

## Background: ANTISENSE TECHNOLOGY

- Proteins are fundamental components of all living cells and include many types of molecules necessary for carrying out the body's functions, such as enzymes, hormones and antibodies. The over production or abnormal production of proteins is implicated or associated with many diseases. Antisense technology prevents the production of a protein involved in a disease process, which results in a therapeutic benefit to patients.
- Genes contain the information necessary to make proteins. A gene is made up of 4 different bases (nucleotides) which are linked together to form a two-stranded structure called DNA. The nucleosides on one strand interact with complementary nucleotides on the other strand (called hybridization). One of the DNA strands is called the sense strand and the other is called the antisense strand. Protein production occurs in two phases called transcription and translation. In the transcription phase, the DNA strand is used as a template for the manufacturing of an RNA molecule. Messenger RNA (mRNA) is responsible for communicating the genetic message found in DNA to other areas of the cells so that protein production can take place. In the translation phase, the mRNA travels to the ribosome, which is the cell's machinery that assembles proteins based on the instructions it carries.
- Antisense technology interrupts the translation phase of the protein production process by preventing the mRNA instructions from reaching the ribosome. When an antisense drug binds (hybridizes) to its target mRNA, the mRNA is degraded and therefore is not translated by the ribosome into a functional protein.
- ISIS 13650 is a short, chemically-modified complementary nucleotide chain that hybridizes to a specific complementary area of mRNA.
- The benefits of antisense drugs include high specificity since they interact with their intended target based on information in the genetic code. In contrast, traditional drugs bind based on the shape of proteins and charge interactions, creating more opportunity for unwanted interactions, and, often undesirable side effects. Therefore, antisense drugs have the potential to be safer than other types of drugs.

- Many advances have been made in antisense chemistry in recent years. ISIS 13650, which is a second generation antisense compound, has increased target binding affinity and resistance to degradation. Increased affinity increases potency which allows for more activity at lower doses which in turn can reduce the overall cost of therapy. Slower clearance of the drug from the body through reduced degradation should allow for less frequent dosing and better patient compliance and convenience.
- Antisense drugs have already been shown to be effective in treating ocular diseases with the commercialization of Vitravene, approved for the treatment of CMV Retinitis.