

## **Thalidomide History Backgrounder**

### **Origins As a Safer Tranquilizer**

Thalidomide was first synthesized in Europe, and in 1954 pharmaceutical chemists in Germany began testing it for potential use as a new anti-allergy drug. It did not work as an antihistamine, but when the laboratory rats being used to test the drug fell asleep, the scientists realized they had discovered a new tranquilizer. What's more, the drug seemed safe even when overdoses were administered. Clinical and regulatory requirements for testing new drugs were limited in the 1950's, and by the following year the new drug was marketed as Distaval in Europe and prescribed for a variety of symptoms including anxiety, insomnia and morning sickness in pregnancy. It should be noted that thalidomide was not approved for use in the U.S.

### **Link to Birth Defects**

In late 1956, the first baby was born with defects that would later be attributed to thalidomide. In all an estimated 12,000 affected babies were born with serious deformities in their legs, arms, hands, ears and internal organs; and across Europe the virtual epidemic of birth defects was attributed to everything from radioactivity to a virus to a chemical cleaner. It wasn't until 5 years later that Australian obstetrician William McBride made the connection between the birth defects and thalidomide taken early in pregnancy. His findings were published in 1961 and the drug was withdrawn worldwide in 1962.

### **New Use in Leprosy**

In 1965 Dr. Jacob Sheskin in Jerusalem revived thalidomide in a desperate effort to help patients suffering from ENL, a painful side-effect of leprosy. Sheskin was just hoping his patients would be able to get some rest, but thalidomide provided important unexpected benefits, clearing the patients' debilitating skin lesions literally overnight. A few years later, thalidomide received World Health Organization designation as the therapy of choice for patients with ENL.

### **U.S. Approval**

For 20 years thalidomide was available for ENL in the United States at just one clinic, which often had to formulate high-grade doses itself. That changed in June 1998 when the Celgene Corporation of Warren, New Jersey, received FDA approval to market thalidomide in the United States as THALOMID<sup>®</sup> for use in leprosy, along with a rigorous patented program it developed to help ensure that female patients of child-bearing age are protected from the possibility of becoming pregnant while on the drug. Called S.T.E.P.S.<sup>®</sup>, this *System for Thalidomide Education and Prescribing Safety* requires physicians and pharmacists to register for the program before being able to prescribe or dispense THALOMID. It is only with this strict closed-loop distribution system of protections that thalidomide can be prescribed and used in the United States. THALOMID is not substitutable under the S.T.E.P.S. program.

### **New Uses: Thalidomide and Multiple Myeloma**

Beginning in the 1970's, Harvard cancer researcher Dr. Judah Folkman began developing a theory that cancers can be blocked by cutting off the blood supply to malignant cells, a process called anti-angiogenesis. By the 1980's he began looking for a drug that could safely prevent a tumor from building its own blood supply, and in 1994 he began researching the anti-angiogenic properties of thalidomide in solid tumors. In 1997 Dr. Folkman first referred a patient with

multiple myeloma for treatment with thalidomide, and the treatment was then tried on a group of multiple myeloma patients who had failed all other therapy. Positive results from this and from subsequent studies conducted by Dr. Kenneth Anderson at the Dana Farber Cancer Institute helped establish thalidomide as a powerful agent in the treatment of multiple myeloma.

### **Thalidomide Today**

Today physicians are learning, through clinical data presented at key medical and scientific meetings around the world, that thalidomide fights cancer through multiple mechanisms including disrupting the blood supply to the cancer and stimulating the patient's immune system. To date, THALOMID is only 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. That said, THALOMID, driven by peer-reviewed publications 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. THALOMID continues to be evaluated in more than 200 clinical cancer studies worldwide for hematological and solid tumor cancers (~65% of the trials). In 1992 Celgene began a program to develop a new class of Immunomodulatory drugs (IMiDs™) as safer and more effective analogues of thalidomide. Two of these offspring drugs, Revimid and Actimid, which in laboratory tests have been shown to be more powerful yet lacking the side effects of thalidomide, are already being tested against several types of cancer including multiple myeloma, MDS, 5Q minus syndromes, melanoma, prostate cancer and others.

*I first heard this story from Dr. Zeldis over a dinner table in Athens, at the 2002 International Workshop on Waldenstrom's. I found this tale of medical serendipity fascinating, and I asked Dr. Zeldis if he would write it down for publication in the Torch. I think you will find it as absorbing as I did.*

*Ben Rude*

## THE THALIDOMIDE STORY

By Dr. Jerry Zeldis, Vice President, Medical Affairs  
Celgene Pharmaceuticals

The story of how thalidomide was discovered to be active in the treatment of multiple myeloma and, ultimately, in Waldenstrom's macroglobulinemia is illustrative of keen-minded physicians who were dedicated to finding hope for their patients.

Thalidomide was marketed in the 1950s as a safe sleeping pill that would not cause death if overdosed. By the late 50s, thalidomide was one of the most commonly prescribed drugs in Europe. As it was also used as an anti-emetic for the nausea and vomiting associated with pregnancy, the rising incidence of malformed babies eventually led to the drug's being banned in 1962.

At the time, the only hypnotics available were barbituates, which could result in death if overdosed. Professor Sheskin in Jerusalem was a physician who cared for patients with leprosy. A common complication of this disease is a painful deforming condition. One patient with this condition was suicidal and could not sleep because of his discomfort. Professor Sheskin was reluctant to give him barbiturates. Instead, he gave him some old thalidomide. To the professor's amazement, after a week on the drug the patient had completely healed. Thalidomide was thus re-born as the drug of choice for treating this complication of leprosy.

Since the mid-1960s a variety of clinicians experimented with thalidomide to treat a number of conditions, including cancer and graft-versus-host disease. By the mid-1990s, thalidomide was understood to be an immune modulatory drug (IMiD) that

could suppress the overexpression of tumor necrosis alpha and to be anti-angiogenic; that is, it could inhibit the production of blood vessels in malignant tumors.

Dr. Bart Barlogie of the University of Arkansas had a patient, a cardiologist in his mid-thirties, who was dying of multiple myeloma. His wife searched the internet for ideas for treatment and discovered the concept of angiogenesis. She called Dr. Judah Folkman, the father of this concept and a professor at Harvard Medical School. He told her that he had observed excess new blood vessel formation in the bone marrow of multiple myeloma patients and that thalidomide was a drug that could treat this. She asked Dr. Barlogie to try it.

I received a phone call from Dr. Barlogie in November 1997. He told me that Judah Folkman advised him that Celgene would give him thalidomide to try and treat a multiple myeloma patient. I told Dr. Barlogie that if he obtained permission from the FDA and his institution, Celgene would give him the drug. "Actually," he said, "I have three patients I would like to treat."

Normally it takes a week or two to complete the paperwork and to deal with the bureaucracies involved in approving the use of a non-licensed drug. The next day Bart called me and told me to ship the drug to Arkansas. After I verified his authorizations, I asked him how he got them so quickly. "I am Bart Barlogie," he replied.

Three weeks later, Bart called me to report that one of the three patients had an unprecedented response to thalidomide. The patient's bone marrow

had been packed with tumor—now it was less than ten percent packed. In addition, a variety of abnormalities were normalizing. Dr. Barlogie asked me if he could treat 10 more patients, then 20 more, then 180, then 1,600! Each time he was able to produce the necessary documents with amazing speed. When I asked how he could do it, he would answer, "I am Bart Barlogie!"

With the help of Dr. Ken Anderson of the Dana Farber Cancer Center, Dr. Ray Alexanian of M.D. Anderson and Dr. Robert Kyle of the Mayo Clinic and their colleagues, within a year thalidomide was recognized as the most promising new agent for multiple myeloma. It was also being tested in related conditions such as Waldenstrom's, Castleman's disease and lymphomas.

If it had not been for Professors Sheskin, Barlogie, Anderson, Alexanian and Kyle, who were willing to keep an open mind, thalidomide and the IMiDs would not have so quickly been found to be active in Waldenstrom's.

*[Editor's note: The above does not imply that thalidomide is licensed for the treatment of any medical condition other than the non-ocular complications of acute and chronic erythema nodosum leprosum. Thalidomide is a known human teratogen that can cause irreversible peripheral neuropathy.]*