

# Computational Methods for the Discovery of Novel Inotropic Agents for the Treatment of Cardiovascular Diseases

## Background

Extensive research in the field of cardiovascular medicine has increased our understanding of biochemical and physiological events that lead to cardiac failure. This has led to remarkable advances in cardiovascular diagnostic and surgical procedures. Since the discovery of cardiovascular effects of *Digitalis purpurea* in 1785, Digitoxin and Digoxin continue to be among the most widely used cardiovascular agents. These agents, however, have narrow therapeutic indices with toxic side effects such as ventricular arrhythmia.

Na<sup>+</sup>, K<sup>+</sup> ATPase, the receptor for digitalis glycosides such as Digitoxin and Digoxin, is the pharmacological target for cardiac glycoside treatment of congestive heart failure. Despite extensive search for substitute cardiotonic agents with wider therapeutic index and positive inotropic effects, none has been found to date. One limitation that has impeded the discovery of new cardiotonic agents has been the lack of 3D structural coordinates of Na<sup>+</sup>, K<sup>+</sup> ATPase. A major advance in this field has been the determination of the high-resolution crystal structure of SERCA 1a (skeletal muscle sarcoplasmic reticulum/endoplasmic reticulum Ca<sup>2+</sup>-ATPases). The Na<sup>+</sup>, K<sup>+</sup> ATPase and other ATPases are believed to have key evolutionarily conserved structural features. Although it is common knowledge that cardioglycosides inhibitors bind the extracellular domain of the receptor, the exact mechanism of inhibition has largely remained unresolved.

**Based on the published crystal structure of SERCA 1a, UMDNJ researchers have developed a 3D structural model for the Na<sup>+</sup>, K<sup>+</sup> ATPase. Furthermore, they have elucidated the key structural features (i.e., the pharmacophore) that dictate drug-receptor binding. This knowledge can be utilized for the *de novo* development of high potency cardiotonic drug candidates.**

## Description of the Technology

Utilizing the recently published crystal structure of SERCA 1a and computational modeling techniques, UMDNJ researchers have derived the 3D-structures for the extracellular and transmembrane domains of the 1 $\alpha$  subunit of sheep and human Na<sup>+</sup>, K<sup>+</sup>ATPases. Using these models and the specific mutations in the extracellular domains that affect cardioglycoside binding, the mechanism of inhibitor-receptor binding has been elucidated. Additionally, a pharmacophore that describes the common types of atoms and their geometric arrangement for cardioglycosides has been developed.

The models and structural data obtained from this study can be utilized in the rational design of low-toxicity inhibitors of Na<sup>+</sup>, K<sup>+</sup> ATPase. The data obtained from the present study can also be used to evaluate synthetic feasibility of the drug candidates as well as in the *in vitro* testing of the inhibitory effects of potential inhibitors.

## Advantages

- Public and commercial chemical libraries (ACD, Maybridge, NCI, and WDI) can be searched for new molecules
- Evaluation of drug candidates selected from computer-aided design for synthetic feasibility

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### **Applications**

- de novo* design of novel inotropic candidates for the treatment of cardiac failure.

### **Patent Status**

- PCT application filed.
- Application was published on May 27, 2004 (Publication Number: WO 2004/043384 A2)

### **Licensing Opportunity**

- This technology is available for non-exclusive or exclusive license.

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