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SYMPOSIUM: MOLECULAR GENETICS IN SARCOMA

Editorial Comment

Cancer Biology – Lessons Learned From Sarcoma

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Sarcoma biology has been the foundation of our understanding the molecular, immunologic, and viral bases of cancer. In the premodern era of orthopaedics, before arthroplasty and arthroscopy, bone and soft tissue sarcoma research established basic concepts of cancer biology. Virtually every major advance in our understanding of how genetic code aberrations cause cancer originated in investigations of sarcoma. Retinoblastoma gene and osteogenic sarcoma [1, 4], Rous sarcoma virus (src gene) [7], Harvey and Kirsten sarcoma viruses (H-ras and V-ras) [8], and Li-Fraumeni syndrome (p53) [6], are important examples. Despite these contributions, during the last quarter-century most serious investigators focused on liquid (hematopoietic) cancers and eschewed the more difficult solid tumors.

Because sarcomas—particularly bone sarcomas—are so rare, many investigators historically were deterred from working on musculoskeletal tumors. However, technologic advances in gene and nucleic acid sequencing, polymerase chain reaction, gene array platforms, si-RNA, and other experimental approaches allow us to probe the elusive causes of and treatment for sarcoma. The discovery of specific targeted therapy against Gastrointestinal Stromal Tumor (GIST) transformed the field [2]. In cancer research, sarcoma is relevant again. There has been a resurgence of interest in the molecular basis of sarcoma.

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The current symposium presents representative original examples of the high-quality investigations illuminating the pathogenesis of sarcoma and inspiring optimism about new treatment strategies. Nevertheless, the articles also highlight the daunting obstacles we face in curing sarcoma, some of which are itemized below.

"Sarcoma" is a conceit that is convenient. In the US each year, there occur only about 8,000 soft tissue and 2,000 bone sarcomas, from well over 70 different histologic subtypes. This makes it difficult to diagnose the cancers and seemingly impossible to collect enough of one histologic type to power a basic molecular study. Historically, the response was to lump the cases together to generate sufficient case volume. If one were really desperate to accrue enough cases, even melanomas (cared for in joint melanoma sarcoma services) were thrown in. It has become increasingly obvious that this approach is antiquated. Cytogenetic and molecular genetic characterization of tumors has become the gold standard for diagnosing the many translocation-based sarcomas (eg, Ewing's family of tumors, synovial sarcoma, myxoid chondrosarcoma, liposarcomas, and others.) Modern genetic techniques have established that the term "sarcoma" does not describe one specific disease but, at best, a collection of diseases.

Molecular pathology provides knowledge of and power over these disparate diseases. We now know what the patient has, what we are treating, and what we are investigating. This is especially important for low-incidence diseases when sample size is limited. Given the dramatic heterogeneity within the same cancer subtype, accurate diagnosis is even more essential. Unfortunately, there remain certain cancers, such as chondrosarcoma, for which the diagnosis and grading are still crude and for which expert pathologists fail to agree at a statistically meaningful level: diagnoses in this area have a kappa value of less than

0.40 [9]. How can we make progress faced with this dismal state of affairs? Traditional histopathology is not capable. Molecular correlates of clinical behavior are direly needed.

Progress in sarcoma research depends on having sufficient tissue from which we can extract high-quality RNA and proteins. The tissue is fundamental. Without tissue, we cannot validate cell line data. Without sufficient tissue, we cannot retest archival tumor samples when the next great discovery is made. Limitation of biopsy tissue compromises diagnostic and research goals. In the words of the late Memorial Sloan-Kettering sarcoma pathologist Andrew Huvos, "Small biopsy, small diagnosis; big biopsy, big diagnosis." Ample biopsy tissue is essential for diagnosis, treatment, and research.

It is a tragedy that a mere 10% of pediatric patients on national cooperative group trials and as few as 2% of adult sarcoma patients have fresh tissue preserved for scientific study. Such a low rate of cooperation is an embarrassment. It is certainly not because we already know enough about these cancers. Every tissue sample of a rare cancer such as "sarcoma" is an invaluable resource. It is well established that oncology patients are generous and cooperative with cancer investigations. In fact, we have never had a patient refuse tissue donation in our collective 35 years of surgical oncology practice. The mandate is simple: we must capture every patient sample. We must overcome institutional obstacles and surgeon inertia. Consumer demand will force the issue. The unique nature of each tumor will ultimately require tailored treatment. It will not be adequate just to cut out the tumor and refer the patient to a medical oncologist. Surgeons will need to harvest the tissue necessary to characterize the disease. The times are changing. As Bob Dylan wrote, "Your old road is rapidly agin'. Please get out of the new one if you can't lend your hand" [3].

Tissue acquisition is the linchpin between clinical care and translational research—if tissue is collected, translational research will ensue. The proud tradition of molecular research about sarcoma will thrive. Even if surgeons do not personally perform the genetic research, they have a moral obligation to contribute to this work that will improve the lives of all of our patients.

Thirty-eight years have passed since Bishop and Varmus started publishing on the role of retroviruses in carcinogenesis (see the Classic Article in this issue of CORR), 15 years since *Science* proclaimed p53 the "Molecule of the Year" [5]. Knowledge and therapeutic prospects that have stemmed from these landmarks are growing explosively. In the near future we will identify the unique biologic profile of each sarcoma and craft a customized treatment for each patient. It will be a fitting translation of the original genetic research regarding cancer. The work presented in this symposium furthers that goal.

To this end, we thank all participants for submitting their exciting work and for remaining patient throughout the review process. We would also like to express our gratitude to the Editor-in-Chief, Dr. Dick Brand, for his utmost devotion and numerous suggestions to bring this special symposium to fruition.

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