Cancer Stem Cells and Cancer/Stroma Interactions
Summary of BCRF think-tank session

Moderator:
Martine J. Piccart-Gebhart, MD, PhD
with the help of Christos Sotiriou, MD, PhD

Attendees:

Stuart Aaronson
Craig Allred
Graham Colditz
Albert Deisseroth
H. Shelton Earp
Silvia Formenti
David Gorski
Rachel Hazan
Mien-Chie Hung
Stephen Hursting
Tan Ince
Charlotte Kuperwasser
Eva Lee
Marc Lippman
Hyman Muss
Funmi Olopade
Kornelia Polyak
Peggy Porter
Thomas Rohan
Hope Rugo
Rachel Schiff
Robert Schneider
Carrie Graveel (attending on behalf of Vande Woude)
Robert Vonderheide
Robert Weinberg
Max Wicha
Eric Winer

This two-hour meeting gathered a number of superb basic / translational scientists, pathologists and clinicians.

As a result, a very stimulating discussion took place and involved emerging preclinical and clinical data pertaining to these two exciting topics.

An effort was also made to identify areas of future research and collaboration.

I. Breast Cancer Stem Cells

This fascinating topic was divided into four points of discussion: new theoretical models of breast cancer development and progression, the breast cancer stem cell hypothesis, the current tools to characterize cancer stem cells and the relevant clinical questions to be addressed.

1. New theoretical models of breast cancer development and progression

The models of very early breast cancer cell dissemination (C. Klein : Lancet 2002, PNAS 2002, Cancer cell 2007) and of breast cancer cell self seeding (Norton and Massagué Nature Medicine 2006) were the subjects of lively discussions !

According to the former, breast cancer (stem) cells could escape the primary site much earlier than originally thought. While most of those cells would not survive in the circulation or at distant sites, a few would be able to do so and would generate metastatic foci genetically distinct from the primary tumor site. Dissemination would also occur, although at a later stage, from the primary tumor itself.

This provocative model – based on laboratory data – generated different levels of enthusiasm in the group.

The second model is supported by laboratory and mathematical modeling data.
It sheds light on a number of clinical "mysteries" – including the apparent benefit from local tumor control (by surgery a/o irradiation) in the setting of overt metastatic disease.
A clinical trial designed to strengthen this evidence is being prepared by ECOG.

2. The breast cancer Stem Cell Hypothesis

Pioneered by M. Wicha, this hypothesis provides elegant concepts for the development of the different breast cancer subtypes (Stem Cell Rev. 2007).

- Triple negative and Luminal B subtypes would derive from an ER negative cancer stem cell.
- Luminal A breast cancer – a markedly different disease – would originate from an ER+ cancer progenitor cell.

An animated discussion took place: Is there a cancer stem cell to start with, or are cancer cells able to acquire "stem cell" properties ?

Independently from the answer to this question, there was a consensus that cancer cells with stem cell features do exist and that their clinical relevance becomes a high priority for future research.

3. The tools to characterize cancer cells with stem cell features

Stem cell markers have been the subject of a recent review (Visvader & Lindeman : Nature Rev. Cancer 2008).
For breast cancer, they include CD44 or CD133 positivity, CD24 negativity, ALDH-1 positivity.
None of these markers is relevant for the luminal A putative progenitor cell.

There was agreement that further progress is needed in the molecular characterization of the stem cells likely to play a role for the different breast cancer subtypes and in the molecular pathways critical for the survival of these cells.

4. The relevant clinical questions that need to be addressed

Two lines of clinical / translational research generated enthusiasm:

- The molecular characterization of circulating cancer cells, according to the different breast cancer diseases. While not all these circulating cancer cells might be clinically relevant, there are emerging technologies that should allow for their in depth molecular characterization and this knowledge might lead to molecular targeting of these cells with an anticipated (although hypothetical) clinical benefit in early breast cancer.

- The study of cancer cells with stem cell features as part of neoadjuvant clinical trials. Preliminary data indeed suggest enrichment for such cells as a result of preoperative chemotherapy and potential eradication of these cells by targeted agents such as lapatinib (J. Chang, J Natl Cancer Inst, 2008).

  There was enthusiasm in the group for broadening this type of studies, as the knowledge gained here might lead to innovative clinical trial designs.

II. Tumor – Stroma Interactions

Basic scientists have done a wonderful job at dissecting these interactions and identifying their role in the creation of a "permissive environment" that allows breast cancer cell dissemination and colonization of distant metastatic sites.

The discussion here was split into two parts : the importance of the stroma at the primary site and the role of the stroma at distant sites.

1. Tumor – stroma interactions at the primary site

- The hard work of our German colleagues that led to the recognition of UPA – PAI-1 as prognostic and predictive markers was alluded to ; of note a drug targeting this invasiness pathway has entered clinical testing (N. Harbecq et al).

- Ch. Sotiriou shared some results of his work with the group (C Desmedt, Clin Cancer Res. 2008). In silico developed gene expression modules, based on publicly available gene-expression profiling data of more than 2000 breast primary tumors, and representing an "activated stroma" or an "active immune component" were found to strongly correlate with patient clinical outcome : namely, the stromal module conferred a poor outcome to the HER2 positive subtype while the immune module identified a subset of triple negative breast cancers with an improved prognosis.

These intriguing results were further corroborated by the development of specific stroma/immune signatures using isolated CD10+ cells (fibroblasts) and CD4+ cells (leukocytes) from freshly microdissected patient tumor samples ; similarly to the in silico results, the stromal signature identified a worse outcome for HER2 positive disease while the immune signature was associated with better outcomes both in the triple negative and HER2 positive subtypes.

While still in need for fine-tuning, these data produced by two different lines of research generate the interesting hypothesis of a differential benefit from future stromal or immune-directed therapies according to the breast cancer molecular subtype.

- Organ-prone multigene metastatic signatures were briefly discussed.
A lung metastasis signature has been discovered by the group of Massagué.
While this work carries the hope for site-directed therapy in the future, the group felt that a lot more work was needed in order to identify the key molecular discriminants and to develop the correspondent anti-metastatic targeted therapies.

2. Tumor – stroma interactions at distant metastatic sites

- The critical role of the stroma at distant sites has long been suspected. Perhaps its most striking clinical demonstration comes from the recent positive results of the Austrian adjuvant bisphosphonate trial (ASCO 2008).

The following points were made about this trial :

1) The magnitude of benefit from adjuvant zoledronic acid given every month appears to be substantial (HR for DFS : 0,643!).
2) Intriguingly the risk of all types of relapses appears to be reduced (including loco regional !).
3) These striking results, however, are based on only 137 events among 1803 highly selected patients – e.g. premenopausal women with highly endocrine responsive tumors receiving an LHRH agonist with either tamoxifen or anastrozole.
   A confirmatory trial in a broader patient population is eagerly awaited.
4) While this trial is bringing fuel to the old "seed and soil" hypothesis formulated by S. Paget more than 100 years ago, it remains unclear whether the treatment benefit (e.g. zoledronic acid) is explained by an effect on the seed, the soil or both.

Everybody agreed that, if confirmed, these results would open the door to a new line of clinical investigations aimed at manipulating the bone microenvironment.

It was also suggested to move from the bedside back to the bench and to study in more depth the potential antimetastatic effect of bisphosphonates in preclinical models.
In particular, it would be of great interest to explore whether bisphosphonates have any impact on the trafficking of key bone marrow cells.

In conclusion, the group felt confident that innovative treatment approaches aimed at manipulating tumor / stroma interactions would be developed successfully in a not too distant future.