GUEST EDITORIAL

JUST SAY YES TO NEW DRUGS

DENNIS LIU

Predatory snails, glowing bacteria, and bad-smelling mosquitoes probably don't make you think "medical breakthroughs!" The list is from the realm of basic research, which has been compared to shooting an arrow into the sky and then painting a target where it lands. It's easy to lampoon basic research. In a culture of ultra-this and cutting-edge-that, "basic" sounds cheap. Of course, in the case of research "basic" means fundamental. Most science teachers are deeply curious about the natural world and can appreciate scientists driven to explore seemingly obscure corners of life. The general public, however, doesn't necessarily appreciate the value of curiosity-driven research that has a high chance of failure. If forced to make a choice on how tax dollars are to be spent, most people would go for applied research. So how is it that the lion's share of research supported by the U.S. Government's National Institutes of Health (NIH) is basic research? The short answer is that basic research is the best compass for applied research. The mission of the NIH is to gain fundamental knowledge about living systems and to apply that knowledge to improving health. At the heart of this mission is the principal of investigator-initiated research, which is bureaucratic code for "let smart, driven, curious people follow their nose." Don't try and tell them what they should be researching. The NIH is the envy of the global research community with a budget of about $30 billion a year. No other nation on earth comes close to this level of public support for biomedical research. In 2008, when vice-presidential candidate Sarah Palin disparaged federally funded research on flies, she was expressing a common public concern about basic research, that it's academic, irrelevant to real-world problems, frivolous. However, as a person interested in helping children with Down syndrome, for example, Ms. Palin should understand that in part it's those fruit flies that are lighting the way toward better treatments. Speaking of illuminating, let's have a closer look at that weird list from the annals of basic research.

You'll be pleased to learn that bacteria have a surprisingly active social life and, in fact, love a good meeting. Bonnie Bassler at Princeton University and others have been studying a phenomenon in colonial bacteria evocatively named "quorum sensing." Pathogenic bacteria send and receive chemical signals to coordinate the launch of virulent attacks on their hosts, attacking only when they have strength in numbers. This stand-up-and-be-counted phenomenon was first discovered in a "helpful" bacterial species that uses quorum sensing to produce bioluminescence in a symbiosis with bobtail squid. Some compounds that interfere with quorum sensing have progressed to the applied-research phase with a shot at becoming new drugs. Bonnie Bassler entered the field fascinated by bacterial communication and is now turning basic research insights into a strategy to develop new antibiotics. In the early days, some were dismissive of bacteria that glowed and did not cause disease, but they've seen the light as Bonnie's research has moved into the preclinical stage and is the next great hope for a new generation of antibiotics and a way out of the terrible problem of growing resistance to current antibiotics. See Figure 1, and search the NOVA scienceNOW website or visit BioInteractive.org to learn more.

Although a run-in with predatory snails could ruin a nice dive among coral reefs, research on these snails is producing new drugs for treating chronic pain, Parkinson's disease, and cardiac arrhythmia. Cone snails (genus *Conus*) hunt worms, other snails, and even fish. These pokey predators nab strong, fast prey by harpooning and injecting a brew of peptide toxins, throwing the kitchen sink at the fish neuromuscular system, causing rapid rigid paralysis and then a limp state for easy ingestion. Since fish are our vertebrate cousins, the toxins also affect the human nervous system. One of the leading scientists in cone snail research, Baldomero "Toto" Olivera at the University of Utah, began his research wanting to find new chemical reagents for understanding how the nervous system works, but three decades on he's seen a new painkiller come to market (Prialt) and several more drugs in clinical trials. It takes a lot of research to turn a toxin into a medicine, and cone snail research is a good example of the back-and-forth between basic and applied research. For example, clinical studies have revealed new types of receptors in the human brain that basic researchers are now studying

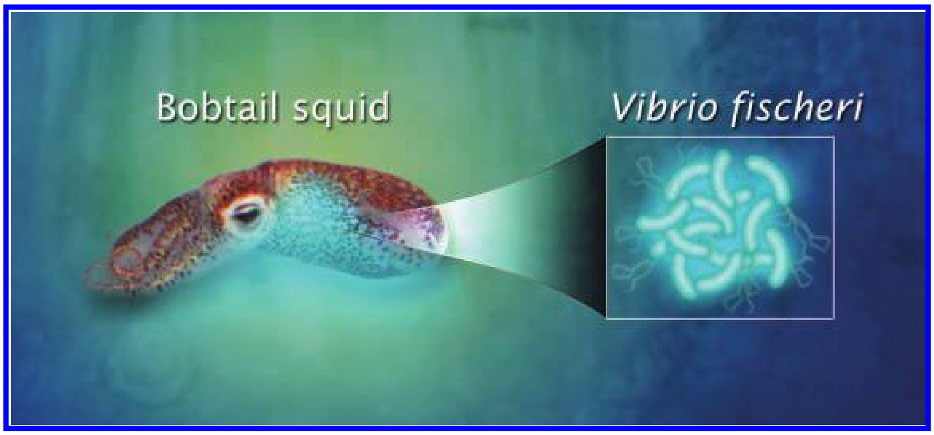

Figure 1. The Hawaiian Bobtail squid has a remarkable symbiotic relationship with a species of marine bacteria that can produce light via a communal signaling system. Pathogenic bacteria use the same system, called quorum sensing, and researchers are studying how to disrupt the signals to stem infections. © Howard Hughes Medical Institute. See *ABT* online for video clip.[1]

Figure 2. Venomous cone snails hunt fish, marine worms, and other snails. Each cone snail species has a unique mix of toxins, typically more than 200 different peptides. Researchers have turned these toxic peptides into medicines (e.g., a new drug for intractable pain in people). © Howard Hughes Medical Institute. See *ABT* online for video clip.[2]

Figure 3. Understanding and disrupting the olfactory systems of insects like a malaria-carrying mosquito could save millions of lives each year. © Howard Hughes Medical Institute.[3]

to understand fundamental principals of how neurons function. See Figure 2, and learn more at TheConeSnail.com and BioInteractive.org.

In the case of bad-smelling mosquitoes, I'm guilty of bad grammar in referring to the ability of mosquitoes to find us by smell and then suck our blood. If we could interfere with their ability to smell, perhaps they would leave us alone. Leslie Vosshall of The Rockefeller University has been studying insect olfactory systems to learn fundamental things about how the nervous system processes information, including molecular signaling mechanisms. The strategy is to understand how a simpler, insect nervous system functions in order to gain insights into our own, more complex nervous system, including identifying molecules that may have similar functions across evolutionarily diverse nervous systems. But there's another potential benefit that's related to thwarting biting insects. For many years, the insect repellent of choice has been the organic compound known as DEET, a blunderbuss of a chemical that has serious negatives for human health and the environment. New insights into the function of the mosquito olfactory system are being used to design a new generation of insect repellents that can interfere with the insect olfactory system in a highly specific manner. The goal is to develop longer-lasting, more effective insect repellents with fewer negative side effects. New repellents would be a godsend not just to picnickers, but to the millions worldwide living in areas blighted by malaria, dengue fever, and other mosquito-borne diseases. See Figure 3, and search the Rockefeller University website or visit HHMI.org to learn more.

Each researcher has their own set of motivations that make them passionate about their work. Some care more about eventual practical benefits than others; all want to learn fresh things about the world. Good scientific communication powers the research enterprise and enables basic research to be cumulative and progressive. We need good dialogue as well among scientists, science teachers, and the public. I'll close by quoting Canadian scientist John Polanyi, who said, "it is folly to use as one's guide in the selection of fundamental science the criterion of utility. Not because scientists despise utility. But because useful outcomes are best identified after the making of discoveries rather than before." Bull's-eye, Dr. Polanyi!

References

[1]The video clip featured in Figure 1 can also be found at http://www.hhmi.org/biointeractive/biodiversity/click.html

[2]The video clip featured in Figure 2 can also be found at http://www.hhmi.org/biointeractive/biodiversity/video.html

[3]The video clip for Figure 3 is at http://www.hhmi.org/biointeractive/disease/malaria-human.html

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