

## THE DAWN OF PERSONALIZED MOLECULAR MEDICINE IN CANCER CARE

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For most patients, the diagnosis of cancer carries the realization of one's biggest health fears. Treatment may invoke almost as much trepidation as the illness itself. Though we have made advances in care such as powerful anti-emetics, bone marrow stimulators and less toxic agents, chemotherapy still is a blunt instrument that carries multiple side effects.

The search for a better mousetrap has begun to yield exciting results. Molecular diagnostics once used as laboratory tools have made their way to patient care. The prototype of such a treatment is with the antibody rituximab. This is a monoclonal antibody against a B lymphocyte cell surface marker named in the laboratory CD (cluster designation) 20. The CD 20 protein is expressed on normal B lymphocytes, but is over-expressed on the cell surface of lymphoma cells. Rituximab is a mouse-human chimeric (fusion) antibody with the variable portion targeting CD 20 made from the mouse genome. The majority of the antibody (the conserved portion) is made from a human gene to avoid recognition of this protein by our own immune system as foreign. Intravenous infusion of rituximab has been shown as a single agent to control the growth of low grade lymphoma and allows one to completely avoid chemotherapy in some instances. It can notably increase the cure rate of aggressive lymphomas when added to standard chemotherapy agents. Patients receiving single agent rituximab sit about three hours for their infusion for symptomatic lymphoma and leave without side effects (barring a rare infusion reaction). They feel steadily better during treatment without nausea, hair loss or fatigue.

Several other antibodies have been developed against such 'liquid' tumor circulation in the bloodstream. This concept has been advanced to use technologies to conjugate proteins such as potent cytotoxic agents to direct a lethal dose selectively to the malignant cell, sparing the normal cell. It mitigates the need to deliver agents solely based on cell division rates. Similarly, radioactive iodine conjugated to the targeting antibody can be targeted to cells not only in the bloodstream, but also the bone marrow or

reticuloendothelial system. There are few side effects excepting the rare infusion reaction and little long-term toxicity. They have greatly widened the therapeutic window for cancer treatment.

Treatment of so-called 'solid tumors' has also benefited from such research. Proteins on the surface of these cancer cells can be targeted by antibodies such as cetuximab (binds to the epidermal growth factor receptor-EGFR) and can increase the control rate of colon cancer and cure rate of head and neck cancers.

One of the most remarkable advances in cancer care has been the development of trastuzumab. This antibody targets Her-2, a cousin of EGFR, classified in the same epidermal growth factor family of proteins, and is over-expressed on the cell surface of breast cancer cells. Trastuzumab was shown first to add to the control rate of metastatic breast cancer in the late 1990s and was available only by lottery until produced in sufficient quantities. Perhaps the only thing more remarkable than the use in metastatic breast cancer of this non-toxic antibody was the 50 percent increase in cure rate in the adjuvant treatment of breast cancer when added to chemotherapy. This was such an unprecedented and unequalled finding in cancer treatment that two weeks after the data were presented at the 2005 American Society of Oncology International meeting, it became a standard of care.

A clue to the future of such treatments was the selection of patients who might benefit from this antibody. To that point in time, clinicians would like to have had a tool based on molecular pathways to select patients who would respond to biological therapies, less toxic than chemotherapy. For example, trastuzumab is effective only for the 20 percent of patients who have the Her-2 protein overexpressed or amplified on their tumor cells. This is as measured by protein levels on tissue biopsy or by analysis of the gene duplication itself. Thus the analysis of other molecular pathways to target cancer cell growth, division, resistance to chemotherapy, the ability to metastasize and the ability to set up residence in other tissues are needed, and are yielding exciting results.

*(next month: Targeting Cancer in Novel Ways)*

## THE DAWN OF PERSONALIZED MOLECULAR MEDICINE IN CANCER CARE PART 2

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Last month, we looked at molecular diagnostics that are changing the way cancer is treated. This article continues with an examination of additional new means to success.

### *Unlimited Potential*

Recently, a clever means to treat cancer was derived with a molecular pathway in mind that was not tumor-specific. Clusters of cancer cells cannot grow beyond a millimeter in diameter as they outstrip their oxygen need supplied by passive diffusion. However, tumor cells have taken advantage of a normal physiologic process by producing and secreting vascular endothelial growth factor (VEGF). When VEGF is produced by malignant cells, host endothelial cells are recruited to form new blood vessels (angiogenesis) in the tumors to allow nutrient delivery and further the growth and spread of cancer. The first antibody targeted against VEGF, bevacizumab, was developed and used in mice, and cured otherwise fatal tumors transplanted from human tumors into the so-called xenograft model. Perhaps nothing engendered more excitement than the presentation at the American Society of Oncology Meeting in 2004 when it was shown that this non-chemotherapeutic agent extended survival from 15 months to 21 months when added to the standard treatment of metastatic colon cancer. There were few side effects (rare increase in intestinal perforation) and thus a new standard of care was created. This antibody has now been approved based on randomized controlled trials in colon cancer, lung cancer, renal cell cancer and breast cancer. It is highly active in other malignancies, as one might expect, such as ovarian cancer and brain cancer (glioblastoma multiforme) and likely many more to come as it is pathway-specific, not tumor-specific. The dawn of the new age of treatment paradigms has arrived.

### *Small Molecule Smart Bombs*

While antibodies have the advantage of being engineered and screened quickly and then produced in large quantities, they are limited to cell surface or extracellular

targets. Small molecule inhibitors have thus been developed in parallel to target the intra-cellular pathways. The classic example of molecular medicine comes from the development of imatinib. This small protein was developed as part of designer protein technology. Chronic myelogenous leukemia (CML) is a cancer that is caused by the recombination of two genes (bcr and abl) that have been translocated to be next to each other (called the Philadelphia chromosome) causing the continued expression of the bcr-abl fusion protein. This new protein is now expressed on the cell surface of CML cells and allows unregulated cell proliferation. The protein serves as a growth signal that is the single cause of this cancer, so was a logical target; shut it off and shut off the cancer. Scientists used molecular modeling of the aberrant bcr-abl protein to develop imatinib to bind to the activation pocket of the intracellular portion of this transmembrane protein. Once bound to the bcr-abl fusion protein, imatinib shuts it off. A disease once fatal in two to three years now can be treated for more than a decade with a pill once a day. This is truly amazing.

Physicians and researchers turned their attention back to solid tumor treatment with these small molecules that could penetrate the cell membrane, and are at work on the signaling cascade that drives cancer cells to multiply and spread. One such target was the signaling pathway of the EGFR protein. EGFR is overexpressed in many tumor types such as pancreas cancer and non-small cell lung cancer. When combined with standard chemotherapy, erlotinib has been shown to extend survival in pancreas cancer. While the average survival in this rapidly fatal disease is only extended a few weeks, in absolute terms at one year six more people are alive by taking this oral tyrosine kinase inhibitor than would otherwise survive (23 percent versus 17 percent). Diarrhea is the major side effect but is manageable and the other toxicity, an acne-like rash, is ironically linked to a better response. In lung cancer treatment, erlotinib as a single agent was shown to extend survival in second-line treatment. We have now even

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gone to use of totally non-chemotherapeutic approaches in first line metastatic lung cancer combining erlotinib with bevacizumab. It does not, however, work for all, and thus refining our new molecular tools is the next goal.

Tumor characteristics play a role in how we can target cellular growth signals. Renal cell cancer is a classic example of this. The clear cell subtype of renal cell cancer develops from a mutation in the von-Hippel-Lindau (VHL) tumor suppressor gene. This mutation allows unregulated growth of this tumor, but the development of small molecule inhibitors aimed at the downstream targets has now been developed. These small molecules are anti-angiogenic (inhibits new blood vessel formation) and target multiple tyrosine kinases that are unregulated due to the mutation of the VHL gene and stop this tumor's growth, extending patient survival. A disease with little hope and with only one FDA approved, very toxic treatment (interleukin-2) up until two years ago now has six FDA-approved biological agents to be implemented.

### *Patient Selection Might be the Key*

We have already discovered that breast cancer cells that do not overexpress Her-2 will not respond to trastuzumab. We have now tools looking at the expression of genes in breast tumor cells that can better predict response to chemotherapy. Two licensed tests are now available. One test is the Oncotype Dx, which looks at the RNA expression of formalin-fixed breast cancer tissue. Tumors can be analyzed from specimens routinely obtained from lumpectomy or mastectomy samples. Although not universally accepted, it is a tool for clinicians to help guide patients in the decision process of whether chemotherapy may be of benefit. More in line with the molecular profiling, there are now tools that look at individual genes in lung cancer. The one that holds the most predictive power is the presence of EGFR over-expression. Lung cancer cells that express the EGFR activation mutation tend to respond to erlotinib, while those cancers that do not express this EGFR mutation will not respond; a great negative predictive tool. One of the most important molecular findings of recent times is defining tumors that will not respond to antibodies against the EGFR

surface protein, again another negative predictive tool. The signaling protein produced by the K-ras gene is the gear that engages the EGFR and allows it to direct RNA expression and promotes cellular growth. However, some cancer cells do not use that pathway and thus using cetuximab will not inhibit tumor cell growth in colon cancer though the drug was approved for all these patients. Obviously we need more tools and more tests to target all cancer cells, but this is indeed a daunting task.

### *The Future*

The concept underlying much of cancer therapy is that patients with specific types and stages of cancer should be treated with chemotherapy based on population-based studies of "all comers." However, the recent advances in drug development, pharmacogenomics, and the molecular characterization of tumors — including sequence analyses, RNA expression and proteomic profiling — have placed individualized cancer care at the forefront of medicine. I look forward to what the next decade of discovery has to offer.

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## IMPORTANT NEWS ON LAB REQUISITION SIGNATURES

The laboratory is experiencing a high volume of requisitions having illegible physicians' signatures. As a result of improper registration of patients in our computer system our personnel are in jeopardy of being reported to the State for HIPAA violations. We are requesting that each Pathology Requisition and each Discharge Requisition have a legibly printed physician's first and last name, including the physicians who are to get copies. This process will ensure that reports are routed to the appropriate physician and the level of patient care complies with the standards mandated by John Muir Health.

We are implementing new requisition forms for both laboratory and pathology that will have a line for the printed name as well as one for the signature. Until then, please insert the printed name above the signature field. Thank you for your compliance with our request. If you have questions feel free to contact either Marianne Niessner, Pathology Manager at (925) 381-9385 or Dorie Ruhe, Laboratory Manager at 925-941-4544.