Small Molecules Targeting for ESX-Sur2 Proteins' Interaction

Youngjoo Kwon

College of Pharmacy & Division of Life & Pharmaceutical Sciences, Ewha Womans University

It's been known that overexpression of the oncoprotein Her2 (eu/ErbB2), transmembrane receptor protein, occurs in human breast cancer. Her2-positive breast cancer patients who have Her2 overexpression show less therapeutic efficacy with enhanced metathesis and increased resistance to chemotherapy. So far, a humanized monoclonal antibody against Her2 protein called Herceptin is the only drug approved by Food and Drug Administration for treatment of Her2-overexpressing breast tumors. However, antibody therapy of Herceptin may not be ideal method for therapeutic intervention of Her2 protein expression. The therapeutic intervention of Her2 protein expression may be more efficiently achieved by inhibiting the expression of Her2 gene rather than by down-regulating the Her2 protein already overexpressed. Here, we found that the interaction of two proteins of ESX (an epithelial-restricted transcription factor) and DRIP130/CRSP130/Sur2 (a Ras-linked subunit of human mediator complexes) mediates the expression of Her2 gene. The association of ESX with Sur2 is mediated by a small hydrophobic face of 8-amino acid helix in ESX, suggesting that the ESX-Sur2 interaction can be a new novel target for Her2-positive cancer. The process to develop potent ESX-Sur2 interaction inhibitors targeting for Her2-positive cancer therapeutics will be discussed.

Small Molecules Targeting for Esx-Sur2 Proteins' Interaction

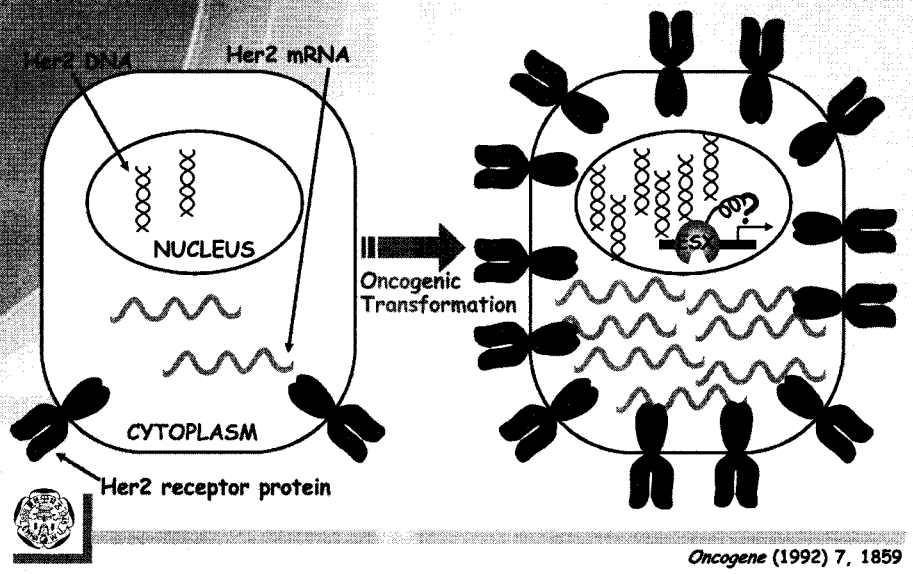
Youngjoo Kwon

College of Pharmacy & Division of Life & Pharmaceutical Sciences Ewha Womans University

Outline; discovery of potent anticancer-like ligands against Her2-positive human breast cancer

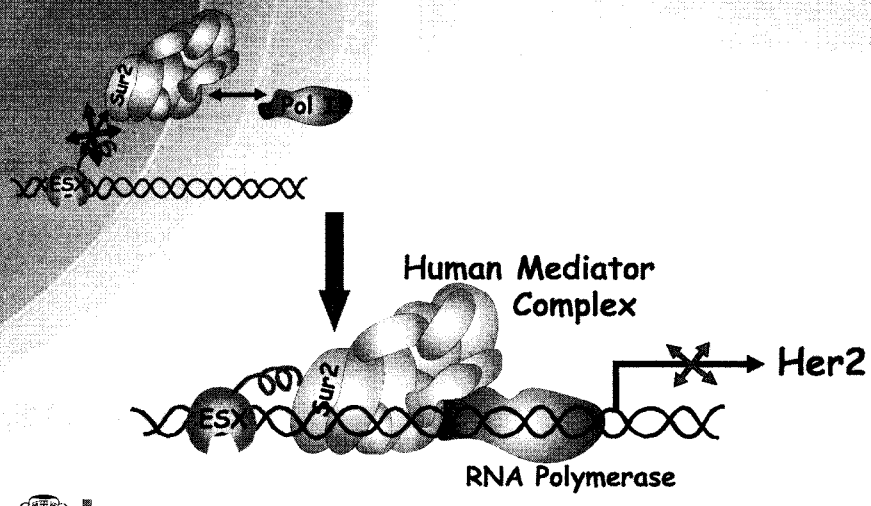
- Identification of the protein-protein interaction target related to Her2-positive human breast cancer
- Study on the binding core between ESX and Sur2 proteins
- Screening small molecules to inhibit ESX-Sur2 interaction
- Optimization of inhibitory activity of ligands against ESX-Sur2 interaction
- Future plan

Her2 is an oncogene in malignant breast cancer and activated by ESX, an epithelium-specific transcription factor



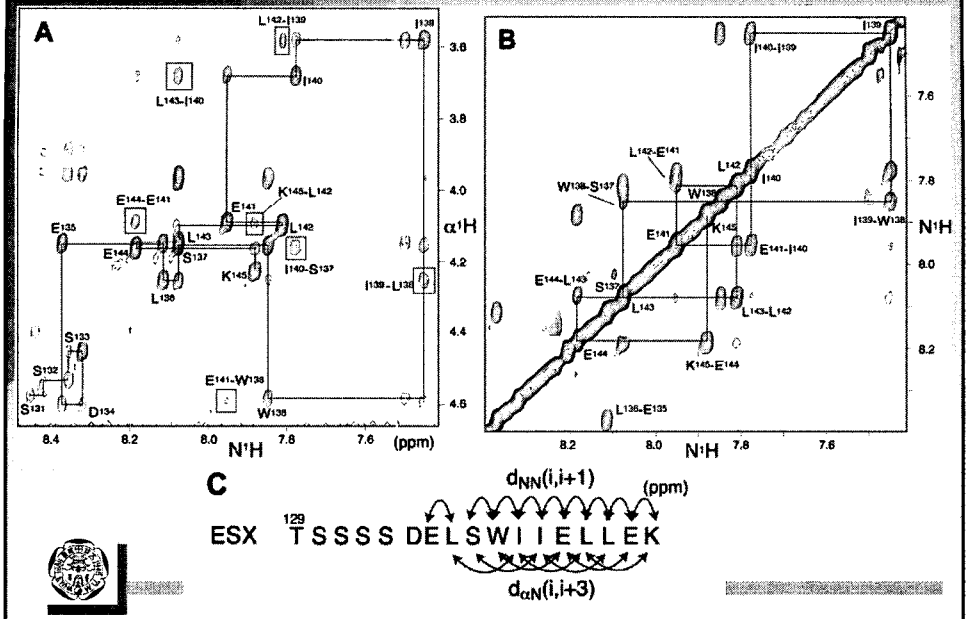
Oncogene (1992) 7, 1859

Sur2-ESX interaction could be a potential target for Her2-overexpressing breast cancer

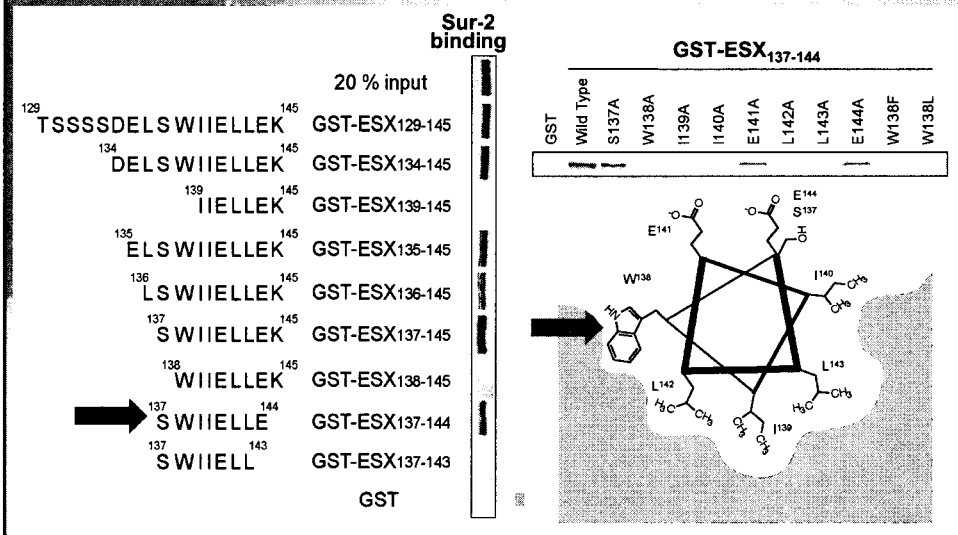


M. Uesugi, *Proc. Natl. Acad. Sci. USA* (2002) 99, 12747

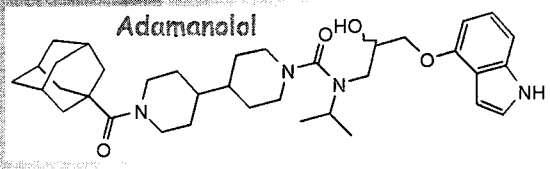
NMR Studies of $ESX_{129-145}$: α-helical structure

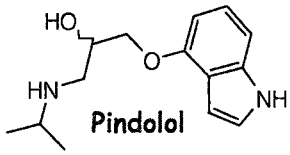


An 8-amino acids helical peptide is sufficient for the interaction with Sur2

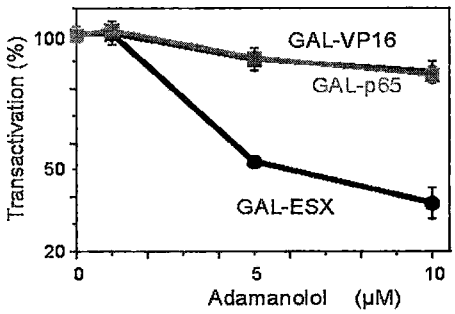


Screening indole-containing compounds: Discovery of adamanolol that impairs Sur2-ESX interaction



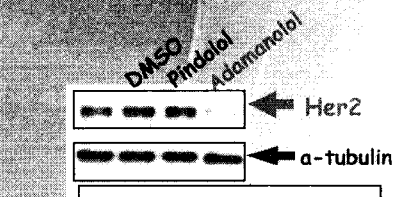


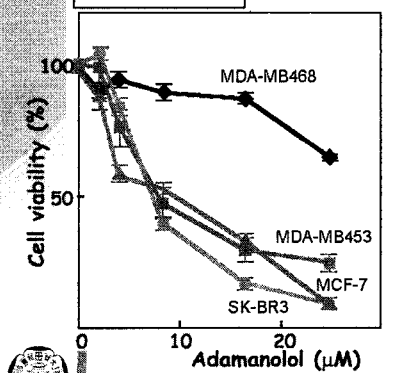
Focused chemical library
- Less than six N atoms
- clogP is between -1 & 6
- 2,433 compounds

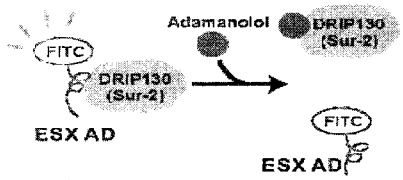


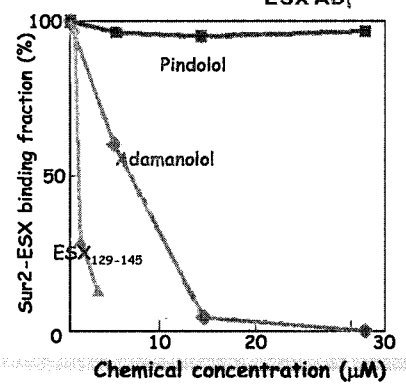
M. Uesugi, *J. Am. Chem. Soc.* (2003) 125, 4992

Discovery of adamanolol that impairs Sur2-ESX interaction (continued)

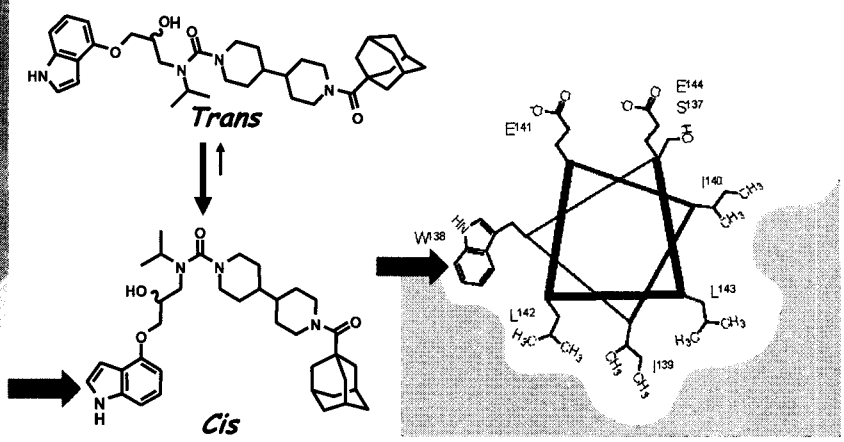




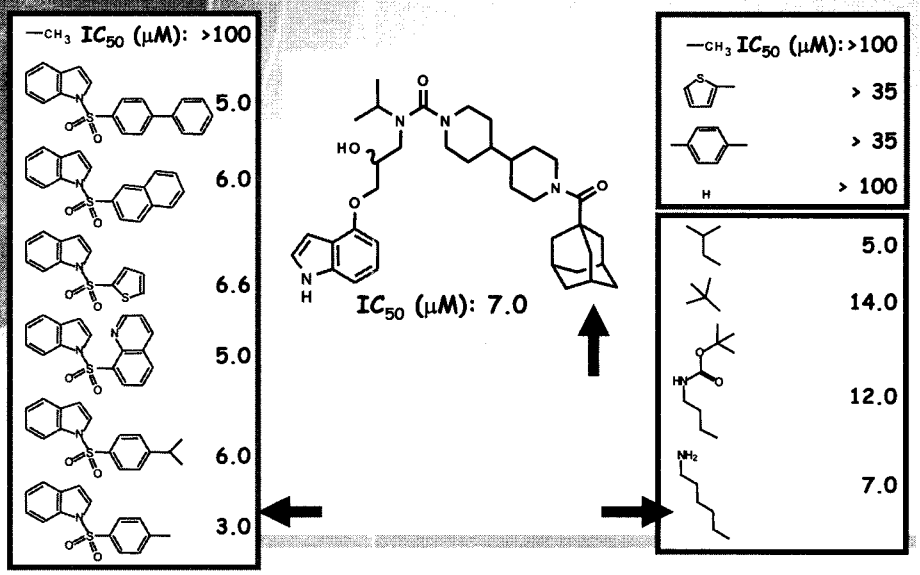




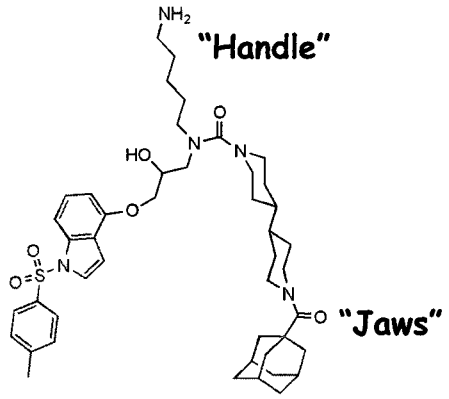
How does adamanolol inhibit the Sur2-ESX interaction?

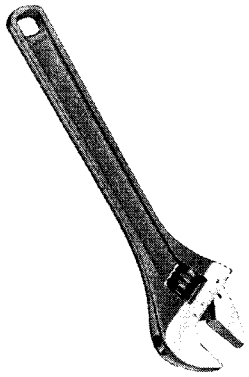


Study of structure-activity relationship among adamanolol derivatives



Discovery of second generation of adamanolol derivative: Wrenchnolol

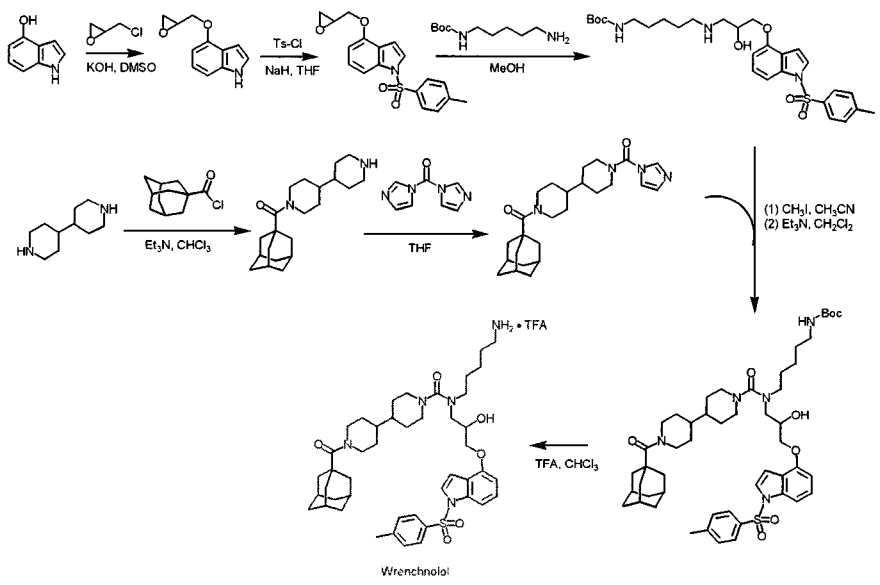


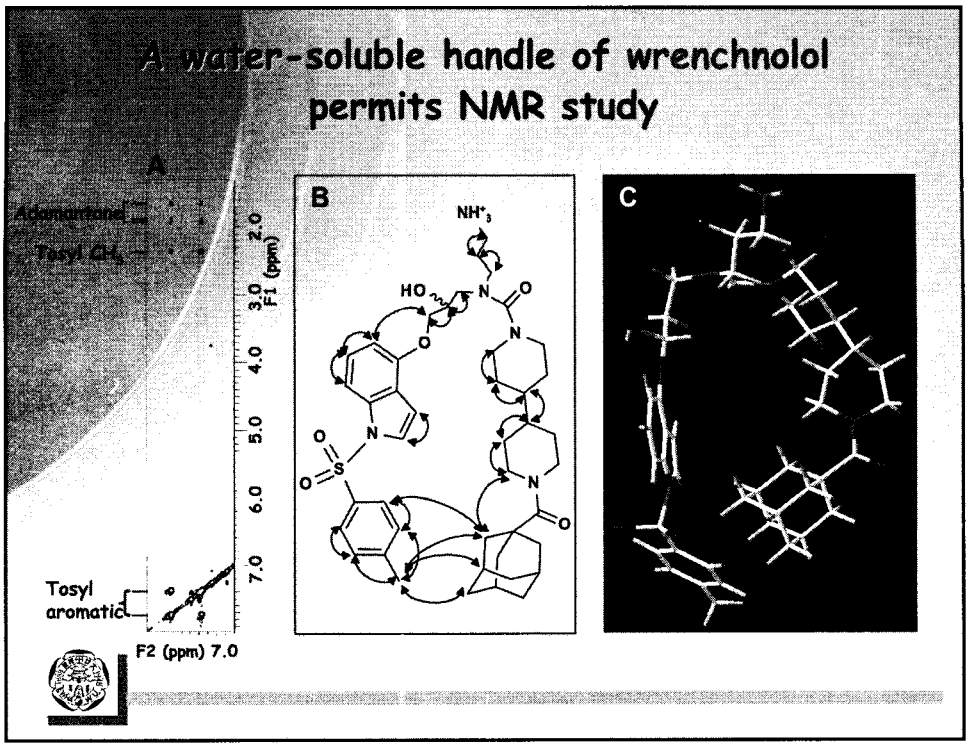


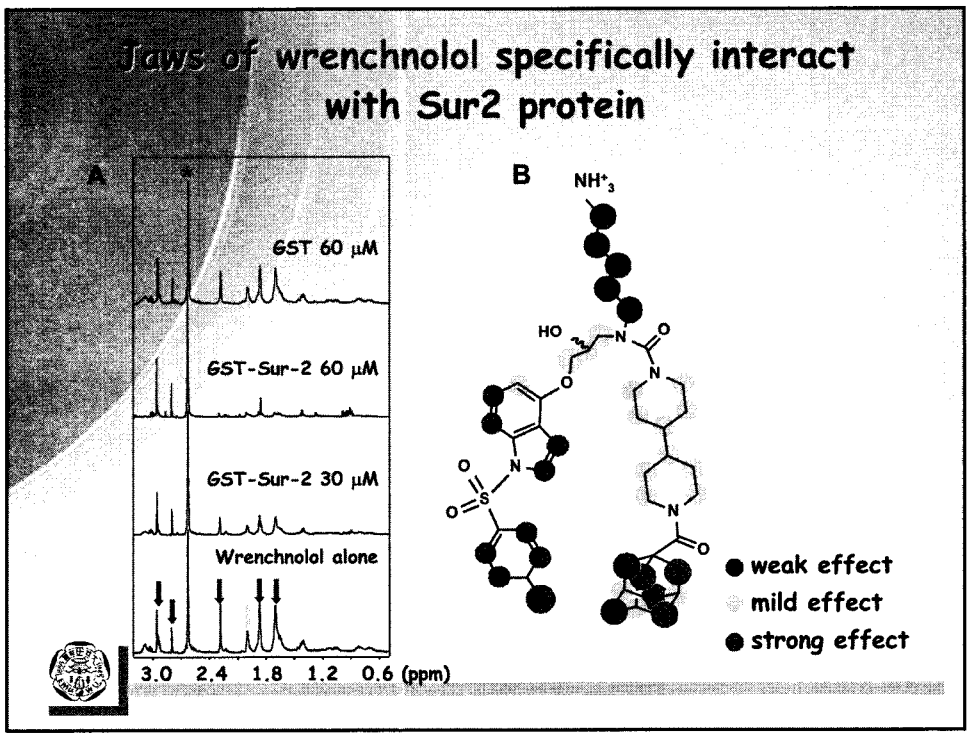
Water-soluble, IC_{50} in cells = 7 μM
In vitro binding inhibition is greater than adamanolol

J. Am. Chem. Soc. (2004) 126, 3461.

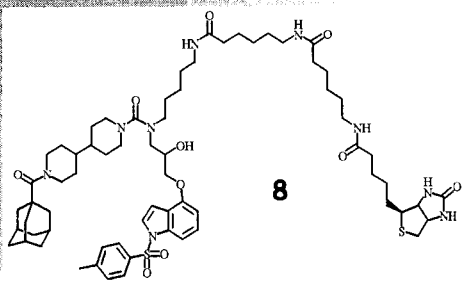
Wrenchnolol synthesis

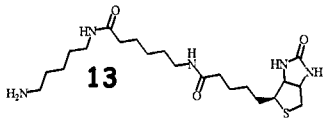


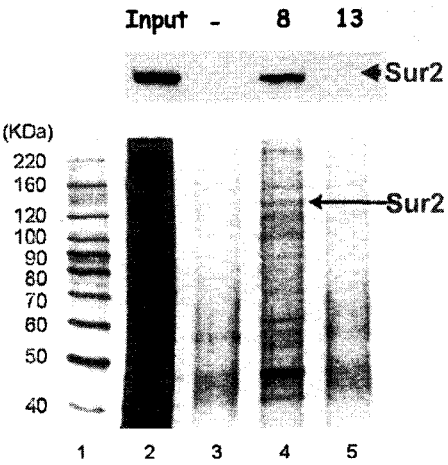

A water-soluble handle of wrenchnolol permits NMR study
A
Adamantanol
Tosyl CH3
Tosyl aromatic
F2 (ppm) 7.0
F1 (ppm)
2.0
3.0
4.0
5.0
6.0
7.0
B
NH+3
HO
C


Jaws of wrenchnolol specifically interact with Sur2 protein
A
GST 60 μM
GST-Sur-2 60 μM
GST-Sur-2 30 μM
Wrenchnolol alone
3.0 2.4 1.8 1.2 0.6 (ppm)
B
NH+3
HO
weak effect
mild effect
strong effect

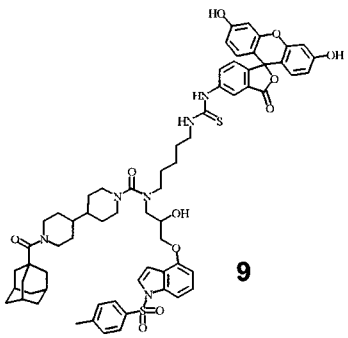
Wrenchnolol specifically interacts with Sur2 protein (continued)



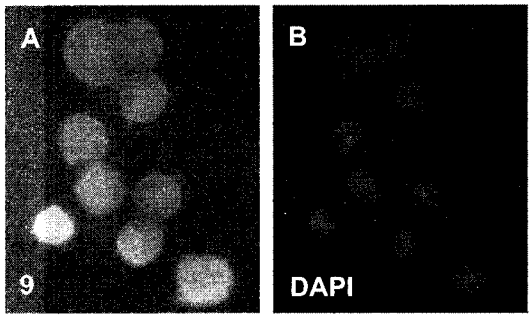


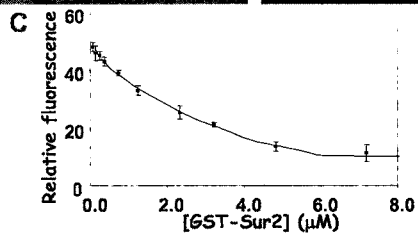


A fluorescent handle confirms cell permeability and enables K_d estimation

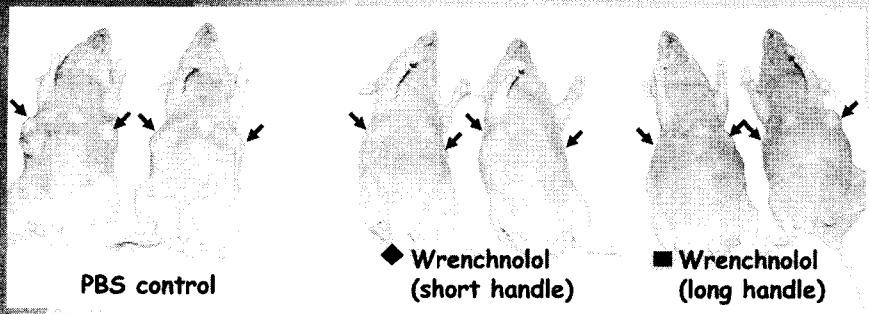


K_d = 1.8 μM





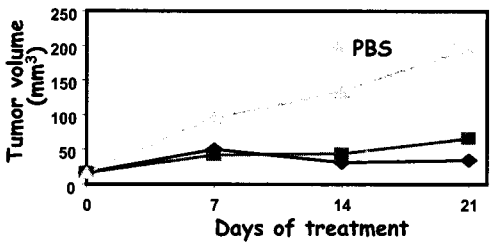
Wrenchnolol reduces tumor size in animal tests

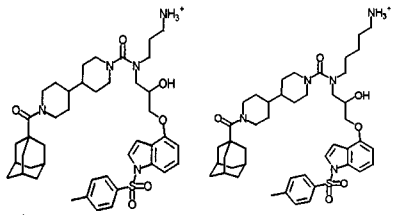


PBS control

◆ Wrenchnolol (short handle)

■ Wrenchnolol (long handle)





◆ Wrenchnolol (short handle)

■ Wrenchnolol (long handle)

Future Plan

- Possible utility of wrenchnolol as an activation domain of natural transcription factor
- Discovery of artificial non-peptidic transcription factor
- Structure determination of ESX-Sur2 complex
- Discovery of more potent inhibitor against ESX-Sur2 interaction