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# Na,K-ATPase isoform-selective cardiac glycosides: A potential anti-cancer drug?

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Na, K-ATPase is present in the membrane of most eukaryotic cells and creates trans-membrane gradients of Na and K ions, which control directly or indirectly essential physiological functions of all animal cells. Regulation of this enzyme and its isoforms is believed to play a key role in various pathological processes, including cancer. The Na+, K+-ATPase consists of two subunits, α and β, in addition to a single membrane-span FXYD regulatory protein. There are four isoforms of α (α1-4) and three isoforms of β (β1-3), which are expressed in a tissue-specific fashion. Cardiac glycosides (CG) such as digoxin or ouabain are specific inhibitors of Na,K-ATPase. CG's display distinct *in vitro* anti-cancer effects, but the full anti-cancer potential of this drug has not yet been addressed. In order to improve selectivity and affinity of cardiac glycosides for the different α isoforms of the human Na,K-ATPase we synthesized new digoxin derivatives, modified in the sugar moiety. We have investigated the effects of CG's and the digoxin derivatives on cell growth and survival of different human cancer cell lines. The IC50 values for growth inhibition of human cancer cells *in vitro* are linearly correlated with the number of binding sites of NaK-ATPase and with the Ki for inhibition of the purified human NaKα1β1 complex. Together, these observations imply that the IC50 values by the different compounds are a consequence of binding to and inhibition of the pump, andquestion the potential of cardiac glycoside as selective anti-cancer drugs.

## Biography

Adriana Katz is an Associate Staff Scientist at the Biological Chemistry department, at Weizmann Institute of Science in Israel, with expertise in membrane proteins, structure-function and protein interactions. The research mainly involves characterization of membrane transport systems, structure and regulation. She has specialized in proteomic analysis - 2D gels, Blue native gels, membrane protein separations and identifications by Mass Spectrometry aimed to identify interacting proteins in the membrane. She is now extending her work to the mammalian Na,K-ATPase including structure-function analyses, inhibition by cardiac glycosides and drug design. She holds a PhD in Biochemistry from the Hebrew University in Jerusalem.

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