Mitochondria-Sequestered Anti-Cancer Compounds: Mitochondria-sequestered anti-cancer compounds represent a new class of targeted cancer therapeutics. One example is MitoVES11, which we synthesized in non-racemic form at LSUS last year. Currently, this compound is in pre-clinical development as an anti-cancer agent. MitoVES11 is a lipophillic compound, but it bears a positively-charged phosphonium salt group that causes it to be sequestered at the inner mitochondrial membrane. It resides there in high concentration and renders its biological activity on the nearby mitochondrial redox complex II (succinate dehydrogenase). MitoVES11 has demonstrated very potent anti-tumor activity in a transgenic mouse breast cancer tumor model in a study conducted by our collaborator (Jirka Neuzil, Griffith University, Gold Coast Campus, Southport, Queensland Australia). We are now set to explore structure-activity relationships within this class of molecules. We will synthesize two new analogs of MitoVES11, which we have termed, MitoVEM11 and MitoVEF11. These new structural analogs will have variations in their "functional domain", which we believe is the portion of the molecule that binds within the active site of succinate dehydrogenase. When the chemical syntheses are complete, we will send both target molecules to Dr. Neuzil, who will test them in cellular assays with a variety of cancer cells and also in a transgenic mouse breast cancer tumor model. The results of these assays will be compared to those previously obtained with Mito VES11.

Faculty Director - Dr. Brian Salvatore; undergraduate - Dakota Boston; high school student - Meghan Mussehl

Novel synthesis of non-racemic MitoVES11: This is a mitochondrially-sequestered compound that targets cancer cells and fast growing endothelial cells. It was important for us to develop a non-racemic synthesis of this compound, because all of our previous studies had been performed with racemic mixtures (i.e. 50/50 mixtures of both enantiomers). The synthesis we devised begins with the commercially available D- and L- Trolox enantiomers, and it was a total of 8 steps from beginning to end. The synthesis was completed in late December 2008. Both enantiomers, as well as the racemic compound were sent to our collaborator (Jirka Neuzil, Griffith University, Australia). In vitro testing in U937 cancer cells revealed that the R-isomer was more potent than the S-enantiomer in inducing apoptosis in these cells. This is an impotant piece of data, which will be included in a paper that we will submit together with Dr. Neuzil to "Nature Medicine" later this year. The synthesis that we developed last year will also be helpful in preparing future analogs, including a fluorescently-labeled derivative that we will be able to track inside of living cells using confocal microscopy.

Faculty director - Brian Salvatore; undergraduates - Jacob Lowring and Jay Story; high school student - Meghan Mussehl.