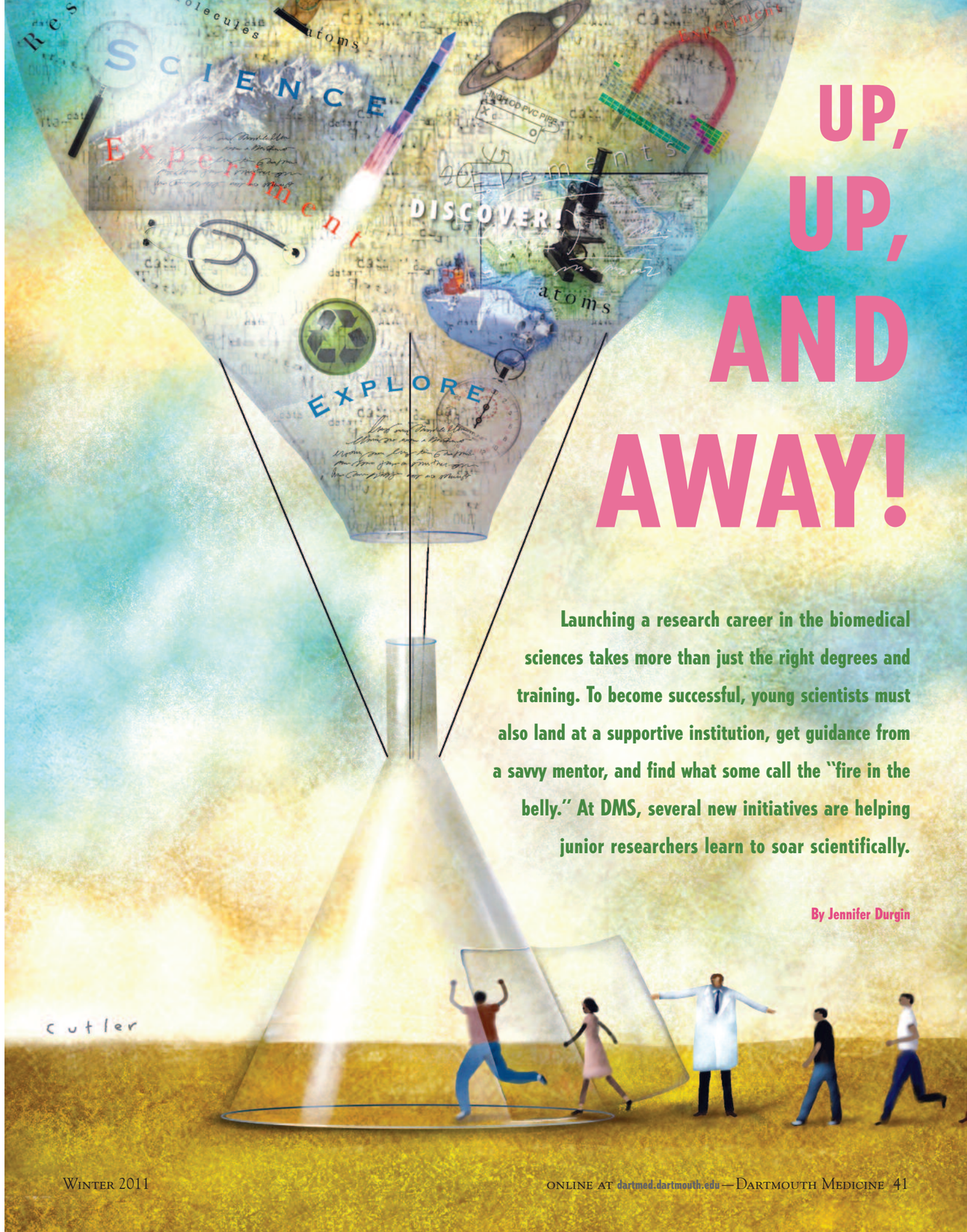
UP, UP, AND AWAY!

Launching a research career in the biomedical sciences takes more than just the right degrees and training. To become successful, young scientists must also land at a supportive institution, get guidance from a savvy mentor, and find what some call the "fire in the belly." At DMS, several new initiatives are helping junior researchers learn to soar scientifically.

By Jennifer Durgin



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At first, there seemed to be plenty of entry-level faculty openings for a young neuroscientist like Farran Briggs, Ph.D. It was 2008, and Briggs was in the fifth year of a postdoctoral fellowship, studying neuronal circuits in the early visual system of mammals. She had already coauthored several papers in reputable neuroscience journals and had been able to secure funding during her entire fellowship—and even for graduate school. Her career seemed poised to take off.

But as the U.S. financial system collapsed during the fall of 2008, universities began pulling their ads for faculty positions, Briggs recalls. "More than half of the job ads that were posted were withdrawn after Lehman Brothers" filed for bankruptcy, she says, adding that "2008 was a very interesting year to get my feet wet."

In order to land a job as an assistant professor at a top research university, Briggs figured, she'd have to prove that she was *the* best candidate out there in her specialty—even though she knew that many talented postdocs in her field were already on the market and many more were coming up behind her.

"You get in the back of the line of these incredible applicants, and everyone is fighting for like five positions in the country," Briggs says. "It's kind of insane!"

The backlog of postdocs in neuroscience (and other biomedical disciplines) has continued to swell, in part due to the stagnant budget at the National Institutes of Health (NIH) and in part due to the weak economy. The NIH—which underwrites the majority of biomedical research at U.S. universities and draws its funding from the federal government—hasn't seen a major budget increase since 2003. As a result, it has become harder and harder to secure NIH funding, certainly for new researchers and even for experienced ones, and thus harder for institutions to hire new research faculty. New faculty often need a few years of start-up funding to get their labs going, but since institutions' endowments shrank in 2008, it's been tougher for them to come up with those funds.

Another sign of the times is the declining rate of approval for grants with a single researcher as the lead investigator (known as R01 or R01-equivalent grants). In 2001, the success rate for original NIH R01 or equivalent applications was 25%. By 2008, that rate had fallen to 8%, though it did rise slightly, to 10%, in 2010.

For a young scientist like Briggs, who is just starting out and who has learned to regard R01 grants as a significant measure of research success, those odds are daunting. Concerned about the challenge, but undeterred, Briggs "made a big push" near the end of her training, she says, and got an important paper published in a

Early guidance on the journey toward scientific success

Behind every successful scientist is a platoon of hard-working scientists-in-training: postdoctoral fellows, Ph.D. and M.D. students, and even undergraduates. For researchers on the Ph.D. track who intend to go into academic medicine, doing a postdoctoral fellowship is a key stop on the way to becoming a principal investigator—but postdocs don't always get the recognition they deserve. For those on the M.D. track, gaining experience in a lab, as well as in the clinic, is essential—but other aspects of becoming a physician-scientist aren't as clear. At DMS, two relatively new initiatives are helping both groups of future scientists reach their goals.

The Dartmouth College Postdoctoral Association (DCPA—see http://www.dartmouth.edu/~provost/postdoc/) is run by and for postdocs. It was established in 2008 and is funded by the Provost's Office (in addition, Dartmouth has for many years had a similar organization for graduate students, the Graduate Student Council—see http://www.dartmouth.edu/~gsc/newwiki/pmwiki.php). The DCPA sponsors workshops and seminars on topics ranging from grant-writing to career-planning and also hosts social events.

Postdocs, who have already earned a Ph.D., are neither students nor regular employees, so they may fall into cracks in an institution's personnel systems. But, points out Salvador Almagro-Moreno, Ph.D., the president of the DCPA and a postdoc in microbiology and immunology, postdocs often stay at an institution for several years—sometimes longer than graduate students or even regular employees. Now, thanks to the DCPA, Dartmouth postdocs have a stronger institutional voice and an organization focused solely on their needs. As a result, "the whole postdoc community is starting to agglutinate," says Almagro-Moreno.

Among M.D. students at Dartmouth, a sense of community and class cohesion has never been lacking. But for those medical students who dream of conducting research as well as treating patients, the path to achieving that goal can be murky. A new program called DMS Science Scholars is helping such students chart a course to their goal, beginning in their first year of medical school. Each Science Scholar is paired with an M.D.-Ph.D. student mentor; is given funding to work in a research lab after Year 1 of medical school; and is taught the basics of grant-writing, preparing a scientific poster presentation, and other related skills.

The Science Scholars benefit from "some of the meat" of the Ph.D. curriculum, but within the constraints of the M.D. track, explains Pablo Valdes, an M.D.-Ph.D. student and the codirector of the program. Seven first-year medical students were selected as Science Scholars this year—the first of many to follow on this guided journey toward becoming a physician-scientist. J.D.

"It really is trial by fire," observes Briggs, who is now several months into making the transition to independence. "You can try to pick the brain of your advisors as best you can. I certainly did." But, she adds, "You can't necessarily prepare for everything. . . . You just sort of dive in and do it."

top journal. She also applied for and landed an ultracompetitive NIH grant aimed at launching the careers of promising young scientists. Known as the K99/R00 Pathway to Independence Award, the grant provides one to two years of funding for postdocs while they're still working under a mentor, followed by up to three years of independent funding—contingent on their securing a tenure-track or equivalent research position.

With a strong publication on her CV and a prestigious grant in her pocket, Briggs's chance of being offered one of the few coveted faculty positions in her field seemed good. But in the end, it wasn't her impressive publications record or the fact that she had snagged a K99/R00 award that convinced Dartmouth Medical School's chair of physiology, Hermes Yeh, Ph.D., to hire Briggs in 2011. It was her "chalk talk."

It's standard practice for researchers interviewing for a faculty position to give a "job talk," a formal presentation about the nitty-gritty details of their research. It's less common, says Yeh, to also ask a candidate to do a "chalk talk," an informal research presentation using only a piece of chalk (or a dry-erase marker) and a few visual aids.

"Our department is very diverse," says Yeh. "It was actually Farran's job to make her research directions and programs clear enough so that somebody who is not in her immediate field can understand and get interested in it."

Finding the right candidate is "not just a simple matter of looking at the CVs and counting the papers or number of grants" a person has, explains Yeh. "Our department takes teaching very seriously. We put the same kind of emphasis on whether we think the person has the ability to stand in front of medical students and explain clearly some fairly difficult concepts and principles."

It was Briggs's chalk talk, Yeh says, that ultimately made her rise to the top of the applicant pool (and the same was true of Bryan Luikart, Ph.D., another neuroscientist whom Yeh recently recruited).

Briggs will do some teaching during her first few years at DMS, but her primary focus right now is on setting up her lab and getting established as a researcher. That's no simple task. Making the transition from postdoc to independent investigator is perhaps the steepest learning curve along a scientist's career path. In one step, Briggs went from being one of many subordinate researchers in a lab run by someone else, to having a long list of responsibilities, not the least of which is hiring and managing a laboratory staff.

"It really is trial by fire," observes Briggs, who is now several months into making that transition. "You can try to pick the brain of your advisors as best you can. I certainly did." But, she adds, "You can't necessarily prepare for everything. . . . You just sort of dive in and do it."

Ten years ago, James DiRenzo, Ph.D., an associate professor of pharmacology and toxicology at DMS, was where Briggs is now—just starting out as an assistant professor at DMS. Economic times were better and funding was easier to come by. Even so, the growing pains of trying to figure out how to be a successful independent investigator were as real then as they are now.

"When it came to the actual process of establishing myself as an independent investigator," says DiRenzo, "99% of the mentoring I received, I received here." And most of that mentoring came from the chair of his department, Ethan Dmitrovsky, M.D., the Andrew G. Wallace Professor of Pharmacology and Toxicology.

Dmitrovsky doled out advice on how to set up a lab, how to hire and manage staff, how quickly to grow the lab, what grants to apply for, and much more, says DiRenzo.

One thing DiRenzo learned "absolutely nothing about" during graduate school and his postdoctoral fellowship, he admits, was managing people. There were opportunities to learn those things, he says, but he was always so focused on conducting the research that he passed up those chances.

Hiring and managing a laboratory staff "is very hard," he soon realized. "You're not simply hiring a scientist or simply accepting a trainee into your lab. You're becoming involved with another person and a person who has all these other sorts of interests and issues." Most of all, when an independent investigator takes on a student or a postdoc, that investigator is signing up to be a mentor and advisor for the young scientist. It's a great responsibility, but also a great joy for many investigators.

"The thing I probably most enjoy is watching the maturation process," says DiRenzo, "when you see students . . . hit that level of independence where they're already making the right calls for themselves."

Good mentoring is widely acknowledged as essential for graduate students and postdoctoral fellows, but it's also critical for junior faculty.

One pearl of wisdom that Dmitrovsky shared with DiRenzo, who studies normal and cancerous stem cells in the breast, was to not be in a rush to get his first R01 grant.

"The problem is that for most people their first R01 gets [them] four years of funding, sometimes [only] three," says DiRenzo. To bring in further sup-

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Farran Briggs, Ph.D.
Assistant Professor of Physiology

Education: Dartmouth College (B.A. in biology, 1997); University of California, San Diego (Ph.D. in biology, 2003); University of California, Davis (postdoctoral fellowship)

Research: Exploring the structure and function of neurons in the visual cortex of the brain and determining how they respond to changes in attention

Came to DMS: 2011

Career stage: Newly appointed to her first faculty position, Briggs is still in the process of unpacking supplies and setting up her lab.

Even now, in the middle of his career, DiRenzo says he has no shortage of questions for Ethan Dmitrovsky, the chair of his department. "I was very fortunate to have a chair who believed strongly in the mentoring aspect" of his role, says DiRenzo. "It made a big difference, that's for sure."

port, investigators have to submit an application for a grant renewal, which includes describing what they've accomplished in the first round of funding. "As you're starting a lab," he says, "that two- to three-year period . . . simply isn't long enough to really get yourself established."

Another reason for DiRenzo to hold off on chasing his first R01, Dmitrovsky advised him, is that many private foundations that support cancer research specifically target young investigators. This is especially true in the breast cancer arena.

The strategy worked well for DiRenzo. He garnered support from several private foundations during his first decade at Dartmouth, including the V Foundation for Cancer Research, the Mary Kay Ash Charitable Foundation, the Susan G. Komen Breast Cancer Foundation, and the Elsa Pardee Foundation. He's only this year nearing the end of his first R01 grant, and he's optimistic about his chances for renewal.

Still, even now, in the middle of his career, DiRenzo says he has no shortage of questions for Dmitrovsky. "I was very fortunate to have a chair who believed strongly in the mentoring aspect" of his role, says DiRenzo. "It made a big difference, that's for sure."

Duane Compton, Ph.D., DMS's senior associate dean for research, agrees. "Junior faculty success can almost be one-to-one correlated with the amount of mentoring—the time and quality of mentoring—that they get," says Compton, a biochemist.

That's why he and others at DMS are looking at ways to match junior faculty with senior faculty whose research is in a similar field and who have the time and willingness to mentor a young investigator. Often the chair of a department is able to fill this role, as was the case with Dmitrovsky and DiRenzo. Likewise, Briggs frequently turns to her chair, Yeh, for advice on such matters as writing a budget and hiring lab staff.

But, as DMS Dean Wiley "Chip" Souba, M.D., Sc.D. points out, the chair of a department "can't do it all alone," and there may be other senior faculty who know more about a given junior faculty member's line of research. For those and other reasons, it's important to have ways to link junior faculty to senior faculty, not just within departments but also among different departments and across the whole institution.

In addition to mentoring, part of supporting new research faculty, points out Souba, is making sure that they have good lab space and a sizable start-up package that will fund their salary and research expenses—which range from technicians, postdocs, and graduate students to research animals, equipment, and supplies—for a few years.

After five years, junior faculty should have been able to secure their own funding, but many achieve that goal sooner. And sometimes, new faculty members arrive at DMS with their own start-up money, like Briggs's K99/R00 award.

DMS is currently recruiting junior scientists in several key areas, such as cancer, neuroscience, lung biology, inflammation, biostatistics, and bioinformatics. To aid in recruiting and supporting new faculty, DMS is also focusing on getting more so-called "mega-grants." These are multimillion-dollar awards that go to teams of investigators rather than to individuals. They can be used in a variety of ways to support junior faculty, as well as senior faculty and young scientists still in training.

For example, DMS computational geneticist Jason Moore, Ph.D., is overseeing a recent $11-million grant from the NIH to assist a network of northern New England institutions in recruiting, training, and supporting young quantitative biologists. Moore, the Third Century Professor of Genetics and of Community and Family Medicine, says that the grant will encourage junior faculty to examine different aspects of the way genes and environment interact in causing or preventing diseases. Other DMS-led mega-grants secured in recent years include a $6-million renewal from the NIH for immunological research; a $10.5-million renewal from the NIH for lung disease research; and a $29.8-million U.S. Department of Health and Human Services grant to develop readily deployable devices that can measure levels of radiation in survivors of radiological and nuclear catastrophes.

Mega-grants, says Souba, act as magnets, attracting the best young scientists, postdoctoral fellows, and graduate students to an institution.

The increasing focus on team science and mega-grants is not unique to DMS, but "the willingness to collaborate and work as a team" is unusually high at Dartmouth, says Souba, who arrived at DMS a year ago. That's a message that Souba delivered directly to Farran Briggs, when he met with her recently.

"People are very open to collaborate [at DMS]," he told her. "You can call them up and they'll say, 'Oh, yeah, let's get a cup of coffee.' And that's so critical for a young person like yourself."

Briggs had already found that to be true. "Within a few weeks of being here," she told the dean, "I was already solicited to be a part of three other grant proposals."

Although DMS faculty may seem less concerned with who's going to get the credit for a research

JON GILBERT FOX

James DiRenzo, Ph.D.
Associate Professor of Pharmacology and Toxicology

Education: University of Notre Dame (B.S. in biological sciences, 1988); University of California, San Diego School of Medicine (Ph.D. in biomedical sciences, 1996); Dana Farber Cancer Institute (postdoctoral fellowship)

Research: Investigating cellular and genetic mechanisms of adult epithelial stem cells and cancer stem cells in the breast

Came to DMS: 2001

Career stage: DiRenzo credits his department chair, Ethan Dmitrovsky, with teaching him how to survive and thrive as a PI.

"Not everybody can be an investigator," says Green, who holds DMS's Raymond Sobel Professorship of Psychiatry. "What it takes is what scientists tend to call 'fire in the belly.' . . . You have to be willing to submit things that get turned down . . . to keep batting your head against the wall a little bit."

finding or for obtaining a grant than faculty at other places, they still want to get promoted and advance their careers. And collaborative, team science doesn't always fit well with the rules that have historically governed promotions.

The tradition in academic medicine has been that faculty are promoted based largely on the success of their individual research programs, as measured by the number of high-profile papers they were the lead author on and the number of large grants they were the principal investigator (PI) for. But at DMS, the rules are changing.

"Team science is something that is to be not only accepted but actually encouraged," says Leslie Henderson, Ph.D., DMS's senior associate dean for faculty affairs. Over the past three years, Henderson has led a revision of the criteria according to which DMS appointments, promotions, and titles are bestowed. Under the new guidelines, team science is highly valued, says Henderson.

In fact, working as a team is not just highly valued but critical to doing translational research. Translational science bridges the gap between laboratory investigations and clinical applications. Translational science has become a major focus for top academic medical centers across the country, including Dartmouth, and for the NIH.

At the heart of translational research is the physician-scientist, a medical doctor who treats patients but also spends some time doing research. Physician-scientists have been conducting what amounts to translational research for centuries, long before the phrase was coined. In fact, some of the greatest discoveries in the early days of modern medicine were made by physicians who ventured from the clinic into the laboratory to investigate illnesses or peculiarities they had observed in their patients. For example, it was a physician and a medical student who discovered insulin, the life-saving treatment for diabetes.

But today, physicians' translational role more often works in the other direction—a process known as "bench-to-bedside" research. Andrew Schafer, M.D., a professor of medicine at Weill Cornell Medical College, has written about this process in a book titled *The Vanishing Physician-Scientist*. In either the lab-to-clinic or the clinic-to-lab model, physicians play "the pivotal role of applying the findings of basic science to patient care," Schafer notes. So it follows, then, that for an academic medical enterprise to have a thriving translational research program, it must support and nurture young physician-scientists.

That's something that Alan I. Green, M.D., the chair of psychiatry at DMS, knows about firsthand.

When Green began his career in research, in the early 1980s, he had just finished his clinical training in psychiatry, and research funding was nearly as tight as it is today. But he was determined to find a way to both practice psychiatry and conduct research. At first, he applied for and received some small grants and collaborated with others on their grants. It was several years before he got his first R01, and his application wasn't even accepted on its first submission. The NIH review committee ranked it very favorably—in the 12th percentile—yet it still didn't make the cut its first time around.

"Not everybody can be an investigator," says Green, who holds DMS's Raymond Sobel Professorship of Psychiatry. "What it takes is what scientists tend to call 'fire in the belly.' . . . You have to be willing to submit things that get turned down and not get offended, not get disappointed, or not lose hope because the competition is extremely tight. And you have to be willing to keep batting your head against the wall a little bit, until you figure out how to do this and . . . get good at it."

Green learned how to "get good" at research from one of his mentors, Joseph Schildkraut, M.D., a Harvard psychiatrist and physician-researcher.

"He used to say to me," recalls Green, that "at that point in his career, my career was more important to him than his own career. So he was willing to read what I put out and critique it and give me ideas . . . point out problems that he saw in it."

Since a mentor has to be willing to put the interests of the junior person first, says Green, it's not always easy to find someone willing to do that. That's one of many reasons that Green is leading the new Dartmouth Center for Clinical and Translational Science, dubbed SYNERGY.

SYNERGY aims to provide resources, technologies, training, and expertise to scientists working in clinical and translational research at Dartmouth. It has already made more than two dozen pilot grants to DMS translational scientists since 2008. In 2011, SYNERGY launched the Mentored Career Development Program and named two SYNERGY Scholars: Auden McClure, M.D., an assistant professor of pediatrics, and Matthew Havrda, Ph.D., an instructor in pediatrics.

As SYNERGY Scholars, McClure and Havrda are matched with at least two senior scientists who oversee their progress in developing their own translational research programs. The award also covers 75% of their salaries and provides funding for research assistants, supplies, and tuition expenses.

The Hitchcock Foundation, an internal Dartmouth-Hitchcock research funding organization,

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JON GILBERT FOX

Alan Green, M.D.
Raymond Sobel Professor and Chair of Psychiatry, Professor of Pharmacology and Toxicology

Education: Columbia College (premed and A.B. in history, 1965); Johns Hopkins School of Medicine (M.D., 1969); Beth Israel Hospital, Boston (internship); Massachusetts Mental Health Center (residency)

Research: Understanding the brain circuitry in patients with co-occurring disorders—schizophrenia *and* alcoholism, for example—and developing psychopharmacological treatments for them

Came to DMS: 2002

Career stage: Green says that he's "gotten better" at juggling research with his other responsibilities, but even he admits that grant-getting can be a challenge.

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also has a program that funds junior investigators who do clinically oriented research.

"To be a top-rate academic institution," says Green, "we need to be able to provide opportunities for our brightest junior people." Those opportunities can then launch them to the next level—securing outside funding for clinical translational research.

Jim DiRenzo agrees. As the scientific director of the Comprehensive Breast Program at Dartmouth's Norris Cotton Cancer Center, he serves as a conduit between clinicians and basic scientists who are conducting breast cancer research.

"Translational research is so hard and it's so multidisciplinary that any mentorship that you can get [is] of value," says DiRenzo. "It's one thing to say, 'I know how to operate my lab and I know which research questions I think are interesting.'" But it's "much more demanding" to do research involving many different specialists—such as clinicians, epidemiologists, statisticians, and pathologists.

Succeeding as a translational researcher can be even more difficult if you've got a full or nearly full clinical schedule, which is often the case for physician-scientists. Carving out the time for research has always been a struggle for practicing physicians.

For over 20 years, Dean Souba was a practicing cancer surgeon and a scientific investigator, researching amino acid metabolism. So he understands the competing demands of the clinic and the laboratory. But times were different when he was starting out, Souba admits. "I came up at a time when the pressure or the mandate to produce clinically was not as great," he says.

Today, because of declining reimbursements from governmental and private payers, physicians are under enormous pressure to see as many patients as possible to bring in more revenue. But "to do science," says Souba, "you've got to have time. So part of our strategy going forward is to create time—not for everybody, but for select people." (Giving faculty protected time, free of clinical responsibilities, applies not only to research faculty, Souba adds. It also applies to those focused on teaching.)

"People usually come to an academic medical center because they want to do more than just take care of patients," Souba says. So figuring out how much time a physician-scientist is going to spend seeing patients versus doing research is part of recruitment negotiations. Many clinical departments at DMS have funds to support physician-scientists when they're doing research and not seeing patients. For example, Green established such funds in psychiatry some years ago.

To be sure, having protected time, good mentors, and collaborative colleagues are all key to developing a successful research career. But in the end—and no matter whether a researcher has an M.D., a Ph.D., or both—those elements are secondary to a far less tangible attribute. Green calls it "fire in the belly." DiRenzo calls it persistence.

"Of course you have to be smart," says DiRenzo, "but there are lots and lots of very smart people. The ones who are really successful are persistent."

That's heartening to a young scientist like Farran Briggs. She may shrug off her tenacity as "just a part of being a PI." But she clearly knows how to set a goal and pursue it. ■