Lost in Translation: The Future of Cancer Research?

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"When Lord Lucan received the order from Captain Nolan, and had read it, he asked, 'Where are we to advance to?' Captain Nolan pointed with his finger to the line of the Russians, and said, 'There are the enemy, and there are the guns'."

Alfred, Lord Tennyson
The Charge of the Light Brigade, October 25, 1854

The formula was very simple: discover the secrets of the cancer cell, identify molecular targets, develop specific drugs, and cure the disease. It was the hand-off from laboratory to clinic that proved much more challenging. Translating scientific discoveries into improved therapies for cancer patients turned out to be one of the most difficult human endeavors ever attempted. Other challenges, like sequencing the human genome, landing a spaceship on Titan, or overcoming "The Curse of the Bambino," have been handled in stride by application of appropriate resources and a winning combination of human ingenuity and hard work. Thus, why is the cure for cancer apparently still lost in translation?

It is true that the scientific problem is daunting; we are only just beginning to grasp some of the complexities of the cancer cell. In fact, the more we learn about the molecular diversity of tumors, the more we realize that cancer therapies must be tailored to molecularly defined subsets of tumors. Therefore, patients must be segregated into ever-smaller groups for appropriate treatment. This scenario does not match the current business model in the pharmaceutical industry that requires large numbers of patients to benefit from new drugs so that the return on investment is sufficient to cover the significant drug development costs. The ability of the cancer cell to escape from almost any treatment by mutation or epigenetic disguise reduces the success rate of even the most potent targeted therapy. Thus, it is likely that successful cancer therapies will involve the use of multiple drugs, attacking different targets, in concert. However, it is problematic to use drugs from several companies in combination trials under the existing practices and regulations. Certainly, the classic clinical trial design, which was optimized for testing cytotoxic therapies, needs to be updated and adapted to the needs of molecular targeted therapies. Significant efforts are under way in laboratories, clinics, and government offices to understand and overcome all of these hurdles. However, there may be a more fundamental and endemic problem that must be addressed by a change in the culture of biomedical research. This is the problem of perception and communication.

Developing new treatments for cancer requires an unprecedented level of integration of all aspects of cancer research. Population biology and laboratory science must be integrated with clinical medicine. Leads uncovered by large-scale science projects must be picked up and investigated by small laboratory groups. Industry, big pharma, as well as small biotech, must work in harmony with academic scientists and with government officials. Patients and patient advocacy groups need to be clearly informed so that they can participate in the decisions that have such a profound impact on their lives. All artificial barriers that are impediments to progress must be removed to accelerate translation of new ideas into clinical treatments for the prevention and cure of cancer. However, we still communicate with each other in obsolete terms emphasizing differences that may no longer exist and creating boundaries where there should be an open range for free interaction. We describe ourselves in archaic terms, such as basic-scientists, applied-scientists, translational-scientists, and physician-scientists, as if these defined distinct species. Sometimes, we even use these monikers as pejorative terms when debating resource allocation. This misunderstanding and mistrust promotes fierce competition for limited resources and an attitude of protectionism that can be very damaging. How is it possible to build a transdisciplinary team in this polyglot boarding house? I submit that there is no place in cancer research for hyphenated scientists.

By definition, all research supported by the National Cancer Institute is applied. According to the mission statement, the National Cancer Institute,"...supports research, training, health information dissemination, and other programs with respect to the cause, diagnosis, prevention, and treatment of cancer, rehabilitation from cancer, and the continuing care of cancer patients and the families of cancer patients."

Indeed, the NIH supports this mission in many ways and, of course, a host of biomedical organizations, fundraisers, volunteers, etc., combine to support the cause of cancer research. The broad base of support is a principal strength of our system, as it is hard to predict from where the key idea or finding will emerge that significantly impacts the National Cancer Institute mission. For example, some of the critical information that unraveled the cell death pathways usurped by mutations in many cancers came from pioneering studies of the humble worm, *Caenorhabditis elegans* (http://nobelprize.org/medicine/laureates/2002/).

There is no doubt that the link between laboratory and clinic is the place where most is lost in translation. Perhaps our expectations are too great. We place an unacceptable burden on individuals who are required to treat patients, coordinate clinical trials, compete successfully for several grants (this will be more difficult in the future in the wake of the announced reduction in the payline for RO1 applications), and conduct the highest-quality laboratory research while managing a complex, multitechnology workplace environment (to say nothing of the many required committees and reviewing activities). The exceptional individuals who successfully manage this high-wire balancing act cannot be used as career models because they each followed unique paths to achieve their present positions. Investing more into M.D./Ph.D. programs may not be the best way to generate more of these rare leaders. We need to look at our entire biomedical training program with a fresh eye, as we cannot expect a single person

to attain the highest level of excellence in all of these endeavors simultaneously. In addition, we need to consider new avenues for exposing young graduate students and postdoctoral fellows to the problems facing cancer patients in the clinic. The inspiration and motivation they experience may change career direction for a lifetime. There has been an interesting demographic change at the annual AACR meetings over the past few years. Based on a nonstatistical personal survey, it seems that scientific sessions dealing with advances in treatment, which used to be the denizen of aging physicians, are now populated by fellows, first-year graduate students, and even undergraduate students seeking knowledge and inspiration for future career tracks. There is no shortage of enthusiasm and energy in cancer research, there are many opportunities to make a real difference, the science challenges the best and the brightest from across the board, but the Byzantine career structure makes them shy away.

How does a young medical student maintain the dream of discovering a cure for cancer when she or he is channeled through such a long training path involving multiple clinical specialties before being offered a chance to pursue research? Or worse, is the M.D./Ph.D., supremely talented at exam skills and multitasking, ready at the age of 30 to compete with the best of the Ph.D. graduates in postdoctoral laboratory science? When in their training do we provide those fresh-faced Ph.D.s with exposure to the real-life problems of medicine and the practical difficulties encountered attempting translational research? Instead of promoting teamwork, we teach competition and suspicion, and we create barriers to collaboration.

At the very least, we should acknowledge that cancer research is a broad continuum and that diverse approaches are not only equally valid, they are essential if we are to succeed. Perhaps we can be a little more inclusive in our definitions of translational research and we can be careful not to pigeonhole individuals, allowing more investigators to cross-traditional boundaries? Most importantly, we need to encourage teamwork, cooperation, and open communication. Cancer research thrives from a constant influx of new ideas and perspectives in an atmosphere that promotes debate. Let all the ideas compete in an open arena so that the best can be selected for support. In this age of "big science," it is even more important to choose our targets carefully, to select the best people, and pick out the most deserving projects for investment of major resources. This investment is not just the dollars and cents of grant support, it also includes the hopes and dreams of cancer researchers and patients alike. The guiding principle must be quality, as resources become tight it will become harder to prioritize only the best and most promising science for support. But the alternative is to squander our resources by rushing headlong into the fray without thinking, valiantly attacking the wrong target, because of miscommunication.

"*Forward, the Light Brigade!*
Charge for the guns!' he said:
Into the valley of Death
Rode the six hundred."
Alfred, Lord Tennyson
The Charge of the Light Brigade,
October 25, 1854