

Human Genome Neil Senzer, MD

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“The most common way people give up their power is by thinking they don’t have any.” Alice Walker could just as well have been talking about the sense of hopelessness and dread that so many cancer patients experience when they are confronted with their diagnosis. Although in the past this was a justifiably appropriate response, the technological explosion in the new millennium, has paved the way to

- 1) Deciphering the human genome,
- 2) Doing so in less than a week at a constantly decreasing cost,
- 3) Unlocking the molecular components and functionality of the immune machinery,
- 4) Applying computerized systems analytic techniques to integrate all this information and
- 5) Modeling cancer progression and growth using novel evolutionary concepts. All of these are now bringing hope and empowerment to cancer patients, their physicians and their health support teams.

The Mary Crowley Cancer Research Center did not just climb aboard this bandwagon; it helped create it through establishing as founding mission statements attentiveness to personalized cancer therapy, rapid and responsible application of new findings to patient treatment, and, in collaboration with the other research and development organizations, development and integration of multiple modes of treatment.

As a result of the expanding genomic (pertaining to genes) and proteomic (pertaining to proteins) cancer database in a variety of cancer types, we now estimate that 3-12 mutations (alterations in the gene sequences that encode proteins) are necessary and sufficient to cause cancer. We have also learned that mutations in different genes can have a similar effect if they are in the same signaling (relaying information from the cancer cell surface membrane to the genes in the nucleus) or functional pathway. However, despite the existence of hundreds of known cancer mutations, there are only 12 core pathways thereby enabling us to focus attention on how a subset of these pathways that are rewired by the mutations interact with each other and to better understand how to design therapies to interfere with these cancer promoting networks.

Unfortunately, there is a lot of cross-talk both between and within these pathways which requires computerized systems analysis to delineate key targets, “bottlenecks”, defined by being major sites of molecular information transfer. Mary Crowley continues to explore this approach by offering patients “designed” multi-targeted therapeutics such as small molecular inhibitors of TORC1+TORC2+PI3k and TORC1+TORC2+DNA-PK. In the former, for example, if only the protein TORC1 is inhibited the cancer cell compensates by increasing TORC2. However, if both TORC1 and TORC2 are inhibited, the cancer cell becomes capable of increasing the protein PI3k that is upstream of both proteins and eventually overcomes the intended inhibition: thus, the triplet combination.

Approximately ten percent of the genes responsible for maintaining cancers are called “oncogenes”; these are genes that produce proteins that control functions necessary for cancer growth and/or survival. The remaining

90% are “suppressor genes” that normally inhibit pro-cancer biological functions. There is abundant evidence that restoring the function of some of these suppressor genes can have therapeutic benefit. One such gene is p53 that acts as a “gatekeeper” preventing the accumulation of mutations, repairing errors in genes occurring during cell division, and initiating a cell kill process called apoptosis in cells containing genes with errors that cannot be repaired. Mary Crowley was singularly responsible for helping to design, implementing, and successfully completing a “first-in-man” study of p53 restorative therapy. Not only were we able to show that the gene could be delivered to cancer cells but, in addition, that by using a nanoparticle carrier system it could be ‘selectively’ delivered to the cancer cells and not the surrounding normal cells and that, most importantly, it produced clinical responses. This study has now been published and has led to Phase II testing in different cancer types in combination with other treatments. The rationale for these combinations is based on the role the p53 protein plays in initiating the cell kill pathway in cells with significant DNA (the structural basis of genes) damage. By selectively using chemotherapy agents that damage cancer DNA and/or radiation that can be physically focused to target and damage cancer cells, restoring p53 function should allow for enhanced cell death. Mary Crowley has designed and implemented a treatment protocol combining p53 restorative therapy with docetaxel (a chemotherapy agent) in selected patients.

As noted above, gene mutations are detected in biopsied samples of patient’s cancers. In addition, multiple biopsies of the same cancer site as well as biopsies of the same cancer that has spread to different parts of the body (metastases) in each individual patient show different or modified mutation patterns. This genetic diversity within each cancer is called “genetic heterogeneity”. To make matters more complicated, not only do cancers undergo heritable mutations (passed from cancer cell to cancer cell during the process of cell division) that result from structural changes in DNA, they also undergo epigenomic changes that, as a result of biochemically activating or deactivating genes without affecting structure, also result in heritable change. As a result, the different genetic/epigenomic groups of cancer cells (called clones) within each cancer have a complicated ecology (the relationship between groups and their environment). Although they can interact with each other to enhance survival and/or proliferation (growth due to reproduction) necessary for adaptation, they also compete with each other for space to grow as well as for access to blood vessels delivering oxygen, amino acids (to form proteins) and glucose (for energy). Thus, every cancer evolves! Generally speaking, evolution involves complex tradeoffs between the two processes; proliferation rate and survival. Cells that are highly plastic (phenotypic plasticity is the ability of an organism to change its expressed traits) are highly adaptable in that they respond conditionally to changes in their environment (other cancer cells and surrounding normal cells). The traditional use of chemotherapy is more likely to affect cancer cells with a high proliferative rate leaving behind cancer cells with a different proliferative pattern but more adept at survival. This phenomenon is called “competitive release” and results in treatment resistance. An important component of survival is the ability to hide from the immune system.

Considering all this, Mary Crowley in collaboration with bio-tech companies, has embarked on a “one-two punch” developmental strategy: combining an attack on cancer cell proliferation using combinations of novel targeted agents that interfere with the individually identified mutated gene pathways in the cancer with immunotherapy to decrease the survival advantage of the cancer. This latter approach has now completed Phase I evaluation in the clinic with the demonstration of safety, the ability to elicit an immune response, and with a strong suggestion of improvement in patient survival. The results of this FANG™ vaccine have been recently published. The vaccine uses the cancer cells from the patient into which are inserted one gene to produce an immune stimulating protein (GM-CSF, granulocyte-macrophage cell stimulating factor) and a second to produce a novel agent to block the ability of the cancer genes to encode proteins that suppress the immune response. Mary Crowley has now activated a series of treatment protocols in patients with selected cancer types to study the combination of this FANG™ vaccine with chemotherapy—attacking both cancer cell proliferation and survival. Our expectation is that these studies will lead to studies of combinations of FANG™ vaccine and individualized targeted therapeutics—a truly personalized combined modality approach based on

genomic and epigenomic findings integrated with revised concepts in evolution and ecology.

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