Research: The Moving Parts

Vincent T. DeVita Jr, MD

In the process of going through transformation, the American Cancer Society (ACS) convened a group called Research 3.0 that made recommendations to the ACS Board about how to transform its research programs in the next decade. It is worth looking at Research 3.0 to examine how it will affect 2 of the moving parts of research programs: the investigators who do the research and the grants or other instruments that support their research.

A good place to start is by defining what we mean by research. How does clinical research differ from basic research; what is translational research, and what do we mean by applied research and applied science? Louis Pasteur said there is no such thing as applied research, only research and the application of the results of research. The latter is applied science, the application of what we know to diseases. The failure to distinguish between research and applied science causes much confusion when trying to interpret science budgets and could potentially be a problem in interpreting the recommendations of Research 3.0.

Research is really a methodology. All good research is characterized by the use of strong inference, a term coined and described in detail by John Platt in 1964.1 It involves setting up alternative hypotheses, the designing of an experiment or experiments that will exclude one of the hypotheses, developing new hypotheses, and repeating the process until only one hypothesis remains standing. In other words, it involves keeping the facts and throwing away hypotheses. This is true in the clinic as well as in the laboratory, but this is not easy to do. Many researchers get attached to their hypothesis and design studies to prove it, rather than disprove it. Because of this, the literature is filled with studies defending hypotheses that could have been easily disproved in a properly designed study. All good researchers use strong inference to ask fundamental (basic) questions regardless of the size of the particle under study. Science administrators have struggled for decades trying to define the difference between clinical research and basic research but, as you can see, there really is none, methodologically speaking, if both are testing hypotheses using strong inference.

It is easier to test hypotheses in the laboratory where experiments can sometimes be set up and completed in days or weeks compared to the years required for clinical studies. Yet, there are some classical examples of fundamental (basic) research in the clinic, such as in Bernard Fisher’s studies testing the hypothesis that lymph nodes were not a barrier to metastases in breast cancer but a sign that a tumor had already spread,2 and in the experiments that proved it was possible to cure childhood leukemia and advanced Hodgkin’s disease with combination chemotherapy in adults.3,4 It is also much more difficult to design experiments to exclude a hypothesis in the clinic when the particles are whole humans who can talk back to you.

When I was Director of the National Cancer Institute (NCI) Treatment Division, I reviewed about 1500 of NCI’s clinical protocols and looked for those that were using strong inference. Only 5% to 10% of them were actually testing a hypothesis; the rest were applied science. Now, there is nothing wrong with applied sciences as long as it is identified as such, but when good scientists are offered examples of applied science as clinical research, they are understandably confused at what passes for research by clinicians.

Finally, translational research was a term introduced by my successor as NCI Director, Sam Broder. It simply refers to laboratory research that has visible potential applications in the clinic, although the time span from discovery to application is never clear. At the time he coined the phrase, in the early 1990s, it was often difficult to see the clinical application of a study on what might have been an obscure molecule. Translational research has lost much of its meaning today, because virtually all laboratory science has visible clinical applications and most grants are categorized as translational research. Yet, translational research is different from applied science, because it involves the use of strong inference.

The most important recommendation of the Research 3.0 group was to urge the ACS CEO to double the funds devoted to research in the ACS budget over 5 to 7 years. That requires no explanation. It does require that the ACS raise substantially
more funds. The extramural grant program will be the main beneficiary of any increase in funding, and the recommendations of Research 3.0 for the extramural research program are shown in Table 1. There are 2 points to note from Table 1. The first is that 50% of extramural funds are to be devoted to basic science. Presumably, this means all studies that ask fundamental questions, using strong inference, whether they take place in the laboratory or the clinic. The second point is the awards in this category will be made only to those in their early careers, who are under the age of 45. The logic for this is that in order to assure the future of research, we need to assure that young scientists are provided the stable support they need to encourage them to stay in the field. But it can be argued that supporting young investigators is really the job of the National Institutes of Health (NIH) and NCI, because the ACS’s research program is too small to affect the long-term needs of the nation’s young scientists, and NIH and NCI have special programs for young investigators. In addition, other organizations such as the American Association for Cancer Research, the American Society of Clinical Oncology (ASCO), and the ASCO Foundation and others have substantial special grant programs for young investigators. It can also be argued that the ACS should be focused on discoveries that help eradicate cancer. In that case, discovery knows no age barrier, and major discoveries have been made at both ends of the age spectrum. By recommending age discrimination in awarding grants, the ACS could be hindering progress toward its basic goals.

My favorite example of great research at the nether end of the age spectrum was the discovery that information is transmitted by DNA, not proteins, which laid the foundation for Watson and Crick’s work on the structure of DNA and the molecular revolution that followed.5,6 It was made by a retired scientist at the Rockefeller University, Oswald Avery, and has often been referred to as the most important discovery that never won a Nobel Prize. Linus Pauling won his Nobel Prize for work he did in his 50s, and he was the close runner-up to Watson and Crick for the discovery of the structure of DNA; thus, he might have been the first person to win 3 individual Nobel Prizes. He continued working productively in the lab into his 80s. E. Donnall Thomas and Joseph E. Murray won a Nobel Prize for the definitive and fundamental clinical research they did on organ transplantation while in their 50s and 60s.

A truth in mathematics is that if you haven’t done anything major by the time you are 40, then you probably never will. Not so in biology. Biology is very complex and it takes time to develop the insight and wisdom to solve biological problems. Leó Szilárd, the famous nuclear physicist, who gave us the nuclear chain reaction, decided at age 47 to become a biologist. After that, he quipped, “I never had a decent bath.” While a physicist, Szilárd thought through the mathematics of a problem while soaking in a bathtub and could solve complex problems in one bath. But when he became a biologist, he said, he often had to interrupt his bath to go look things up! Senior physician-scientists do much of the best work in clinical investigations, as was the case with E. Donnall Thomas and his work on allogeneic marrow transplantation. They need years of experience to marshal the resources to design and carry out novel clinical experiments that use strong inference.

The remaining half of funds, as shown in Table 1, will be in support of grants in response to Requests for Applications (RFAs) that will attempt to align our supported research with ACS mission-critical questions. But notice that half of those funds will go to mission-critical questions in “applied research” or, strictly speaking, applied science. These monies will not support fundamental research, the lifeblood of discovery. In this category of applied science, no age restriction will apply. Finally, the other half of funds allocated in response to RFAs will go to support in areas designated as mission-critical but these funds will also be restricted to young investigators receiving research scholar awards. In all, 75% of ACS extramural research funds will be allocated to young investigators. The 25% for which scientists of any age are eligible would be funds devoted to the application of the results of research, or applied science, not discovery.

Much of research today is called “Big Science” because addressing major issues often requires millions of dollars typically not provided in small research grants such as the research scholar awards provided by the ACS. The type of support instrument to foster discovery has been a subject of heated debate for years. At the NIH, the preferred grant instrument is called the RO1 grant, which has supported

| TABLE 1. Recommendations for the Extramural Grant Program Made by the Research 3.0 Group Extramural Program |
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| 1. 50% of funds allocated toward basic science—only early career investigators, no RFAs |
| 2. Allocation of remaining 50% |
| a. 25% for Requests for Applications (RFAs) for mission-critical questions in applied research |
| • Includes funding for program evaluation |
| • Collaboration with American Cancer Society scientists a consideration, but not required |
| • No age restrictions |
| • Transdisciplinary |
| • New funding mechanisms |
| b. 25% for RFAs for research in mission outcome priority areas |
| • Only early career researchers |
| • All Research Scholar Grants (RSGs) |

Program Made by the Research 3.0 Group Extramural Program
investigator-initiated research, ideas springing from the fertile mind of a single scientist, and typically supports a small laboratory run by a single investigator. ACS research scholar awards are similar to RO1 grants. Research 3.0 recommended the ACS reexamine the use of large program project grants to accommodate the current collaborative nature of science. These grants would support teams of scientists each doing a part of a project focusing on one area or a specific tumor. Because these kinds of grants are large and expensive, their resurrection will depend on the ability of the ACS to raise the funds to support them or require a reduction in the support for research scholar grants.

There is often conflict between program directors who want to see the science of their programs advance quickly and need a more structured approach, and those who feel that investigator-initiated research remains the future of science. This is not a new issue. Years ago, when the author was Director of the NCI and the National Cancer Program, the institute faced criticism for siphoning monies away from RO1 grants into other instruments to support research. The other instruments were Program Project grants (PO1) of the type recommended by the Research 3.0 group, and even research contracts, an instrument generally disliked at the NIH and research universities because it implies external direction of the scientist doing the work.

To address this question, we designed a special study. The NCI assembled a panel of elite scientists who were experienced in both laboratory and clinical sciences and asked only that they meet and deliberate to identify what they thought were the 10 to 15 most important advances in cancer science and medicine in the preceding 20 years. After several weeks of in-person and phone meetings, they identified 13 different discoveries. We then thanked them for their work and disbanded the committee and hired an external contractor to work backward from each discovery, to trace the papers they produced in the scientific literature, to the funding instrument that supported the initial work. The results were surprising. No single grant mechanism dominated. Many different mechanisms supported the traced work (Fig. 1). The figure shows the percent of NCI-supported trace papers by funding mechanism and type of advance. For studies considered laboratory-based, 3 mechanisms dominated: the RO1 grant, the NCI Intramural Program, and the surprising one, the research contract. However, even the P30 grant, which is the cancer center support grant, through its pilot project grant mechanism, supported the initial work of one investigator who went on to win a Nobel Prize. Only the R10 grant, which supported the clinical trials program, did not, by definition, play a role in laboratory-based studies.

For the clinical advances, the dominant grant was the program project grant, the PO1, followed by the R10, the P30, and NCI Intramural Program. The RO1 grant comes in last, which has not been a support instrument that has worked well for clinical investigations. Finally, fundamental advances in epidemiology were most often supported by research contracts, with equal but lesser support coming from PO1 and RO1 grants and even cancer center core grants.

Actually, this was a data-rich study and is presented here in its most simple form to illustrate the central message that research flourishes when there are multiplicities of ways of supporting it. This is due to the fact that different kinds of projects require different types of support to carry them out at different times in their evolution. One shoe doesn’t fit all. This is especially true in the era of Big Science. The most surprising finding was how often the research contract, often considered an inferior instrument, played an important role in the identified projects. This may be due to the tight focus and flexibility contract support provided to investigators, which allowed research projects to move forward more rapidly. These findings highlight the importance of the recommendation that the ACS reexplore different grant mechanisms to match the needs of modern research.

There is another important point about larger project grants. Although more senior scientists generally direct them, because they have the experience to coordinate...
complex projects, they often include support for young scientists as part of the project. This important means of support is often overlooked and needs to be considered as one of the other ways to support young scientists in the age of modern science. The Research 3.0 recommendation that 25% of funds go to support mission-critical areas in applied science, with no age restriction, is important but needs clarification of the definition of applied research to be sure it includes projects that support fundamental research with clinical application, or translational research, and not just applied science.

Everything we do that works was developed through research. As volunteers for the ACS, we need to be reminded of this when the temptation is to shy away from research support in favor of programs to provide access to care. As sophisticated as cancer care has become, it is still what Lewis Thomas referred to as “half way technology.” In this sense, cancer is unique as a discipline. Other fields are much more settled in their ways, able to focus on one organ or a small group of disorders affecting one organ, rather than the hundreds of entities affecting every organ in the body. The cancer field is unsettled and is likely to be that way for some time.

Although the ACS spends about 15% of its budget on research, only about 10% is devoted to its most visible component: the extramural research grants. There could be a better balance of resources between what we know works and the allocation of resources to research programs that can deliver the next generation of advances.

Research 3.0, in its totality, represents the beginning of a major new thrust for ACS in the area of research support. If the Society can double the funds in the research program in the next 5 to 7 years and broaden the ways it supports research to match the extraordinary pace and opportunities of modern research, it will play an increasingly important role in unraveling the mysteries of cancer and fulfill our mission to create more birthdays, and meet the expectations of our donors and volunteers.

References
1. Platt JR. Science, strong inference – proper scientific method (the new Baconians). Science. 1964;146:347-353.
2. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med. 2002;347:1233-1241.
3. Frei E III, Karon M, Levin RH, et al. The effectiveness of combinations of antileukemic agents in inducing and maintaining remission in children with acute leukemia. Blood. 1965;26:642-656.
4. DeVita VT Jr, Serpick AA, Carbone PP. Combination chemotherapy in the treatment of advanced Hodgkin’s disease. Ann Intern Med. 1970;73:881-895.
5. Avery OT, Macleod CM, McCarty M. Studies of the chemical nature of the substance inducing transformation of pneumococcal types: induction of transformation by a desoxyribonucleic acid fraction isolated from pneumococcus type III. J Exp Med. 1944;79:137-158.
6. Watson JD. The Double Helix: A Personal Account of the Discovery of the Structure of DNA. New York, NY: Atheneum; 1968.
7. National Institutes of Health. An Assessment of Factors Affecting Critical Cancer Research Findings. NIH Publication 90-567. Bethesda, MD: NIH; May 1990.
8. Thomas L. The Lives of a Cell: Notes of a Biology Watcher. New York, NY: Viking Press; 1974.