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Spotlight

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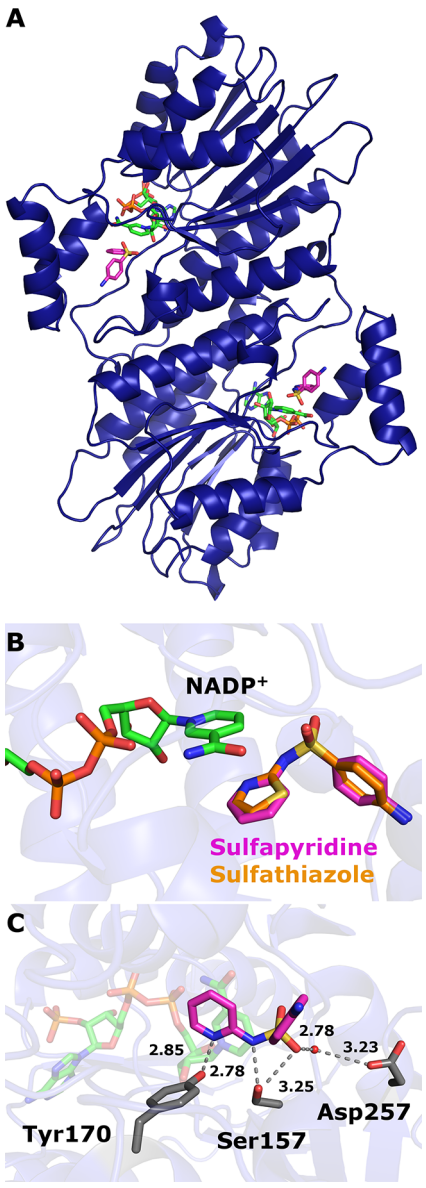
SORTING OUT THE SIDE EFFECTS OF SULFAS

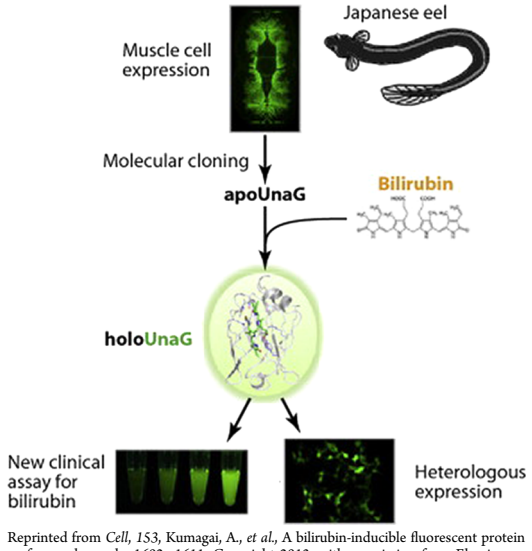


From Haruki, H., *et al.*, *Science*, 2013, *340*, 987. Reprinted with permission from AAAS.

Sulfa drugs, defined by their sulfonamide moiety, comprise the first class of antibiotics ever to be discovered and also encompass other drugs types including antiinflammatory, antidiabetic, and anticonvulsant agents. Though they exhibit significant therapeutic benefits, sulfa drugs can cause a variety of adverse gastrointestinal, neurological, and dermatological side effects. Yet, the molecular underpinnings of these effects are not well understood. Haruki *et al.* (*Science* 2013, *340*, 987−991) now report the identification of the enzyme sepiapterin reductase as a target for many sulfa drugs, a finding that may explain some of their off-target activities.

The recent finding that sepiapterin reductase is the target of the potent antiinflammatory agent sulfasalazine prompted interest in whether other sulfa drugs also inhibited this enzyme. Sepiapterin reductase performs the final step in the biosynthesis of the enzymatic cofactor tetrahydrobiopterin, and preventing this transformation can have a variety of biological consequences including inhibiting the biosynthesis of certain neurotransmitters. The authors screened a library of known drugs and identified 10 sulfonamide-containing therapeutics that inhibited sepiapterin reductase. X-ray crystal structure analysis shed light onto the binding mode of the compounds in the enzyme active site, and in cellular assays, addition of the inhibitors led to a decrease in tetrahydrobiopterin levels. In addition, treatment of a neuroblastoma cell line with the inhibitors led to decreased levels of the dopamine precursor L-DOPA and the dopamine metabolite 3-methoxytyramine, suggesting a potential mechanism for the neurological effects of some sulfa drugs. Together, the findings offer a molecular basis for the off-target effects of sulfa drugs and could guide the design of improved therapeutic agents with enhanced selectivity for their intended targets. **Eva J Gordon, Ph.D.**

AN UNUSUAL FLUORESCENT PROTEIN IN UNAGI



Reprinted from *Cell*, *153*, Kumagai, A., *et al.*, A bilirubin-inducible fluorescent protein from eel muscle, 1602−1611. Copyright 2013, with permission from Elsevier.

The Japanese fresh water eel unagi, aside from being a common ingredient in the Japanese diet, travels impressive distances in the open ocean and rivers over the course of its life cycle. Little is known about how the eel sustains the extensive physiological demands of this journey, but the recent discovery that unagi muscle fibers are fluorescent presented an intriguing entree for further investigation of its musculature. Now, Kumagai *et al.* (*Cell*, 2013, *153*, 1602−1611) report that the fluorescence in unagi musculature is derived from a protein that resides in the small-diameter muscle fibers of the eel.

Starting with strongly fluorescent samples from five eels, the authors cloned the fluorescent protein and named it UnaG. They determined that it contains 139 amino acids, emits green fluorescence that is independent of the presence of oxygen, and is a member of the fatty acid binding protein family.

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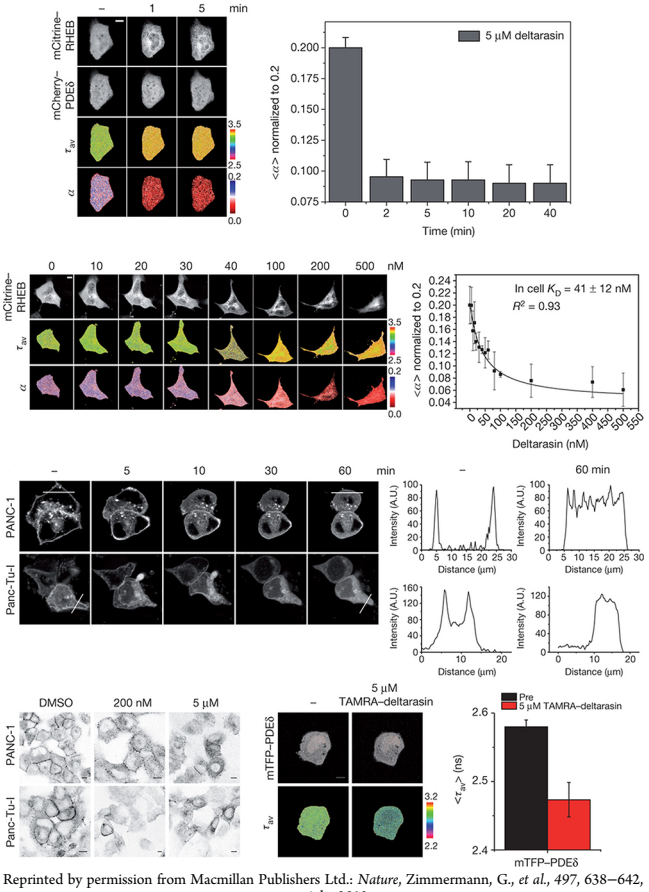
Notably, this class of proteins is known for its role in oxidative metabolism, which may offer clues about the role of UnaG in eel muscular physiology. Surprisingly, the investigators also found that the protein is not intrinsically fluorescent; rather, it fluoresces upon binding the heme metabolite bilirubin. Analysis of the crystal structure of UnaG in complex with bilirubin suggests the importance of hydrogen bonding and offers insight into the high affinity and selectivity of the interaction. Importantly, as bilirubin is a marker for several pathologic conditions such as impaired liver function and jaundice, UnaG could serve as a diagnostic biosensor for bilirubin detection. To this end, the authors demonstrate proof of principle by developing an assay that enables the rapid detection of bilirubin in human serum, an improvement over the current method which is insensitive and out of date. This study illuminates the exciting potential of UnaG as a tool for exploring unagi physiology, for general biological discovery applications, and for the diagnosis of bilirubin-related disorders. **Eva J. Gordon, Ph.D.**

GETTING TO KRAS THROUGH ITS CHAPERONE

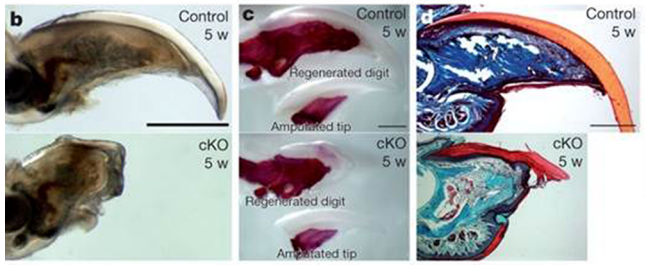


Reprinted by permission from Macmillan Publishers Ltd.: *Nature*, Zimmermann, G., *et al.*, *497*, 638–642, copyright 2013.

The *KRAS* oncogene encodes a GTPase that has been widely implicated in cancer development. Despite intense efforts, direct inhibition of KRAS activity has yet to result in the generation of successful therapeutic agents. Now, Zimmermann *et al.* (*Nature*, 2013, *497*, 638–642) devise a new approach for disrupting KRAS function by targeting the interaction between KRAS and the prenyl binding protein phosphodiesterase delta (PDEδ).

PDEδ functions as a chaperone for KRAS, escorting it through the cytoplasm to the cell membrane. This journey is necessary in order for the protein to perform its membrane-proximal signaling functions that promote cell growth and survival in both normal and cancerous cells. To find inhibitors of the KRAS-PDEδ interaction, the authors develop a high-throughput screen for small molecules that prevent binding between a biotinylated and farnesylated KRAS4B peptide and a His-tagged PDEδ. Several benzimidazoles were identified as hits and were subsequently validated through a variety of secondary assays. X-ray structure analysis revealed that two benzimidazole molecules bound to a hydrophobic tunnel in PDEδ. Further structural analysis guided the design of a small library of dimeric benzimidazoles, leading to the identification of a potent inhibitor referred to as deltarasin. Addition of deltarasin to human pancreatic cancer cells disrupted the interaction between KRAS and PDEδ, resulting in a loss of KRAS spatial organization and signaling capacity. In addition, in mouse models of pancreatic cancer, deltarasin treatment resulted in substantially decreased tumor growth. This study identifies the PDEδ-KRAS interaction as novel cancer target and lays the foundation for new discovery efforts toward novel anticancer agents for RAS-dependent cancers. **Eva J. Gordon, Ph.D.**

HAMMERING NAIL REGENERATION



Reprinted by permission from Macmillan Publishers Ltd.: *Nature*, advance online publication 12 June 2013, DOI: 10.1038/nature12214.

Breaking off a fingernail can be a painful moment followed by months of waiting for the nail to regrow. Interestingly, in mammals, amputating the fingertip near that nail will actually result in regeneration of the tissue and bone as well. This curious phenomenon has never been well understood, but it has long been known that the two events must be related. Now, a group has used a combination of gene expression profiling, imaging, and transgenic animals to better understand the molecular relationship between nail and digit tip regeneration.

Takeo *et al.* (*Nature* 2013; DOI:10.1038/nature12214) began with a mouse strain that harbored an inducible marker for Keratin 14-expressing cells, a hallmark of the nail stem cells (NSCs). Using this approach, the researchers could see that descendants of these stem cells either maintained this stem marker in the case of proximal cells or differentiated into other cell types in the distal cells. This observation was interesting because amputation in the proximal region does not support tissue regeneration, while distal region amputations result in regrowth. Proximal and distal cells were then compared in their gene expression profiles by microarray analysis to ask the important question. Which mRNA levels are different between cells that support regeneration versus those that do not? The best clue came from the proximal region cells displaying low levels of transcripts for the Wnt signaling pathway when compared to the distal cells. Wnt signaling, long studied in early embryonic limb development, represented an excellent candidate for the tissue regeneration phenotype of distal cells. By using a mouse strain with conditional nail epithelial knockout of the critical Wnt signaling factor, β-catenin, the researchers went on to show that the Wnt pathway is required for both nail and digit regeneration. These findings highlight a new role for

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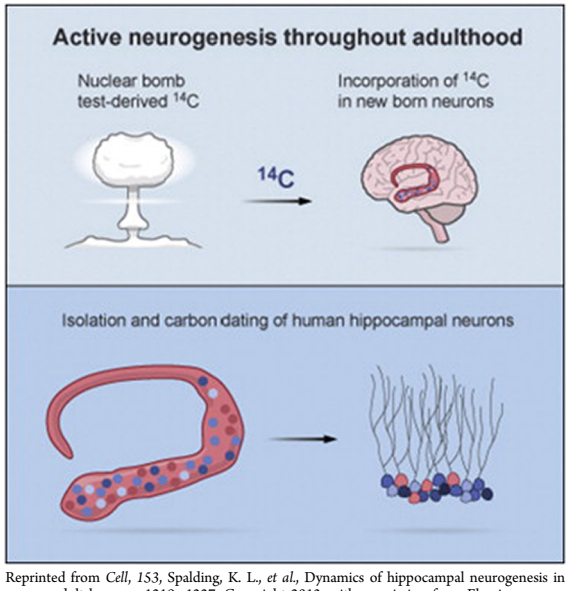
nail stem cells in regeneration of the adjacent digit and armed with the knowledge of what pathway is at play, targeted therapeutic approaches may become a reality for more serious amputations. **Jason G. Underwood**

CALCULATING NEURON AGE USING C-14



Reprinted from *Cell*, *153*, Spalding, K. L., *et al.*, Dynamics of hippocampal neurogenesis in adult humans, 1219−1227. Copyright 2013, with permission from Elsevier.

Fifteen years ago, neuroscientists overturned the long-held idea that adult human brains could not form new neurons. Now Spalding *et al.* (*Cell*, 2013, *153*, 1219−1227) have used a ^{14}C dating technique to date the formation of neurons in the human hippocampus. Their results suggest that neurogenesis involves a significant fraction of neurons in the human hippocampus and occurs within specific regions.

The research takes advantage of the elevated levels of ^{14}C in the atmosphere during the 1950s and 1960s when aboveground nuclear testing produced higher level of that isotope that were incorporated in plants and into the animals that ate those plants. Those higher isotopic levels were incorporated into the genomic DNA of humans. By looked at post mortem slices of human brains from subjects ages 19 to 92, they used mass spectrometry and mathematical modeling to date when the cells in the brain were "born" based on the levels of ^{14}C incorporated in their genomes.

When the researchers compared the formation of non-neuronal cells with the formation of neurons, they observed that 35% of the neurons in the hippocampus of adults were added in adulthood. These cells are primarily concentrated in the dentate gyrus, the area of the brain responsible for building new episodic memories and for exploring new environments. Neurons in other areas of the human hippocampus do not exchange. These results differ starkly from mice, where just 10% of the neurons in the dentate gyrus are formed in adulthood. Neurogenesis slows as humans age, but that process is slower in humans than in mice. Middle-aged neurons are relatively rare: Older neurons are not typically replaced as they die, but the body will produce new neurons as younger neurons die.

The results show variability among individuals. As a result, these isotopic patterns could help researchers understand how patterns of neurogenesis are linked with psychiatric diseases such as anxiety and depression. **Sarah A. Webb, Ph.D.**

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