Preface

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In the last decade, researchers have made a concerted effort to move beyond their restrictive silos so as to practice cross-discipline studies in ways that have led to some paradigm-shifting observations and practices. This is an exciting era of discovery as so-called system approaches become multi-system studies. The new discoveries and methods highlighted in this issue will likely expedite solutions for some of the more enigmatic diseases, such as ophthalmic and male breast cancer, for example.

Early and accurate cancer detection as well as targeted treatment are obvious goals, and the quest to achieve these has been relentless, but has followed predictable paths. We have benefited tremendously from omics-type studies over the years, but the power of combining data sets from these types of studies with novel spectral data sets is really just beginning to be appreciated despite the foresight that led to pioneering pilot studies decades ago.

Raman spectroscopy capitalizes on scattered light in response to targeted laser exposure that yields spectral patterns that are surprisingly unique and that allow for accurate discrimination between samples. These include everything from tissues and cells, and even subcellular components that are within intact cells or free in body fluids. The power of this approach is that a sample can be interrogated even without having known, validated biomarkers up front. Cognitive software can be groomed to link known samples of malignant tissue with the associated Raman spectra. These patterns can ultimately be associated with disease states and response to therapy. Eventual pairing of handheld Raman spectroscopy with femtosecond-pulsed laser technology allows micro- and nano-ablation at the cellular level, which will make it possible to conserve valuable tissue while insuring destruction of diseased areas.

Internationally, there are only a handful of programs equipped to generate archived spectral atlases for general use. One such program is headed by Greg Auner at Wayne State University. Dr. Auner's group has deep expertise in this field. His group has teamed up to provide for this issue a compendium that brings together valuable clinical applications such as, for example, ovarian cancer screens from patient serum as well as technical parameters for conducting Raman screens and introductory information for the uninitiated. It is an excellent reference resource for experts and novices alike.

Herst et al. have given us greater insight to the metabolic plasticity of mitochondria and have challenged the dogma that genes remain within individual cells, as mitochondrial DNA and entire mitochondria are now found to transfer between cells to impact many cancer phenotypes, and mitochondrial-nuclear cross-talk has been demonstrated. This new paradigm is expanded further by Beadnell et al. who have provided a dense primer on the role of mitochondrial genetics in cancer metastasis, where mitochondrial genome changes are thought to be metastasis modifiers rather than drivers *per se*. For example, various trait differences such as organ tropism can be mapped to specific mitochondrial DNA polymorphisms (SNP). Models to study the contributions of mitochondrial DNA quantitative trait loci (QTL) are covered by Vivian et al. The mitochondrial-nuclear exchange or MNX mouse model allows for combinatorial studies in which the influence of mtDNA on tumor phenotypes can be examined by pairing nuclear DNA with mitochondrial genomes from other strains of mice. There are profound differences in the frequency of mammary gland neoplasms developing in MNX mice depending on the source of mtDNA. They explain by example how mitochondrial polymorphisms were found to contribute to age-related tumor phenotypes. Collectively, this group of reviews also offers the reader food for thought in the era of mitochondrial replacement therapy.

Additionally, while important for glycolysis, the exciting moonlighting roles of GAPDH are completely underappreciated. This so-called housekeeping gene that is a common reference standard, functions in many other capacities beyond metabolism. Michael Sirover has given an abridged

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accounting of these functions as they relate to cancer, from the inhibition of apoptosis and promotion of angiogenesis to GAPDH as a protein co-factor for regulation of transcription factors including stem cell markers (such as Sox2, ALDH1, OCT4, NOTCH1), and its role in post-translational regulation of CSF-1 mRNA through direct binding to the decay element.

Maheshwari and Finger have provided an in-depth overview of rare and diverse ophthalmic cancers with detailed clinical considerations in diagnosis and treatment. Likewise, Leon-Ferre et al. review another rare cancer type, male breast cancer, and provide a contemporary look at the key biological commonalities and differences between male and female breast cancer. Clinicopathological features as well as treatments for early and late-stage disease are covered in great detail. Important gaps in the knowledge-base are highlighted along with suggestions for improving our understanding of the unique biology of this disease through models and male breast cancer cell lines.

When modeling tumor microenvironment, cancer-associated fibroblasts (CAFs) must be considered. Houthuijzen and Jonkers provide a detailed review of the state of research related to the interplay of CAFs and breast cancer to enhance invasion and metastasis, impact immune function

and modulate therapy resistance. They explore the challenges of targeting CAFs to improve therapy efficacy and provide rationale for possible mechanisms of pro- and anti-tumorigenic effects of CAFs in breast cancer.

Sheng et al. tackle tumor heterogeneity and phenotypic plasticity in personalized medicine and expound on the importance of model selection for improving cancer-specific approaches by illustrating the virtues of 2D/3D/mammosphere culture in teasing out the vulnerabilities shared by all tumor cells in heterogeneous tumor masses, such that more curative cancer drugs can be fast-tracked in development pipelines.

As a final note, it has become apparent from educating both undergraduate and even graduate students that while periodicals are highlighting these breakthrough findings, core curriculum in higher education is not always keeping pace. It is hoped that articles in this issue find their way into STEM syllabi and that creative applications of this new knowledge continue to emerge for therapeutic benefit.

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