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BINARY CANCER THERAPIES

(See also Scherz & Salomon p. 198)

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In binary tumor therapy the concomitant application of two non-toxic agents is selectively synergized in-situ to provide highly efficient anti-tumor effects otherwise unattainable by either one of them.

Phototoxicity of Bacteriochlorophyll derivatives (Bchld): from cell killing to cancer therapy:

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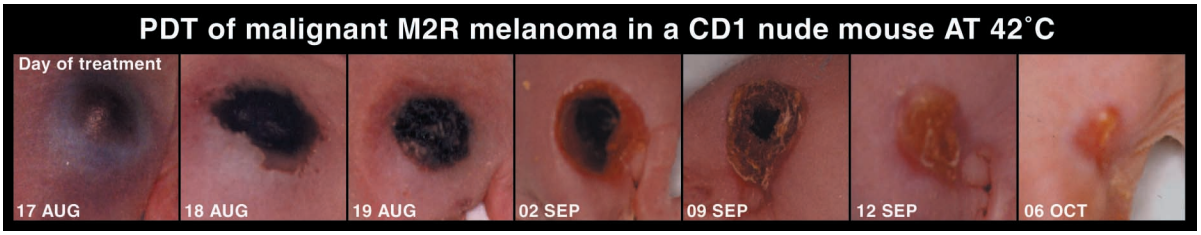
Photodynamic therapy (PDT) is a novel mode of chemotherapy in which drug action is locally controlled by light. In PDT, a non-toxic pigment (sensitizer) is photosensitized in-situ (by non-hazardous light) to generate cytotoxic Reactive Oxygen Species (ROS) that cause cell death and necrosis of tumor components, with minimal damage to the surrounding tissue (see also previous abstract). Selective treatment is achieved by proper sensitizer delivery and by precise local illumination of the treatment sites (directly or via optic fiber) at practically any part of the body. The clinically used sensitizer (hematoporphirin derivative) that absorbs in the visible light window, as well as other pigments still in the pharmaceutical pipeline, have various drawbacks that we wish to overcome by introducing Bchlds as photosensitizers for PDT.

Research Objective

Development of BChl-based PDT agents, with superior therapeutic properties, lacking in current clinically used sensitizers. Particularly, the new sensitizers: (i) strongly absorb (for minimal drug dose) in the Near Infra Red (NIR) (for treatment with maximal depth of penetration); (ii) are highly photocytotoxic, with minimal dark toxicity, (iii) are more water-soluble and therefore rapidly clear from the circulation (to avoid coetaneous phototoxicity), and (iv) maintain photocytotoxicity even under hypoxic conditions, therefore yielding enhanced effects in and around hypoxic tumor domains that are often resistant to conventional anti-tumor therapies.
The research included the design, synthesis and testing of Bchlds with the aim of achieving the above properties. Included is also the elucidation of the photophysical and photochemical mechanisms underlying phototoxicity and the mechanisms of cell kill and tumor destruction.

Research achievements

Synthesis of a novel family of photosensitizers based on Bchl derivatives was achieved. These substances strongly absorb in the NIR (λ= 760-800nm, ε_{max}~10^5) and are ~1000 times more toxic than clinically used sensitizers. Their LD_{50} values are in the nM range, they rapidly clear from the circulation (2-16 hrs in mice), and are phototoxic under hypoxic conditions (Chl-Ser: kills anaerobic bacteria). Singlet oxygen is generated by Chl-Ser via Type II and OH radicals are generated by Bchl-Ser through a novel type-III mechanism. Protocols for PDT of solid tumors in mice resulted in a high rate of cure (85% for melanoma, 80% for DS sarcoma, and 60% for C6 glioama). The depth of effective treatment was found to be 1.5 cm with a reasonable light intensity



(150 mW/cm^2). The new sensitizers enabled the development of a new concept in PDT that aims at the tumor vasculature. Importantly, treatment is completed within 30 min, a tramendous advantage over clinically used PDT protocols which may last 24-48 hrs. The materials were patented, licensed, and the lead-compound is scheduled to enter clinical trials in the year 2000. The development of targeted Bchl-conjugates aimed at endothelial-cell markers for anti-tumor and non-oncologic anti-vascular therapy (Age Related Macular Degeneration) is underway.

Commitment to cell-death is achieved within 1 min of illumination, with cytolytic and other visible morphological changes developing within 20-30 min. Cell death observed by vital stains becomes apparent within hours. Bacterial death with Bchl-Ser and with targeted Bchl-IgG was also successful. The mechanism of tumor destruction is primarily anti-vascular leading to hypoxia, necrosis and tumor eradication. Tumor response to PDT is substantially augmented by hyperthermia at 43°C (with P. Vaupel). Vascular perforation in the tumor allowed the selective release of blood-borne substances into the tumor a finding that led to a new concept we termed "light-enhanced drug delivery".

Boron Neutron capture therapy (BNCT): pharmacology and non-invasive imaging of ^{10}B-agents for cancer therapy:

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BNCT is an experimental cancer treatment in which a neutron beam is used for irradiating ^{10}B-labeled substances previously accumulated in the tumor, to locally release cytotoxic alpha particles.

Research Objective

(i) To investigate the chemistry and the pharmacology of candidate boron delivery agents in tumor models
(ii) To develop boronated substances for clinical use and
(iii) To develop non-invasive in-vivo detection methods based on Magnetic Resonance Spectroscopy (MRS) and imaging (MRI).

Research achievements

We have developed a method for NMR detection of the ^{10}B-enriched compound, borocaptate Sodium (BSH), and have used MRS and spatially localized-MRS to investigate the pharmacokinetics and metabolism of BSH and borono-phenylalanine (BPA) in cultured melanoma cells, and in tumor-bearing mice. These results form the basis for future efforts toward successful clinical implementation of BNCT.

Involvement of ROS in cell physiology: Simulating cell-signaling with BChlds and light.

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Research objectives

Stimulation of signaling cascades by photogenerated ROS.

Research achievements

Light-dependent stimulation of signal transduction pathways by Bchld + light (stimulation of phospholipase A_2 and selective phosphorylation of p38 MAPK, secretion of von Willibrand factor and depolymerization of actin cytoskeleton and microtubules) has been demonstrated in our laboratory. These effects appear to be mediated by ROS and form the basis for identification enzymes and physiological processes in which ROS may be involved. The ability to control ROS production by light (photo-switch), permits a novel approach to study the general effects of ROS on cells, their role in PDT and in particular their potential role in cellular signaling.

Acknowledgements

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