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Building a Translational Research Portfolio: Promise and Pitfalls

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Introduction

Because the Carle Foundation Hospital, its affiliates and collaborators are working towards building a robust translational research portfolio, this is the perfect moment to contemplate the implications of charting that path. The promise is noble; the potential pitfalls many. The promise of translational research, be it at Carle or elsewhere, is simple, clear and compelling. Translational research is anticipated to bring more effective, less toxic medical diagnostics and treatments to patients faster than ever.

It is not, however, on the promise that one needs to focus. Focusing on the promise of such an exciting innovation in medical research just happens of its own accord. Rather, the contemplation needed is about the pitfalls posed by our eager embrace of this new research paradigm. Only in so doing can we realistically hope to fulfill the promise.

Needing to contemplate the balance between rushing forward and engaging in deliberative thought about the possible pitfalls in research is not specific to the translational arena. Some of the translational research pitfalls mimic those throughout all of research. Others mimic the problem seen primarily in the clinical research setting. Only some are unique to the translational research paradigm. But because our scientific focus has become so trained on the translational research engine and because Carle is at the beginning of its own translational leap forward, serious attention to all these potential pitfalls is timely and necessary. In addition to helping Carle and its partners avoid some of these pitfalls, moving forward thoughtfully can establish Carle as a model for how best to transition an historically clinically

centered community hospital system into a community hospital system respected for both its clinical care and its research.

Pitfalls Generic to All Research: Being Too in Love With the Research

Investigator bias is an insidious problem that permeates the scientific world. Too often, scientists become overly enamored of their hypotheses, their data, and their conclusions. Their enthusiasm dulls their ability to be alert to the fallacies in the assumptions on which their hypotheses are based, to the flaws in data collection and recording, and to the confounds lurking in their conclusions. The blind spots produced by the natural optimism about one's own work adds bugs into the scientific literature and endangers research subjects, slowing down the progress of science rather than speeding it up.

Pitfalls in the Clinical Research Setting: Being Overly Hopeful About Finding the Magic Bullet

The one, irreconcilable ethical tension inherent in all clinical research is that the goals of clinical care and the goals of research are different. It is confusion about these differences that lead us down paths strewn with all sorts of research problems. The goals of clinical care are to diagnose, treat, cure or prevent disease in an individual patient. The goal of clinical research is to produce new knowledge that will help diagnose, treat, cure or prevent disease in future patients. Clinical research is never treatment. If a research subject is benefited by the experimental aspects of research participation, it is a happy accident. It is a happy accident that happens often, but it is a statistical accident, nonetheless. Clinical research, no matter how excellent the research care provided,

lacks the component of personalization that is the hallmark of clinical medicine. That is, if a research subject's clinical care needs move beyond the pre-set interventions permissible in the research protocol, that subject will have met off-study criteria and will be discharged back into the care of his or her community treating physician(s). While the ends of research must never supersede the rights and welfare of a research subject, protecting subject rights and welfare is not the same as providing personalized clinical care.

This confusion, however, seems to be sunk in concrete into the psyche of patients, clinicians, investigators, the media and the public. That is why protocols invariably refer to research subjects as patients and experimental drug administration as treatment. Why this confusion is so firmly embedded in people's minds is a topic well beyond the scope of this article. But suffice it to say that hope – hope for a cure to terrible and lethal diseases, hope for the personal emotional and intellectual reward of contributing to finding such cures – is a powerful driver. Couple hope with the commercial and non-financial material rewards that accompany medical progress and one can see why emphasizing the promise of translational research is so easy and why it is such a struggle to devote time and resources to addressing the concerns.

Pitfalls Specific to Translational Research: Coupling the Bench and the Bedside Too Tightly

Finally, translational research poses its own, novel pitfalls. Left to its own devices, translational research can turn out to be its own worst enemy. The intellectual bonus that the translational paradigm offers is its characteristic bi-directionality. That is, the heart of the translational advance is that the needs of clinical care are to be used to better shape the questions being addressed on the bench and the insights that emerge from the bench are anticipated to spark the creative capabilities of those closer to the bedside. But we must be cautious about knitting these threads too tightly. More often than not, scientific advances come from serendipity. If we become overly concerned about coupling the bench to the bedside we run the risk of drying up the pools of thought and imagination and surprise that feed medical progress.

Recommendations for Avoiding the Pitfalls and Realizing the Promise

Conceptual Recommendations: Resist just following the money. Advance the Carle research portfolio in the direction of truly unmet medical need. Practically speaking this means not necessarily undertaking every research protocol that is suggested or offered. Conducting research is such a time-consuming, resource-intensive activity that it is a good thing to cherry pick. Pursue only the most excellent protocols focused on the most important scientific and medical questions.

Avoid coupling the bench with the bedside too tightly. Encourage the most creative investigators to stretch themselves. Support seemingly disparate and commercially impractical science. In time, the fruits of this kind of inquiry may be the juiciest of all.

And above all, don't become too hopeful. Remember that the process of science is multiple dead-ends before an opening is found in the thicket of human disease. Our innate tendency towards optimism will be enough to drive the curiosity and perseverance needed to sustain the research enterprise. Be humble about the prospect for success of any individual project or research path. Avoid the positive hype and spin that is so common in the media and proposals for funding.

Procedural Recommendations: Sweeping, conceptual recommendations, without procedural means of implementation, are little more than platitudes. Policies and procedures will need to be put in place to manage Carle's growing translational portfolio. These will need to include guidance documents on disclosure, management and in some circumstances, prohibition of activities that produce not only frank financial conflicts of interest but the appearance of conflicts of interest. Carle's oversight bodies and officials will need to be alert to their responsibilities to decide whether or not a protocol's question or hypothesis is of sufficient import to allow the protocol to go forward, not merely whether or not the protocol is safe. Resources might be well-spent by having a highly skilled clinical veterinarian serve as a member of the Institutional Review Board (IRB) and have a scientist-member of the IRB serve as a member of the Institutional Animal Care and Use Committee (IACUC). Such reciprocal membership can be expected to strengthen the quality of basic research

protocols and the review of early phase clinical trials, assuring that the bi-directional character of the move to translational research is maximized scientifically while increasing protections and care of the human and animal subjects.

Finally, Carle and its partners might want to take a page out of the book on nationally funded genetics research. When Congress created the Human Genome Project in 1990, it appreciated that research progress in this scientific area held out the promise of rich advances in human well-being but raised, also, ethical, legal, and social concerns that ought to be explored and addressed. This appreciation was operationalized into what is commonly referred to as the ELSI Program. ELSI stands for the ethical, legal, social implications of genetic science. Since the beginning of the Human Genome Project, the ELSI Program has had a carved-out budgetary set-aside; monies applied to research into the ELSI implications of the new genetics. This model has been replicated in the patient advocacy community. The Alpha-1 Foundation, a not-for-profit patient advocacy group devoted to advancing research into the treatment and cure of alpha-1-antitrypsin deficiency (A1AD), a hereditary disorder that affects the lungs, liver and other organs, has created what they call the Alpha-ELSI Committee which funds ELSI research related to Alpha-1. Carle could set the example for other community hospitals building translational research portfolios by creating the Carle Translational-ELSI Program, budgeting regularly for, and soliciting protocols to, study the ELSI aspects of areas of research interest in which the Carle group specializes.

Conclusion

In sum, that the Carle Foundation Hospital and its affiliates and collaborators are excited about moving vigorously into the world of translational research is not surprising. Given Carle's rich traditions in clinical care, embracing research that holds out the promise of increasing the pace of progress in clinical care is a logical direction for investment of Carle's intellectual capital. But one wants to remember, as the drumbeat of hope and success moves the research program forward, that there are many loose stones on which to trip along the way. That Carle and its partners give thoughtful attention to moving with sufficient caution not to slip will go a long way towards avoiding the pitfalls and fulfilling the promise.

Glossary

Basic Research: Research involving living animals or biological samples from living animals.

Bench Research: Either basic or clinical research.

Clinical Research: Research involving living persons or biological samples from living persons.

Durable Power of Attorney for Research

Participation: A document signed by a decisionally-capable adult assigning another person the authority and responsibility for decision-making for the signed person's research participation if the research subject should be decisionally unable to make his or her own decisions.

Research: A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

Translational Research: A relatively new term, translational research is used to describe both an individual research study and a strategy for a body of research designed to turn basic and bench science discoveries more quickly than in the past into practical medical interventions.

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