The history of Irofulven, MGI Pharma’s novel anti-tumor drug-candidate, unfolds like a suspense story. It involves toxins, great expectations and crushed hopes, and a promise for a better future. The journey of Irofulven from a natural toxin isolated from a mushroom to a chemotherapeutic drug has involved people and places that have influenced American mycology in the 20th century, and has left its mark on mycological taxonomy.

In 2001, the Food and Drug Administration (FDA) granted fast track status to the novel anti-tumor drug-candidate Irofulven (also known as hydroxymethylacylfulvene, HMAF, and MGI-114). Irofulven is a chemically modified version of the fungal toxin Illudin S. It is a DNA-alkylating agent that has an unusual mechanism. Irofulven is a DNA and protein-damaging agent that targets rapidly dividing cells of malignant tumors, and in some cancers even poorly differentiating malignant cells. It enters the tumor cells where it interferes with DNA replication and cell division by binding to DNA and to protein targets. This leads the tumor cells to shut down and consequently die (apoptosis). A study conducted at the University of Texas Cancer Therapy and Research Center (2002) determined that at certain doses tumor cells were highly susceptible to Irofulven’s dual damaging activity while normal cells showed only marginal response to the cell-killing drug. The Texas study concluded that agents with this unique dual mechanism could be the basis for the development of tumor selective anticancer drugs.

In Phase I and Phase II clinical trials, conducted by MGI Pharma and the National Cancer Institute, Irofulven exhibited particularly promising results in shrinking malignant solid tumors, including those of drug-resistant cancers. It demonstrated remark-
Figure 1. Structure of Irofulven and Illudin S

able results on patients with pancreatic cancer that had stopped responding to drugs, offering new hope for patients with this deadly disease. Based on these favorable results, a Phase III clinical trial of Irofulven for the treatment of pancreatic cancer was started. Gaining the FDA’s fast track designation for an expedited review and approval process was an important milestone for the drug-candidate.

Irofulven is unique also for its remarkable history. It was developed by Trevor McMorris, Professor of Chemistry at the University of California, San Diego (UCSD), and Michael Kelner, Professor of Pathology at the UCSD School of Medicine. It is an acylfulvene, a family of potent semi-synthetic anticancer compounds, which was derived from Illudin S, a fungal metabolite too toxic to be used as a drug. The illudins were isolated over 50 years ago at the New York Botanical Garden in the Bronx from 

Completely bioluminescent in the dark and toxic to wildlife, the Jack O’Lantern mushroom was isolated from the poisonous and bioluminescent Basidiomycete Lampteromyces japonicus (Kawamura) Sing. This compound was soon found to be identical to Illudin S, isolated earlier from 

A few months earlier a compound called “Lampterol” was isolated from the poisonous and bioluminescent Basidiomycete 

This confirmed the valuable taxonomic character of illudins for the genus Omphalotus. Employing a molecular approach, Thorn (et al.) suggested a close relationship of the genera Omphalotus and Lampteromyces and later noted that the two illudin-containing genera form a monophyletic group in the clade Omphalotaceae. In 2004, Kirchmair et al. published the phylogeny of the genus Omphalotus, based on nuclear ribosomal DNA-sequences. The writers, who set out to clarify the phylogenetic relationships within the genus Omphalotus, indicated that the presence of illudins in both Lampteromyces japonicus and species of Omphalotus had a hand in the placement of L. japonicus in the genus Omphalotus.

In 1987, after Trevor McMorris joined the University of California, San Diego, he and Michael Kelner published a pre-clinical evaluation of the illudins as anti-cancer agents. The illudins, in particular Illudin S, were found to be highly cytotoxic (cell-killing) against a number of human cancer cells. But there was a problem. While the illudins demonstrated marked antitumor activity, in vitro and in vivo, they also demonstrated poor therapeutic index. The therapeutic index compares the amount of a therapeutic agent that causes the measured therapeutic effect, to the amount of the same agent that causes toxic effects.
The illudins’ therapeutic index was particularly poor when they were tested against solid tumors, where they have previously shown the most promise. Better understanding of their mechanism led to the development of a novel family of semisynthetic strong antitumor agents, acylfulvenes, which were derived by reverse Prins reaction from Illudin S. Acylfulvenes demonstrated far better therapeutic indices than Illudin S, while maintaining its marked antitumor activity toward solid tumors. Next generations of acylfulvenes proved to be even more effective antitumor agents, and their therapeutic indices kept improving. In an article published in 1999, McMorris and Kelner wrote, “acylfulvene is 100 fold less toxic in vitro and in vivo than Illudin S but possesses marked antitumor efficacy in vivo, thus displaying opposite properties from Illudin S.”

In the late 1990s Trevor McMorris submitted a patent application for total synthesis of antitumor acylfulvenes to the USPTO. The compounds yielded by the patented process could be formulated as pharmaceutical compounds, used in different concentrations, and administered on their own or in conjunction with other pharmaceutical compounds to humans with malignant tumors. In the description of the patent, McMorris noted that in tests of Irofulven on human metastatic lung carcinoma in mice, complete tumor regression was observed in the animals. He also noted that Irofulven exhibited outstanding activity against breast, colon, and skin cancers.

In 2001, with the FDA’s fast track status and a Phase III international clinical trial for Irofulven on refractory pancreatic cancer patients on the way, Irofulven generated much excitement. It showed promise in shrinking tumors of drug-resistant pancreatic cancer, a particularly deadly form of cancer with limited treatment options. The side effects associated with Irofulven were not much different than those of other chemotherapeutic agents. It had the potential to be the highly effective tool in the armament against cancer that its developers had hoped for.

However, MGI Pharma stopped the Phase III clinical trial a few months after Irofulven received its fast track status. MGI Pharma announced that a preliminary analysis by an independent safety monitoring board (DSMB) reported that the comparator agent (5-FU) demonstrated greater than expected survival benefit, making it statistically improbable for MGI to achieve its objective for the trial. It was a grave disappointment on many levels. Another problem became clear: patients enrolled in other Irofulven clinical trials reported serious visual disturbances. In a Phase II study of Irofulven in women with recurrent and heavily pre-treated ovarian cancer conducted at the Dana Farber Cancer Center in Boston in 2005, the Irofulven dose had to be lowered in mid-trial because of unexpected retinal toxicity. The retinal damage, in some cases significant, was associated with the dose and administration of the drug. This has been another stumbling block for Irofulven.

Irofulven continues to be evaluated in clinical trials for the treatment of solid tumors of a variety of cancers, both alone and with other chemotherapeutic drugs. Its unique DNA damaging mechanism has been tried in combination with other DNA damaging agents and these trials have yielded favorable results. They indicate that the antitumor activity of Irofulven is enhanced by this method, particularly when combined with platinum-derived and select-alkylating agents. The FDA lists a number of Irofulven trials, involving a variety of cancers, including an open trial for recurrent, pretreated, ovarian cancer.

Any antitumor agent must first demonstrate that it is both effective and safe enough to be used on humans. Toward this end it has to pass a long and tortuous path of testing and clinical trials before it can be approved. Streptomycin, the first antibiotic to prove effective against Tuberculosis, was almost shelved because it also caused severe loss of hearing. The efficacy and safety of Irofulven, the drug derived from the toxin of the “glow in the dark” Jack O’Lantern mushroom that beacons Halloween, is still being tested. Only time and further clinical trials will tell if it will take its place in the armament against cancer. But whether it is called Clitocybe or Omphalotus, the Jack O’Lantern’s place of honor in the annals of Pharmacological research is no Halloween trick.

Bibliography


