

Innovations

Cancer gets the red light

Pharmacyclics, Inc.

The triumvirate of cancer therapy — chemotherapy, radiotherapy and surgery — is being challenged by a new method of treatment. Photodynamic therapy (PDT) uses red light to activate otherwise benign drugs, and its specificity is winning over clinicians. “Photodynamic therapy is going to be well accepted because of the minimal side effects and low cost,” says David Dolphin of QLT PhotoTherapeutics, Inc. (Vancouver, Canada).

QLT is marketing Photofrin®, the only PDT drug to be approved in the USA. But several other companies are racing to get the next generation of drugs onto the market. As with Photofrin®, these drugs are based on porphyrins, the four-pyrrole rings seen in heme and chlorophyll (Figure 1).

One of QLT’s future competitors is Pharmacyclics, Inc. of Sunnyvale, California. The Pharmacyclics drugs are based on the expanded porphyrin ring of texaphyrin, synthesized by Jonathan Sessler (University of Texas, Austin). The larger ring of conjugated bonds increases the wavelength of absorption, and so clinicians can use light that penetrates deeper into tissues. The improved localization of texaphyrin to tumors was an unexpected bonus.

From clinic to chemist and back again

Sessler has more reason than most to be motivated in his work. While a graduate student in chemistry, he got first hand experience of the imperfect and imprecise nature of

cancer treatments as he fought off Hodgkin’s disease. The physician who pulled him through was Richard Miller, now the President and CEO of Pharmacyclics. “Someday,” says Sessler, “we will write the book and make a fortune.”

Sessler originally planned to fill the larger hole in texaphyrin with radioisotopes. The combination could then be linked to an antibody targeted to a cancer cell. In the end the texaphyrin localized to cancer cells better if there was no antibody, probably because the porphyrin has a high affinity for lipoprotein particles in the bloodstream. Rapidly dividing cancer cells make large amounts of membrane, so they have hefty appetites for the cholesterol in lipoprotein particles. The texaphyrin gets pulled in as a passenger.

Sessler says that local attitudes colored his decision to make texaphyrin. “In Texas, everything is bigger,” he says. “When I arrived here I quickly realized that making something bigger would be the way to go. Besides, if you name a molecule after your state you get early tenure.”

The upshot for PDT is that a larger metal, in this case lutetium, can fit into the texaphyrin to yield the final drug Lu-Tex. The lutetium improves the efficiency with which the Lu-Tex, excited by light, undergoes a process called intersystem crossing. Instead of re-emitting the energy as fluorescence, the Lu-Tex is converted to an excited triplet spin state. It can then undergo spin exchange with unreactive triplet oxygen, converting

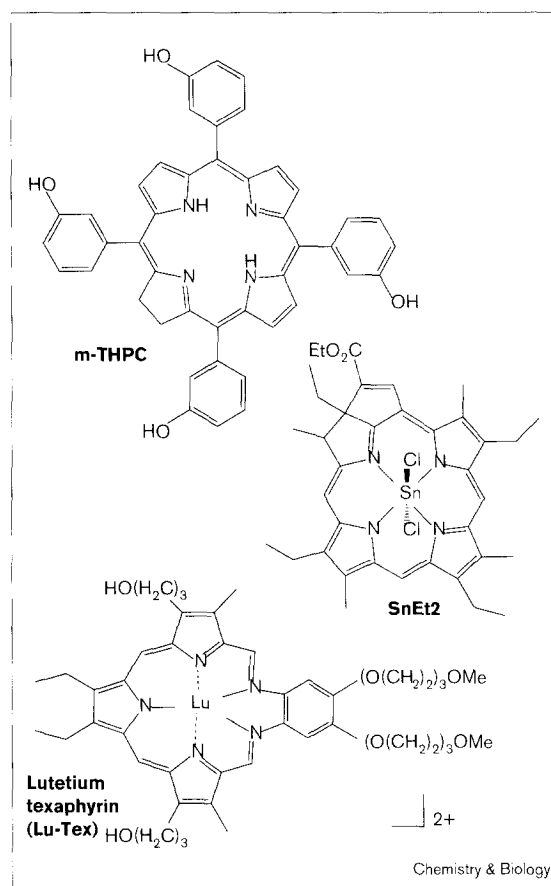
it to highly reactive singlet oxygen even while the Lu-Tex reverts to its original singlet state.

Singlet oxygen “oxidizes whatever it hits,” says Sessler, with membrane lipids perhaps its most important target. A proportion of the target cells die soon after, often from ion leakage, but many more die from necrosis after various signaling molecules cause the destruction of the surrounding blood vessels.

Texaphyrin as an electron sink

Gadolinium is another lanthanide ion that can fit into the texaphyrin hole. The resulting Gd-Tex is being used to increase the power of treatments with radiation or chemicals such as adriamycin or bleomycin. When these agents encounter water they produce

Figure 1



Some of the porphyrin-based drugs used for photodynamic therapy. Shown are Scotia’s m-THPC, Miravant’s SnEt2, and Pharmacyclics’ lutetium texaphyrin.

hydroxyl radicals and solvated electrons. With Gd-Tex around, the radicals have a longer life and so can do more damage. The imines of the texaphyrin probably act as an electron sink, preventing the radicals from recombining with the electrons to form inactive hydroxide ions.

Unlike lutetium, gadolinium is paramagnetic, meaning that the oscillations of its unpaired electron can be detected by magnetic resonance imaging. An imaging agent made of gadolinium and zeolite is providing Pharmacyclics with some cash while Lu-Tex winds its way through cancer trials.

Texaphyrin on trial

A Phase II trial is underway using Lu-Tex for recurrent breast cancer, and Gd-Tex is in a Phase II trial for the treatment (with radiation) of cancers that have metastasized to the brain. The National Cancer Institute (NCI) has also recognized the potential of Lu-Tex and Gd-Tex, and is funding grants for investigators wanting to run trials with these drugs for bladder, ovarian, pancreatic and primary brain cancers (Lu-Tex) and head and neck, pancreatic, lung and primary brain cancers (Gd-Tex). "It is wonderful for us," says Markus Renschler, the Director of Clinical Research, "because we are tapping into the brain trust of the country through the NCI."

Pharmacyclics also has promising preclinical data on the use of Lu-Tex for atherosclerosis. The foamy macrophages that are part of atherosclerotic plaques ingest large amounts of cholesterol, and once again the Lu-Tex comes along for the ride.

After local delivery, the drug is concentrated ~35-fold in the plaques as compared to neighboring tissue (the concentration in tumors is 10–15-fold over background). The light is delivered using lasers and fiber optics, and because of its high wavelength it is not absorbed by passing red blood cells.

Competitors

While trials are ongoing, QLT has the market to itself. "Photofrin probably has at least three to four years, probably more than that, before any competing drugs can be approved," says Dolphin. It is currently approved for esophageal cancer, and approval for small cell lung cancer is pending. Photofrin®, a mixture of porphyrin oligomers, was developed after early experiments with natural product isolates. It is excited by lower wavelengths of light than the new drugs, and patients who use Photofrin® are photosensitive, and so have to avoid the sun for up to a month after treatment. The photosensitivity may not be acceptable for non-life-threatening diseases, says Dolphin, but for chemotherapy patients it is small fry. And the lower wavelengths are good enough for the many applications that do not require deep penetration. "It works on most solid tumors," says Thomas Dougherty, a PDT pioneer at Roswell Park Cancer Institute in Buffalo, New York. "That's the bottom line."

That doesn't stop companies like Pharmacyclics from claiming many advantages for their drugs. According to Pharmacyclics, Lu-Tex shows almost no photosensitivity, but has higher selectivity, allowing the treatment of tumors that are spread over wide areas. Lu-Tex is water soluble and easily clears the body, and it homes to tumors rapidly, so that light treatment can be on the same day as the drug injection (this is not the case for Photofrin®).

Other companies claim similar advantages for their drugs. Scotia Quanta Nova of Guildford, UK, has a drug called m-THPC that has very high activity, and so light treatments can be very brief. Unfortunately severe photosensitivity accompanies this increased activity. QLT's second drug, BPDMA, causes very little photosensitivity and is being used in trials for age-related macular degeneration (AMD), the most

common cause of blindness in the elderly. QLT hopes that the drug treatment will seal the leaky blood vessels that cause AMD. A drug promoted by Miravant Technologies (Santa Barbara, California) is also being used for AMD. The drug, called tin ethyl etiopurpurin (SnEt₂) or Purlytin®, is also in Phase II/III studies for the treatment of metastatic breast cancer, basal cell carcinoma, and Kaposi's sarcoma.

The perfect drug

Saturation of one of the four pyrrole units of porphyrins (to form a chlorin) has boosted the absorbance maximum for the PDT drugs from the low to the high 600 nm range. The next step in raising the absorption maximum is to saturate a second pyrrole unit, as in bacteriochlorophyll. Pharmacyclics has bypassed this mechanism with the novel texaphyrin, which absorbs at 732 nm. (Another advantage of the higher wavelength is that the light used for treatment is not absorbed by melanin, so pigmented melanomas can be targeted.)

But the longer wavelengths are not desirable for all disease applications. "While there is this perception out there that long wavelengths are better, it's not necessarily true," says Byron Robinson of Miravant. "The shorter wavelengths of light can help you better limit the depth of light penetration at the target area." Eventually, he says, the different drugs may complement each other, with the shorter wavelength drugs used for the more accessible conditions.

The next step in PDT drug development will be to bring more logic to drug design. "For the therapy to evolve," says Robinson, "we need to understand structure-activity relationships and what controls localization. The company that gets a grasp on that will be successful."

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