

Therapeutic Targets/Targeted Therapeutics
Summary of BCRF think-tank session

Moderator:

Gabriel N. Hortobagyi, MD

Attendees:	Susan Horwitz
Joaquin Arribas	J. Dirk Iglehart
Alan Ashworth	Nancy Lin
Jill Bargonetti	Philip Livingston
Jose Baselga	Hayley McDaid
Robert Benezra	Kathy Miller
Fatima Cardoso	Kent Osborne
Lisa Carey	Ben Ho Park
Vincent Cryns	Edith Perez
Francisco Esteva	Lori Pierce
Zhen Fan	Neal Rosen
Monica Fornier	William Sikov
William Gradishar	George Sledge
Mark Greene	Richard Zellars

With excellent attendance, and a good mix of medical specialties and scientific areas of interest, this was a lively group.

Initial discussions focused on the interpretation of “targeted therapies”, with some members of the group emphasizing the effect of a potential therapeutic, with others requiring a clear therapeutic effect in a population enriched for the target. This discussion highlighted the importance of bringing all stakeholders together and enhance communication between clinical and laboratory investigators.

Next, the discussion turned to the inefficient drug development process in general use today, with the need to implement large, multi-thousand patient clinical trials to reach definitive conclusions about the clinical usefulness of a new therapeutic. This led to a vigorous discussion about preclinical models. Some members of the group indicated that preclinical models were largely inadequate and not predictive of clinical events. Others, to the contrary, emphasized the need to understand that every model has definite strengths and weaknesses, and that in order to have models predict the clinical effects of a new therapeutic, both the model and the specific question being asked have to be carefully selected. It was pointed out that far too many experiments are fundamentally flawed, because the model selected is not representative of the clinical reality, or has a peculiar molecular characteristic not found in clinical breast cancer, or simply because the researcher does not understand the shortcomings of the model. It was emphasized that

it was highly desirable to perform experiments in multiple, well-selected models to make sure that the observed effects were indeed related to the target and drug under evaluation, and not to a single model's idiosyncrasy.

Action plan: There was consensus about the need to write a review or position paper about the status of breast cancer models and the optimal selection and utilization of such models in drug development. Potential authors: Alan Ashworth, Neal Rosen, Edith Perez, Jose Baselga, and Jill Bargonetti.

The next topic for discussion was novel trial designs to expedite drug development. "Window" trials and neoadjuvant trials were highly favored following the necessary evaluation for safety, since such trials provide an excellent opportunity to obtain serial biological samples. There was enthusiasm about this strategy, although several participants brought up the problem of obtaining IRB approval for "mandatory" procedures, including biopsies.

The discussion further emphasized the critical importance of obtaining biological material, especially tumor biopsies during the assessment of targeted therapeutics to ascertain tissue pharmacokinetics and pharmacodynamics. Furthermore, it was emphasized that biopsying metastatic disease immediately before participation in a new drug clinical trial would enhance the available biological information and would preclude erroneous assumptions of marked expression based on the (often remote) primary tumor.

Action plan: Because of the perceived heterogeneity of IRB positions on this matter, it was proposed that the IRBs relevant to BCRF awardees research be polled regarding their position on mandatory interventions in clinical trials.

Because breast cancer was increasingly a conglomerate of smaller and smaller molecular subgroups, multicenter, multinational collaborations will be increasingly important for timely drug evaluation. One of the potential obstacles mentioned was the international transport (export) of biological materials. It was stated that the US is one of the most restrictive countries in terms of exporting biological material, thus making it particularly difficult to participate in multinational trials with biological endpoints.

The final discussion related to the development of a biological material repository to serve all BCRF investigators. Such a repository could be virtual, but it would require sophisticated informatics support, as well as appropriately trained personnel.

Action plan: Promote discussion of biomaterial repository with the Scientific Advisory Board.