Ask your students where they think new medicines come from. For that matter, how about old medicines? Aspirin, perhaps the most famous medicine, has a very interesting history that entails folk medicine, chemistry, clinical research, and molecular biology. Bayer has a website called Wonderdrug (www.wonderdrug.com/pain/asp_history.htm), where you can see a timeline of aspirin’s history, which reaches back to before ancient Greece. On the subject of painkillers, I was musing over the yin and yang of basic and applied research the other day while in the endodontist’s chair for a root canal. My “endo” was telling me about all the different “medicines” he was using. To keep myself occupied, I tried ticking off what was primarily the fruit of basic versus applied research. The procaine injections were a result of mostly applied research, but using basic chemistry to improve cocaine. Sodium hypochlorite as well as the drill and tiny canal files were definitely the products of applied research. The microscope has its origins in basic research but has matured into applied technology. EDTA and osteoclast-osteoblast modulating factors are the fruits of basic research. But none of my determinations were really tidy or definitive.

The research enterprise is confusing to most people, even for advanced students. How do results get transferred to medical advances? Converting basic research into new treatments has many names such as translational, clinical, applied, and disease-oriented research, to name just a few. Clearly, we need all these kinds of research, and they depend on one another. In this Web-review feature, my primary interest is to consider three research stories that highlight the importance of basic research to improving medicine because basic research is fundamental to health advances and yet often underappreciated. After all, it’s not that long ago that the National Institutes of Health (NIH) and National Science Foundation (NSF) were regular recipients of Senator Proxmire’s Golden Fleece awards for wasting taxpayer money. While emphasizing the critical importance of basic research, these stories reveal how important and interdependent the various categories of research are.

Analgesics like aspirin are an important group of painkillers primarily for treating relatively minor aches and pains. There is also a great need for treating pain-associated chronic debilitating illness as well as the intense pain that can follow certain traumatic injury or some surgical procedures. The best-known drugs for chronic pain management are the opioids and other narcotics, which also have the well-known downside of being addictive. Have a look at the University of Utah Learn Genetics website for an excellent feature on addiction (http://learn.genetics.utah.edu/content/addiction). There is a long-standing need for drugs that manage chronic pain more effectively, with fewer side effects, and without being addictive. The opening scene of my first story features a consummate predator stalking her prey (Figure 1). But this predator is a snail, of the genus Conus. The cone snails are a large and diverse group of marine mollusks. They prey on worms, other snails, and even fish, but like all snails, their locomotion is slow. Unlike more familiar predators, they don’t have strong jaws and sharp teeth. The cone snails have evolved several fascinating hunting

Figure 1. A cone snail hunting and ingesting a fish. The Biodiversity pages of the BioInteractive website have videos of several different species hunting.
strategies that include netting and harpooning prey. They
depend on delivering a complex mixture of toxins that
disrupt the nervous and neuromuscular systems of their
prey. The venom must work quickly to overcome prey that
are fast and strong. To avoid delay or failure, the toxins
overpower the prey’s neuromuscular system with dozens
of different peptide toxins. It’s memorable to watch these
hunters in action, and you can find several videos on the
Howard Hughes Medical Institute (HHMI) BioInteractive
webpages at www.hhmi.org/biointeractive/ biodiversity/video.html (Figure 1). Jason Biggs of the University
of Guam has a very nice 14-min video presentation on the
diversity of hunting styles of different cone snail species
(www.hhmi.org/biointeractive/biodiversity/2009_versatile _hunters.html).

Baldomero “Toto” Olivera has done pioneering research
on cone snail venoms, motivated by the triple purpose
of learning new things about how the nervous system
works, developing new research tools, and discovering
new medicines. Toto talks about his research in his 2009
HHMI Holiday Lectures (www.hhmi.org/biointeractive/ biodiversity/lectures.html) and has developed a website
aimed at providing teachers and students with information
about cone snails (www.theconesnail.com). Each cone snail
species mixes a unique cocktail of up to 200 peptide toxins.

Given that there are hundreds of cone snail species, there
are estimated to be tens of thousands of peptides targeting a
variety of cellular targets such as ion channels, transmitter
vesicles, and receptor complexes. In addition to Toto’s
Holiday Lectures, aimed at a high school audience, you
can view a more technical version of the story delivered by
Toto on Ron Vale’s iBioSeminars website (www.ibioseminars
.org/lectures/chemicalbiologybiophysics/baldomero-olivera .html) (Figure 2).

Although Conus toxin research has uncovered previously
unknown types of ion channels in the name of basic re-
search, I’m telling this story because new medicines have
come from this research. Toto began purifying peptide toxins
from cone snail venom in the early 1970s. Research psychi-
atrist Michael McIntosh, then an undergraduate working in
Toto’s lab at the University of Utah in the early 1980s, had
found that one peptide—ω-conotoxin—caused an interesting
“shaker” phenotype when injected into mice (view a short in-
terview with Dr. McIntosh at www.hhmi.org/biointeractive/
biodiversity/McIntosh_bio.html). ω-Conotoxin turned out
to be a calcium channel blocker and in the mid-2000s
was approved for the management of chronic, intractable
pain. Currently a number of other peptide toxins derived
from cone snails are in development to treat Parkinson’s
disease, epilepsy, heart disease, and pain. The animation

Figure 2. The iBioSeminars website has dozens of introductory and research-level seminars by research scientists, including Toto Olivera, pictured here.
New Medicines

Figure 3. The Hawaiian bobtail squid has a symbiotic relationship with a bioluminescent bacterium.

found at www.hhmi.org/biointeractive/biodiversity/2009_prialt_blocks_motor.html shows the physiological action of ω-conotoxin. To learn more about the synthesized medical form, trademarked as Prialt, search the European Medicines Agency website (www.ema.europa.eu) or use a direct link to the Prialt pages (http://tinyurl.com/4pouwgh). Prialt’s current patent holder, the French company Ilan, has produced a website aimed at doctors and patients (www.prialt.com/patients/product_info/about_prialt).

The nearly three-decade time frame from basic discovery to a clinical drug approved for use with patients might surprise students. There is of course lots of information about the drug approval process on the U.S. Food and Drug Administration (FDA) website, but I found one of the best concise graphics, including time frames, on the website of the pharmaceutical industry publication NGP (www.ngpharma.com/news/Glenmarks-new-drug-fails-in-trials). The time frame ranges from 12 to 25 years to go from the discovery process to FDA approval, and they present time estimates for each phase of the process. You might challenge students to come up with ways to streamline this process while maintaining patient safety.

For conotoxin researchers, it’s been a long journey from the reefs of the Indo-Pacific to new pharmaceutical treatments. Students are likely aware that there is a huge public health problem concerning antibiotic resistance, a perennial search for new antibiotics, and hopes for entirely new classes of antimicrobial agents. The next story has not reached the point of a new drug for patients yet but holds great promise. By sheer coincidence this story also features a predatory mollusk, the diminutive bobtail squid. Bobtail squid bury themselves during the day and come out at night to prey on crustaceans and fish. You can see videos of how they bury themselves on the vimeo website (vimeo.com/15490567) and on the Biointeractive Biodiversity pages (www.hhmi.org/biointeractive/biodiversity/2009_bobtail_squid.html). These night hunters have a challenge when the moon is out. Moonlight causes them to cast a perceptible shadow as they cruise along the sandy shallows in search of prey. Their adaptation to this situation is to deploy a form of countershading by emitting luminance that they can tune to the amount of moonlight. They counter being silhouetted by the moon to avoid detection by the eyes of upward-glancing prey. The problem is that squid don’t have the genes to directly produce light. Instead, they have evolved a symbiosis with *Vibrio* bacteria that can produce light. The *Vibrio–squid* symbiosis is a classic example of curiosity-driven basic research aimed at understanding life on our planet. Learn more about the symbiosis from two researchers at the University of Wisconsin in a feature at www.hhmi.org/biointeractive/biodiversity/Bioluminescence_01.html (Figure 3). Margaret McFall-Ngai and Ned Ruby have devoted their careers to understanding the squid–*Vibrio* symbiosis. Students at Davidson College have put together a website on bioluminescence that includes information on the symbiosis as well (www.bio.davidson.edu/people/midorcas/animalphysiology/websites/2005/plekon/
index.htm). The Microbial Life Educational Resources pages also have information on the squid–Vibrio symbiosis (http://serc.carleton.edu/microbelife/topics/marinesymbiosis/squid-vibrio/collection.html), as do the Why Files webpages (http://whyfiles.org/2010/sustaining-symbiosis-new-clues).

An important aspect of the phenomena is that bacterial cells do not waste energy producing light during the day. So how do they turn light production on and off, how is it regulated, and what are the signals? It turns out that the answer is simply cycles of population growth. When bacteria multiply to a certain density, the community begins to produce light. The mechanism for this coordinated activity has come to have the catchy name “quorum sensing.” Bonnie Bassler, now at Princeton University, had heard about this fascinating symbiosis and as a microbiologist became particularly interested in understanding the genetics and biochemistry of light generation as well as the molecular signals for turning the lights on and off. Ultimately Bonnie turned to a free-living luminescent species of Vibrio bacteria that are easier to culture. You can view an animation of the signaling phenomena in action at www.hhmi.org/biointeractive/biodiversity/2009_QS_molecular_cascade.html (Figure 4) as well as a molecular animation of its genetic control at www.hhmi.org/biointeractive/biodiversity/2009_lux_operon_light_prod.html.

As a budding scientist launching a career, Bonnie had challenges for those who dismissed bacterial light production as an interesting phenomenon not in the mainstream of biomedical research. The PBS program NOVA scienceNOW has an excellent video profile of Bonnie on its website (www.pbs.org/wgbh/nova/body/bonnie-bassler.html). Bonnie talks about the challenges, her good fortune, and her desire for her very basic research to lead to new drugs. In this regard, Bonnie has had good instincts and good fortune. It appears that quorum sensing is a universal phenomenon among bacteria of every species studied, including many important pathogenic species from Vibrio cholera to Salmonella and Escherichia coli.

Most bacterial species use quorum-sensing signaling, not to coordinate light production, but to turn on virulence factors and coordinate attacks on their hosts when they have sufficient population. Bonnie presents her science at length in her iBioSeminars (www.ibioseminars.org/lectures/chemical/biology/biophysics/besslar.html), in her Holiday Lectures (www.hhmi.org/biointeractive/biodiversity/lectures.html), and in an energetic 18-min TED talk that should appeal particularly to students (www.ted.com/talks/bonnie_bassler_on_quorum_sensing.html).

A main thrust of the quorum-sensing drug development research is to identify molecules that can disrupt quorum-sensing systems of pathogens and therefore perhaps disrupt the production of toxins. The Bassler lab and collaborators are screening large chemical libraries and have identified some interesting compounds that disrupt quorum sensing and when administered to mice have had some success in fighting off bacterial infections. This research is now in the highly unpredictable preclinical phase of medicine development.

The first story described basic research to clinical applications while the second story is still in the preclinical phase of drug discovery. My third story relates to a blockbuster drug, one that’s making a lot of money and saving a lot of lives. Cardiovascular disease is a leading cause of illness and death globally. Perhaps it’s no surprise then that the biggest blockbuster drugs of all time are the statins, developed to fight atherosclerosis, a leading factor in heart disease. The PharmaLive website has a report on the world’s best-selling medicines (www.pharmalive.com/special_reports/sample.cfm?reportID=314). Over 40 million people take statins worldwide, generating many billions of dollars in revenue for the pharmaceutical industry annually. Despite some leveling off of individual brands, the class continues to dwarf the sale of more famous drugs, like Viagra. Understanding how statins work and developing new statins that are more effective with fewer negative side effects are highly dependent on basic research. However, our initial interest in controlling cholesterol levels and developing statins originated in the field of clinical medicine.

Statins act to lower the level of serum cholesterol. Cholesterol is a lipid, and many studies find lipid chemistry difficult, or at least hard to remember, perhaps because hydrophobic molecules get short shrift in the science curricula on a watery planet. Of course their hydrophobicity is what makes them so important and interesting. Without lipids
New Medicines

Figure 5. Wiley has a good interactive feature on their website that covers the structure and physiology of cholesterol, including the health implications.

there would be no cellular and subcellular compartments, no way to sequester all that watery chemistry, not to mention the interesting signaling functions of lipids. I think cholesterol is a good entry point into lipid chemistry because students can be motivated by the health connections. Wiley has a good interactive tutorial on cholesterol that you can find at www.wiley.com/college/boyer/0470003790/animations/cholesterol/cholesterol.swf (Figure 5). The graphics are highly schematic, but it's a good overview of cholesterol with some emphasis on aspects that relate to heart disease and statin action. The occasional pop-up quizzes help keep students’ attention and discourage just clicking through. It’s good that this feature puts cholesterol in the context of the steroid family of molecules, but it’s unfortunate that they don’t put them in the broader context of fat and lipid molecules. William Reusch in the Department of Chemistry at Michigan State University has put together a nice online primer on organic chemicals, including lipids (www2.chemistry.msu.edu/faculty/reusch/VirtTxtJml/biomol.htm). It’s not interactive or graphics driven, but it has excellent information, clearly and concisely presented. Satoshi Amagai has developed a pair of very nice features for the BioInteractive website on the molecular structure of fats (www.hhmi.org/biointeractive/obesity/obesity_molecular/01.html) and how the body uses fat (www.hhmi.org/biointeractive/obesity/obesity_proc sing_fat/01.html). The “How the Body Uses Fat” feature in particular helps clarify that the much discussed “good” (HDL) and “bad” (LDL) cholesterols are not cholesterol; they are large lipoprotein particles that transport cholesterol through the blood. Our understanding of the chemistry of cholesterol, its metabolism, and its physiological regulation is a triumph of basic research. But importantly, the earliest concerns about the potential health hazards of cholesterol came from physicians. To understand the relationship between clinical and basic research, it’s necessary to consider some history.

By the 1950s and 1960s, research had associated atherosclerosis with heart disease and established that artery-clogging plaques were composed largely of cholesterol. It was also known that HMG-CoA reductase was the rate-limiting enzyme on the path to making cholesterol. These facts led to a search for an inhibitor of HMG-CoA reductase that could be used to reduce cholesterol in the body and perhaps slow or stop plaque formation. For a review of the plaque formation process, have a look at the animation produced by pharmaceutical company AstraZeneca and available on YouTube (www.youtube.com/watch?v=fLonh7ZesKs). The graphics are much better than the narration. By the early 1970s, drug company employee Akira Endo was screening bacterial and fungal cultures to find inhibitors of HMG-CoA reductase. He soon found a candidate, the first member of the class now known as statins. In 2003 John Simons published an article in Fortune Magazine (http://money.cnn.com/magazines/fortune/fortune_archive/2003/01/20/335643) covering the fascinating commercial aspects of these drugs.

In the late 1960s, physicians Michael Brown and Joseph Goldstein saw their first patients suffering from a severe
form of inherited hypercholesterolemia called familial hypercholesterolemia (FH). These individuals can have serum cholesterol levels 10 times that of an average person, and they develop thick deposits of cholesterol called xanthomas that can be seen on various parts of the body (Figure 6). Brown and Goldstein’s approach was to use this genetic disease as a way to understand the more general phenomena of high cholesterol affecting the general population. They were also interested in the basic research problem of how insoluble cholesterol could be delivered to cells—“the delivery problem.” I recommend visiting their Nobel Prize webpages and in particular reading the transcript of their Nobel lecture (http://nobelprize.org/nobel_prizes/medicine/laureates/1985/goldstein-lecture.html). Their lab website presents a good short history of this work as well (www4.utsouthwestern.edu/moleculargenetics/pages/gold/past.html). Although I think Brown and Goldstein would probably call themselves disease-oriented researchers, it’s significant that they sought training in basic research and have followed a basic research approach to understanding disease. As a result, their work established important concepts in cell biology, a case of medically oriented research contributing to basic research advances. Their cholesterol work has elucidated receptor-mediated endocytosis, recycling of membrane receptors, and feedback regulation of receptors. These principles are outlined in a review article on their website (www4.utsouthwestern.edu/moleculargenetics/pdf/msb_cur_res/2009%20ATVB%20Brown%20431.pdf). Brown and Goldstein discovered the answer to the delivery problem: Cells had receptors on their surface that bound cholesterol-rich LDL particles. Bound particles were subsequently internalized and processed (coated pits and vesicles) to make the cholesterol available to the cell to make new membrane. Once separated from the LDL, the receptor could be recycled to the cell surface. The simple animation found on the W.H. Freeman website (http://bcs.whfreeman.com/thelifewire/content/chp05/0502003.html) illustrates endocytosis and recycling of LDL receptors, but not feedback regulation. Cells deprived of cholesterol increase the number of receptors on their surface and decrease the number of receptors when cholesterol is plentiful. Goldstein and Brown’s hook for finding and cloning the LDL receptor was that their FH patients had a paucity of LDL receptors. Understanding these various genetic and biochemical equilibria in the context of cellular function led to a hypothesis that was experimentally validated. Lowering the cholesterol content in liver cells could up-regulate LDL receptors, providing more receptors for taking LDL out of the bloodstream, thus lowering serum cholesterol levels and inhibiting plaque formation. Brown and Goldstein’s work has been essential to understanding the action of statins and forms the rational basis for ongoing statin development. They received the 1985 Nobel Prize in Physiology or Medicine, and the lab continues to work on cholesterol regulation.

There are so many more stories that could be used to hone students’ appreciation for the multifarious dimensions of the research enterprise, and I think these stories help students realize how many different sorts of research and research careers there are. Cancer is one story that really needs an article all its own. There is continuing controversy about the war on cancer that dates to Nixon’s 1971 National Cancer Act. Because of the devastating and far-reaching nature of cancer, the government and various nongovernmental organizations are under continuous pressure to be waging a war. The National Cancer Institute has published a useful cancer timeline (http://dtp.nci.nih.gov/timeline/noflash/index.htm) emphasizing therapeutics. There are many versions of why the war on cancer failed: Cancer is so many separate diseases; the research emphasis was wrong; environmental factors can cause cancer. A much-discussed article published in Fortune Magazine in 2004 (http://money.cnn.com/magazines/fortune/fortune_archive/2004/03/22/365076/index.htm) blamed the failure on faulty animal models, in particular mice, while a 2007 Washington Post article suggested that the $100 billion spent on cancer drug development is wasted because cancer is predominantly an environmental disease (www.washingtonpost.com/wp-dyn/content/article/2007/11/02/AR2007110201648.html). A 2008 Newsweek article
All of these popular press articles present a piece of the story that has some truth but entirely misses the nature of basic research. I think this also underlines why waging war on a disease is not a good metaphor for what research does. Dueling metaphors aside, it probably was premature to focus on eliminating cancer in the 1970s before we understood enough about the biology of cancer and before we had enough information from basic research. Due to a large body of research done on model systems starting in the 1970s, we now understand that what all cancers have in common is faulty cell cycle regulation. Because of the Nobel Prize–winning basic research of Paul Nurse, Leland Hartwell, Tim Hunt, and many others on cell cycle regulation (http://nobelprize.org/nobel_prizes/medicine/laureates/2001/nurse-lecture.html), we understand the biology of cancer and finally have a chance to develop rational therapies. As a 2010 article published in the journal PLoS ONE documents (www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0009584), deaths due to cancer are declining in the United States. Although these gains are most likely due primarily to reduced smoking, basic research has helped and is likely to accelerate gains as therapies for specific cancers become available.

I’ll close with a short list of websites of related interest:

- FASEB has a Breakthroughs in Science section (www.faseb.org/News-and-Publications/Breakthroughs-in-Science.aspx) with some good examples, including hypertension research. I think the common media usage of “breakthrough” is a problem, but I understand why we fall back on that language.
- The NIH National Institute of General Medical Sciences has a good website describing the use of model organisms in research (www.nigms.nih.gov/Publications/modelorg_factsheet.htm).
- The University of Wisconsin has a website that focuses on using Caenorhabditis elegans in teaching but also includes information on other model systems and the general approach of using model organisms (www.wormclassroom.org/teaching-model-organisms).
- A thoughtful EMBO report is available (www.nature.com/embor/journal/v9/n8/full/embor2008142.html) that discusses animal models and their future as human stem cell science and computer modeling matures.
- In a Science Perspective (www.sciencemag.org/content/307/5717/1885.full), Stanley Fields and Mark Johnston have authored a succinct and specific statement of how model organisms will continue to be important for biomedical research in the coming decades.
- An excellent 2006 Perspective published in the New England Journal of Medicine (www.nejm.org/doi/full/10.1056/NEJMcp068050), by Joseph Loscalzo, describes the NIH budget, comparing it to industry spending, and spells out the difference between drug development research and basic research.
- BioCentury published a very good report on the politics of the 2011 NIH budget (www.biocentury.com/promotions/budgetfight/us-budget-fight-over-basic-translational-research-spending-by-nih-a1.htm) and the political battle between basic and translational research priorities.
- The Science Coalition, primarily representing U.S. research universities, has published a thorough report on how basic research pays an investment dividend in jobs and new companies (www.sciencecoalition.org/successstories). The report points out that 55% of basic research takes place at universities and that 60% of the funding is federal.
- The Journal of Clinical Investigation publishes a review series (www.the-jci.org/publications.php?list=review_series) that presents bundles of articles on particular diseases or organs. Reproductive Biology is an interesting example; it includes articles on reproduction in placental mammals focusing on getting bench-to-bedside insights.
- The NSF has been conducting an annual poll of citizen attitudes toward science and engineering for many years, and the results are quite consistent. Americans trust scientists and think science is important, but they don’t understand science very well. The 2010 report is available online (www.nsf.gov/statistics/seind10/c7/c7s3.htm).
- Virginia Commonwealth University conducts an annual survey focused on attitudes toward the life sciences, especially controversial issues like cloning and stem cells. The most recent report is available online (www.vcu.edu/lifesci/centers/cen_lse_surveys.html).
- Scientific American, now published by Nature America, conducted a web survey in 2010, published online (www.scientificamerican.com/article.cfm?id=in-science-we-trust-poll).

Email me at dliu@hhmi.org to tell me your favorite bench-to-bedside story.

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