THE HARTWELL FOUNDATION

2006 Individual Biomedical Research Award

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Novel Drug Targets for Leukemias

Dr. Wells proposes innovative technology for direct and simultaneous identification of as many as 1000 newly cleaved proteins that appear in cells during programmed cell death, the pathologic process referred to as apoptosis. While in normal tissues cell growth is in balance with apoptosis, in cancer the balance is gradually perturbed to favor rampant cell growth. One of the key problems in cancer management is how to recognize and readjust this stepwise loss of cellular self-control as the disease progresses. Wells proposes a systematic study of apoptosis by creating a global profile of the degradation products that occur normally and in a model cell line derived from acute lymphocytic leukemia (ALL). He hypothesizes that certain enzymes deliberately degrade specific proteins to force cell death. The task of identification however, is daunting. With over 800 potential enzymes capable of degrading one or more of the 16,000 plus proteins in the human genome, estimates suggest more than one million derivatives are possible. To overcome this challenge and determine whether any particular protein functions as either an apoptotic or prosurvival factor, he will take advantage of RNA interference to limit gene controlled protein expression, as well as available computation and bioinformatics resources. The comprehensive profiles should reveal for the first time novel targets for potential chemotherapeutic intervention in ALL, which alone accounts for 78% of childhood leukemias and half of related deaths. Many important possible applications of the *degradomics* approach offered by Wells include those associated with disease processes of metabolism, inflammation, neurodegeneration, thrombosis, and infection.