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Characterization of the pharmacological effects of cardiac glycosides on lung epithelial cells

PhD dissertation defense by

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Introduction

- Lung cancer alone accounts for 15% of cancer incidences and 30% of cancer related mortality.
- Lung cancer has poor prognosis due to an intrinsic wide signaling array, and limited therapeutic approaches.
- Developing new therapeutic alternatives for lung cancer is of critical need.
- Cardiac glycosides are potential candidates.

General outline

- Digitoxin, a cardiac glycoside with the potential to provide a new hope for cancer therapy.

- Digitoxin and a synthetic monosaccharide analog inhibit cell viability in lung cancer cells.

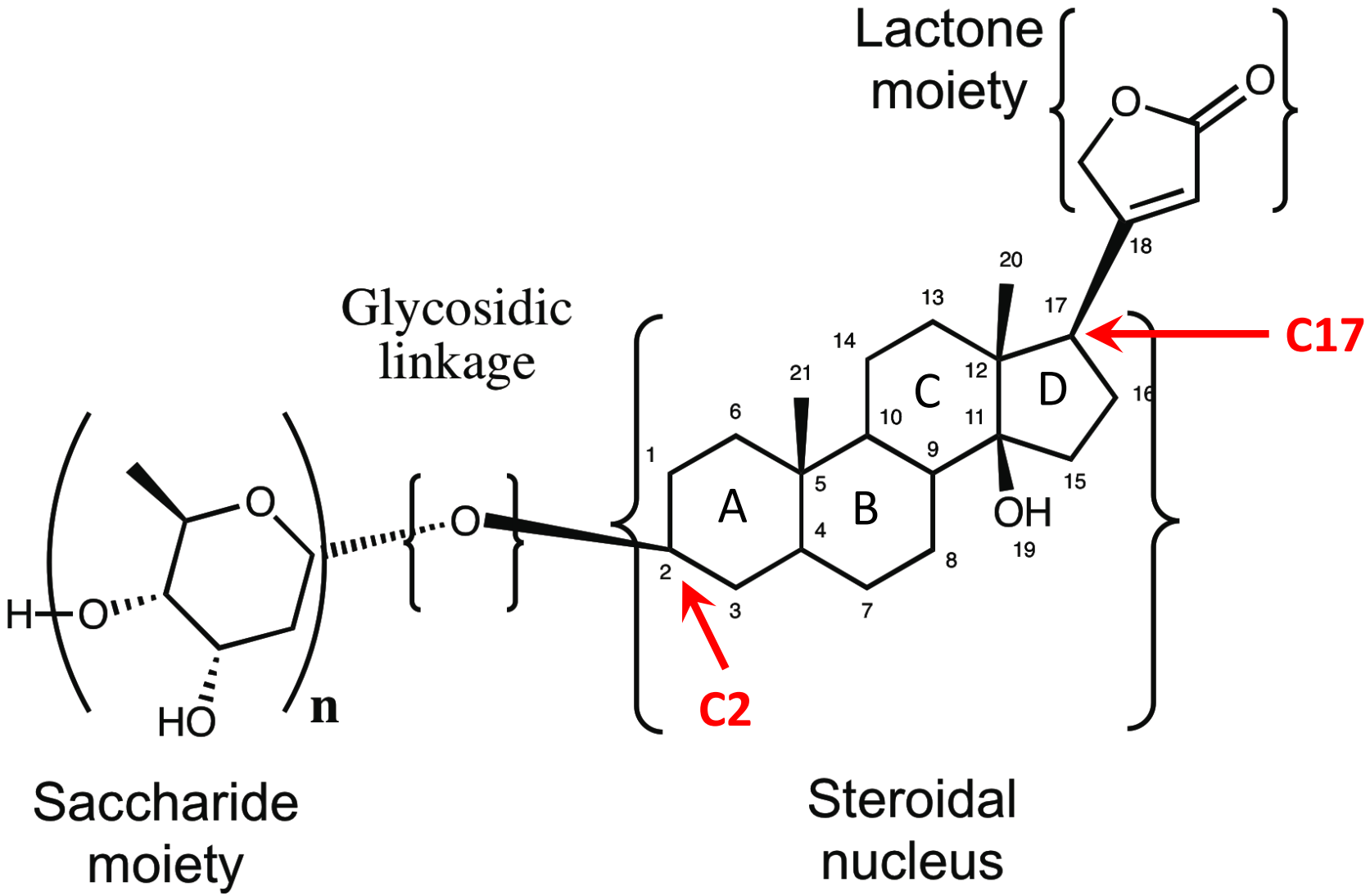
Digitoxin, a cardiac glycoside with the potential to provide a new hope for cancer therapy

- Outline
  1. What are CGs?
  2. Evidence for anticancer effect.
  3. Potential CGs candidates.
  4. Differential effects on Na+/K+ATPase.
  5. Structural manipulation enhanced digitoxin's cytotoxic activity.
  6. Potential mechanism for CG's selective cytotoxicity
  7. Conclusions and future directions

What are cardiac glycosides?

- A large family of chemical compounds found in several plants and animal species.
- Known for more than 1500 years for several medical conditions as diuretics, emetics, abortifacients, antineoplastics, and heart tonics .
- Patients with congestive heart failure, “dropsy””, improved after administering foxglove extract (*Digitalis purpurea L.*)

Cardiac glycosides share a common structural motif



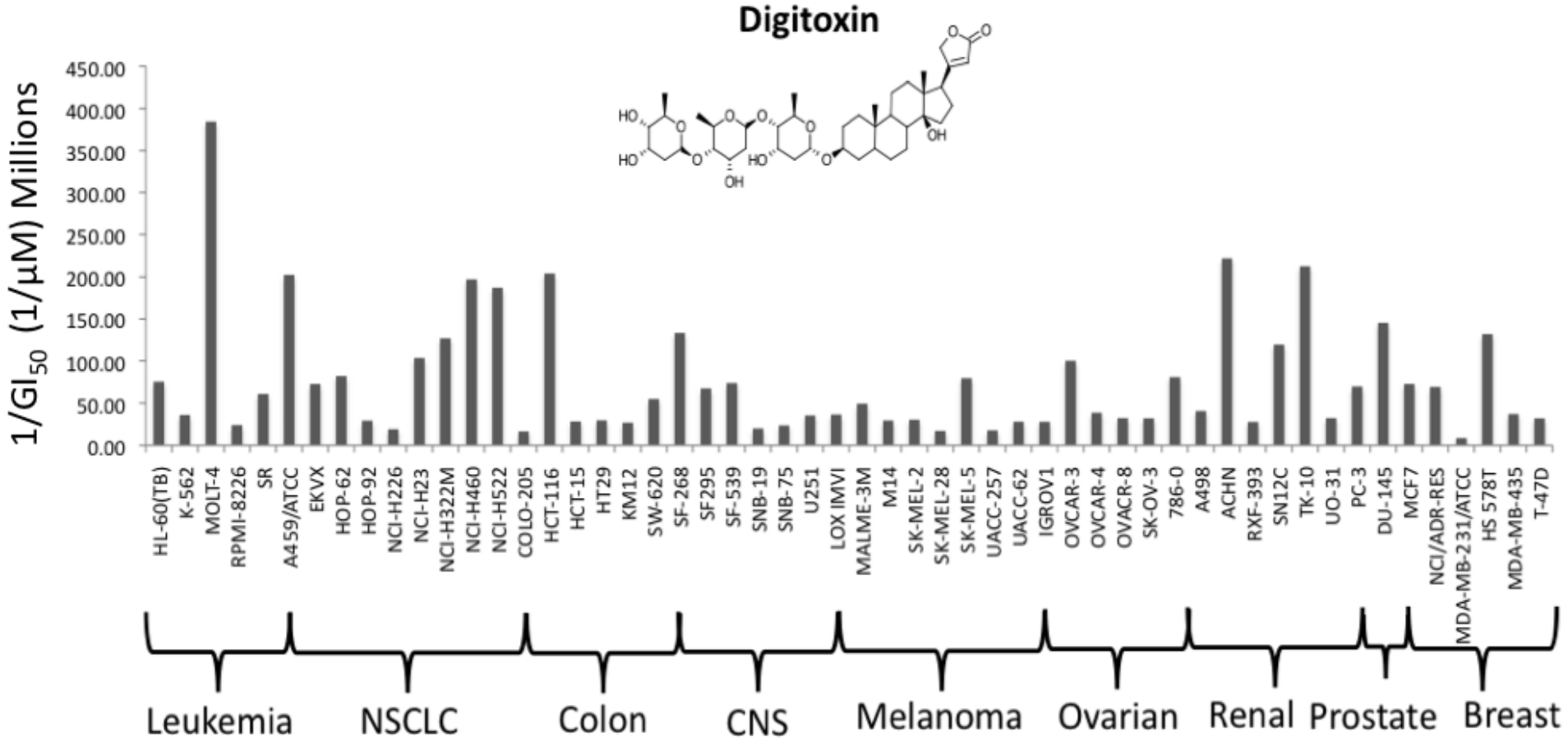
Evidence for anticancer effect for cardiac glycosides

- Historical records indicated CGs extracts for treating malignant conditions.
- Shiratori et al., (1967) found anticancer potential for CGs on rodent cancer models.
- Stenkvist et al. (1979-2001), and Goldin et al., (1984) showed that women on digitalis therapy
  - developed more benign forms of breast tumors, and
  - 9.6-times lower cancer recurrence rate when compared to control patients.
- CGs mediate a significant anticancer effect.

What are potential candidates from cardiac glycosides?

- Digitoxin is an ideal candidate as an anticancer drug because:
  - Anticancer effect at therapeutic concentrations
  - Long half life (7days)
    - 97% bound to plasma proteins
    - Large V_d
  - Complete clinical profile

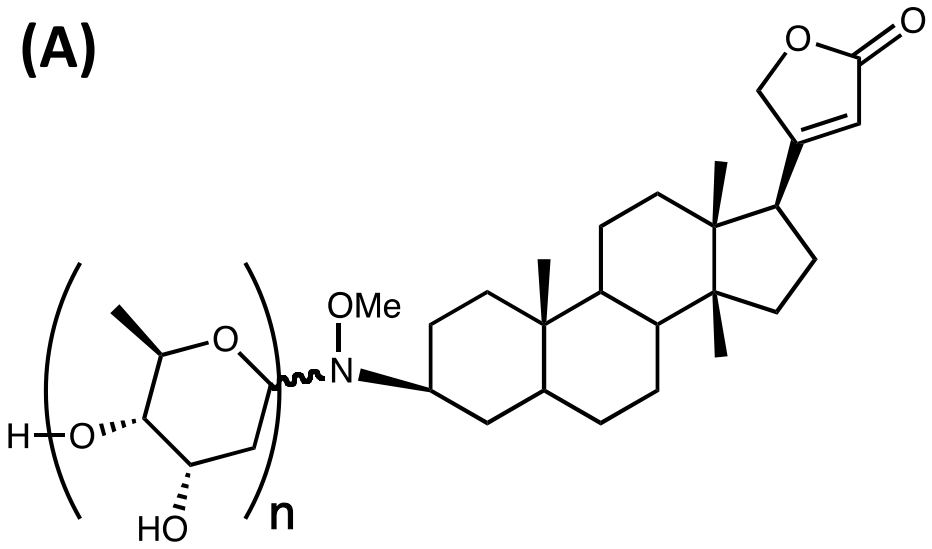
What are potential candidates from cardiac glycosides?



Iyer *et al.*, 2010, Wang *et al.*, 2010

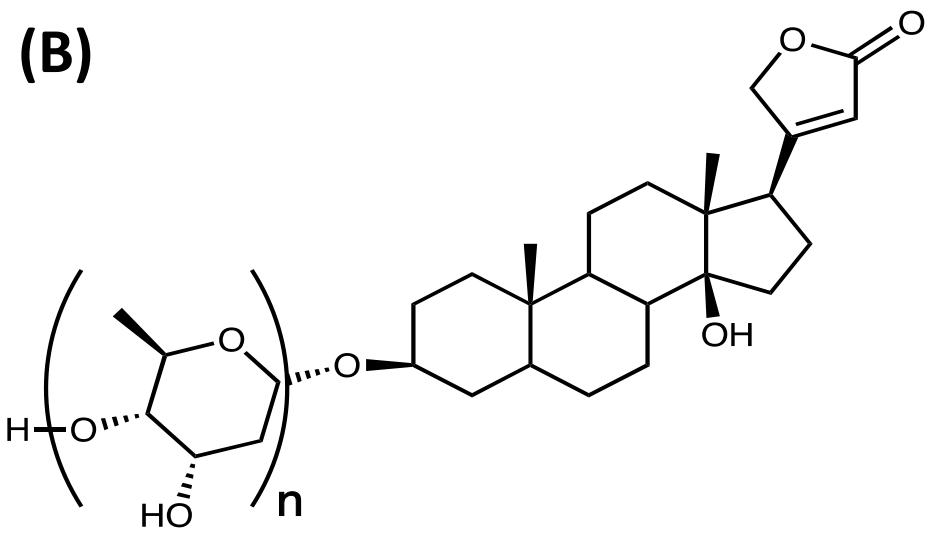
Manipulation of the glycosidic linkage and saccharide moiety of digitoxin

(A)



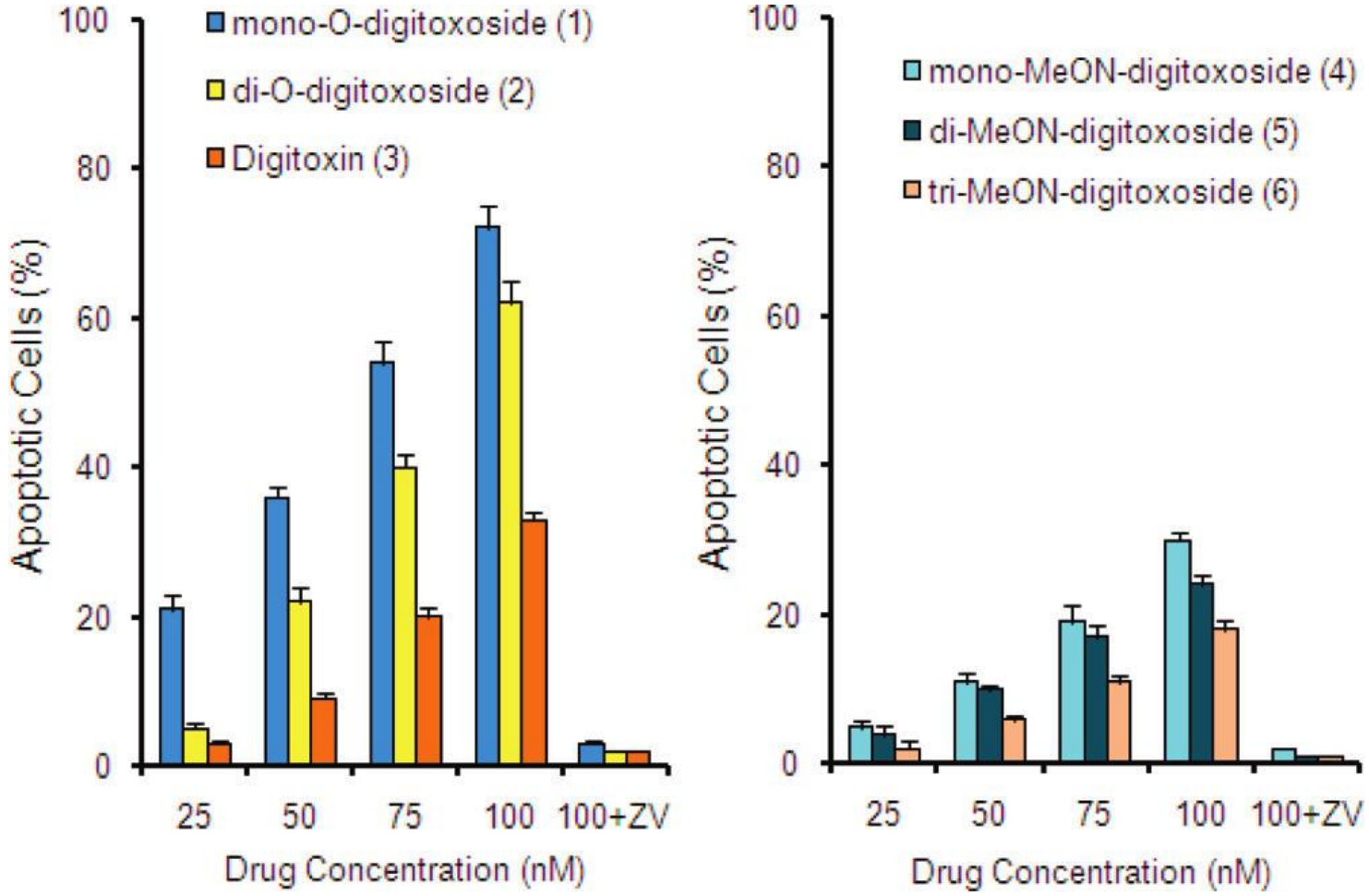
n=1; Digitoxin mono-MeON-saccharide
n=2; Digitoxin di-MeON-saccharide
n=3; Digitoxin tri-MeON-saccharide

(B)



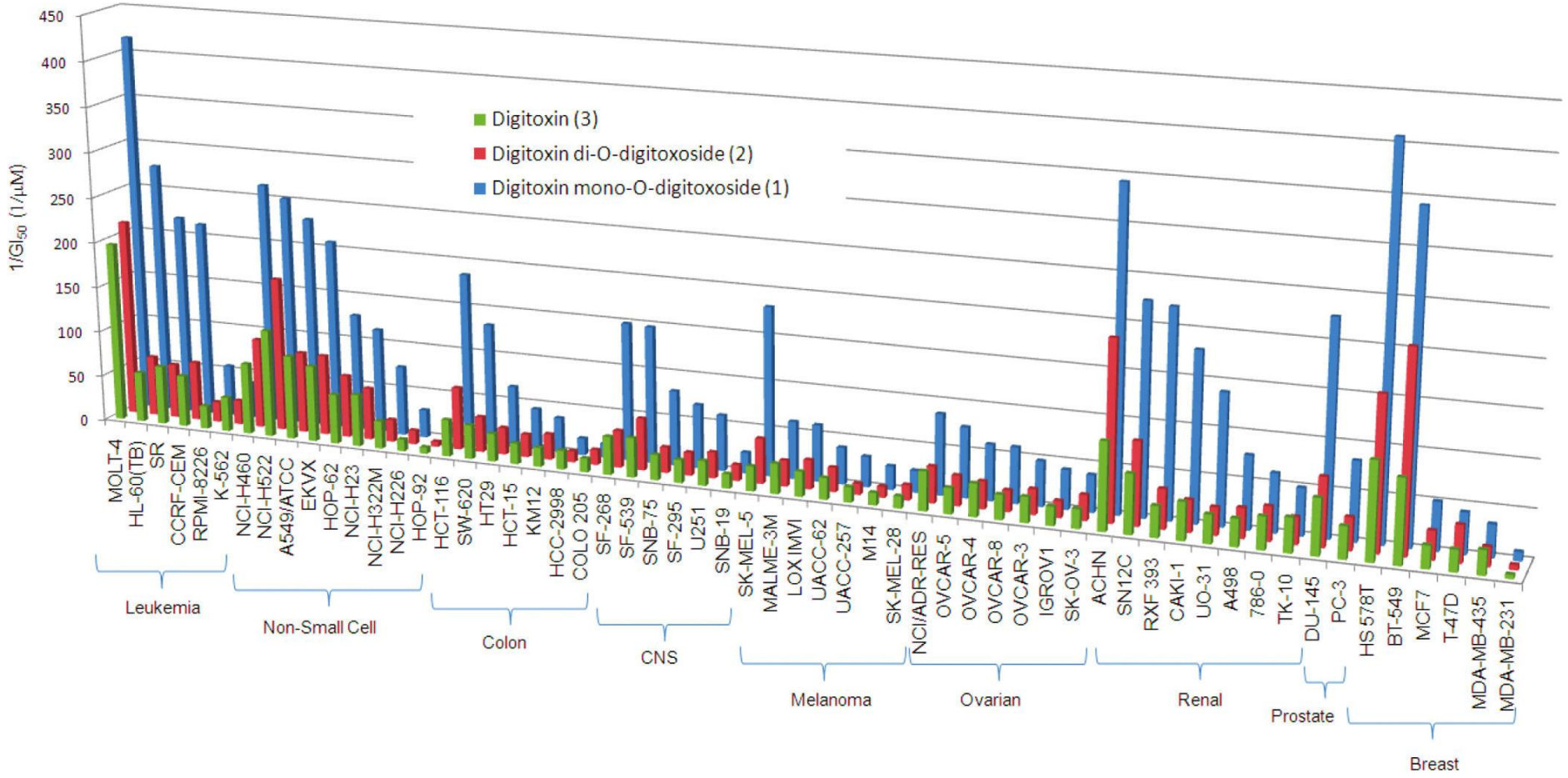
n=1; Digitoxin mono-O-saccharide
n=2; Digitoxin di-O-saccharide
n=3; Digitoxin
n= *alfa-L-rhamnose;* *D6-MA*

Digitoxin O-saccharides are more potent than digitoxin MeON-saccharides



Iyer *et al.*, 2010

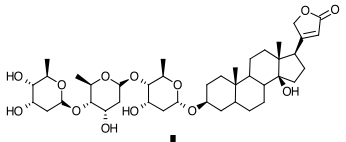
Digitoxin monosaccharide analogs are more potent anticancer agents than their disaccharide and trisaccharide counterparts



Iyer *et al.*, 2010

Digitoxin affects Na^+/K^+ATPase differently depending on its concentration

Digitoxin (0.5-5µM)



Na^+/K^+ ATPase inhibition

↓

Intracellular Na^+ ↑↑

↓

Na^+/Ca^{2+} exchanger activation

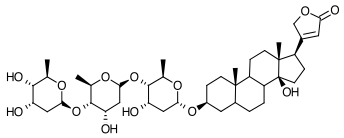
↓

Intracellular Ca^{2+} ↑↑

↓

Intracellular events

Digitoxin (10-100 nM)



↓

Na^+/K^+ ATPase signalosome (MAPK, SRC, Akt, and PLC signaling)

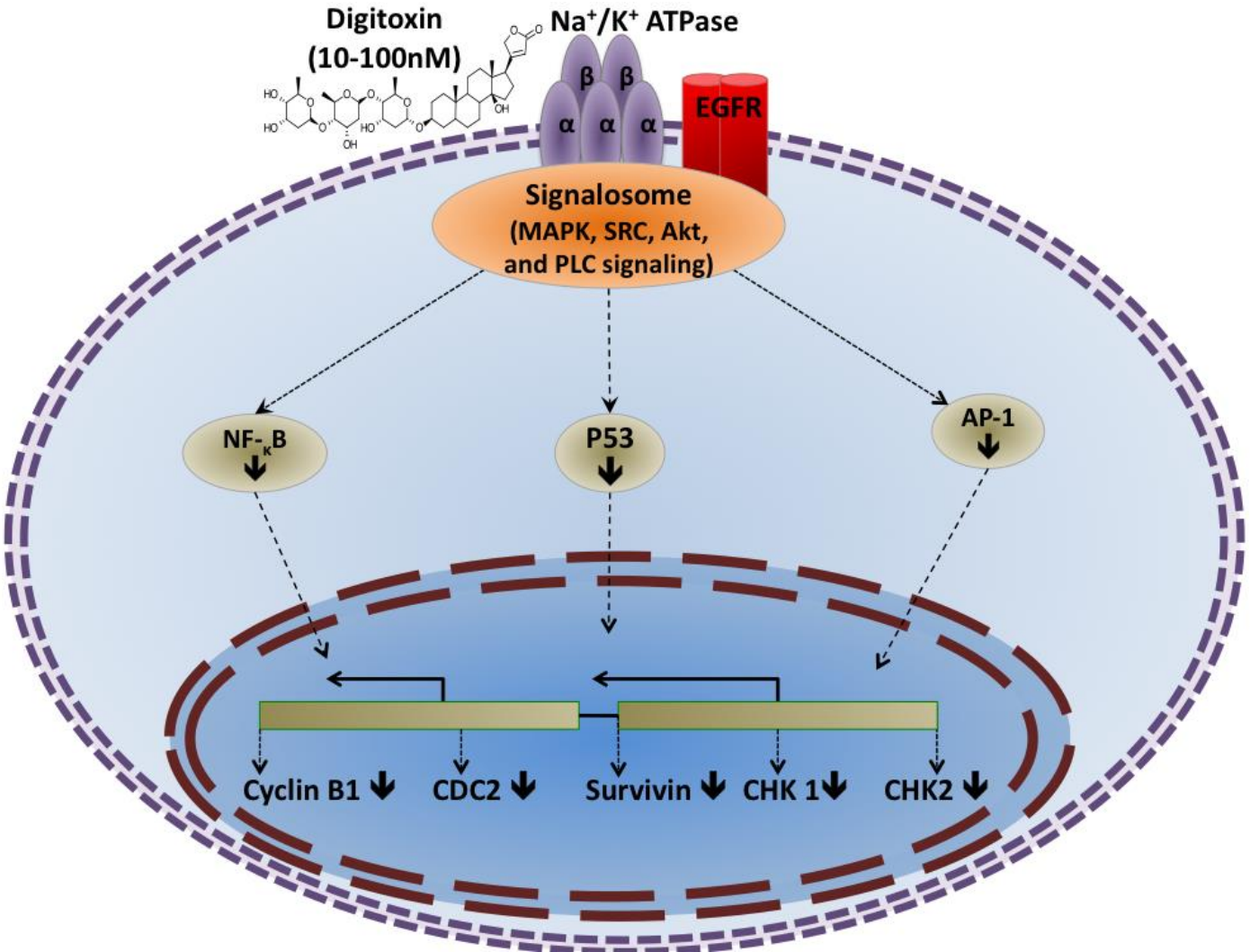
↓

Intracellular events
Manipulated gene expression
Cancer specific genes ↓↓

↓

Cell death

CGs reduce cell cycle regulatory proteins that are specifically overexpressed in cancer cells by blocking AP-1 and NF-κB signaling



Conclusions and future directions

- How do digitoxin and analog cause G2/M phase arrest and apoptosis in cancer cells?
- What are potential p53-independent therapeutic target(s) that mediate cancer cell death?
- How do digitoxin and D6-MA inhibit survivin and p53 expression in cancer cells?
- Would digitoxin and D6-MA induce mitotic catastrophe in cancer cells? if so, how?

Digitoxin and a synthetic monosaccharide analog inhibit cell viability in lung cancer cells

- Outline
  - Introduction
  - Objectives and hypothesis
  - Results
  - Discussion and conclusions

Introduction

- Appropriate cell cycle progression is crucial for cell viability.
- *In vitro* CGs studies showed apoptosis, autophagy, and cell cycle arrest; however, mechanism is unclear.
- Wang et al. synthesized and compared several digitoxin monosaccharide analogs for lethal and growth inhibitory effects.
- Three monosaccharide analogues showed at least a 5-fold increase in antineoplastic potency in NSCLC.
- Understanding the cytotoxic mechanism of CGs in NSCLC will help in developing safer and more effective anti-cancer drugs.

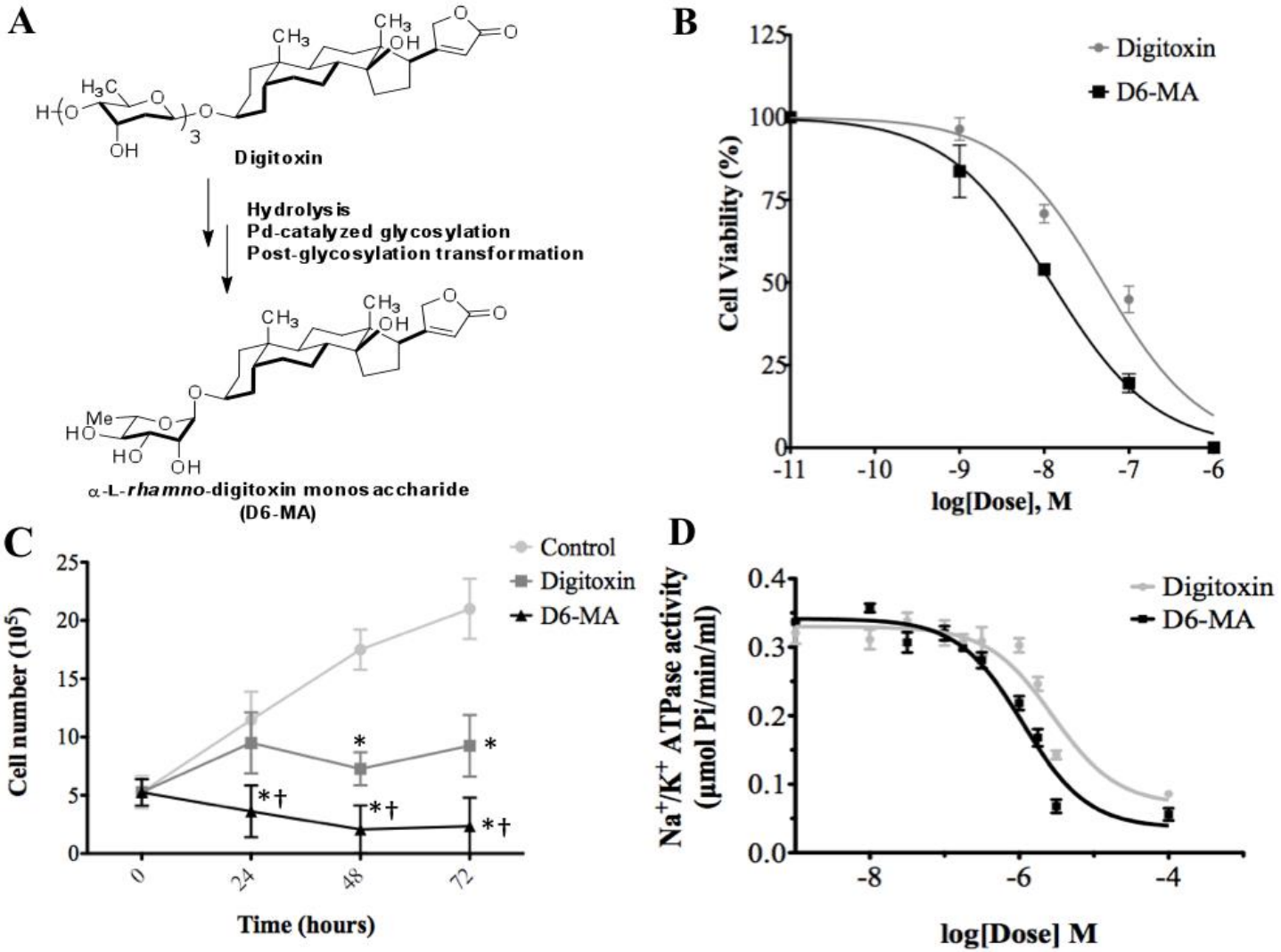
Objective and Hypothesis

- NCI-H460 cells were chosen as a model for NSCLC because
  - NSCLC cells are more sensitive to digitoxin and D6-MA
  - Recalcitrance of NSCLC cells to chemotherapy

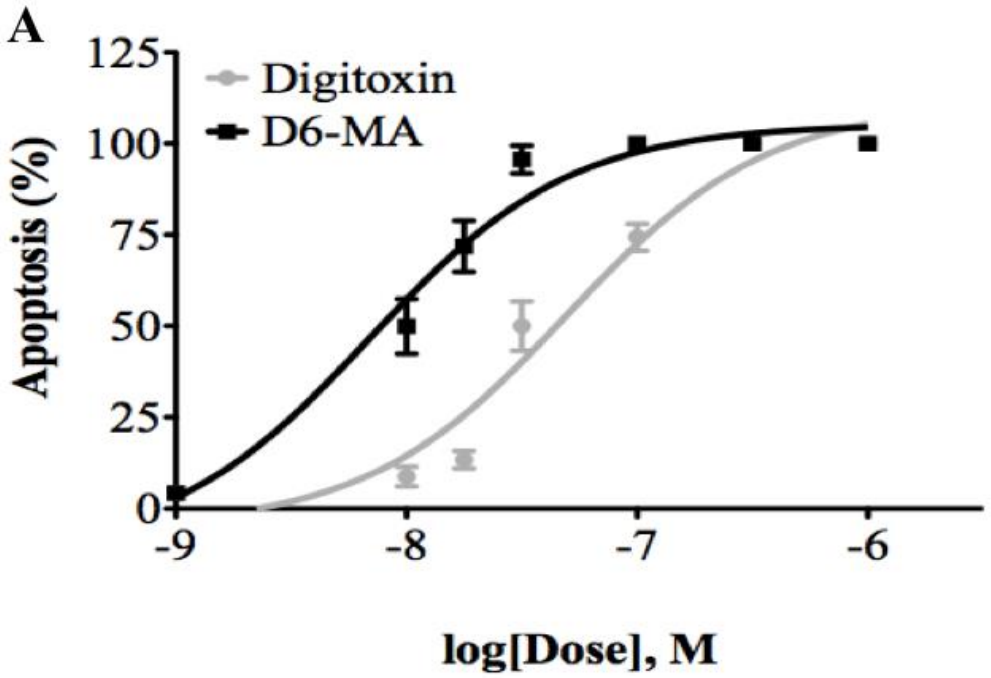
- Objective:
  - compare digitoxin with D6-MA with respect to their cytotoxic mechanisms

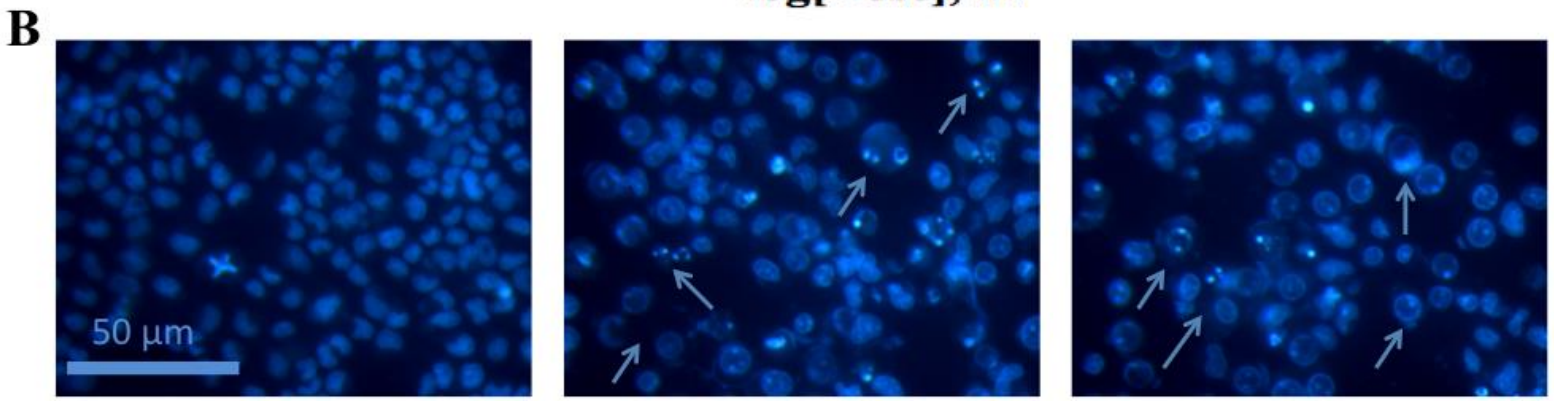
- Hypothesis:
  - therapeutically relevant doses of digitoxin and D6-MA would decrease cell viability due to G2/M arrest and induce apoptosis in NCI-H460 cells , with D6-MA being more potent.

Digitoxin and D6-MA causes inhibition of NCI-H460 cell viability and Na^+/K^+ATPase enzyme activity

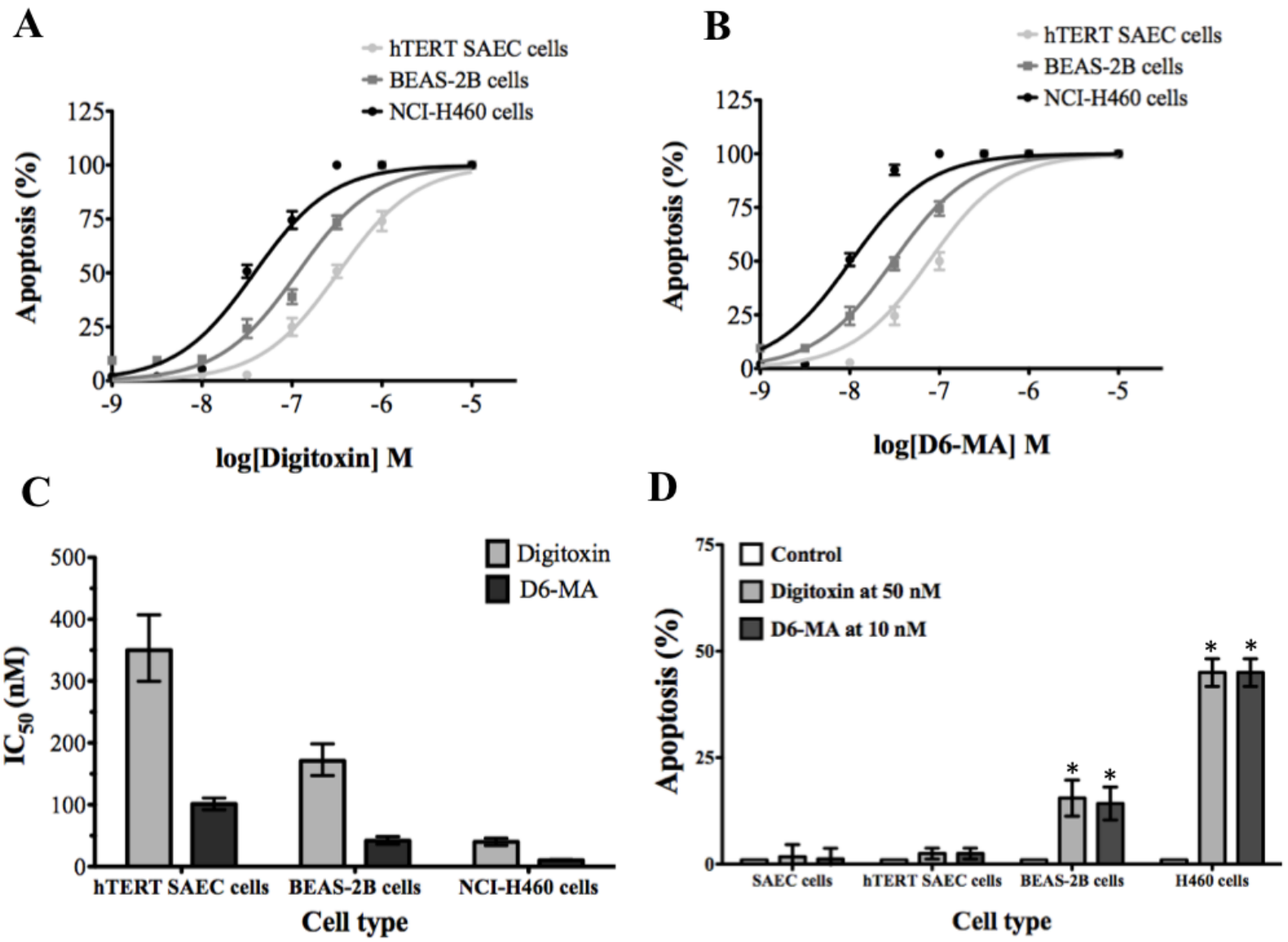


Digitoxin and D6-MA induces apoptosis in NCI-H460 cells

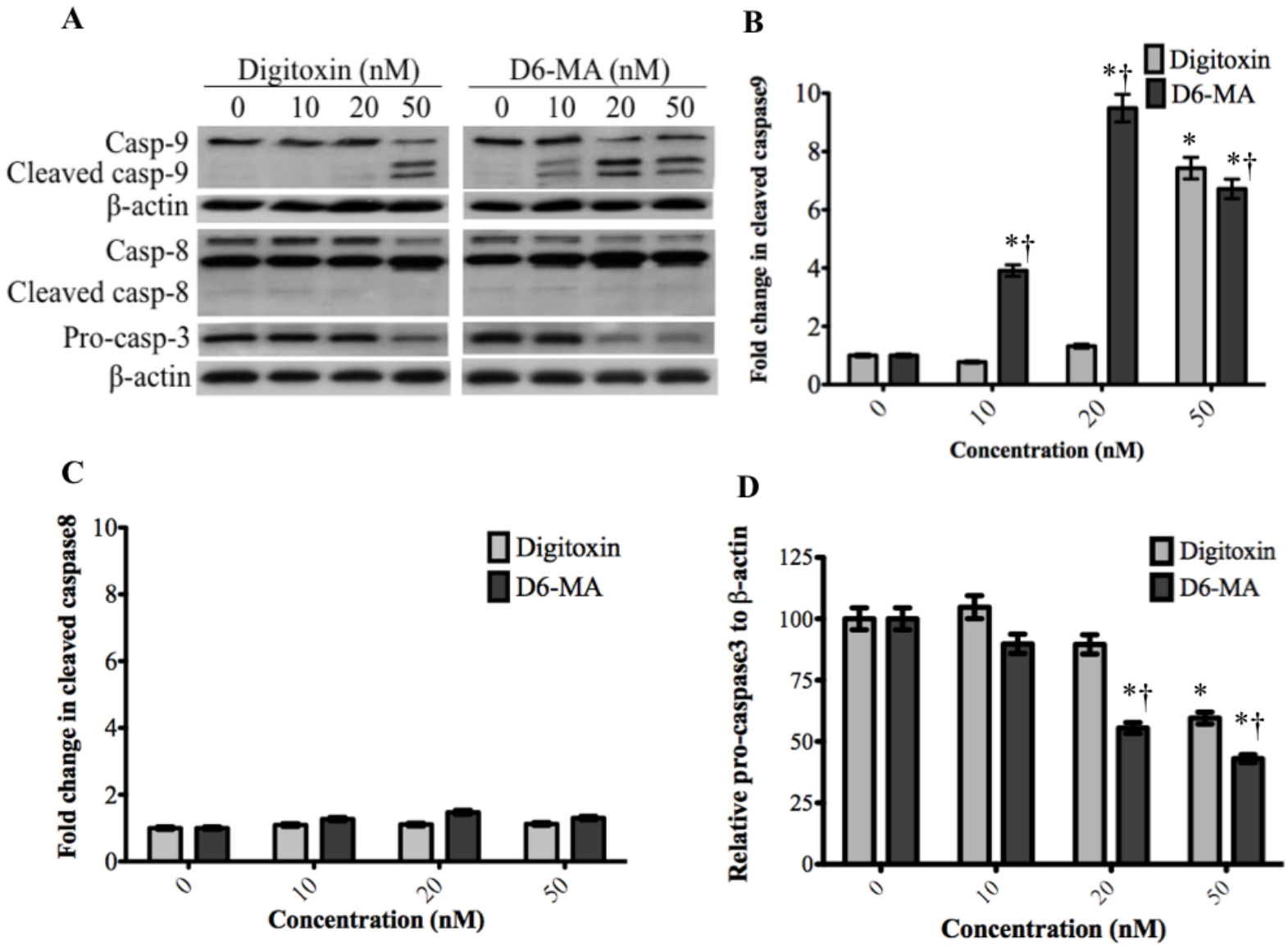




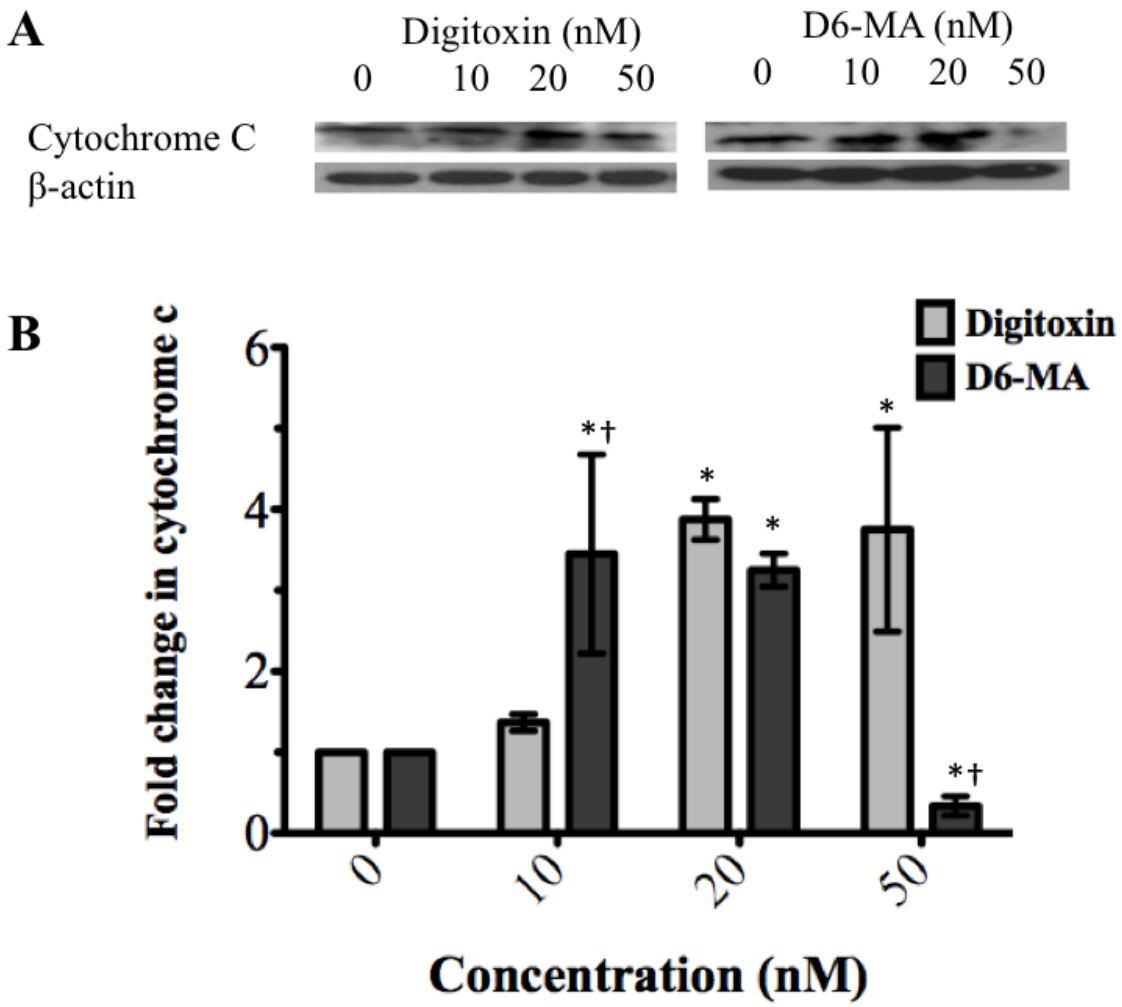
D6-MA exhibits selective cytotoxicity to NSCLC cells



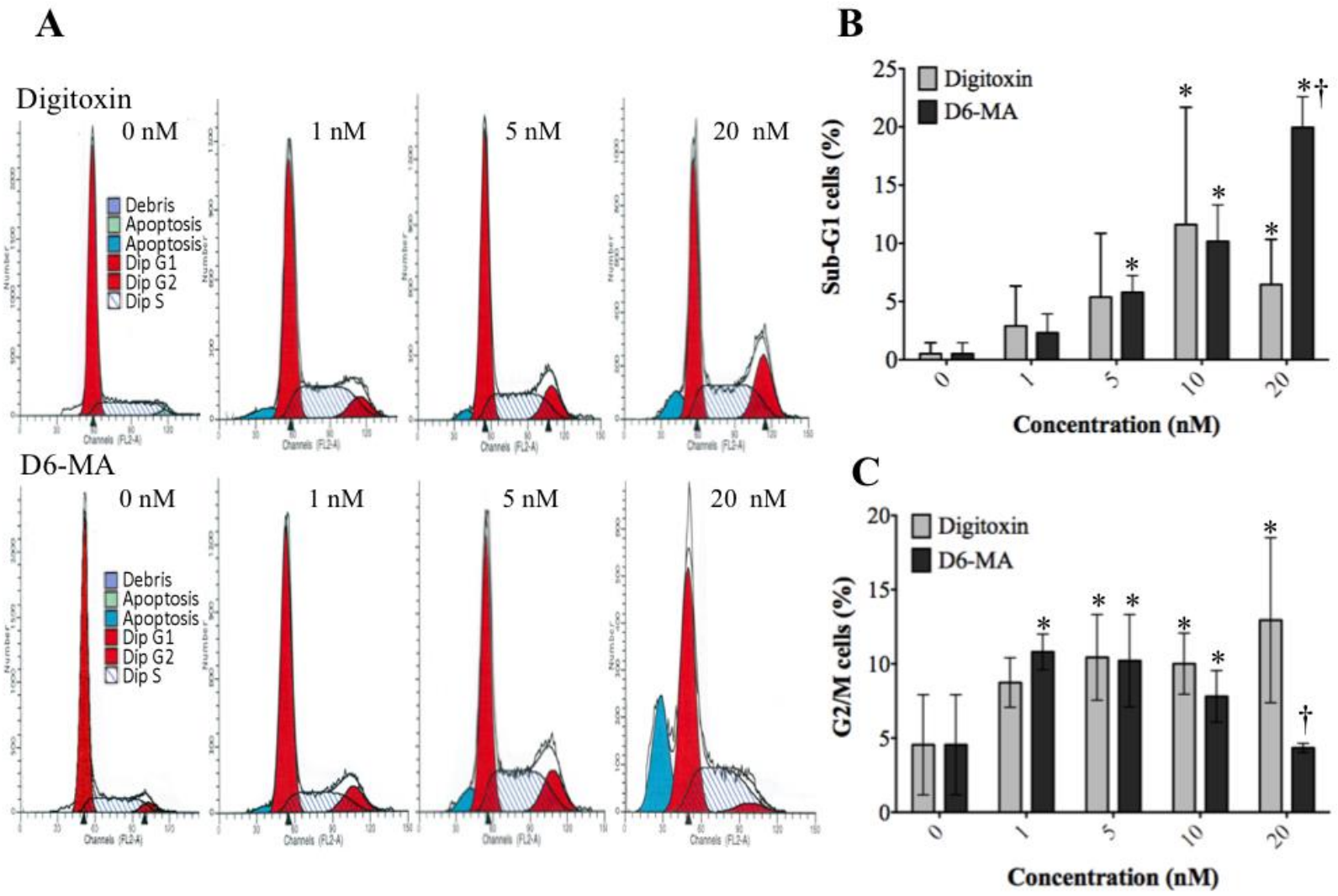
Digitoxin and D6-MA induces extensive caspase-9 cleavage



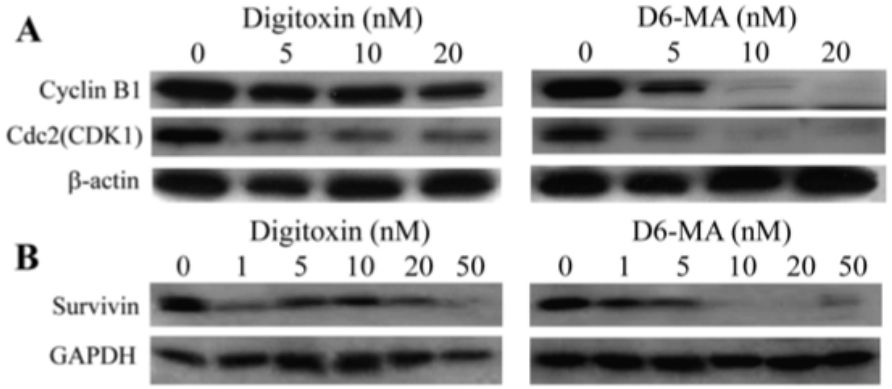
Digitoxin and D6-MA induces expression of cytochrome c

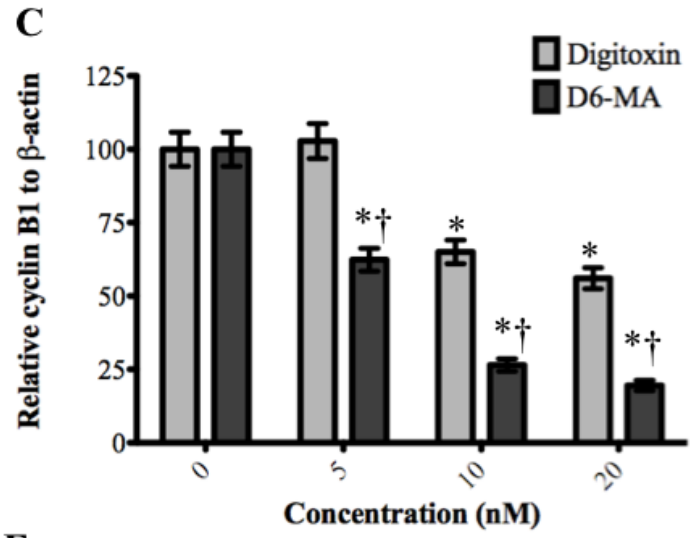


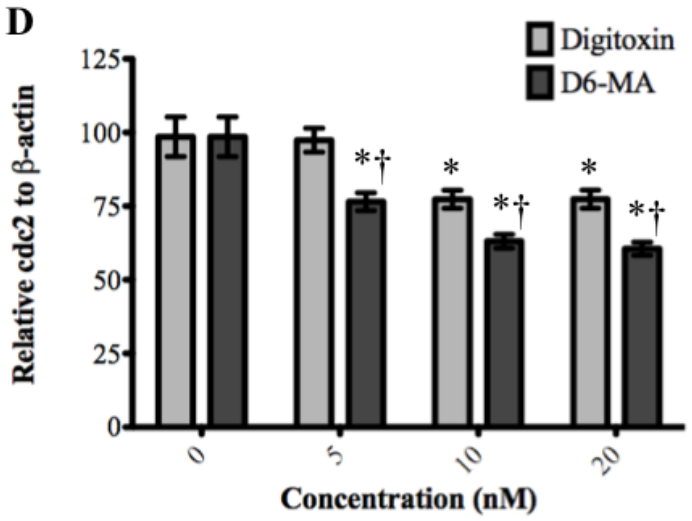
Digitoxin and D6-MA induce G2/M phase arrest

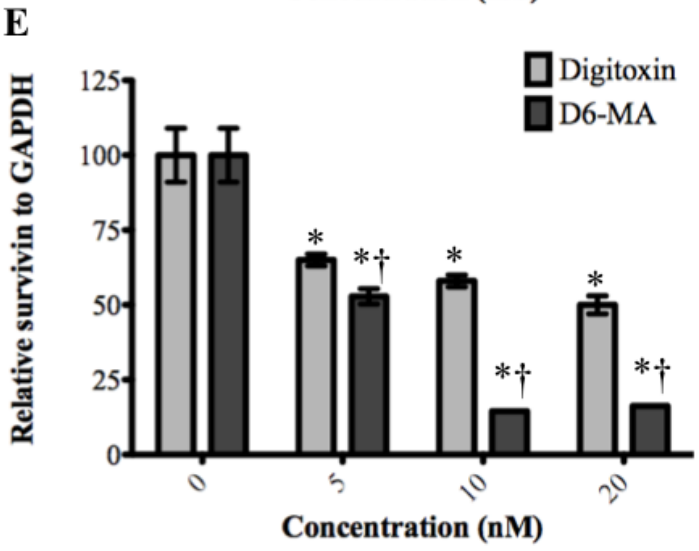


Digitoxin and D6-MA induced down-regulation of cyclin B, cdc2, and survivin

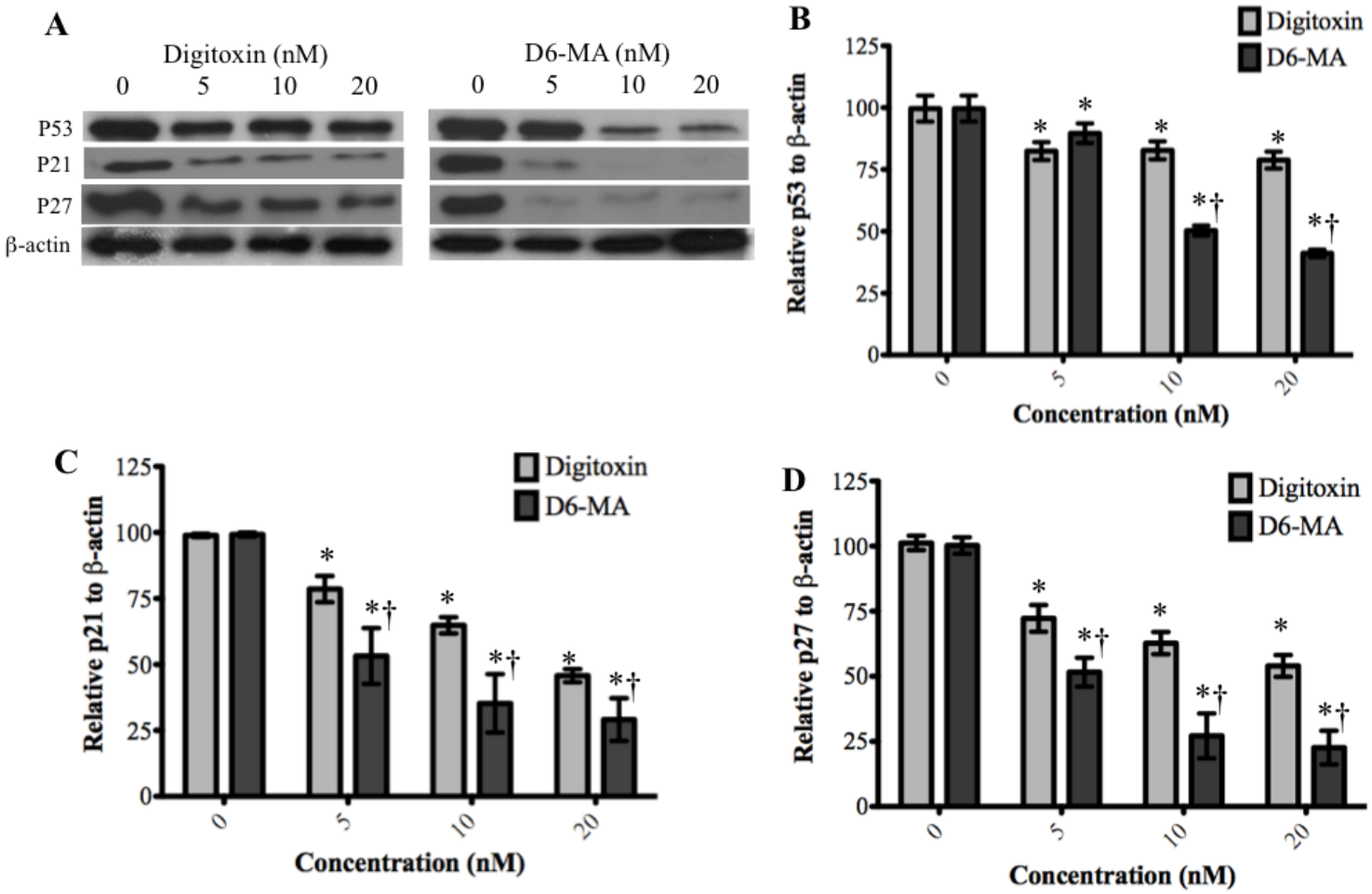




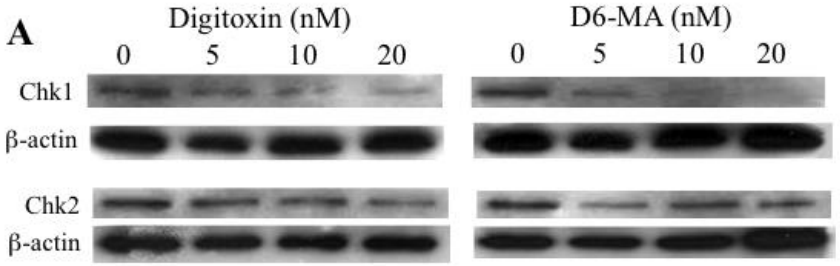


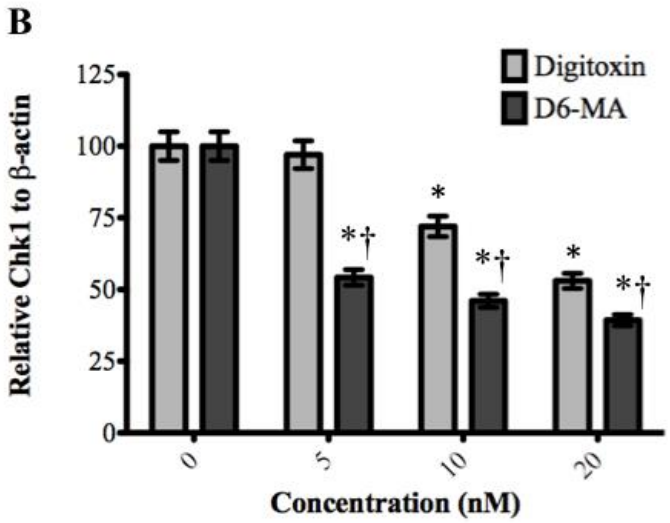


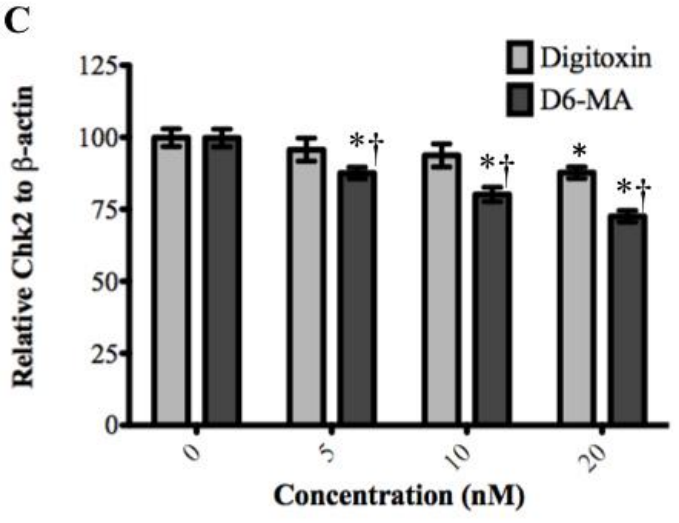
Digitoxin and D6-MA-mediated G2/M phase arrest does not correlate with up-regulation of p53-related signaling



Digitoxin and D6-MA-mediated G2/M phase arrest does not correlate with up-regulation of Chk1/2







Discussion and Conclusions

- Na+/K+ ATPase inhibition by either digitoxin or D6-MA does not account for drug or analog cytotoxic effects.
- Na+/K+ ATPase signalsome activation is a viable possibility.
- Digitoxin and D6-MA are selective to NSCLC cells.
- Digitoxin and D6-MA induced differential caspase-9 cleavage, but not caspase-8.

Discussion and Conclusions

- Digitoxin and D6-MA induce cytochrome c expression which contrasts previous claims of general inhibition of protein synthesis.

- Inhibiting the expression of cyclin B1, cdc2, survivin, and Chk1/2 explain the potent and selective cytotoxic effect of digitoxin and D6-MA at therapeutic concentrations.

- Digitoxin and D6-MA induce G2/M phase arrest and cyclinB1 and cdc2 down-regulation.

- G2/M phase arrest and down regulation of cyclinB1 and cdc2 are not directly controlled by up-regulation of p53 signaling or checkpoint kinase signaling.

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