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An Engineering Approach to Translational Medicine

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In the years since the completion of the Human Genome Project, physician-scientists have applied new energy to translating findings from the laboratory into better treatments for patients. Yet this accelerated, unidirectional transfer of knowledge from the bench to the bedside, a practice that goes by the name of translational medicine, is hitting an obstacle: The generation of data is far outstripping scientists' ability to convert it into usable knowledge. I believe that, paradoxically, this problem stems from the tightly focused approach that gives science much of its power. Genomics, proteomics and other high-throughput technologies are seductively powerful, but that seduction may limit our view of the complex problems of physiology and disease.

For example, scientists can now correlate a disease with a specific pattern of gene expression. Such experiments are straightforward and fairly quick when the tools are available, and they provide a massive quantity of data. However, by diverting limited resources of time, money and personnel, mining this wealth of data may actually lead investigators away from grasping the governing laws from which they could build predictive models of the disease.

I am not suggesting that investigators should give up high-throughput, brute-force methods. Today's technology is a boon to science and a powerful component of my own research. However, as clinical investigators, we stand to reap significant benefits on behalf of society by expanding our focus and viewing translational medicine not through the eyes of a scientist, but as an engineer might.

Physician-scientists may benefit from an approach that emphasizes solving problems over generating hypotheses

Why an engineer? Because an engineer uses the fruits of science to feed the appetite of technology. Unlike scientists, who tend to approach problems from a "bottom-up" perspective by collecting data and seeking patterns, engineers take a "top-down" approach, probing a specific system for clues, taking it apart and considering how each component can be handled in a tailored solution. An engineer is a problem solver rather than a hypothesis generator.

The two perspectives are neatly symbiotic in physics and chemistry, for which fundamental laws yield predictive models. But in the life sciences, biologists, including physicians, must be more aware of the gap between science and technology—we still know too little about the complexity of living systems to make many generalizations from first principles.

I propose that an engineering approach, what might be called "real systems analysis," may be a better way for scientists to identify and develop solutions for biomedical problems. This kind of problem solving requires that translational-medicine research place more emphasis on going from the bedside to the bench, rather than the other way around. The Clinical Breast Care Program (CBCP) is a collaboration between Windber Research Institute and Walter Reed Army Medical Center, and it is the prototype for an integrated approach to the study of breast cancer. Here, I present some examples of how top-down problem solving in the CBCP has provided unique insights.

Disease Is a Process, Not a State

For the purposes of diagnosis, analysis and experimentation, academic physicians tend to focus on disease at a single point in time. But disease needs to be treated as a process that evolves over time through the interaction of genetic, environmental and lifestyle factors. This view puts a premium on understanding the complex history of a patient, and it acknowledges that most disease cannot be tied to a single cause.

When physicians make a diagnosis, it's natural to focus on the patient and symptoms at the time of presentation. The doctor's knowledge of a patient's past is typically limited to major illnesses, allergies and family history. Yet clinical assessments could be much more meaningful if we understood the way that genes and environment interact to produce disease. For example, we know that certain biomarkers, such as mutations in the genes BRCA1 or BRCA2, indicate higher risks of breast cancer. But the fact that a woman has a mutation in BRCA1 doesn't mean that she will develop breast cancer—it only

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indicates that she needs to be monitored more closely.

Likewise, smoking, high alcohol consumption and obesity are correlated with an increased risk of breast cancer, but we know little about how each factor raises the risk—much less about how two or more might work in concert to increase risk. This situation leaves us with a circular argument: To justify the cost of collecting a comprehensive patient history, we need proof that such data are relevant, but we can't evaluate which data are relevant because we don't have a database of comprehensive patient histories.

We in the CBCP think that detailed information will prove useful, although we don't know exactly what connections will emerge from the mass of variables. We are collecting from each patient a lengthy history that includes her exposures to tobacco and alcohol, details about pregnancy, childbirth and breastfeeding, and a record of changes in her body mass. We also try to include information about the timing of these events in a person's life. The chronology is particularly relevant for breast cancer because the breast develops continuously from birth through old age. This lifetime of changes also presents an additional challenge: Not only do these factors influence risk differently over time, but their interactions with one another also vary with age.

An engineering perspective treats the patient as a system, or a set of subsystems, that has been acted on, differentially, by many elements that influence its state at critical points over time. Our job is to identify these critical points so that they might be controlled. Whereas many current studies identify correlations between isolated variables, we hope that the wider scope of the CBCP's systems-based approach will help us determine causality, thereby improving diagnosis and treatment.

Victoria & Albert Museum, London/Art Resource, NY

Breast-cancer diagnosis and treatment might improve if physician-scientists knew more about a patient's life experiences prior to her diagnosis. For the ancient Greeks, the Fates who governed each person's life were incarnate as a girl, a woman and a crone, as shown in this 16th-century tapestry.

Aging as a Background to Disease

The breast changes between a woman's time *in utero* and her post-menopausal years. This maturation process is different for women who have had children than for those who have not, and it also varies under the influence of several variables: age of menarche, use of hormonal birth control, number and timing of children, the practice of breastfeeding, age of menopause and use of hormone-replacement therapy. Thus, our definition of "normal" varies with age and experience, and an optimal diagnosis must use a systems-based approach to compare an individual cancer patient's baseline (which we must guess at) to her disease state (which we can measure during diagnosis and treatment). The immediate aim of our project is to determine background levels of gene and protein expression in breast tissue and to find out how these numbers vary in a healthy population. This information will be a significant step in the development of molecular diagnostics.

Note that a woman's life stages are not separated by fixed boundaries. Rather, each represents a unique intersection of a woman's age and an event. Given this complexity, it was crucial to sieve the scientific literature for data that we could integrate into a systems approach. This was more difficult than one might think. Scientists have studied these stages for decades, producing a tremendous body of work in physiology and pathology—more than any one scientist can master. Furthermore, we recognized that even the most encyclopedic and fair-minded review article cannot escape the inherent bias of its author. Thus, we have harnessed some computing power, employing text data-mining to cull the literature. This effort has two aims: to refine the definitions of these stages and to extract information about the underlying physiological and developmental changes. This information becomes the foundation for our molecular analyses and helps integrate clinical and molecular data. We plan to augment this computational approach with a community-based longitudinal study that includes molecular and behavioral components.

Tumor Classification and Staging

Tumor classification is critical to the assessment and treatment of cancer. To optimize this process of classification, the physician must determine both the present disease state and its potential for progression. This is a difficult task, and it will become more difficult as more relations are established between genes, environment and disease; an ideal representation of cancer would reflect all of these variables. With this idealized tool, a person's disease would become a vector in multi-dimensional space, with each of tens or hundreds of axes representing a clinical or molecular parameter. Perhaps we will realize this vision.

In the meantime, oncologists use three concrete variables to define the stage of a tumor—tumor size (T), metastasis (M) and nodal involvement (N), the finding of cancer in nearby lymph nodes. One problem with this system is that the mapping of some TMN triples to fixed stages is ambiguous, perhaps because the terms are imprecise or insufficient to describe the disease. Another flaw is that these numbers do not reflect the history of a patient's disease and treatment. Yet the TMN system could be made into a better assessment tool simply by setting each variable on its own axis to create a three-dimensional TMN space. Each person's clinical trajectory can be viewed as a unique vector in TMN space. This method highlights the fact that although the stages of tumor progression are linear, there are different "paths" through the disease; not all stages may be encountered on each patient's path. Furthermore, as we see how different vectors turn toward the origin (cancer-free) vs. the extremity of poor outcome or reoccurrence (10,10,10 in a TMN space where the axes run from zero to 10), we can identify paths through TMN space that represent different responses to a given treatment. The result is better information for clinicians to make the best decisions for each patient.

Heterogeneity of Breast Disease

Breast tumors are usually composed of more than one type of cancer. This is a problem when the cancers do not all respond to the same treatment. Although scientists know about this phenomenon, it has been difficult to quantify because pathologists use differing diagnostic criteria. In the CBCP, we have the advantage of having a single pathologist review all patient samples. We think it likely that when a tumor biopsy has a specific combination of subdiagnoses, it is more accurate to describe the tumor in terms of its heterogeneity rather than noting only the severest cancer (the current convention). The CBCP categorization scheme contains 135 potential subdiagnoses for tissue sections. Among 891 patient samples, we have observed 75 of these. Although most combinations are rare or nonexistent, others are extremely common: We found two cancers that had a 92 percent likelihood of showing up paired rather than alone. This finding suggests that we may need to review the tumor-classification system to reflect this heterogeneity, thereby refining our evaluations of tumor stage and grade and improving treatments for patients.

An engineering perspective analyzes breast cancer by viewing the whole patient and applying customized treatments that reflect each person's unique confluence of biology and experience. We hope that this practice reinvigorates the study of breast cancer and other diseases to enhance patient care—the ultimate goal of translational medicine. To my basic-science colleagues, I say that our engineering counterparts have been looking at the world through somewhat different glasses, and perhaps it is time to share the view.