Cancer stops at red light

Place a bright light against your hand and look at the opposite side. Your hand will be illuminated in an eerie red glow, because only the red portion of the visible spectrum penetrates sufficiently to make it all the way through the tissues of the hand. To Mirivant Medical Technologies (Santa Barbara, CA, USA) this deep penetrating property of red light is much more than just a novelty; it is the key to new therapies under development for a wide variety of indications including cancer, eye diseases, benign prostatic hyperplasia, atherosclerosis, dysfunctional uterine bleeding, and various dermatological conditions.

The term Mirivant uses for this photodynamic approach is 'PhotoPoint'. The numerous indications for PhotoPoint therapy are so far being pursued with a single photoactive compound, tin ethyl ethipurpurin ($SnET_2$) (Figure 1).

In September 1997 Mirivant changed its name from PDT Inc., the name by which the company had been identified since its inception in 1989, when it acquired the rights to the $SnET_2$ compound from the University of Toledo (OH, USA). In addition to drugs for PhotoPoint, Mirivant also produces light sources and various devices for delivering the activating red light to specific tissues.

Selective accumulation

Dr David Crean, Manager of Biophysics and Extramural Affairs at Mirivant, has explained how $SnET_2$ works – being hydrophobic it readily binds to circulating lipoproteins. Rapidly metabolizing cells, such as cancer cells, have an abundance of surface lipoprotein receptors. Therefore, $SnET_2$ is readily and selectively assimilated into such cells in concentrations that are as much as tenfold those observed in more quiescent cells. $SnET_2$ has no effect on the cells in which it accumulates, but when activated by low-energy red light, it produces highly reactive oxygen metabolites. The combined requirements of drug accumulation and activation by red light allow the highly specific destruction of target tissues.

Applications that are immediately apparent for such an approach include the treatment of skin conditions such as psoriasis and skin cancers. The patient is first given a photoactive drug, such as $SnET_2$, that collects in the rapidly dividing skin cells, and then each lesion on the surface of the skin is exposed to red light, leading to the selective destruction of the abnormal cells. The utility of this two-step approach is that tissue destruction is limited to those areas that receive a dose of the red light, a procedure sufficiently mild to allow it to be used on an outpatient basis. The photoactive drug also accumulates at a lower level in normal skin cells, making it necessary for the patient to stay out of bright sunlight for several weeks following treatment. The most frequent side effect of the therapy is a mild, transient sensitivity to the sun or light in some patients, causing a flushing of the skin. In October 1997, Mirivant announced an agreement with Medicis Pharmaceuticals (Phoenix, AZ, USA) to develop and commercialize the PhotoPoint technology for the treatment of both psoriasis and skin cancer.

Other applications

Mirivant is also investigating the use of PhotoPoint for the treatment of advanced eye diseases, particularly those involving the neovascularization associated with macular degeneration and diabetic retinopathy. This area of research is being conducted in collaboration with the ophthalmology group of Pharmacia & Upjohn (Uppsala, Sweden) and with Iris Medical Instruments (Mountain View, CA, USA), a provider of semiconductor-based ophthalmic lasers, which will be used to irradiate damaged tissues with precise amounts of the red-activating light.

This therapeutic approach can also be used anywhere in the body where red light can be applied, in some cases facilitated by endoscopy, catheterization or surgery, to activate the photoactive compound. One example is benign prostatic hyperplasia (BPH), the gradual enlargement of the prostate, which affects more than half of the men aged over 60 years. Surgical BPH treatment is one of the most frequently performed procedures in the USA. The photodynamic approach may provide a nonsurgical option for the treatment of BPH. As with the dermatologic indications, a dose of photoactive compound will be administered followed by irradiation of the prostate tissue with red light using catheter technology. Mirivant is working with the oncology section of Pharmacia & Upjohn (Milan, Italy) and Boston Scientific (Watertown, MA, USA), a major manufacturer of catheter-based medical technology, to develop PhotoPoint for the treatment of BPH; they have recently applied to the US Food and Drug Administration (FDA) to begin Phase I/II trials using $SnET_2$ as the photoactive compound.

Mirivant also has agreements in place to collaborate with Chiron Diagnostics (Emeryville, CA, USA), on the application of PhotoPoint to the early detection and treatment of lung cancer, and with Cordis Corp. (Miami, FL, USA) for the development of catheters for cardiovascular applications, where PhotoPoint may find a use in the prevention of restenosis. In the area of gynecology, the PhotoPoint therapy is being explored for the treatment of the uterine endometrium to stop dysfunctional bleeding. Cells of the endometrium divide rapidly and readily take up $SnET_2$. When red light is then applied to the interior of the

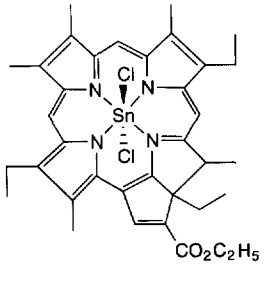

Figure 1. *Tin ethyl ethipurpurin.*

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uterus, the endometrial tissue is destroyed. Mirivant scientists believe that this treatment will eventually lead to a reduction in the 600,000 hysterectomies that are performed each year in the USA.

Identifying new photoactive agents

Although all of these applications are currently being pursued with $SnET_2$ as the photoactive agent, Mirivant has an aggressive chemistry program to discover new photoactive agents. According to Crean, the ideal photoactive agent for use in PhotoPoint therapy would require the following properties:

- Easily manufactured, in only two or three steps from inexpensive materials ($SnET_2$ is produced in a five-step synthesis).
- Photostable, so that it is not necessary to work under darkened conditions.
- Chemically well defined.
- Easily formulated.
- Not accumulated in the skin, because the presence of sunlight causes photosensitization.

Crean also points out the utility of having a library of compounds with different maximum activation wavelengths in the 440–650 nm range. Light in this region of the spectrum penetrates human tissues to very different extents. Therefore, use of compounds with different absorption maxima would allow the activation of a photoactive agent in superficial lesions with shorter wavelength light or activation in deeper or denser tissue with light of a longer wavelength.

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Combinatorial technologies – the 'nuts and bolts'

The 3rd IBC Interactive 'Nuts and Bolts' Forum on Combinatorial Technologies was held on 23–24 October 1997 at Coronado, CA, USA. The main conference was followed by a workshop on the 'Advances in Analytical Characterization and Purification of Compounds'. The aims of the meeting were to present practical experiences in the development of chemistry for the generation of libraries and to highlight possible solutions to the problems of purification, analysis and data handling. Some of the presentations during the conference included honest accounts of the difficulties encountered during the development of synthetic protocols for library generation, particularly the development of solid-phase chemistry.

Novel linkers

The linker groups used in solid-phase chemistry usually leave a residual functional group within the final molecule, and there are increasing numbers of reports of linker groups having been developed to leave more pharmacologically acceptable moieties. Dr David Rees (Organon Laboratories, Newhouse, UK) gave an overview of linking strategies, before outlining the development of the REM linker, which produces a tertiary amine[1]. Although the initial linker allows preparation of libraries, it is unstable under certain conditions and as a result modification of the ester group to an amide and sulphone have been investigated (Figure 1)[2].

Dr Jeff Jacobs (Versicor, San Francisco, CA, USA) described the work on the benzyl bromide linker, which highlighted issues concerning the supports used in solid-phase chemistry[3]. During the development of chemistry on the benzyl bromide resin, a common impurity was observed in failed reactions because of cleavage of the linker group

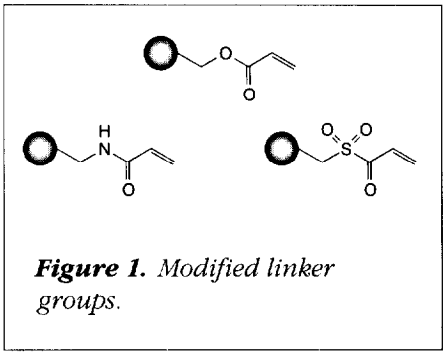

Figure 1. *Modified linker groups.*

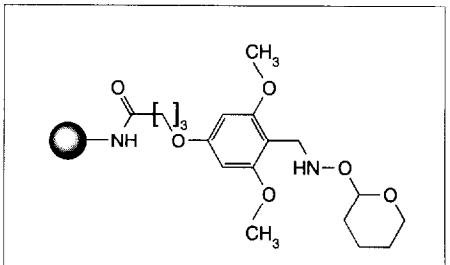

Figure 2. *Hydroxamic acid-producing linker.*

from the support. This problem could be circumvented by the use of ArgoWang™ (Argonaut Technologies, San Carlos, CA, USA), as subtle changes in the support affect the susceptibility of the linker group to cleavage. Jacobs also described a new linker for the preparation of hydroxamic acids using Tentagel S NH resin (Rapp Polymere, Tübingen, Germany) (Figure 2)[4].

The preparation of libraries based on a ketoproline by solid-phase chemistry using the Kenner Safety Catch linker[5] was described by Dr Matthew Plunkett (Arris Pharmaceutical, San Francisco, CA, USA). One of the key steps was the reductive amination of the ketone functional group (Figure 3). Although the reaction on solid phase has been well documented in the literature, optimization of the reaction conditions was necessary for the particular resin-bound substrate. Parameters that were

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