

## Cancer Metabolism Overview

### What Is Cancer Metabolism?

Cancer cell metabolism is an exciting and promising area for the development of drugs to treat cancer. In 1924, Nobel laureate Otto Heinrich Warburg discovered that cancer cell metabolism is distinct from the metabolism of normal or healthy cells. While normal cells rely on oxygen for metabolism, cancer cells rely largely upon an oxygen independent form of metabolism to produce the energy necessary for survival and growth. This altered metabolism is both unique to cancer and critical to cancer cell survival. Moreover, this metabolic shift is considered to be **fundamental** to the transformation of normal cells into cancer cells including solid tumors, lymphoma and leukemia.<sup>1</sup> Metabolic function in cancer cells, as with any living cell, is essential to survival. With recent scientific insight, we now better understand these processes and can envision targeting the unique aspects of cancer metabolism to find drugs to revolutionize the treatment of cancer.

James Watson, Nobel Laureate who discovered the double helix, recently wrote in a *New York Times* Op-Ed piece, that research efforts over the last 40 years for new treatments have not been focused in the right areas and that targeting cancer metabolism is the best current hope for a miracle drug.<sup>2</sup> This perspective has been gained significant support in the past few years.

### Why Is Cancer Metabolism A Promising Arena For Investigation?

There are three reasons why this is considered among the most exciting areas in cancer drug research today.

- **Potential Efficacy:** Since metabolism is essential for cell survival, the development of agents that disrupt metabolic processes, could lead to a treatment that is a powerful cell killer. Many of the largest selling cancer drugs today are not cell killers (cytotoxics), but agents that work only to slow tumor growth and traditional cytotoxic agents do not distinguish between normal and cancer cells which can lead to severe side effects.
- **Potential Safety:** Since the metabolism of cancer is different from that of healthy cells, drugs that target this metabolic difference have the potential to selectively impact cancer cells, bypassing normal cells. A drug that is catastrophic to cancer cells, but safe to normal cells, would be superior to any cancer drug known today.
- **Broad Potential Applicability:** Preliminary data suggests that the unique metabolism of cancer is consistent across cancer types, from solid tumors to lymphoma and even leukemia. Therefore, drugs targeting cancer metabolism may have a wide potential application. This novel approach to cancer treatment is fundamentally different from current treatments and has the potential to treat even drug-resistant and other difficult-to-treat cancers.

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<sup>1</sup> Vander Heiden, et al. (2009): "Understanding the Warburg Effect: The Metabolic Requirements of Cell Proliferation." *Science* 324(5930) 1029-1033

<sup>2</sup> Watson, James D. (Aug. 6, 2009): "To Fight Cancer, Know the Enemy." *New York Times*, Op-Ed

### **Is Cancer Metabolism Being Leveraged Today In Medicine?**

A key feature of cancer cell metabolism is an enhanced appetite for glucose and certain other nutrients, including certain lipids, proteins and amino acids. Current medical practice uses this enhanced demand for glucose by cancer cells to identify live tumors through PET imaging (Positron Emission Tomography.) This technology utilizes a glucose molecule that is labeled with a radioactive isotope, fluorine-18. Tumors preferentially take up much more glucose than normal cells (as a result of their altered energy metabolism.) When they take up more of the radio-labeled glucose than normal cells, they become visible to scanners that see this radioisotope, distinguishing them from most normal cells.

### **Who Is Working To Develop Drugs In This Area?**

As the potential of this therapeutic area gains recognition, many companies, including big pharmaceutical companies, are exploring cancer metabolism or the potential to re-brand and reevaluate their science in the context of cancer metabolism. However, only a small group of companies with a focus on cancer energy metabolism as a primary target for therapeutic intervention, have a meaningful presence in this area. Many current drugs and drug candidates being developed by these companies do indirectly target aspects of cells that relate to energy production processes or target aspects of these processes that are also displayed in healthy cells. These drugs do not act directly on the unique enzyme targets involved in cancer's energy metabolism.

### **Why Target The Mitochondrial Processes?**

The primary cellular organelles responsible for generating the majority of the energy used by a cell are the mitochondria. The structure, function and quantity of cancer cell mitochondria, however, are vastly changed in cancer cells. Instead of functioning primarily to make energy, cancer mitochondria are largely repurposed to make biosynthetic intermediates, or cellular building blocks required for cell survival and proliferation. The mitochondria are also a key player in the cellular pathways that determine if a cell should live or die. New drugs that can halt mitochondrial function will cause catastrophic death through a variety of mechanisms, including starvation, blocking reproduction, programmed cell death (apoptosis) and necrosis. Since normal cell mitochondria do not exhibit certain key enzymes involved in these processes, the potential exists to design a drug that targets these enzymes and kills cancer cells. Since normal cells don't have these targets, such drugs would leave normal cells unaffected, resulting in drugs with superior efficacy and safety.

### **What Should We Know About Cornerstone Pharmaceuticals?**

Cornerstone is a leader in the discovery and development of cancer therapies that capitalize on and disrupt the unique metabolic processes of cancer cells.

While cancer metabolism has recently become a hot area of cancer research, the scientists at Cornerstone Pharmaceuticals have been quietly working nearly alone in this specialized area of cancer research for over 15 years.

Unlike other companies who are only now searching for selective drug targets in order to find and subsequently develop drugs for this area, Cornerstone already has a drug candidate in clinical development. By disrupting vital cancer-specific metabolic processes, Cornerstone's drug candidates have the potential to safely and selectively kill cancer cells *irrespective of cancer type*.

Cornerstone's founding members, management and scientific and advisory team comprise some of the most preeminent scientists in the field of cancer cell metabolism and cancer research:

- Cornerstone's CEO Rob Shorr, Ph.D., - Co-founder of Cornerstone, began his career at Smithkline & French (now GSK,) and was Chief Scientist at Enzon and United Therapeutics. Dr. Shorr has published extensively and won numerous awards for his research in cancer and drug delivery. Dr. Shorr has also contributed to the discovery and development of standard of care drugs and technologies that are being marketed today, including G-protein coupled receptor identification and mechanisms of signal transduction, helping to open the door to the field of GPCR targeted drugs, and PEGylation for enhanced drug delivery, and separation materials for nucleic acid and genomics research. At Enzon, Dr. Shorr contributed to the development and FDA approval of PEGylated asparaginase (Oncaspar) and PEG INTRON A for the treatment of hepatitis C and the discovery of PEGylated arginine deiminase for the treatment of cancer. The PEGylated enzymes are among the first biologics based drugs that target cancer metabolism. PEGylated arginine deiminase received the NJ Cancer Society Gallo Award for innovation. At United Therapeutics Dr. Shorr contributed to the discovery and development of PEGylated small molecule drugs for the treatment of pulmonary hypertension and other diseases.
- Paul Bingham, Ph.D. and Zuzana Zachar, Ph.D. - lead academicians who have been researching cancer metabolism since the mid 1990's.
- Gregg Semenza, Ph.D. -an acknowledged world leader in the space who discovered Hypoxia Inducible Factor 1 (HIF1)
- Robert Weinberg, Ph.D.,- one of the leading cancer researchers in the world and credited with the discovery of the human oncogene.

The Company's unique approach to targeting cancer metabolism has led to the discovery of first-in-class drugs that have the potential to revolutionize the way cancer is treated. Its platform technology that targets and disrupts cancer metabolism is known as its AEMD platform, or Altered Energy Metabolism Directed platform.

Cornerstone's lead drug candidate from its AEMD platform, CPI-613, is a first-in-class, small molecule drug. CPI-613 is currently being evaluated in three clinical trials, (i) a Phase I/II clinical study in cancer patients designed to determine its maximum tolerated dose, and evaluate its safety and efficacy, (ii) a Phase I/II trial evaluating CPI-613 in first-line treatment for pancreatic



cancer in combination with Gemcitabine and (iii) a Phase I study evaluating CPI-613 in hematologic malignancies, including acute myelogenous leukemia (AML.)

Key features of CPI-613 shown in preclinical testing:

- Demonstrated broad spectrum anticancer activity in all tested cancer cell types, solid tumor and hematologic
- Is very well tolerated at therapeutically useful doses, with none of the side effects typically observed with traditional small molecule anticancer drugs
- Easy to manufacture

The three clinical trials for CPI-613 are all currently enrolling patients. The Phase I/II trial in hematologic malignancies is being run by Wake Forest University Baptist Medical Center, while the other trials are being funded and run by Cornerstone. For more information about trials please contact: [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

For more information about cancer metabolism or the work Cornerstone Pharmaceuticals is doing in this area please visit [www.cornerstonepharma.com](http://www.cornerstonepharma.com) or contact: Meghan Weber at (917) 399-8713.