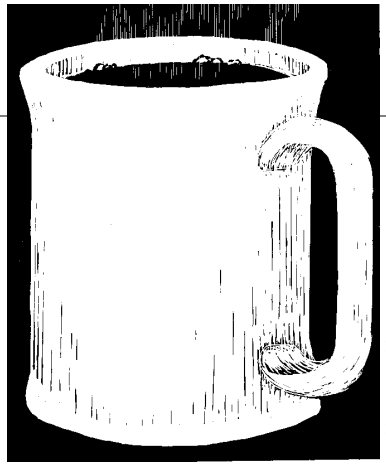
A research itinerary

By Alan Eastman, Ph.D.



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Research is always a journey, but the destination is just a hypothesis. When researchers write grants, they propose grandiose destinations—perhaps even a cure for cancer. But for most investigators, such promises are simply a means to market the grant proposal; otherwise, funding agencies are unlikely to provide the money for the journey. The investigator and the reviewers know only too well that no individual grant is apt to have a significant impact on disease; it is in the aggregate that research advances knowledge.

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Unknown: One reason for this skepticism is that when a basic scientist—someone grounded in the lab—proposes a potential cure for cancer, the need for animal and eventually human studies can present a void too challenging to cross. What if the results suggest experimentation outside of your expertise? You can stick to the known or head for the unknown. A change of course becomes possible when friends you've made en route—people with experience in unfamiliar territory—become collaborators.

This is the story of one such journey, in which laboratory experiments spanned research cultures to help cancer patients. The story starts in 1979, when I began to investigate the mechanisms of action of the anticancer drug cisplatin. Chemical and biochemical techniques helped us to characterize the lesions in DNA brought about by cisplatin. Cell biology led to the realization that cisplatin perturbed normal cell-cycle progression. However, following cisplatin treatment, cells accumulated at the G2 phase just before mitosis, which allowed the cells to repair the DNA damage caused by cisplatin. If tumor cells undergo mitosis too soon they die—the intended effect—but after adequate time for repair they can recover and grow anew.

Mechanism: We became aware through other published studies that caffeine could overcome this arrest in the cell cycle, force cells through mitosis, and enhance cell-killing. Intrigued, we began to attack the mechanism by which caffeine enhanced the cisplatin-induced cell-killing. It did not seem to work in all cells, and this was attributed to a defect in the p53 tumor suppressor gene. More than 50% of tumors have defects in this gene, and it is these cells that are sensitive to the action of cisplatin plus caffeine. So caffeine appeared to be a wonder drug that selectively killed tumor cells without increasing toxicity to normal cells. Unfortunately, the amount of caffeine required for this effect far exceeds what a human can tolerate. Back to the lab.

Studies on how caffeine worked led us to screen other likely compounds, and in 1996 we reported that UCN-01 was 100,000 times more potent than caffeine at overcoming cell-cycle arrest and enhancing cisplatin-induced cell-killing. And animal experiments suggested these concentrations were well tolerated.

The National Cancer Institute (NCI) has just completed a Phase I trial of UCN-01 alone, defining safe doses for subsequent studies. The next step is drug combination trials, and the NCI has approved two so far. One, of cisplatin plus UCN-01, will be performed at Dartmouth because of our role in developing the original hypothesis. A major component of this trial will be proof-of-concept in the patient. This will require frequent biopsies of accessible tumors to determine whether cisplatin causes the anticipated cell-cycle arrest and whether UCN-01 overcomes this arrest. Furthermore, we hope to confirm that this abrogation of arrest occurs only in tumors with defective p53 genes. We hypothesize that the maximum tolerated dose of UCN-01 won't be needed to produce the beneficial effect, and indeed it may be detrimental to the activity of this drug combination. Determining these pharmacodynamic endpoints will be critical to the success of future clinical trials.

Travelers: My fellow travelers on this journey have included numerous dedicated students, postdocs, and technicians. As the results suggested new directions, Dr. Julia O'Hara collaborated on animal experiments. Next, Dr. Lionel Lewis helped us to understand how the drug was distributed in mice and humans. As we begin to administer UCN-01 to cancer patients, Dr. Ray Perez is serving as our clinical oncologist. Finally, we discovered that UCN-01 has certain limitations, so Dr. Gordon Gribble is helping with the chemical synthesis of potentially better analogs. Fortunately, all these experts were already at Dartmouth and were willing and able to work with us.

Of course, every step of this journey has required funds. The studies on UCN-01 were initiated with a small grant from DHMC's Norris Cotton Cancer Center, which has been an invaluable resource in other ways as well. This led to three years of funding from the American Cancer Society to perform the cell biology and animal experiments. This summer, we were awarded a three-year NCI grant to synthesize and test novel analogs. Finally, the NCI has just provided funds to support the clinical trial. So far, over a million dollars has been committed to this project.

The journey continues, thanks to fellow travelers without whom the idea would never have moved beyond the bench. I am indebted to all who have made this such an exciting voyage. Now we await results that will surely suggest more new avenues of exploration. ■

Eastman, a professor of pharmacology and toxicology at DMS, has been on the Dartmouth faculty since 1989. He is also associate director for basic sciences of DHMC's Norris Cotton Cancer Center and directs the pharmacology and toxicology graduate program.