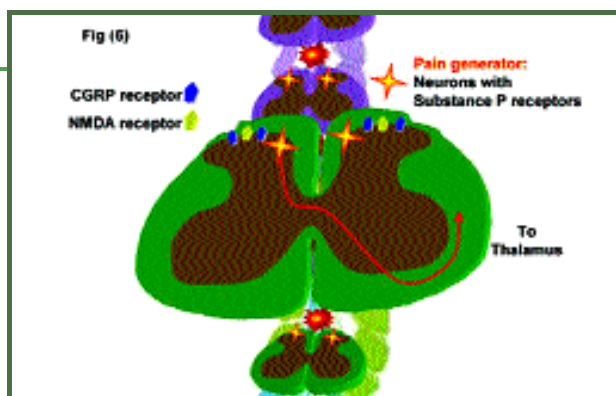


## Drug Development Update

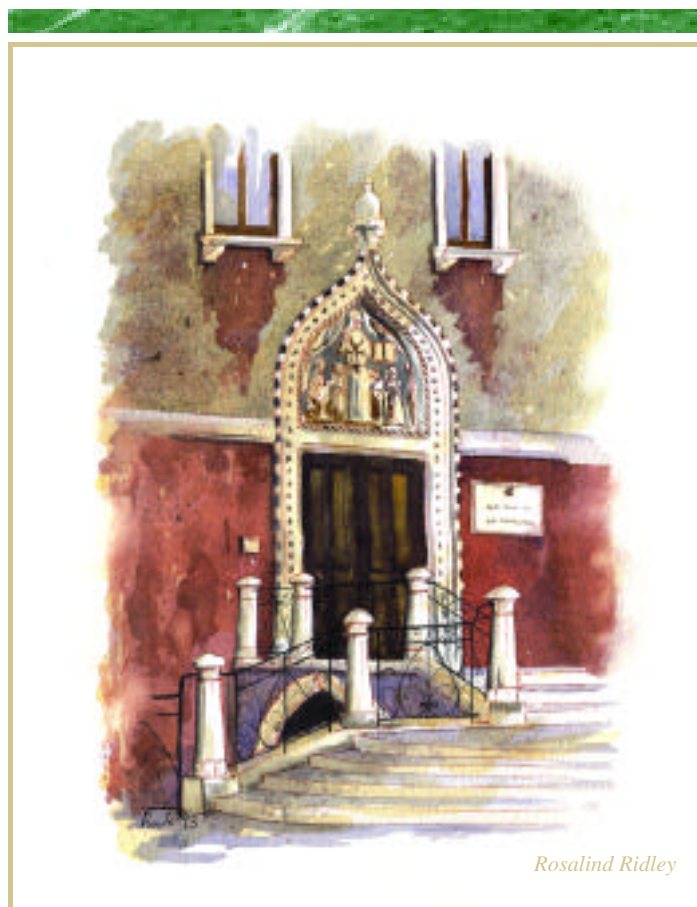
Chronic pain conditions are often caused by ongoing disease states or tissue damage that create sensitization of both the primary afferents (nerves that convey impulses from the outer part of the body) and spinal cord neurons. This sensitization results in a persistent increased sensitivity to both noxious (hyperalgesia) and non-noxious (allodynia) stimuli. Many persistent pain states have proven difficult to treat using currently available pharmacological or surgical approaches that may cause significant unwanted side effects, and often result in significant reduction in quality of life.

Advanced Targeting Systems is continuing to develop Substance P-Saporin (SP-SAP) as a chronic pain therapeutic. The first of two toxicology studies has begun and we expect to have results from that study in early 2005. All of the preclinical data and scientific publications support the idea that SP-SAP eliminates the chronic pain signal. It accomplishes this by removing a small subset of neurons in the spinal cord.

One patient population that should be targeted is terminal cancer patients who are unresponsive to opioid treatment. These patients have run out of options. The surgical and chemical interventions that are often made by physicians destroy more neurons in a less-specific manner and can even cause a central pain state. We believe SP-SAP can greatly reduce the perception of chronic pain in patients with minimal or no side effects. We believe this because we have seen the effects in two animal models in preclinical studies. Once we have toxicology results the FDA accepts, clinical trials in humans can begin.



**Location and Function of Substance P receptor (SPR)-positive neurons in the spinal cord.** SP-SAP specifically targets and eliminates cells that express SPR. Intrathecal administration in the spinal cord kills these spinothalamic neurons that make up less than 5% of the neurons in the spinal cord. These SPR-positive neurons also express CGRP (calcitonin gene-related peptide) and NMDA (N-methyl-D-aspartate or glutamate) receptors. These SPR-positive neurons are labeled "Pain Generators" and it has been shown that their elimination greatly reduces the perception of chronic pain in animal models.



Rosalind Ridley

*Doorway of Campo Sant'Angelo*

## Accomplished Scientist. . . Talented Artist - Rosalind Ridley

*As promised, we are pleased to present another drawing from Dr. Rosalind Ridley, internationally recognized expert on prion diseases and learning and memory in primates.*

The doorway is the 15th century entrance to an older Augustinian mendicant friary in the corner of the Campo Sant'Angelo next to the Ponte dei Frati. The Campo Sant'Angelo is situated in the western part of the San Marco district. Being in the inner curve of the meander of the Grand Canal, this area was the most marshy and unstable in Venice. Many campanile in this area collapsed under subsidence and earthquake. The *campanili* of San Michele Arcangelo, which stood a few feet from this doorway, fell in 1347. Its replacement fell on its day of completion and a third attempt was finished in 1456, damaged by a thunderbolt in 1487, and finally demolished in 1837.