

**Molecular Classification, Prognostication and Prediction**  
**Summary of BCRF think-tank session**

**Moderator:**  
**Clifford Hudis, MD**

**Attendees:**

Angelo Di Leo  
Laura Esserman  
Bruce Haffty  
James Hicks  
(for Michael Wigler)  
Kim Hirshfield  
James Ingle  
Benita Katzenellenbogen  
Gordon Mills  
Monica Morrow  
Soon Paik  
Charles Perou

Michael Press  
Lajos Pusztai  
Gad Rennert  
Stuart Schnitt  
Ian Smith  
Christos Sotiriou  
Fraser Symmans  
Zoltan Szallasi  
Laura Van 't Veer  
Charles Wang Zhigang  
Walter Willett  
Antonio Wolff

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This group consisted of an interesting mix of medical oncologists, laboratory investigators, pathologists, surgeons, and informatics experts. This provided a useful range of insights and complementary skills and knowledge.

As our discussion unfolded, each member of the group presented their area of expertise, their BCRF-funded research project, and a summary of research they are currently excited about. We used each introduction as an opportunity to pull in new discussants, points of view, and areas for possible inquiry and collaboration.

Our initial focus was on the use of molecular classifiers. We compared the use of newer genetic profiling using arrays to the historical use of “single gene” markers, such as the estrogen and progesterone receptors and HER2 status. We then considered the clinical meaning of the finer classification offered by gene profiling. This led to a careful consideration of the differences between purely prognostic factors and those that are predictive (or both). Relating to these issues, we had an extended review of the two commercially available gene expression profiles, with particular attention to both how clinicians might use them today and how investigators might extend their utility. We contrasted these tests with the molecular classification expression profiling provides (luminal A, B, basal, etc...) and noted that even these categories are likely to be further subdivided. A key issue we need to keep in mind is the link between classes of breast cancer and therapeutic implications and interventions. Specifically, a distinct subset of breast cancers is only relevant if it describes a different natural history or points to a differentiated treatment approach. We ended this area of discussion by considering the interesting lack of direct overlap for the several well-described gene profiles and the implications for translational scientists and targeted drug development.

We next turned to a variety of single genes, generally presented by members of our group as the focus of their research. Some of these genes, such as those regulating the metabolism of tamoxifen, have functional normal variations in the form of SNPs (single nucleotide polymorphisms) and others, such as PTEN are only distinct when they are mutated and/or dysfunctional in tumors. This allowed us to consider the overall utility of single-gene research in experimental systems as opposed to whole genome approaches.

The group recognized the herculean task that molecular studies can represent, both because of the complexity of the systems within single cells and clonal masses but also because of the heterogeneity we see across animal tumor models and humans with breast cancer. At the same time we recognized that we have never before had the opportunity to perform such precise molecular studies at a relatively affordable cost. This evolved into a consideration of society's obligation to support appropriate tissue banks of human breast cancers. A critical issue that the group considered was the utility of large tissue repositories linked either to broad populations (i.e., the national or regional tissue banks developed by several European countries) or to individual clinical trials. The differential value and utility of each approach led to agreement that, at a minimum, annotated tissue banks linked to prospective clinical trials should be a very high societal priority.