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Membrane-active Synthetic Organic amphiphiles that enhance the efficacy of antibiotics and are useful as direct Injection Agents

We have developed a number of novel amphiphilic molecules that partition into bilayer membranes and form ion conducting pores. These compounds show many of the sophisticated properties of natural protein channels. The hydraphiles are toxic to cells because they disrupt the osmotic balance of such bacteria as E. coli and B. subtilis. Unfortunately, they are also toxic to yeast and mammalian cells, diminishing their utility as antibiotics. However, at lower and non-toxic concentrations, the compounds we call "hydraphiles" show synergistic activity with a range of FDA-approved antibiotics, enhancing the efficacy of, for example, erythromycin against E. coli by 16-fold. In recent work, we have found that the hydraphiles can be used in direct injection chemotherapy. This type of therapy involves a direct assault on the site of pathology. It requires toxicity but also controlled diffusion of the toxin so that peripheral tissue damage is minimized. These studies were conducted in mice. In order to determine both the efficacy of the hydraphile as therapeutic and to monitor the progress of the studies, a zinc-based, near infrared fluorescent biosensor was injected. This sensor detects phosphatidylserine flip-flopping to the external leaflet of the bilayer during apoptosis and provides an optical record of cell damage and death. The hydraphiles proved to be superior to simpler and more diffusable reagents such as ethanol.

Biography

George Gokel obtained the Ph.D. in chemistry from the University of Southern California. He did post-doctoral studies at UCLA in the laboratory of Donald Cram. He has authored or coauthored over 400 papers, ten monographs, and is named as an inventor on 15 U.S. patents.

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