Development of Artemisinin Compounds for Treatment of Cancer

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Summary

We will develop novel medical and food/supplement technologies based on artemisinin, a natural product isolated from Artemisia annua L. Artemisinin is a part of the current standard treatment for malaria infection in humans. Artemisinin contains an endoperoxide group that reacts with intracellular iron to generate toxic radical species. Cancer cells undergoing rapid proliferation intake large quantities of the essential nutrient iron through up-regulation of transferrin receptor. Artemisinin has demonstrated highly selective cytotoxicity towards cancer cells in vitro and in vivo. We have found that the anti-cancer activity of artemisinin can be greatly enhanced by delivering the compound directly to the cellular iron uptake machinery. Also, dimers of artemisinin have shown highly potent anticancer activities that are equivalent to that of Taxol in cell-based assays. Recently, we discovered that artemisinin derivatives induce a specific down-regulation of survivin, an anti-apoptotic protein, that is highly expressed in humans including breast cancer cells. We will characterize the apoptotic and other cellular responses of both cancer and normal cells, and identify the protein targets in order to elucidate the mechanism of action of artemisinin-based compounds. We will synthesize an artemisinin dimer-biotin conjugate that will help us to isolate and identify the initial reaction product(s) of artemisinin derivatives in cancer cells.

Development of Artemisinin-based Cancer therapeutics

We will synthesize novel artemisinin dimers, and artemisinin conjugates of transferrin receptor (TfR) binding peptides. We will examine in vitro cytotoxicity and selectivity of these newly synthesized artemisinin derivatives and conjugates on human breast cancer cells, and will compare them with those of normal breast cells. We have already found that artemisinin dimers specifically down-regulate survivin, an anti-apoptotic protein, that is highly expressed in human cancers including breast cancer. We will characterize the apoptotic and other cellular responses of both cancer and normal cells, and identify the protein targets in order to elucidate the mechanism of action of artemisinin-based compounds. We will synthesize an artemisinin dimer-biotin conjugate that will help us to isolate and identify the initial reaction product(s) of artemisinin derivatives in cancer cells.

Canine Clinical Trial of Artesunate

Artesunate is a water soluble derivative of artemisinin, and is currently being evaluated in Phase-1 human clinical trial in Germany for treatment of breast cancer. We have obtained bulk artemesunate, and, after confirming the purity, prepared artesunate capsules for our study. We have sent out over 100 letters to practitioners in the Eastern Washington area advertising the trial. We will analyze serially collected biopsies from dogs with naturally occurring NHL treated with oral artemisinin or placebo administration to demonstrate molecular response. Survivin levels are dramatically decreased upon incubation of human cancer cell lines with artemisinin derivatives. Because survivin is overexpressed in canine NHL and high expression levels confer a poorer prognosis than low expression, this model is ideal for proof-of-principle examination of this mechanism. Along with survivin, our preliminary data demonstrates high levels of transferrin receptor in canine NHL samples by Western blot. Survivin and TfR expression levels will be compared in tumor specimens from dogs receiving artemisinin and placebo.

Clinical Trial

Criteria
- B cell phenotype
- Stage II and IIIa
- Willing to return

End-points
- Molecule
- Response
- Remission duration

Cultivation of Artemisia annua L.

The primary goal of this year’s trial was to determine the optimum planting date for our region. Every year is different in Washington, and this spring was long and cold. We didn’t plant until May 20th (the three plants closest to the camera). We included two other planting dates, one in early June and one in mid June, corresponding to plants 4-6 and 7-9 in the picture, moving away from the camera. Since the beginning of June, we have been destructively harvesting plots to determine the sesquiterpene profile (and total artemisinin content). The largest plants are currently nearly 2 meters tall and mass half a kilogram. In total, we have 700 plant in the field, with harvest occurring every week through the end of September.

Artemisia annua L. growing near Pullman, WA. The plant has been selected for high artemisinin content. A nursery is shown in the background has about 100 plants. Those would be used for potential breeding/cloning efforts and for initial chicken feed development.