EDITORIAL

From the Editor's Desk: The emergence of "personalized medicine" in medical care

Medical students throughout their education are taught to consider the patient as a whole. We are reminded through our course work and by our course instructors that understanding the pathophysiologic basis of disease and responding with clinical interventions are only part of healing a person who is ill. So we must consider what makes both the patient and the disease presenting to us typical. Or better perhaps would be posing the opposite question: what makes this patient and their disease different from others? To be sure, socioeconomic and lifestyle factors, past medical and family histories, medications, etc. all contribute to making each patient unique. As editors, though, we note the emergence of another titratable parameter in this process of "personalization:" genetic constitution. We have invited and published in this issue of the McGill Journal of Medicine, four expert reviews from leaders in the field of an emerging approach to medical care referred to as "personalized medicine." We find them individually well-written and insightful, and complementary *en masse*.

This introductory editorial offers some specific examples of what we feel are the three most important elements of this field as presented by the reviews herein: molecular diagnosis, treatment prediction, and prognosis-making. With this structure, we hope to equip the reader with a bird's-eye view of "personalized medicine," elements of which will be further developed by the four invited expert reviews herein. We must note that there is no indexed entry for "personalized medicine" in the 16th Edition of Harrison's Principles of Internal Medicine, and that this is very much an evolving field. In early January, 2007, a PubMed search for "personalized medicine" returned 532 results, over 80% of which were published after 2000. Our goal is thus to involve our readers in this dialogue, by way of introduction, and to empower them to help chart a course for personalized medicine.

Personalized medicine aims to consider the genetic constitution of a patient and their disease in the process of diagnosis, prognosis, and predicting treatment response. The process begins with molecular analysis of the disease entity and patient's genetic constitution, upon which further subtype diagnosis can sometimes be made. The utility of molecular diagnosis is exemplified by defining colorectal cancer subtypes based on tumorigenic pathways of genetic instability. It is understood that characteristic serial mutations frequently underlie the progression of a colorectal adenoma to an invasive carcinoma - namely, mutations in tumor-suppressor genes APC, K-ras, and p53. More recent work has demonstrated that some, about 70%, of colorectal neoplasia are aneuploid, meaning that they have an abnormal complement of genetic material in their neoplastic cells. Those cancers with demonstrated aneuploidy states (a state also referred to as "chromosomal instability") manifest a loss of these so-called tumor-suppressor genes - that is, a loss of heterozygosity at this locus - and are designated Group 1 colorectal cancer. Conversely, other forms of colorectal cancer - the remaining 30% - fail to demonstrate this aneuploid state in their nuclei. Rather, in these cancers inactivation of DNA mismatch repair mechanisms results either from direct mutation of mismatch repair genes (hereditary non-polyposis colorectal cancer or Lynch Syndrome) or from hypermethylation of CpG islands in the promoters that drive the expression of these mismatch repair genes, thus attenuating their expression (Group 2). Clinically, Groups 1 and 2 colorectal cancers differ in many important ways. One prominent difference is that Group 1 colorectal cancers are mainly well to moderately differentiated adenocarcinomas (invasive cancer of glandular cells), whereas Group 2 cancers are generally more poorly differentiated, and associated with a poorer prognosis. Molecular diagnosis of colorectal neoplasms is therefore becoming a focus of not only diagnosis, but could also provide substrate for subtype-specific treatment design and prognosis-making. Such analysis is an example of "molecular diagnosis," and is an important component of personalized medicine.

Another important concept under the umbrella of "personalized medicine" is predicting treatment response based on molecular diagnosis. Several new pharmaceuticals have emerged very recently that are referred to as "targeted therapies." Perhaps the best-known example is that of the monoclonal antibody trastuzumab (Herceptin®). Trastuzumab has offered great promise to many women with a sub-type of invasive breast cancer. Invasive breast cancer is most frequently ductal (80%) or lobular (10%) carcinoma, and is believed to arise from a progression that includes carcinoma in situ. Treatment generally consists of local - radiation-based and surgical - and systemic - chemotherapeutic, including the microtubule-stabilizing drug paclitaxel - treatments. The toxicity of systemic chemotherapeutic drugs can be high, and is largely due to systemic inhibition of more rapidly proliferating tissues: bone marrow suppression, gastrointestinal dysfunction, hair loss. Trastuzumab

was developed based on the observation that some breast carcinomas appear to have evolved in part due to an over-expression of the epidermal growth factor receptor 2 (HER2). Over-sensitivity through over-expression of the receptor HER2 leads to excess cell stimulation of cell proliferation, the hallmark of cancer. Trastuzumab is a purified human monoclonal antibody that inhibits the dimerization of the tyrosine kinase subunits of the HER2 protein. Patients are tested to determine if their cancer is HER2-positive, using one of two tests approved by the American Food and Drug Administration: immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH). Thus, by specifically targeting an important basis of this subtype of breast carcinoma, physicians can predict if a patient will likely respond to trastuzumab treatment, and can improve outcomes for many of these patients. A similar mechanism of action - inhibition of receptor tyrosine kinase activity - underlies the beneficial effects of another anti-cancer drug, imatinib mesylate (Gleevec®), which has shown great success in treatment of Philadelphia-chromosome positive chronic myelogenous leukemia (CML). To many, these drugs represent a thrust of cancer biology, and underlie the mantra of physician-scientists: "from bench to bedside."

The third constituent of the approach underlying "personalized medicine" is prognosis. Here again, the reader can find examples of the utility of personalized medicine in the management of breast cancer patients. Prognostic value of molecular diagnosis is well established in the case of the her2/neu mutation that underlies HER2-positive invasive breast cancers - which are found in about 20 to 25% of breast cancers, according to the American Association for Cancer Research. Studies have demonstrated that HER-2/neu amplification is an independent predictor of shorter disease free survival in both node-negative and node-positive patients, and hence confers a worse prognosis. HER2-positive breast cancer and Herceptin are discussed in depth by the reviews herein.

This rationale behind personalized medicine is tantalizing, as it elegantly integrates a seemingly discursive body of knowledge about pathology, genetics, and pharmacology into a clear improvement in treatment options for patients - many of whom with significantly morbid and mortal diseases. This is a beginning for personalized medicine, though: whether these drugs and diagnostics herald the beginning of an era of new genetically-tailored drugs, or instead are "beginner's luck" innovations for doctors and scientists, remains to be seen. We hope that this arguably agnostic conclusion is not disappointing to the reader: we feel that it will be up to the reader to consider personalized medicine as an emergent approach to medical care. We hope that the four articles herein will provide sufficient flint and steel to spark such a discourse on this topic for you, and will invite perspective on what helps define the patient and their disease. Please enjoy these reviews - and all the excellent articles in this issue of the MJM - and accept our warm wishes.

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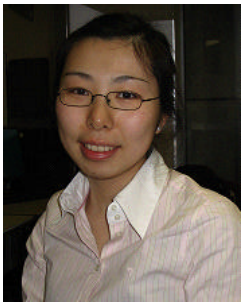

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