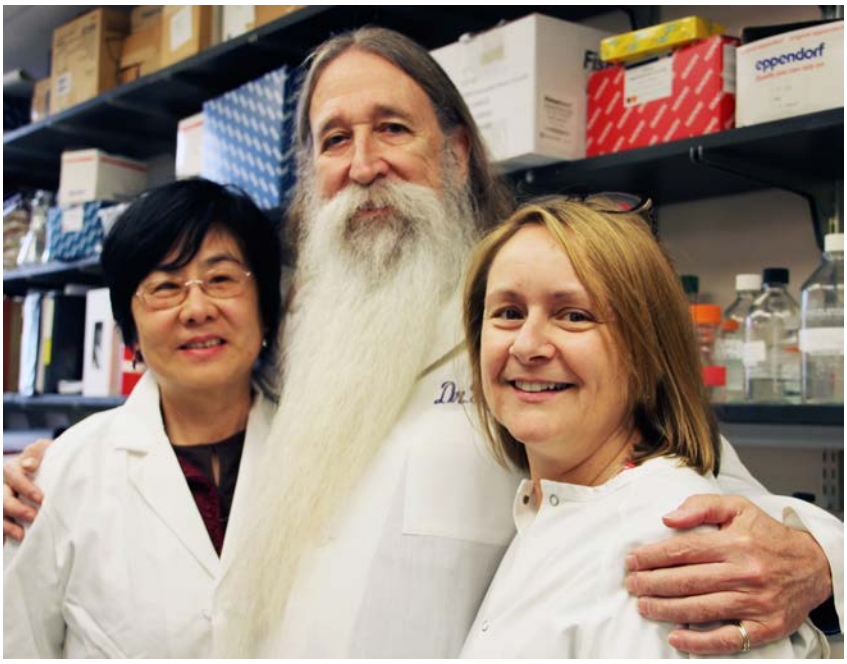
NEWSLETTER

Animal models

of human genetic disease



Dr. Mark Haskins with coworkers Ping Wang and Patty O'Donnell

Dr. Mark Haskins earned his VMD in 1969 and his PhD in 1977. In 1974 he joined the faculty of Penn Vet in the Department of Pathobiology. Like many people with a 40-year research program, the questions he has focused on have remained reasonably consistent, while the techniques used to address the questions have changed dramatically. **Continued on page 2**

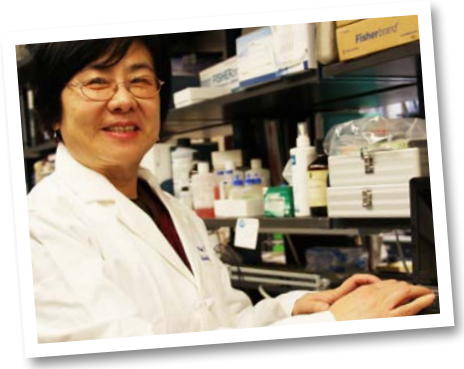
NIH Changes & Updates

Investigators who submit grant applications to the National Institutes of Health are alerted to updates regarding significant changes to the biographical sketch format. Use of the new format is encouraged now and *required* for applications submitted on or after May 25, 2015 (NOT-OD-15-032).

The NIH has also updated how substantial scientific changes' are identified in resubmission applications. It is now sufficient to outline the changes made in the introduction attach-ment, which in most cases still cannot exceed one page (NOT-OD-15-030).

DARKO STEFANOVSKI, PhD, *JOINS* CLINICAL STUDIES, NEW BOLTON

Dr. Darko Stefanovski, Assistant Professor of Biostatistics in the Department of Clinical Studies-New Bolton Center, joined the faculty of the School of Veterinary Medicine in August 2014. Dr. Stefanovski's research focus is on Type 2 Diabetes and Obesity. He is interested in the molecular mechanism of insulin independent glucose disposal, also known as Glucose Effectiveness (GE), in the liver and in brain/liver communication. Modulating GE may aid in glycemic control without the side effects of insulin therapy such as weight gain and hypo-glycemic episodes. He is working on early detection of problems with GE and their relationship to Type 2 diabetes and obesity.



Ping Wang has worked with Dr. Haskins for 25 years

DR. MARK HASKINS....*continued from page 1*

For example, when the veterinary genetics pioneer, Don Patterson, a professor in the department of Clinical Studies, Philadelphia, hired Mark to evaluate lesions in animals with genetic diseases, the focus was mostly descriptive - clinical and biochemical. Today, due to advances in our understanding of the genetic basis of these diseases, coupled with advances in molecular biology, descriptive analyses have given way to more mechanistic assessments that form the basis for therapeutic strategies to ameliorate diseases- interventions that could not have been imagined in 1974.

The history of the genetics group at Penn Vet began in 1974 with Don Patterson, who had a project in the medical school's first NIH human genetics center grant to develop a screening laboratory to identify large animal models of human genetic disease. Don made it quite clear that finding the models was just the beginning; the ultimate goal was to use these animal models to understand the underlying causes of these diseases. After identifying the first animal with any mucopolysaccharidosis (a cat with MPS VI), Patterson's group found a cat with MPS I and were sent a dog from California with MPS VII. This led to a focus by the group on animals with what can generally be referred to as lysosomal storage diseases (LSDs). LSDs are inherited metabolic disorders caused by reduced activity of a single lysosomal enzyme and deficient catabolism of large substrates in lysosomes. As most lysosomal enzymes are

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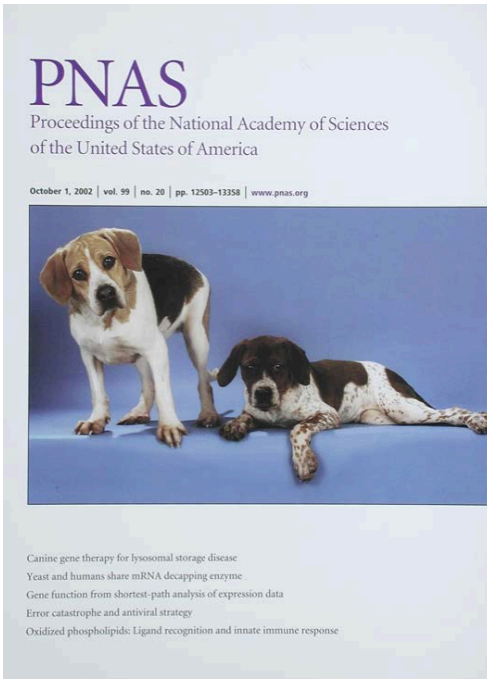

Fig. 1 Canine Gene Therapy for Lysosomal Storage Disease
PNAS USA 99(20):13102-7 (October 2002)

PENN VET'S EBOLA RESEARCH *and* RESOURCES

As Ebola continues to dominate in the news, Penn Vet provides the latest information on Penn Vet faculty involved in research discovering novel therapeutics to treat viral disease. Visit the site and see the faculty who study host pathogen interactions, viral signaling mechanisms, treatment of zoonoses, and the public health impact of Ebola (http://www.vet.upenn.edu/about/press-room/press-kits/ebola-source-kit) In November, Penn Vet's **Ron Harty**, Department of Pathobiology, spoke on the subject in Rowan University's Deans Distinguished Speaker Series.

MARK HASKINS continued from page 2

ubiquitously expressed, a deficiency in a single enzyme can affect multiple organ systems. More than 50 forms of inherited LSDs occur in humans and are associated with high morbidity and mortality. As the Haskin's group discovered that disease progression in these naturally occurring animal homologues of LSDs closely resembled that observed in humans, their utility in evaluating the efficacy and safety of therapy for both animal and human patients became even more apparent.

Mark's initial NIH grants were to investigate the cats with MPS I and VI, and the dog with MPS VII. After 30 years, Mark converted a grant first funded in 1979 to one focused on gene therapy for MPS I and VII dogs, which is now funded to 2017. Don Patterson was awarded a P40 grant (Referral Center for Animal Models of Human Genetic Disease) in 1985 that was subsequently inherited by Mark upon Don's retirement. This grant also has a remarkable legacy, as it was just successfully renewed in 2013 – leading to funding for Don's initial vision for 43 years. There are few programs at Penn Vet that has had anywhere near this longevity in success, and its continued achievements represent a team effort involving Drs. Margret Casal, Peter Felsburg, Urs Giger, Paula Henthorn, Meg Sleeper, Charles Vite, and John Wolfe, as well as long-term technicians, Ping Wang (25 years) and Patricia O'Donnell (15 years), other individuals providing technical help, (Jessica Bagel, Therese Ruane, Tom O'Malley, Ulana Prociuk, Caitlin Fitzgerald, Shurnevia Strickland, and Juli Sorenson), and many veterinary students. Continued on Page 4

WAGNER FREE INSTITUTE HOLDS BENEFIT HONORING PETER DODSON

The Wagner Free Institute of Science honored Penn Vet's **Peter Dodson,** professor in the Department of Animal Biology and one of the world's leading dinosaur paleontologists. Dr. Dodson has led dinosaur expeditions around the globe, including to China where in 2014 his team discovered a new titanosaurian, *Yongjinglong datangi*, one of the largest animals to have ever lived. As a teacher, Dr. Dodson has inspired generations of paleontologists and dinosaur lovers. His commitment to rigorous research, combined with his infectious joy of discovery, embody William Wagner's goals for the Institute - making high-level science accessible to everyone. The benefit entitled "A Sip of Science" was held on November 14, 2014 in the historic lecture Hall at the Wagner Free Institute of Science in Philadelphia.

Peter Dodson, MSc, PhD

PENN'S PANCREATIC CANCER RESEARCH CENTER

Dr. Ellen Puré, chair, Department of Animal Biology, was a featured speaker at the November 17th inaugural scientific symposium of the **Penn Pancreatic Cancer Research Center (PCRC)** held at the Smilow Center for Translational Research. Her topic was "Remodeling the tumor micro-environment to treat pancreatic cancer".

DR. MARK HASKINS

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In the late 1960s and early 1970s the MPS diseases were shown to be caused by deficient activity of enzymes involved in the degradation of glycosaminoglycans (GAGs, previously called mucopolysaccharides). In their continued studies on MPS disorders, many carried out in collaboration with investigators at Penn and elsewhere they learned that the GAGs that are stored in the lysosome produce an inflammatory response, suggesting one approach to therapy could be to modulate the immune response. A more direct approach, and one that Mark's research currently focuses on, is to provide the gene using viral vector gene delivery. As these enzymes have a mannose 6-phosphate (M6P) moiety that allows them to be trafficked to the lysosome and also to be taken up from the extracellular fluid by cells by plasma membrane localized M6P receptors, initial therapy focused on purifying these enzymes from human urine and more recently from transfected CHO cells, followed by intravenous administration. Haskins assisted in testing these enzymes, primarily in cats with MPS. This work had important One-Health implications, as the Haskins group has recently determined that shorter infusion periods are as effective as longer infusions, reducing the time children need to be in therapy each week. However, enzyme therapy costs more than $300,000 a year and requires infusions once a week for life, prompting a continued search for less inconvenient and more cost-effective therapeutic options.

With the advent of gene therapy, viral vectors were developed to transfer DNA encoding the normal enzyme to the patient's own cells. Working with Kathy Ponder at Washington University, Haskins and his group evaluated neonatal retroviral gene therapy in dogs with MPS VII. Untreated dogs cannot stand or walk by six months of age, but Haskin's successfully treated a group of dogs - one of which made the cover of the PNAS (Figure 1) and maintained mobility. Indeed, Preston (one of the treated dogs) was still able to run down the hall 11 years after treatment. While remarkably successful, challenges with gene therapy remain. For example, retroviral vectors randomly integrate and, thus, have the potential to disrupt tumor suppressor genes or turn on oncogenes. This led Haskins and his colleagues to turn their attention to adeno-associated virus (AAV) vectors, which generally do not integrate. Another challenge in treating LSDs by gene therapy is that the enzymes do not cross the blood brain barrier. Thus, transducing somatic cells provides enzyme to many tissues but not the brain. This issue may be solved, since recently two AAV serotypes (AAV9 and AAVrh10) were found to cross the blood brain barrier and transduce cells in the CNS when injected IV in mice. While Haskins has now treated dogs and cats with MPS I and dogs with MPS VII using these serotypes, he has also found that intrathecal injection of vector into the cerebral spinal fluid (CSF) in the foramen magnum not only leads to high amounts of enzyme in the CSF, but due to the ability of these vectors to cross the blood brain barrier in the other direction, results in the transduction of somatic cells, thus, increasing serum enzyme levels to improve systemic disease.

Haskins and his group are currently assessing the ability of concurrent IV and intrathecal gene therapy to drive long-term replacement enzyme expression in LSD patients,

continued on page 5

DR HASKINS

continued from page 4

thereby ameliorating disease progression that lead to cognitive and developmental defects, hearing and vision problems, cardiac defects, aberrant skeletal formation, and ultimately premature death. His identification of large animal models in which such therapies can be translated for clinical use and his continuing assessment of gene therapeutic approaches in these models has given hope to a large number of families affected by these devastating, and currently untreatable, diseases.

Dr. Haskins' office is located in 4020 Ryan.

Recent publications

Cubizolle A, Serratrice N, Skander N, Colle M-A, Ibanes S, Gennetier A, Mazouni K, Mennechet F, Kalatzis V, Jousemet B, Cherel Y, Lajat, Y, Bernex B, Vite C, **Haskins ME**, & Kremer EJ Corrective GUSB transfer to the canine mucopoly-saccharidosis VII brain. *Molec Therapy* 22:762-773. (2014)

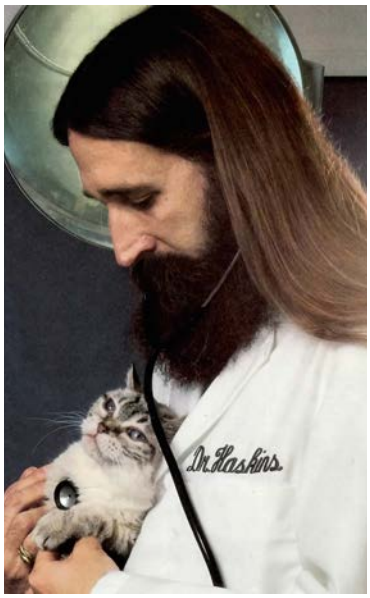
Simonaro CM, Sachot S, Ge Y, He X, DeAngelis VA, Eliyahu E, Leong D, Sun H, Mason JB, **Haskins ME,** Richardson DW, & Schuchman SH Supplementation of media with acid ceramidase improves the quality of primary and stem cell-derived chondrocytes for cell-based cartilage repair. *PLoS ONE* [Electronic Resource]. 8(4):e62715 (2014)

Serratrice, N, Cubizolle, A, Ibanes, S, Mestre-Francés, N, Bayo-Puxan, N, Creyssels S, Gennetier A, Bernex F, Verdier J-M, Haskins M E, Couderc, G, Malecaze F, Kalatzis V, & Kremer E J. Corrective GUSB transfer to the canine mucopolysaccharidosis VII cornea using a helper-dependent canine adenovirus vector. *J Control Release* 181:22-31. (2014)

Chiaro KA, O'Donnell P, Shore EM, Malhotra MR, Ponder KP, **Haskins ME,** & Smith LL Effects of Neonatal Enzyme Replacement Therapy and Simvastatin Treatment on Cervical Spine Disease in Mucopoly-saccharidosis I Dogs. *J Bone Miner Res*. Jun 4. doi: 10.1002/jbmr.2290. [Epub ahead of print]. (2014)

Hinderer C, Bell P, Gurda BL, Wang Q, Louboutin J-P, Bagel J, O'Donnell P, Sikora T, Ruane T, Wang P, **Haskins ME**, & Wilson JM Intrathecal gene therapy corrects CNS pathology in a feline model of mucopoly-saccharidosis I. *Gene Ther*, Jul 16. doi: 10.1038/mt.2014.135. [Epub ahead of print] (2014)

Hinderer, C, Bell, P, Gurda, BL, Wang, Q, Louboutin, J-P, Zhu, Y, Bagel. J, O'Donnell P, Sikora, T, Ruane, T, Wang P, **Haskins ME**, & Wilson, JM Liver directed gene therapy corrects cardiovascular lesions in feline mucopoly-saccharidosis type I. *Proc Natl Acad Sci* USA Sep 29. pii: 201413645. [Epub ahead of print] (2014)



Dr. Haskins in the 1983 issue of the *Smithsonian*

Penn Vet Publications

Comachione AS, Leite FS, Wang J, Leu NA, Kalgonov A, **Volgin D,** Han X, Xu T, Cheng YS, Yates Jr, Rassier DE & **Kashina A** (2014) Arginyl-ation of myosin heavy chain regulates skeletal muscle strength. *Cell Rep* 8(2):470-476

Gaub BM, Berry MH, Holt AE, Reiner A, Kienzler MA, Dolgova N, Nikonov S, Aguirre GD, **Beltran WA,** Flannery JG, Isacoff EY. (2014) Restoration of visual function by expression of a light-gated mammalian ion channel in retinal ganglion cells or ON bipolar cells. *PNAS USA Pii: 201414162 Epub ahead of print*

Volgin DV, Lu JW, Stettner GM, Mann GL, Ross RJ, Morrison AR, **Kubin L** (2014). Time- and behavioral state-dependent changes in posterior hypothalamic GABAA receptors contribute to the regulation of sleep. *PLoS ONE* 9(1): e86545.

Dipti Pitta, N Parmar, A Patel, N Indugu, S Kumar, K Prajapathi, AB Patel, B Reddy & C Joshi (2014) Bacterial diversity dynamics associated with different diets and different primer pairs in the rumen of Kankrej Cattle. *Plos ONE* 9(11):1-15.

GLOBAL COLLABORATIONS ~ CHILE-USA

The 5th Annual Meeting of **Nexos Chile-USA** was held at the Perelman School of Medicine on October 17-18, 2014. Nexos Chile-USA aims to establish connections and collaborations between Chilean scientists working in the US and those established in Chile. The meeting was organized by**Dr. Carolina López,** assistant professor, Department of Pathobiology and **Dr. Daniela Gómez Atria**, a postdoctoral researcher in the School of Veterinary Medicine, together with postdocs and Ph.D. students from other schools at the University of Pennsylvania and other American universities. The event was financed in part by the Ministry of Foreign Affairs of Chile through the Chilean Embassy in Washington D.C., the Biomedical Post-doctoral Programs, the Vice Provost Office of Research, University of Pennsylvania, and supported by Penn Vet. Dr. López opened the meeting with a keynote lecture sharing her career path and was joined by several established Chilean scientists. Participating in this meeting were Dr. Cecilia Hidalgo, the first Chilean woman awarded the National Prize of Natural Science and the Chilean Ambassador for the United States, Juan Gabriel Valdés.

Carolina López

Student Research Day is on Thursday, **March 26, 2015** REGISTER here:

http://survey.vet.upenn.edu/index.php?sid=47561&lang=en

The Martin M Kaplan V'40 Keynote Speaker will be:

John Clifford, DVM,

Chief Veterinary Officer for the USDAand the Animal and Plant Health Inspection Service (APHIS), Deputy Administrator for Veterinary Services

SYMPOSIUM on AQUATIC ANIMAL HEALTH

Dr. Oriol Sunyer, professor, Department of Pathobiology, was the keynote speaker at the 2014 Seventh International Symposium on Aquatic Animal Health held in Portland, Oregon. He spoke on "Novel mucosal B and T cell immune responses of teleost fish to pathogens and vaccines".

RECENT AWARDS

(Direct Costs)

Gargoyle on Old Vet exterior

Gudrun Debes
American Association of Immunologists
The role of T cell egress from the effector site in regulating inflammation
10/1/14-9/30/15 $47,244

Carolina Lopez
American Association of Immunologists
Molecular Mechanisms Behind the Potent Immunostimulatory Activity of Defective Viral Genomes 10/1/14-9/30/15 $43,680

Shelley Rankin
U18-FD-005164 FDA
Companion Animal and Animal Food Diagnostic Sample Analysis in Support of FDA Vet-LIRN Activities and Investigations
9/1/14-8/31/19 $75,000

Rachel Kreisler Stanton Foundation
Study of Economic Reasons for Surrender of Dogs to Animal Shelters
1/1/2015--12/1/2015 $58,524

Thomas Parsons
Commonwealth of PA—USDA Swine Enteric Coronavirus Disease Cooperative Agreement
7/1/2014 – 9/30/2015 $31,483

Thomas Parsons
Kraft Food Group—New tools for measuring welfare: Cognitive bias and sleep patterns in swine.
11/5/2014-5/5/2016 $79,573

Kendra Bence
NIH/NIDDK R01 DK082417
Neuronal protein tyrosine phosphatases in metabolism 9/14/15- 6/30/18 $675,000

Charles Vite
NIH/NINDS Novel Therapies for Globoid Cell Leukodystrophy
Sub contract, Washington University
10/1/14-3/31/15 $36,800

Dorothy Brown
AlcheraBio LLC--Clinical Study: A dose ranging study to evaluate the field safety and effectiveness of a single intra-articular injection of CNTX-4975 in companion animal dogs with chronic, moderate to severe stifle joint pain associated with osteoarthritis
8/5/14-8/4/16 $51,200

William Beltran
NIH/NEI Translational Research Program on Therapy for Visual Disorders (R24)
University of Washington subcontract
9/1/14-8/31/19 $1,890,144

William Beltran
FDN Fighting Blindness
Development of Optogenetic tools with increased light sensitivity for vision-subcontract.
9/1/14-8/31/17 $198,585

Gustavo Aguirre
AGTC
Gene Therapy Clinical trial for RPGR-XLRP
9/15/14-9/15/16 $633,477

CHMI PILOT AWARDS

Penn Vet's **Center for Host-Microbial Interactions** (CHMI) awarded three pilot grants:

Thomas Schaer & Dipti Pitta
A Minipig Model of Oral Dysbiosis to Investigate the Etiology of Periodontal Disease. 12/1/14--11/30/15 $48,750

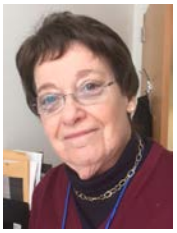
Dieter Schifferli
GWAS to differentiate intestinal from septicemic *Salmonella*
12/1/14--11/30/15 $50,000

Narayan Avadhani
CHMI: Intestinal microbiota and barrier dysfunction in alcoholic liver disease
12/1/14--11/30/15 $50,000

A new study by Gary Smith, professor of population biology and epidemiology used epidemiological modeling methods to determine the proportion of schizophrenia cases that may be attributable to *T. gondii* infection. The work, published in *Preventive Veterinary Medicine*, suggests that about one-fifth of cases may involve the parasite. *Prev Vet Med.* online October 2014

Recent Publications

Fecteau, M-E, Aceto HW, Bernstein, LR and **Sweeney RW** (2014) Com-parison of the antimicrobial activities of gallium nitrate and gallium maltolate against *Mycobacterium avium subsp. paratuberculosis in vitro. Vet J.* 202(1): 195-7.



Whitbeck JC, Huang ZY, Cairns TM, Gallagher JR, Lou H, Ponce de Leon M, Belshe RB, **Eisenberg RJ** & Cohen GH. 2014. Repertoire of epitopes recognized by serum IgG from humans vaccinated with herpes simplex virus 2 glycoprotein D. *J.Virol.* 88(14):7786-7795

Yildirim O, Hung JH, Cedeno RJ, Weng Z, **Chris Lengner,** and Rando OJ (2014) A System for Genome-Wide Histone Variant Dynamics In ES Cells Reveals Dynamic MacroH2A2 Replacement at Promoters *PLoS Genet* 10(8);e1004515.

Signaling pathway leading to obesity

Ceren Ozek, graduate student in Dr. Kendra Bence's Laboratory

Research from Penn Vet was well received at the Obesity Society's Annual Scientific meeting held in Boston, MA on November 6, 2014. **Ceren Ozek**, graduate student in the laboratory of **Dr. Kendra Bence**, associate professor in the Department of Animal Biology, was awarded the *Ethan Sims Young Investigator Award*. Ceren was selected from a group of five finalists. Her presentation at the meeting was entitled "PTP1B is a Novel Physiological Regulator of BDNF/TrkB Signaling in the Brain". Concurrently Dr. Bence's paper entitled "Protein Tyrosine Phosphatase 1B is a Novel Regulator of Central Brain-Derived Neurotrophic Factor and Tropomyosin Receptor Kinase B Signaling" was published in the *Journal of Biological Chemistry* (Ozek C, Kanoski SE, Zhang ZY, Grill HJ, **Bence KK**. *J Biol Chem*. 2014 289(46):31682-31692.

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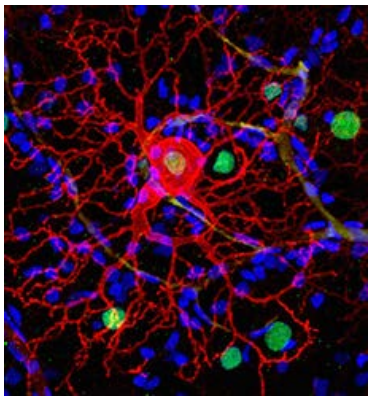

Image courtesy of Dr. William Beltran—A dog's retinal ganglion cell expressing LiGluR (red) can be controlled by light after delivering a chemical photoswitch.

TO: