

EXECUTIVE SUMMARY [NON-TECHNICAL ABSTRACT FOR PUBLIC INFORMATION OR PROGRAM PROMOTION]: State **in layman's terms** the application's broad, long-term objectives and specific aims, making reference to the potential public benefits of the project relevant to California. This should NOT be a duplicate of the Technical Abstract above.

Several studies put the cost of antibiotic resistance at \$4 – 5 billion/year. Developing and testing a new antibiotic can take about ten years and cost between \$800 million and \$2 billion. Furthermore, bacteria can rapidly develop resistance rendering it all but useless after a relative short period of time. Therefore, it is very important to develop strategies to extend the useful life of existing antibiotics.

A common strategy used by bacteria to resist the therapeutic action of antibiotics is to inactivate it by enzymatic modification of the antibiotic molecule. We have been working on antisense strategies to prevent the synthesis of an enzyme that confers resistance to a variety of aminoglycoside antibiotics. We have been successful in designing oligonucleotides that reduce synthesis of the resistance enzyme. However, we have observed that a residual amount of enzyme that can be enough to help bacteria survive the treatment is always synthesized. In this project we propose to search for compounds that inhibit the action of the resistance enzyme. These kinds of compounds could act synergistically with antisense oligonucleotides to completely eliminate the ability of the bacterial cells to modify the antibiotic, rendering them susceptible. We will use different strategies to screen a large number of compounds of different chemical nature to isolate those with the most potent inhibitory effect.

Since drug resistance is a major obstacle in the conquest of bacterial infections, this proposal targets a critical issue in the treatment of bacterial infectious diseases: the need to develop strategies aimed at preserving the effectiveness of currently available antibiotics.