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Translational/Personalized Medicine, Pharmaco/Surgico/ Radiogenomics, Lymphatic Spread of Cancer, and Medical Ignoromes

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Abstract

In the elusive quest for “personalized” cancer treatments based on pharmacogenomics, diverse challenges must be overcome: questionable validity of “molecular models of life,” obstacles to bidirectional translation of scientific advances from bench to bedside to community, and limitations of bioinformatics to recognize and deal with “ignoramics/ignoromes” (expanding unknowns in cancer biology, theranostics, and therapeutic choices). These considerations apply to lymphatic system functioning—lymphatic vessels, lymph, lymph nodes, and lymphocytes—in diseases like cancer.

Keywords

personalized medicine; translation; pharmacogenomics; surgicogenomics; lymphology; ignoramics

“The term proteome was introduced only in 1994 to describe the total protein content of a cell produced from its genome. Unlike the latter, it is not even approximately a fixed feature of a cell (let alone an organism), changing as it does during development. Deciphering the proteome, and following its temporal development during the life cycle of each tissue of an organism has emerged as the major challenge for molecular biology in the post-genomic era”... “The model [molecular model of life] assumes that the cell is the locus of agency, that is, the level at which it is appropriate to model and tabulate benefits, costs, and accidents. But is what is good, bad, or neutral, for the cell also the same at higher level of organization in multicellular organisms? Cancer trivially shows that it is not always so.”

—Sahotra Sarkar in “Molecular Models of Life: Philosophical Papers on Molecular Biology”[1]

OVERVIEW

Among the latest megatrends in medicine are: (1) redoubled emphasis on “forward translation,” that is, bringing discoveries more rapidly from the laboratory into the clinic and to the general public [“bench to bedside to community (trench)”], and (2) exploding interest in the promise of “pharmacogenomics,” that is, more “personalized” medicine based on tailoring specific drug regimens to the patient’s sequenced genotype. These megatrends have converged most notably in cancer biology, theranostics, therapeutics, and public policy and encompass efforts to target the lymphatic system’s multifaceted yet nuanced role in cancer growth, spread, and control (Fig. 1).

Nonetheless, diverse obstacles and complexities need to be acknowledged and overcome before the “DNA code defines the man” model and personalized treatment regimens/cures become an accepted reality. In this new world of -omes, -omics, and molecular signatures, these challenges include but are not limited to: over-simplification of the “molecular model of life” [1]; differential gene expression in time and space; epigenomic influences; phenotypic variation genomics dictating and modulating non-drug treatments (e.g., surgery or radiation instead of or as adjuncts to pharmaceuticals); translational missteps, pitfalls, and conflicts of interest (things “found, lost, and sold in translation”); the inherent reverberating bidirectional nature of translation (the round-trip and side trips from bedside to bench and back again); and excessive reliance on but inherent limitations of bioinformatics along with inadequate appreciation of its mirror image—“ignoramics” [2]. Ignoramics involves recognizing and dealing with “what we know we don’t know, don’t know we don’t know, and think we know but don’t”—the unanswered/unasked questions and unquestioned answers (“ignoromes”). Mix fractals, chaos, and complexity into the picture, and pat explanations and confident predictions become even more tenuous [3].

Examples of these foregoing challenges in proceeding from “genes to man” abound in medicine’s past and present, and specifically in lymphology—or rather in the latest fashionable terminology, “lymphatomics”—the study of the domain or “ome” of everything known (and unknown!) about the integrated system of lymphatic vessels, lymph, lymph nodes, and lymphocytes in health and disease. And these knowns and unknowns bear directly—for good or evil—on cancer biology, theranostics, and therapeutics, and serve as cautionary notes for any concrete blueprint drafted for the future.

TRANSLATION AND REVERSE TRANSLATION: BENCH TO BEDSIDE OR BEDSIDE TO BENCH? THE TRUE ORIGIN OF THE HUMAN GENOME PROJECT

The chain of medical discovery is often misleadingly portrayed as an orderly sequence proceeding from bench to bedside to community. But this portrayal is belied by the history of medical science, perhaps most conspicuously in the popularly accepted culmination of the bench to bedside evolution of the Human Genome Project from the Double Helix [3,4] (Fig. 2, left). This epic “forward translation” was marked by an international 50-year celebration in 2003. However, according to many prominent scientists, the true seminal discovery—the

sine qua non—in genetics discovery occurred quietly a decade earlier with a prescient 1944 publication identifying a simple sugar molecule—desoxyribonucleic acid (DNA), rather than the widely postulated but undiscovered complex protein, as the elusive stuff of heredity [5,6].

This neglected example of “reverse translation”—not bench to bedside but bedside to bench (then back again)—was based on the demonstration that DNA was the “Transforming Principle” in pleural effusions of Bellevue Hospital patients with pneumococcal pneumonia [5,6] (Fig. 2, right). The bacterial capsular material was shown to be responsible for the inherited pathogenicity of the smooth encapsulated pneumococcus in contrast to the non-pathogenicity of its rough unencapsulated counterpart. The multidisciplinary research team (largely physician–scientists without PhDs)—included two of my New York University (NYU) medical school professors (Colin MacLeod, MD, and William Tillett, MD), working with Rockefeller Institute scientists (Oswald Avery, MD, and Maclyn McCarty, MD). They braved a firestorm of criticism and objection from chemists of the day mocking the very notion of such a simple sugar encoding such sophisticated genetic information. (Subsequent crystallography and other evidence revealed the double helix nucleotide sequences that form the backbone of DNA.) No Nobel prize was ever awarded to this physician-dominated team—at the time or subsequently—for identifying DNA as the transforming principle—nor has there been clear recognition since that the Human Genome Project really began with pressing unanswered questions posed at the bedside by sick patients to their perplexed physicians. Nonetheless, Nobelist Joshua Lederberg, who had a lifelong fascination with biomedical ignorance and prescient discovery [7], along with a small cadre of other distinguished scientists (some of whom credited the inspiration for their careers to the seminal 1944 paper), quietly celebrated the 50 years anniversary of the Human Genome Project earlier, in 1994 not 2003!

REVERSE TRANSLATION (BEDSIDE TO BENCH): FROM MAN TO MOLECULES

The dynamic interrelationship of translation and “reverse translation”—now thought also to be a bona fide biochemical/molecular phenomenon, that is, proteins and mRNA can alter DNA—has thus been key albeit neglected in examining medical discovery. Again, another of my physician–scientist–teachers at New York School of Medicine, Severo Ochoa, MD brought his clinical background to bear when he won the Nobel prize in 1959 [8], in part for delineating the enzymes in the Krebs cycle of glucose metabolism but largely for describing key biochemical pathways in “transcription” and “translation”—the conversion of the message from the DNA helix through RNA templates into proteins, thereby providing the foundation of proteomics. Ochoa laid the groundwork for understanding the mechanisms of translational processes in protein synthesis, particularly the *direction of translation* and an array of initiation factors [8]. Marshall Nirenberg won a subsequent Nobel prize for further delineating these processes. This triple meaning of the word translation—molecular, clinical, and societal (including linguistic)—and accordingly the triple meaning of reverse translation runs through discoveries that have shaped modern medicine (and other sciences) from biomarkers of disease (e.g., newborn screening for phenylketonuria and other inborn errors

of metabolism) to the limitless potential of proteomics to mark, track, and target disease including cancer.

PERSONALIZED MEDICINE AND PHARMACO/SURGICO/RADIOGENOMICS

Sound medical practice has always been personalized with decisions based on observation and involvement of the individual patient. The extent of the “phenotypic profile” has been limited only by the powers of observation and intellect and by the knowledge and technology of the day. So to suggest that only reasoning from a genomic/proteomic basis qualifies as “personalized medicine” shows an ignorance of the historical progression of medicine and a limited vision of the future potential of even molecular (and submolecular) science. At this time, public disappointment in the pace of translation of genetic advances and drug discoveries is mounting—that is, the clinical application of advances from molecular biology. Indeed, the impact of pharmacogenomics in the clinical arena including applications in personalized medicine for cancer treatment could be considered in a more preliminary and limited stage than “surgicogenomics” (Table I). The use of genomics to define and select patients and populations vulnerable to rare hereditary cancers such as those arising in familial endocrine neoplasia syndromes and intestinal polyposis as well as more commonly for high risk breast and ovarian cancer has led to diagnostic genetic tests with relatively clear surgical therapeutic implications, that is, removal of the thyroid, polyp-ridden intestine/colon, breast and ovaries to prevent deadly cancers or to eradicate them early by removing the vulnerable organ [9]. It is to be expected that as drugs tailored to genomic profiles proliferate for the targeting and management of cancer, further surgicogenomic applications (including highly sophisticated technical “procedures” for gene therapy, organ/composite tissue/cell transplantation, and tissue engineering) will also develop along with “radiogenomics.” The genotype—and specific gene profiles—will then influence or even determine the choice or effectiveness of operations or radiation therapy or special sensitivity to different operations or forms of radiation treatment/radioprotection and/or require the expertise of future surgeons and radiologists/radiation oncologists. The end result will likely be an evolution of medicine and medical specialties in the genomic and post-genomic era that involves all current modalities of therapy and new ones not just “pharma” – informed by the patient’s and specific cancer tissue’s genomic profile but also mediated and modified by the epigenomic and proteomic profiles as well as metabolomics, systemomics, etc., thereby integrating genotype as one important element contributing more or less influentially to the patient’s phenotype and outcome (Fig. 3).

Whereas “translational medicine,” may be a new or reinvigorated paradigm for some medical specialties, it is nothing new for lymphology and lymphologists [10,11]. Since before the founding of the discipline and the formation of the 42-nation International Society of Lymphology in Zurich in 1966, clinical lymphology has transcended the boundaries of medical specialization, language, politics, and geography. Translational lymphology has been embodied by pioneers like Ernest Starling exploring the physiologic principles governing lymph formation and edema [12] or Florence Sabin meticulously dissecting the lymphatic sacs of human embryos [13], with profound clinical implications and applications arising from their basic science findings. On the other hand, astute clinicians, like British vascular surgeon John Kinmonth (Fig. 4) sought out geneticists and imaging scientists for

better documentation and explanation of the inheritance patterns and hidden pathologic processes manifest by the recorded images of dysfunctional lymphatic vessels and pathological lymph nodes he was seeing for the first time in patients with lymphedemaangiiodysplasia syndromes studied with oily contrast lymphography [14]. Or the Földis, framing the boundaries of lymphology with their ideas, experiments, teachings, and clinical practice to define and treat lymphostatic disorders in experimental animals and man [15].

In a similar fashion, fresh insights in clinical lymphology, especially those provided by non-invasive lymphatic system imaging including lymphangioscintigraphy and sentinel node mapping and more rational classification of the spectrum of lymphatic disorders, should reinforce the forward translation and reverse translation that sheds light and leads to new management approaches for patients afflicted with these disorders including cancer. As pointed out previously, lymphatic system involvement in cancer is not simple but more multifaceted and nuanced than once thought with both beneficial and harmful interacting influences of lymphatic vessels (including lymphangiogenesis and lymphogenous route of spread), lymph (fluid/composition), lymph nodes (cancer cell proliferation and containment, immune responses), and lymphocytes (and other immune cells like dendritic cells/macrophages trafficking in tissues and through “lymphoid” structures) (Fig. 1) [16,17].

Furthermore, key lymphatic developmental genes/proteins involved in lymphvasculogenesis and lymphangiogenesis (e.g., angiopoietin 2 [18] and *FOXC2* [19–21]) have also been implicated in cancer development and progression with potential usefulness as diagnostic/prognostic biomarkers as well as for targeted anti-cancer drug development. Indeed, the discovery of *FOXC2*'s role in lymphatic development is another classic example of reverse bedside to bench rather than forward translation—a surprising, unsuspected fruitfly gene found by a singleton chromosomal rearrangement in an infant, subsequent family pedigree analyses, genome sequencing, and positional cloning in the autosomal dominant syndrome of lymphedema-distichiasis [19]. Lymphedema-distichiasis manifests as pubertal onset of limb lymphedema and a congenital double row of eyelashes. Only after this discovery in patients was a reexamination of the *Foxc2* haploinsufficient and null transgenic mouse model undertaken and striking similarities in the human and mouse phenotypic spectrum noted (Table II) [19–21].

LYMPHATOMICS, IGNORAMICS, AND IGNOROMES

With the recent explosion of information in “molecular lymphology,” highlighted at this conference (and reviewed in Refs. [22,23]), a diverse array of genes and proteins involved in lymphatic development, growth, and function along with parallel advances in tumor biology, it is tempting to mold these latest molecular discoveries into a “molecular model of life” or at least a “molecular model of cancer” [1]. Such a premature untranslated model, however, would, as mentioned earlier, ignore the symmetrically and geometrically expanding domain of ignorance—the “ignorome”—what we know we don't know, don't know we don't know and think we know but don't—surrounding the lymphatic system and the complex interactions among body systems [24]. Indeed, the answers may change but the most basic questions about cancer persist (What is cancer—really?, What makes it spread?, and Can we

cure it?). In connection with the University of Arizona's Summer Institute on Medical Ignorance [2,25] (Fig. 5), these are by far the most common beginner's questions (high school student researchers) and also the Nobelists' same unanswered questions albeit at a different level of sophistication in their ignorance. In future years, our NIH project's Virtual Clinical Research Center with its cornerstone "Questionarium" will provide a venue for medical ignoramics—exploration of ignorance by students and experts and a virtual interface for collaborative research and learning (Fig. 6) [26].

The rush to reduce biology and disease to molecules, to turn a blind eye and shun direct translation without molecular mechanistic explanations and then adapt informatics to manage the growing information stockpile, needs to be balanced, as discussed here, by an equally energetic effort in "medical ignoramics"—the familiar terrain of the clinician who must decide what to do when lives hang in the balance and it is unclear what best to do. Indeed, the mountain of information, meta-analyses, and competing algorithms, may actually obscure progress and promote inaction. Ignoramics questions dogma, reevaluates neglected insights, identifies key gaps and unknowns, and develops approaches to explore complex systems and reconstruct them in diverse environments such as human health and disease and where necessary, to act appropriately on limited information. Indeed, even a simplistic "genes to man" (Fig. 7) concept is already confounded at the molecular level by recent discoveries in epigenomics, and differential gene expression patterns in space and time (and in vivo and in vitro compared to in silico). DNA methylation, and the latest RNA reverse influences on the expression of the DNA code (reverse translation). What greater chasm of the unknown must lie between genotype and phenotype and the promise of personalized genomic medicine! The field of cancer genomics embodies this complexity, promise, and challenge.

Epilogue:

As physicist David Gross commented as he accepted the 2005 Nobel Prize:

"Fortunately, nature is as generous with its problems as Nobel was with his fortune. The more we know, the more aware we are of what we know not. Indeed, the most important product of knowledge is *ignorance*. The questions we ask today are more profound and more interesting than those asked years ago when I was a student. There is no evidence that we are running out of our most important resource – ignorance. How lucky for science, how lucky for scientists. How lucky for the Nobel Foundation." [27]

But often, on the other hand, how unlucky for us as physicians and for our patients!

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Fig. 1.
Complex interrelationships among the various processes (arrows) taking place in the lymphatic system provide the context confounding the implications and interpretation of cancer genomics (modified with permission from [Ref. 17]).

Fig. 2. Bookcovers of the celebrated “Double Helix” by Nobel Laureate James Watson (left) and less well-known “DNA: The Transforming Principle” by Maclyn McCarty describing seminal discoveries (1953 and 1944, respectively) and contrasting origins (bench to bedside vs. bedside to bench) in the path to the Human Genome Project. See text for further explanation.

Fig. 3. Schematic depicting the current vision of “personalized medicine” and pharmacogenomics.

Fig. 4.

British vascular surgeon John Kinmonth, MB, FRCS (1916–1982) made pioneering contributions to translational lymphology by providing valuable imaging methods for contrast lymphography and this technique was used for characterizing lymphatic disorders, including not only staging of lymphomas but also for clarifying hereditary primary lymphedema syndromes based on lymphatic structural and functional abnormalities. He also predicted that improvement in methods to study chromosomes (he was only able to count them then) would shed light on hereditary lymphedemas.

Fig. 5.

Collage of Summer Institute on Medical Ignorance teaching tools. Clockwise: Questionator interactive game, Ignorance Log, Ignorance Research Report, Ignorance Map, and “Grow Your Own Organ” questioning exercise, which can be used as starting points for curricular ventures into medical ignorance. Background, SIMI “ignorami” [high school (left) and medical student (right)] ponder questions while conducting research together [reproduced with permission from [Ref. 25]].

Fig. 6. Design of our NIH-funded Virtual Clinical Research Center/Questionarium provides a virtual interface to enhance interaction between real-life clinical research centers and the public, nurture student questioning, and expedite bidirectional translation of laboratory findings to the bedside ([Ref. 26] abstract).

Fig. 7. Frontiers of ignorance in lymphology (LS) depicting the steps and connections in both directions (forward and reverse) between molecular and clinical research, that is, translating from “genes to man” [23].

TABLE I**Surgicogenomics Related to Prophylactic Surgery in Hereditary Cancer Syndromes**

Syndrome	Genes
Familial breast/ovarian cancer	BRCA1 and BRCA2
Familial medullary thyroid carcinoma (multiple endocrine neoplasia, MEN-2)	RET
Familial intestinal Polyposis and Gardner's syndrome	APC, MUTYH, SMAD4/DPC4
Hereditary colorectal cancer	MSH2, MLH1, MSH6, PMS2, PMS1, MLH3, APC
Pancreatic islet carcinoma (MEN-1)	MEN 1, CDKN2A

TABLE II

Clinical Phenotypic Spectrum of Human Lymphedema-Distichiasis Mimicked in FoxC2 +/- and -/- Mouse Models

		Mouse	
	Human, <i>FOXC2</i> +/-	<i>Foxc2</i> +/-; +/-, +Tg^{**}	<i>Foxc2</i> -/-[*]
Ocular	Distichiasis ptosis, cataracts	Distichiasis ptosis, cataracts	
Lymphatic	Lymphedema praecox	Lymphedema	Incompetent valves
	Hyper/dysplastic phenotype	Hyper/dysplastic phenotype	
	Increase in lymphatics	Increase in lymphatics	
	Increase in lymph nodes	Increase in lymph nodes	
	Lymph reflux	Lymph reflux thru incompetent valves	
Cardiac	Tetralogy of fallot		Aortic arch defect
	Ventricular septal defect		Ventricular septal defect
Skeletal	Cleft palate		Cleft palate

* In embryos.

** Similar lymphatic but not ocular phenotype in +/-, +Tg.