Perspectives on Physiology and Medicine from Nobel Prize Winners: The 64th Lindau Nobel Laureate Meeting

"Educate. Inspire. Connect." Those are the missions of the annual Lindau Nobel Laureate Meeting. Since 1951, Nobel laureates have gathered in the picturesque town of Lindau, Germany, to discuss science. Starting in 1953, the meetings incorporated young scientists from across the world to instill in them enthusiasm for and knowledge of science, while also providing an atmosphere for collaboration. From 29 June to 4 July 2014, approximately 600 young scientists representing nearly 80 countries gathered in this small town on the shores of Lake Constance and in view of the snow-capped Swiss Alps to directly interact with 37 Nobel laureates. Given this year's theme of Physiology and Medicine, it was a great privilege to attend this meeting as a young dermatologic investigator. Although it was a general scientific meeting, many of the insights into research, publication, funding, and professional development offered by the Nobel laureates are relevant to dermatology. My goal in this Editorial is to share these insights and to increase awareness of this unique scientific meeting.

The immune system

The immune system underlies many dermatologic diseases. Jules Hoffmann (2011 Nobel Prize in Physiology or Medicine) described his research on the activation of innate immunity in insects, which led to the discovery of the *Toll* gene and how recognition of fungi and Gram-positive bacteria generates host antimicrobial defenses. He further examined the role of the Drosophila immune deficiency pathway in recognizing Gram-negative bacteria. He explained that the hallmark of the two pathways is activation of NF-κB followed by control of gene expression. His career studying insects was influenced by two observations: insects represent 80% of living species and insects are resistant to infection.

Bruce Beutler, who shared the Nobel Prize with Hoffmann, detailed how his work on lipopolysaccharide led to the identification of its receptor, Toll-like receptor 4, as a sensor for mammalian microbial infection. He then described his current research using "forward genetics": he generates numerous random mutations in mice to create a phenotype of deficient or altered immune system function and then works to elucidate the molecular basis of the phenotype. His goal is to understand all genes needed for proper immune function.

Robert Huber (1988 Nobel Prize in Chemistry) discussed the structure and function of the proteasome in protein degradation, focusing on the immunoproteasome. Characterized by incorporation of inducible factors LMP2, MECL-1, and LMP7, the immunoproteasome is increasingly becoming a target for drug inhibition. For example, LMP7 inhibitors have decreased differentiation of T helper cell types 1 and 17 in experimental autoimmune encephalomyelitis and are being studied in a mouse model of multiple sclerosis.

Infectious disease

Hand in hand with the immune system are infectious agents. HIV and tuberculosis were two hot topics addressed by several Nobel laureates, with a strong emphasis placed on the need for drug development for both diseases. Françoise Barré-Sinoussi (2008 Nobel Prize in Physiology or Medicine) recounted her background in retroviruses and the opportunity this training afforded her when discovering HIV as a cause of AIDS. She stressed the importance of investigating the mechanisms by which HIV persists in the human body and the reservoirs it uses. Rolf Zinkernagel (1996 Nobel Prize in Physiology or Medicine)

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translated his experience studying cytotoxic T-cell recognition of infected cells into a hypothesis as to why vaccines against HIV or tuberculosis are difficult to achieve. He challenged our understanding of "immunologic memory" and discussed the important role of preexisting neutralizing antibodies and preactivated T cells in robust immunity.

Barry Marshall (2005 Nobel Prize in Physiology or Medicine) entertained attendees with his research on *Helicobacter pylori* and its link to gastritis and peptic ulcer disease. After recounting self-administration of *H. pylori* to aid in his discovery, Marshall reminded young researchers of the importance of internal review boards and the safety protocols they establish. Connecting the immune system with infectious disease and dermatology, Marshall discussed evidence suggesting that childhood infection with *H. pylori* protects against atopic diseases, including asthma and atopic dermatitis. He believes that more research into a possible link between *H. pylori* and regulation of the immune system in atopy is needed; a recent longitudinal birth cohort study supports this association (Amberbir *et al*., 2014).

Hamilton Smith (1978 Nobel Prize in Physiology or Medicine) discovered type II restriction enzymes, but lectured on his fascinating work in the field of "synthetic biology." He is creating an engineered *Mycoplasma* organism by chemically synthesizing a genome reduced to only its essential genes. Peter Agre (2003 Nobel Prize in Chemistry) described his personal development as an investigator and his discovery of aquaporins. Aquaporin research ultimately led him to study malaria, a parasitic disease for which Agre emphasized the need for more investigation and drug development.

Cancer

Several Nobel laureates discussed their research on various types of cancer. J. Michael Bishop (1989 Nobel Prize in Physiology or Medicine) outlined how the malfunction of genes leads to cancer through gain-of-function (protooncogene) or loss-of-function (tumor suppressor genes) mutations. He provided a history of several milestones in cancer research, including Ernest Kennaway's identification of carcinogens in coal tar and James Cleaver's work showing that deficiencies in DNA-repair enzymes underlie the accumulation of UV-induced DNA damage in xeroderma pigmentosum. Bishop was driven by the question of how Rous sarcoma virus transformed cells, leading to the observation that viral DNA can be integrated into the host cell.

Because dermatologists face the consequences of human papillomavirus (HPV) infection every day in the clinic, the discussion by Harald zur Hausen (2008 Nobel Prize in Physiology or Medicine) of the role of HPV infection in cervical cancer as well as the impact HPV vaccines will play in decreasing HPV-induced disease was of particular interest. For dermatologists, these vaccines will be beneficial in both male and female populations for reducing genital warts and cancers. Martin Evans (2007 Nobel Prize in Physiology or Medicine) described work on malignant cells, particularly mouse teratocarcinomas, which led to an excellent system for identifying and isolating embryonic stem cells.

Elizabeth Blackburn (2009 Nobel Prize in Physiology or Medicine) approached cancer from the "end," describing her discovery of telomerase in maintaining telomeres. Telomerase mutations are associated with dyskeratosis congenita, and Blackburn emphasized that, whereas some cancers have too little telomerase activity, melanoma can have too much. About 400 genes contribute to the balance of telomere length, with telomerase levels being crucial. Her recent work on the epidemiology of telomere length has yielded interesting observations, including a dose-dependent reduction of telomere length in smokers and a direct correlation between level of education and longer telomeres.

Translational research

This year's lectures unintentionally developed a recurrent theme: translate basic science discoveries into either applications or medical advances that benefit mankind. Ironically, the Nobel laureates emphasized the need for more basic-science research and encouraged young researchers to tackle fundamental problems. Yet the amount of translational research being conducted by these scientists led me to conclude, "Excellent science will itself generate opportunities for translational applications." Thomas Steitz and Ada Yonath (2009 Nobel Prize in Chemistry) exemplified this notion because their years of fundamental structural studies of the ribosome are now a platform for the development of new antimicrobial agents and understanding antibiotic resistance. Aptly, the final panel discussion was entitled "Science for the Benefit of Mankind."

Publication and funding

All the Nobel laureates agreed on the current state of publication and funding mechanisms in science—namely, they think major reform is needed. Randy Schekman (2013 Nobel Prize in Physiology or Medicine) stressed to young researchers that it is the quality of the science that matters, not impact factor or journal title. He, along with many others, believes that the impact factor is a flawed metric that "devalues scholarly achievement" and receives improper emphasis in the funding process. Schekman encouraged all researchers to read and sign the "San Francisco Declaration on Research Assessment," available online (http://am.ascb.org/dora). Interestingly, many of the Nobel laureates had saved old rejection letters from various journals and showed them at the meeting, the point being that their own groundbreaking research was at times rejected or dismissed. They offered this as encouragement to young researchers that, in time, excellent science prevails.

Career development

The goal of the Lindau Nobel Laureate Meeting is to inspire young scientists from across the world; with that inspiration comes much-needed practical advice for those beginning their careers. Oliver Smithies (2007 Nobel Prize in Physiology or Medicine) offered five basic pearls of wisdom for young researchers: (i) choose excellent mentors; (ii) read, read, and read some more; (iii) enjoy what you do ("It is pointless to do something you don't enjoy"); (iv) learn to do "good science" first, because this matters more than *what* you do; and (v) share willingly.