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Targeting Cancer

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Physicians have been treating advanced cancer patients with surgery, radiation and chemotherapy for 60 years. In 1970 patients with advanced cancer that had spread from its original site in the body, had less than 50% survival at 1 year. Today less than 50% of advanced cancer patients survive 1 year. Nothing dramatic has changed. And yet, hope exists. Technologic advances in molecular biology and particularly genomics are revolutionizing cancer therapy. (Ginsburg, *Personalized medicine: revolutionizing drug discovery and patient care*. Trends Biotechnol. 19, 491-496, 2001.) The personalization of oncology treatments demands the ***alignment*** of patients' molecular cancer growth mechanisms with the drugs which have been designed to target the cancer specific molecular signals.

"No two cancer patients are the same, the genetic alterations in different cancers are heterogeneous according to each tumor." (American Society of Clinical Oncology, 2009 Annual Meeting.) This explains why two patients with the same cancer diagnosis, cancer stage and treatment often have very different responses which range from complete remission to rapid progressive disease. This variance in patient response is due to the historical inability to identify and target the treatment to the core mechanism of the individual's cancer. (Gerlinger, et al N Engl J Med 366:10 March 8, 2012.) Newly developed molecular diagnostics are increasing our understanding of the genomic makeup of an individual's cancer and how that cancer differs from normal, but therapeutic development in order to target these molecular (genomic, proteomic) targets lags behind. Therefore, it is time for new methods to harness this technology.

Aligning Patient-specific Targets to Targeted Therapy

The uniqueness of each individual is mirrored by the uniqueness of cancer cells, which have evolved from normal cells. Rapid processes to screen each patient's molecular diagnostic information, including next generation genomic sequencing, have become standard practice for cancer physicians. This new process of identifying molecular target signals and corresponding new targeted therapies will allow physicians to exquisitely ***align*** each patient to a therapy that attacks their cancer cells without harming healthy cells. ***However, while patient molecular diagnostic information has become readily available, the targeted therapies are slow in development. And the process to interpret the new molecular diagnostic information and match a patient to a targeted therapy is still in a very early stage of development***. Discoveries lay dormant without the tools needed to translate them into a treatment plan, or a compass to guide physicians' alignment of molecular treatments to cancer patients who will most likely to benefit. FDA has called for a new "product development tool-kit." (http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathOpportunitiesReports/ucm113411.pdf.)

At Mary Crowley Cancer Research Centers, ("Mary Crowley") research physicians are developing a *tool-kit*. The tool-kit represents a process which guides physicians to interpret patient-specific molecular information, and to align relevant targeted therapies for individual patient's treatment plans. The molecular biology of the patient's tumor instructs physicians with the information necessary to treat the tumor. The transformation is in the ***alignment***: diagnostic targets aligned to targeted therapies,

which is the essence of personalization. The result will be treatments most likely to halt each patient's cancer cell growth. Consequently, the most beneficial patient outcomes will occur when the knowledge of the bedside clinician is paired with the expertise of the molecular scientist. Mary Crowley acts as the bridge between treating physicians, molecular scientists who provide next generation diagnostic information, and pharmaceutical companies that develop next generation targeted drugs.

Background on Molecular Cancer Targets

"Though cancer has been known to be associated with abnormal chromosomes for over a hundred years, the causes of cancer were nearly a complete mystery until the first half of the 20th century when genes of DNA were shown to control the behavior of cells. Therefore, cancer is due to very specific changes or mutations in one of more than 25,000 genes, particularly genes that produce proteins that influence the rate and extent of cell division. The genetic damage can arise in any cell of any organ, making cancer the most frequent disease of the human genome," says David G. Nathan, M.D., Past President of the Dana Farber Cancer Institute and author of *The Cancer Treatment Revolution*.

Genes are made up of DNA that is found in every cell of our body. DNA holds within it, the information that instructs cells to develop specific features, which enables cells to perform specific roles in the body. DNA exists within the nucleus of every cell of our body. A chromosome is an organized package of DNA, supported by proteins that are found in the nucleus of the cell. DNA mutations can result in the mutated gene causing too much or too little of a given protein, which foster cancer cells. When DNA or protein behaves abnormally, uncovering such abnormal signals can aid in cancer diagnosis, prognosis, prediction of treatment response and recurrence. Evidence of abnormal molecular signals is also informing the development of drug targets for new cancer treatments.

We now know that cancer cells from one patient can show dozens of mutations that may be different from the dozens of mutations shown by cancer cells from another patient. Because it is difficult to target all gene mutations, cancer pathways carrying the mutated genes can also be targeted. A pathway is similar to a relay race in which one runner (usually a protein) hands off the baton to the next, and so forth. Each pass of the baton plays a vital role necessary for the success of the cancer cell: growth, proliferation, survival and/or metastasis. By intervening with a drug at the on-off switch, we may be able to make a drug to stop every runner in the race.

Revolution in Drug Development

Non-targeted therapeutics, like chemotherapy, work in some cases to slow cancer growth, but can result in toxicity. In addition, prior to chemotherapy treatment, no measureable accuracy exists to predict who will benefit. Furthermore, non-targeted therapeutics can enable cancer to molecularly re-evolve and generate a new resistance strategy. In many cases this is an additional factor allowing more aggressive tumor rebound. However, six key alterations exist within cancer cells, which are controlled by molecular signaling and which dictate malignant growth. These include:

- Self sufficiency
- Insensitivity to natural immune function and resulting growth inhibition
- Independence from programmed cell death
- Unlimited replicative potential
- Sustained angiogenesis or growth of blood vessels
- Capacity for local and distal tissue invasion

Scientists believe that blocking any one of these six cell process alterations will *halt* cancer growth. This provides justification for molecular-targeted therapeutics. Next generation targeted drugs in development are designed to target these six key cancer cell processes by attacking molecular signals. Molecular signaling is governed by a limited number of mutational events, which create *high degree nodes* in the cancer-signaling network and thereby create an *attack vulnerability*, i.e., an Achilles' heel.

Most oncology focused pharmaceutical companies have shifted toward development of targeted therapies, which seek to apply recent advances in molecular information in order to achieve better patient outcomes. If a drug is targeting the core mechanism of the cancer, it will be more likely to stop cancer cell growth and less likely to harm patients' healthy cells. One of the largest obstacles in translation is interpretation of molecular diagnostic information. The core mechanism which drives cancer cell growth, sometimes called the *driver gene*, is not always known. Scientists have now developed individual tests, which originally took years to complete, to map the genome and other relevant molecular information for each patient within weeks. These tests are far less expensive than the $1 billion cost of the original genome map developed in the Human Genome Project, and are often covered by insurance plans as validated sources of diagnostic information. Resulting diagnostic reports are called the *patient molecular profile*. However, the process for uncovering relevant genes, pathways or signals to block cancer cell growth remains in its infancy. For example, multiple molecular signals may be relevant, or a gene mutation may be unrelated to the proteins driving the cancer. This can lead researchers toward blocking the wrong gene targets, until further research uncovers the correct target. *Physicians treating cancer patients need a tool-kit that enhances their ability to interpret molecular information, to determine the relevance of cancer targets, and to have the expertise to select new drugs that block the patient-specific target.*

Several targeted therapeutics are now available as standard treatments, having achieved FDA product approval. Below is a partial list of targeted therapeutics and the molecular signals they are designed to block.

Therapeutic	**Target**
Herceptin, Tykerb	Her2neu
Gleevac	cKIT, BCR-ABL-tyrosine kinase (TK)
Tasigna	BCR-ABL-TK
Rituxas, Bexxar	CD20
Avastin	VEGF
Tarceva, Iressa, Vectibix, Erbitux	EGFR
Velcade	Proteasome
Sutent, Nexavar	PDFGR, VEGFR, KIT-FLT3, RET-TK
Vemurafenib, Dabrafanib	BRAF
Crizotinib	ALK, ROS1
Vismodegib	Shh
Everolimus, Torisel	mTOR

While this is a good start, many more targeted treatment options are needed.

The Secret Sauce: Alignment of Targets

The tool-kit in development at Mary Crowley will guide physicians toward the best targeted treatments for their patients, in standard therapy, as well as clinical trials. The process begins and ends with the patient. First, the treating physician obtains the molecular profile of the patient which is determined from a tissue sample to understand

the most relevant genetic information that drives the patient's cancer. If no *Driver Gene* is readily apparent, bioinformatic experts may need to further assess the genes and proteins in a patient's molecular profile report in order to uncover signals and pathways that the cancer is taking or that could provide the resistance to established therapies. This can produce a roadmap to help physicians determine the best juncture at which to turn off the genetic switch.

Finally, the patient-specific molecular information is used to ***align*** each patient with a custom target-specific drug, which uses a molecular signal-blocking technology. If no approved product fits the patient need, many more investigational molecular targeted therapies are available through clinical trials. New targeted drugs in clinical trials all undergo a rigorous process under FDA oversight in order to prove that they can stop cancer cell growth and provide a patient benefit. The first step is identification of a prognostic target. Cancers are often suspected to have multiple relevant targets along the genomic pathway. Once a target discovery proves relevant to cancer cell growth, scientists endeavor to attack the target with an investigational drug. FDA requires proof that the investigational drug controls the molecular target with potency. For example, most successful targeted drugs have achieved greater than 50% knockdown (turning off) of the intended molecular target. This means that the molecular mechanism implicated in cancer cell growth is disabled more than half the time. Some investigational drugs have shown greater than 90% knockdown of a molecular target in early testing. After an investigational drug has shown potency against the intended target, the FDA requires validation in the laboratory and in animal testing that the drug demonstrates cancer inhibitory activity. This is closely tied to whether the targeted therapy successfully *delivers* its payload to the cancer cells. The delivery mechanism has proven a key obstacle to many targeted therapeutics. If an investigational drug passes these milestones, and shows that its mechanism of action is correlated with benefit and tumor response, it can move on to clinical testing. The clinical testing phase constitutes Mary Crowley's area of expertise.

Clearly, matching a targeted therapy to the diagnostic target, involves multiple targets, which are based on pathway crosstalk and feedback. Each step is a complicated process. However, while our personalized treatment capabilities continue to expand, patients are in need of care. Our first step, genomic diagnostics application to target assessment has now become patient-ready and can supplement existing tools in order to provide further benefits to treatment planning and, ultimately, to better patient outcomes. Although advanced cancer patient survival has not dramatically changed since 1970, the physician toolbox is improving. With better tools, outcomes will improve. Hope exists.

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