Developing cardiac troponin modulators to treat heart failure

Systolic heart failure, also known as heart failure with reduced ejection fraction (HFrEF), is a condition in which cardiac contraction is impaired. Although the most common cause is ischemic cardiomyopathy secondary to coronary artery disease, other etiologies include hereditary dilated cardiomyopathy, infiltrative diseases, and various causes of cardiac inflammation.

Positive inotropes are drugs that increase cardiac contractility. They are not used in the treatment of chronic heart failure because they have been associated with increased mortality. However, compounds known as "calcium sensitizers" show promise for increasing the efficiency of cardiac contraction without increasing cardiac oxygen demand. The best known calcium sensitizer drug is levosimendan (Orion Pharma), a potent type 3 phosphodiesterase inhibitor. It has been shown to improve cardiac function in systolic failure, but it also lowers blood pressure and provokes cardiac arrhythmias, similar to other type 3 phosphodiesterase inhibitors.

The troponin complex turns muscle contraction on and off in response to calcium. Compounds that bind to troponin can act as calcium sensitizers or desensitizers. Tirasemtiv (Cytokinetics) is a fast skeletal muscle troponin activator that has been tested in clinical trials for improving skeletal muscle function in myasthenia gravis, amyotrophic lateral sclerosis (ALS), and peripheral vascular disease.

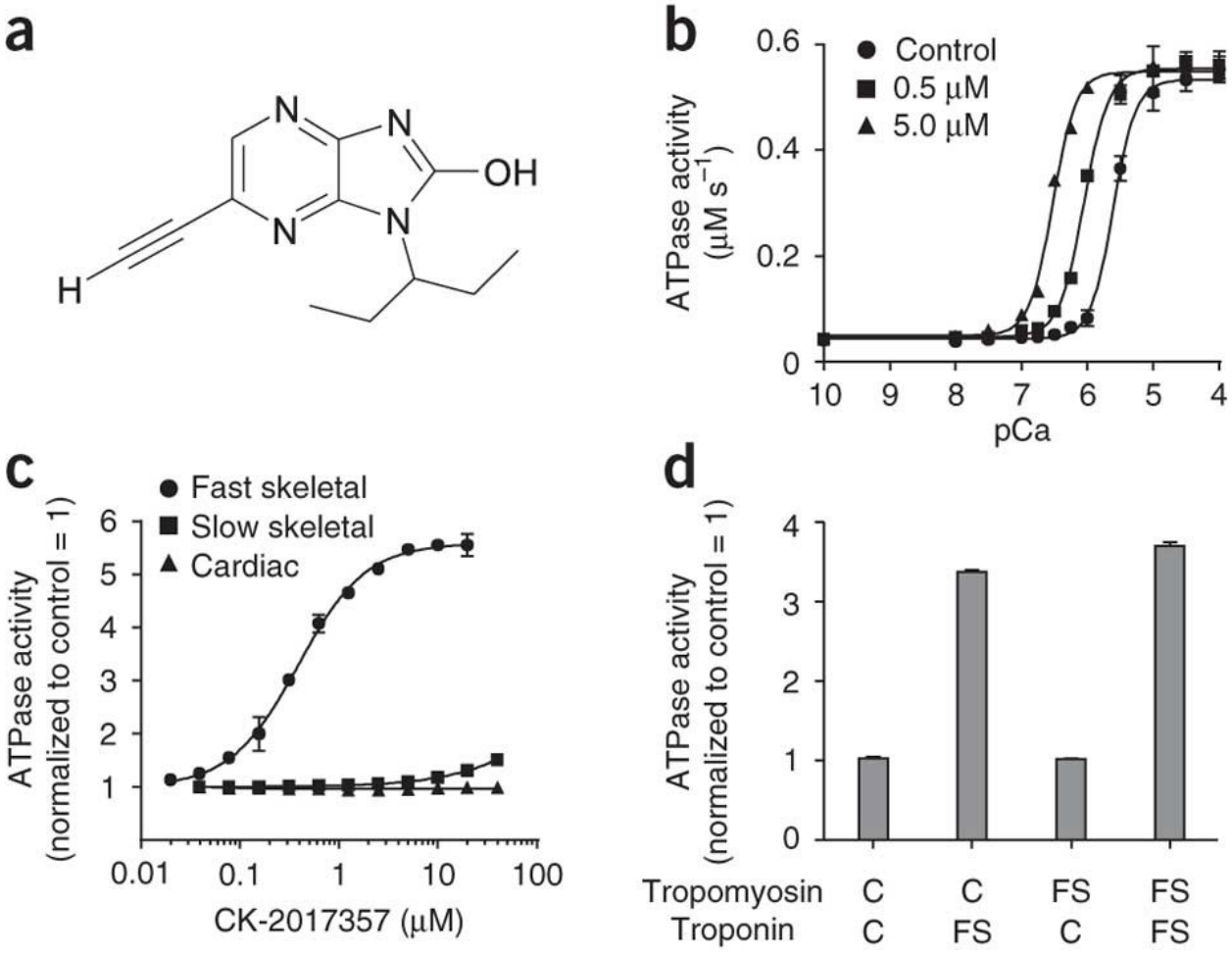
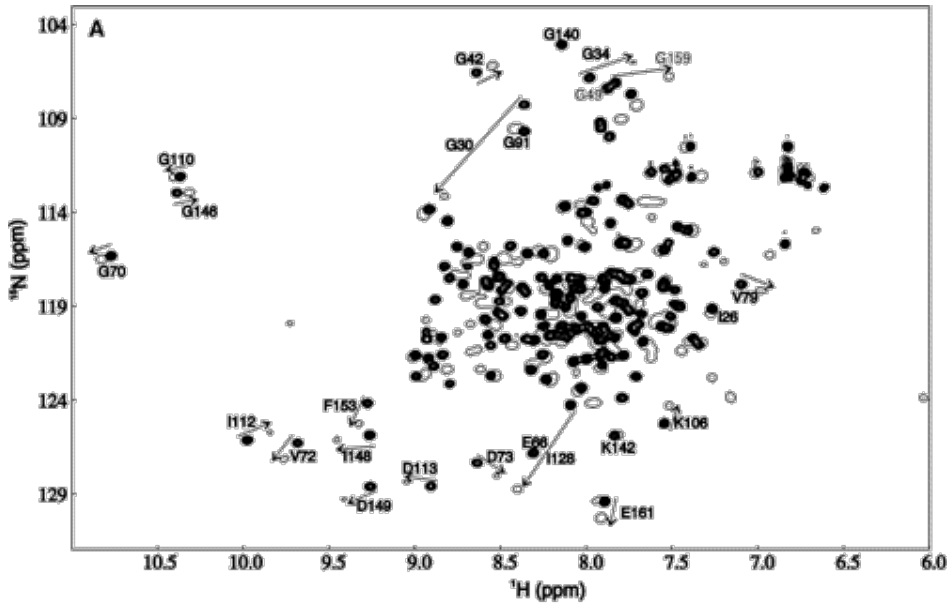


Figure 1. a) Chemical structure of tirasemtiv, a fast skeletal troponin activator. **b)** Tirasemtiv acts as a calcium sensitizer of actomyosin ATPase activity.

*Figure reproduced from Russell AJ et al. 2012. Activation of fast skeletal muscle troponin as a potential therapeutic approach for treating neuromuscular diseases. Nat. Med. **18**, 452-455.*

To date, there is no high affinity cardiac troponin activator. We are using NMR spectroscopy to screen and develop compounds to bind cardiac troponin to function as calcium sensitizers.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G34
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G91
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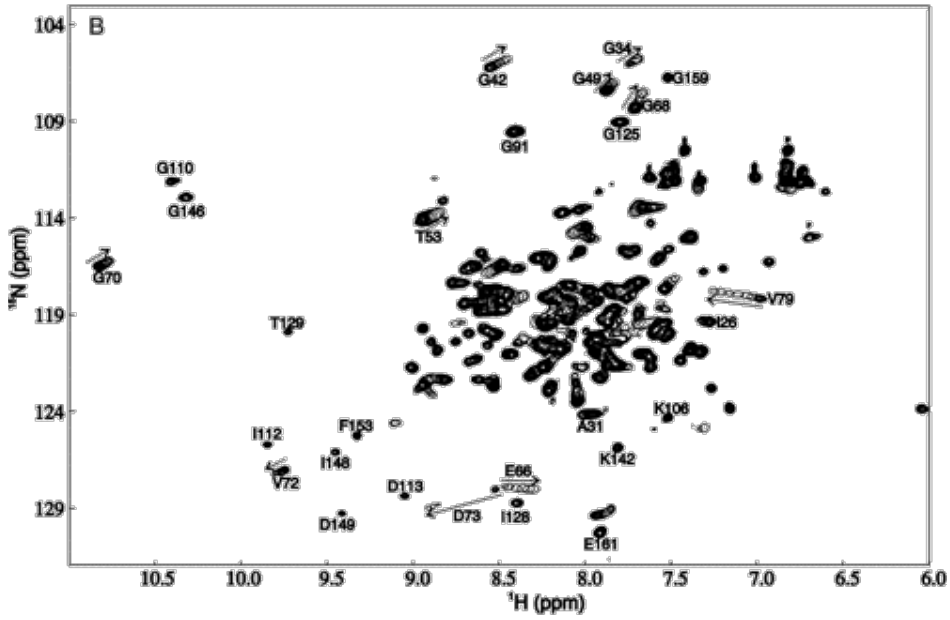
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V79
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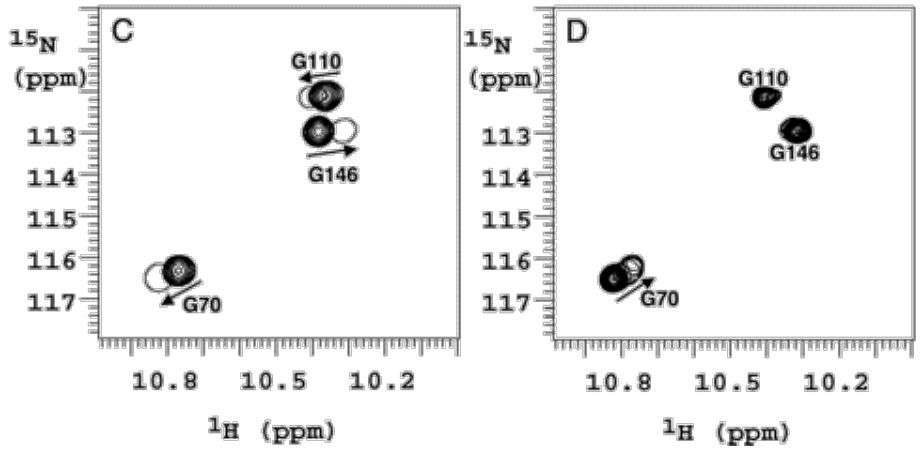
C
D
^{15}N (ppm)
^{1}H (ppm)
G110
G146
G70

Figure 2. 2D $^{1}H,^{15}N$-HSQC NMR spectra are used to monitor cardiac troponin C binding to **a)** troponin I, followed by **b)** calcium desensitizer compound W7.

Figure reproduced from Li MX, Hoffman RM, and Sykes BD. 2006. Interaction of cardiac troponin C with calmodulin antagonist W7 in the presence of three functional regions of cardiac troponin I. Biochemistry **45**, 9833-40.

Troponin modulating compounds bind to the interface between the N-terminal regulatory domain of troponin C and the switch region of troponin I.

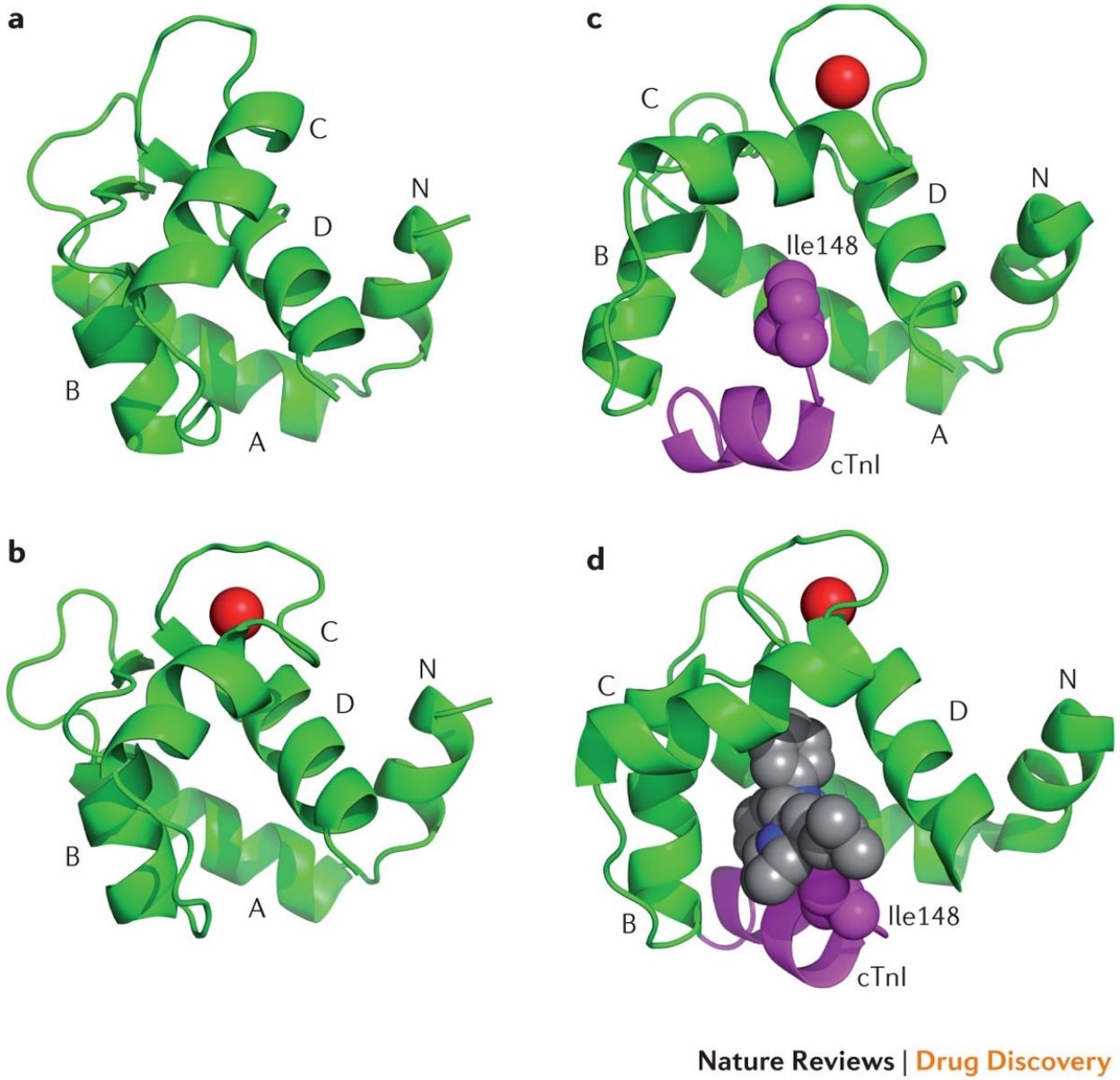

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Figure 3. Structures of the N-terminal regulatory domain of troponin C in the a) apo closed state, b) calcium-bound closed state, c) troponin I-bound open state, and d) troponin I-bound open state bound to the compound bepridil.

Figure reproduced from Hwang PM and Sykes BD. 2015. Targeting the sarcomere to correct muscle function. *Nat. Rev. Drug Discov.* 14, 313-328.