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Spotlight

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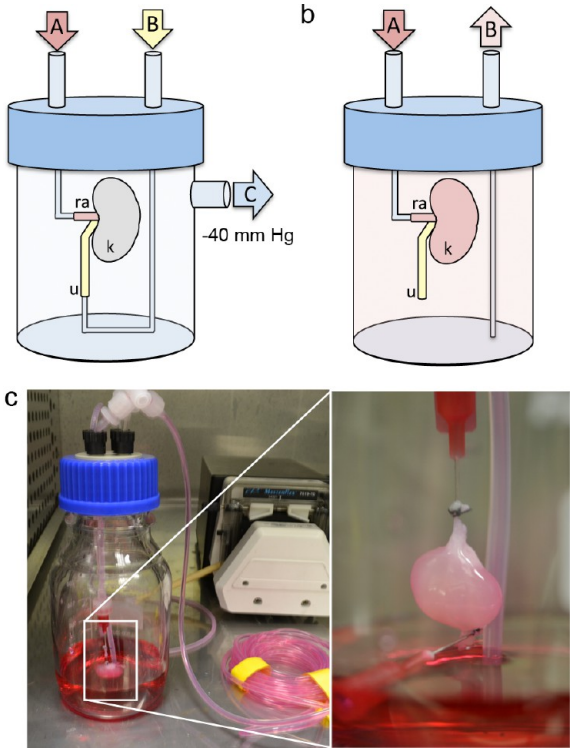
KIDNEY CREATION



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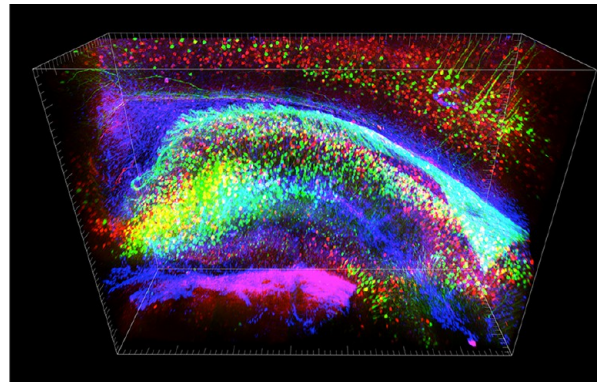
Of the nearly 1 million people living with end-stage kidney disease, 100,000 of them are waiting for a donor kidney, and only 18,000 transplants are performed each year. Clearly, the math substantiates the urgent need for alternative methods to treat kidney disease. The availability of bioengineered kidneys would provide restoration of kidney function while mitigating the side effects of immunosuppression that necessarily accompany kidney transplants. Toward this goal, Song *et al.* (*Nat. Med.* advance online publication April 14, 2013; DOI: 10.1038/nm3154) report the creation of decellularized kidney scaffolds, the regeneration of live tissue in the scaffolds, and the demonstration of the functional potential of the bioengineered kidneys when transplanted into a rat.

Their approach first involves removing all cellular components from a kidney using detergent. This process, which was achieved in rat, pig, and human kidneys, preserves the tissue architecture of the kidney but strips the organ of any functional capabilities such as blood filtration or generation of urine. Rat kidney scaffolds were then repopulated with endothelial and kidney cells by instilling the endothelial cells through the renal artery and the kidney cells through the ureter, and transferring the constructs to a perfusion bioreactor suitable for whole-organ culture. Remarkably, the regenerated kidneys could perform kidney-like functions *in vitro*, including filtering perfused fluid, clearing metabolites, reabsorbing electrolytes, and producing urine. Finally, a kidney regenerated in this manner was transplanted into a rat, and was shown to produce urine, clear creatinine, and excrete urea, glucose, and albumin, albeit not as efficiently as a native kidney. These findings showcase the exciting potential of this approach toward the development of bioengineered kidneys suitable for treatment of individuals with kidney disease. **Eva J. Gordon, Ph.D.**

IMAGING INTACT BIOLOGICAL SYSTEMS WITH CLARITY



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Though molecular imaging technologies have greatly advanced our understanding of biological processes, use of these methods in investigation of intact biological systems, such as a whole brain, remains a major challenge. The presence of lipid molecules is a major culprit in preventing effective imaging of intact systems, as lipids scatter light and hinder macromolecule diffusion into the tissue, though they provide a necessary structural framework that holds the tissue together. To overcome this challenge, Chung *et al.* (*Nature* advance online publication April 10, 2013; DOI: 10.1038/nature12107) develop a method to remove lipids from tissue while preserving the structural integrity of the system.

Their method, called CLARITY, relies on the infusion of hydrogel monomers, formaldehyde, and thermally triggered initiators into the tissue. Temperature-induced polymerization, followed by a specially developed method for ionic extraction of the lipids called electrophoretic tissue clearing, leaves a structurally supported, lipid-free biological system appropriate for molecular labeling and imaging. CLARITY was tested on the brain of a 3 month old mouse expressing enhanced yellow fluorescent protein in a subset of projection neurons. High-resolution fluorescence imaging of long-range projections, cellular and subcellular structures, protein complexes, nucleic acids, and neurotransmitters, was achieved in the intact tissue. CLARITY was also successfully used on a human post-mortem brains for the imaging of neurons and projections over large volumes, demonstrating the potential of this approach for examining the structural and molecular features of the normal brain as well as those afflicted with neurological disorders. This study

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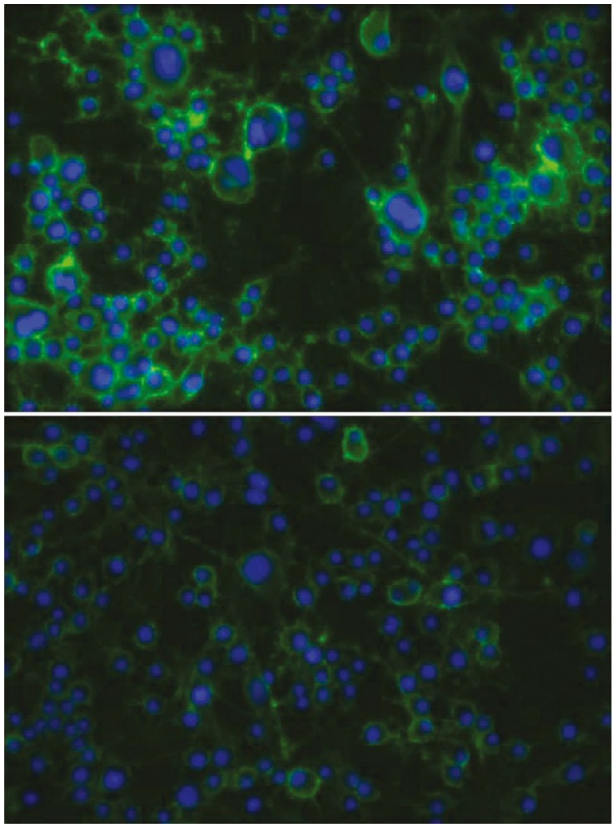
illustrates the exciting potential of CLARITY to offer an inclusive view of intact biological systems at a molecular level. **Eva J. Gordon, Ph.D.**

A REASON NOT TO FRET ABOUT PRION DISEASES

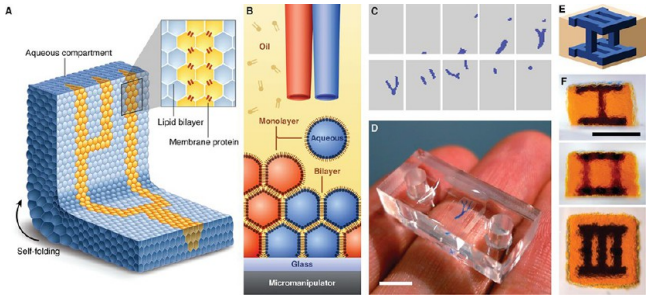


Karapetyan, Y. E., *et al., Proc. Natl. Acad. Sci. U.S.A., 110,* 7044−7049. Copyright 2013 National Academy of Sciences, U.S.A.

Prion diseases such as mad cow disease and Creutzfeldt-Jakob disease are caused by prions, infectious, misfolded, aggregated forms of prion protein (PrP). PrP is a cell surface protein normally found in the brain and other tissues, and mice that do not express PrP are resistant to prion diseases. This suggests diminishing PrP levels in cells as a potential therapeutic strategy for these devastating neurological disorders. To this end, Karapetyan *et al.* (*Proc. Natl. Acad. Sci. U.S.A.* 2013, *110*, 7044−7049) report a novel high throughput screen for identifying small molecules that reduce cell surface expression of PrP.

The screen is a based on fluorescence resonance energy transfer (FRET) using two fluorescent antibodies that bind to distinct regions of PrP. A collection of 1280 approved drugs was screened, and of 9 hits identified, 2 were investigated further. Tacrolimus, an immunosuppressant, and astemizole, an antihistamine, were each capable of inhibiting prion replication in neuroblastoma cells. Investigation into the mechanism of their activity suggested that tacrolimus inhibits translation of PrP, while astemizole appears to prevent prion propagation by inducing autophagy, a catabolic process in which the cell degrades unnecessary substances using its lysosomal machinery. When tested in mice infected with prions, astemizole, but not tacrolimus, prolonged survival. The screen presented in this study is a promising general strategy for finding drug leads for prion diseases, and the favorable drug profile of astemizole points to the rapid potential of this compound for prevention and treatment of these conditions. **Eva J. Gordon, Ph.D.**

TOWARD TISSUE-LIKE MATERIALS



From Villar, G., *et al., Science,* 2013, *340,* 48−52. Reprinted with permission from AAAS.

Though researchers would like to build flexible, biocompatible, and programmable materials for novel electronic devices or synthetic tissues, building these types of networks in three dimensions has proved challenging. Now Villar *et al.* (*Science,* 2013, *340,* 48−52) have used a printing technique to construct a tissue-like material from lipid-encased water droplets.

Using a double nozzle on a micromanipulator, the researchers can squirt out aqueous droplets into an oil bath that includes lipid molecules. As the 65 pL droplets land in the bath, they acquire a lipid bilayer on their surfaces and add to a growing network of droplets. In addition, the printing mechanism allows the researchers to embed specific membrane proteins into the lipid bilayers separating selected droplets to create patterns of droplets with specific characteristics. In one set of experiments they embedded staphylococcal α-hemolysin (αHL) into the bilayers of a set of droplets within a printed structure. These proteins form channels within cell membranes that allow ions and other small molecules to permeate. With electrochemical experiments, the researchers saw increases in current along a pathway that included the αHL droplets, but not in regions with insulating droplets that do not contain αHL. This movement of electrical signal mimics the function of nerves.

Villar *et al.* also made droplet networks that could change their shape after printing as a way to mimic muscle action. The lipids surrounding the droplets allow water to pass through them. So the researchers used different ion concentrations in droplets in different layers, and the subsequent movement of water by osmosis prompted droplets to expand or contract. In one experiment they induced lines of droplets to curve into a circle, and in another they printed layers in a petal shaped array that closed into a hollow sphere.

The work is just a first step, and the ability to incorporate other proteins or even cells into such networks could create devices with therapeutic properties, such as the ability to repair or augment tissues. **Sarah A. Webb, Ph.D.**

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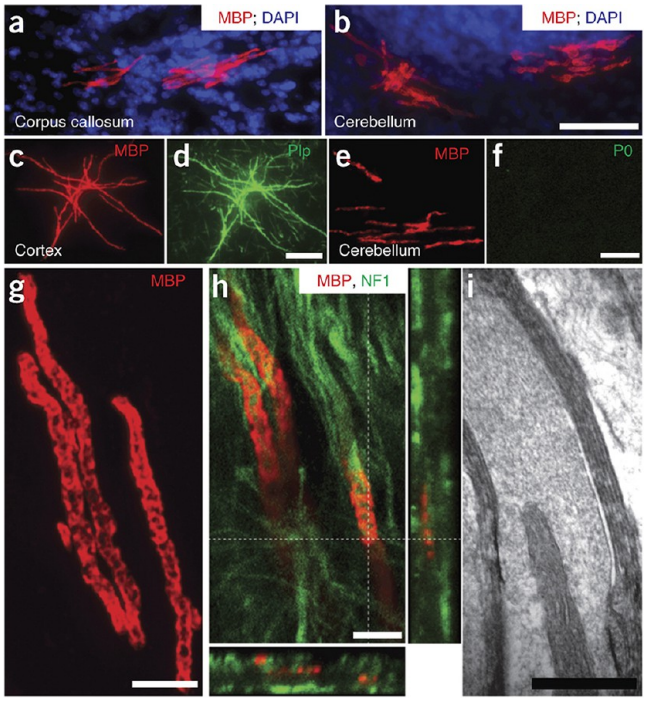
FROM LIMB TO MYELIN



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Oligodendocytes are glial cells in the nervous system that provide myelin, a critical insulation around neuronal axons. Defects in myelination occur in diseases such as multiple sclerosis and cerebral palsy, or from injuries to the spinal cord. Oligodendrocyte precursor cells (OPCs) represent a possible therapy for the human diseases and results in mouse model systems have shown striking promise. Remyelination was observed when researchers took mouse OPCs generated from embryonic stem cells and injected them into a mouse carrying a myelin defect. Bringing this to the human is difficult, but a new study indicates another promising route for generating those precious OPC cells. Inspired by induced pluripotent stem (iPS) cell reprogramming, Yang *et al.* (*Nat. Biotechnol.* advance online publication 2013; DOI: 10.1038/nbt.2564) went hunting for transcription factors that could reprogram fibroblast cells into induced OPC-like cells (iOPC).

Using gene expression data comparing oligodendroglia to other neural lineages, candidate OPC-specifying factors were identified. Ten factors were selected, all of which were known to exhibit severe defects when mutated. Then, mouse limbs served as a source for fibroblasts since they contain no neural lineage cells that might contaminate the analysis. The mouse strain encoded the green fluorescent protein, GFP, under the control of a promoter specific for OPCs and mature oligodendrocytes. Fibroblasts were transduced with a lentivirus pool carrying the 10 different genes and the cells were screened for GFP expression. A reductionist approach uncovered a minimal combination that yielded robust GFP expression; Sox10, Olig2 and Zfp536. The researchers then moved to the rat, a model system suitable for comparing the iOPCs to primary cultures of OPCs. Gene expression profiling indicated that the iOPCs were far more similar to primary OPCs than to fibroblasts. The group went on to show that iOPCs could further differentiate into myelinating oligodendrocytes, both in a neuronal coculture system and in a transgenic mouse model harboring a genetic myelination defect in the nervous system. As with other induced stem cell systems, there's still a long way to go before this can move into humans, but this study indicates that defined factors can shift mammalian fibroblasts into yet another precursor cell type. If human iOPCs can one day be generated, using grafted cells for remyelination could have tremendous therapeutic potential. **Jason G. Underwood, Ph.D.**

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