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Sarcoma–The standard-bearer in cancer discovery

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ABSTRACT

Sarcoma is a rare tumor type that occurs most frequently in connective tissue. Despite its uncommon occurrence, sarcoma research has provided the means for groundbreaking research that has advanced our understanding of general cancer mechanisms. It is through sarcoma research that the pioneering efforts of cancer immunotherapy were explored, that we understand the inherent genetic nature of cancer mutations, and that we appreciate the subclassification of general cancer types to make more accurate prognoses. This review explores the brief history of sarcoma research and what sarcomas can still teach us about the future of cancer research, especially in regard to novel immunotherapy targets, the role of epigenetics in disease progression and chemoresistance, and the benefits of more focused clinical trials.

1. Sarcoma–the standard-bearer

In battle, the standard-bearer honorarily carries the flag, which represents the nobility and purpose of continuing the fight. In the war on cancer many advances have been made that surround the more common cancers such as breast cancer, prostate cancer, colon cancer, and lung cancer. However, there are these rare tumors of mesenchymal origin, sarcomas, which have disproportionately advanced the front lines of our understanding of cancer mechanisms. It is because of sarcoma research that we even know what oncogenes and tumor suppressor genes are. It is because of sarcomas that we appreciate that there are many subclassifications under a given umbrella of disease that can indicate different prognostic information. Even in the proliferating field of cancer immunotherapy, the first applications were performed 126 years ago in sarcoma patients. What can sarcoma research teach us in the future about cancer mechanisms and therapies? How can a focus on this rare and often overlooked cancer advance the army of cancer researchers into new and promising research? First we will review where we are and what sarcoma research has taught us in the past.

2. Sarcoma research–the present, past & future

In the recent 2017 cancer progress report (www.cancerprogressreport.org), produced by the American Association for Cancer Research, there is reason for optimism as progress against cancer is evident. Since the 1990s, the cancer death rate among adults and children in the United States has decreased 25 and 35%, respectively. Despite these positive trends, cancer remains the second leading cause of death in the United States and a sobering global health concern. The predictions for the future rise in new cancer cases per year is projected to be 35% more in the United States and 60% more worldwide by the year 2030. More needs to be done to accomplish the goals of the cancer moonshot initiative and win the war on cancer.

Many recent advances in cancer therapy have come through basic science research efforts that strive to understand the mechanisms that drive cancer and uncover its unique vulnerabilities. Targeted therapies designed to attack the Achilles heel of specific cancers are demonstrating promising results with fewer side effects than traditional chemotherapies (Camidge, 2014; Baudino, 2015; Sawyers, 2004). To emphasize this point in shifting the approach to more targeted and personalized therapies, in the past 12 months the FDA has approved 16 new anticancer therapeutics, each designed and approved for a cancer with a specific molecular indication (Table 1).

In spite of these advances in therapeutics, there are cancer subtypes that suffer from dismal outcomes due to a lack of response to current therapies. Even among and common and treatable cancer types, certain patients do not respond because the cancer has advanced and metastasized beyond the point of a curative treatment by the time the patient presents to the healthcare system (Miller et al., 2016). There remain significant gaps in knowledge about these disparities between the biology of individual cancer cases; why some tumors respond and others do not. Vulnerabilities specific to advanced and metastatic cancers are yet poorly understood. Possibly by studying the rare cases and exceptions, we can come to understand the mechanisms that are currently enigmatic and preventing the next major advancement in cancer care.

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Table 1
FDA approved anticancer therapeutics.

Generic name	Trade name	Molecular target	Approved indication
Regorafenib	Stivarga	VEGFR2;TIE2	Liver cancer
Brigatinib	Alunbrig	ALK;EGFR	Lung cancer
Ibrutinib	Imbruvica	BTK	Lymphoma
Midostaurin	Rydapt	FLT3;KIT	Leukemia
Olaratumab	Lartruvo	PDGFRα	Soft-tissue sarcoma
Ribociclib	Kisqali	CDK4/6	Breast cancer
Dabrafenib	Tafinlar	BRAF	Lung cancer
Trametinib	Mekinist	MEK1/2	Lung cancer
Neratinib	Nerlynx	HER2/EGFR	Breast cancer
Niraparib	Zejula	PARP1/2	Ovarian cancer
Rucaparib	Rubraca	PARP1/2	Ovarian cancer
Atezolizumab	Tecentriq	PD-L1	Lung cancer
Avelumab	Bavencio	PD-L1	Bladder cancer, skin cancer
Durvalumab	Imfinzi	PD-L1	Bladder cancer
Nivolumab	Opdivo	PD-1	Head and neck cancer, bladder cancer
Pembrolizumab	Keytruda	PD-1	Head and neck cancer, bladder cancer, lymphoma

Outliers teach us what we don't know and lead us to new questions and discoveries. In medical oncology, each sarcoma patient is an outlier. Sarcomas make up about 1% of all cancers and with over 70 different subtypes of sarcoma it is unusual to have a high volume of patients with any single sarcoma type, even at the largest cancer centers (Bridge, 2014; Demetri et al., 2010). However, through sarcomas we have learned fundamental truths about all cancers: (1) the relationship between the immune system and cancer and the idea that it may be harnessed to target cancer, (2) the conceptual discovery of oncogenes and tumor suppressor genes, (3) personalized medicine, treating subsets of cancer as unique diseases.

Are there still lessons that can be learned from studying this outlier, a sometimes overlooked disease, that can teach us about general cancer mechanisms and the barriers that prevent further therapeutic success? We think the answer is yes. It is not unprecedented for sarcoma to lead the way in groundbreaking cancer research.

2.1. History of groundbreaking sarcoma research

Cancer immunotherapy is arguably one of the most promising new therapeutic avenues in oncology. Despite the recent advancements of immune checkpoint inhibitors as evidenced by the 3 recently approved PD-L1 inhibitors and 2 PD-1 inhibitors in the past year (Table 1), the first attempts to harness the body's immune system to fight cancer was conducted in the 1890s. It was not for another 120 years that the first cancer vaccine and the first immune checkpoint inhibitor were approved by the FDA. In the last six years, numerous other vaccines and immune checkpoint modulators have been pushed through preclinical and clinical testing to receive FDA approval.

The father of immunotherapy is considered to be Dr. William Coley. He observed spontaneous remissions of rare sarcomas in patients that simultaneously developed erysipelas. In 1891, Dr. Coley injected streptococcal organisms, also called Coley's Toxins, into patients with the hypothesis that a mounted immune response to the bacteria would also attack the tumor. The ensuing immune response from the infection resulted in the shrinking of some tumors deemed inoperable. These responses were especially evident in bone and soft-tissue sarcomas. Over 1000 patients were treated with Coley's Toxins over a forty year span (McCarthy, 2006).

While these studies did not earn Dr. Coley a Nobel Prize, others have made revolutionary discoveries in cancer by studying sarcomas and for their efforts they have been awarded the Nobel Prize. The discovery of an oncogenic retrovirus led to the fundamental tenet of cancer initiation that overexpression of genes can transform cells to become cancerous. This was performed by Dr. Peyton Rous in the early 1900s in which he demonstrated cell-free extracts from a chicken tumor could promote sarcomas in a healthy chicken by transmission of the retrovirus carrying the oncogene *src* (Weiss and Vogt, 2011).

Another cancer biology breakthrough occurred in sarcoma research in 1976 when Michael Bishop and Harold Varmus published a paper which concluded that the oncogenes in Rous sarcoma virus (RSV), which could infect cells to cause sarcomagenesis, were in fact of cellular, not viral origin (Stehelin et al., 1976). The gene that led to sarcomagenesis had originated in normal cells. They hypothesized that RSV had taken up the gene during replication and had carried it afterwards. The impact of this and subsequent papers published by Bishop and Varmus was to show that the root of many cancers lay in the mutation of genes already found within a healthy cell (Varmus et al., 1989; Bister, 2015). This discovery has shifted much of modern cancer research towards discovery of the mechanisms by which normal cells and cancer cells regulate expression of various oncogenes of cellular origin and away from a sole focus on viral and external carcinogenic causes.

With the idea that genetic mutations cause cancer, the most important cancer gene discovery was made while studying sarcoma. Li-Fraumeni syndrome, named after doctors Frederick Li and Joseph Fraumeni, Jr. who first reported the syndrome in 1969, is an autosomal dominant disorder that greatly increases the risk of developing several cancers (Li and Fraumeni, 1969). A common diagnosis in patients with Li-Fraumeni syndrome includes rhabdomyosarcoma, a rare childhood cancer developing in skeletal muscle tissue. After identifying multiple rhabdomyosarcoma patients with other cases of childhood sarcoma within their close families, Li and Fraumeni hypothesized a hereditary cause to explain the familial link, as more than one occurrence of these diseases within one family was statistically unlikely. In a research study published in 1990, the doctors examined DNA samples from five Li-Fraumeni syndrome carrying families, ultimately finding an autosomal dominant inheritance of the mutated *TP53* gene, which is translated into the p53 tumor suppressor protein (Malkin et al., 1990). This research provided a strong link between p53 and tumor suppressing function and represents the most commonly mutated gene across all cancers.

Sarcomas are a collection of genetically distinct diseases that are parsed into two subcategories of being sarcoma of the soft-tissue or the bone (Bridge, 2014; Demetri et al., 2010). Among these classifications, molecular genetic testing often accompanies a diagnosis to further subtype the sarcoma. Soft-tissue sarcomas, for example can be divided into two major genetic categories: 1) sarcomas with identifiable gene abnormalities (*i.e.* chromosomal translocations or point mutations), and 2) sarcomas with unknown gene mutations. This latter group typically harbors complex genetic alterations that likely result from an unstable genome. Soft-tissue sarcomas with identifiable gene mutations can be subtyped even further to the specific translocation or point mutation that provides useful diagnostic and prognostic information (Demetri et al., 2010). With the completion of the human genome project, many efforts have been implemented to sequence and subcharacterize cancer. Breast cancer is a quintessential example of a complex group of diagnostic entities that were once considered a single disease, until they were divided into ER/PR +/-, HER2 +/-, triple negative, claudin low or high. One of the most cited works in cancer research, "Molecular portraits of human breast tumours," (Perou et al., 2000) underlines this point. However, decades before this publication, soft-tissue sarcoma was already being subdivided and characterized to help physicians understand and predict the behavior of specific types of sarcoma (Russell et al., 1977; Brennan et al., 1991).

What is left to learn about cancer that sarcomas can teach us? Has cancer become so individual that the study of general oncogenic mechanisms has become moot? We believe that sarcoma still can teach us about general cancer mechanisms that can help us delineate the epigenetic processes that regulate transformation, metastasis, and resistance. Due to the genetic simplicity of several sarcomas driven by