This Week's Citation Classic®

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Matsui H & Schwartz A. Mechanism of cardiac glycoside inhibition of the (Na^+-K^+)-dependent ATPase from cardiac tissue.
Biochim. Biophys. Acta **151**:655-63, 1968.
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The studies revealed specific binding of H^3-digoxin to a heart Na,K-ATPase, with K_D of $3x10^{-8}$M; ATP and Mg^{2+} were required; Na^+ stimulated and K^+ inhibited the binding reaction. [The *SCI*® indicates that this paper has been cited in over 280 publications since 1968.]

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In 1964 one of us (A.S.) presented an early paper of his at the Sixth International Congress of Biochemistry in New York City. The subject was cardiac Na,K-ATPase (NKA). It was an example of good fortune that the other author (H.M.) became interested in the work and decided to join Schwartz's laboratory as his first professional colleague.

When a decent preparation method became available,[1] we studied the mechanism of inhibition by digitalis. We believed, as suggested by Repke,[2] that the positive inotropic action of digitalis involved inhibition of Na/K transport. We studied influences of K^+ and Na^+ on inhibition of NKA by ouabain. It turned out that K^+ *reduced* while Na^+ *increased* inhibition.[3] It appeared that digitalis probably worked by "stabilizing" a phosphorylated intermediate. How to prove this concept? We reasoned that digitalis would "bind" more firmly to a phosphorylated NKA. Schwartz called Stanley Bloomfield at Burroughs-Wellcome, who kindly supplied us with H^3-digoxin in July 1966. Matsui tried a number of methods but finally used a simple centrifugation procedure. Our first successful experiment was completed on September 26, 1966. Matsui presented our abstract at the 51st Federation of American Societies for Experimental Biology meeting in April 1967, at which time we also wrote a paper. The data were very exciting because they contained very good evidence that the binding of H^3-digoxin was saturable with a very low dissociation constant ($3x10^{-8}$M). H^3-digoxin was highly specific in that it was not inhibited by noncardiac steroids. The binding required Mg^{2+} and ATP, was markedly stimulated by Na, and was inhibited by K^+. The first journal to which the paper was submitted, *Proceedings of the National Academy of Sciences*, rejected the paper after six months of waiting. It was a question of relevance. We next sent it to *Biochimica et Biophysica Acta*, which happily, after a few corrections, accepted it. So, after almost two years, our paper was finally published. We, and our families, have remained very close friends, and, in fact, we dedicate this essay to Midori, Matsui's daughter who has passed away.

The importance of this paper is probably multiple. It has provided a reasonable mechanism by which digitalis inhibits the enzyme. It is likely that the NKA is the therapeutic receptor for digitalis.[2,4] Hence, this paper describes either the first or among the first drug receptor-radioligand binding experiments. Further, how nice that the paper was selected as a *Citation Classic* in 1985, for it is the bicentennial anniversary of William Withering's classic treatise on the foxglove,[5] a drug that still enjoys widespread use.

1. **Matsui H & Schwartz A.** Purification and properties of a highly active ouabain-sensitive Na,K-dependent adenosine triphosphatase from cardiac tissue. *Biochim. Biophys. Acta* **128**:380-90, 1966. (Cited 240 times.)
2. **Repke K R H.** The biochemical action of digitalis. *Klin. Wochenschr.* **42**:157-65, 1964. (Cited 125 times.)
3. **Matsui H & Schwartz A.** Kinetic analysis of ouabain-K^+ and Na^+ interaction on a Na,K-dependent adenosine triphosphatase from cardiac tissue. *Biochem. Biophys. Res. Commun.* **25**:147-52, 1966.
4. **Schwartz A, Lindenmayer G E & Allen J C.** The sodium-potassium adenosine triphosphatase: pharmacological, physiological and biochemical aspects. *Pharmacol. Rev.* **27**:3-134, 1975. (Cited 645 times.)
5. **Withering W.** *An account of the foxglove, and some of its medical uses: with practical remarks on dropsy, and other diseases.* Birmingham, England: Printed by M. Swinney for G.G.J. and J. Robinson, 1785. 207 p.