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SYMPOSIUM

The Importance of Student Initiative Both In and Out of The Lab

The Second Immunobiology Student Symposium

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In September 2013, graduate students from the Yale Immunobiology Department hosted the second Yale Immunobiology Student Symposium. It was an eclectic and thought-provoking event that encouraged scientists to think outside the box both in their research and in their endeavors outside of the laboratory. The speakers ranged from a government representative to a *New York Times* science journalist and included four research scientists at the cutting-edge in their field. Speakers discussed their current research, from the role of our gut microbiota in causing colorectal cancers to the biochemical modifications in histone tails that give rise to our unique human biology. The overarching message was to let scientists, especially those of the younger generation, know how to approach, think, and talk about science.

INTRODUCTION

The Yale Department of Immunobiology introduced the first Yale Immunobiology Student Symposium in 2012. The second took place in September 2013. The unique characteristic of this annual symposium is that it is organized from start to finish entirely by graduate students in the Department of Immunobiology. The committee usually includes five to six students as well as a faculty advisor whose role predominantly consists of providing insight when asked by the students to do so. I was one of the five students who organized this year's symposium. It was an extremely challenging yet rewarding experience.

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†Abbreviations: NSF, National Science Foundation; STEM, Science, Technology, Engineering, and Mathematics; NSF BIO, NSF's Directorate for Biological Sciences; BioMaPs, biology, mathematics, the physical sciences, and engineering; SEES, science, engineering, and education for sustainability; AAAS, American Association for the Advancement of Science; IBD, inflammatory bowel diseases; MS, multiple sclerosis; PCR, polymeric chain reaction; ChIP-Seq, Chromatin immuno-precipitation sequencing; TAMs, tumor-associated macrophages; Ang II, Angiotensin II; S1P1, signaling molecule sphingosine-1-phosphate.

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The speakers for this year's symposium were Dr. Joann Roskoski, Deputy Assistant Director, National Science Foundation Directorate for Biological Sciences; Dr. David Hafler, Professor of Immunology and Neurobiology at Yale University; Dr. Wendy Garrett, Assistant Professor of Medicine, Immunology, and Infectious Disease at the Harvard Medical School; Dr. James Noonan, Associate Professor of Genetics at Yale Medical School; Dr. Mikael Pittet, Associate Professor of Radiology at Harvard University; and Carl Zimmer, *New York Times* science columnist. Each speaker presented the audience with a new way of looking at science, be it in the context of science policy, science writing, or scientific research.

GETTING INVOLVED IN SCIENCE POLICY

Dr. Roskoski from the National Science Foundation (NSF†) talked about the federal perspective toward fostering scientific progress and encouraging graduate students who do not feel particularly politically inclined or empowered to contribute to setting national science priorities. The first and most important point she highlighted was that when we talk about science policy, we really mean resources for research. As such, the NSF sets priorities that reflect in which areas they want to further invest. What stood out among this year's NSF priorities was a desire to engage with the technological advances in the field of scientific research, such as the impact of nanoparticles on the environment, and to foster innovations in translational sciences. Of note was the organization's goal to encourage citizenship development via enhancement of postgraduate programs and training future Science, Technology, Engineering, and Mathematics (STEM) teachers.

The major investments of the NSF's Directorate for Biological Sciences (NSF BIO) included "Five Grand Challenges" focusing on topics ranging from the role of genomes in phenomes — the collection of phenotypes at the different organizational levels in an organism [1] — to synthesizing life by looking at biological processes at the smallest scale. Also among these investments were projects aimed at better understanding the brain's inner intricacies, creating a platform for collaborations at the interface of biology, mathematics, the physical sciences, and engineering (BioMaPs), providing researchers with the technological tools they require (Cyberinfrastructure), as well as promoting the NSF's science, engineering, and education for sustainability (SEES) initiative.

Dr Roskoski not only presented how the NSF works — which committees do what and how they do it — but also introduced the idea that as scientists we have a great role to play in the public sphere by engaging with the government in a much more direct fashion. The basic requirements for this are to remain informed, engage in professional societies, organize for action (e.g., mentoring programs), and educate the public about "our" science. On top of that, the NSF provides several platforms for policy-enthused scientists to further develop their skills in this field by becoming Science and Technology Fellows. In addition, two seminal programs — the Presidential Management Fellows and the American Association for the Advancement of Science (AAAS) Science and Technology Policy Fellowships — provide the opportunity for accomplished scientists and engineers to participate and contribute to federal policymaking while learning firsthand about the crosstalk between science and government agencies. These programs have the goal to develop a cadre of potential astute government leaders well-versed in the sciences. Past the histrionics of Washington lies a whole field of opportunities for budding and established scientists to contribute to science policy and advocacy.

NURTURING NATURE — THE DIFFERENT LEVELS OF INVOLVEMENT OF ENVIRONMENTAL FACTORS IN DISEASE DEVELOPMENT

In the past decades, our understanding of the interplay between the environment

and our genetic makeup has greatly increased. We better understand how these interactions contribute to a number of physiological and immunological processes, including the development of cancers and autoimmune diseases. This theme was addressed in four talks with different contexts: Dr. Hafler talked about how a high salt diet can contribute to the development of autoimmune diseases by its impact on specific cell subpopulations of the immune system; Dr. Garrett illustrated how components of our gut microbiome can promote the development of colorectal cancer; Dr. Noonan explained how the interface between the environment and our DNA (i.e., the epigenome) plays an essential role in defining our human biology; and Dr. Pittet illustrated via breathtaking *in vivo* imaging data how the immune environment drives the production and migration of tumor-associated macrophages. What stood out was the originality and thought-provoking approaches these researchers adopted in order to tackle such complex topics.

High Salt Diets and the Development of Autoimmune Diseases

Several environmental factors can foster the development of autoimmune diseases. Recently, Dr. Hafler's group showed that high salt diets — preponderant in the West — play a particularly important role in priming the immune system in the development of autoimmunity [2]. In his talk, he presented data published in the journal *Nature*, in which his group showed that salt drives autoimmune diseases by the induction of pathogenic Th17 cells, which are a subset of T helper cells. Using both *in vitro* and *in vivo* experiments, they demonstrated that a high sodium chloride diet results in a high concentration of this mineral in the tissue interstitium. This leads to increased expression of IL-17A by naïve $CD4^+$ T cells in a dose-dependent fashion. This effect is specific to the sodium cation as experiments using other anions or cations did not yield the same results. Microarray analysis confirmed that the high salt environment resulted in a clear Th17 phenotype with signature Th17 cytokines being expressed by these cells (e.g., CCL20, RORC) as well as pro-inflammatory cytokines.

These data indicate that a high salt diet triggers the activation of pathogenic Th17 cells that are involved in autoimmune responses. It therefore seems that such a diet results in the induction of the inflammatory secretion program in response to high concentrations of the sodium chloride cation. In fact, genome-wide association studies have shown that salt-induced genes are enhanced in inflammatory bowel diseases (IBD) and multiple sclerosis (MS). Further results from the Hafler group should be published soon and promise to shed more light as to the precise immunological mechanisms involved in MS and, more generally, autoimmune diseases. What truly stands out from the research he presented was that his laboratory was able to dissect out the mechanisms underlying how salt can set the scene for the development of autoimmune diseases and the immune cell subpopulations at the center of this process.

The Role of the Host Microbiota in Disease

Dr. Garrett spoke about her research on the bacterial species that inhabit our intestines, also collectively known as our microbiome. Her research has two main themes: one is to identify the human colorectal cancer microbiomes and the other is to use mouse models to parse microbiota-immune interactions. Her group focuses more specifically on colorectal cancer. There are numerous well-established associations between microbes and cancer [3,4]. One means of identifying such associations is to mine cancer genomes from microbial signatures by deep-sequencing tissue samples from cancer patients. Using such an approach coupled to 16S rRNA sequencing and polymeric chain reaction (PCR), Dr. Garrett's group has worked to identify a causal role for *Fusobacterium nucleatum* — a symbiotic bacterial species that lives in our gut — in colorectal carcinogenesis.

Colorectal cancers develop through a progressive series of discrete histologic and genetic changes. In order to better understand if *F. nucleatum* was functioning to po-

tentiate the development of colorectal cancer at the earliest stages of carcinogenesis, Dr. Garrett's group focused on adenomas, which are lesions that can progress to cancer. The results revealed an enrichment for *F. nucleatum* in these lesions. Based on these association studies, her laboratory then fed this bacterial species to mice and observed that the phenotype seen in humans recapitulated in their animal model, with mice developing colon cancer. More precisely, it seems that *F. nucleatum* contributes to colorectal cancer development by expanding the myeloid-derived immune cell populations and allowing their infiltration into tissues, which contributes to tumor development [5]. Thus, this bug reshapes the gut environment to promote tumorigenesis. Our endogenous microbiota, therefore, has the potential to assume a much darker role.

The Contribution of Epigenetics in Making Us Human

Dr. Noonan's talk focused on the genetic and epigenetic elements that make us human. More particularly, he highlighted the importance of gene regulation in human development and evolution. His research uses a genomics approach to understanding human developmental programs and how they evolve through time, in order to better understand which of our genomic features contribute to our unique human biology. Gene regulation is critical for pattern development in the embryo. In fact, modifications in the spatial and temporal expression of specific gene transcripts are a prerequisite for evolutionary and developmental changes.

Regulatory changes in modular genes allow major developmental changes without changing protein function. Based on this rationale, Dr. Noonan presented research from his laboratory in which his group adopted a sequence-driven analysis in order to shed light on this issue. They focused on conserved sequences among different species, tested for fixed changes of nucleotides in humans, and used transgenic mouse strains to identify the effect of mutations that are fixed in humans. Chromatin immuno-precipitation sequencing (ChIP-Seq) allows them to use histone modifications (e.g., H3K27ac) as a quantitative readout of genomic sequences with regulatory functions. This method enables them to identify evolutionarily relevant tissue-specific functions of regulatory regions by identifying human-specific changes in promoters and enhancers.

Their research shed much light on limb- and brain-specific *cis* changes in regulatory elements that give rise to our unique human features. In the limb for instance, 13 percent of promoters and 11 percent of enhancers have gained activity when compared to rhesus macaques [6]. In the brain, this rationale has allowed Dr. Noonan's team to identify five transcriptional programs required for the unique formation of the cerebral cortex in humans [7]. Thus, through this innovative use of functional genomics, Dr. Noonan's group is capable of mapping regulatory changes during embryonic development that allow us to be humans.

Reshaping the Tumor Environment

The last research-related speaker of the symposium was Dr. Pittet. His research aims to delve deeper into cancer's idiosyncrasies by looking at tumorigenesis not just as a cell-autonomous process, but also as a cell-extrinsic mechanism. More specifically, his talk focused on macrophage pathways in lung cancer and what he called "the effect of long-distance relationships" between immune cells and the cancer environment. Using non-small cell lung cancer models, his lab's broader goal is to better understand the basic immune functions involved in cancer development *in vivo* and identify effective anti-cancer therapies. His interest in this model stems from the fact that non-small cell lung cancer is the most commonly diagnosed form of cancer, yet patients lack therapeutic options. Moreover, the mouse model recapitulates what is seen in humans, making findings in this animal model directly relevant to better understanding the disease pathogenesis in humans.

Building on the fact that the number of tumor-associated macrophages at time of di-

agnosis correlates with patients' survival, his group used nanoparticles to label and track tumor-associated macrophages (TAMs). This allowed them to track the flux, numbers, and functional states of macrophages in various tissues [8]. Their interest was to figure out where TAMs come from and, more precisely, how far they come to the tumor environment. They identified the levels of the Angiotensin II (Ang II) hormone as a good predictor of disease outcome, with patients that express it at relatively lower levels tending to survive longer [9]. Ang II production also amplifies hematopoietic stem cells and macrophage progenitors, thereby promoting the accumulation of new macrophages in tumors. Regulating the pathway that involves Ang II, which includes the signaling molecule sphingosine-1-phosphate (S1P1) in hematopoietic stem cells [10], could be amenable to treating cancer.

KNOW YOUR AUDIENCE

"There are a lot of people outside these walls who are highly interested in what you guys do here," said Carl Zimmer, a science columnist at *The New York Times* and the last speaker of the day. He very wittily described what our role was in explaining science to the wider public. "Some of you might become frustrated and prefer to completely disengage from this endeavor because you know how hard it is to explain an extremely complex process in simple terms without losing accuracy," he said. He pointed out that in a world where Jenny McCarthy, an infamous celebrity who wages a war against vaccines, is hired by *The View* and has access to 3 million viewers, we, as scientists, have a duty to speak out and as loud as we can. But to do so requires knowledge of the mismatch between esoteric scientific vocabulary and how people actually speak in the real world.

Many scientists have achieved the seemingly arduous task of sharing arcane scientific findings with the larger public and getting them to engage with the world of scientific research. One of the most notable among them is Peter Medawar, whose *Pluto's Republic* was published in 1982. In the book, Medawar discusses a range of topics from concerns with the field of psychoanalysis to a Jesuit priest's ventures into paleontology, but the key here is that he does it with wit, sometimes glib, and great inspiration. Scientists should take note of such successful instances of engagement with the wider public and realize that it is not all that hard to do the same. The key, perhaps, is not so much content, but semantics. Scientists have a tendency to use needlessly formal phrases, write in the passive voice, and use words whose colloquial meanings do not match the definitions in science.

A spate of resources exists to help scientists in their attempts to write for the larger public rather than just their department. Zimmer suggested we should not use the word "novel" unless we are talking about *War and Peace*. In fact, he put together a list of banned words [11]. Zimmer also pointed out a number of books that would help in this regard: *Am I Making Myself Clear* by Cornelia Dean, *Don't Be Such a Scientist* by Randy Olson, and *The Elegant Universe* by Brian Greene. "If Brian Greene can write a bestseller about string theory, don't tell me that your research is too complicated to write about it for a lay audience," Zimmer said. The question then becomes: Is your research more complex than string theory?

CONCLUSION

To borrow a phrase used during a Yale talk in October 2013 by the popular science writer David Dobbs, the symposium truly left the audience with "a state of heightened [desire for] inquisition," be it inside their laboratory or outside when trying to present the wonders of science to a larger audience. The main message was that one should be inspired to look at one's own research differently. Each speaker used tools and rationales at the cutting edge in their field in order to shed light on complex and oftentimes impenetrable processes such as the development of autoimmunity, cancer, and what makes us human. A desire to tackle today's burning questions in the field of im-

munology and genetics brought Drs. Hafler, Garrett, Noonan, and Pittet to reach beyond the realm of everyday experimental tools to bring about the beauty of science. Dr. Roskoski and Carl Zimmer's speeches reflected a desire to move science forward through government agencies and engaging scientists in policy in the case of the former and through inspired writing about esoteric scientific topics in the latter.

REFERENCES

1. Judson O. The Human Phenome Project. The New York Times [Internet]. 2010 June 8. Available from: http://opinionator.blogs.nytimes.com/2010/06/08/the-human-phenome-project.
2. Kleinewietfeld M, et al. Sodium chloride drives autoimmune disease by the induction of pathogenic TH17 cells. Nature. 2013;496(7446):518-22.
3. Li M, et al. Helicobacter pylori Infection Synergizes with Three Inflammation-Related Genetic Variants in the GWASs to Increase Risk of Gastric Cancer in a Chinese Population. PLoS One. 2013;8(9):e74976.
4. Khan AA, et al. Normal to cancer microbiome transformation and its implication in cancer diagnosis. Biochim Biophys Acta. 2012;1826(2):331-7.
5. Kostic AD, et al. Fusobacterium nucleatum Potentiates Intestinal Tumorigenesis and Modulates the Tumor-Immune Microenvironment. Cell Host Microbe. 2013;14(2):207-15.
6. Cotney J, et al. The evolution of lineage-specific regulatory activities in the human embryonic limb. Cell. 2013;154(1):185-96.
7. Ayoub AE, et al. Transcriptional programs in transient embryonic zones of the cerebral cortex defined by high-resolution mRNA sequencing. Proc Natl Acad Sci USA. 2011;108(36):14950-5.
8. Keliher EJ, et al. 89Zr-labeled dextran nanoparticles allow in vivo macrophage imaging. Bioconjug Chem. 2011;22(12):2383-9.
9. Cortez-Retamazo V, et al. Remote control of macrophage production by cancer. Oncoimmunology. 2013;2(5):e24183.
10. Cortez-Retamazo V, et al. Angiotensin II drives the production of tumor-promoting macrophages. Immunity. 2013;38(2):296-308.
11. Zimmer C. Phonemena: The Loom. National Geographic [Internet]. Available from: http://phenomena.nationalgeographic.com/2009/11/30/the-index-of-banned-words-the-continually-updated-edition/.