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Why so blue?

Researchers examine seasonal affective disorder

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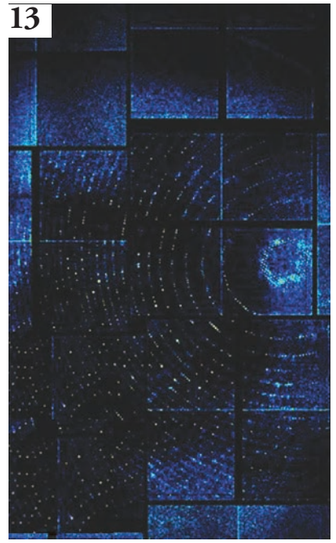

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The impact of the sequester: 1,000 fewer funded investigators

By Jeremy Berg

The Rock Talk blog recently featured a post titled "FY2013 by the numbers: research applications, funding and awards" (1) in which National Institutes of Health Deputy Director for Extramural Research Sally Rockey noted that the number of competing R01 awards dropped from 5,436 in fiscal year 2012 to 4,902 in FY13 and that the number of competing R21 awards fell from 1,932 to 1,771. These results reflect the impact of the sequester, which resulted in a $1.5 billion, or 5 percent, decrease in the NIH appropriation.

While these data capture one important aspect of the sequester's impact, they do not reflect a more integrated evaluation of the effect on investigators. As I detail below, such an evaluation reveals that the number of funded investigators dropped by about 1,000 from FY12 to FY13, substantially more than the drop of 150 from FY11 to FY12. Given the investments these investigators and society have made in developing their scientific skills, these data provide a quantitative measure of the inefficiencies created by erratic support for biomedical research.

Examining R grants held by each investigator

I analyzed data from NIH RePORTER for R-series grants (2). These included all funding mechanisms from R01s to R56s (including SBIR and STTR, or R41 to R44, grants) but excluded R13 (conference awards) for FY11, FY12 and FY13. Data for other mechanisms, such as P01s, DP1s (Pioneer awards) and larger mechanisms, were not included.

For each year, data for about 35,000 awards were downloaded. The number of awards is made up of about 75 percent R01s, 10 percent R21s, 5 percent SBIR/STTR awards and 10 percent other mechanisms, with R01s accounting for approximately 80 percent of the funds. The awards for each investigator were aggregated for each year. Some of the key parameters from this analysis, together with those reported on Rock Talk, are summarized in the table.

Examination of these data reveals that from FY11 to FY12 the total amount of funding going to the R mechanisms increased slightly while the number of investigators decreased by 151, resulting in a slight increase in the average funding per investigator.

In contrast, from FY12 to FY13 the total amount of funding going to these mechanisms decreased by $1.2 billion (compared with the $1.5 billion cut across the entire NIH appropriation and $1 billion for all research project grants). This drop has two components: The number of investigators decreased by 1,001, or 3.8 percent, and the average funding per investigator dropped by 5 percent.

Year-to-year dynamics of the investigator pool

These trends can be analyzed further by examining the dynamics of investigators into and out of the system as shown in the figure.

Of the 26,513 investigators funded by these mechanisms in FY11, 5,287 were no longer funded by these mechanisms in FY12. However, 5,136 investigators who were not funded in FY11 were awarded grants in FY12, with the difference accounting for the small decrease of 151 investigators. The number of investigators for whom funding ended and was not renewed in FY12 grew by 219 to 5,506. More strikingly, the number of investigators who were not funded in FY12 but who were awarded grants in FY13 dropped by more than 600 to 4,505, a decrease of more than 12 percent from the previous year.

Who are the unfunded investigators?

Examination of the parameters for the applicants who received funding in FY12 but not in FY13 revealed the following:

- More than 2,900 investigators of the 5,506 who lost R funding had R01 grants in FY12. The median duration of these R01 grants was five years, with more than 750 having durations of eight years or more and with more than 180 with durations of 20 years or more.
- More than 110 investigators had R00 funding in FY12 but did not show any R funding in FY13. Given that there have been about 180 K99/R00 awards per year, this indicates that more than half of the K99/R00 awardees are not transitioning to other R funding, at least in the first year after the completion of their R00 awards.
- Nearly 900 investigators had R21 funding in FY12 but did not show any R funding in FY13. Given that there have been about 1,800 R21 awards per year, this indicates that about half of the R21 awardees are not transitioning to other R funding in the next year.

What about the more than 600 investigators who would have been expected to be funded without the sequester but who weren't funded? Of course, we do not know who these investigators are. However, based on the data recently posted on Rock Talk, we can estimate that about 50,000 investigators competed for these mechanisms in FY13.

Also, based on previous years (3), we can reason that about 30 percent of those who would have been funded without the sequester would have been new investigators. Thus, the sequester may have resulted in the loss of about 200 new investigators who normally would have received their first major NIH funding and may have interrupted funding for more than 400 more established investigators.

R series versus research project grants

In her post, Rockey notes that the total funding for all research project grants, or RPGs, dropped from $15.92 billion in FY12 to $14.92 billion in FY13, a decrease of 6.3 percent. The total funding going to the R series awards that I examined (which makes up about 85 percent of the RPG pool) dropped by 8.9 percent.

What accounts for this difference? U01 awards comprise the largest remaining portion of the RPG pool (4). These are cooperative agreements rather than grants for which NIH staff members are involved in guiding the research. The funds devoted to U01 awards remained essentially constant from FY12 to FY13 at $1.57 billion.

Characteristics of funding through R mechanisms and all research project grants (RPGs) for FY11 through FY13

	FY11	FY12	FY13	Sources
Total funding for R mechanisms	$13.38B	$13.51B	$12.31B	This study
Number of investigators with R funding	26,513	26,362	25,361	This study
Average R mechanism funding per investigator	$505K	$512K	$486K	This study
Total funding for all research project grants (RPGs)	$15.82B	$15.92B	$14.92B	(1) and (2)
Average size of a research project grant	$450K	$455K	$441K	(1) and (2)
Number of research project grants	35,173	35,029	33,796	(1) and (2)

SOURCES: 1. HTTP://1.USA.GOV/1HT40KY 2. HTTP://1.USA.GOV/1ET5MQQ

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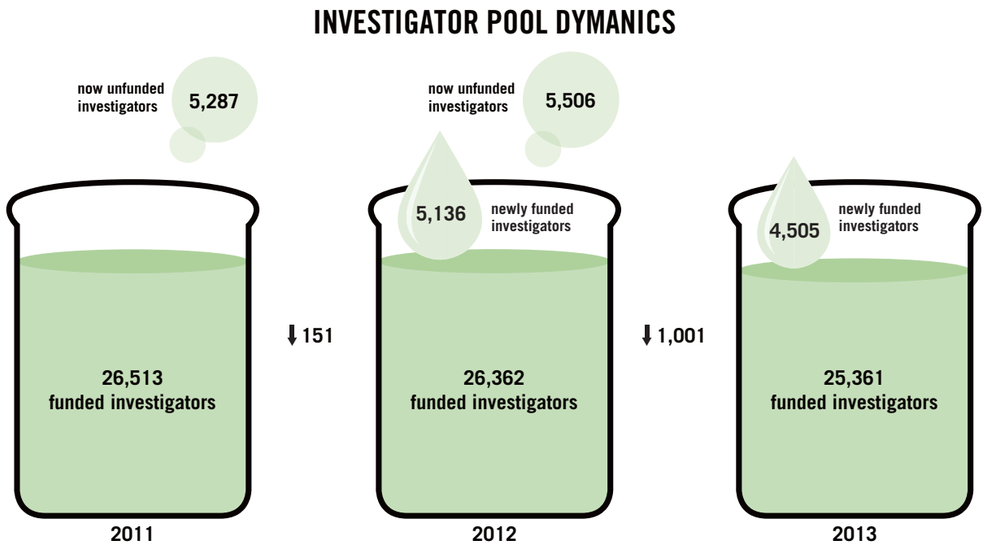

Shrinking pool of R-series-funded investigators: Of the 26,513 investigators funded by R-series mechanisms in fiscal 2011, 5,287 were no longer funded by those mechanisms in FY12. At the same time, 5,136 investigators who had not been funded by these mechanisms in FY11 ended up being funded in FY12. As a result of this give-and-take, 151 fewer investigators were in the pool. This downward trend continued in FY13, when 5,506 investigators did not receive funding and only 4,505 investigators were added to the mix. Ultimately, 1,001 fewer investigators than in FY12 were in the pool.

CONTINUED FROM PAGE 3

What does it all mean?

First, let me offer a disclaimer. While I have done my best to ensure accuracy in this analysis, these are not official NIH data and some minor differences likely would be observed with a more detailed analysis due to a range of technical issues. Furthermore, I have focused on R-series awards and have not included other mechanisms that also contribute to the support of specific investigators.

With that said, the analysis does place the impact of the sequester in relatively sharp focus: There were about a thousand fewer investigators funded by these mechanisms in FY13 compared with FY12. This represents more than six times the number of investigators who lost this funding from FY11 to FY12 and a 3.8 percent drop in the R-mechanism-funded investigator cohort.

The NIH took steps to reduce the drop in the number of grants awarded in FY13. This can be seen in the cut in the average level of R funding going to each funded investigator by 5.2 percent. This figure reflects both the effect of cutting noncompeting grants, estimated to average 4.7 percent across NIH (5), and the limited number of new grants going to already-funded investigators. The 5.2 percent decrease in R funding going to each investigator can be compared with the increase of 1.5 percent of funds going to each investigator from FY11 to FY12.

The NIH leadership and staff had a great challenge in trying to operate with the reduced appropriation associated with the sequester. The results described, wherein R series awards absorbed a disproportionate amount of the sequester, do not appear to be a matter of clearly articulated policy decisions but rather the accumulated impact of a large number of individual decisions. Only through analyses like the first-pass analysis that I have described here can the real effects of the sequester be appreciated.

The results of this analysis highlight the inefficiency associated with having a large number of individuals, both productive established investigators and talented young scientists at the dawn of their careers, struggling to obtain even modest resources to realize their contributions to science and to the health of the nation.

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When agreement isn't enough

By Benjamin Corb

The U.S. Congress is now entering appropriations season — that exciting time of the year when the House and the Senate dole out funding to federal departments, agencies and pet projects for fiscal 2015. This time of year has advocates like me scheduling meeting after meeting to fight for funding for our constituencies. On one hand, this kind of dialogue with members of Congress represents democracy at its best. On the other hand, this dialogue can be one of the most frustrating aspects of science advocacy.

The case for increased federal investments in research and development is, on its face, an easy argument to make. You'd be hard-pressed to find a member of Congress who doesn't see value in investing in research on diseases like cancer, Alzheimer's and diabetes. Likewise, the economic argument in support of investments in research is clear, concise and widely accepted. If the argument is that clear, and support is bipartisan, then why are increases so hard to come by?

This answer has many parts. The first is legal. In 2011, Congress passed the Budget Control Act, which established hard caps on how much money Uncle Sam can appropriate for discretionary programs between 2011 and 2021. This statute was an effort to curb growing debt and deficits and was championed successfully by conservative House members. In addition to discretionary appropriations caps, the act established automatic, across-the-board budget cuts, commonly known as sequestration, which have so negatively impacted research.

Advocacy efforts like those by the American Society for Biochemistry and Molecular Biology's Public Affairs Advisory Committee were a part of the reason a bipartisan accord was reached last December that relieved the cuts of sequestration for FY14 and FY15. The Bipartisan Budget Agreement last December delayed some spending cuts and raised some fees to an extent that relieved the majority of budget cuts slated for these fiscal years. However, the budget caps remain. As a result, appropriators are still limited in the amount of money they can disperse, including funds for research funding agencies.

The second issue is politics. The National Institutes of Health is funded in the appropriations bill for Labor, Health and Human Services, Education and related agencies. Sadly, while supporting biomedical research at the NIH is easy regardless of political party, this bill has been arguably one of the most politically charged bills in the appropriations process because it includes funding for controversial groups and programs, such as the nonprofit Planned Parenthood and President Obama's Affordable Care Act. One side of the debate will argue for increased funding for the NIH by taking money away from other programs under this particular appropriations umbrella, but the other side will oppose bitterly the reduction of funding for the other programs. As such, NIH funding ends up in a political quagmire.

Finally, there are the issues of history and optics. Regarding history, the NIH budget doubled from the late 1990s to the early 2000s, which was a blessing and curse. This budget growth led most members of Congress to develop a "you already got yours" attitude toward the NIH. Regarding optics, the NIH receives the second-largest appropriation in the entire government, after the Department of Defense. Significantly increasing NIH funding, when that money could fund dozens of other programs, is politically very difficult.

But change is possible. As a result of our efforts and other factors, the NIH received a $1 billion increase in FY14 over FY13. This boost didn't make up for sequestration entirely, but it again demonstrates Congress' understanding that biomedical research is a worthy investment of the taxpayers' money. These successes ensure that the PAAC and the ASBMB Public Affairs Office will continue to strongly advocate for increases in the budgets of federal science funding agencies, even in the face of the obstacles listed above.

Advocacy efforts like those by the American Society for Biochemistry and Molecular Biology's Public Affairs Advisory Committee were a part of the reason a bipartisan accord was reached last December that relieved the cuts of sequestration for FY14 and FY15.

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Zuk tapped to oversee division focused on policy and communications at NCATS

ZUK

Dorit Zuk in January became director of the National Center for Advancing Translational Sciences' Office of Policy, Communications and Strategic Alliances. In this position, Zuk oversees the development of policy solutions intended to hasten the delivery of new drugs, diagnostics and devices to patients. She also oversees the office's communication arm, which serves the general public and scientific community by disseminating information about NCATS programs, policies and partnerships. "I am very excited to be joining NCATS, the newest center at NIH," Zuk said. "I look forward to helping transform the translational science process so that new treatments and cures for disease can be delivered to patients faster." Before joining NCATS, Zuk spent four years as a science policy adviser to the National Institutes of Health's deputy director for extramural research, Sally Rockey. Before that, she was a science policy fellow at the American Academy of Arts and Sciences and at the American Association for the Advancement of Science. Zuk, who earned her Ph.D. in cell biology at the Weizmann Institute, is a member of the American Society for Biochemistry and Molecular Biology's Education and Professional Development Committee and chairs the advisory committee on AAAS Science and Technology fellowships.

Greider and Agre among first at Hopkins to secure Bloomberg professorships

GREIDER

AGRE

Two members of the American Society for Biochemistry and Molecular Biology are among the first faculty members at Johns Hopkins University granted appointments under the Bloomberg Distinguished Professorships program. Carol Grieder and Peter Agre, both Nobel laureates, secured the endowed chairs funded last year by Hopkins alumnus and business magnate Michael R. Bloomberg. The program is intended to promote interdisciplinary research in line with the university's initiatives. "This university is committed, as much or more than any other, to assembling experts from divergent disciplines to attack humanity's most important problems from every angle," explained Hopkins' president, Ronald J. Daniels, announcing the appointments. Hopkins' provost, Robert C. Lieberman, added: "There is already a tremendous spirit of collaboration at Hopkins. That is one of our hallmarks. I think this program institutionalizes it all in a way that nothing else could." Greider won the 2009 Nobel in physiology or medicine for the discovery of telomerase, which safeguards genetic information by capping off the ends of chromosomes. Agre won the 2003 Nobel in chemistry for his discovery of aquaporins, which move water molecules through the cell membrane.

AAAS recognizes Tsin for his dedication to mentoring throughout his career

TSIN

Andrew Tsin of the University of Texas at San Antonio received the 2013 Lifetime Mentor Award from the American Association for the Advancement of Science at the organization's annual meeting in February in Chicago. AAAS officials cited Tsin's dedication to "facilitating dramatic education and research changes at his institution, leading to a significant production of Hispanic American doctorates in the biological sciences." Tsin has been described as going above and beyond in support of his students, many of whom are first-generation college attendees. George Perry, a dean at UTSA, pointed to an undeniably powerful statistic: "The significant contribution of Dr. Tsin's mentoring is evidenced in the successes of his mentees: 100 percent of his undergraduate and graduate students completed their degrees and have continued in their educational track or have entered successful scientific careers." In a statement, the university noted that during his tenure at UTSA, Tsin has helped bring in $68.5 million in funding for programs for underrepresented minorities. Tsin previously received the Presidential Award for Excellence in Science, Engineering and Mathematics Mentoring from President Obama and is a fellow of the Association for Research in Vision & Ophthalmology.

Effects of follistatin on brown fat

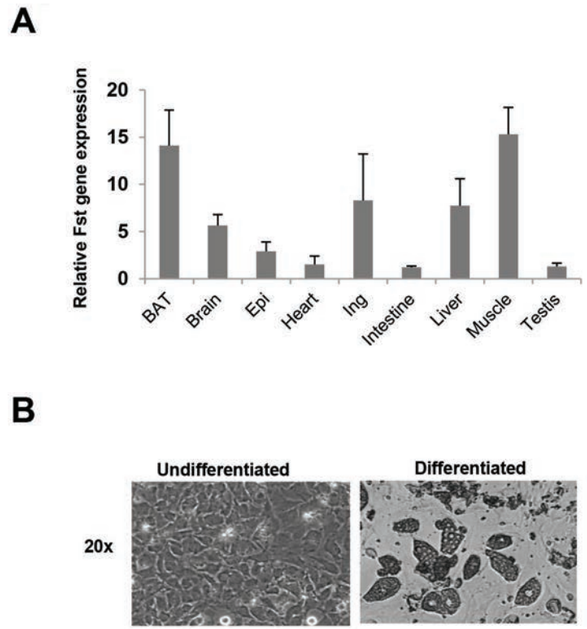
By Mary L. Chang

Nary a week goes by without a new fad diet limiting or directing the intake of sugars, fats or proteins — or a combination of any or all three. So it's rather interesting that a study in the March issue of the **Journal of Lipid Research** seems to indicate that a glycoprotein known to be involved with promoting growth of muscle mass may have an unexpected relationship with brown adipose tissue, more commonly known as brown fat.

Brown fat generates and maintains body heat in warm-blooded animals, and its activity affects energy metabolism and therefore could be a determinant in predicting obesity and metabolic syndrome. In an article by Melissa Braga of the Charles R. Drew University of Medicine and Science and colleagues, the activity of a glycoprotein called follistatin in brown fat was examined.

Braga et al. had noted that follistatin expression levels are significant in some brown adipose tissue and wanted to know its functions there. So first, they examined mouse brown pre-adipocytes allowed to differentiate under controlled conditions; follistatin levels went from undetectable from baseline to substantial levels once the adipocytes differentiated.

From there, the team looked at adipogenesis in vitro in mouse embryonic fibroblasts, comparing the differences between those isolated from wild-type embryos or embryos in which the follistatin gene had been knocked out. The levels of key brown adipocyte proteins, including uncoupling protein 1, or UCP1, were found to be much lower in the knockout mouse fibroblasts compared with wild type. The decrease in the amounts of these proteins suggests that follistatin influences adipogenesis and differentiation of brown adipocytes and that severe metabolic defects may occur without normal follistatin function, including defects that could prove fatal.



Tissue distribution of follistatin and its induction during adipogenic differentiation of mouse brown pre-adipocyte cells. (A) Real-time quantitative PCR analysis of follistatin gene expression in mouse tissue panel (n=3). (B) Photomicrographs of mouse brown pre-adipocyte cells grown either in regular growth medium (undifferentiated) or in BAT-specific adipogenic medium (differentiated) for 8 days.

By treating both kinds of cells with follistatin, the researchers confirmed it was the lack of the glycoprotein that was causing the decreased levels of key brown adipocyte proteins. Addition of the glycoprotein to follistatin-deficient fibroblasts also increased cellular respiration.

Global gene-expression profiling also was conducted on fibroblasts of both types during the early stages of brown adipocyte induction. Expression levels of genes were reduced by 3.5-fold or more in the knockout fibroblasts compared with the wild-type cells and indicated that follistatin is a key modulator of lipid and energy metabolism.

The researchers say more detailed studies of follistatin's functional role in vivo are the next logical step. The development of in vivo models hopefully will help identify potential tissue targets of follistatin and therefore provide novel therapeutic approaches for treating obesity, diabetes and metabolic syndrome.

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Channeling pain

The role of resurgent currents in inherited pain syndromes

By Sapeckshita Agrawal

Nociceptors are nerve cells that sense potentially harmful stimuli and report to the brain and the spinal cord to effect an appropriate defense response. The reporting is relayed in the form of action potentials transmitted by voltage-gated sodium channels on these nerve cells. Interestingly, the nerve cells can be rendered hyper-excitable by various mutations in the SCN9A gene that encode the sodium channel subtype Nav1.7. As a result, two distinct types of inherited pain syndromes can arise: inherited or primary erythromelalgia, called IEM for short, and paroxysmal extreme pain disorder, or PEPD.

To date, IEM has been linked to at least 20 mutations of the SCN9A gene, all of which reduce the depolarizing potential needed to activate the mutant channel, thus facilitating hyperexcitability of the nerve cell. Consequently, seemingly innocuous activities such as exercise can trigger episodes of excruciating pain.

PEPD, on the other hand, has been linked to 10 (and potentially more) separate mutations, also on the SCN9A gene, all of which obstruct channel closure by inducing a depolarizing shift of steady-state inactivation. The result is, again, a hyperactive nerve cell causing debilitating pain.

The apparent dichotomy between IEM mutations affecting activation and PEPD mutations affecting inactivation of the sodium channels recently has been challenged after the characterization of a new mutation of the SCN9A gene published in the **Journal of Biological Chemistry** by Mirjam Eberhardt and collaborators in Germany.

The study highlights the case of a 22-year-old female suffering from canonical symptoms of

IEM. Sequencing her SCN9A gene identified the responsible mutation, A1632T. However, instead of affecting activation of Nav1.7 as expected, the mutation, when tested in transfected human embryonic kidney cells, shifted steady-state fast inactivation to depolarizing potentials – a phenomenon expected from PEPD mutations.

This surprising result led Eberhardt and her team to determine what bifurcates pain syndrome from SCN9A mutations into IEM or PEPD. To do so, the team took advantage of a previously characterized mutation of SCN9A gene, A1632E. Interestingly, that mutation gives rise to overlapping symptoms of IEM and PEPD, displaying shift of voltage-dependence for both activation and fast inactivation.

Using whole-cell voltage-clamp recordings of human embryonic kidney cells transfected with mutant versions of the SCN9A gene, the team determined that the difference in electrophysiology between A1632E and A1632T was in the decay time constants of the current. While A1632T and wild type had similar decay constants, A1632E had a slower current decay. Based on this observation, the team hypothesized that the slower current decay also would lead to resurgent currents in the system.

Resurgent currents, an unusual phenomenon in which sodium channels briefly open during depolarizing currents in the decaying phase of an action potential, arise as a result of occlusion of the sodium channel during inactivation by a blocking particle, which is different from the intracellular loop responsible for routine channel inactivation. Thus, to test the hypothesis that A1632E mutation led to an increase in resurgent currents, the team added a peptide with the sequence of the blocking particle to the transfected cells.

They observed that resurgent currents do, indeed, increase in A1632E mutation but not in A1632T mutations. Thus they concluded that IEM results from increased inactivation of Nav1.7 without an increase in resurgent currents, while PEPD results from increased inactivation with increased resurgent currents.

The results are significant, because they offer insights into the key difference between the electrophysiology of IEM and PEPD, both of which are debilitating conditions that cause episodic pain. These findings provide a novel target area for the development of therapeutic strategies; drugs counteracting the action of the blocking particle that gives rise to resurgent currents could be developed.

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A broader look at the proteins involved in learning and memory

By Rajendrani Mukhopadhyay

Learning is complicated business. But typical research studies into the molecular basis of learning and memory measure only one or a few proteins. In a study just reported in the journal **Molecular & Cellular Proteomics**, researchers cast a wider net and looked at 80 proteins in the brain of mice. By looking at more proteins, the study's leader, Katheleen Gardiner at the University of Colorado in Denver, says researchers can get a better appreciation of "the greater complexity of molecular events underlying learning and memory, how components of a single pathway change in concert, and how many pathways and processes respond."

Gardiner's research focus is on Down syndrome, two characteristics of which are that patients suffer from some level of intellectual disability and that they eventually develop Alzheimer's disease. Gardiner's group aims to find drugs that can lessen the learning disability. But in order to do that, researchers need to better understand the molecular events associated with learning, memory and neurodegeneration.

To get a grasp of the proteins involved in a particular learning process, the investigators studied context fear conditioning in mice. In this type of experiment, mice are put in a new cage and given a small electrical shock. Researchers can tell when a mouse has learned to be fearful of the same cage when the mouse freezes when put back in the cage. This approach "has the advantage that it requires only a single trial, lasting less than five minutes, for mice to learn," explains Gardiner. "This means that we have a clear window in time where we know molecular events associated with successful learning occur."

Context fear conditioning demands that the hippocampus, a region of the brain important for memory formation, be functional. The hippocampus is also a part of the brain that degenerates in Alzheimer's disease.

The investigators gave the mice a drug called memantine, which is used to treat moderate to severe cases of Alzheimer's disease. The drug has been shown to correct for learning impairment in a mouse model of Down syndrome.

Gardiner's group used proteins arrays to see how protein expression changed in the brains of mice that underwent context fear conditioning and were given memantine compared with control mice. They found levels of 37 proteins changed in the nuclear fraction of the hippocampus. Abnormalities in 13 proteins had been reported in brains of Alzheimer's patients. "One surprise was that many proteins that increased in level with normal learning also increased, although not as much, with treatment with memantine alone," says Gardiner. "Memantine induces responses in a substantial number of proteins that we measured, and it does this without impairing or enhancing learning. This indicates that there is considerable flexibility in the timing and extent of protein responses that still result in successful learning."

In particular, Gardiner's group identified the MAPK and MTOR pathways to be affected in their experiments as well as subunits of glutamate receptors and the NOTCH pathway modulator called NUMB. NUMB is known to be essential for some aspects of brain development.

Gardiner says her group is now looking at data from a similar experiment done with a mouse model of Down syndrome. Those mice were unsuccessful with context fear conditioning, but they did as well as wild-type mice when they were treated with memantine.

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Identification of ceramide-1-phosphate transport proteins

By Robert V. Stahelin

Recently, investigators have identified the protein that carries the important sphingolipid ceramide-1-phosphate in humans. This finding helps us understand how C1P is transported inside cells to carry out its critical signaling functions for processes such as cell proliferation and migration.

Sphingolipids play key roles in cellular signaling and membrane trafficking — with sphingosine, sphingosine-1-phosphate, ceramide and C1P acting as the main players (1).

C1P is an anionic sphingolipid containing a phosphomonoester headgroup (see Figure 1A) and in mammalian cells is synthesized from ceramide by the enzyme ceramide kinase. CerK was discovered more than 20 years ago by a team that co-purified it with brain synaptic vesicles (2); to date, it remains the only kinase known in mammalian cells to convert ceramide to C1P.

In 2002, CerK was cloned and found to be expressed in the brain, heart, kidney, lung and hematopoietic cells (3). Since then, the many bioactive roles for C1P have been elucidated. These include macrophage migration, cell proliferation, stem cell mobilization and regulation of eicosanoid production (4, 5).

'An exciting finding'

CerK is localized to the trans-Golgi network, where it generates C1P from ceramide. At the trans-Golgi network, C1P has been shown to activate the pro-inflammatory enzyme cytosolic phospholipase $A_2\alpha$, or $cPLA_2\alpha$ (6). More recently, C1P has been shown to regulate other proteins (7, 8); however, the cellular mechanisms and localizations are not well understood. C1P may be transported via vesicular transport from the trans-Golgi network (9), but for the most part, how specifically C1P is disseminated from the trans-Golgi network to other cellular membranes, where it interacts with effector proteins, remained unknown until recently.

Last year, a multidisciplinary team reported in the journal Nature that it had identified a putative C1P transfer protein, or CPTP, in humans (10).

The team screened the National Center for Biotechnology Information's human genome and identified a predicted transcript with 17 percent sequence identity with glycolipid transfer protein, or GLTP.

The authors demonstrated that the mRNA for this construct was found in most tissues and that the recombinant protein can transfer C1P selectively between phosphatidylcholine vesicles. This is an exciting finding for the lipid research community, as lipid-transport proteins for sterols, ceramide, glycolipids and glycerophospholipids have been studied intensely (11 – 13), and yet those for lipids such as C1P had remained unexplored.

Structural details for CPTP

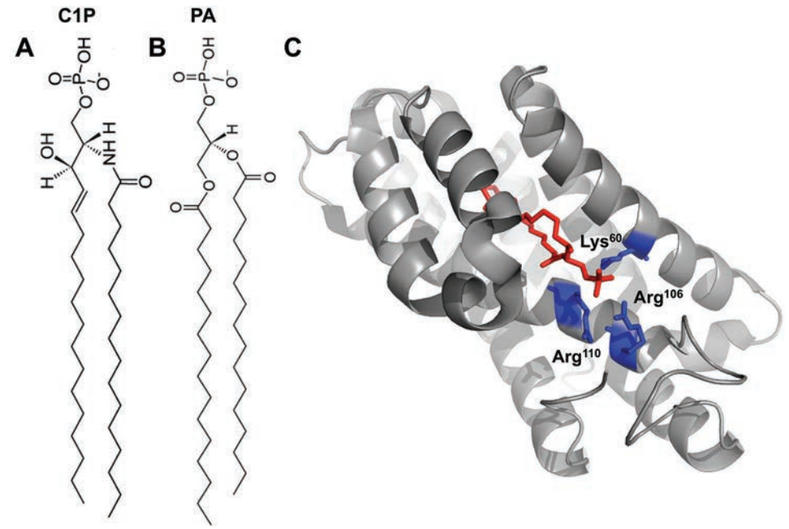
The authors went on to solve the structure of CPTP bound to several lipids, including C1P, with varying acyl chains. The structure revealed an α-helical topology and a fold homologous to that of GLTP (figure 1C).

CPTP has one surface enriched in cationic residues, which contains three amino acids (Lys^{60}, Arg^{106} and Arg^{110}) critical for binding to the C1P phosphate headgroup. Mutation of these residues greatly diminished the ability of CPTP to transport C1P.

Below this surface cationic patch lies a portal to a deep hydrophobic cavity that can accommodate both acyl chains of the C1P molecule. This hydrophobic pocket is highly flexible and can expand to accommodate the sphingosine and acyl chains of 16:0- and 18:1-C1P. The authors demonstrate that this pocket wasn't as adaptable to accommodating longer acyl chains (such as lignoceryl) and thus propose that CPTP may serve to transfer 16:0- and 18:1-C1P selectively in cells.

The structure of CPTP with phosphatidic acid bound (figure 1B) also was solved to investigate why a different anionic phosphomonoester was not transferred efficiently by CPTP.

Phosphatidic acid interacts with the same residues as the C1P headgroup but with a slightly different H-bonding arrangement. Additionally, the lack of the acyl amide moiety on phosphatidic acid precluded the interaction with residues in CPTP that bound the acyl amide of C1P. Thus, phosphatidic acid had altered headgroup and acyl chain positions compared with C1P, which was determined to loosen the phosphatidic acid binding. This distorted orientation likely dampens transfer of phosphatidic acid.



Crystal structure of CPTP in complex with 16:0-C1P (PDB ID: 4K84). Cationic residues (Lys^{60}, Arg^{106} and Arg^{110}) that bind the phosphate headgroup of C1P are shown in blue. The C1P acyl chains are ensheathed in the deep hydrophobic pocket beneath the surface cationic residues that interact with the phosphate headgroup.

Cellular studies of C1P transport

In cells, CPTP visualized by antibody or enhanced green fluorescent protein tag was found in the cytosol but also associated with the trans-Golgi network, endosomes, nuclei and plasma membrane. Thus, the authors propose a C1P-sensing role for CPTP at the trans-Golgi network during CERK signaling.

Silencing of CPTP in human cells resulted in elevated cellular 16:0-C1P and 24:1-C1P as well as fragmented Golgi cisternal stacks. Subcellular fractionation showed that C1P levels were increased in the trans-Golgi network, endosomal and nuclear fractions but were decreased in the plasma membrane. CPTP overexpression could rescue these effects.

CPTP involvement in C1P effector $cPLA_2\alpha$ activity was also assessed. When CPTP was silenced, arachidonic acid levels increased, consistent with C1P accumulation and therefore increased $cPLA_2\alpha$ activation at the trans-Golgi network. Metabolites of cyclooxygenase, lipoxygenase and CYP450 pathways also were increased. Conversely, eicosanoid levels decreased upon overexpression of wild-type CPTP but not dominant negative mutations.

The authors suggest that CPTP acts as a C1P sensor, transferring C1P from the trans-Golgi network to the plasma membrane as levels increase such that C1P does not build up in the trans-Golgi network. This would also allow for fine-tuning of cPLA2α activity and the ability to regulate arachidonic acid generation. CPTP depletion also had effects on other sphingolipids, namely decreased cellular levels of sphingosine, sphingosine-1-phosphate and sphingomyelin.

While metabolism of C1P back to another sphingolipid (ceramide or S1P) is still a controversial subject, this new study suggests that perhaps deacylation of C1P may occur as silencing of CPTP reduces cellular levels of S1P and sphingosine.

CPTP does not appear to be limited to mammalian cells. A CPTP was found in Arabidopsis (14). In that model, cell death 11 mutant, or ACD11, is able to transfer C1P or phyto-C1P, the major component of plant cells.

The structure of ACD11, like that of CPTP, revealed a surface cationic patch for C1P headgroup recognition and a hydrophobic pocket that can accommodate the lipid chains. In null ACD11 cells, normally low levels of phyto-C1P greatly rise, leading to an increase in phyto-ceramides and programmed cell death.

What's to come?

Many questions about C1P-mediated signaling and cellular transport remain unanswered.

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For instance, which lipids CPTP binds at the trans-Golgi network and plasma membrane is unknown, and how specifically it transports C1P from the Golgi to the plasma membrane is not understood. However, these represent exciting questions for future studies.

C1P also has unique biophysical properties that may play roles in its signaling and transport (15). In closing, these new studies identifying the existence of CPTPs will generate much excitement toward further unraveling the mechanism and role of C1P signaling in normal and pathological processes.

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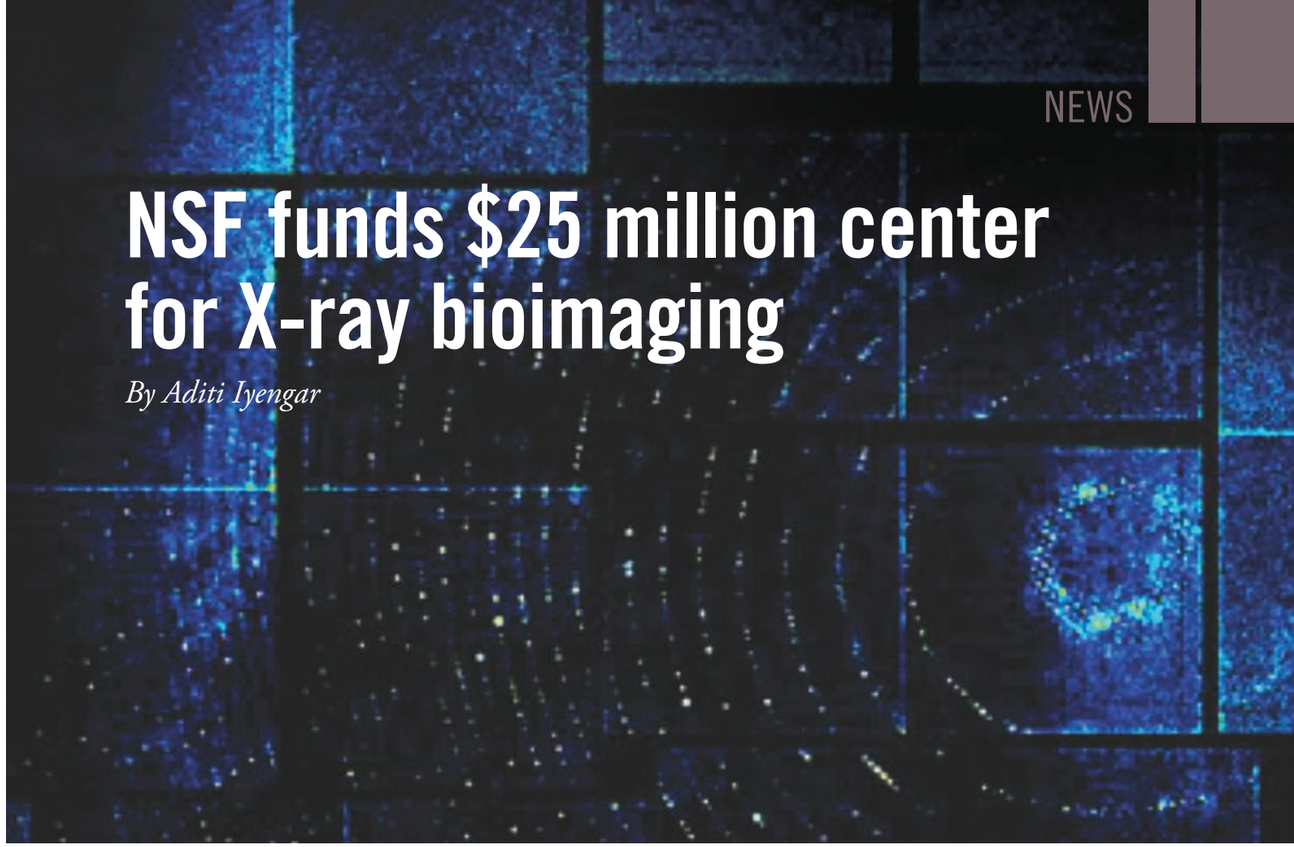
NSF funds $25 million center for X-ray bioimaging

By Aditi Iyengar



The first high-resolution diffraction pattern results from the X-ray free electron laser at LCLS in February 2011. NSF BIOXFEL SCIENCE AND TECHNOLOGY CENTER

The University of Buffalo won a prestigious science and technology center grant conferred every four years by the National Science Foundation for the establishment of innovative and interdisciplinary research centers across the country. This $25 million grant will go toward launching the Center for Biology with X-ray Laser, or BioXFEL, which will focus on developing new bioimaging techniques using the immensely powerful X-ray free-electron laser technology.

Researchers affiliated with the BioXFEL center anticipate new breakthroughs in the field of biomolecular crystallography using this kind of X-ray beam, originally developed at the SLAC National Accelerator Laboratory at Stanford University.

"With this (technology), the center will provide the biology research community with tools to study an enormous number of biological systems that are currently inaccessible by current X-ray methods," says NSF Chemistry of Life Processes Program Manager David Rockcliffe. "Once the center develops the measurement tools to fully utilize the XFEL source, the scientific payoffs are expected to be extraordinary."

The use of XFEL technology could enable scientists to develop advanced forms of X-ray bioimaging, including the serial femtosecond crystallography method for the characterization of biological structures. This particular technique, with its ability to predict the structure and motion of extremely small and previously uncrystallizable molecules, could provide structural biologists with a valuable tool to analyze accurately biological function of proteins and their dysregulation in disease. Such research would boost current methods employed to identify molecular targets for drug development and improve the current understanding of drug design.

The University at Buffalo and Hauptman-Woodward Medical Research Institute will host this center in partnership with Arizona State University; the University of Wisconsin, Milwaukee; Cornell University; Rice University; Stanford University; the University of California, San Francisco; and UC, Davis.

Eaton E. Lattman, a professor in Buffalo's structural biology department and medical school and chief executive officer of the Hauptman-Woodward Medical Research Institute, will be director of the BioXFEL center.

For more information on this center and its research, visit www.bioxfel.org.

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In the April issue:

ALICE AND C.C. WANG AWARD IN MOLECULAR PARASITOLOGY

Stuart recognized for his work with trypanosomes

By Sarah Perdue

Ken Stuart, founder and president emeritus of the Seattle Biomedical Research Institute and an affiliate professor of global health at the University of Washington, is the recipient of the American Society for Biochemistry and Molecular Biology's Alice and C.C. Wang Award in Molecular Parasitology.

The award is given to researchers who are making significant contributions to the field. Stuart was nominated for his work on post-transcriptional mRNA editing in trypanosomes as well as the sequencing and annotation of their genomes.

Trypanosomes include the causative agents of African sleeping sickness, Chagas disease and Leishmaniasis. More recently, Stuart has begun to study the interactions between the malaria parasite and its human host. His work has led to a broad understanding of trypanosome biology as well as the identification of hundreds of potential drug targets to combat the diseases.

Stuart showed that some transcripts in trypanosomes are edited by the addition or removal of a nucleotide and that that process alters how the pathogen regulates energy generation. He also found that this editing is differentially regulated throughout the organism's life cycle and that this editing is essential during the disease stage, making the so-called "editosome" an ideal target for therapies.

"Dr. Stuart's RNA editing discoveries expanded the central dogma of molecular biology by showing that the protein-coding sequence of mRNAs can be precisely changed after their transcription from DNA," said Thomas Wellems, chief of the Laboratory of Malaria and Vector Research at the National Institute of Allergy and Infectious Diseases. "His lab determined the crystal structures of some of the editosome proteins and is testing compounds as potential leads for drug development."

Stuart's editing work has led others to find additional types of editing in such diverse organisms as plants and humans, said Stefan Kappe, the Seattle Biomedical Research Institute's malaria program director. Kappe noted that in humans, for example, post-transcriptional editing has been shown to function in resistance to HIV infection as well as in the regulation of channel receptors in the brain.

Stuart was also a leading force in the sequencing and annotation of the so-called "TriTryp" genomes, and he has since used genetic and biochemical approaches to characterize and assign function to more than 1,000 mitochondrial proteins as well as many of the cellular proteins in Trypanosome brucei. His characterization of the proteome, including structural prediction and enzymatic analysis, has helped identify inhibitors that could lead to the development of anti-trypanosome drugs.

"Now that many genes of these parasites are mapped, researchers can more easily identify genes that are critical for parasite survival, and new knowledge about the similarities between each trypanosome suggests the potential to develop a class of drugs that can target all three parasitic diseases," said Wellems.

In addition to Stuart's work on trypanosome pathogenesis, he is studying the malaria parasite Plasmodium falciparum. He recently characterized a protein complex in that organism that metabolizes hemoglobin and detoxifies heme, and he is using RNAseq to characterize lymphocyte gene expression in response to malarial infection and immunization against the parasite.

I am honored to receive this award from the Wang's, who have made pioneering contributions to molecular parasitology and are committed to improving global health.

– KEN STUART

"In the late 1970s, 'global health' was not a term in common use, and there was almost no research in the U.S. on neglected diseases," said Wellems. "(Stuart) had the vision to build a new organization (Seattle BioMed) and partnerships that would attract leading principal investigators to this research."

Stuart will receive his award during the Experimental Biology 2014 conference in San Diego, where he will deliver an award lecture. The presentation will take place from 3:45 to 6 p.m. Monday, April 28, in the San Deigo Convention Center Room 1A.

Sarah Perdue (sp366@cornell.edu) received her Ph.D. in microbiology from Cornell University, spent two years teaching at different colleges as a visiting professor and now is a postdoctoral researcher at the University of Minnesota.

ASBMB/MERCK AWARD

Cravatt lauded as 'gem of the scientific community' for his work on activity-based protein profiling

By Mark Stewart

Benjamin Cravatt of The Scripps Research Institute in La Jolla, Calif., has been named the winner of the American Society for Biochemistry and Molecular Biology/Merck Award.

Cravatt, professor and chair of the chemical physiology department at Scripps, received this award based on his groundbreaking contributions to the development and application of post-genomic methods for the functional annotation of mammalian enzymes. "Cravatt pioneered the use of the now widely practiced activity-based protein profiling technology, which utilizes site-directed chemical probes to profile active enzymes in complex proteomes," said Chaitan Khosla of Stanford University, who nominated Cravatt for the award.

Most proteomic technologies measure protein abundance and therefore provide only an indirect estimate of protein activity. Cravatt's work has led to the development of a chemical strategy to profile the functional state of enzymes through the development of active site directed probes, known as activity-based protein profiling, or ABPP.

During his graduate work, Cravatt discovered fatty acid amide hydrolase, or FAAH, an endocannabinoid-metabolizing enzyme. ABPP revealed important roles for endocannabinoid-metabolizing enzymes in pain, inflammation and neuropsychiatric disorders. In collaboration with the pharmaceutical company Pfizer, a highly potent and selective FAAH inhibitor was developed and today is in human clinical trials. This FAAH inhibitor represents a potential new class of analgesics and a novel treatment for nervous system disorders.

James Wells of the University of California, San Diego, describes Cravatt as "a star at the chemistry-biology interface and a worthy recipient of this important award."

Cravatt attended Stanford University, earning a B.A. in history and a B.S. in biological sciences. He then pursued a Ph.D. at The Scripps Research Institute under the mentorship of Dale Boger and Richard Lerner. At Scripps, he became an assistant professor in 1996 and rose through the ranks to become professor and chair in 2007.

"His love of science is overflowing and contagious. If you haven't had the chance to hear him speak about his work, there's nothing I'd recommend more highly," says Daniel Herschlag of Stanford University.

I am tremendously honored to receive the 2014 ASBMB-Merck Award, which is a tribute to the many talented and hardworking graduate students, postdoctoral fellows and collaborators with whom I have had the pleasure of working during my career at TSRI.

– BENJAMIN CRAVATT

Cravatt will receive his award at the Experiment Biology 2014 conference in San Diego. He will present his award lecture at 2:55 p.m. Tuesday, April 29, in Room 6A of the San Diego Convention Center.

Mark Stewart (mdstew@uab.edu) is a Ph.D. student in the University of Alabama at Birmingham's cancer biology program and works in the pathology department.

WALTER A. SHAW YOUNG INVESTIGATOR AWARD IN LIPID RESEARCH

Kraft 'has changed our understanding of lipid organization'

By Shaila Kotadia

Mary Kraft, assistant professor of chemical and biomolecular engineering at the University of Illinois Urbana-Champaign, is the winner of this year's American Society for Biochemistry and Molecular Biology Walter A. Shaw Young Investigator in Lipid Research award.

Established by the ASBMB's Lipid Research Division and named after the founder of Avanti Polar Lipids, the award recognizes outstanding research contributions by investigators with 10 or fewer years of experience.

Kraft's colleague at UIUC, Jonathan Sweedler, said that Kraft's work "has changed our understanding of lipid organization within the cellular plasma membrane and the mechanisms that produce it."

Kraft devised a novel method for imaging using high-resolution secondary ion mass spectrometry in conjunction with metabolic isotope labeling, which opened an unexpected new view of lipid composition in the cellular plasma membrane. One key finding demonstrated that cholesterol is not enriched in sphingolipid domains but rather evenly distributed throughout the cell membrane.

Kraft is continuing her excellent efforts, said Bill Bement at the University of Wisconsin-Madison, who supported Kraft's nomination for the award: "I cannot think of anyone who is better suited to this award, aimed as it is at young researchers who have not only attained prominence but also hold considerable promise for future work."

Kraft started her career as a cooperative education student at the Nalco Chemical Company and completed her graduate work at UIUC. She took a four-year hiatus from the Midwest to do her postdoctoral fellowship at Stanford University, where she was willing to try what many other researchers could not achieve.

Her postdoctoral adviser, Steven Boxer, explained: "Everything she was doing was new. There is little precedent for the application of the method to any soft material, let alone biological membranes, and the consensus was that it would be impossible to pull off." Kraft overcame those obstacles and established the high-resolution SIMS technique for lipid membranes. Kraft soon returned to UIUC for an assistant professor position.

Kraft not only has excelled in the laboratory but also in the classroom and in advising, receiving multiple awards from her institution for her attentiveness to student needs.

She will receive her award at the 2014 ASBMB annual meeting in San Diego, where she will give a presentation. The presentation will take place at 3:45 p.m. Sunday, April 27, in Room 6C of the San Diego Convention Center.

I'm honored to receive the Walter A. Shaw Young Investigator Award in Lipid Research for my lab's work on lipid organization in the plasma membrane. I'm especially grateful to my students, collaborators, colleagues, the ASBMB and Walter A. Shaw for making this possible.

– MARY KRAFT

Shaila Kotadia (skotadia@asbmb.org) is an ASBMB science policy fellow.

MILDRED COHN AWARD IN BIOLOGICAL CHEMISTRY

Gierasch lauded as 'phenomenal mentor' and 'rigorous biophysical chemist'

By Anna Shipman

The American Society of Biochemistry and Molecular Biology has awarded Lila Gierasch the 2014 Mildred Cohn Award in Biological Chemistry for her extensive work in protein folding, structure and function. This award recognizes scientists who have made substantial advances in the field of biological chemistry through the use of innovative physical methods.

Gierasch's early research into the relationship between amino-acid sequence and peptide and protein structure resulted in the development of fundamental principles for reverse-turn conformation features as well as the establishment of several biophysical methods commonly used today to characterize protein turns, such as nuclear magnetic resonance, quantitative nuclear Overhauser effects, circular dichroism and computational modeling. This research was also the basis for Gierasch's later research with GnRH analogs and the use of peptide fragments to examine protein recognition motifs. Gierasch also has studied how protein folding occurs within the cell, using transferred nuclear Overhauser effect, or trNOE, methods to show how chaperone proteins recognize the folded state of a protein substrate.

"Lila is a rigorous biophysical chemist, but unlike most chemists who avoid complexity and prefer reductionist type studies, Lila's whole career has been focused on applying chemistry and biophysical methods to the study of peptides and their role in biology as well as protein folding and trafficking in vivo," says Jeffrey W. Kelly at The Scripps Research Institute. "Her work is insightful, revealing and is well ahead of its time."

Some of Gierasch's more recent work has been focused on developing and testing experimentally a computational model of cellular protein homeostasis in E. coli in collaboration with Evan Powers of The Scripps Institute. This collaboration has resulted in FoldEco, an online modeling program used to examine how protein folding in the cell is facilitated by chaperone and degradation networks. Gierasch's lab also uses fluorescent reporters to study how protein sequence may affect protein aggregation and folding.

Gierasch earned her A.B. in chemistry in 1970 from Mount Holyoke College in South Hadley, Mass., and earned a Ph.D in biophysics from Harvard University in Cambridge, Mass., from the lab of Elkan R. Blout in 1975.

Today Gierasch is a distinguished professor at the University of Massachusetts Amherst. She has mentored many undergraduate and graduate students and postdoctoral fellows; served on many editorial advisory boards; and played leadership roles in several scientific societies.

"To me, Lila is not only an outstanding scientist who has made milestone and unique contributions to her own research field but also a phenomenal mentor who never ceases to inspire and help many of her mentees to launch success in their careers," says Ning Zheng, Professor at University of Washington and an Howard Hughes Medical Institute Investigator. "Her achievements as a scholar, a leader and a mentor are extraordinary at every level."

Gierasch will receive the award at the 2014 ASBMB annual meeting in San Diego, where she will give a presentation. The presentation will take place at 8:30 a.m. Monday, April 28, in Room 6A of the San Diego Convention Center.

I am thrilled to be chosen to receive the Mildred Cohn Award from ASBMB. She was one of my heroes; her contributions reflect her deep physical understanding, her experimental boldness and her willingness to deploy any biophysical approach that would answer the key questions underlying a biological system.

My laboratory's contributions reflect the energy, creativity, enthusiasm, hard work and dedication of the wonderful students and postdocs I have worked with through the years. I thank them! In addition, thanks to many collaborators who worked with us to tackle daunting problems, who elevated our science and who shared the pleasures of garnering meaningful results.

– LILA GIERASCH

Anna Shipman (alsnpc@mail.umkc.edu) received her B.S. in biology–biotechnology from Missouri Western State University and is a Ph.D. student in the School of Biological Sciences at the University of Missouri–Kansas City.

AVANTI AWARD IN LIPIDS

Hofmann honored for her contributions to the field of protein lipidation

By Mark Stewart

The American Society for Biochemistry and Molecular Biology has named Sandra Hofmann at the University of Texas Southwestern Medical Center at Dallas the winner of the Avanti Award in Lipids.

Hofmann, a professor in the internal medicine department at UT-Southwestern, focuses her research on fundamental questions in lipid metabolism and protein lipidation, which has led to novel insights into the treatment of human diseases.

When Hofmann set up her own lab at UT-Southwestern, the enzymology of palmitoylation, which is the attachment of fatty acids to proteins, was unknown. Hofmann's research led to the purification of palmitoyl protein thioesterase, or PPT1, an enzyme that removes these fatty acids from proteins. This was the first enzyme identified with a role in protein palmitoylation. The PPT1 gene eventually was mapped to a region in chromosome 1p, which also had been linked to infantile neuronal ceroid lipofuscinosis, or INCL, a devastating neurodegenerative disease in children. Her training as a clinician-scientist helped her make this link and discover that deficiencies in PPT1 cause INCL.

"Hofmann's research is a superb example of how tackling a fundamental basic science question can lead to discoveries of great clinical significance," explains Maurine Linder of Cornell University, who nominated Hofmann for the award.

Hofmann later developed the first mouse model of INCL. That mouse model allowed her to develop enzyme-replacement therapy. The addition of intravenous recombinant PPT1 has led to modest improvements in mice and provides the basis for further studies.

Robert Deschenes of the University of South Florida says that "Hofmann's work is a model of translational science at its best" and that he even uses her work as an example when teaching graduate and medical students.

Hofmann earned her B.A. in chemistry with the highest distinction at the University of Virginia in Charlottesville. She proceeded to earn an M.D. and Ph.D. at Washington University School of Medicine in St. Louis under the mentorship of Philip Majerus. In the Majerus lab, she made seminal contributions to the enzymology of phosphatidylinositol hydrolysis. That work provided her experience in the isolation and characterization of novel enzymes. She left Washington University to pursue postdoctoral training in the laboratory of Nobel laureates Michael Brown and Joseph Goldstein at UT-Southwestern. Hofmann has since remained at UT-Southwestern, where she has risen through the ranks to professor.

In recognition of her research, Hofmann was inducted as a member of the American Society for Clinical Investigation and the American Association of Physicians. She also chairs the Scientific Advisory Board for the Batten Disease Support and Research Association, which allows her to have a sustained influence on the field of disorders of the nervous system.

Hofmann will receive her award in San Diego at the Experimental Biology 2014 meeting, where she will deliver an award lecture. Her lecture will be at 8:30 a.m. Wednesday, April 30, in Room 6A of the San Diego Convention Center.

I am honored to have received this award and am grateful to my colleagues for the nomination and to Avanti Polar Lipids for their support of this award. Lipid enzymology is a difficult and rewarding field pioneered by a number of courageous individuals and it has been a privilege to continue to work in this great tradition. It is particularly exciting to see protein lipidation being recognized. The potential for new discovery in this area is enormous. It would not surprise me to be treating future patients with cancer or neurological disorders with protein palmitoylation inhibitors in the same way that protein kinase inhibitors are used today.

– SANDRA HOFMANN

Mark Stewart (mdstew@uab.edu) is a Ph.D. student in the University of Alabama at Birmingham's cancer biology program and works in the pathology department.

ASBMB YOUNG INVESTIGATOR AWARD

Jaffrey called 'a tremendously gifted thinker' for having accomplished so much so quickly

By Anna Shipman

Samie R. Jaffrey of Weill Medical College of Cornell University has been awarded the American Society for Biochemistry and Molecular Biology's 2014 Young Investigator Award for his advancements in RNA technology and mRNA regulation. The award seeks to recognize outstanding research done in the field of biochemistry and molecular biology by scientists with fewer than 15 years of postdoctoral experience.

The Jaffrey lab researches how RNA regulation affects neuronal growth and development – and especially how novel functions of RNA are involved in intracellular signaling pathways needed for growth and development.

One point of interest is how RNA localization to specific regions of a cell may influence the pattern of protein expression; however, there previously were no simple methods available to visualize RNA in live cells. Jaffrey's lab developed fluorescent-tagged RNA molecules to determine the location of RNA within live cells. These RNA-fluorophore complexes are composed of an RNA aptamer that binds to a target ligand and an RNA aptamer that binds and activates a fluorophore.

These complexes could aid in the study of splicing, RNA editing and degradation, as well as visualization of metabolite levels and interactions that cannot be detected by Förster Resonance Energy Transfer and the detection of signaling molecules within cells. Through the use of these fluorescent-tagged RNA molecules, Jaffrey's lab has identified novel RNA mechanisms that may control protein expression.

The recent focus of his lab has been the role of adenosine methylation in mRNA regulation and modification using a novel sequencing approach that targets N6-methyl adenosine residues to target their presence in the transcriptome.

"I know of few individuals who combine Samie's level of understanding of chemistry, molecular biology and biochemistry and have been able to leverage deep understanding in all of these areas to transform our understanding of RNA biology," says Rajiv R. Ratan of Weill Medical College of Cornell University and Burke Medical Research Institute. "Samie is a tremendously gifted thinker who has accomplished as much in the first 10 years of his laboratory's existence as many of us endeavor to achieve in a lifetime."

Jaffrey earned his B.S. in biology from the Massachusetts Institute of Technology in 1992 and then his Ph.D. in neuroscience and M.D. from the Johns Hopkins University School of Medicine in 1999 in the lab of Solomon H. Snyder. Jaffrey is currently a tenured professor of pharmacology at Weill Medical College in New York City.

It's a great honor to be included in the company of the previous recipients ASBMB Young Investigator Award. This award would not have been possible without the remarkable students and fellows who have been members of my laboratory.

– SAMIE R. JAFFREY

Jaffrey will receive his award at the ASBMB annual meeting in San Diego. The presentation will be at 9:05 a.m. April 29 in Room 6A of the San Diego Convention Center.

Anna Shipman (alsnpc@mail.umkc.edu) received her B.S. in biology–biotechnology from Missouri Western State University and is a Ph.D. student in the School of Biological Sciences at the University of Missouri–Kansas City.

DELANO AWARD FOR COMPUTATIONAL BIOSCIENCES

Nobel laureate Levitt: 'an intellectual leader'

By Preethi Chander

Michael Levitt of the Stanford University School of Medicine is the recipient of the DeLano Award in Computational Biosciences awarded by the American Society for Biochemistry and Molecular Biology.

The award recognizes scientists for their innovative development of computational technologies that enable life-science research at the molecular level.

Levitt, who won the Nobel Prize in chemistry in 2013, is well known for his pioneering work in modern computational biosciences – work that embodies the key elements of the DeLano award: the productive use of computers to accelerate research and ready access to these programs for the scientific community.

Raised in South Africa and later in England, Levitt earned his bachelor's degree in physics from King's College London. He studied at the Medical Research Council Laboratory of Molecular Biology, Cambridge (a part of Cambridge University), where he earned his Ph.D. in computational biology. He then did his postdoc at the Weizmann Institute of Science in Israel, where he later became a citizen and did a few weeks of basic service in the Israeli Defense Forces.

In the year that he spent in Israel before starting his Ph.D., Levitt published the first protein simulation using Cartesian coordinates. That revolutionary paper laid the groundwork for molecular simulations.

Later, with Arieh Warshel, Levitt described a framework for simulation studies combining quantum mechanical and classic mechanical methods.

In other work done at the same time with Warshel, Levitt introduced coarse-grained models of the polypeptide chain for rapid simulation of protein folding. As a staff scientist at the MRC Laboratory of Molecular Biology, he worked with Tony Jack and laid the groundwork for modern approaches to crystallographic refinement.

Levitt's work on protein modeling combining segments of known protein was adapted and extended by David Baker's group at University of Washington, leading to the development of Rosetta, software widely used by the protein-modeling community. Many of the fundamental architectural principles of protein structure and protein-classification schemes taught in protein biochemistry courses stem from classic papers that Levitt authored in the 1970s along with Cyrus Chothia while he was at the MRC.

Barry Honig of Columbia University, a past recipient of the DeLano award, described Levitt as "an intellectual leader in computational structural biology." It is notable that, apart from a an award in 1985 from the Federation of European Biochemical Societies, the DeLano Award in Computational Biosciences was the only prize awarded to Levitt before he was recognized in Stockholm.

Honig said of Levitt: "(He) has taught the practitioners new ways to apply computational tools to structural biology and that it is possible to have impact if theoretical rigor, algorithmic novelty and deep understanding of experimental reality are combined."

This is the only prize I received in the decades preceding the Nobel Prize. Warren DeLano showed exceptional foresight in his pioneering use of Python, a trend adopted by much modern scientific software. His is a remarkable legacy I am proud to honor.

– MICHAEL LEVITT

Past recipients of the DeLano award include Helen Berman and Axel Brunger.

Levitt will receive the award at the ASBMB annual meeting in April in San Diego. His award lecture, tentatively titled "Solving large and difficult structures with less experimental data," will be on Tuesday, April 29, in Room 6A of the San Diego Convention Center.

Preethi Chander (chander.preethi@gmail.com) earned a Ph.D. in structural biology from Purdue University and completed a postdoctoral fellowship at the National Institutes of Health. She works at the National Institutes of Health, Bethesda, MD, as a health science program administrator.

EARL AND THRESSA STADTMAN SCHOLAR AWARD

Regev recognized for rigorous integration of experimental and computational approaches

By Sarah Perdue

Aviv Regev of the Broad Institute at the Massachusetts Institute for Technology and Harvard University won the American Society for Biochemistry and Molecular Biology's Earl and Thressa Stadtman Scholar Award.

The award is given to researchers with outstanding achievement in the fields of biochemistry and molecular biology who have fewer than 10 years of postdoctoral experience.

Regev, a Howard Hughes Medical Institute early career scientist, was nominated for her insightful work on the evolution of regulatory networks in cells and for her development of cutting-edge techniques that have broad implications in diverse fields of molecular biology.

"At the conceptual level, Aviv is interested in one of the deepest and most general of biological questions: how biological circuits function and rewire – from the rapid responses of immune cells within hours, to developmental commitments by cells in the blood system, to genetic changes in cancer, to long-term evolutionary changes over millions of years," said Eric Lander, president and director of the Broad Institute, who nominated Regev for the award.

The bulk of Regev's work focuses on the short timescale responses of dendritic cells to pathogen challenge. "Dendritic cells were a superb choice for deciphering cell circuits," says Jonathan Weissman, an HHMI investigator and professor at the University of California, San Francisco, School of Medicine, who also nominated Regev. "First, the dendritic cell response is physiologically and clinically important its own right and more broadly serves as a model for other impulse responses to environmental challenges that are ubiquitous in biology. Second, the well-characterized stimuli provide unique handles with which to resolve regulatory relations computationally."

It is this rigorous integration of experimental and computational approaches that Regev's nominators emphasize. "Her strategy starts by monitoring the transition in exquisite detail. She then uses these data to drive her model-building efforts. And finally she perturbs the system in a manner designed to test and challenge her models," Weissman said. "When applied iteratively, this approach leads to robust models that explain the observed data and have true predictive value."

Lander added, "Aviv was an early pioneer in the reconstruction of networks using probabilistic models, and her work has defined the field today. In the past few years, she has expanded these models to the dynamic setting, where the network components and connectivity change with time, a very difficult computational problem."

Regev also has been a pioneer in RNA sequencing to elucidate these complex changes in regulatory networks. She noted that the bulk responses she observed in her dendritic cell work may be concealing important changes at the single-cell level; thus, she and her colleagues adapted a single-cell RNA sequencing approach and found that, even within a homogeneous population of cells, there were subpopulations that responded at different times and in different manners.

Weissman said this work is just one more example of Regev's commitment to staying at the forefront of cutting-edge technologies.

Regev and her colleagues had to develop algorithms to handle these novel types of data sets, writing programs (such as Trinity) that allow for data analysis without prior knowledge of an organism's genes or even a sequenced genome. Trinity today has more than 20,000 users.

Regev will receive her award during the Experimental Biology 2014 conference in San Diego, where she will deliver an award lecture. Her presentation will take place at 9:05 a.m. Sunday, April 27, in Room 6A of the San Diego Convention Center.

I am tremendously honored to receive the award, highlighting the importance of the interface between genomic and more focused approaches to biological circuits.

– AVIV REGEV

Sarah Perdue (sp366@cornell.edu) received her Ph.D. in microbiology from Cornell University, spent two years teaching at different colleges as a visiting professor and now is a postdoctoral researcher at the University of Minnesota.

Why so blue?

Researchers examine seasonal affective disorder

By Diedre Ribbens

Each year, many people experience the "winter blues," the layman's term for a particular mood disorder called seasonal affective disorder, or SAD. There's a lot of information swirling around in popular media about the cause of SAD, but what does science have to say about it?

Researchers have been looking into SAD since it was first defined in the 1980s. Early studies were focused on finding treatment options, because alleviating the symptoms of SAD was a top priority. Since the early 2000s, scientists have been looking at the genetic, epigenetic and biochemical causes that underlie SAD, along with other mood disorders, and they've been finding some pretty interesting stuff.

Genetic studies of the circadian clock

One of the earliest suspects linked to SAD was dysregulation of the circadian clock. The circadian clock is housed in a part of the hypothalamus called the suprachiasmatic nucleus, or SCN. The SCN controls many functions of the body that fluctuate over our natural circadian period, which is about 24 hours long, including sleeping and waking cycles, body temperature, appetite, and many others.

"The SCN is the master oscillator, and it can be considered to be the conductor of a symphony," says David Klein, chief of the neuroendocrinology section at the National Institutes of Health. "You can imagine what happens if you go to the symphony and the conductor walks off stage: The music falls apart. The same thing happens when you travel and get jet-lagged. The conductor lost control of all the separate rhythms in your body." Klein adds that keeping tight control of the circadian clock is a contributing factor to mental health.

It is known that disruption of the circadian rhythm is associated with mood disorders, including SAD and bipolar disorder, and this is thought to be due to the body's inability to adapt its internal clock to match the external environment. In the winter, especially in more northern climates, the body is exposed to substantially less sunlight than in the summer. The SCN can sense this change in light and, subsequently, alter the timing of the body's natural rhythm in response to this change.

Chris Ciarleglio, a postdoctoral fellow at Brown University, believes there are strong genetic and epigenetic components to the body's ability to alter circadian rhythms.

Ciarleglio studied circadian rhythms in the lab of Doug McMahon at Vanderbilt University during his graduate work and retains an interest in the intersection of neurobiology, circadian rhythms and mood disorders. In a 2011 study, the group looked at the effects of light exposure during development on epigenetic changes that affect circadian rhythms.

"What we were focusing on in the 2011 Nature Neuroscience paper was the connection between season of birth and subsequent circadian function, with the view that any imprinting from the environment that might happen during your development might impact your subsequent circadian and/or other functions," he explained.

Other researchers have pinpointed specific genes in the circadian rhythm pathway that have polymorphisms linked to patients with SAD that are not present in healthy controls. These genes include CLOCK, Period 2, Period 3 and NPAS2, among others.

Whether polymorphisms in these genes are causative in the case of SAD remains to be shown, but current studies suggest they may contribute to a predisposition to developing SAD and that epigenetic changes induced by light exposure during development may tip the balance toward or away from the development of SAD.

However, genetic predisposition is only one component of a larger picture, and other components of the circadian clock (such as enzyme activity and hormone production) also contribute to this mood disorder.

The rhythmic hormone melatonin

SAD research also has focused on melatonin, a hormone primarily synthesized by the pineal gland in the brain. Melatonin levels fluctuate throughout the day, with increased synthesis at night. In organisms like humans, who are diurnal and thus awake and more active during the day, melatonin helps to trigger the onset of sleep.

The production of this hormone is tightly linked to the amount of daylight exposure an animal receives, so in the winter, when daylight hours wane, melatonin synthesis begins earlier and lasts longer, allowing for a greater fluctuation in the overall amount of melatonin produced.

Klein describes the changes in melatonin synthesis, which he learned from his studies of the enzyme that produces the hormone: "The pattern of activity looks like a hill, because it goes up, then down during the course of the night. When we look at (the

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pattern of activity) more closely, we see that this one hill that goes up and down is actually two hills of activity that overlap."

Klein explains that in the summer, when the nights are short, these two overlapping hills get closer together, so the activity of the enzyme is highest at only one point during the night. In the winter, when nights are longer, the peaks of the two hills separate, meaning the enzyme activity fluctuates more and reaches the highest point for a longer period of time. As a result, the period of melatonin production is longer.

"There's a lot of research in SAD that shows that dysregulation of your melatonin rhythm, how much melatonin your pineal gland produces over the course of the day, will influence your mood," says Ciarleglio.

The extent that melatonin production contributes to SAD is still debated, and studies using animal models are one way researchers are starting to address this question.

Challenges in using animal models to study SAD

Some scientists question the use of mice as models for SAD, because lab mice are nocturnal and therefore respond differently to light-dark cycles, melatonin secretion and other common factors that are used in the studies of SAD and other mood disorders. Research by Serge Daan argues that the nocturnal nature of lab mice is due to polymorphisms in their circadian clock genes and that their counterparts in the wild are more diurnal. Both of these opinions point to the need for other animal models to study SAD.

Haim Einat, a behavioral scientist at Tel Aviv-Yaffo Academic College, has begun vetting several species of diurnal rodents for use in the study of SAD. Einat has studied fat sand rats, Nile grass rats and, most recently, small rodents called degus as candidate model organisms.

Einat and colleagues have shown that all three of these diurnal species develop SAD-like symptoms when exposed to shorter periods of daylight, indicating that they make appropriate models for seasonal mood disorder studies.

The study of SAD and other mood disorders has seen great progress in the past 20 years, and recent genetic, epigenetic and biochemical studies indicate that there is still much to be learned. The increased knowledge and detailed understanding hopefully will lead to more specific and varied treatments — right now the most popular treatment for SAD is bright light therapy — and ultimately will be a boon to those who live with mood disorders.

Studying the Timezyme and ancient melatonin production

David Klein, director of circadian biology research at the National Institute of Child Health and Human Development, studies the enzyme that produces melatonin.

Although the technical name of the enzyme is arylalkylamine N-acetyltransferase, or AANAT, Klein refers to the enzyme colloquially as "the Timezyme." This nickname comes from the role of melatonin in regulating the body's internal clock, and because AANAT manufactures melatonin, it is crucial to maintaining proper control of the body's daily rhythm.

Klein recently led a study, published earlier this year in the Proceedings of the National Academy of Sciences, that showed the form of AANAT in vertebrates originated 500 million years ago. Other studies have shown that vertebrates and nonvertebrates have distinctly different forms of AANAT.

Vertebrate AANAT is found mostly in the pineal gland, where it produces the melatonin precursor N-acetylserotonin from serotonin via the addition of an acetyl group. Nonvertebrate AANAT enzymes are generally similar and are thought to add acetyl groups to a broad range of potentially harmful, serotonin-related compounds. This is in contrast to vertebrate AANAT, which acts more selectively, adding acetyl groups to one specific compound.

"Many enzymes that are involved in neurochemical signaling were originally detoxifying enzymes," explains Klein. Nonvertebrate AANAT was "sort of a shield," he says, part of a group of proteins that evolved to protect the light-absorbing vision molecule retinaldehyde. AANAT acted as a shield by acetylating serotonin and related compounds, thereby preventing them from inactivating retinaldehyde via Schiff base formation.

Today, vertebrate AANAT is still expressed in small amounts in the retina, but melatonin production occurs primarily in the pineal gland. In this way, the high levels of serotonin required to make melatonin are separated from retinaldehyde, preventing destruction of this vision molecule in the eye.

"The Timezyme evolved just to make melatonin. Pineal melatonin synthesis also requires a very high capacity to synthesize serotonin. Although serotonin synthesis occurs in other tissues, the concentration in the pineal gland is much higher, consistent with the knowledge that it is a melatonin factory. For example, serotonin concentrations in the pineal gland are more than 100-fold higher than those in the retina."

Klein's study bridges the gap between nonvertebrate and vertebrate AANAT, showing how a gene-duplication event of nonvertebrate AANAT that occurred 500 million years ago led to the branching and evolution of the two separate enzymes. Before the PNAS paper, the gene duplication event was only a hypothesis due to lack of evidence.

At some point, vertebrates stopped making the nonvertebrate form, so Klein and a group of international collaborators tracked down an organism with both forms present to help confirm the idea and put a timeline on the Timezyme's evolution. The team eventually located both forms in the genome of the elephant shark. Using samples from the elephant shark and related aquatic species, Klein's team used RNA sequencing, 3-D structure modeling and other tools to show that the vertebrate form of AANAT was derived from the nonvertebrate form.

Elephant shark

PHOTO COURTESY OF: WIKIMEDIA COMMONS USEER FIR0002/FLAGSTAFFOTOS

Klein's work has implications for the study of melatonin-related disorders, such as SAD, and also for vision disorders in which harmful chemicals are accumulating in the retina.

Diedre Ribbens (diedre.johnson@gmail.com) is a freelance science writer based out of Minneapolis. Visit her website, dribbens.com, to contact her or learn more about her writing.

Q&A with Jonathan Weissman

By Rajendrani Mukhopadhyay

The plenary speaker for this year's American Society for Biochemistry and Molecular Biology annual meeting is Jonathan Weissman of the University of California, San Francisco. An investigator with the Howard Hughes Medical Institute, Weissman is a biochemist whose laboratory focuses on protein folding, amyloid formation and next-generation genomic sequencing. ASBMB's science writer, Rajendrani Mukhopadhyay, spoke with Weissman to learn more about his scientific interests and influences. The interview has been edited for length and clarity.

What does your research focus on?

We're interested in how proteins fold in cells, especially how chaperones assist protein quality control and how a cell distinguishes between correct and incorrect proteins both in the cytosol and endoplasmic reticulum. We also have a broad interest in developing general approaches for querying biological systems, especially around next-generation sequencing. The most mature of those efforts is an approach we call ribosome profiling. It allows us to globally monitor translation in cells at single-nucleotide resolution.

This idea of using deep sequencing techniques to define the information encoded with these genomes and to watch it being expressed in space and time is really exciting. Ribosome profiling is one example of these techniques. We get to watch, with exquisite precision, the ribosome get in the act of converting an informational molecule, the RNA, into a functional molecule, the protein.

I'll be talking about our ribosome-profiling work during my plenary lecture.

What was the genesis for ribosome profiling?

Our original interest was on the yeast prion phenomenon called [PSI+]. The phenotype of [PSI+] is that when the cell contains this prion, or self-propagating infectious protein, it increases the rate of translation read-through. We wanted to develop an assay that let us watch where ribosomes were reading through stop codons in vivo. But then, once we developed ribosome profiling, it was clear it was a much broader tool.

What are some of the technical challenges with ribosomal profiling?

The biggest challenge is interpretation and data analysis. We get huge amounts of data. It takes longer for us to analyze the data and ask the right questions than it does to actually collect the data. The other technical challenge is working with relatively small amounts of cells. We'd really like to optimize the amount of sample we use in our system.

How do you balance your scientific efforts between asking fundamental biological questions and developing techniques?

For my lab, it's very important that the techniques we develop be driven by fundamental questions that we want to answer. My lab is very interested in seeing what happens to a protein as it's synthesized and how it is recognized by the cell's quality-control systems and doing this in an in vivo setting. Although the ribosome profiling is an -omics tool and it broadly looks at protein translation, I'm personally most excited about its value as a high-precision tool for looking at mechanisms of how proteins are synthesized and folded. I see the methods development as something that drives our ability to ask questions that we want to ask.

To put your work in a larger context, what do you think are some of the big-picture questions in biochemistry and molecular biology?

One of the things is: How do cells maintain integrity of their proteome and detect misfolded proteins? How do the different quality-control systems work together in a coherent way to allow cells to function, and when and why do they break down?

I think there's another, broader question of how we define the function of a protein. What do we mean when we identify protein X to do job Y? A lot of this has been classically done, arguably, in an ad hoc way where you look for some activity in a cell and you try to find the proteins that are responsible for it.

This type of reductionist, top-down approach has been incredibly successful, but it has some inherent flaws and biases to it. We're trying to develop more systematic and less ad hoc, more principled and faster approaches to finding gene function.

The other general area, which is related, is that we have built tools with which we can sequence any individual or organism's genome rapidly and at low cost. There's now a huge challenge to define the information encoded in genomes and how it's expressed in time. Ribosomal profiling is a part of that effort. It lets you know what proteins are being encoded for in a cell in an objective way and see how much is made at a given time. If we really want to test our ideas and try to use this information to design new systems, we have to have much better ways of turning on and off genes and to engineer genomes. I'm very excited about approaches that we and others are working on using the CRISPR system.

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Tell me more about the CRISPR system.

CRISPR is an adaptive-immunity system from bacteria that's been known for some time. It's turned out to be a very useful system for engineering genomes. The CRISPR system that has become particularly popular now is the CAS9-based system. In a nutshell, when a cell becomes infected with a phage, it grabs part of the phage's DNA and inserts it into its own genome in these special cluster repeat regions. It then later transcribes that copy of the phage DNA as RNA and uses that RNA to guide an endonuclease (called) CAS9. Now, if the bacterium is ever infected with the same phage, the CAS9 plus this guide RNA will specifically cut up that phage DNA by hybridization.

What revolutionized things is that Emmanuelle Charpentier (at Molecular Infection Medicine Sweden) and Jennifer Doudna (at University of California, Berkeley) showed that a single protein, CAS9, and a single engineered guide RNA are sufficient to guide the CAS9 endonuclease to a given sequence. So if you give me a piece of DNA, I can design the complementary guide RNA. If you then express that guide RNA plus CAS9, the CAS9-guide-RNA complex will cleave that piece of DNA.

At UCSF, working with Stanley Qi and Wendell Lim, among others, we have made a catalytically dead version of CAS9, the so-called dCAS9. Now the guide RNA guides the dCAS9 to a specific place on the DNA, but instead of cutting it, it just sits there. You can then use this (dCAS9) to fuse gene-activator domains to turn on genes; if you fuse repressors, it will turn off genes. If you fuse GFP, it will mark that part of the chromosome. It lets us turn on and off genes and mark chromosomes without actually causing any changes in the DNA blueprint itself. I think it may even be a competitor to RNAi approaches.

I will also mention the CRISPR work during my talk.

Your undergraduate degree and Ph.D. were in physics from the Massachusetts Institute of Technology. How did you make the switch from physics to biology?

To be honest, I did get my Ph.D. in physics, but what really happened is that, after a year of doing hardcore physics in phase transitions and all that, I decided I was much more interested in biological questions. I found Peter Kim, who was then a professor at MIT in the Whitehead Institute of Biomedical Research. I rotated and then joined his lab. I did all my qualifying exams in physics, but I did my research in a mainstream biological laboratory. That meant I had to take a lot of courses and spend a lot of time catching up, because I had very little biology (training). But, by the time I had graduated (with my Ph.D.), I was pretty well immersed in modern molecular biology. But fast-forward 15 years later, all the quantitative tools, like deep sequencing, are incredibly valuable. There has been this convergence where biology has become an information-rich science. All that training I had in physics and math actually ended up being extremely useful.

You did your postdoctoral fellowship with Arthur Horwich at Yale University. How did that experience influence you?

Enormously. We did great work on the biochemistry of GroEL and really got into the structure-function aspect. It was a terrific time. I wasn't there all that much time, about 2 ½ years, but I published four papers from that time that, in many ways, cemented the standard model for GroEL and how proteins fold inside the central cavity of GroEL. It was a wonderful time because the structures were coming out from Art's lab so we were able to exploit the structural information.

I read in Horwich's "Reflections" in the Journal of Biological Chemistry that you kept chameleons in the lab. He described them as even more finicky eaters than children.

I did indeed have a Jackson's chameleon, Lance. It required taking crickets and coating them with vitamin D and calcium and holding them in front of it every day. (Chameleons) apparently don't get much vitamin D and calcium when they are in captivity, so you have to give them vitamin D and calcium.

Who are your scientific influences?

Obviously, my Ph.D. adviser, Peter Kim, and my postdoctoral adviser, Art Horwich. Also, I used to go to group meetings of Ari Helenius' laboratory (at Yale University). I really learned a lot about how cell biologists think. My father, who is a molecular biologist, is a huge influence. He's Sherman Weissman, and he's at Yale. We talked a lot about science when I was growing up. We still do. Here (at UCSF), I've had many mentors and collaborators. Marshall Nirenberg (who worked at the National Institutes of Health) was certainly a big influence as well. We talked a lot about translation. I came into translation independently and then had the good fortune of being able to talk with Marshall about it. I learned that many of the ribosome experiments we were doing were done back in the 1960s. They had fewer good tools, but they understood the concepts. *(Editor's note: Nirenberg had married Weissman's mother, who was divorced from Sherman Weissman.)*

What is your guiding principle in science?

Try to find new questions that are fundamental and important, but they should be ones we can answer in a clean and crisp way. I really like problems that lend themselves to very clear, definitive answers rather than problems where one ends up going back and forth with arguments because it's hard to resolve anything. The GroEL work illustrated that nicely: When I was a postdoc in Art's lab, a big question, and it was quite controversial at that time, was if proteins fold inside the GroEL/GroES cavity or on the outside. It was an incredible idea that a protein could get encapsulated in another protein and fold in this protected environment. But I liked the problem, because it was easy to explain to anyone and it was going to be one way or the other. I was quite confident that we, or other people, would be clever enough to figure it out. I also like developing approaches, especially when they let you ask questions in a deeper and more defined way and much more rapidly. I always worry about spending our time doing hard work on something when, if we had a new approach, it would make what we do obsolete.

What are your hobbies?

Since I spend pretty much no time now doing experiments, I really love to cook, especially things that are based around techniques. I've been perfecting using my grill as a pizza oven, getting the temperature up to about 700 degrees and making the perfect dough. My lab just gave me a 40-pound slab of steel for my pizza stone because it conducts heat much better. But it's also great at inducing back pain.

Rajendrani Mukhopadhyay (rmukhopadhyay@asbmb.org) is the senior science writer and blogger for ASBMB. Follow her on Twitter at www.twitter.com/rajmukhop.

Meet John Denu

A new associate editor of the Journal of Biological Chemistry

By Rajendrani Mukhopadhyay

John Denu at the University of Wisconsin–Madison joined the ranks of the Journal of Biological Chemistry associate editors in July. His laboratory focuses on the roles of reversible protein modifications that are involved in modulating signal transduction, chromatin dynamics and gene activation. In particular, the group studies histone modifications. The American Society for Biochemistry and Molecular Biology's science writer, Rajendrani Mukhopadhyay, interviewed Denu to learn more about his scientific interests, career and hobbies. The interview has been edited for length and clarity.

Briefly explain what your research group is studying?

We are broadly interested in the mechanisms and functions of reversible protein modifications that control signal transduction, chromatin dynamics and metabolism. More specifically, one major goal is to understand the basic biochemical principles that govern epigenetic information written onto histones. This information dictates gene-expression programs and takes the form of a diverse array of histone post-translational modifications, which are added and removed by chromatin enzyme complexes.

Also, we are investigating the links between metabolism and epigenetic mechanisms that regulate gene expression. Chromatin-modifying enzymes rely on coenzymes and substrates derived from metabolic pathways, suggesting coordination between nuclear events and metabolic networks. We are testing the hypothesis that certain chromatin-modifying complexes have evolved to exquisitely sense metabolite levels and respond accordingly, modifying specific chromatin loci for altered gene expression.

Another major effort involves understanding the mechanisms and functions of sirtuin deacylases and reversible protein acetylation. Accumulating evidence suggests that reversible lysine acetylation is a major regulatory mechanism that controls protein function.

Sirtuins are a conserved family of NAD^+-dependent protein deacetylases that have emerged as important players in modulating protein acetylation. Compelling genetic evidence implicates sirtuins in genome maintenance, metabolism, cell survival and lifespan. We are examining the central hypothesis that reversible protein acetylation is a major regulatory mechanism for controlling diverse metabolic processes and that, at the molecular level, site-specific acetylation alters the intrinsic activity of targeted proteins. We are exploring sirtuin function as a means to tackle these questions and uncover their role in these processes.

You recently had a JBC paper selected as a Paper of the Week. It was about SIRT6's activation by long-chain fatty acids. What is the significance of the work?

We are very excited about this discovery and the impact it might have on human health. SIRT6 is linked with aging, cancer and metabolism. The protein is an extremely inefficient histone deacetylase in vitro, suggesting that there is an activating mechanism in cells. In this paper, we demonstrated that SIRT6 is directly activated by free long-chain fatty acids, including ones linked to the health benefits of dietary polyunsaturated fatty acids. These results suggest the SIRT6 is stimulated to downregulate carbohydrate and lipid metabolism during conditions that increase levels of particular omega-3 and omega-6 fatty acids, such as fasting and dietary supplement intake. The discovery of these endogenous, small-molecule activators of SIRT6 suggests the therapeutic potential of compounds that promote SIRT6 function, particularly for improved metabolism, anti-inflammation and decreased tumorigenesis.

Tell us about your academic background and research training.

My (bachelor's) was in biochemistry from the UW–Madison, where it became clear that I wanted to grow up and be a biochemist. My Ph.D. with Paul Fitzpatrick at Texas A&M University provided training as a classical enzymologist. Postdoctoral training at the University of Michigan with Jack Dixon allowed me to use those skills to tackle new enzymological questions in the signaling field. In Jack's lab, I became enamored with protein modifications and the idea that PTMs communicate critical cellular information.

What does it mean to you, on a personal level, to be an associate editor for the JBC?

It was a tremendous honor to be asked to serve the JBC in this capacity. In addition to previously serving as an editorial board member, I have authored JBC papers throughout every stage of my career, so the JBC occupies a very special place in my life. To me, the JBC represents a community, and now I get to contribute to this community in a new way as an associate editor.

How is the new role going so far? Have you been surprised by anything during your tenure with the JBC?

So far so good, but the first two months were a very steep learning curve. One of the best aspects of being an AE is the ability to tap into the collective wisdom of the other

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JOHN DENU

(Left) Denu with his brother after a half-marathon. (Above) Denu before a Warrior Dash with his son and daughter-in-law.

When I'm not in lab, I'm still thinking about the lab. Obviously, this can be a problem if you want to have a so-called normal life. But there is nothing very normal about the life of a scientist. It is important to try and press pause routinely. I try to pick nonscience activities that force me to refocus my attention on something completely different. I do this one of several ways: go for a vigorous run, play basketball or work on mechanical problems like fixing or modifying cars. It's worked for me: I'm still married to the same understanding woman after 25 years, and the two boys turned out fine.

For scientists in training, do you have any words of wisdom or a favorite motto?

Enjoy the work. This is an awesome career, but not everyone is cut out for it. At different stages of your career, do the 50-percent test. If you're miserable more than 50 percent of the time, it's time to change your line of work. If you enjoy your work most of the time, keep doing it. I prefer to operate near 90-percent job satisfaction, where the missing 10 percent represents time spent trying to keep the lab funded. Congressional sequester can greatly affect that percentage.

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AEs. The board is an amazing group of scientists, and our discussions on JBC matters are enjoyable with plenty of give-and-take. Perhaps most surprising to me is how we handle manuscripts. Of course, there are important policies and guidelines to follow, but it's not an impersonal operation where a computer weighs the reviews and spits out a decision. Each of us can bring our own unique perspective to the editorial process.

What do you do outside of the lab? Do you have any advice for balancing life in the lab with life outside of the lab?

Rajendrani Mukhopadhyay (rmukhopadhyay@asbmb.org) is the senior science writer and blogger for ASBMB. Follow her on Twitter at www.twitter.com/rajmukhop.

An open letter to my younger self, an aspiring graduate student in the sciences

Dear Paul,

I know what you're thinking: "This will be a snap. I'll be out in four years!"

You can brush up on your class schedule, fill up your book bag with shiny new notebooks and highlighters with more colors than a Skittles packet, and march into your new endeavor with determination. However, there are a few words of wisdom that I would like to share with you before you take this long, strenuous and, yes, sometimes crazy journey as a graduate student.

If there's one thing you should do immediately, it's to immerse yourself in the academic and scientific community. These people are not only your colleagues and friends but also your potential collaborators. The scientific community is a tight-knit collective. But its members will be there for you when you are feeling down on your luck or need advice (which will happen often!) or even help you procure jobs. Networking, networking, networking. Do it now or else learn the hard way why it isn't just a buzzword.

Balance work and play. It's easy to be sucked into lab life — slaving away at the bench, trying to finish just one more experimental replicate to show that your amazing results are reproducible. But don't forget to engage your peers and attend social gatherings or even just take coffee breaks to catch up. Many people struggle with separating work life and social life. Why can't it be combined? After all, we are all here, presumably, because we want to be, so why not make it productive and enjoyable now and for the rest of your career?

Diversify and volunteer. Many times the research problems you are trying to solve are so specific and narrow that it becomes easy to lose track of the bigger picture. Even more tragic: You might lose the ambition to develop skills outside your field. Public speaking, presentations, scientific writing and networking are crucial skills that can be helpful not only in your research but in your social life as well. You can develop these skills by helping others with projects, listening

Many times the research problems you are trying to solve are so specific and narrow that it becomes easy to lose track of the bigger picture. Even more tragic: You might lose the ambition to develop skills outside your field.

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to your peers' presentations, or even proofreading essays and papers. These skills will be even more important if you decide to search for a career outside of basic research.

Before I close, I want to talk about something that may seem unfathomable at this moment. Your experiments that you thought were foolproof will sometimes fail and may even cause you to doubt yourself. It will be discouraging, time and time again, having one positive result for every five failures. Or there may be a time when you get some questionable results that will have you stumped for weeks on what to do next. Having only three classmates in your Ph.D. program to ask questions can be difficult when no one has an answer for you, and being in an unfamiliar and disorienting new setting only adds to the initial struggle. While it's normal to doubt yourself and wonder why you are putting yourself through such hardships when things consistently don't go as planned, your failures are really what make you a better and more informed person. Perseverence, determination, patience and a sense of humor will help you get out of any mishaps unscathed and will make you a stronger person.

Graduate school, and much of life from here on out, is much less structured than you have experienced previously. But it can be summed up with brevity: You get out what you put in.

If there's disorganization, then take the initiative to make sense of things, even if it's a little extra work. Be confident, take action and don't procrastinate. You'll find your way. Life can be difficult at times, but it also can be rewarding and wondrous! So make the most of your time and enjoy the ride.

Oh, and your geek T-shirt collection is getting out of hand, so try to save your money for something more useful, like a house.

Sincerely,
Your older and wiser postdoctoral fellow self

Paul Sirajuddin (psiraju1@jhmi.edu) is a first-year radiation oncology postdoctoral fellow at The Johns Hopkins School of Medicine. A native of Michigan, he ventured to the East Coast for a postbaccalaurate fellowship at the National Cancer Institute in 2008 and then earned his Ph.D. from the Georgetown University Lombardi Comprehensive Cancer Center in 2013.

Enjoying the Open Letters series?

We've extended the submission deadline to Oct. 1, 2014. Send yours to asbmbtoday@asbmb.org.

Teaching science and social justice

Project seeks to promote social consciousness in the classroom

By Morgan Thompson, Jon Beckwith and Regina Stevens-Truss

When did you first learn about the American eugenics movement and the Tuskegee syphilis studies? How long were you culturing HeLa cells in the lab before you heard of Henrietta Lacks? What do you say to a family member who has chosen not to vaccinate his or her child after finding extensive pseudoscience masquerading as evidence online?

Most scientists gain their first research experiences as undergraduates, prior to any formal training in ethics or social justice in science. Though we train scientists to be technically and theoretically critical of their own work and that of others, critical examination of the societal context of research or active engagement in public discourse rarely is encouraged.

The Science and Social Justice Project — a joint effort of faculty members at the Arcus Center for Social Justice Leadership at Kalamazoo College and at Harvard Medical School — seeks to remedy the segregation of science from its value-laden historical, social and political context in undergraduate and graduate classrooms. Together, we are building a Web-based repository of curricula and activities that integrate science and social justice topics into scientific training programs.

While continued efforts to expand and improve the mandatory ethics training and guidelines of the National Institutes of Health Office of Research Integrity are laudable, those courses continue to vary widely in quality and depth and are diminished in importance by being tacked onto, rather than woven into, curricula. It is our belief that substantial experience with relevant materials from the social sciences and humanities must be incorporated into the scientific curriculum. Yet, to date, incorporation of these topics in science courses is left exclusively to the personal motivations of individual educators. We hope to raise the profile of these individual efforts, highlighting stellar exemplars of integrating science and social justice that often go undetected and uncovering best practices that can ultimately bolster mandatory ethics training and make substantial exposure to the social sciences standard throughout science curricula. The Science and Social Justice Project will present a compendium of curated models that span the sciences and offer a range of depth so that you, the user, can easily

Actors in "Edge of the Map" portray Alice Wexler and her father, Milton Wexler, discussing whether she should have children, given that her mother suffered from Huntington's disease.

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extract, adapt and integrate social justice components in your science classroom.

Courses with science and social justice content:

• include science-communication training to improve the public discourse about science,

• bring relevant examples of social justice issues into introductory science survey courses and advanced topics courses,

• incorporate social justice issues into laboratories, class activities, or field trips, and/or

• focus on scientific ethics.

At the University of Minnesota, Sehoya Cotner has incorporated social justice issues into her introductory biology course, "Evolution and Biology of Sex." In the course, Cotner moves beyond the basic biological definition of sex to what science can and cannot tell us about such things as gender identity, mating preferences and kin selection. By pushing to the boundaries of what is currently known, Cotner introduces her students to discovery science. As she states, "It's an opportunity for me to say that science isn't about answers; it's about questions and about refining your hypotheses and figuring out what data you really need."

The "Social Issues in Biology" course taught by Jon Beckwith at Harvard Medical School also incorporates societal factors within a science setting. Last spring, the course allowed students to participate in a collaborative, multimedia theater production called "The Edge of the Map." Calla Videt, a writer and director of the SIGHTLINE theater company in New York, developed an experimental production with the input of students and Beckwith.

During a five-week residency, Videt and the course teaching assistant led students in art-making activities to produce content, such as audio recordings and visual artwork. These materials were publicly exhibited in conjunction with the final production. The course and performance also incorporated a Twitter campaign to engage audiences in discussions about the social implications of science.

"The Edge of the Map" focused on genetics, interweaving four stories that tackled questions about what genetics can and cannot tell us about identity using present-day and near-future innovations in genetic testing and engineering. "Connecting a theater production with a course on social issues in biology energized the class in its discussions of the social implications of genetics and of how theater could communicate these issues to the public," Beckwith says.

You can help us gather and enlarge the community of scholars devoted to making social science training an explicit and desegregated part of science teaching and research in one of two ways:

• by contributing syllabi and other course materials that you have developed and/or

• by participating in the Science and Social Justice Think Tank, as part of the Kalamazoo College Arcus Center's upcoming conference, WITH/OUT – ¿BORDERS?, which will take place Sept. 25–28. Conference participants will contribute to workshops and have broader conversations about scientific culture, interdisciplinary boundaries and globalization.

Embedding social responsibility and engagement in the science classroom will create a community of scientists who are able to distill and present nuanced perspectives on how science can and cannot inform decisions in our daily lives and public policy. Together we can firmly integrate social consciousness within the scientific culture.

To read more about the Science and Social Justice Project and find out how you can get involved, visit www.kzoo.edu/praxis/category/science.

Principles of practicing social justice in science

• Develop awareness of current and historical injustices and injuries promoted or perpetrated by science and scientists.

• Use science as a tool to improve the human condition and create more just communities.

• Speak out in defense of sound science and against scientific abuses and unreasoned attacks on science.

• Challenge the work of scientists that entrenches inequities in power and resources or harms, divides or discriminates against people.

• Involve those who are the subjects or stakeholders of scientific study in the design and implementation of solutions.

• Foster discourse between those in the natural sciences and those in the social sciences to promote a critical examination of scientific endeavors, broader accountability, the communication of science and solidarity.

Morgan Thompson is a geneticist and consultant of the Science and Social Justice Project. Jon Beckwith is a microbiologist and longtime social activist in science who has taught the "Social Issues in Biology" course at Harvard Medical School for three decades. Regina Stevens–Truss is a chemistry professor at Kalamazoo College and a member of the ASBMB Minority Affairs Committee and Educational and Professional Development Committee, as well as the faculty adviser of the Kalamazoo ASBMB Undergraduate Affiliate Network chapter.

Reader comments

Re: "The promise vs. the payoff of the NIH intramural program" by Jeremy Berg, President's Message, February issue

As usual, Jeremy, so well-framed. How can we ensure that intramural investigators are evaluated with the same rigor as (Howard Hughes Medical Institute) investigators or (National Institutes of Health) Pioneer Awardees? Should they be reviewed in parallel with extramural applications? Is the intramural program on par with the well-funded science going on at Janelia Farm? We need to demand uniform excellence, as the program represents a major investment and a significant proportion of NIH research expenditures.

– SUZANNE PFEFFER

I agree wholeheartedly with the argument that peer review of intramural labs needs to be at a comparable level to extramurally funded labs. And the inclusion of budgets for intramural labs in the NIH RePORTER is a great step toward more transparency in how funds are distributed internally. However, as a former section chief in the intramural program, I also urge caution in how those numbers are interpreted.

It is far too easy to look at the budgets of a laboratory and take offense at the number of "R01 equivalents" spent in one lab at the NIH. However, I would first question their accuracy. Do the RePORTER numbers agree with internal budgets that each (principal investigator) may have access to, or do miscellaneous items (some quite substantial) get lumped into those budgets at the discretion of administrators or those higher up the food chain? Although I left the intramural program >15 years ago, this was commonplace when I was there.

Second, I would question whether they are indeed directly comparable to extramural grants. Are they expected to pay for the same supplies, services, salaries, etc.? Universities subsidize extramural grants in ways that do not show up in grants and that cannot be done intramurally. Yes, some of the numbers are staggering and insupportable. But I simply urge caution in their interpretation and, again, strongly encourage the use of the same level and type of peer review for internal and external funding.

There are simply too many outstanding investigators in the intramural program to paint them all with one brush. I urge moving quickly to the use of (the Center for Scientific Review) to review internal funding. The internal review system at the NIH is simply too tarnished by a long history of abuse and politics.

– RICHARD A. KAHN

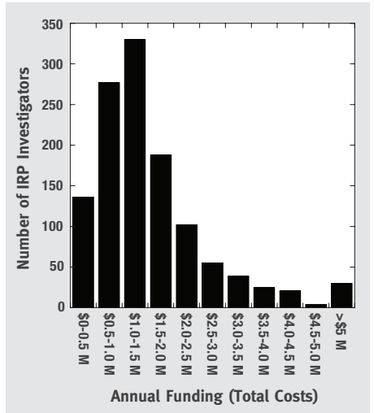

Figure from President's Message, February issue

I have several comments at this point. First, the apparent growth in the (NIH Intramural Research Program) between 2003 and the present is due, in part, to an accounting change regarding the National Library of Medicine that occurred in 2006-2007. This accounts for some, but not all, of the growth that I noted. The IRP grew from 9.6 (percent) of the overall NIH appropriation in 2006 to 10.5 (percent) in 2007 due, in large part, to this accounting change.

Second, with regard to Dr. Kahn's comments, I realize and agree that intramural and extramural budgets for a given laboratory are hard to compare due to differences in accounting practices. Indeed, comparing one extramural grant and other (or likely one intramural budget and another) requires care. My purpose in this column was to put the best available data to which I had access out to stimulate discussion and the gathering of more and better data. I know from my own time in the IRP that there are many outstanding and productive scientists in the IRP. Thanks, Rick, for sharing your insights.

With regard to Dr. Pfeffer's comments, I do not pretend to know the answers about how best to review the intramural program. Simply imposing the CSR-based extramural review system is, in my opinion, likely to be problematic. I am simply trying to encourage transparency and rigorous processes for all (intramural and extramural) research investments for the good of our national scientific enterprise.

– JEREMY BERG

2014

ASBMB ANNUAL MEETING

April 26–30, 2014 • San Diego, CA

ASBMB SPECIAL EVENTS

Saturday, April 26

Fostering Partnerships Among Colleges, Universities and K-12 Schools*
San Diego Marriott Marquis Hotel
9 a.m. – 1 p.m.

Start Trek the Next Generation of Scientists: Undergraduate Program
San Diego Convention Center
Events all day

Professional Development Program for Trainees*
San Diego Convention Center
9 a.m. – 4:30 p.m.

Opening Reception & Science Outreach Posters
San Diego Marriott Marquis Hotel,
North Tower, Marriott Hall 3
7:30 p.m. – 9 p.m.
(immediately following the Opening Lecture)

Sunday, April 27

ASBMB Twitter Breakfast*
San Diego Convention Center, Room 14A
(Mezzanine Level)
7 a.m. – 8:15 a.m.

Building A Sustainable Research Enterprise
sponsored by the ASBMB Public Affairs Advisory Committee
San Diego Convention Center, Room 6B (Upper Level)
12:30 p.m. – 2 p.m.

ASBMB Welcome Reception
hosted by the ASBMB Minority Affairs Committee
San Diego Marriott Marquis Hotel, Marina Ballroom D
7:30 p.m. – 9:30 p.m.

Monday, April 28

Science Communication Training Workshop "You Can't Say That on Television (or to Congress, or to Students)"
Sponsored by the ASBMB Public Outreach Committee
San Diego Convention Center, Room 14A,
Mezzanine Level
12:30 p.m. – 2:30 p.m.

ASBMB Science Cafe
San Diego location TBD
7:30 p.m. – 9 p.m.

Tuesday, April 29

Women Scientists Networking Event
San Diego Convention Center, Room 14A
(Mezzanine Level)
6 p.m. – 8 p.m.

** Pre-registration is required*

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