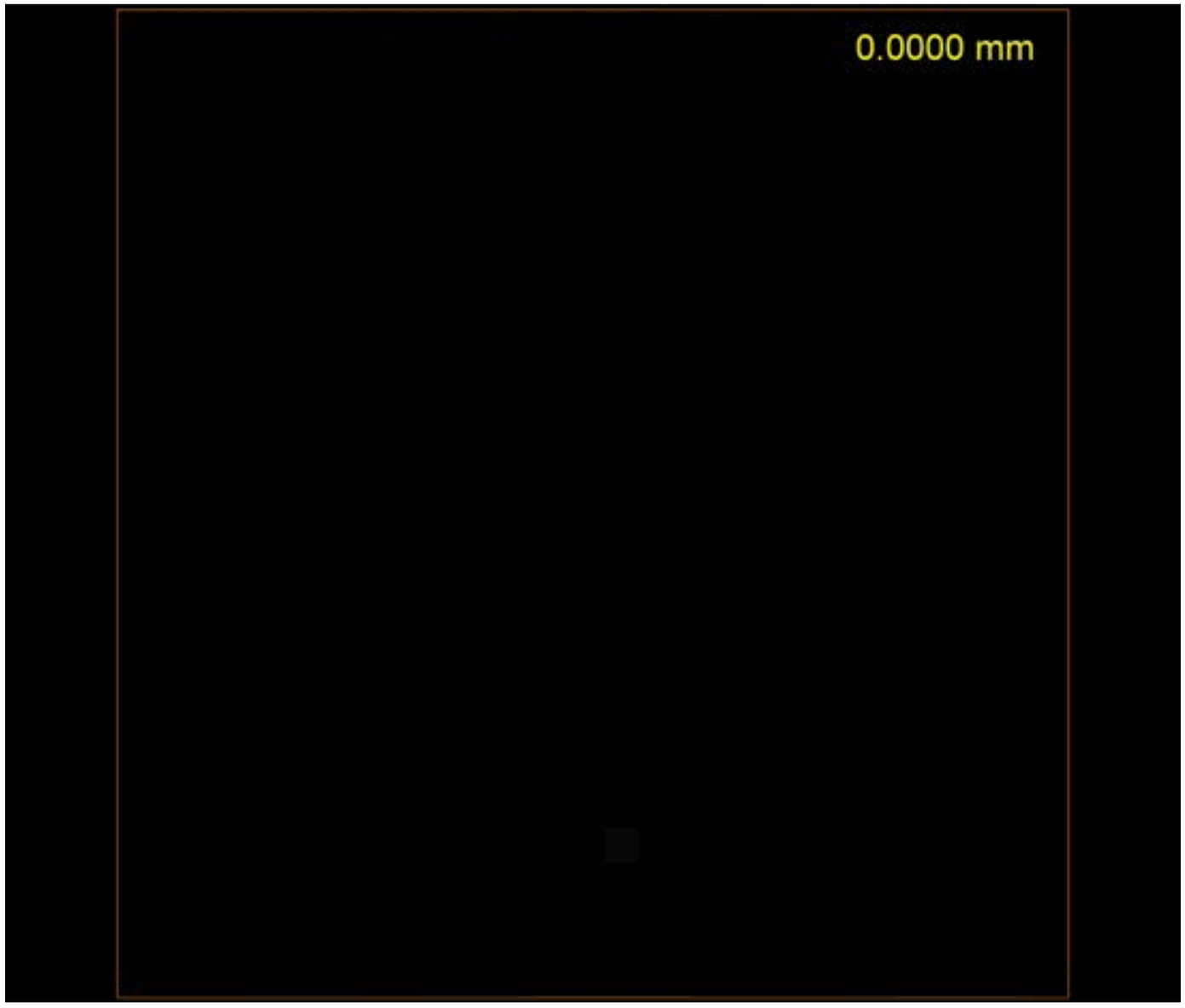
If you are really patient, you can reconstruct a whole mouse brain



Tomer et al Nature Protocols 2014

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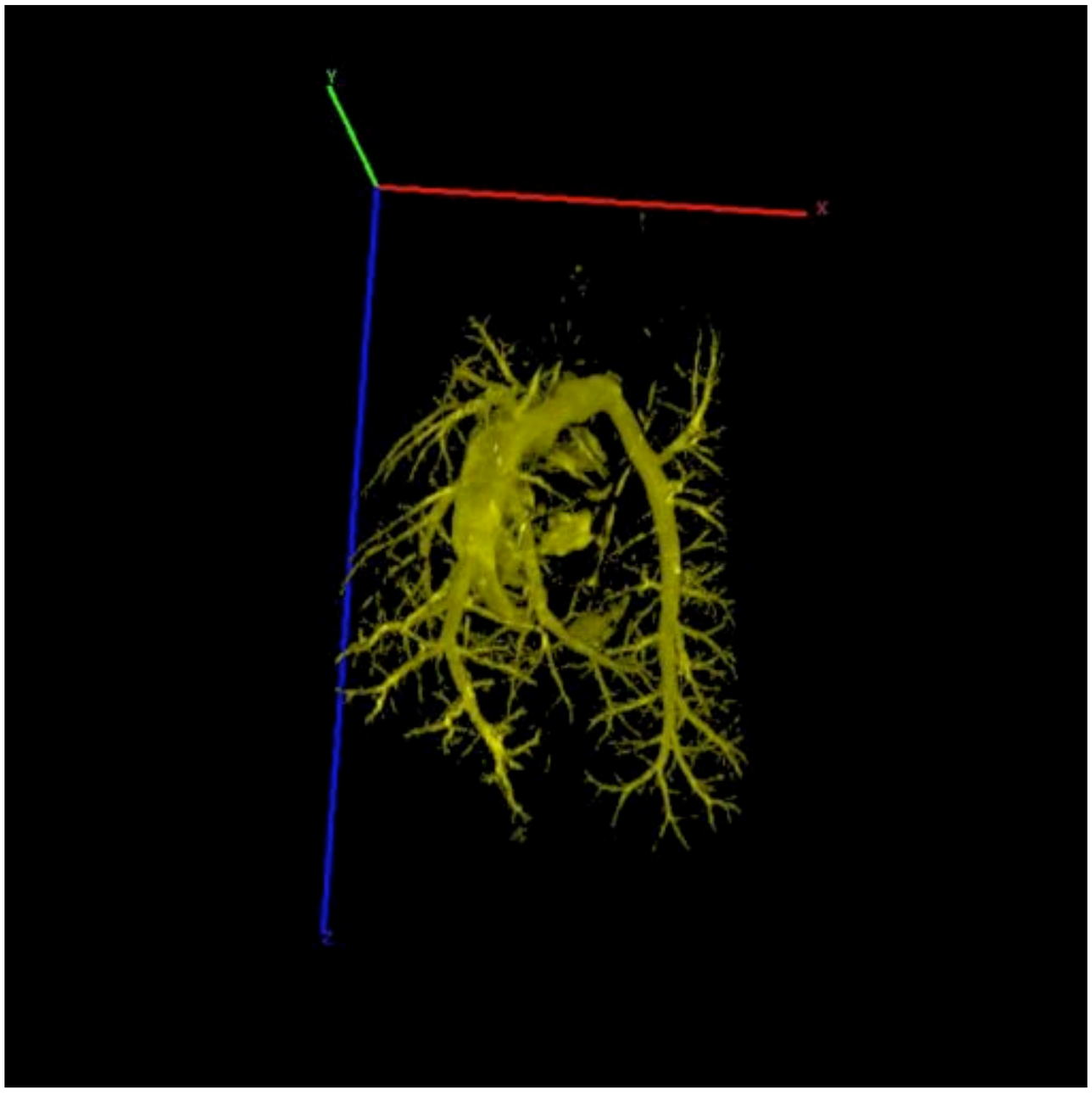
We can also measure lung structure



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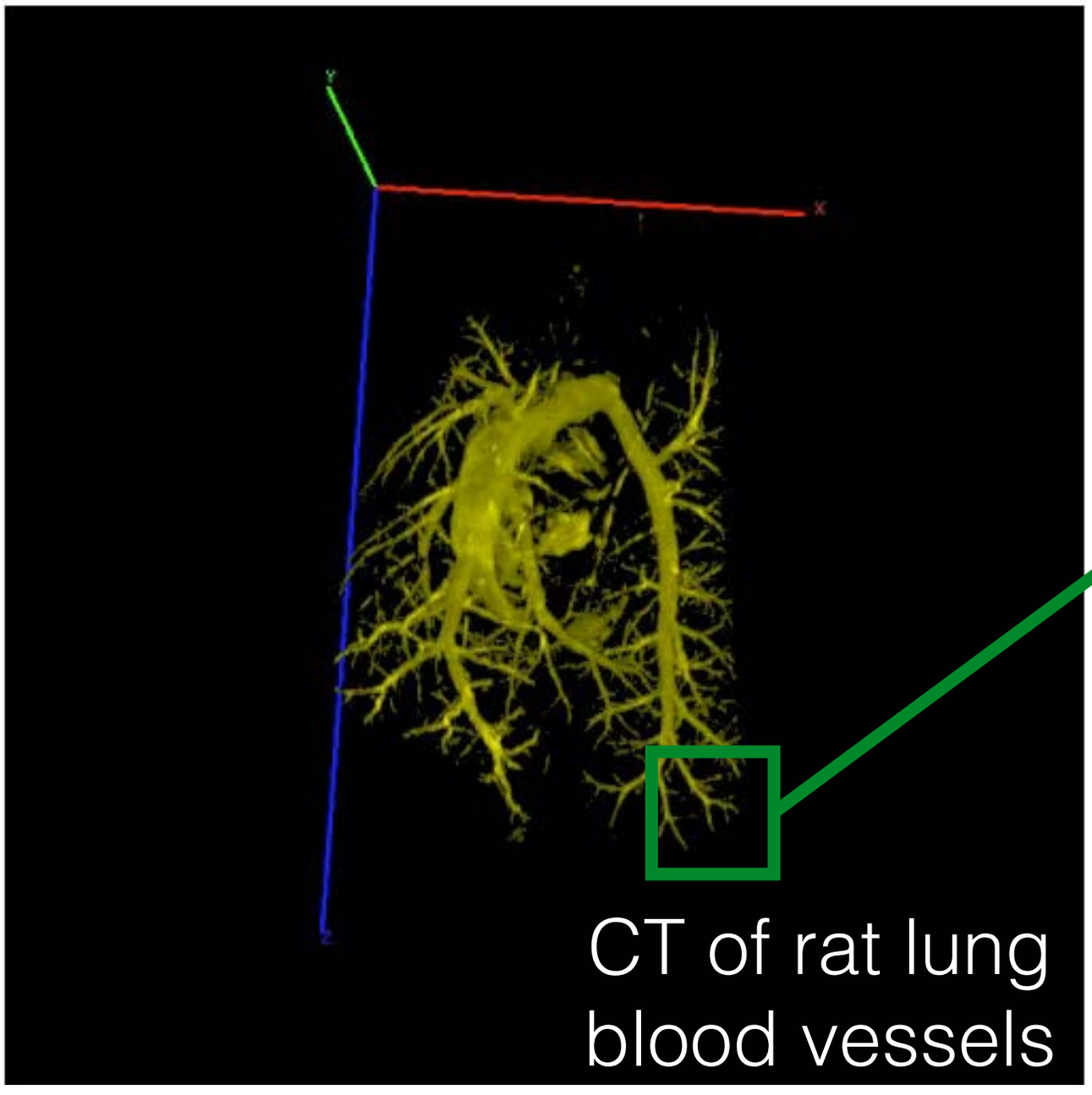

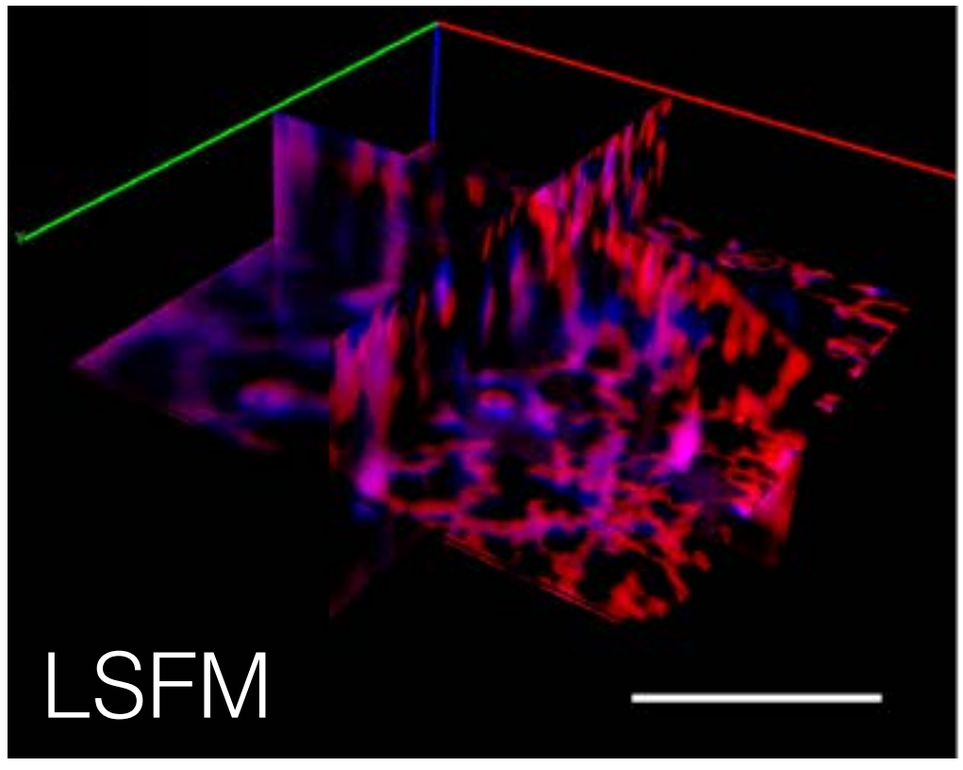

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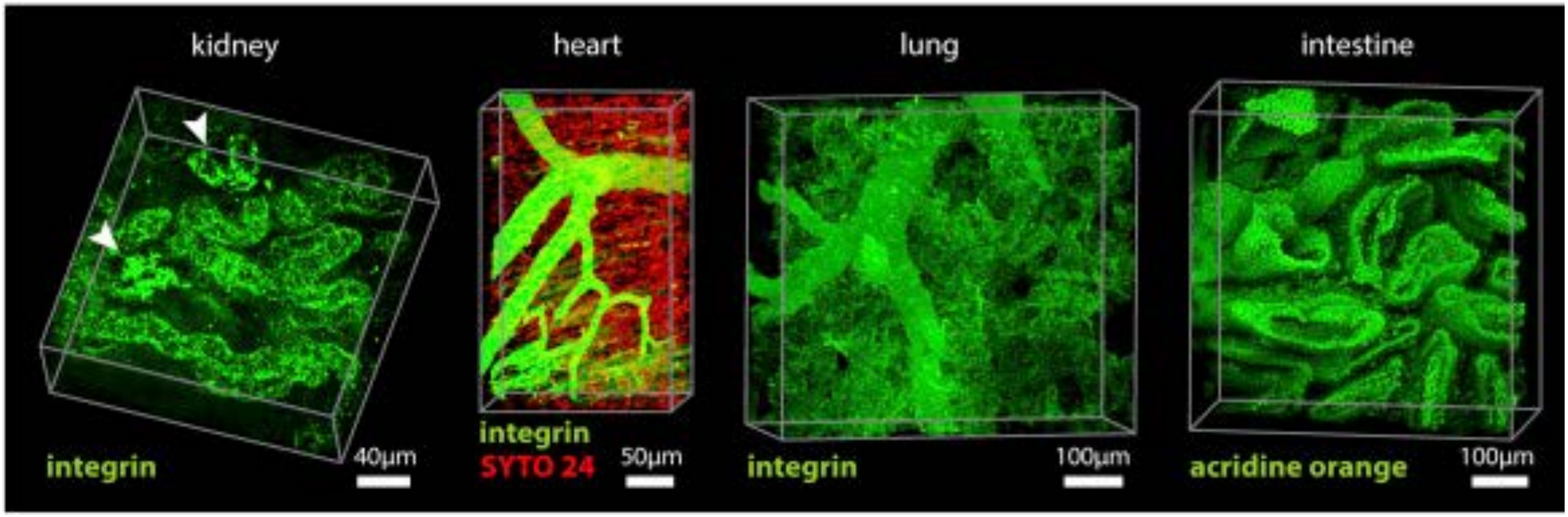
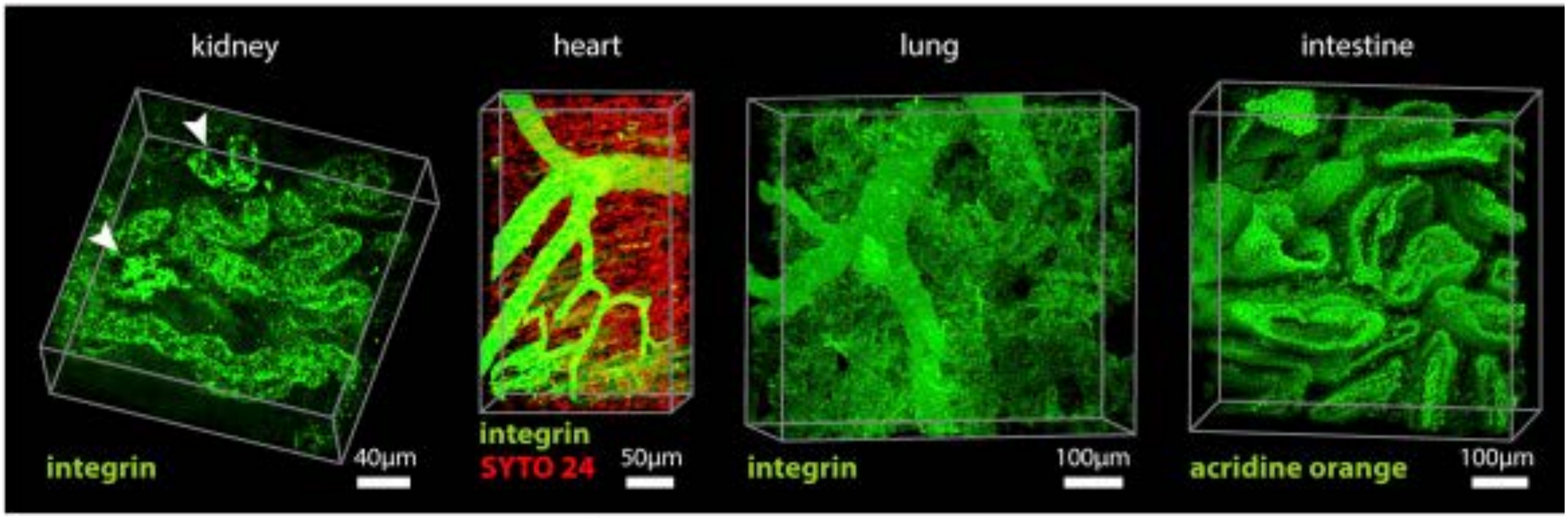
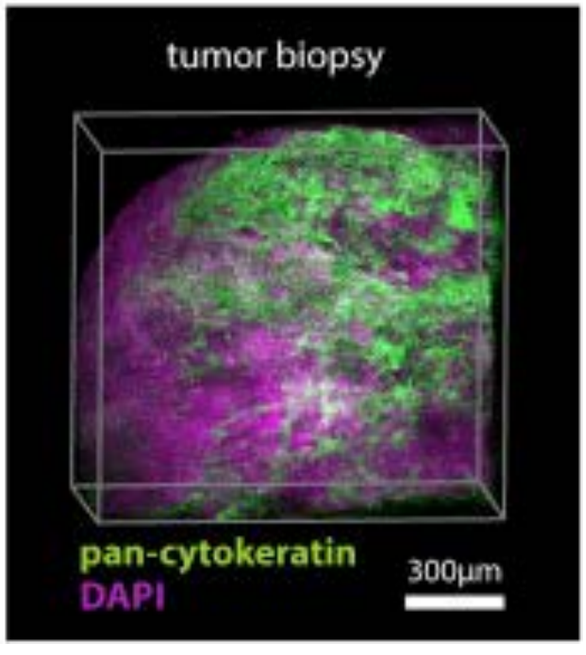
Application to animal models of disease



Yang et al Cell 2015

Application to animal and human models of disease





Yang et al Cell 2015

Application to analyzing structural changes in the brain from external events

ARTICLE

doi:10.1038/nature15698

Basomedial amygdala mediates top-down control of anxiety and fear

Avishek Adhikari[1,2]*, Talia N. Lerner[1,2]*, Joel Finkelstein[1]*, Sally Pak[1], Joshua H. Jennings[1,2], Thomas J. Davidson[1,2], Emily Ferenczi[1,3], Lisa A. Gunaydin[1,3], Julie J. Mirzabekov[1], Li Ye[1,2], Sung-Yon Kim[1,3], Anna Lei[1] & Karl Deisseroth[1,2,3,4,5]

Application to analyzing structural changes in the brain from external events

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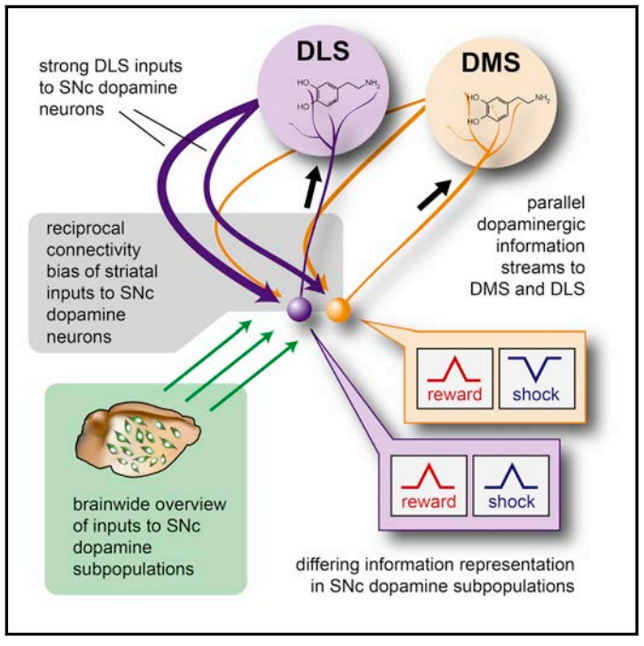
Cell

Article

Intact-Brain Analyses Reveal Distinct Information Carried by SNc Dopamine Subcircuits

Graphical Abstract



Authors

Talia N. Lerner, Carrie Shilyansky, Thomas J. Davidson, ..., Liqun Luo, Raju Tomer, Karl Deisseroth

Correspondence

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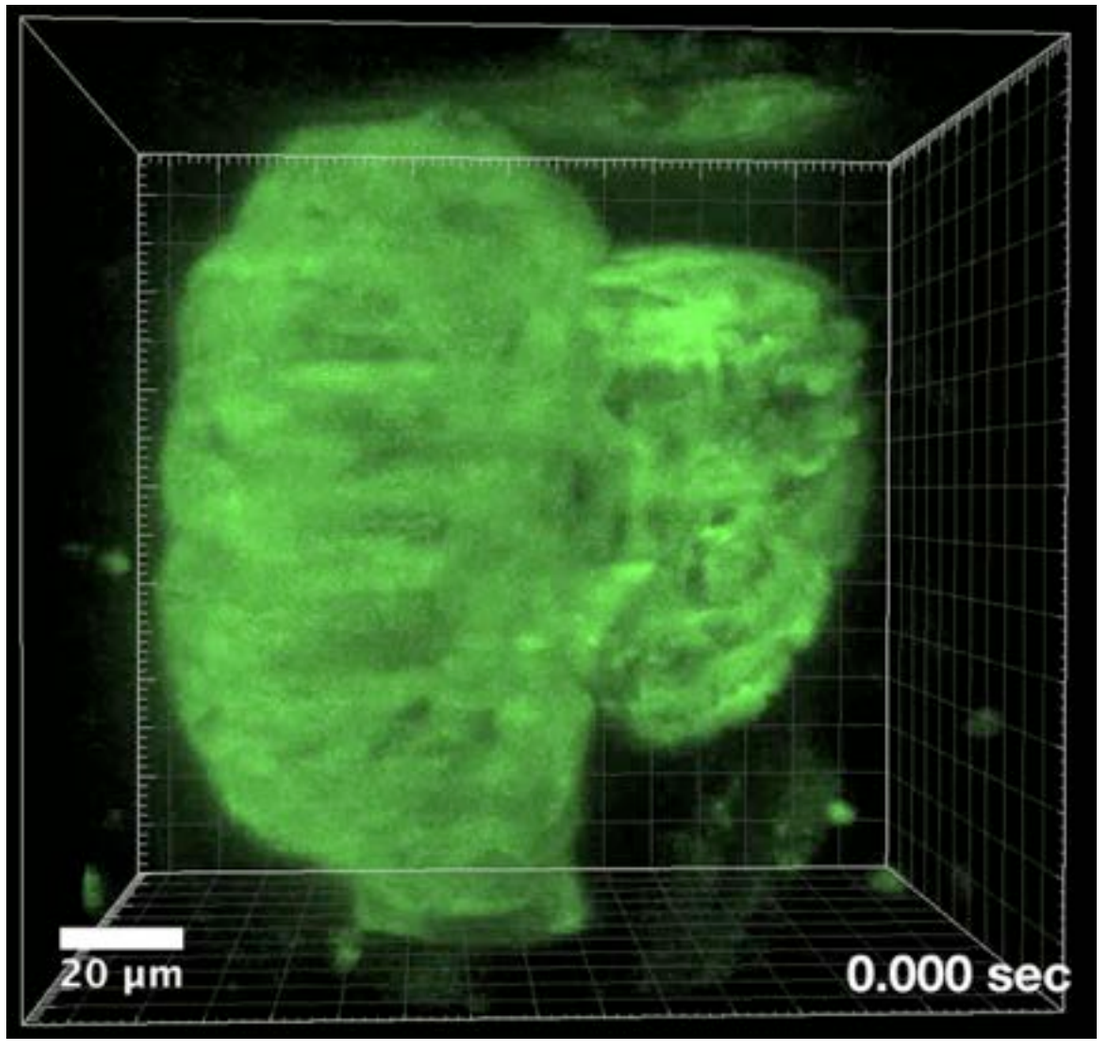
In Brief

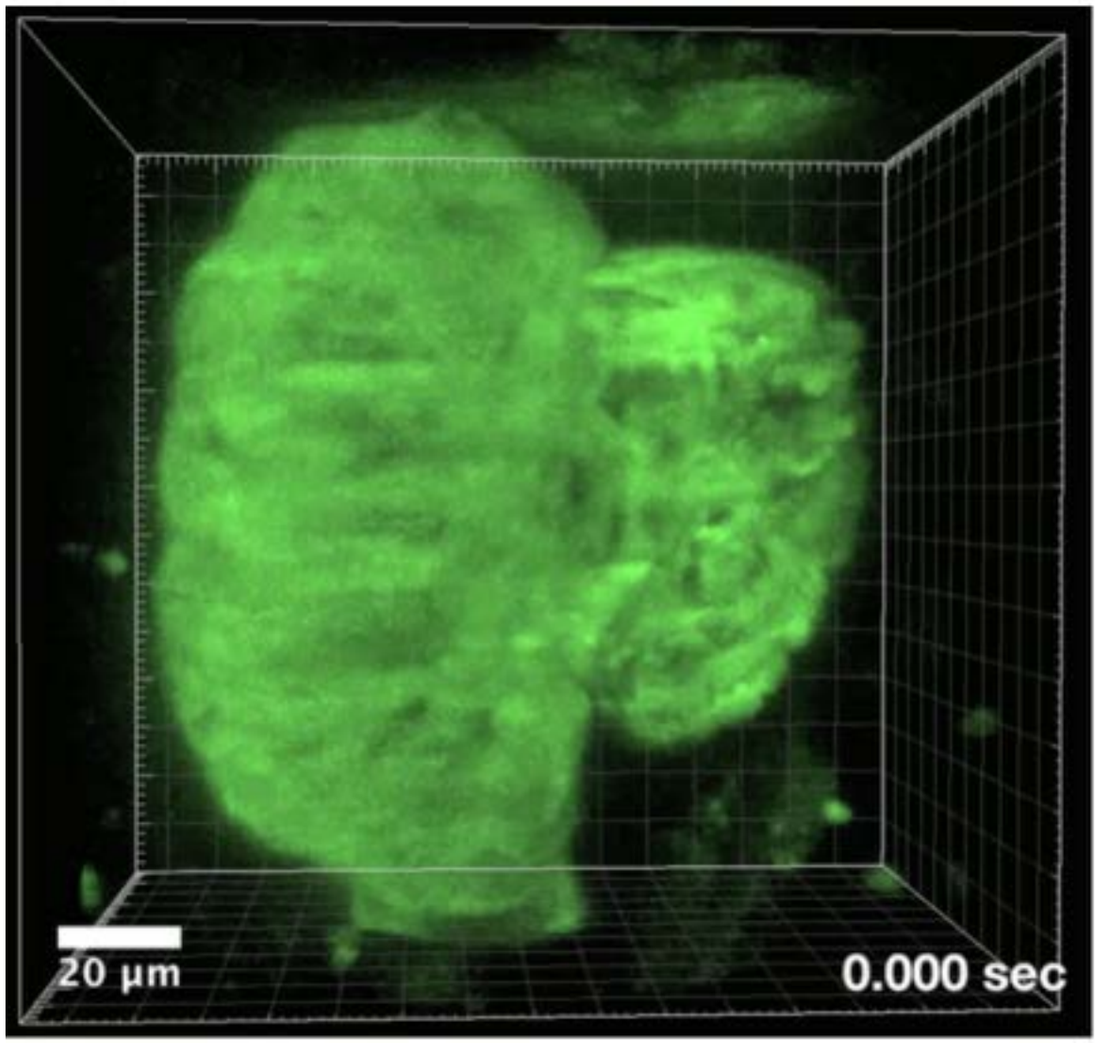
Exploring the mammalian brain with an array of intact-brain circuit interrogation tools—including CLARITY, COLM, optogenetics, viral tracing, and fiber photometry—reveals that neurons in the SNc region present different biophysical properties, wiring of inputs and outputs, and activity during behavior, despite signaling through the same neurotransmitter.

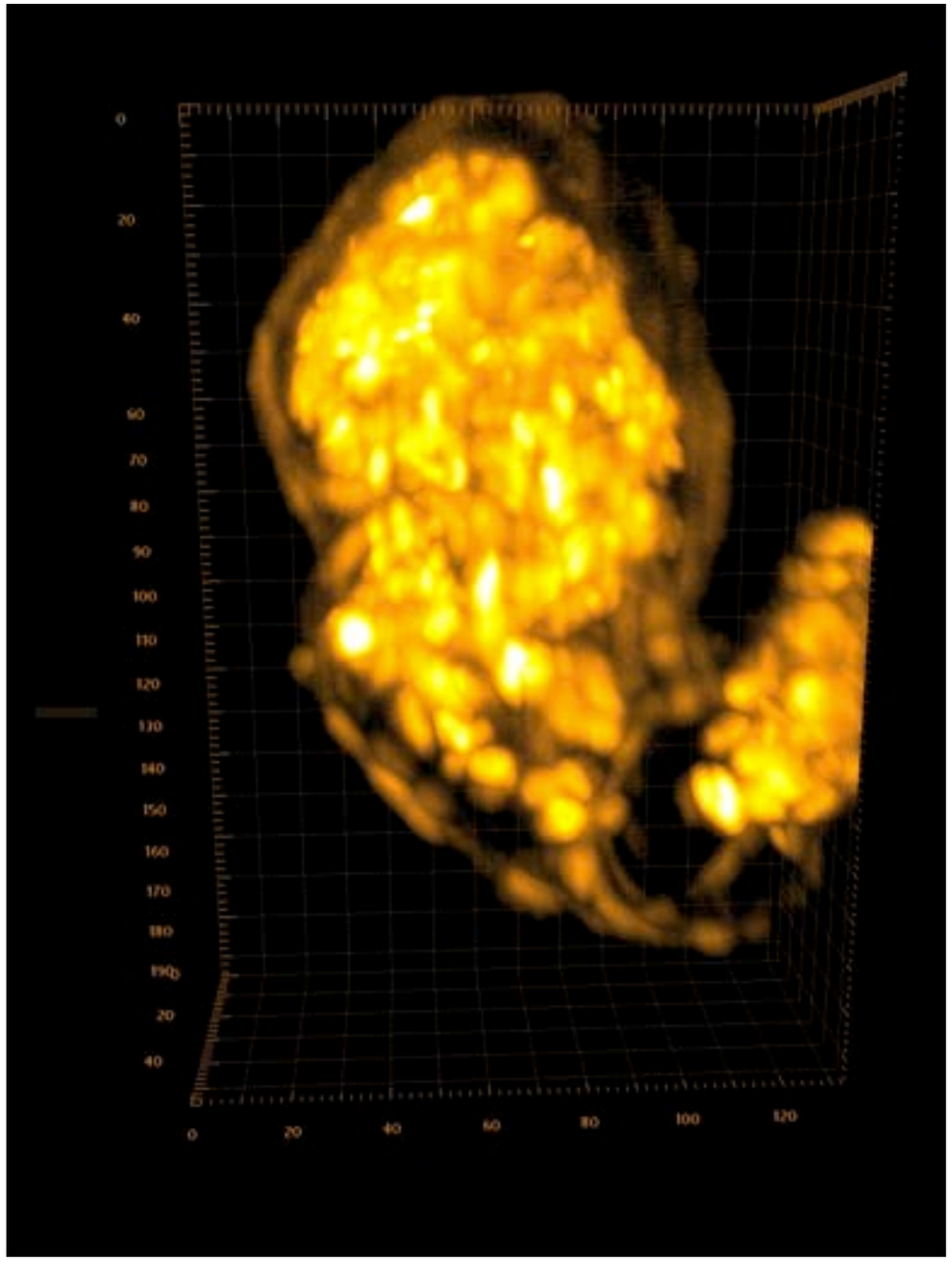
Application to the dynamics of development



Trivedi et al Biomedical Optics Express 2015

Application to the dynamics of development - we can measure even faster!





Trivedi et al Biomedical Optics Express 2015
Fahrbach et al Optics Express 2014

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Jasmine Singh

Pediatric Heart Lung Center
Research Therapy Laboratory Education Training
Innovation
PHLC
Collaboration

Gregory Seedorf
Dr. Steven Abman

Colorado State University

Duncan Ryan
Dr. Alan Van Orden