It is widely anticipated that the sequencing of the human genome, the characterization of the human proteomic map and the underlying advance in technological know-how will give rise to an unprecedented leap in biomedical science over the next half century. It may be that the bottleneck in the equation is the availability of staff trained to understand the scientific data generated and transform it successfully into something with medical value. Such people must have detailed knowledge both of medicine and the practice of scientific investigation. Here, we present three commentaries that endeavor to explain how such hybrid researchers can be recruited, trained and retained.

Training PhD researchers to translate science to clinical medicine: Closing the gap from the other side

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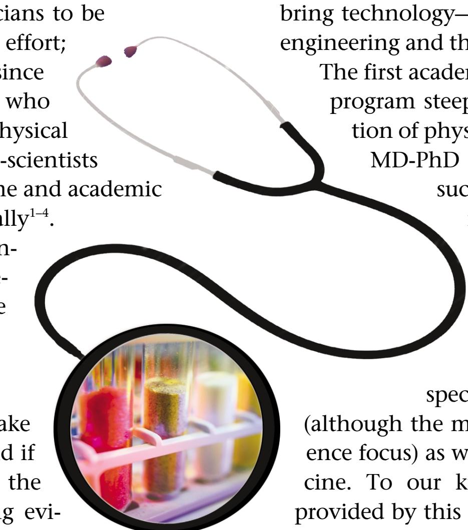
At no time in the history of the biological and physical sciences have the prospects for advancing clinical medicine been so great. However, the translation of the burgeoning scientific advances to clinical medicine remains a formidable challenge, not only because of intellectual and practical hurdles involved in implementing knowledge gained at the bench to a bedside setting, but also because of the uneven balance of experts on either side of the equation—the number of people involved in basic research is much greater than the number of people involved in its clinical translation.

We must address this growing divide, and we can do this in part by enhancing efforts to train and nurture individuals who can identify unmet medical needs and implement, or translate, new findings and technologies in their solutions. Generally speaking, we have depended on physicians to be the prime movers of the translational effort; however, as has been well documented since at least 1979, the number of physicians who are trained in the biological and/or physical sciences and the number of physician-scientists who participate in both clinical medicine and academic research have decreased dramatically[1–4]. Largely overlooked thus far is the potential of another group to be at the forefront of translational medicine: the non-physician scientists.



Teaching medicine to scientists

Is it possible to train PhD scientists to make superior contributions to medicine? And if so, how? Would such training attract the very best scientists? There is increasing evidence that the answer to the first and last questions is a resounding yes. In this commentary, we address the middle question by discussing several training models that provide a perspective. The overarching philosophy of these programs is essentially the same as that for MD-PhD training programs: if one is going to be translating laboratory research to clinical practice, one must have substantial training in both domains.

Accepting that we have robust and effective training models for basic research, the question becomes the degree to which we train basic scientists in clinical medicine. The possibilities range from a full clinical program, as for MD-PhDs such as medical scientist training programs (MSTPs), to in-depth experience in pathopysiology and clinical medicine, to short, targeted exposure to pathophysiology/pathobiology (where the short duration is relative to their entire training program or to an MD program). Below, we discuss two prototypical training models that represent alternatives to the MD-PhD option. Although the curriculum and the potential impact of these programs are outlined, we wish to emphasize that there are limited outcome data available on the programs. We close with comments about the nature of the training environment—something that we feel to be as crucial to a successful outcome as the specific curricular components of training.

HST-MEMP model

The Harvard-MIT Division of Health Sciences and Technology (HST) was established in 1970 as a joint effort between the Massachusetts Institute of Technology and Harvard University to bring technology—especially as this term reflects innovation in engineering and the physical sciences—to biology and medicine.

The first academic program offered by HST was a unique MD program steeped in basic science and geared to the education of physician-scientists, with up to 40% receiving dual MD-PhD qualifications. This program has been highly successful in producing individuals who integrate research with clinical medicine[5,6].

In 1978 the Medical Engineering Medical Physics (MEMP) PhD program was launched. Central to the mission of this program is the training of PhD scientists both in the fundamentals of their chosen subspecialty of engineering and the physical sciences (although the model can apply to trainees with a natural science focus) as well as with a firm foundation in clinical medicine. To our knowledge, the in-depth clinical experience provided by this program is unique for graduate students who will not be physicians.

The goal of the MEMP PhD program is to educate students at the interface of engineering, physical sciences and the biomedical sciences via a flexible structure that permits exploration of all the intersections of those disciplines. Students are jointly admitted by HST and a collaborating department selected from the traditional engineering or physical science departments at MIT or Harvard. Presently, we accept 10% of applicants yielding a class of 18–22 students each year depending on available fellowship funding.

Because the program accepts students with quantitative backgrounds who want to solve human health problems, we attract individuals who are comfortable in multidisciplinary environments. They are comfortable with the notion that they can navigate both the basic science and clinical enclaves at Harvard and MIT, including the teaching hospitals, in deciding on mentors, collaborators, courses and research laboratories. Applicants also are attracted to the concept of taking classes with, and working in the clinic with, medical students. The most compelling evidence we have that this program attracts the very best students is that HST-MEMP is generally the first choice of our applicants, with over 75% of admitted students matriculating, all of whom select this program over others at MIT, Harvard and other top-ranked institutions.

Depending upon their interests and career goals, students follow diverse curricular paths. The student begins with an intensive grounding in a sub-discipline of engineering or physical science at MIT or Harvard, and then passes a doctoral qualifying examination in the collaborating department, at which point HST becomes their primary institutional association.

In addition to their thesis research, students must complete seven pre-clinical courses in one of two tracks: a systems physiology or cellular/molecular track. PhD students take these courses side-by-side with HST's MD and MD-PhD students, providing a rich environment for cross-fertilization between PhD students and physician-scientist trainees. Courses are structured much like a graduate-school subject to include basic science foundations, progressive science and clinical correlates in recognition of the goals of the students, whether they are pursuing an MD or PhD degree, with the ultimate aim that research is an important part of their career. Medical subjects are integrated with physical science/engineering subjects throughout training.

Clinical work

After concluding the set of preclinical courses, students then complete a total of four months clinical training, including a longitudinal patient-care experience in one of the Harvard teaching hospitals. This opportunity to participate in clinical training, through coursework with medical students and hands-on experience, is a distinctive hallmark of the MEMP program. The clinical experience of the PhD student is divided into three parts. The first six-week period is an intensive introduction to clinical medicine. Students develop skills in patient interviewing and physical examination, they become proficient in the organization and communication of clinical information in both oral and written form and work on correlations of clinical issues with basic pathophysiology. Finally the students become familiar with the multiple components of clinical decision making and the broad economic, ethical and sociological factors that influence this decision making process.

In the second six weeks, students enhance their recently acquired clinical skills by working with a hospital ward team and are expected to function like a third-year medical student. They are directly involved in acute and longitudinal patient care, participate in patient management decisions with the house staff and attending staff, and attend regularly scheduled teaching conferences. Students take call in turn with their fellow students, including night call. They are involved in the assessment and medical management of many common diseases seen on a medical ward, such as chronic obstructive lung disease, atherosclerosis, congestive heart failure, renal failure and hepatitis. (As such, they are exposed to what is largely adult medicine; however, we are currently establishing an alternative clinical experience for those PhD students in the Cellular and Molecular track that will be more focused on human genetics and metabolic diseases in a pediatric setting.)

This frontline clinical experience has a profound influence on the student, who comes away from it with an insight into the

Table 1 Career choices by HST-MEMP biomedical engineering graduates compared with biosciences PhD and MD-PhD students

Model type:	**In-depth experience**		**Targeted exposure**		**Combined degree**	"Typical" PHD
Cohort description	PhD (engineering) with in-depth clinical experience		PhD (bioscience) with one-semester exposure to pathobiology		PhD (mostly bioscience) with full MD training	PhD (mostly bioscience) matched to MSTP cohort
Data source	HST-MEMP Alumni (1984–2001)		Tufts Alumni * (1984–1998)		NIH MSTP study ** (1971–1990)	
	#	%	#	%	%	%
Basic science/engineering department	36	39	27	30	19	53
Clinical department	26	28	23	25	43	8
Both	-	-	-	-	20	5
Total academic positions	62	67	50	55	83	65
Industry/consulting	24	26	38	42	6	30
Other	7	8	3	3	11	5
Total	93	100	91	100	100	100

* U.C. Tufts data from NAS/Arias report[8]. **, NIH data (www.nigms.nih.gov/news/reports/mstpstudy).

Table 2 Journals in which HST-MEMP graduates have published frequently

Journal name	Number of articles	Rank*
Proc. Natl. Acad. Sci. USA	35	1
Magn. Reson. Med.	33	2
Radiology	31	3
J. Orthop. Res.	29	4
J. Biomech.	28	5
J. Appl. Physiol.	27	6
J. Biomech. Eng.	27	6
J. Magn. Reson. Imaging	24	8
Ann. NY Acad. Sci.	21	9
Am. J. Physiol.	19	10
*Nature series***	18	
IEEE Trans. Biomed.	16	11
Lasers Surg. Med.	16	11
Biophys. J.	14	13
Invest. Radiol.	14	13
J. Biomed. Mater. Res.	13	15
Am. J. Roentgenol.	11	16
Circulation	11	16
Neuron	9	21
Science	9	21
Circ. Res.	8	25
Nature Biotechnol.	8	25
J. Clin. Invest.	6	37
Nature Med.	6	37

*Rank of journal in publication frequency among the PubMed-listed journals authored by MEMP grads (out of 1295 articles in 436 journals).

** Includes *Nature*, *Nature Med.*, *Nature Biotechnol.*, *Nature Neurosci.* and *Nature Immunol.*

health-care system and how physicians make decisions. They witness the successes and failures of modern medicine's diagnostic and therapeutic approaches and often formulate their goals for how their future research can affect individual patient care. Attending physicians often comment that the performance of the PhD student is indistinguishable from an MD candidate early in their third year of medical school when clinical medicine is still new to them. There are numerous formal and informal interactions between PhD and MD candidates, interactions that provide a foundation for long-term networking opportunities that facilitate future research at the interface of science and medicine.

A third bout of clinical experience comes later in the PhD training. At this point, the student constructs, with faculty advice, a one-month preceptorship that is conducted in a clinical environment. In some cases, students use this preceptorship to design or launch a pilot clinical study. In others, they seek to understand the medical management of a particular class of diseases. And in others still, they seek to define how an emerging science or technology might influence clinical medicine. The experience involves patient contact and a term paper is required.

The end result

The total time from matriculation to awarding of the PhD degree is a mean of 6.1 years—a duration similar to that for typical PhD candidates in collaborating departments at MIT and Harvard.

Table 1 illustrates the career choices of the 93 graduates who had complete training as of summer 2001 and whose positions are known. While 25% have pursued work in business or consulting, the majority (67%) of our alumni have selected academic positions. Appointing departments are quite diverse and are nearly evenly split between engineering and physical sciences in a university-based setting, and clinical departments in a medical-center setting. Recent trends have strongly favored industry and academic bioengineering programs (where there has been an abundance of open faculty positions). This trend can be seen by comparing data in the table for all graduates with the career choices of the cohort that graduated between 1995 and 2001 for whom 3 out of 4 in academia have selected basic science and engineering departments. Only five alumni are in positions not directly related to the biomedical enterprise.

Although MEMP is still a relatively young program, its graduates have been very successful in careers that reflect their training at the boundary of science, engineering and clinical medicine. The impact of MEMP on medicine is difficult to assess quantitatively. However, we do know that at least 17 of the 59 alumni (25%) from the 1981–1995 cohort are directly involved in moving their scientific discoveries to the clinical arena, clearly supporting the notion that investigators without an MD can become actively involved in 'bench-to-bedside' applications.

Those graduates who have entered academia have been successful in garnering grant support. Of our graduates in US academic departments, 60% of those who graduated before 1990 presently have active NIH grants. This compares very favorably to graduates of MSTP programs, where 50% of those more than 10 years post-PhD have held an NIH grant (http://www.nigms.nih.gov/news/reports/mstpstudy/mstp-print.html#sources). MEMP alumni publish in leading basic science and clinical journals, with the most frequent journals including this one and PNAS as well as specialty publications (Table 2).

The value of the extensive clinical training for our PhD students has been questioned and assessed in several ways over the past decade, and in every instance has resulted in an overwhelming endorsement. For example, one advisory group concluded, "the value of the MEMP clinical experience is inestimable. For engineers, medicine is demystified, and the interface between engineering and the health sciences is erased. In the process, the intimidation of the clinical arena is dispelled… There was a resounding positive endorsement from students, alumni, and faculty alike."[6] In an alumni survey completed in 1996, we asked the following question: "MEMP requires a particularly heavy dose of medical courses, including a substantial clinical experience. The latter is unique in biomedical engineering doctoral programs. Should this aspect of the MEMP curriculum be maintained? Has it been relevant to your own career?" The experience was unanimously praised as an essential element of the program, one that had attracted them originally and had affected their careers in important ways.

The targeted exposure model

The notion of incorporating clinical concepts into graduate training is not new. From their inception dating back to the early 1960s, formal biomedical engineering (BME) doctoral programs have embraced (patho)physiology as a core requirement. For instance, at Johns Hopkins, one of the oldest and most prominent programs—and to our knowledge the only BME department within a US medical school—BME PhD students are required to join medical students in taking first-year basic science courses

(Molecules and Cells, Immunology, Neuroscience and Physiology/Histology). Although basic in their orientation, these courses include clinical correlates.

Some programs, such as the BME program offered by the Joint Graduate Group in Bioengineering at University of California (UC) San Francisco and UC Berkeley, have established an elective course whereby students are exposed to patient interactions. In addition many students elect to expand their medical knowledge by taking medical courses with medical students. Although many other programs have options similar to those at Johns Hopkins and UC San Francisco/Berkeley, in many cases the courses are taken within BME and do not include medical students (http://www.whitaker.org).

Although most BME programs use a targeted exposure model to provide a medical perspective, to our knowledge the new BME program at Purdue University, where students have a summer clinical internship, is the only program other than HST-MEMP requiring both substantial coursework and an extended in-depth clinical experience. It is interesting to note that with the rapid growth in the number bioengineering programs, some are expanding the medical science opportunities while others are moving away from medical science choosing not to include pathophysiology/pathobiology courses.

In a parallel trend, several PhD programs in the biological sciences have introduced targeted medically relevant material into their curriculum. To our knowledge, the most longstanding of these is the program introduced in 1983 by Irwin Arias at Tufts University in which selected PhD students take a one-semester course in pathobiology. Students interact with patients, handle pathological specimens and see major diagnostic and therapeutic facilities, as a basis for delving into pathobiological mechanisms[7,8]. Washington University launched a similar program in 1992 wherein students have a two-semester experience in human pathology.

Other efforts to address the need for clinical training have been short-lived and abandoned due to lack of funds. For example, Harvard Medical School has twice had such programs. From 1978-1983 some 50 graduate students were offered a pathobiology course. More recently, 16 newly-admitted students in the Division of Medical Science, were provided the opportunity to augment their studies with several preclinical courses and organized regular visits to hospitals to meet clinical investigators. This, and the Tufts and Washington University programs are three of eight that were funded briefly by the Markey Charitable trust. Their goal was to enhance the knowledge of clinical medicine of PhD students through one or more additional courses. Each of these programs seems to be viewed as extremely attractive and successful by the students, but the only program for which outcome data are known to be available is the Tufts program (Table 1)[7]. The success of the Pathobiology course offered by Tufts in influencing career decisions can be appreciated by noting the substantial number of graduates who have selected academic positions—especially in medical centers—compared with the graduate cohort in the MSTP study.

Conclusions

Two key conclusions can be drawn from these graduate programs with experiences in medical science. These programs attract exceptional candidates and draw many more qualified applicants than available positions. Although outcome data are incomplete, alumni of these programs are overwhelmingly retained in their positions and successful in biomedical careers. Many are in positions where they can connect with the patient-care enterprise during the course of their research, and thus have the potential to create a vibrant link between the clinic and basic research.

There are several important lessons learned that are not obvious from a cursory look at curricula. First, giving students first-hand knowledge of human disease through direct interactions with patients is crucial. This can happen in a more passive fashion, such as bringing patients into classes in graduate courses, or more actively by bringing students to the clinical setting. Such experiences lack the power of a period of total immersion in the clinical milieu but certainly have had positive effects in decreasing the gulf between the bench and the bedside. Second, there are benefits to teaching graduate students clinical medicine and medical science in the same way one teaches medical students. In other words, it is not necessary (and is in fact undesirable) to ask an instructor to modify what and how they teach to accommodate the fact that these students are not medical students. Third, as any student making the transition from preclinical to clinical work can testify, there is a world of difference between learning in the classroom and implementation on the wards. The opportunities, limitations and constraints of the clinical environment are far more difficult to appreciate for students who have not had to function in that environment.

Finally, one of the most important lessons has come through our organizational structure. We have had the benefit of training MDs, PhDs and MD-PhDs—with about 120 of each enrolled at any given time—under the auspices of a single academic unit, thus they all quite naturally traverse between bench and bedside. By contrast, MD and PhD students are usually in wholly separate departments and even institutions, and there are many pressures to maintain that segregation.

In summary, students who augment their graduate training with in-depth experiences in clinical medicine are, by many measures, as successful as the MD-PhD cohort in terms of retention in academic biomedical careers, in the scope of contributions ranging from basic science to clinical, and in involvement in the process of translating scientific advances to the bedside.

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