

## Why We Do What We Do!

Cancer. Few words are able to stir as much dread in the imagination. Perhaps this is because nearly every family in the United States has been affected by this hideous disease in some shape or form. Indeed, the high incidence of the various forms of cancer makes this disease an increasing reality for Americans. Furthermore, there are roughly 1.2 million new cases of cancer diagnosed each year in the United States. Additionally, there are a staggering 550,000 cancer-related deaths in this country alone. To put things into perspective, on a typical day in America there are approximately 11,132 births; on that same day, approximately 3,500 people will be diagnosed with cancer, and approximately another 1,500 people will die from it.

The pursuit for a cure for cancer remains one of modern medicine's greatest quests. The complexity and aggressive nature of the disease has made this quest more difficult than ever imagined. No example can demonstrate this point better than President Nixon's now famous speech given for the inauguration of the National Cancer Institute on May 6, 1971. This turning point in modern medicine ushered in the relentless war on cancer by proclaiming that the United States would find a cure for cancer within five years. In retrospect, this date has marked only the beginning of our understanding of this incurable disease.

Indeed, much of the trial and error that has defined our 30-year war on cancer has served to characterize the unique traits that make cancer so resistant to conventional treatment. Cancer is highly autonomous, produces its own growth factors, is adaptable, has redundant and overlapping systems, develops its own blood supply, and is highly heterogeneous. It is this heterogeneity that has emerged to define the mixed patient responses to traditional treatment regimens and guides us in our pursuit of cancer drugs that demonstrate multiple mechanisms of action acting singularly or in concert against tumor biology.

- Cancer is the second leading cause of death in the United States, surpassed only by heart disease.
- According to the American Cancer Society (ACS), about 553,000 Americans die from cancer each year — an average of more than 1,500 cancer deaths each day.
- The National Institutes of Health estimates that cancer costs Americans \$156.7 billion each year: \$56.4 billion in direct medical costs, \$11 billion in lost productivity due to illness, and \$59 billion in lost productivity due to premature death.

Celgene scientists are studying potential treatments for hematological and solid tumor cancers, including the following:

- **Colorectal cancer** is the third most frequently diagnosed form of cancer in the United States (when all forms of skin cancer are excluded). The ACS estimates that about 107,300 new cases of colon cancer and 41,000 new cases of rectal cancer were diagnosed in 2002, with approximately 48,100 and 8,500 deaths respectively from these cancers.
- **Metastatic melanoma** is a very serious form of skin cancer. It begins in melanocytes - cells that make the skin pigment called melanin. Although melanoma accounts for only about 4% of all skin cancer cases, it causes most skin cancer-related deaths. The chance of developing melanoma increases with age, but it affects all age groups and is one of the most common cancers in young adults. The number of new melanomas diagnosed in the United States is increasing. Since 1973,

the incidence rate for melanoma (the number of new melanomas diagnosed per 100,000 people each year) has more than doubled from 5.7 to 14.3. The American Cancer Society estimates that about 53,600 new melanomas will be diagnosed in the United States during 2002. About 7,400 people in the US are expected to die of melanomas during 2002.

- **Multiple myeloma** is a cancer of antibody-producing cells normally found in bone marrow. It is the second most prevalent hematologic cancer, accounting for about 1% of all cancers, according to the Multiple Myeloma Research Foundation. About 50,000 Americans have multiple myeloma. There is no known cure; the ACS estimates that 14,600 new cases were diagnosed in the United States in 2002, and that more than 10,800 patients would die from the disease during the same period.
- **Myelodysplastic syndromes** are a group of hematologic conditions that affect approximately 300,000 people worldwide. The five types of MDS are refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in formation, and chronic myelomonocytic leukemia. Myelodysplastic syndromes occur when blood cells remain in an immature or "blast" stage within the bone marrow and never develop into mature cells capable of performing their necessary functions. Eventually, the bone marrow becomes filled with blast cells until there is no room for normal cells to develop. According to the American Cancer Society 14,000 new cases of MDS are diagnosed each year in the United States (approximately 87,000 worldwide), with survival rates ranging from six months to five years for the different types of MDS.
- **Renal cell carcinoma** Renal cell carcinoma (RCC, or kidney cancer) is the sixth leading cause of cancer death in the United States, accounting for 3% of adult malignancies. The average age at diagnosis is between 50 and 70 years of age, with a 2:1 male predominance in the disease. An estimated 31,800 new cases of RCC are projected to be diagnosed in the United States in 2003. One third to one half of these patients will present with metastatic or advanced disease. Although the 5-year overall survival rate in RCC is approximately 50% of patients, patients with metastatic disease have a median survival of about 11 months.
- **Prostate cancer** is a leading cause of cancer death in men in the United States, second to lung cancer. Prostate cancer accounts for about 11% of all cancer-related deaths in men, or about 31,500 deaths in the United States annually.

### **Development Candidates**

Celgene has a number of product candidates being evaluated for their potential roles in treating various forms of cancer:

- **THALOMID<sup>®</sup>** our lead commercial product is being evaluated in more than 200 clinical cancer studies worldwide for hematological and solid tumor cancers (75% of the trials). THALOMID, driven by peer-reviewed publications and clinical studies such as the Mayo Clinic and M.D. Anderson studies published in *The Journal Of Clinical Oncology* (JCO) in November 2002 and January 2003, respectively, is used primarily to treat all stages of multiple myeloma and several solid tumor cancers including prostate, melanoma and renal cell carcinoma. To date, THALOMID is FDA approved in the United States for the treatment of acute cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL), a complication of Leprosy.

- **REVIMID™ (CC-5013)** is a member of a new class of novel immunomodulatory drugs, or IMiDs™, which may demonstrate, in clinical studies, anticancer response. Ongoing clinical trials are evaluating REVIMID in the treatment of a broad range of conditions, including; the malignant blood cell disorders known as myelodysplastic syndromes (MDS), as well as multiple myeloma and solid tumor cancers. REVIMID has received a Fast Track Designation from the FDA both for the treatment of MDS and the treatment of multiple myeloma. REVIMID is believed to affect multiple biological pathways within the cell, which ultimately may be responsible for the clinical response observed in multiple studies. The IMiD pipeline is covered by a comprehensive intellectual property estate of U.S. and foreign issued patents and pending patent applications including composition-of-matter and use patents.
- **ACTIMID™ (CC-4047)** is a second-generation immunomodulatory drug, or IMiDs™, which may demonstrate, in clinical studies, anticancer response. Ongoing clinical trials are evaluating ACTIMID in the treatment of prostate cancer, as well as multiple myeloma. ACTIMID is believed to affect multiple biological pathways within the cell, which ultimately may be responsible for the clinical response observed in clinical studies. The IMiD pipeline is covered by a comprehensive intellectual property estate of U.S. and foreign issued patents and pending patent applications including composition-of-matter and use patents.
- **Kinase (CC-401)** successfully completed a Phase I trial in healthy human volunteers. Our pipeline of JNK inhibitors holds enormous promise for the treatment of a wide range of chronic and acute diseases. A versatile target, JNK is involved in the onset and progression of diabetes, stroke, rheumatoid arthritis, asthma and cancer.
- **Benzopyran (CC-8490)**, is the lead compound from our class of benzopyrans, markedly inhibits the growth of glioma (a brain tumor originating from the nervous system) in in-vivo studies and promotes apoptosis (cell death) in preclinical glioblastoma models. Based on these preclinical data, we have initiated a Phase I/II trial of CC-8490 in patients with glioblastoma in partnership with the National Cancer Institute and we continue to explore other molecules from this class.
- **Ligases** - Our ligase modulators made the important transition from target discovery to drug discovery and demonstrated anti-cancer activity in preclinical models.
- **Tubulin Inhibitors** - Celgene scientists discovered a new class of tubulin inhibitors, anti-proliferative compounds offering medically meaningful potential through multi-faceted anti-cancer mechanisms of action. These small-molecule anti-cancer compounds demonstrate activity against drug-resistant cancer cells, inhibition of inflammatory cytokines and anti-angiogenic activity. Our tubulin inhibitor pipeline contains numerous compounds that could improve the lives of patients challenged by cancer.

The above mentioned compounds have not been approved by the FDA or any other regulatory agencies as a treatment for hematological and solid tumor cancers and they are currently being evaluated in preclinical and ongoing clinical trials for efficacy and safety for future regulatory applications.

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