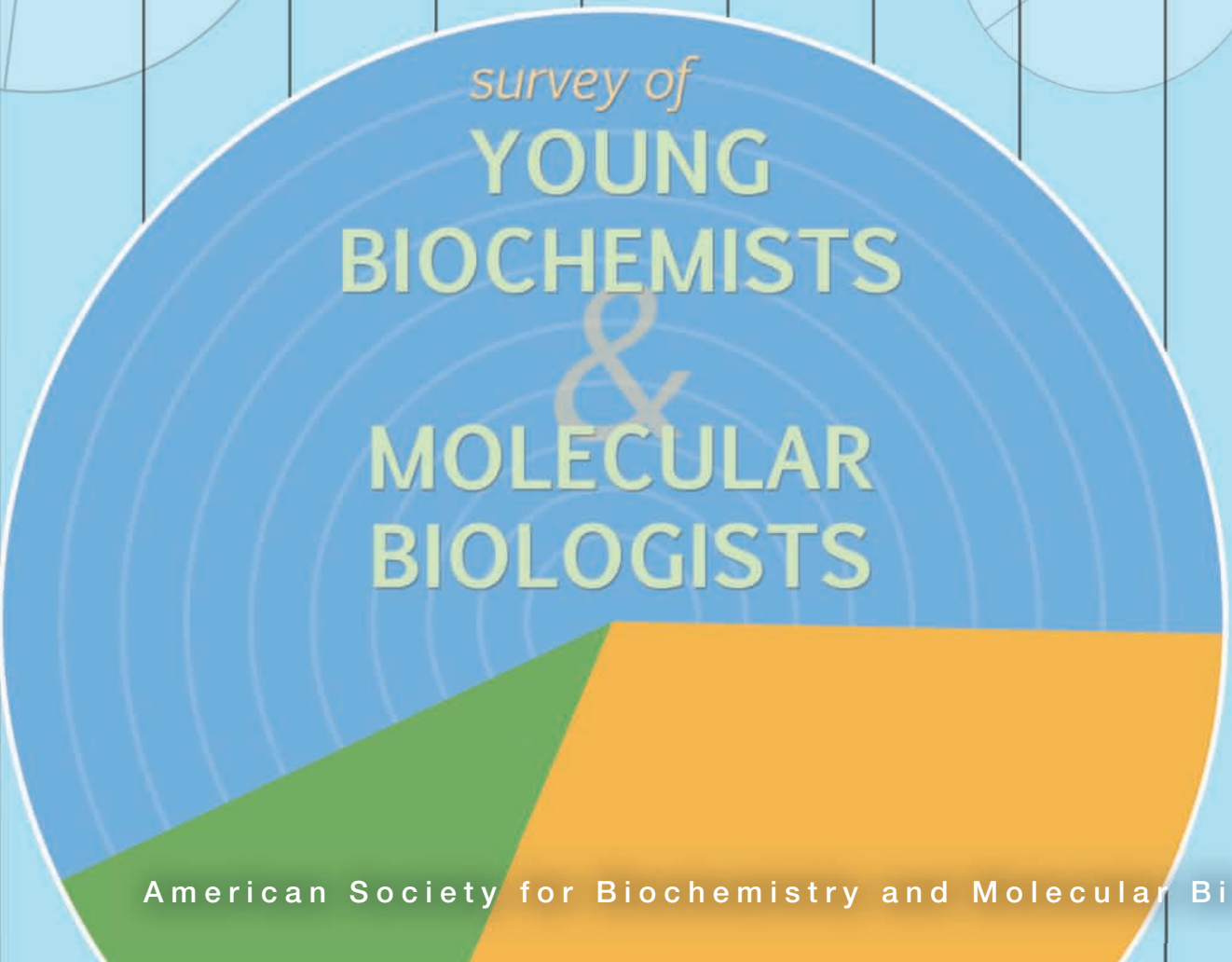
ASBMB today

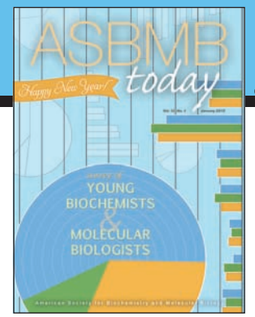
Happy New Year!

Vol. 12 No. 1 January 2013



American Society for Biochemistry and Molecular Biology

contents



JANUARY 2013

On the cover:
In this issue, we offer a snapshot of the ASBMB survey of young scientists. 22

news

essay

features

departments

2013 ASBMB SPECIAL SYMPOSIA

Focused Meetings in Your Field

The ASBMB Special Symposia program was established to provide specific or underrepresented segments of the scientific community with opportunities to present unique, cutting-edge science and to engage in active networking opportunities. Find out about the 2013 lineup.

retrospective

Charles "Chuck" Sweeley Jr., who made major contributions to the fields of sphingolipids and mass spectrometry, died on Sept. 21 in Lansing, Mich., after a long battle with a rare form of bladder cancer. See more on page 8.

ASBMB today

A monthly publication of
The American Society for
Biochemistry and Molecular Biology

ASBMB
www.asbmb.org/asbmbtoday

online exclusives

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Research Spotlight

Education and Professional Development Manager Weiyi Zhao interviews Lehigh University's Jennifer Swann.

Tabor award winners

Contributor Kevin McPherson writes about two new recipients of the Journal of Biological Chemistry/Herb Tabor Young Investigator awards: Vijay Rathinam and Susanne Horvath.


RATHINAM


HORVATH

Top articles of 2012

Find out which essays, editorials and reports were read online the most last year. You might be surprised by some of the results!

NATURE'S PATHWAYS

In her latest article for her online-only column, contributor Shannadora Hollis writes about a Journal of Biological Chemistry paper and explores the fungus-fighting potential of ornamental tobacco.

president's message

(Not so) sudden impact

BY JEREMY BERG

When I started as a postdoctoral fellow in biophysics at Johns Hopkins School of Medicine in 1984, I had the good fortune to attend some lab meetings involving groups from the adjacent department of molecular biology and genetics. Among the scientists whom I had a chance to know were Professors Hamilton Smith and Dan Nathans, who had shared (with Werner Arber) the Nobel Prize in physiology or medicine in 1978 for "the discovery of restriction enzymes and their application to problems of molecular genetics."

While exploring genetic recombination in bacteria, Ham (as he is nearly universally known) and his graduate student discovered the restriction enzyme now known as HindII. Ham and his coworkers showed that this enzyme could cleave DNA at specific sites, and Nathans realized how such enzymes could be harnessed as tools to map and later to modify DNA molecules. Nathans and his co-workers applied these tools to study the tumor virus SV40. These studies were powerful in their own right and were full of possibilities; Nathans concluded his Nobel lecture (1) with the statement, "It should be possible to make out the basic regulatory mechanisms used by plant and animal cells, and eventually to understand some of the complex genetic programs that govern the growth, development and specialized functions of higher organisms, including man."

This prediction of the impact of this basic discovery was, of course, right on the mark. Restriction enzymes became one of the key tools fueling major revolutions in molecular, cellular and developmental biology and other areas. One of Nathans' major interests was cancer biology, and this revolution facilitated the identification of genes that regulate cell growth and the cell cycle. Biochemical insights gleaned from analysis of this collection of genes included the central role that enzymes known as protein kinases play in controlling these processes.

This insight, in turn, extended the trail of impact. Brian Druker, an oncologist working on leukemia, chose to pursue the observation that the great majority of cases of chronic myelogenous leukemia are characterized by a chromosomal abnormality, the Philadelphia chromosome identified by Peter Nowell and David Hungerford and characterized by Janet Rowley involving a reciprocal translocation between chromosomes 9 and 22. Using the tools of molecular biology, this translocation had been shown to generate a novel gene fusion between the beginning of the Bcr gene from chromosome 22 and the Abl protein kinase gene from chromosome 9. The import of this fusion was that the Abl protein kinase is expressed in an inappropriately regulated manner, stimulating white blood cells to grow out of control.

Druker saw this as a potential opportunity to develop a drug to treat leukemia based on the logic that inhibitors of this protein kinase should block this inappropriate growth signal. Druker and his collaborators, including Nicholas Lydon from the pharmaceutical company then known as Ciba-Geigy, identified a compound that would block the enzyme activity by competing with ATP for the enzyme active site and demonstrated that this compound largely would prevent colony formation by leukemia cells in culture (2). However, Druker encountered considerable challenges when trying to push this project further into the clinical arena due to concerns that it would be difficult to generate an ATP analog that would be sufficiently specific for the Bcr-Abl kinase to avoid side effects. Nonetheless, when a clinical trial was performed to test the safety of the compound in patients with CML, the compound was found to be quite well tolerated and, most importantly, remarkably efficacious, with 53 of 54 patients who took doses over 300 miligrams per day showing complete hematological responses, typically within four weeks (3). This compound, imatinib (marketed as Gleevec in the United States) is now the first-line treatment for CML and has transformed the prognosis for CML patients. Furthermore, this development represents a key landmark in the development of personalized, or precision, medicine (4) and has fueled considerable research and development efforts in both the academic and private sectors.

Examples such as the development of imatinib are crucial in discussing the impact of biomedical research in our society, as they illustrate the ultimate effects of such research on people's lives. They also illustrate the cumulative nature of such advances, as they involve

concepts and tools developed by many scientists over many years or decades (often with different goals in mind) and the interactions between basic scientists, clinicians and the private sector in converting a set of discoveries into a tangible benefit for patients worldwide.

The National Institutes of Health recently launched a useful webpage (5) that aggregates papers, reports and other items that illustrate the impact of NIH-supported research. The collection covers four major areas: our health, our economy, our communities and our knowledge. This is a valuable resource for American Society for Biochemistry and Molecular Biology members when they discuss the impact of their research and the research of their colleagues with their families, friends and government representatives.

Two examples of the reports available are "Economic impact of the human genome project" (6) and "Leadership in decline: assessing U.S. international competitiveness in biomedical research" (7). The first report concludes that a $3.8 billion investment in the human genome project has resulted in $796 billion in economic activity. While I would quibble that including only the human genome project itself and excluding the underlying investigator-initiated basic research that made the genome project possible and enhanced it along the way underestimates the investment, even if you triple the investment to $11.4 billion, this represents a 70-fold return on investment over a 22-year period (from 1988 to 2010) for an annualized return of more than 300 percent. The second report surveys the aspirations, strategies and investments that other countries have been involved in over the past decade while the American investment in biomedical research has been falling due to nearly flat NIH appropriations (with any increases well below the rate of inflation) and discusses some of the implications of these trends.

After I completed my postdoctoral fellowship, I continued my career at Johns Hopkins and had further opportunities to interact with Nathans on both scientific and administrative projects. After winning the Nobel Prize, he continued his research at full throttle, focused primarily on the examination of genes induced in response to growth factors. When several of these genes turned out to encode zinc-binding proteins, our laboratories collaborated, contributing to the discoveries that members of one class of these proteins are sequence-specific, single-stranded, RNA-binding proteins that regulate RNA turnover.

Nathans was a remarkable man, one of the most clear-headed individuals I have ever met. When the president of Johns Hopkins left relatively suddenly to pursue a different opportunity, Nathans was asked to step in as acting president, and he did a remarkable job, guiding the university through some turbulent times, including a major reorganization involving the School of Medicine and Johns Hopkins Hospital. He was successful because his judgment was universally trusted, despite (or maybe, in part, because of) his relative lack of administrative experience.

A year after turning over the reins to a new president, Nathans was diagnosed with leukemia. His diagnosis coincided with the period when clinical trials of imatinib were getting under way, although he had a different form of leukemia that is not treatable with the drug. Regardless, I am certain that he would have been thrilled by this development as one of the eventual outcomes from the field of molecular medicine that he helped envision. Furthermore, he would have followed with interest the development of other protein kinase inhibitors that have proved to be effective for the treatment of other cancers, although in many cases the results have been less striking than those with imatinib, because most other cancers are much more genetically heterogeneous and complex than CML. Nonetheless, the development of these drugs highlights the essential nature of the patient determination that has been personified by scientists such as Dan Nathans and Brian Druker. Even more, they reveal the long-term impact of basic research that uncovers fundamental cellular mechanisms when coupled with creative efforts to translate this basic knowledge into clinical interventions.

Jeremy Berg (jberg@pitt.edu) is the associate senior vice-chancellor for science strategy and planning in the health sciences and a professor in the computational and systems biology department at the University of Pittsburgh.

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The ASBMB legislative agenda for 2013

BY CHRIS PICKETT

The 113th Congress will be sworn in on Jan. 2, and there is quite a bit of work to be done on a wide range of issues. The American Society for Biochemistry and Molecular Biology remains committed to voicing the concerns of our members to those on Capitol Hill. To this end, the ASBMB Public Affairs Advisory Committee has begun work on an ambitious plan to develop a sustainable biomedical research enterprise. The goal of this endeavor is to develop a research enterprise that is insulated against boom-and-bust funding cycles, prepares trainees for the jobs available and ensures that the benefits of research are brought rapidly to market. Developing a sustainable biomedical research enterprise will be a multiyear process that will require significant legislative action. The ASBMB legislative agenda for 2013 will merge our current advocacy efforts with the legislative needs of a sustainable research enterprise.

Funding

Federal funding is an essential component of biomedical research in the U.S., and increasing the appropriations for research agencies is always a priority for the ASBMB. Funding for the National Institutes of Health has been stagnant over the past 10 years, and the ASBMB will be advocating for increases to research funding to ease the financial strain on biomedical investigators. Federal funding for biomedical research still will be an essential part of the sustainable research enterprise, and the ASBMB will begin discussions with legislators about a consistent and predictable federal investment in biomedical research that compensates for inflationary changes.

STEM education

The ASBMB is collaborating with several organizations to convince Congress to invest in innovative programs that improve science, technology, engineering and math education around the country. Improving STEM education will ensure that students have the knowledge needed to get jobs once they graduate. An education with a strong STEM component is also necessary for the sustainable biomedical research enterprise, as it trains the next generation of scientists to make the advancements required to improve public health.

Regulatory affairs

The convergence of academia, industry and governmental research forms myriad opportunities to develop treatments and cures that improve the livelihood of all Americans. However, unnecessary governmental regulations and uncertainty around the ownership of intellectual property, for example, often slow the exchange of information between research sectors. In 2013, the ASBMB will be advocating for legislation that removes many of these barriers while ensuring that the outputs of a sustainable research enterprise – cures, treatments and new technologies – are properly vetted before release to the general populace.

Immigration

The immigration of gifted scientists from around the world is essential for the U.S. to remain competitive with rising international competitors. The ASBMB is working to make it easier for foreign scientists to work and stay in the U.S. after obtaining their degrees. The American research enterprise requires having excellent scientists working in all research sectors, and an immigration policy that ensures that the best scientists from around the world do their innovative work here is an integral part of this endeavor.

The ASBMB also will be pursuing legislative action on a number of other fronts, including training and workforce issues, animal use in research and travel restrictions for federal scientists. We will be making a concerted push to achieve significant legislative gains that will improve the abilities of our members to do their important scientific work in the short term while laying the groundwork for the establishment of a sustainable biomedical workforce in the long term.

Chris Pickett (cpickett@asbmb.org) is the science policy fellow at the ASBMB.

Kyoto Prize goes to Ohsumi

Yoshinori Ohsumi, a professor at the Tokyo Institute of Technology, won the Kyoto Prize in Basic Sciences last month for his studies of autophagy in yeast and his contributions toward elucidating the mechanisms of and physiological significance of the cellular process. Each year, three laureates are presented with diplomas, prize medals and 50 million yen apiece from the Inamori Foundation.

OHSUMI

Georgia Tech's García honored by Society for Biomaterials

GARCÍA

Andrés J. García, a professor at the Georgia Institute of Technology School of Mechanical Engineering, won the 2012 Clemson Award for basic research from the Society for Biomaterials. The award recognizes "significant contributions to and understanding of the interaction of materials with tissues within a biological environment." In his nomination of García, the University of Washington's Buddy Ratner cited García's "strong commitment to polymeric biomaterials and to the modern biology of healing and regeneration, coupled with a fine intelligence, a charismatic personality and super-charged energy." On top of the award, one of García's publications was selected as part of a special issue of the Journal of Biomedical Materials Research Part A focusing on the most significant 25 publications since the inception of the journal in 1965. At Georgia Tech, where he is chairman of the bioengineering graduate program, García focuses on engineering biomaterials that promote tissue repair and healing, quantitative analyses of mechanisms regulating cell adhesive forces and cell-based therapies for regenerative medicine. Among his numerous accolades are the National Science Foundation CAREER Award and an Arthritis Investigator Award.

Two members win Columbia University's 2012 Horwitz Prize

LOSICK

SHAPIRO

Members Richard Losick of Harvard College and Lucy Shapiro of the Stanford University School of Medicine were named winners of the 2012 Louisa Gross Horwitz Prize, issued by Columbia University to recognize outstanding basic research in biology and biochemistry. Losick and Shapiro shared the award with Joe Lutkenhaus of the University of Kansas Medical School, and the honorarium will be divided among the three. The Horwitz Prize was established through a bequest to Columbia from S. Gross Horwitz in honor of his mother, the daughter of a prominent Philadelphia surgeon, author and one-time president of the American Medical Association. Losick said that sharing the prize with Shapiro was "a special treat, as we have been close comrades-in-arms in microbial development from the early days of our careers, and each of us has been held spellbound by the bacterium we have been studying." He continued, "It was also a delight to share the Prize with Joe Lutkenhaus, whose contributions to how bacteria divide had a major influence on our studies with Caulobacter and Bacillus."

Carroll wins Pfizer award for young investigators

CARROLL

Kate Carroll, an associate professor at the Florida campus of The Scripps Research Institute, won the American Chemical Society's 2013 Pfizer Award in Enzyme Chemistry. The award, begun in 1945, is given annually to stimulate research in enzyme chemistry by scientists under 40 years old. Carroll, a member of the American Society for Biochemistry and Molecular Biology's mentoring committee, was selected for this award on the basis of her work using the tools of chemistry and biology to elucidate protein cysteine oxidation as a new paradigm for the regulation of cell-signaling pathways. Carroll will give an award lecture at the ACS annual meeting to be held in the fall in Indianapolis.

Fuchs gets N.Y. Academy of Medicine medal

FUCHS

The New York Academy of Medicine named Elaine Fuchs of the Rockefeller University the 2012 winner of the Academy Medal for Distinguished Contributions in Biomedical Science. In a statement, the academy said it was acknowledging Fuchs "for her innovative and imaginative approaches to research in skin biology, its stem cells and its associated human genetic disorders." The academy has issued the medal to biomedical researchers since 1929 and has put a special emphasis on recognizing those working on translating their findings to improve human health. Fuchs, a Howard Hughes Medical Institute investigator, was honored at the academy's 165th Anniversary Discourse and Awards event last month.

IN MEMORIAM:

Parithychery R. Srinivasan

Parithychery R. Srinivasan, professor emeritus at Columbia University, died Oct. 23 at the age of 84. Srinivasan, who immigrated to the United States in 1953 as a Fulbright scholar, spent six decades at Columbia and served as acting chairman of his department in the 1970s. After retirement, he continued teaching a graduate seminar for the medical school. He was an active member of the New York Academy of Sciences, holding various leadership positions over the years, including the presidency in 1980. A longtime resident of Hastings-on-Hudson, N.Y., Srinivasan was also very involved with the Temple Beth Shalom community.

IN MEMORIAM:

Marilyn Rosenthal Loeb

Marilyn Rosenthal Loeb, a childhood disease and vaccine researcher at the University of Rochester Medical Center, died Aug. 24 from complications of thyroid cancer at age 82. Loeb, who trained under virologist Seymour Cohen, first joined the pediatrics department as a faculty member in 1978 and focused her work on the role of cell-surface molecules in bacterial infections and on the characterization and evaluation of vaccines. Loeb was a lifelong advocate for women in science and enjoyed traveling widely and participating in outdoor activities.

Please submit member-related news and accolades to asbmbtoday@asbmb.org

Högbom among the first class of fellows for Wallenberg Academy

HÖGBOM

Martin Högbom, an associate professor at Stockholm University, was named one of the first Wallenberg Academy fellows by the Knut and Alice Wallenberg Foundation. The inaugural cohort of the program, established by the foundation in collaboration with five Swedish royal academies and 16 Swedish universities, includes 30 young researchers of various disciplines. At Stockholm, Högbom focuses on structure–function studies of proteins that use metal cofactors. In particular, his group works with membrane proteins and ones involved in the lipid metabolism of M. tuberculosis. The fellowship program aims to provide long-term support, including mentoring, for up to 125 young researchers by 2016. Each fellow receives a five-year grant worth between $750,000 and $1.13 million (in U.S. dollars), and that grant can be considered for renewal for another five years after that.

Retrospective

Charles Crawford Sweeley Jr. (1930 – 2012)

BY ALFRED H. MERRILL JR., ROBERT C. MURPHY, WILLIAM L. SMITH, DENNIS E. VANCE, JOHN E. WILSON AND ROBERT K. YU

Charles "Chuck" Sweeley Jr., who made major contributions to the fields of sphingolipids and mass spectrometry, died on Sept. 21 in Lansing, Mich., after a long battle with a rare form of bladder cancer. He was 82.

A native of Williamsport, Pa., Chuck earned a bachelor's degree in chemistry at the University of Pennsylvania in 1952 and a Ph.D. in biochemistry at the University of Illinois, Urbana-Champaign, in 1955, working under the direction of Herbert Carter. After training with Evan Horning at the National Institutes of Health, Chuck took a position at the University of Pittsburgh in 1960 and was promoted to professor in 1966. He moved to Michigan State University in 1968, served as chairman of the biochemistry department from 1979 to 1985 and retired in 1992.

Here we highlight some of his accomplishments, which are described in greater detail in a recent review (1).

Chuck's illustrious research career began during his Ph.D. training. His thesis was on the chemistry of antibiotics, one of the major interests of the Carter laboratory. However, he spent most of his career studying the chemistry and biochemistry of sphingolipids and glycosphingolipids, the other major focus of the Carter laboratory (1).

Chuck was the first to develop a sensitive method for determining the sphingoid bases using periodate oxidation and analysis of the resultant long-chain fatty aldehydes by gas-liquid chromatography, or GLC, then a novel technology that Chuck played a key role in developing. Chuck wrote:

> *"An unexpected, career-altering opportunity came to me when Horning ordered the first gas chromatograph at the National Institutes of Health and I was given the task of setting up this machine … Later, I set out independently to apply gas-liquid chromatography … to other lipids. We reported a new method to analyze sphingolipid bases in sphingomyelin and glycosphingolipids by conversion of these long-chain bases to aldehydes with periodate and separation by GC … Human plasma sphingomyelin was found to contain sphingosine, dihydrosphingosine, and two unknown bases which were later shown to be sphinga-4,14-dienine and hexadecasphing-4-enine"(1).*

His method to hydrolyze sphingolipids is still used today to analyze the de novo biosynthesis of sphingolipids by following labeling of the sphingoid base backbone or to quantify sphingolipids on the basis of the amount of the sphingoid bases released. Chuck was the first to characterize a novel unsaturated sphingoid base, sphinga-4,14-dienine, in the sphingomyelin fraction of human plasma.

With the characterization of sphingoid bases as a background, he further investigated the biosynthesis of sphingosine as a condensation product of palmitoyl Co-A and serine, and, employing elegant biochemical tools, he elucidated the stereochemistry of the reaction intermediates and products. These elegant studies led to a proposed mechanism for how the first sphingolipid intermediate, 3-ketosphinganine, is formed by removal of the α-proton from serine as the Schiff base with pyridoxal 5-phosphate, displacement of the coenzyme A moietly from palmitoyl-CoA to form the carbon–carbon bond and then decarboxylation. This mechanism has been borne out by subsequent spectroscopic and X-ray crystallographic studies. His lab also demonstrated that double bonds in the sphingoid base and the 4-hydroxyl group of phytosphingosine are added after 3-ketosphinganine has been made.

Chuck was also the first to introduce derivatization of complex and simple sugars by the trimethylsilyl, or TMS, hydroxyl protecting group. This chemical maneuver rendered these and related compounds sufficiently volatile and thermally stable that they could pass through a gas chromatograph. Conversion to TMS derivatives greatly facilitated analysis of nonvolatile compounds owing to the ease in sample preparation and predicable elution profiles. Previously, these natural products were converted to volatile peracetyl or permethyl derivatives for GLC analysis. Chuck's 1963 paper on TMS derivatization of carbohydrates (2) was one of the 500 most-cited papers of the 1960s. The success of his strategy to derivatize sugars also was made possible by his introduction of the stationary phase, SE-30, for GLC.

With Dennis Vance, then one of his doctoral students, Chuck was one of the early investigators to utilize stable isotopes, especially deuterium, to assist in elucidating the metabolism of glycosphingolipids and carbohydrates.

Chuck first recognized Fabry's disease as a lysosomal glycolipid-storage disease and went on to isolate and partially characterize one of the major accumulated glycosphingolipids as trihexosyl globoside. He wrote of his good fortune in meeting Bernard Klionsky, who told him "about a rare genetic disorder called Fabry's disease, supposedly a sphingomyelin disorder." Chuck wrote, "I was pleased that he was willing to give me a piece of formalin-fixed kidney from a Fabry patient … It did not take long to find that this kidney contained abnormal amounts of two novel glycosphingolipids" (1).

Although the glycosidic linkage of the terminal galactosyl residue was wrongly assigned the β configuration, Chuck always acknowledged at scientific meetings and in publications the contributions from other investigators who showed it was actually of the α configuration – a true reflection of his graciousness and generosity. His work on the lysosomal glycosphingolipid-storage disorders led to the characterization of many serum neutral glycosphingolipids and to the study of a variety of glycosidases in animal and plant sources. These studies provided insights into the nature of lysosomal glycolipid-storage disorders and paved the way for the development of enzyme-replacement therapy for lysosomal lipid-storage disorders.

Chuck undertook an investigation of the biosynthesis of gangliosides, in particular GM3, or hematoside, and purified a sialyltransferase from rat liver to homogeneity employing classical biochemical techniques and affinity column chromatography. This was a remarkable feat, as glycosyltransferases in general are of very low abundance in tissue. He further elucidated the biological function of the interconversion of GM3 and lactosylceramide in human fibroblasts in relation to cellular proliferation.

He made important contributions to the emerging technique of biochemical MS in terms of analytical instrumentation, applications to the analysis of complex lipids and the use of stable isotope-labeled precursors as a strategy to study lipid biochemistry. By the late 1960s, he was using combined GC-MS in the studies of sphingolipid bases and publishing about the extraordinary power of this approach. His interest in using stable isotope labeling in biochemical studies directly led him to observe a problem caused by a separation of deuterium-labeled molecules from the corresponding protium species by GC. This feature, resulting from an isotope effect, complicated analysis of the isotope ratios of peaks eluting from the gas chromatograph. At this time, Chuck was on sabbatical in Ragnar Ryhage's laboratory at the Karolinska Institute, and Ryhage's lab was developing one of the first GC-MS instruments, the LKB 9000. To address the isotope-effect problem, a method was developed to switch the ion source acceleration potential in a rapid fashion to focus alternatively the appropriate isotope-labeled ions at the detector, thus enabling specific ions to be sampled rapidly at an appropriate time scale for elution from the gas chromatograph. This voltage-alternation approach was published in 1966, and the concept of selected ion recording remains a mainstay of GC-MS and LC-MS techniques.

Sweeley was before his time in promoting the power of time-of-flight MS, or TOF-MS. Using a fast TOF detector, he showed that it was possible to obtain 10 complete mass spectra per second during a GC separation of extracts of biological fluids using a time array detection strategy. While the true speed potential for TOF-MS would have to wait for the development of fast-timing circuits and faster data-acquisition systems, he used this concept of rapid mass-to-charge scanning to reveal the wealth of molecules present in urine and other biological fluids, a type of study he called metabolic profiling and a prototype for what we know now as metabolomics. Indeed, his metabolic profiling was decades ahead of its time. Chuck described it this way:

> *"Our first paper was on the development of an*

on-line computer system for single focusing mass spectrometry (1970). This was followed by a report on computer-controlled multiple ion detection in combined gas chromatography–mass spectrometry (GC-MS) (1973) and development of a computer system for selected ion monitoring of multi-component mixtures by computer control of accelerating voltage and magnetic field strength (1975). This allowed investigators to determine several substances in mixtures at the very high sensitivity obtained by selected ion monitoring. The next step was to develop methods for the automated determination of many substances in a mixture, and this led to the development of MSSMET, a computer system for metabolic profiling (1974 – 1986). We utilized metabolic profiling to examine the urinary organic acid fraction in natural early-onset insulin-dependent diabetic dogs (1988) and in studies of the turnover of [U-14C]-glucose into various metabolites in lactic acidemias (1988). This technique was utilized not only in studies of urinary organic acids but also in the analysis of urinary steroids … Metabolic profiling was also extended to a new and novel detection system using musical sounds instead of graphs or tables to analyze normal and abnormal samples of urine (1987). Intensities at the apex of each GC peak were converted to frequencies and played on a digital keyboard, higher notes reflecting greater concentrations of metabolites. This was one of the first reports on the use of sound as a sense of perception in the field of analytical chemistry and became known whimsically in the press world-wide as 'musical urines.'" (1)

In closing comments, Chuck noted:

"By now the work I have described is ancient history … But I lived in exciting times, times that marked the beginnings in most of the areas of my research. It was the beginning of gas chromatography, nearly the beginning of mass spectrometry in the biomedical sciences, the beginning of chemistry and metabolism of sphingolipids, and certainly the beginning of what we now know about intermediary metabolism in man. Our generation provided a foundation upon which modern investigation in these fields has grown and prospered." (1)

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2013 ASBMB SPECIAL SYMPOSIA

Focused Meetings in Your Field

The multitasking endoplasmic reticulum in health and disease

The endoplasmic reticulum is now recognized as a central control point for compartmental organization of the eukaryotic cell. Beyond managing the biosynthesis, folding and degradation of proteins that make up at least one-third of the eukaryotic genome, it regulates membrane trafficking that drives cell specialization during development. It is essential for compartmentalization of the nucleus and the structure of chromatin. It performs specialized functions such as detoxification by the liver and management of the metabolome by the pancreatic beta-cell. More recently, a flurry of proposed new activities associated with the ER include the regulation of mitochondrial function, peroxisome biogenesis, autophagosome/phagoautosome formation as well as specialized ER domains that link to antigen cross-presentation in the immune system and cross-talk with viral and bacterial pathogens. The apparent old and new multitasking activities of the ER now serve as the catalyst to bring together a diverse pool of investigators to explore in depth and challenge traditional views of ER function that will help define the ER as a heretofore unanticipated central regulator of eukaryotic function through its ability to manage and integrate metabolic, biosynthetic, degradation and signaling pathways. We look forward to your participation.

The multitasking endoplasmic reticulum in health and disease

May 1 – 4

Airlie Center, Warrenton, Va.

Early registration and abstract submission deadline: Feb 1

More information: www.asbmb.org/MultitaskingER

Organizers: John Bergeron, McGill University; Tommy Nilsson, McGill University; and William Balch, The Scripps Research Institute


BERGERON


NILSSON


BALCH

Membrane-anchored serine proteases

The recent availability of the complete genomic sequences of several mammalian organisms has led to an explosion in knowledge of proteolytic enzymes and the realization that proteases make up more than 2 percent of the human proteome. An unexpected outcome was the unveiling of a new family of serine proteases

that are anchored directly to the plasma membrane. This inaugural symposium on membrane-anchored serine proteases will highlight the rapidly expanding understanding of the activities of this family of enzymes in fundamental cellular, developmental and pathological processes. The symposium will explore biochemical aspects of their structure and function, regulation of their activities in cells and tissues, challenges in the identification of their target substrates, and their roles in cellular signaling, proteolytic cascades and receptor activation. Their potentially wide-ranging contributions to diverse human pathologies, such as cardiovascular diseases, inflammation, cancer and viral infections, also will be featured. This abstract-driven meeting will encompass a variety of disciplines, and there will be ample opportunities to interact and share findings in a relaxed, collegial atmosphere.

NEW! Membrane-anchored serine proteases

Sept. 19 – 22

William F. Bolger Center, Potomac, Md.

Early registration and abstract deadline: June 12

More information: www.asbmb.org/SerineProteases

Organizers: Toni Antalis, University of Maryland School of Medicine, and Thomas Bugge, National Institute of Dental and Craniofacial Research


ANTALIS


BUGGE

Student-centered education in the molecular life sciences

Improving science, technology, engineering and math education is a rallying point on the way to improving our competitiveness as a nation. Given the fast pace of research and development, biochemistry and molecular biology are likely to feature prominently in future economic and intellectual opportunities. To increase the number of highly qualified STEM graduates, the President's Council of Advisors in Science and Technology recommends widespread adoption of empirically validated teaching practices and replacement of standard laboratory courses with discovery-based research courses. This symposium will allow educators to explore best practices in BMB education and to bring proven strategies and resources back to their institutions. An overarching goal is to help educators deliberately foster deep learning and development of essential skills for students. A common thread across the symposium will be use of data from instructors' classrooms or broader research projects to inform and improve instruction. Examples include a workshop on the use of Bloom's Taxonomy to promote high-level cognitive skills in large and small classes, a plenary session on design and implementation of a research-based lab curriculum, and a workshop on teaching and assessing molecular visualization. Poster and networking sessions will allow ample time for participants to engage in meaningful conversations, form collaborations and share expertise.

Student-centered education in the molecular life sciences

Aug. 4 – 7

Seattle University, Seattle, Wash.

Early registration deadline: May 1

Abstract submission deadline: June 5

More information: www.asbmb.org/StudentCenteredEducation

Organizers: Vicky Minderhout and Jennifer Loertscher, Seattle University


MINDERHOUT


LOERTSCHER

Transcriptional mechanisms and evolution

Organisms have evolved a diverse set of mechanisms to orchestrate the expression of their genes. The core machinery of gene expression is instrumental to this process but also subject to the ever-changing needs required to survive and reproduce. This special symposium aims to bring together current perspectives on regulatory evolution with mechanistic insights into gene expression. Topics will include complex transcriptional processes, RNA processing and translational machines with an emphasis on evolutionary insights and quantitative models. These topics will be covered by a panel of invited speakers recognized for recent advancements in mechanistic and evolutionary studies of gene expression with the objective of achieving cross-fertilization between disciplines. This focused, three-day meeting will allow extensive informal interactions for participants to gain a better understanding of key challenges in the respective areas of study and to forge collaborations.

NEW! Transcriptional mechanisms and evolution

July 25 – 28

University of Chicago, Chicago, Ill.

Early registration and abstract deadline: May 1

More information: www.asbmb.org/Transcription

Organizers: David Arnosti, Michigan State University; Ilya Ruvinsky, The University of Chicago; Justin Fay, Center for Genome Sciences at Washington University in St. Louis


ARNOSTI


RUVINSKY


FAY

Come and knock on my door

BY NICK D. TSIHLIS

When I introduce myself lately, I have to remember not to say, "I'm a postdoc." About a year ago, I became the only research assistant professor in the vascular surgery division at Northwestern University Feinberg School of Medicine. I'm still learning the ropes.

I'm a Ph.D. who gets emails about scheduling operating-room time, since I'm in a department full of surgeons. I'm a nontenure-track faculty member who has no use for invitations to seminars about new classroom software, because I don't teach. On top of all that, I'm the guy who feels a little awkward at the lunch table, because I got promoted above my postdoc and grad student friends. I still feel strange calling myself a professor, because I don't have my own lab, but that's what's on my new business cards and the placard outside the door to my new office.

And now the professorship is starting to feel more real. When the phone rings on my desk, I know it's for me and not one of five other people in the lab. When I want to hang up my coat, I can use a hook behind the door instead of hanging it on the back of my chair and having it drag across the lab floor. When someone wants to ask me a question, he or she knocks on my door and asks to come in as opposed to just walking up to my desk and firing away.

I was offered this new faculty position after proving myself as a postdoc for five years. Over that time, I acquired quite a lot of responsibilities in the lab, which I am still fulfilling in my new role. These include bench work, data analysis, manuscript preparation, grant writing, equipment repair, computer help, inventory management, and mentoring undergraduate students, postdocs and surgical residents doing research in the lab.

The overall focus of the lab is nitric oxide vascular biology, with an emphasis on keeping blood vessels open after surgical interventions. After a blockage such as an atherosclerotic plaque is removed from an artery, the inflammatory environment causes aggressive cellular proliferation, which often leads to diminished blood flow. We've shown in animal models that administering NO at the site of the intervention prevents cellular proliferation. My research focuses on determining the molecular mechanism by which NO is causing these effects in the vasculature. Specifically, I study the ubiquitin-proteasome pathway, which is responsible for breaking down short-lived proteins in our cells. This includes the cyclins that allow for proper cell cycle progression. NO is known to affect the cell cycle, and we've seen that it does this by regulating the ubiquitin-proteasome pathway. Basically, when the cell cycle is arrested, cells can't multiply and block off the blood vessel.

While the promotion changed my day-to-day life in the lab, I still get to do all the things I did as a postdoc. I still enjoy seeing the light go on in someone's eyes when he or she grasps something I'm explaining to them. I get to keep up on the latest scientific advances and apply them to my work. I still participate in our floor's interdisciplinary journal club. But I am also tasked with more personnel and administrative matters, like interviewing undergrads and running lab meetings, and I am working on more interdepartmental collaborations. I am directly reviewing manuscripts for journals and working on ideas to get my own funding as well as helping my boss with her grants. Lastly, I am gaining some understanding of how the faculty and administration interact.

People ask me all the time, "Don't you want a tenured position where you have your own lab?" The truth is this position is perfect for me, because I don't want to be on the tenure track right now. My wife and I have two young daughters. The next five years should be spent watching them grow up — not toiling in the lab for a tenure-track professorship that may not exist. According to a recent report from the American Federation of Teachers, the percentage of positions at public, four-year universities that were tenured or on the tenure track dropped from 51 percent in 1997 to 39 percent in 2007 (1). While the numbers across all institutions aren't so stark — they dropped from 33 percent to 27 percent — I'd rather see my wife, carve jack-o-lanterns with the kids and take them trick-or-treating while they still want to be seen with me.

The next five years should be spent watching (my daughters) grow up – not toiling in the lab for a tenure-track professorship that may not exist.

As I have stepped into this role over the last year, I have not only been trying to make my own way but also to make a path for others who will fill these positions in the future. So here's some advice. Use your time wisely and find a balance. Take on new challenges, but say no to things if you can't make time to do them well. Use your knowledge and connections to help others, but take time away from the lab for yourself so you don't burn out. Eat lunch with your colleagues, but go to yoga class twice a week on your lunch hour to clear your mind. Make yourself available to others, but don't check work email at home. (This is easier said than done, especially with a smartphone in your pocket keeping you constantly connected.) Finally, try on your new title and walk through that next door, but don't be afraid to leave it open so people can come in and chat.

Nick D. Tsihlis (n-tsihlis@northwestern.edu) is a research assistant professor in the vascular surgery division at Northwestern University Feinberg School of Medicine.

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1. http://www.insidehighered.com/news/2009/05/12/workforce

Parched no more

Bruce Baum's team came up with a gene therapy to help head-and-neck cancer patients with dry-mouth syndrome

BY RAJENDRANI MUKHOPADHYAY

In 1991, Bruce Baum was stuck in the audience of a lecture at which the speaker was just droning on. To kill time, the dentist-biochemist began to sketch out an idea he had for treating dry-mouth syndrome. The idea came to fruition last year as the first successful human clinical trial to treat the syndrome with gene therapy was published (1).

Dry-mouth syndrome is common among patients who undergo radiation therapy for head-and-neck cancers; their salivary glands get damaged by the treatment and no longer produce saliva. Others with dry-mouth syndrome are perimenopausal women and people with Sjögren's syndrome, a poorly understood disease. The sensation of a persistently dry mouth can be uncomfortable and affect quality of life. The patients can't enjoy certain foods because they become hard to swallow and taste.

In 1982, Baum had set up a dry-mouth clinic at the National Institutes of Health in collaboration with oral surgeon Phil Fox. In the mid-1980s, he and Fox decided to test a drug called pilocarpine, which was being used to treat dry eyes, on patients who still had partially functional salivary glands. The drug worked by stimulating the functional portions of the glands to overproduce saliva, and it went on to become the commercial product Salagen.

But Salagen was useless in patients whose salivary glands were almost destroyed. These were mainly head-and-neck cancer patients who had undergone extensive radiation treatment. Baum was frustrated that he was unable to help those patients.

By 1990, gene therapy was getting increasing attention, and Baum was keeping an eye on the research. His former postdoctoral adviser, Ronald Crystal, then at the National Heart, Lung and Blood Institute and now at Weill Cornell Medical School, was investigating gene therapy for cystic fibrosis. Lungs bear many similarities to the salivary glands, so Baum figured that any breakthroughs in gene therapy for a lung disease might be extended to salivary glands.

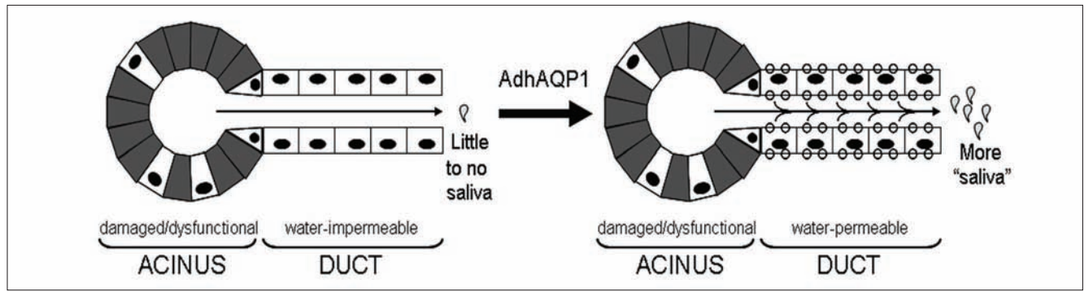
By 1991, Crystal's group had preliminary data that it could transfer the lacZ gene to rat lungs. Baum began to think about how he could transfer genes into salivary glands.

Then came the boring lecture. Baum, who was sitting next to an old friend at the talk, sketched his idea onto a napkin and showed it to his friend. His friend took a look and said it could work.

Baum's idea was based on an old-fashioned dental technique. The largest of the major salivary glands are the pair of parotid glands. Each gland sits below an ear and looks like a bunch of grapes. Each gland has a straight pipe that runs through the cheek and empties in front of the first molar. Dentists have used this pipe to thread in a tiny tube to deliver contrast agents to the parotid glands for diagnostic X-rays. Baum considered using this same technique to deliver a viral vector carrying a gene to the parotid glands and to correct the dry-mouth defect.

But the question remained: Which gene? The answer came from Peter Agre at the Johns Hopkins School of Medicine, whose group had discovered aquaporin-1 (2). Aquaporin-1 is a protein that naturally forms channels for water in the membranes of cells. Agre won the Nobel Prize in chemistry in 2003 for his discovery. "As soon as I became aware of his paper in the [Proceedings of the National Academy of Science], I called him up and we collaborated for a number of years," says Baum.

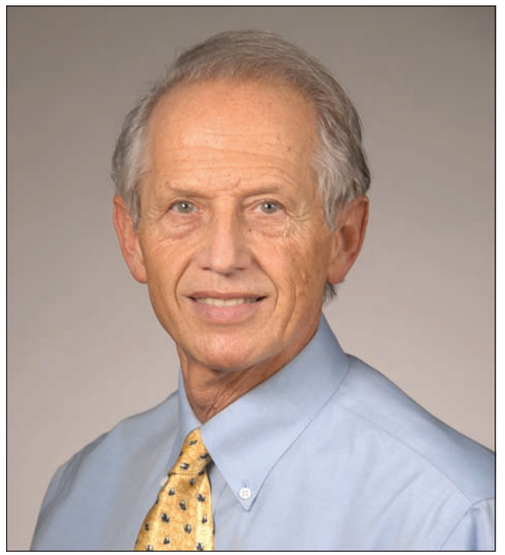
Over the next 15 years, Baum and his collaborators successfully tested his idea on rats and miniature pigs. The parotid glands, as he intuited, were an ideal target for gene therapy. Thanks to the old-fashioned dental technique, they were easily accessible. There was no danger of a gene vector escaping from the glands and wreaking havoc elsewhere, because the parotid glands are covered in a tough, fibrous layer that forms a barrier between them and the circulatory system.



The gene for aquaporin-1 is carried into the parotid gland by a disabled adenoviral vector to help the gland produce saliva again. Image provided by Bruce Baum.

From the animal studies, Baum and his colleagues had sufficient evidence to get approval from the NIH and the U.S. Food and Drug Administration for human testing in 2008. They started a phase I clinical trial with 11 head-and-neck cancer survivors. The investigators infused the aquaporin-1 gene directly into one of the parotid glands. The gene was carried in a disabled, nonreplicating adenovirus.

Within the study's first 42 days, five participants had increased levels of saliva secretion as well as a renewed sense of moisture and lubrication in their mouths. The six who didn't benefit from gene therapy didn't suffer serious side effects.



Bruce Baum, a dentist–biochemist, retired from the National Institute of Dental and Craniofacial Research in 2011.

Two of the five patients who benefited from the treatment particularly struck Baum. One was a man who had complained that his parched mouth stopped him from enjoying his two favorite foods – macaroni and cheese and croutons in salad – because he would end up choking on them. After the first 14 days of the trial, the man's saliva output started to increase, and he was thrilled to report that he could again eat both without difficulty. "He also said to us that he suddenly started drooling on his pillow again," says Baum.

The other patient was a man who routinely participated in triathlons. "He complained it was just so hard for him to run because his mouth would be so dry from breathing through his mouth," says Baum. But once the man started in the clinical trial, says Baum, he reported that "he didn't have to use a water bottle during a race he ran. That was pretty impressive."

Since his retirement from the National Institute of Dental and Craniofacial Research in 2011, Baum has let his colleagues move ahead with subsequent steps of the research. Four of the six patients who didn't benefit from the trial had reactions to the adenovirus vector. The next step will be to try another vector. The patients for whom the adenoviral vector did not work are eligible to enroll for another trial with the different vector once the trial is approved.

Rajendrani Mukhopadhyay (rmukhopadhyay@asbmb.org) is the senior science writer for ASBMB Today and the technical editor for the Journal of Biological Chemistry. Follow her on Twitter at www.twitter.com/rajmukhop.

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Q&A with Jeremy Nicholson

BY RAJENDRANI MUKHOPADHYAY

Jeremy Nicholson of Imperial College London is heading up the U.K.'s government-funded phenome center, which will undertake population-scale metabolic phenotyping and profiling. Nicholson is one of the pioneers in metabonomics, the systemic study of the responses of small molecules or metabolites that are expressed in a cell, tissue or organ to physiological or pathological stimulation or genetic modification. The MRC-NIHR Phenome Center is backed by the U.K. Medical Research Council and the National Institute for Health Research. Two instrument manufacturing companies, Waters Corp. and Bruker BioSpin, are funding partners in the venture and are developing new technologies for high-throughput metabolic analysis with Imperial College London.

Below is the interview ASBMB's science writer, Rajendrani Mukhopadhyay, conducted with Nicholson in late 2012. The interview has been edited for length and clarity.

Is the new MRC-NIHR Phenome Centre opening in January on the site of the London Olympics antidoping laboratory as was reported in the media during the 2012 Olympic Games?

For operational reasons and in agreement with all of our funding partners, we decided to relocate much of the instrumentation used in the Olympic 2012 drug testing laboratory to one of the major Imperial College medical campuses, the Hammersmith Hospital. With the center at Imperial, we will have better high-speed data links with the Imperial computer networks as well as bring the facility into the middle of our new translational medicine and biobanking centers. So there are technical and scientific advantages to the Imperial location [for the MRC-NIHR Phenome Centre]. We are undertaking a major lab refurbishment to allow the center to open in early 2013.

What's the impetus for building a large-scale phenome center?

I've been working in metabolic phenotyping and metabolic profiling for the best part of 30 years. I've been thinking about trying to build a national center for about seven or eight years to broaden and extend the research capacity and capability [for metabolic phenotyping and profiling] to other universities in the U.K., even outside of the U.K. The infrastructure of the Olympic Games 2012 antidoping laboratory offered a window of opportunity. They had 45 mass spectrometers of various types working in parallel. They were doing up to 300 forensic assays for different drugs, metabolites, and other markers of abuse with a turnaround time of about six hours. There is no analytical laboratory in the world with that sort of capacity and throughput

Jeremy Nicholson of Imperial College London.

coupled with that level of forensic quality. The Olympics test lab was developed and run by David Cowan of King's College, and King's remains a strategic partner in the new phenome center.

What will the NIHR-MRC Phenome Centre do?

It has multiple functions. It will function as a research and development laboratory. The industrial investment is to develop the next generation of high-throughput technology so that we can go for faster, cheaper and more efficient analyses of complex biological mixtures.

We will also do population-level human phenotyping in partnership with multiple research groups in epidemiological research but will especially serve the National Institute for Medical Research's biomedical research centers, such as Oxford, Cambridge, University College London, Imperial and King's. From a scientific point of view, we introduced the concept of the metabolomewide association study, or MWAS, in 2008 (1). The idea is that you can measure thousands of metabolic variables in urine or plasma samples taken from epidemiological studies, and you can regress those variables against disease risk factors, such as blood pressure, body mass index, visceral fat. In epidemiology, we try to find metabolic markers associated with the risk of getting a disease. In some ways, we are trying to rewrite the handbook of molecular epidemiology, because we're giving epidemiologists a much wider range of analytical metrics than they ever had before to describe physiological variation.

In an ideal situation, you would have a genomewide association study plus a metabolomewide association study. You can look at those together statistically, and that's one of the things we'll be doing as part of the phenome center. We will be looking at populations that have been quite extensively genotyped and doing complementary metabolic profiling. Genes and environment combine to create your individual risk factor of getting a disease, and this also works at the population level. Your genes are like a set of cards you get dealt with when you are born. How you play them through your life, lifestyle and environment, determines whether you win a game or not. The environment is the most important factor that we might be able to control in our lives, but we need to understand how the interactions work at the physiological level.

Another very important part of the metabolic phenotype is the contribution from the gut microbiome, another exploding area of biological science. The microbes inside us have an enormous influence on our biochemistry. It's only in the last few years that we've discovered really how important those bugs are, in terms of our disease risk factor probabilities and how they are connected with many noninfectious diseases. Again, we're getting a new set of information that previously hasn't been available to epidemiologists – the output of the gut microbial activity in people who are sampled in epidemiological studies.

By the way, one of the things the MRC also wanted us to do is to set up a research training center linked to the phenome center. This will be to train the next generation of clinician-scientists who will be using this technology. We'll be running new medical mass spectrometry/nuclear magnetic resonance courses so we have a national training capability for these technologies generously funded by our industrial partners.

How you do envision integrating all these different types of data and handling the sheer volume of data?

We plan to have a big computational cluster to handle the data volume. We are doing a lot of work, for instance, on using graphical processor unit calculations for ultrahigh speed data analysis. If you go to get an Xbox or a Sony GameBoy, they have unbelievably fast graphic processors to deal with real-time simulations. For instance, a (central processing unit) processor that fits inside a (personal computer) might have four or eight cores or even 12 cores these days. A (graphics processing unit) has up to 3,000 cores in it, so if you can program it in the right way, the performance is outstanding.

IMAGES PROVIDED BY JEREMY NICHOLSON

Two surgeons with two of the new 600 MHz NMR spectrometers at the Imperial Clinical Phenome Center.

Some of my group have been working with other groups around the world stringing together 15, 20, 50 graphic processors. If you can program them correctly, you can do data processing and visualization, like an IBM Deep Blue, at one one-hundredth of the cost.

How did you get to where you are today?

I was an inorganic biochemist in the early 1980s working on complexation and dynamics of potentially toxic metals like mercury and cadmium in biological systems. In one set of experiments, we were trying to measure the kinetics of transport of metals into blood cells. We were using nucleic magnetic resonance spectroscopy. In red blood cells, for instance, you've got glutathione at an intracellular concentration of about 2 millimolar, and as certain metals get into the cell, they complex with the glutathione and the NMR signal starts to change. By measuring the rate of change of signal in the red blood cells, you could measure the rate of absorption of these toxic metals directly. I wanted to do the complexation study in a realistic situation, so we added the metals to whole blood rather than a suspension of red blood cells. Of course, there were lots of extra signals from the blood plasma metabolites. As soon as I saw this, the penny dropped. I thought, "This is a clinical diagnostic tool." Doing NMR of plasma allows you to get a very rapid fingerprint of plasma biochemistry in just a few minutes with no sample pretreatment, so it was easy to try out lots of experiments in just a few weeks. I ran a sample of my own urine in an NMR experiment – even more signals! Then I popped some paracetamol [Editor's note: Paracetamol is known as acetaminophen in the U.S.] and looked at the signals in my urine a few hours later and was able to follow its metabolism and excretion. I was driving my wife completely crazy, because I was doing experiments on myself and it was disrupting the household. I decided to fast completely for 48 hours and look at my urine every few hours. I watched my ketosis develop in near real time. She watched my temper get worse.

My focus then shifted to this new field of spectroscopic diagnostics. It was how many metabolites could you discover? How many diseases can you diagnose using this approach? That's how metabonomics was born for me.

Apparently there is going to be another phenome center for clinical applications at St. Mary's Hospital, which is part of Imperial College London.

The Imperial clinical phenome center is for patient phenotyping. It is funded by consolidating multiple grants from the NIHR, the Gates Foundation, the [U.S. National Institutes of Health] and drug companies. It's a laboratory for patient-journey phenotyping (2). When you go into hospital, there's a work-up procedure, the doctor decides what's wrong with you, what treatment you're going to have, and there is an outcome – recovery or possibly not. That is a patient journey. We're putting together all the technologies we have into every stage of the patient journey and developing new tools for diagnosis and monitoring response to therapy.

The mathematics and analytical chemistry are the same [for the two phenome centers], but the information delivery timescales are different. In epidemiology studies, there are a large number of samples, and the analyses take a long time. In clinical situations, you've got a smaller number of samples, but you have to analyze and model them faster because the doctor needs the information to make decisions. [The two] present different sorts of modeling challenges. You also have to think about how you visualize data so a doctor can make sense of them and make a useful decision. Most systems biology information generated by genomics, proteomics and metabonomics is actually completely useless to doctors, because it cannot be visualized or presented in a medical framework. They need something very simple to help make a decision. Note that I say "help." We are not trying to replace medical decision making, merely augment it. The data need to be built into a decision tree so you take complex data and link them to the therapeutic framework.

Sounds like you've covered all your bases.

We have a core research facility at Imperial, a new clinical phenome center, a new population phenome center and others. I think we have all the bits to do a good job at making systems medicine real. The translational task is still an enormous one but very worthwhile. Ask me how we are doing in three years' time!

Rajendrani Mukhopadhyay (rmukhopadhyay@asbmb.org) is the senior science writer for ASBMB Today and the technical editor for the Journal of Biological Chemistry. Follow her on Twitter at www.twitter.com/rajmukhop.

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The ASBMB survey of young biochemists and molecular biologists

The results from the American Society for Biochemistry and Molecular Biology's survey of young biochemists and molecular biologists are now out. The respondents, who were between ages 20 and 39, ranked intellectual freedom as the most influential factor in choosing a career.

The survey was launched by a special ASBMB task force after its 2011 survey of biochemists in academe found that women and men were represented in equal numbers at all training levels but that the numbers of women seeking and holding various positions after training dropped off significantly. "Particularly striking is the constancy in the distribution of female and male teacher-scholars as applicants (27:73), interviewees (34:66) and appointees (28:72), as well as tenured academic biochemists (28:72)," the task force reported in the previous survey (1). Elizabeth Theil of Children's Hospital Oakland Research Institute, who led the task force, said the group wanted to investigate why, even in 2011, fewer women than men chose to apply for tenure-track positions as teacher–scholars.

The latest survey results suggest that more than half of the respondents, both men and women, felt they received limited support from peers, educators and family in choosing science careers. (See mentoring column on page 34). Reinforcing the data from the 2011 survey, the new survey shows younger women were more concerned about family, children and work-life balance than men. Both men and women were concerned about weak job prospects and low research funding.

Theil says she and her fellow task force members were struck by the large number (nearly half) of the survey respondents who wrote specific comments, surprised by the lack of knowledge (62 percent) of institutional family-friendly policies and concerned about mentoring effectiveness.

"Why were we surprised? For one thing, many institutions have family-friendly policies in place. For another, in the past, teacher-scholars spent a great deal of time mentoring pre- and postdoctoral students with discussions on many issues," she says. "The conversations often occurred during informal coffee breaks, lunch and group meetings in faculty members' homes."

But these days, she adds, the increased professional demands on teacher-scholars have forced them to focus primarily on giving technical advice to their mentees. She also suggests that the growing emphasis on digital communication has inadvertently led to fewer face-to-face discussions between teacher-scholars and their mentees and that the tone and content of the exchanges have become more formal and less likely to cover lifestyle issues and career advice.

Nonetheless, Theil says, she and the task force members were impressed by the passion of the young scientists for creative and independent research and their willingness to commit to the long hours. But they found chilling the widespread fears of failing in the current research climate.

Based on the survey results, the task force has made three recommendations:

1. Mentors should discuss actively with trainees, including postdoctoral researchers, the life of a scientist and help with career development as well as giving technical advice.
2. Granting agencies should permit one-year extensions to grants in progress requested by female principal investigators who are new mothers. Because concerns about child-care were raised more by young female scientists than their male counterparts, Theil says the grant extensions are a clear way to encourage women to become teacher-scholars in biochemistry and molecular biology.
3. The ASBMB should highlight institutions that have effective policies for attracting women to teacher-scholar positions in biochemistry and molecular biology.

Members of the task force were Melanie Cobb at the University of Texas Southwestern Medical Center at Dallas; Judith Klinman at the University of California, Berkeley; Fred Maxfield at Weill Cornell Medical College; Janet Smith at the University of Michigan at Ann Arbor and Joanne Stubbe at the Massachusetts Institute of Technology. Christopher Streeter at the consulting firm Altshuler Gray advised the survey's design and carried out the initial data analyses.

– Rajendrani Mukhopadhyay

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MAJORITY OF RESPONDENTS FROM RESEARCH UNIVERSITIES WITH GOOD MIX OF GRAD STUDENTS AND POSTDOCS

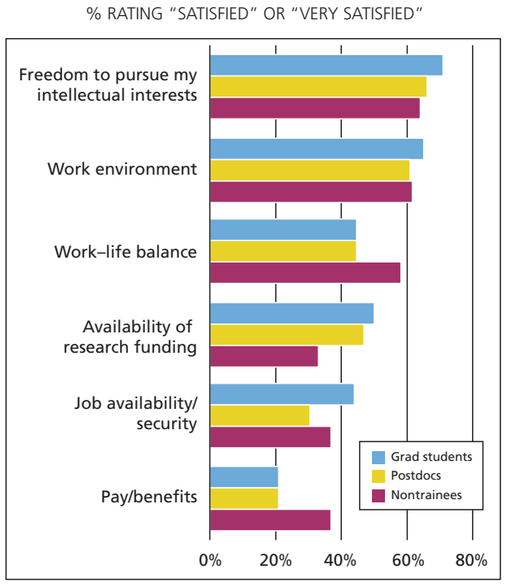
		COUNT	%
INSTITUTION	Academia (research university)	1512	79%
	Academia (primarily undergraduate)	85	4%
	Academia (other professional school)	37	2%
	Academia (other)	36	2%
	Independent research org./nonprofit	153	8%
	Other	80	4%
POSITION	Graduate student (Ph.D., M.D.)	634	33%
	Graduate student (Masters)	57	3%
	Postdoc	790	42%
	Nontenure track faculty	96	5%
	Researcher	161	8%
	Science administrator	13	1%
	Other	148	8%

GOOD REPRESENTATION FROM BOTH WOMEN AND MEN

		COUNT	%
AGE	20-29	734	39%
	30-39	94	50%
	40-49	171	9%
	50-59	27	1%
	60-69	7	0.4%
	Prefer not to answer	12	1%
GENDER	Female	1036	55%
	Male	840	44%
	Prefer not to answer	18	1%
MARITAL STATUS	Married	932	49%
	Single	779	41%
	Divorced	43	2%
	Separated	13	1%
	Widowed	3	0.2%
	Prefer not to answer	22	1%
	Other	106	6%

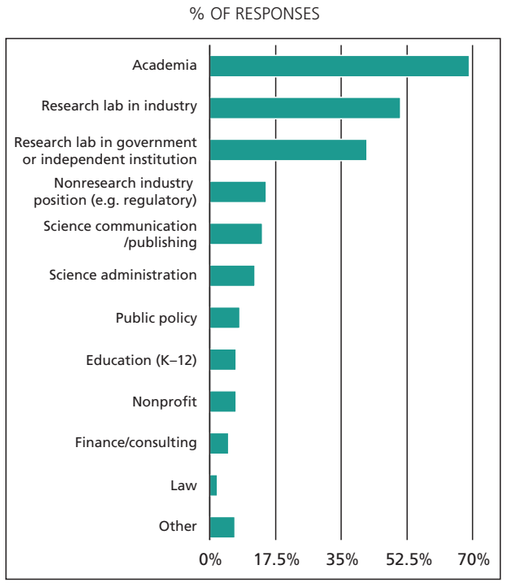
SATISFACTION WITH CURRENT POSITION, BY POSITION

How satisfied are you with the state of the following factors in your current position?



CAREER PLANS AFTER DEGREE, FOR TRAINEES

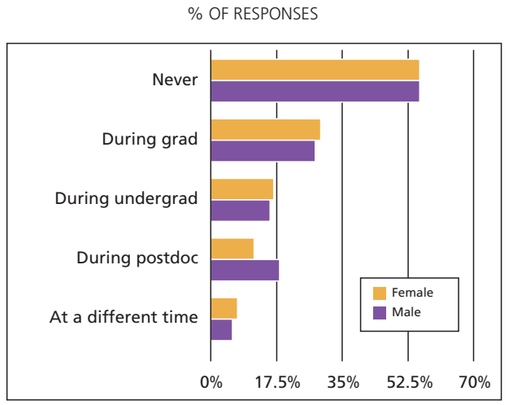
What do you plan to do after your degree/postdoc?



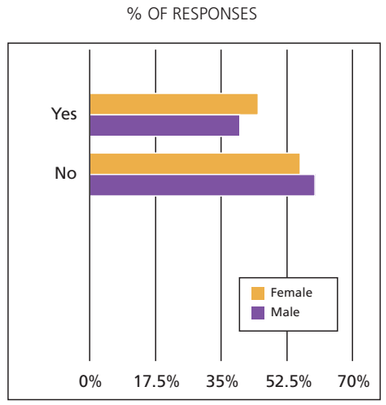
WOMEN AND MEN DISCOURAGED FROM PURSUING CAREERS IN SCIENCE IN EQUAL NUMBERS

With women only slightly more likely to be influenced by these comments

Has anyone ever actively discouraged you from pursuing a career in academic science?

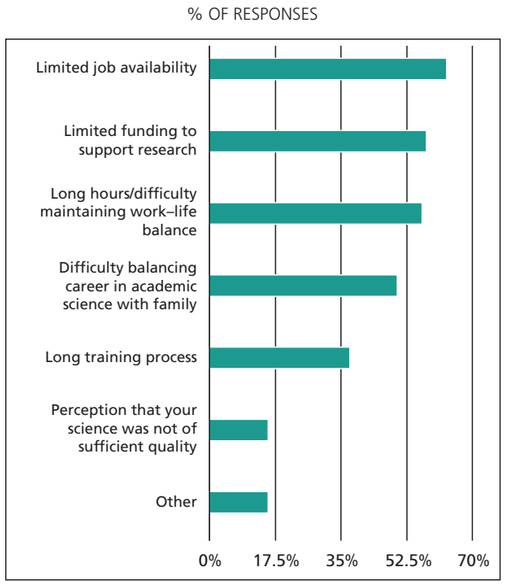


If discouraged, did this influence your career choices?



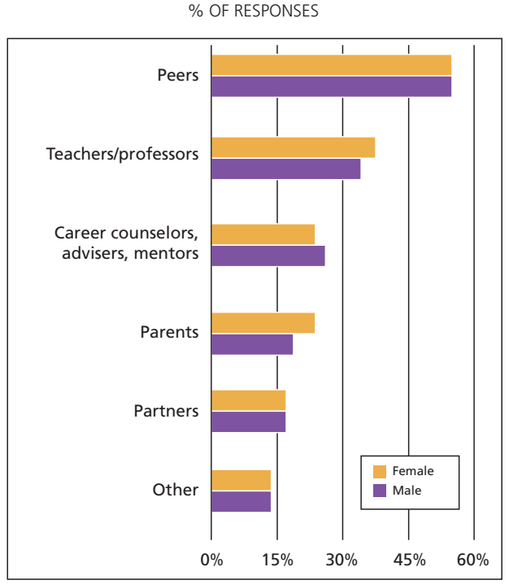
NATURE OF NEGATIVE COMMENTS

What issues did these people cite in their comments to you?



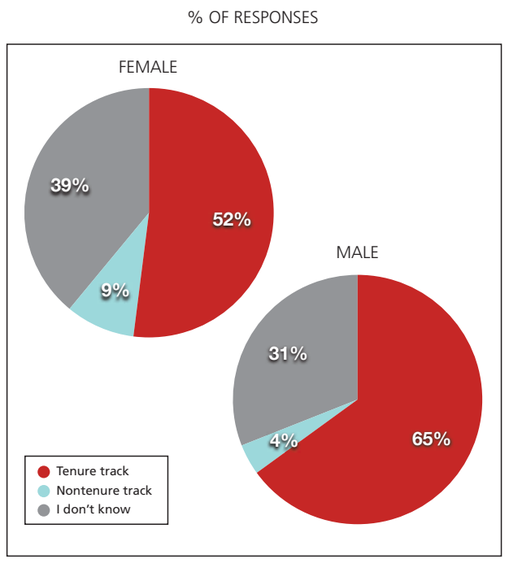
SOURCES OF NEGATIVE COMMENTS ALSO SIMILAR FOR BOTH GROUPS

Who made these comments?



WOMEN APPEAR LESS LIKELY TO CONSIDER PURSUING TENURE-TRACK POSITIONS, FOR TRAINEES

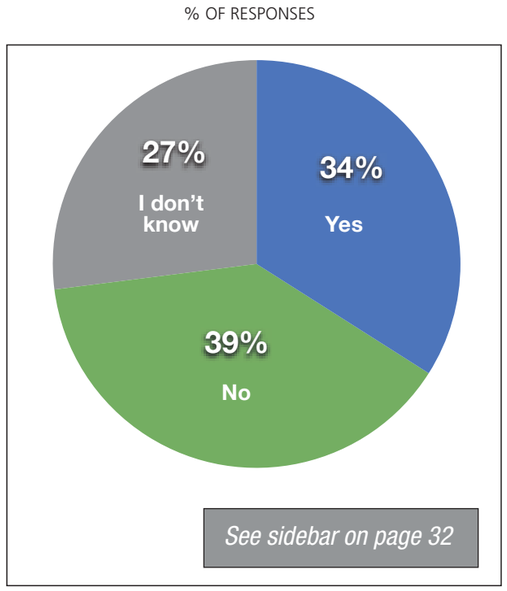
Do you plan to enter a tenure-track or nontenure-track position?



ONLY ONE-THIRD REPORT AVAILABILITY OF FORMAL MENTORING

Though more than a quarter don't know

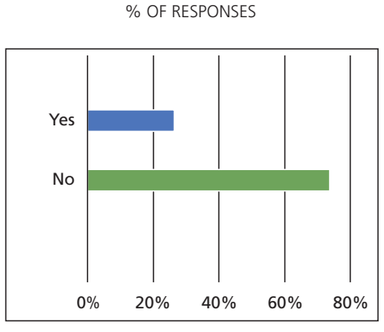
Is there a formal career-development, mentoring process at your organization?

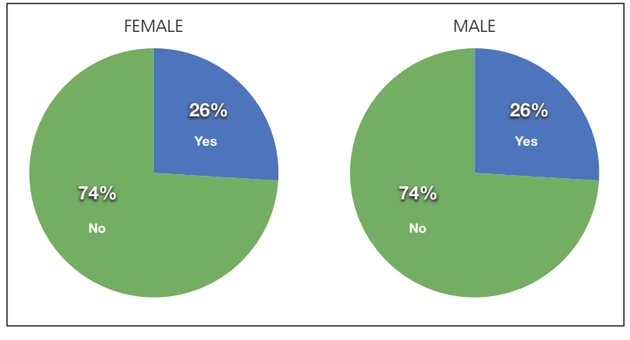


See sidebar on page 32

ULTIMATELY, JUST MORE THAN ONE-QUARTER OF BOTH MEN AND WOMEN CLAIM TO HAVE CAREER-DECISION REGRETS

Do you have any major regrets about the decisions you have made to date regarding your career in science?



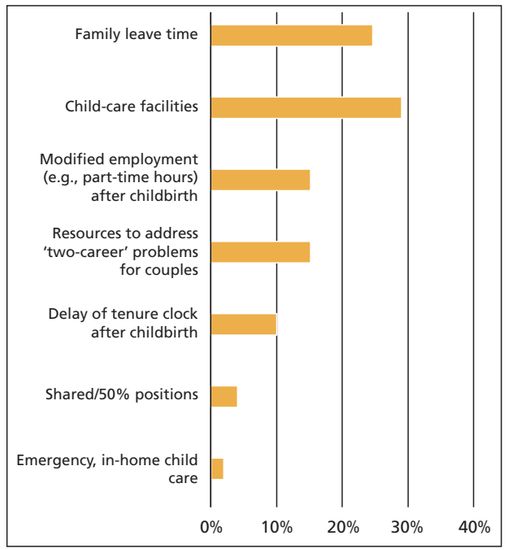


FAMILY LEAVE AND CHILD-CARE FACILITIES CITED AS MOST VALUABLE FAMILY-FRIENDLY POLICIES

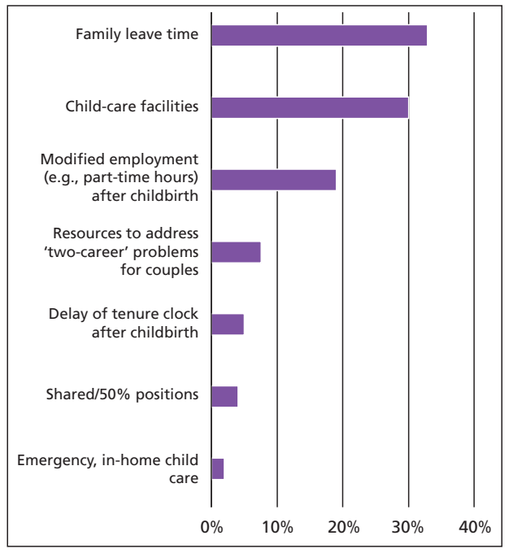
Women also cite two-career resources and delay of tenure clock after childbirth

Which of the family-friendly policies are/would be most valuable to you in supporting your career growth?

FEMALE - % OF RESPONDENTS RANKING TOP CHOICE



MALE - % OF RESPONDENTS RANKING TOP CHOICE

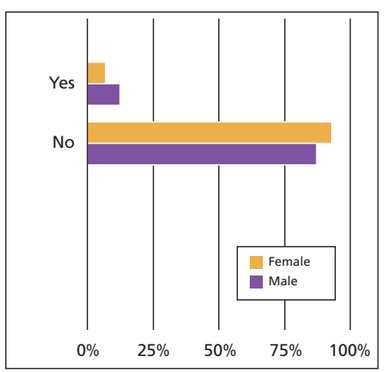


TENURE-TRACK DECISIONS, FOR TRAINEES

Women vs. men

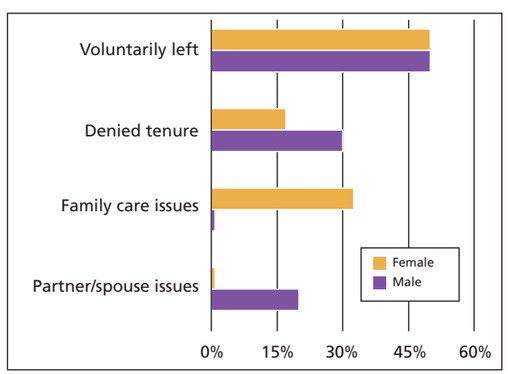
Did you ever hold a tenure-track position?

% OF RESPONSES



What caused you to leave the tenure-track? (For those once on it)

% OF RESPONSES

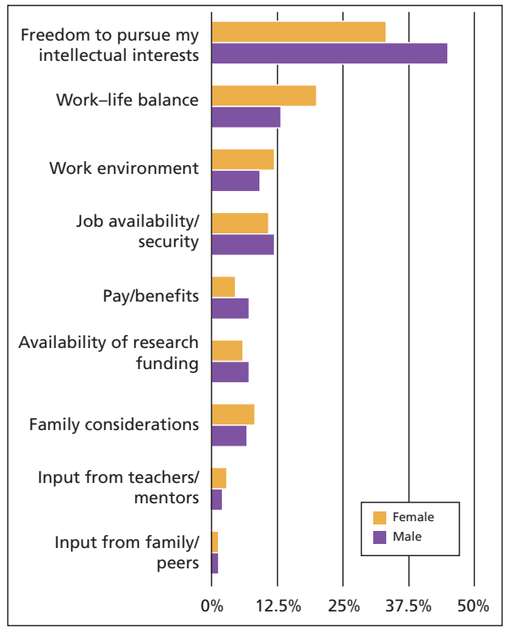


CAREER DECISION FACTORS

Women vs. men

Please rank the following factors based on their influence on your career decision-making process to date?

% RANKING TOP INFLUENCE

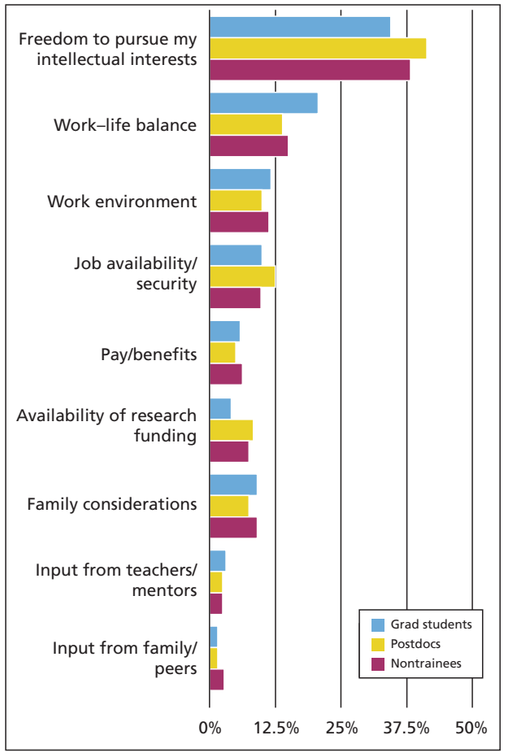


CAREER DECISION FACTORS

By position

Please rank the following factors based on their influence on your career decision-making process to date?

% RANKING TOP INFLUENCE



Biomed workforce recommendations

The Biomedical Workforce Working Group at the National Institutes of Health in June presented a report to the Advisory Committee to the Director detailing the state of the biomedical workforce and suggesting improvements to the education and compensation of trainees. On Dec. 6, the advisory committee made these recommendations to NIH Director Francis S. Collins:

- Implement a new type of grant award for institutions to develop innovative training approaches.
- Require individual professional development plans of graduate students and postdocs.
- Encourage institutions to limit the number of years a graduate student can be supported by NIH funds to five years.
- Increase annual postdoc pay from $39,000 to $42,000 as early as next year.
- Develop an example benefits package for postdocs that institutions could adopt.
- Increase the number of K99/R00 and Early Independence Awards that encourage career independence.
- Institutions are encouraged to track career outcomes of their graduate students and to publish this information for incoming students.
- Study sections should give fair consideration to grants that propose to pay staff scientists.

The NIH will give the community a brief period to comment on these recommendations. However, unless there is strong opposition to specific points, it is expected they all will be implemented in the near future.

Follow the ASBMB Policy Blotter at http://asbmbpolicy.wordpress.com/ to keep track of this and other important science policy issues.

– Chris Pickett

The merits of Google Plus

BY RAJINI RAO

Like many of my generation, I was introduced to the brave new world of social networking through my children. After the initial excitement of discovering long-lost college mates and cousins on Facebook died down, I became disenchanted with the realization that nothing more profound than one's breakfast bagel was on our collective minds. So when my daughter sent me a coveted invitation to the new Google Plus network during its beta stage, I dutifully opened a profile page fully expecting it to languish in the ether. Indeed, my children promptly abandoned the fledgling platform, but a chance encounter with a few science enthusiasts drew me back.

There is an insatiable appetite for quality science among the Google crowd, which is composed largely of tech-savvy and educated readers.

It turns out that Google Plus was designed to function more like Twitter but without the character limitation. This meant that one could broadcast short paragraphs of text (microblogs) paired with eye-catching images or movies on a public platform and acquire a following. I was asked to contribute to ScienceSunday, a Google page that was initiated by two academic scientists. That fateful first contribution unexpectedly turned out to be wildly popular: An animated image of the rotating ATP synthase accompanied by a short description of the mechanism made it to the top of Google's "What's Hot" list, where it was shared by thousands and inspired hundreds of comments and lively debate.

There is an insatiable appetite for quality science among the Google crowd, which is composed largely of tech-savvy and educated readers. I write about anything and everything that catches my interest: how a bee's foot fits snugly into the conical cells of a petunia flower buffeted by the wind, the optics of the compound eye or the gating mechanism of a potassium channel. I recruited one online volunteer to convert movies into attention-grabbing animated GIFs and another to pair science to music. Now I could explain the contractile spring of Vorticella in tune to "Maxwell's Silver Hammer" by the Beatles or showcase the molecular dance of the Ca^{2+}-ATPase with its uncanny resemblance to a couple doing the tango. I try to keep the science real and the language simple without sacrificing the hard numbers by leavening what I write with a generous dose of humor. I joined the curating team that has now expanded to five academic scientists ranging from a college dean to postdoctoral fellows. Today, ScienceSunday is a worldwide weekly event that reliably trends on Google Plus, with thousands of searchable posts tagged with the #sciencesunday hashtag.

The impetus to find and recommend other fellow scientists to follow on social networks led to Science on Google Plus: A Public Database. There, we compile and curate profiles by scientific discipline and promote shared circles ranging from anthropologists to astronomers, mathematicians and neuroscientists along with hundreds of promotional pages for scientific societies and organizations. A popular post on famous female scientists inspired another young scientist to set up a database showcasing STEM Women on Google Plus. More recently, we have been hosting Hangouts on Air, archived on YouTube, where we discuss current scientific events or critique influential papers, such as the largely debunked study linking genetically modified corn to cancer. All this has caught the attention of Google Plus administrators, who have offered us technical assistance and publicity for our science outreach efforts. If you have a taste for science evangelism, do join me on Google Plus!

Rajini Rao is a professor at the Johns Hopkins University School of Medicine and a Journal of Biological Chemistry editorial board member. Follow her on Twitter at www.twitter.com/madamscientist, read her blog at http://madamescientist.wordpress.com, and check out her posts on Google Plus at http://bit.ly/M3r5bY.

Vytas Bankaitis

New director of the Lipid Research Division

BY DANIEL RABEN

Like everyone, I occasionally get the opportunity to write about something that is exciting flavored with a little nostalgia. For me, this opportunity presents itself as I write to tell you about stepping down as director of the American Society for Biochemistry and Molecular Biology Lipid Research Division while introducing our new director. Stepping down is definitely filled with mixed emotion. Yet I'm incredibly excited that Vytas (Vyto) Bankaitis has agreed to take the reins.

The LRD began over breakfast. Yes, it was a breakfast conversation with a number of our colleagues from different lipid fields. What came out of that conversation was a desire to do something that would solidify our community and provide a forum that would help support our common aspirations. After discussing this with a wide number of lipidologists, we began toying with the idea of starting an independent lipid society, which would have been a daunting task indeed. Fortunately, Greg Petsko, president of the ASBMB at the time, encouraged us to organize under the auspices of the ASBMB. I can't tell you how lucky we were to do just that. Executive Director Barbara Gordon and her staff at the ASBMB were, and are, incredible. Launching the society with the ASBMB infrastructure was not only efficient, but it was fun and rewarding.

The LRD, the first division within the ASBMB, is now well established. We have more than 500 member lipid biochemists, chemists, biologists and biophysicists. We have representation on the ASBMB Meetings Committee, contribute a monthly article in ASBMB Today and maintain an LRD website known as the Lipid Corner (http://www.asbmb.org/lipidcorner/). Most importantly, we have begun our efforts to address funding problems lipid researchers face at a variety of agencies with a focus on the National Institutes of Health. In fact, this is one of Vyto's major objectives, and he plans on taking advantage of the expertise of Ben Corb, the ASBMB's public affairs director.

Vyto Bankaitis

Vyto is the E. L. Wehner-Welch Foundation chair in chemistry at the Texas A&M University Health Science Center Department of Molecular and Cellular Medicine in College Station, Texas. He has been involved in lipid research for more than 20 years and has made seminal contributions to the field. They are too numerous to list in this article, but his contributions have greatly advanced our understanding of the biology and biochemistry of phospholipid transfer proteins. Vyto has focused much of his studies on the phosphatidylinositol/phosphatidylcholine transfer proteins, or PITPs. His work has led to new insights regarding the mechanism of lipid-driven metabolic reactions and intracellular signaling pathways in both yeast and mammals.

Most of us who know Vyto are fully confident of one thing: Enthusiasm, energy and creativity will be not be in short supply at the LRD leadership. Vyto has a strong dedication to lipid research and lipid researchers. He is full of ideas and has the skills and energy to accomplish his goals. He already has begun to plan how to move the LRD forward. I will let him write to outline his goals and hopes, but I'm looking forward to the next three years with great excitement.

Daniel Raben (draben@jhmi.edu) is director of the ASBMB Lipid Division and a professor in the department of biological chemistry at the Johns Hopkins University School of Medicine.

A Café Scientifique program for teens

BY MICHELLE HALL AND MICHAEL MAYHEW

How do you capture the attention of teenagers in an age of Facebook, YouTube and iPhones? Given the scientific and technical underpinnings of these 21st century phenomena, it would seem self-evident that science would naturally appeal to teenage minds. Unfortunately, experience shows that teenagers have a limited interest in, and understanding of, the nature of science and the fruits it bears beyond what they learn in school. As scientists and educators, we were motivated to reignite interest in science among teenage audiences by rekindling their curiosity and ability to ask, "Why?" Our solution was to found a science café program for teenagers: Café Scientifique New Mexico.

In 2007, we attended a presentation by Duncan Dallas, an Englishman who had initiated the Café Scientifique model for engaging the lay public in dialogue on science topics. At the time, these programs were rapidly proliferating across North America and elsewhere in the world because of their great success in bringing scientific concepts to the general public. The concept of hosting an informal (but legitimate) scientific presentation while allowing for socializing with peers over refreshments made the Café Scientifique model extremely popular with adults. Listening to the presentation, we were struck by an exciting thought: Could we successfully adapt the Café Scientifique model to serve teens?

Thus was born the Café Scientifique New Mexico. After obtaining funding from the National Science Foundation, we started up the program in 2008 in four host towns of diverse character in northern New Mexico: Los Alamos, Española, Santa Fe and Albuquerque. We began our work with some trepidation: What if we built it and they didn't come? Thankfully, the program has been successful well beyond our initial hopes, proving highly popular with teens as it enters its sixth season. We now have a well-tested and refined model for teen cafés, and as a result we have just received further funding from the NSF to propagate the model at partner sites throughout the United States.

Elements for success

Any organization should be able to start up and operate a teen program by adhering to a number of essential principles:

- **Teen leadership and ownership:** We regard this as one of the key secrets of success. The teens need to feel that it is their program. By building a strong cadre of youth leaders who both guide and help implement programming, the teen cafés have been able to maintain high levels of success.
- **Presentations:** A Café Scientifique program for teens cannot be a lecture series. Sessions need to be highly interactive, must engage teens directly, and have to be pitched at teens' level and stimulate their curiosity. Scientists are vetted and subjected to a practice run with youth leaders before giving their presentations.
- **Institutional relationships:** It is important to develop relationships with a range of institutions that encourage their scientists to participate and to develop personal relationships with individual scientists within these organizations. It is by word of mouth that we get our best referrals of skilled public speakers.
- **Local hero:** A teen café program will require significant organizational and logistical support. There is no substitute for a local hero with the energy and commitment to make the program work smoothly.

- **Teachers:** Relationships with teachers in the high schools are highly beneficial. Teachers can champion the program with their students and encourage them to attend café sessions, while some may allow presentations about the program in their classrooms.
- **Good venues:** The venue must be centrally located and easy to get to. It must be conducive to social interaction and discussion, movement among groups and hands-on activities. Schools are generally to be avoided; teens typically enjoy learning about a science topic so long as it is in an out-of-school setting.

Everyone benefits

Our goals for Café Scientifique New Mexico were for teens to

- acquire a richer, more nuanced understanding of the nature of science,
- come to see scientists as real people leading interesting lives,
- get a better appreciation of the relevance of science to their daily lives,
- acquire increased science literacy concerning current issues in science,
- consider the possibility of a life in science for themselves, and
- develop skills and attitudes for lifelong learning in science.

Our formal evaluations demonstrate that the program has indeed met these goals, positively influencing participating teens' attitudes toward science and their view of the importance of science to their lives. It has increased their understanding of the nature of scientific research, understanding of science issues in the news, and ability to use facts to support scientific points of view. Moreover, teens themselves say that the program has helped them make connections between school and the real world of science research. "Since the Café, I see science everywhere, at the store, on the street, in the park," reported one attendee.

There also has been significant benefit to the presenters, who have uniformly considered their participation in the program to be enjoyable and of personal benefit. One presenter told us that preparing his presentation "forced me to focus on the really basic elements of my research and how to communicate them." Similarly, another felt participating had helped her to "identify the critical issues in my work: why I was doing it, why it is challenging, what we are trying to accomplish."

Best of all, the Teen Café Scientifique program continually renews our own curiosity and keeps us wondering about the nature of so many interesting things.

Michelle Hall and Michael Mayhew are the directors of Café Scientifique New Mexico (cafenm.org) and the Teen Science Café Network at Science Education Solutions (scieds.com) in Los Alamos, N.M.

A wake-up call on mentoring

BY FRED MAXFIELD

In a recent American Society for Biochemistry and Molecular Biology survey of biochemists and molecular biologists in the early stages of their careers, nearly 40 percent reported that they were unsatisfied or very unsatisfied with the career mentoring they had received. In contrast, a strong majority were satisfied or very satisfied with their scientific mentoring.

The survey was conducted by the society's Task Force on Women in Academia, and it was aimed mainly at gathering information about how trainees and people in early stages of their careers make decisions. A report of the results of the survey, including the enthusiastic commitment of young biochemists and molecular biologists to science, is on page 22 of this issue. Mentoring was not a major focus of the survey, but many of the task force members, including me, were struck by the negative review of career mentoring by so many trainees (both male and female).

In addition to the quantitative assessments, the survey asked for comments on some questions. (A few examples of positive and negative comments about sources of career mentoring are shown in an accompanying box.)

The comments provide some insight into why many trainees are disappointed in the quality of career mentoring. The career expectations for young biochemists and molecular biologists are inevitably affected by the current economic and funding climate. Many of today's mentors were trained at a time when the federal science budget was expanding. Medical schools, universities and research institutes were growing, and there was a strong demand for newly trained scientists. In addition, large pharmaceutical companies were expanding their internal research programs, and biotech startup companies were hiring large numbers of young scientists. In such an environment, trainees with good scientific track records had excellent chances of obtaining reasonable jobs. Mentoring was mainly training in how to do science. Mentors and their institutions did not have a strong incentive to provide career counseling, because many people were finding good jobs. I think that very few of my peers at academic medical centers or research universities would say that they ever received much career counseling. What we did receive was guidance in how to conduct science, and apparently today's trainees feel that on average we are still doing a fairly good job of passing on that knowledge. However, in today's world that is not enough.

There are not nearly enough high-quality academic and purely scientific job openings to accommodate the people who are finishing Ph.D.s and postdoctoral training. Mentors and their institutions need to develop ways to provide alternate career counseling. Academic mentors themselves may have limited capabilities, because many of us have worked only in academia or other research laboratories. Nevertheless, we can sit down with our trainees and listen carefully to their thoughts about career options. We also owe it to them to provide honest evaluations of their prospects for various types of jobs. In my own experience, this means that sometimes I may need to be a cheerleader for someone who has extraordinary skills but may lack the self-confidence to push for the top research positions. On the other hand, I have sometimes had discussions in which I suggested that individuals seek

Continued on page 36

BOTH WOMEN AND MEN CITE GRADUATE AND UNDERGRADUATE ADVISERS AS MOST INFLUENTIAL

Which of the following sources of mentorship have been most influential in your career decisions?

% RANKING TOP INFLUENCE

	FEMALE	MALE
Graduate adviser	31%	30%
Undergraduate teacher/adviser	22%	21%
Current PI (if different from graduate adviser)	11%	12%
Current supervisor	8%	11%
Thesis committee member	3%	3%
Off-campus mentor	5%	4%
Other on-campus mentor	3%	3%
Career development office	3%	2%
Career fair	2%	1%
Other	12%	14%

SURVIVING GRADUATE SCHOOL

Things to look for in a thesis adviser

BY PETER J. KENNELLY

On the scale of human interactions, the relationship between a graduate student and his or her thesis adviser (a.k.a. major professor) lies somewhere between that of roommates locked into a long-term lease and a marriage. Finding a good match among the faculty typically is the single most important determinant of the quality of a graduate-school experience. It is therefore critical that entering students get to work early and diligently to learn all they can not only about potential mentors and their research programs but about themselves.

Ask the following questions:

- Is this potential adviser someone you respect, someone you would like to model yourself after?
- Where are the potential adviser's former students? Do they tend to transition to the types of postgraduate and professional opportunities that appeal to you?
- What kinds of skills are you likely to develop in this lab?
- Do students from this lab get their work published in quality journals?
- What is the lab group like? Are they hard-working and enthusiastic? Do they get along with one another?
- What do you need from a mentor? What are your strengths and weaknesses?
- Are you likely to respond well to this person's particular training and managerial style?

Notice that the list does not ask questions about the potential adviser's area of research. The biggest mistake a student can make in selecting a major professor is ignoring the signs of a potentially poor match because he or she is enamored of the faculty member's area of research. A research project is a tool, a vehicle for transforming curious and committed students into capable, independent research scientists whose skills are translatable and evolving. As long as a student finds a project interesting and challenging, labels matter little in the long run.

A student–mentor relationship based on mutual respect, good communication and shared expectations offers a richness and depth that will animate your entire career.

Peter J. Kennelly (pjkennel@vt.edu) is a professor and the head of the department of biochemistry at Virginia Polytechnic Institute and State University and chairman of the ASBMB Education and Professional Development Committee.

jbc THE JOURNAL OF BIOLOGICAL CHEMISTRY

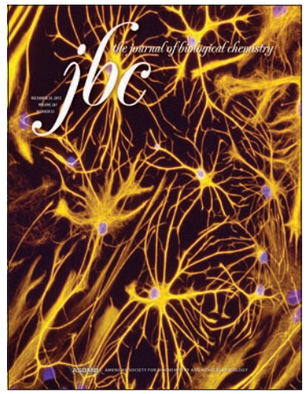
Thematic minireview series commemorates the discovery of the cys-loop ligand-gated ion channel superfamily

BY DANIELLE GUTIERREZ

It has been 25 years since the identification of two proteins that facilitate communication between nerve cells — a significant achievement that revealed a group of related proteins. In recognition of this advancement, the Journal of Biological Chemistry has published a series of articles that assess what we know about each family member in this group and where that research is headed.

This superfamily was recognized in 1987 with the discoveries of the genes that encode two of its members, the $GABA_A$ and glycine receptors, and of the similarity of these proteins to the first characterized family of this group, the nicotinic acetylcholine receptors. F. Anne Stephenson of the University College London School of Pharmacy, an author on one of the two 1987 articles, explains that these findings, in addition to revealing the new superfamily, led to the discovery of multiple protein subtypes within each family. Since that time, two additional protein families have been added to the group — the serotonin-3 receptors and the glutamate-gated chloride ion channels.

Proteins in this group, known as the cys-loop ligand-gated ion channel superfamily, are targeted by neurotransmitters to allow the passage of ions across cell membranes, ultimately affecting functions such as muscle contraction, anxiety, pain, vision, and food digestion and passage. For example, mutations in $GABA_A$ receptor subunits are involved in some forms of epilepsy. Also, certain antianxiety drugs target these receptors, and drugs that affect serotonin-3 receptors treat irritable bowel syndrome and the nausea and vomiting associated with chemotherapy.



The JBC series chronicles the history of this field, highlighting the many advances that scientists have made over the past 25 years. Each review focuses on a different member of the group, covering its structure, regulation and functions. The roles of some of these proteins in diseases and therapeutics are also discussed.

Jean-Pierre Changeux reviews nicotinic acetylcholine receptors in "The nicotinic acetylcholine receptor: the founding father of the pentameric ligand-gated ion channel superfamily." The nicotinic acetylcholine receptor was the first neurotransmitter receptor identified, and Changeux discusses the major breakthroughs that led to the achievement — the acquisition of single cells from the electric organ of the electric eel, advances in membrane fragment purification, the discovery of toxins that bound to the receptor and could be used with affinity chromatography to purify the receptor, the preparation of membranes from the electric ray that were rich in the receptor, and the investigation of the receptor's structure by electron microscopy. The author also reviews the receptor subunits, acetylcholine binding sites, the channel opening mechanism and binding sites for regulatory molecules.

Erwin Sigel and Michael Steinmann focus on $GABA_A$ receptors in "Structure, function and modulation of $GABA_A$ receptors." The review emphasizes the complexity of $GABA_A$ receptors, which are formed by five subunits that enclose a chloride ion channel. For example, the authors note that 19 subunit isoforms exist, with expression patterns varying broadly — some are extensively expressed in the central nervous system, and others are limited to specific cell types or tissues. Additionally, the authors discuss $GABA_A$ regulation through post-translational modification, receptor associated proteins, endogenous compounds and exogenous small molecules. The authors conclude with a discussion of topics for future research.

Sébastien Dutertre, Cord-Michael Becker and Heinrich Betz cover glycine receptors in "Inhibitory glycine receptors: an update." The authors discuss the structure of glycine receptors and their subunits and the binding sites of agonists, antagonists and allosteric modulators. They also review the various isoforms of glycine receptors, which differ in expression in embryos and adults. Many mutations of glycine receptors lead to hyperekplexia (commonly called startle disease), and the authors discuss the role of some of these mutations in preventing proper glycine signaling.

Adrian Wolstenholme discusses glutamate-gated chloride channels — receptors that are similar to mammalian glycine receptors but that are unique to protostome invertebrates. The author describes the structure of these receptors — noting that this was the first eukaryotic ligand-gated anion channel for which a three-dimensional structure was determined — and reviews the roles of these receptors, such as regulating movement, feeding and sensory information. The review highlights the economic and therapeutic significance of these receptors, which are targets of certain pesticides and of parasite-removing drugs.

Sarah Lummis reviews serotonin-3 receptors, starting with the discovery of this receptor family. The author discusses the receptor structure and five known receptor subunits. The review explains how serotonin-3 receptors function and the roles that these receptors play, for example, in regulating intestinal movement. While there are currently serotonin-3 targeting drugs for the treatment of conditions such as irritable bowel syndrome and chemotherapy-induced nausea, the author notes that further understanding of receptor subunits C through E may lead to treatment for a variety of diseases, such as migraines, bulimia and psychosis.

Since 1987, scientists have overcome major challenges and learned where particular protein subtypes of a family are located and what functions they perform. Stephenson emphasizes that the advancements in this field were a boost for the pharmaceutical industry in terms of finding selective drugs that lack undesirable side effects, such as nonsedating antianxiety drugs, which act on a particular subtype of $GABA_A$ receptors.

The JBC series was convened by Stephenson, who today is an associate editor of the journal and whose lab continues to investigate the structures and functions of neurotransmitter receptors, including the $GABA_A$ receptors, in health and disease.

Danielle Gutierrez (daniellebgutierrez@gmail.com) a freelance science writer based in Corpus Christi, Texas.

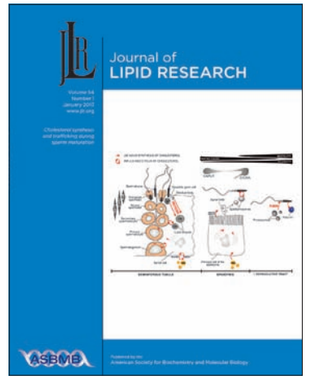
JLR THE JOURNAL OF LIPID RESEARCH

Role of sterols in the formation and function of sperm

BY RAJENDRANI MUKHOPADHYAY

The formation of mammalian sperm involves a complex developmental process. In a recent review in the Journal of Lipid Research, Simon Horvat at the University of Ljubljana in Slovenia and colleagues discuss the dramatic changes that take place in membrane lipid composition during spermatogenesis.

In particular, the authors focus on cholesterol and its intermediates. They describe sterol dynamics in sperm maturation and explain recent technical advances that could help researchers understand the complex process of sperm formation and function.



Cholesterol and its intermediates are one class of molecules whose content greatly differs between the cells of the male reproductive system and cells of nonreproductive systems. For example, in several mammalian species, cholesterol precursors, such as the testis meiosis-activating sterol and desmosterol, have been observed to accumulate in spermatozoa and testes but not in nongonadal cells.

The enzymes involved in production of sterols in the male reproductive system, such as the cytochrome P450 lanosterol 14α-demethylase, show stage-specific expression patterns during the formation of sperm. Studies have indicated there is complex time- and cell-specific regulation of sterol-compound production during spermatogenesis.

Sterols are also involved in sperm transport. Studies have shown that the epididymal transit of sperm and their movement through the female reproductive tract involves changes in the sterol composition in the spermatozoal membrane that are needed for successful fertilization. Despite all the evidence pointing toward the importance of cholesterol and its intermediates in sperm formation and function, Horvat and colleagues note that the exact role of sterols in the male reproduction system is still unclear.

Rajendrani Mukhopadhyay (rmukhopadhyay@asbmb.org) is the senior science writer for ASBMB Today and the technical editor for the Journal of Biological Chemistry. Follow her on Twitter at www.twitter.com/rajmukhop.

MCP MOLECULAR & CELLULAR PROTEOMICS

Metabolic profile of clinical depression

BY RAJENDRANI MUKHOPADHYAY

Clinical depression, also known as major depressive disorder, robs its victims of interest and pleasure, sleep, appetite

Continued on page 36

Continued from page 32

alternative career tracks. I have seen some of these people years later and found that they were pleased with their careers as entrepreneurs, administrators, consultants or patent lawyers. Those are all good career options.

Given that mentors cannot be experts in providing good advice about all possible careers, trainees need other sources of advice. Research institutions need to do a better job addressing these issues. In the survey of trainees, only one-third of respondents were aware of career-training programs at their institutions. Some positive examples of how to provide training were included in the comments.

There are many resources available for individuals and institutions interested in obtaining or providing career advice. A good starting point is the Career Resources link in the ASBMB web site: http://www.asbmb.org/Page.aspx?id=264. Another good source is http://myidp.sciencecareers.org, which was developed by the Federation of American Societies for Experimental Biology, the Medical College of Wisconsin, the University of California–San Francisco, the American Association for the Advancement of Science, and Science Careers with support from the Burroughs Wellcome Fund.

It is essential that we address this problem if we are going to attract the best students into biomedical sciences in the future. We need to do much better than the current level of career counseling.

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Feedback

Comments from survey respondents, edited for clarity and style.

- *One of our faculty members regularly holds seminars on career choices for Ph.D. graduates, inviting successful Ph.D.s who took alternative careers.*
- *Seminars on industry and potential occupations for Ph.D. scientists were highly influential. Peers, friends and colleagues (though not necessarily mentors) were highly influential.*
- *We don't have anyone helping us to figure out what to pursue once we get our degrees.*
- *I feel that, for nonresearch-based academia or industry positions, I have received no career mentorship. Anything besides R01 research is a dirty word.*
- *I feel like I was left floundering to figure everything out on my own. The academic assumption is that you'll follow the standard path for tenure-track professorship, even though this is incredibly impractical for most people these days. Other options are barely discussed and, if discussed, looked down on.*

Continued from page 35

and concentration. Clinically depressed people also suffer from excessive fatigue and dark thoughts. The illness is a major cause of disability, suicide and physical problems. However, a diagnosis for the illness is based on psychiatric reviews, which can be subjective. In a paper in Molecular & Cellular Proteomics, Chinese researchers described a test that could objectively diagnose the illness.

Depression is a complex mental disorder. The disease diagnosis is subjective because it can present a number of different symptoms and the exact causes of it are not understood. "Despite overwhelming efforts to identify the biomarkers for MDD, there were still no empirical laboratory tests available to diagnose MDD," says Peng Xie of Chongqing Medical University, who was the senior author on the MCP paper, adding that the current subjective diagnosis process has a considerable error rate.

The researchers decided to analyze urine, a sample that can be collected easily, for metabolites that could act as markers for depression. By using nuclear magnetic resonance spectroscopy, they were able to identify five molecules in urine that together seemed to sort out people who suffered from depression from those who didn't.

The molecules were malonate, formate, N-methylnicotinamide, m-hydroxyphenylacetate and alanine. Malonate and formate are primarily involved in energy metabolism, m-hydroxyphenylacetate has a role in gut microbial metabolism, and N-methylnicotinamide affects tryptophan-nicotinic acid metabolism. Alanine is one of the 20 amino acids used to make proteins. Xie says, "Based on the previous clinical and basic studies, we suggest that disturbances of these metabolic pathways are implicated in the development of MDD."

Xie says the researchers zoomed in on a few metabolites as markers because, in clinical practice, it is not convenient or economically feasible to measure simultaneously a large number of metabolites for diagnosis. The current work is a proof-of-concept and opens up more avenues of investigation. Xie says, for one, the researchers would like to collect urine samples from depression patients and healthy controls from more ethnically diverse populations to validate further the diagnostic performance of the five metabolites. They also would like to dig deeper into the underlying metabolic pathways of these five molecules to see if they can uncover how these biochemical pathways play into the disease.

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HOUSING

DEADLINE: March 22, 2013

THEMATIC SESSIONS

Catalytic Mechanisms

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SPECIAL EVENTS

Professional Development for Graduate/Postdoctoral Trainees
Saturday, April 20

ASBMB Opening Reception
Saturday, April 20, immediately follows the Opening Lecture

Undergraduate Orientation: A Student's Guide to the ASBMB Annual Meeting
Saturday, April 20

17th Annual Undergraduate Student Research Poster Competition
Saturday, April 20

Beyond College: Coping with Some Common Challenges
Undergraduate workshop, Saturday, April 20

Undergraduate Breakfast with ASBMB Award Winners
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ASBMB Welcome and Networking Reception
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Monday, April 22

ASBMB Women Scientists Networking Event
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Y.E.S. Mixer (Young Experimental Scientists)
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