AACR Annual Meeting—March 31-April 5th, 2006
An Advocate's Perspective

Jane Perlmutter

I was fortunate to attend the American Association of Cancer Research (AACR) annual meeting for the third time as part of the excellent Scientific←→Survivor Program. (See http://www.aacr.org/page5957.aspx for the meeting proceedings, including many webcasts; and http://www.aacr.org/page5845.aspx for information about AACR's Survivor and Advocate programs.) I have commented on the scope of these meetings and the nature of this particular program in previous notes (http://www.gemini-grp.com/index_files/CancerAdvocacyFiles.htm) and therefore will not repeat myself. Rather, I will focus here on several trends I found most interesting this year. Before I do so, however, I should mention AACR's excellent new magazine—"CR: Collaboration → Results" that was launched during the annual meeting (http://www.crmagazine.org/). The magazine's mission is "to strengthen collaborations and communications among cancer survivors, patient advocates, physicians and scientists, with the goal of accelerating the prevention and cure of cancer" and should be of interest to many readers of these notes.

The Promises of Cancer Research

Since the mid '90s we have been hearing that we would soon reach an age of personalized medicine where treatments would be tailored to the biology of individual's cancer. Likewise, we have heard that by understanding the biology of cancer—the processes and signaling pathways—treatments would be targeted to cancer cells, sparing normal tissue and the many side effect that are often associated with cancer treatment.

Over the past fifteen years there have been exciting technical and scientific advances toward these goals, and a few significant clinical applications. Still, the more we learn, the more complicated things seem to become. For example, validating bio-markers that can be used to classify cancer types has been easier to conceptualize than accomplish. Also, targeted therapies are proving to be more toxic than predicted, and cancer cells proving to be smarter than anticipated. Thus, multiple pathways often need to be knocked out to disrupt cancer, and even then genes mutate to resist drugs.

Although the hype surrounding recently approved targeted therapies might lead one to believe the concept is new, it is worth noting that anti-estrogen targeted therapies (e.g., SERMs) have been effectively used against breast cancer for at least 30. Angela Brodie, the winner of this year's award for translational research, talked about the long and often difficult history of bringing Aromatase Inhibitors which are an alternative approach to blocking estrogen, from lab to clinic. Craig Jordan, in an early morning "meet-the-expert" session, talked about sequencing

a variety of SERMs, Aromatase Inhibitors and Estrogen therapies to overcome the tendency of cancer cells becoming resistant to therapies.

Balancing enthusiasm for the genuine scientific progress and frustration with the limited clinical progress is always tricky. What I sensed at this year's at AACR meeting is an increasing sense that it is time to focus more attention on the challenges of translating the basic science into improved patient outcomes. This is not to say that there will be a slowing down of breakthroughs in basic research; indeed, I expect that to continue to accelerate. Rather, that we may also see an acceleration in benefits to patients.

Of the three other topics I will address, the first two—epigenetics and microenvironments—are relevant to both science and treatment. The third—drug development—directly addresses the issue of translating current knowledge into patient outcomes.

Epigenetics and Micro-environments

Epigenetics is defined on the AACR website as "having to do with the chemical attachments to DNA or the histone proteins around which it coils. Epigenetic marks *change the pattern of genes expressed in a given cell or tissue by amplifying or muting the effect of a gene, but do not alter the actual DNA sequence.* Unlike mutations to DNA sequence, epigenetic modifications are typically reversible." Because many cancer cells contain epigenetic abnormalities that are reversible, there is increasing interest in developing therapies aimed at reversing them. This may involve de-methylation, de-phosphoraliation, or removal of ubiquitin peptides. Such therapies, it is hoped, will be less toxic than traditional chemotherapies which kill cancer, as well as other cells. While there was a bit of a buzz about these processes at last year's meeting, this year there was a roar, perhaps most clearly heard in the presidential talk given by the outgoing AACR president, Peter Jones. In addition, many other technical talks and posters were directed at epigenetics.

Another alternative to indiscriminately killing cells is based on understanding the environment surrounding cancer cells. This strategy is based on the insight that cancer flourishes in only selective areas of the primary organ and metastasizes to only selected sites. By changing the micro-environment, the hope is, we can prevent cancer from growing and/or metastasizing.

Angiogenesis, a hot topic for the past several years, is actually an example of focusing on the micro-environment. Angiogenesis is defined in blood vessel formation. The relevance to cancer is that blood vessel development is necessary to support growth of solid tumors. Further, cancerous cells send signals to encourage angiogenesis. Anti-angiogenetic therapies take advantage of this by disrupting these signals. When angiogenesis is knocked out, the tumor cannot continue to grow. Several such drugs are now being incorporated into cancer treatment with modest improvements in outcomes.

Micro-environments are also relevant to metastasis. Cancers only metastasize to a subset of potential sites. Further, the site where metastases are found seems predictable based on genetic properties of both the tumor and host site. Some interesting work was reported that found that mice could be bred to have strong tendencies toward specific metastatic sites, even when injected with identical cancer cells. This finding suggests that manipulation of the biology of potential host sites could interfere with and perhaps prevent metastasis. This is indeed the mechanism by which bisphosphenates reduce bone metastases—that is, by changing the bone structure. Many talks were directed at characterizing properties of the micro-environment that are required for cancer invasion and metastasis.

Drug Development

These meetings, unlike the American Cancer Oncology (ASCO; http://www.asco.org) meetings, focus on basic science. Nevertheless, they increasingly report some translational and clinical research. This year I found increasing attention to biological, methodological, economic and regulatory issues that impact drug development. Two of the opening plenary talks fall into this category. Todd Golub talked about using gene profiles of tumors to identify new applications of already approved drugs. The method led to novel, practical and apparently successful therapies. Also, Gregory Verdine talked about methods to make "small molecule biologics." Chemotherapies use small molecules which can readily penetrate cells, but do not specifically target cancer. Newer, biologics, on the other hand are designed to target cancer processes. However, they are large, making it difficult for them to reach their targets. The chemical approaches Verdine discussed were meant to avoid these issues.

Another session focused on regulatory issues associated with drug development based on targeted therapies. Janet Woodcock discussed the FDA's Critical Path Initiative which is being implemented, in part, to facilitate better selection among targeted agents. The goal is to reduce the proportion of failed phase III trials which are costly in terms of time, money and patients. Phase 0 trials will now allow drug developers to simultaneously test several related compounds in very small, presumably safe doses. The goal of these studies will be to investigate how the drugs are metabolized and reach their targets. Based on these results, phase 1 and 2 trials will be more focused on identifying optimal, rather than maximum dosages. This reflects an important change. In particular, with chemotherapies, higher doses are generally more effective, but also more toxic. Thus, prescribed doses were determined to achieve a reasonable trade-off. With targeted therapies, there is typically a point where higher doses are not only more toxic, but less effective. This is good news for patients, but poses new challenges for drug developers—finding the optimal dose.

Another session focused on economic challenges associated with targeting subsets of cancer patients. As we see prices of targeted therapies skyrocket, we need to ask how they will be paid for. Even well insured patients often cannot

afford co-payments. While there was no resolution to this issue, a very interesting paper by Thomas Roberts presented some economic models that suggest that under many conditions targeted therapies are more, not less economic for drug companies. This occurs because even though fewer patients use the targeted therapies, targeted drugs are more likely to pass regulatory hurdles. Additionally, targeted therapies are usually priced at a premium. The model showed that even if the premium is modest (10-15%), targeted drugs are generally more profitable for drug companies.

Finally, there were a number of sessions that focused on clinical trial design issues. I was very heartened to hear some innovative ideas, including much more interest in and acceptance of Bayesian Approaches. Because this is a particular interest of mine, I am making a significant amount of material on this topic available to advocates on my website (http://www.gemini-grp.com/index_files/Bayesian.htm). Here I will mention two trial designs that I heard discussed which could be more efficient than traditional designs (i.e., take less time, fewer patients and less money to complete) and remain statistically sound. In *adaptive trials* patients are randomized to treatments, but the proportion assigned to each arm changes through the course of the trial, based on early results. Using this approach, on average more patients receive the superior treatment, and the trial can often be completed more rapidly than using traditional approaches. Another interesting design is the *randomized discontinuation trial*. This is a two-phase design. In phase I all patients are treated with the drug being evaluated. In phase II, those who had a positive response are randomly assigned to continue the same treatment or switch to placebo. This design is particularly useful if you can identify characteristics (i.e., biomarkers) that distinguish the responders from non-responders, although the markers would have to be independently validated.

Conclusion

In conclusion, participating in the Scientist←→Survivor program was a wonderful opportunity to obtain a broad perspective on cancer research, learn of the latest trends, and network with inspiring, generous scientists and advocates. Many of the scientists are as interested in learning from advocates as we are in learning from then. This program helps advocates gain the competence, confidence and voice to be more effective on behalf of all those affected by cancer. I encourage you to apply to attend next year's conference which will celebrate AACR's 100th anniversary.