Editorial

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It is a pleasure to provide a brief introduction to this special issue of the Journal of Mammary Gland Biology and Neoplasia devoted to Novel Molecular Targets in Breast Cancer. This issue contains reviews on several targets that have been selected because, in our opinion, they represent areas in which basic science has advanced to the point at which innovative and validating clinical trials can be accomplished. Much of this work is built on a substantial body of prior work and success that it is worth very briefly recapitulating.

Of all the solid tumors afflicting humans, the successful treatment of breast cancer has achieved the greatest gains. This is in part due to the exceedingly well organized clinical trials network which exists for breast cancer trials. And this in turn unquestionably reflects the commitment of a very long and very distinguished list of very courageous advocates who have provided resources for study and encouraged women to participate in clinical trials. The result of these efforts is the dramatic and continuing fall in breast cancer deaths even though the incidence of breast cancer has not declined [1].

Half a century ago there were no systemic therapies for breast cancer aside from endocrine ablation and additive therapies utilizing pharmacologic doses estrogens and androgens. There were no successful adjuvant therapies. And most certainly, there was no adequate mechanistic understanding of the molecular pathogenesis of breast cancer so as to permit the rational development of therapies. This picture has radically changed for the better. [2]

Though occasionally overlooked as the first example of molecular targeting, the identification, purification and

quantification of estrogen receptors provided endocrine therapy with a rational and predictable basis. These seminal discoveries were accompanied by a rapidly expanding appreciation for the multiple sources of estrogens in humans including the critical role of peripheral aromatization of androgen precursors of estrogens, and the ever-increasing options for either antagonizing their effects or reducing their ambient concentrations below those needed to stimulate tumor growth [3]. The application of these approaches to the adjuvant setting has gratifyingly resulted in the cure of many women who would otherwise succumb to breast cancer [4], and has served as a highly effective [though as yet insufficiently employed] means of preventing thousands of breast cancers each year [5].

The next great advance in targeted therapy was the discovery of HER2/neu as an oncogene and as an amplified and overexpressed contributor to the pathogenesis of about 20 % of breast cancers. This discovery led to the development of multiple FDA- approved, or soon to be approved, means for interfering with signaling via this pathway. Once again, the addition of these approaches to the adjuvant setting has greatly enhanced the success of chemotherapy for those women whose breast cancers are stimulated through the HER2 pathway. At the same time it has also unquestionably been curative for a significant fraction of women who, until recently, faced one of the most lethal forms of breast cancer. It is exceedingly gratifying that a subtype of breast cancer once thought to confer a particularly grave prognosis is now transformed to one of the most treatable forms of breast cancer! [6].

One of the great mysteries that remains is an adequate explanation for why therapies that can convincingly cure some women with microscopic metastatic disease fail to provide a similar benefit against overt metastatic disease. For example, tamoxifen given prior to a diagnosis of breast cancer can prevent 50 % of cases. Aromatase inhibitors are

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even more effective. In the adjuvant setting both afford long-term cure of breast cancers that would otherwise be destined to recur. Yet essentially no women receiving these therapies for metastatic disease will be cured.

Part of the explanation for this discrepancy/discordance likely lies in the ability of tumors to “adapt” to the selective pressure of an initially successful intervention. Such alternative pathways may already exist in some of the cells comprising a tumor or, alternatively, the initial therapies themselves may induce exploitation of resistance pathways. Other mechanisms such as failure of immune surveillance may also be at work.

One of the most remarkable aspects of our understanding of breast cancer has been the near universal acceptance of sub-classifying breast cancers into a variety of “species”. Unfortunately while two of these subsets are most clearly associated with specific molecular drivers [luminal A and HER2] the others are not, and even for these two categories, resistance, as mentioned above, is a common occurrence [7].

It is the purpose of this collection of focused communications to delve into several molecular pathways currently under intense investigation that hold significant promise to improve future therapy of breast cancer. All have received significant preclinical validation. They also all have translatable components that are already in a clinical trial or are soon to enter a clinical trial. As such there is appropriate

reason for optimism that even greater success in treatment may be achievable in the near future.

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