While anti-oxidants have long been getting a great deal of attention as prophylactics of and panaceas for cancers, there’s a now a new group of therapeutic compounds in the spotlight — DNA repair promoters. So how exactly do DNA repair promoters and compounds promote the repair of human DNA and what is their role in the enhancement of human health?

BACKGROUND ON DNA REPAIR

A cause of cancer is errors in DNA sequences that manifest in newly replicated DNA. There are two main types of errors: (1) dimmers in the form of and C -> T, DNA and (2) DNA mismatch repair. In normal skin, DNA repair or correction of these dimers and corrupted DNA requires coordination of more than 20 proteins, which together can repair approximately 50 percent of damaged DNA incurred daily.

Ultraviolet radiation causes DNA damage by producing cyclobutane pyrimidine dimers (CPD). Cytosine to thymidine (C to T) transition mutations result, and serve as “molecular finger-
the correct complement ary nucleotide. Thus, an adenine on one strand is normally paired with a thymine on the other, and a guanine on one strand with a cytosine on another.

The process of mismatch repair involves first recognizing the mismatch — for example, of an adenine with a cytosine. The machinery then recognizes a break in the newly synthesized DNA strand, which triggers the machinery to excise the section including the mismatch, starting at the strand break and working toward the mismatch and slightly beyond. The system then replaces the mismatched strand with one containing the correct complementary nucleotide. The power of the DNA repair machinery is highlighted by the fact that the mismatch repair system is flexible enough to recognize such a triggering strand break on either side of the mismatch along the DNA strand.

DNA REPAIR ADJUVANTS

DNA repair promoters or adjuvants can be divided into three categories (1) minerals (e.g. selenium and selenomethionine), (2) carboxyl alkyl esters i.e. AC-11 (formerly known as C-MED-100 derived from Cat’s Claw [Uncaria tomentosa]), and (3) Dimericine, a DNA repair enzyme, (T4 endonuclease V) encased in liposomes. Selenium and AC-11 can be taken orally. AC-11 and Dimericine can be applied topically alone or in combination with other agents — most commonly a sunblock. Of the three DNA repair enhancing agents discussed, only AC-11 can be administered both orally and topically. The DNA repair adjuvants will be discussed herein.

SELENIUM

Selenium has been touted as a substance that can prevent or treat cancer. There are two possible mechanisms for this: antioxidant effects or enhancement of DNA repair. It was noted by Seo that selenium in the form of selenomethionine (SeMet) can activate the p53 tumor suppressor protein by a redox mechanism that requires the redox factor Ref-1. Specifically, using ultraviolet light to damage cellular DNA, the research team found that treatment of the cells with selenomethionine activated a protein called Ref-1 that switched on p53 causing a three-fold increase in p53 activity and a doubling of DNA repair in the cells. As a result, cells with functional p53 can tolerate higher doses of ultraviolet light if grown and maintained in the presence of selenomethionine. Rafferty, more recently in 2003, however, concluded that selenite and selenomethionine protect keratinocytes from UV-induced oxidative damage, but not through creation or formation of UV-induced excision repair sites. So while...
selenium might prevent cancer, it might not be acting to do this by promoting DNA repair.

**AC-11**

Oral AC-11 has been shown to decrease DNA damage and to increase DNA repair capacity in human volunteers. Immune enhancement was observed in response to pneumococcal vaccine in volunteers given oral AC-11 and an in vitro study demonstrated that AC-11 inhibits the nuclear transcription factor, NF-kB, which is activated in inflammatory diseases such as arthritis, asthma and inflammatory bowel diseases.6-9

AC-11, a water-soluble extract of *Uncaria tomentosa*, has been noted effective in repairing both oxidative (8-hydroxyguanine, single- and double-strand DNA breaks) and photochemical (cyclobutyl pyrimidine dimers) DNA damage. *Uncaria tomentosa* grows in the Amazon basin and has been used historically by indigenous tribes for medicinal purposes. The carboxyl alkyl esters in the Cat’s Claw extract found in AC-11 are the main components thought to be responsible for enhancing the repair of DNA. The recommended oral dose is 350 mg/day. AC-11 is applied topically in a 0.5% concentration.

**THE ROLE OF AC-11 IN DNA REPAIR**

While no data exists to support that contention of a beneficial effect on mismatch repair for AC-11, it’s possible AC-11 does exert such a role. AC-11 appears to enhance the normal repair of cyclobutyl pyrimidine dimers following UV-B exposure. We can infer, with some confidence, that AC-11 enhances nucleotide excision repair (or photoreactivation). The observed reduction in oxidative DNA damage (8-hydroxygua-

**Reduced non-melanoma skin cancer** following topical application of AC-11 in hairless mice (unpublished study) is likely due to a reduced dimer burden. Decreased dimers – decreased p53 mutations – decreased acinar ketosis – decreased malignancies.

**MECHANISM OF AC-11**

The mechanism for AC-11 activity has yet to be fully defined; however, research in humans and in human living skin equivalents shows that AC-11 reduces erythema and blistering after ultraviolet exposure.10-11 AC-11 significantly enhanced the repair, but not the formation, of cyclobutyl pyrimidine dimers (TT-dimers) in human living skin equivalents exposed to UV-B light.

In a study of 5 healthy volunteers aged 35 to 55 year old taking 350 mg/day of AC-11 orally for 4 weeks, 8-hydroxyguanine levels were significantly (p < 0.05) decreased. The beneficial effect was noted to persist two weeks after therapy was discontinued. Another study reported a significant (p < 0.05) decrease in DNA single-strand breaks following peroxide-induced DNA damage in monocytes of healthy volunteers who received 8 weeks of AC-11 at 350 mg/day.7

Pero et al, assessed oxidative DNA damage in 14 volunteers, most of which (more than 75%) had chronic diseases, and reported that 9 of the 14 volunteers had decreased 8-hydroxyguanine DNA adducts after 400 mg of AC-11 per day for 4 weeks. Finally, in a in a single-blind, right side-left side, beach sun exposure pilot study that included 42 healthy volunteers there were dramatic and significant (p < 0.0001) reductions in erythema and blistering in volunteers who applied 0.5% topical AC-11 with and SPF-15 sunscreen when compared to the group who just applied an SPF-15 sunscreen.

**AC-11 AND ANIMAL STUDIES**

The DNA data in humans has been supplemented with two animal studies in which the effects of known DNA damaging agents were compared in AC-11-treated and control animals. In the first study, daily doses of 40 mg/kg or 80 mg/kg of AC-11 were administered to 20 rats (an additional 10 rats served as controls) by gavage for 8 weeks. Half the animals from each group were exposed to 12 Gy whole body radiation (137Cs source) and allowed 3 hours to repair in vivo before DNA damage was assessed. AC-11-treated animals almost completely repaired single-strand DNA breaks (p < 0.05) for both AC-11 doses compared to untreated animals. Double-strand DNA breaks were substantially less in animals treated with 40 mg/kg/day of AC-11 and significantly (p < 0.05) less in animals treated with 80 mg/kg/day of AC-11 compared to untreated animals.

In the second study, daily doses of 40 mg/kg or 80 mg/kg of AC-11 were administered orally to 8 rats (4 at each dose) 24 hours after the last of three 2 mg/kg intraperitoneal doses of doxorubicin. Four animals received doxorubicin only. Animals treated with 80 mg/kg of AC-11 had significantly (p < 0.05) reduced DNA damage in the form of single-strand DNA breaks.

More recently Pero12 reported on the combination of a Cat’s Claw water extract (AC-11, carboxy alkyl esters = active ingredients) plus medicinal mushroom extracts (Cordyceps sinensis, Grifola blazei, Grifolfrondosa, Trametes versicolor and Ganoderma lucidum, polysaccharides = active ingredients) plus nicotinamide plus zinc into a formulation designed to optimize different modes of immunostimulatory action in 14 subjects treated for 4 weeks and found patient experienced reduced pain, reduced fatigue, weight loss and a reduced presence of DNA damage in peripheral blood assessed by (8-OH) DNA repair.
NEW
To COMe
guanine DNA adducts and elevation in serum protein thiols.

**DIMERICH**

T4 endonuclease V (Dimerice) is a DNA repair enzyme produced in bacteria that is delivered in liposomes in the form of a topical cream. The liposome utilized in Dimerice is a fat bubble called a T4N5 liposome made from lipid lecithin, from the egg. It is thought to act via two mechanisms.

Immediately, T4 endonuclease V removes DNA dimers, primarily cyclobutane pyrimidine type. In the long-term, it may restore p53 gene function and exert a lasting chemopreventive effect. Dimerice has been studied as a topically applied cream to decrease the development of skin cancer in patients with xeroderma pigmentosum and renal transplant patients on immunosuppressive therapy. Dimerice received orphan drug designation for this indication in 1989.

In patients with xeroderma pigmentosum there is a rare genetic defect in UV radiation-induced DNA repair mechanisms characterized by severe sensitivity to all sources of UV radiation, especially sunlight. Several studies have been done using Dimerice to prevent skin cancer in xeroderma pigmentosum patients.

**STUDIES ON DIMERICE**

One study found the Dimerice lotion reduced the incidence of basal cell carcinomas by 30% and of actinic keratoses by 68%. In another study, in vivo testing involving T4N5 liposome lotion has yielded intriguing results. In a test conducted with 12 xeroderma pigmentosum (XP) patients and 15 patients without this condition who had a history of skin cancer, researchers applied the cream at various intervals after controlled UV exposure. Biopsies conducted 6 hours after UV exposure revealed that patients with XP had achieved approximately 15% fewer CPDs (improved DNA repair) while patients with a history of skin cancer achieved less than 10% fewer CPDs.

Phase I and II trials of Dimerice for prevention of skin cancer in xeroderma pigmentosum patients were completed. Dimerice, however, is not commercially available. The company states, “The XP Trial was registered with the FDA as a Phase III trial because it had a clinical endpoint: reduction of actinic keratoses and skin cancer and that its application is open. The FDA has undergone reorganization twice in the last 3 years and our application has been moved. We are discussing the number of XP patients required for market approval.”

New studies of Dimerice are ongoing. Craig A. Elmets, M.D., Chair of the University of Alabama at Birmingham’s Department of Dermatology and Senior Scientist at the UAB Comprehensive Cancer Center is leading a 3-year, multicenter, Phase II, randomized, double-blind controlled study of T4N5 liposome lotion, or Dimerice, to determine its success in preventing recurrence of non-melanoma skin cancer in 100 renal transplant patients. Enrollment is ongoing.

It would seem that the most useful role for Dimerice would be its inclusion in sun-block. Since it has no reported side effects, Dimerice is promising. Whether it will change clinical outcomes will become clearer as Phase III trials are completed.

**PROMISING FUTURE**

We now know that anti-oxidants and anti-inflammatory adjuvants are not the only ways to enhance the health of patients and retard the development of skin cancer. DNA repair adjuvants appear to be promising health aids. AC-11 and Dimerice appear to be best used in conjunction with other agents to optimize their health promoting utility. While promising, the ultimate clinical effectiveness and effect on outcome, mode of administration and mode of utilization with other agents remains to be fully defined.

Dr. Scheinfeld is currently an alternate of the Investigational Review Board at St. Luke’s Roosevelt Hospital in New York City.

**Disclosure:** Noah Scheinfeld is a consultant for Optigenex, the maker of AC-11.