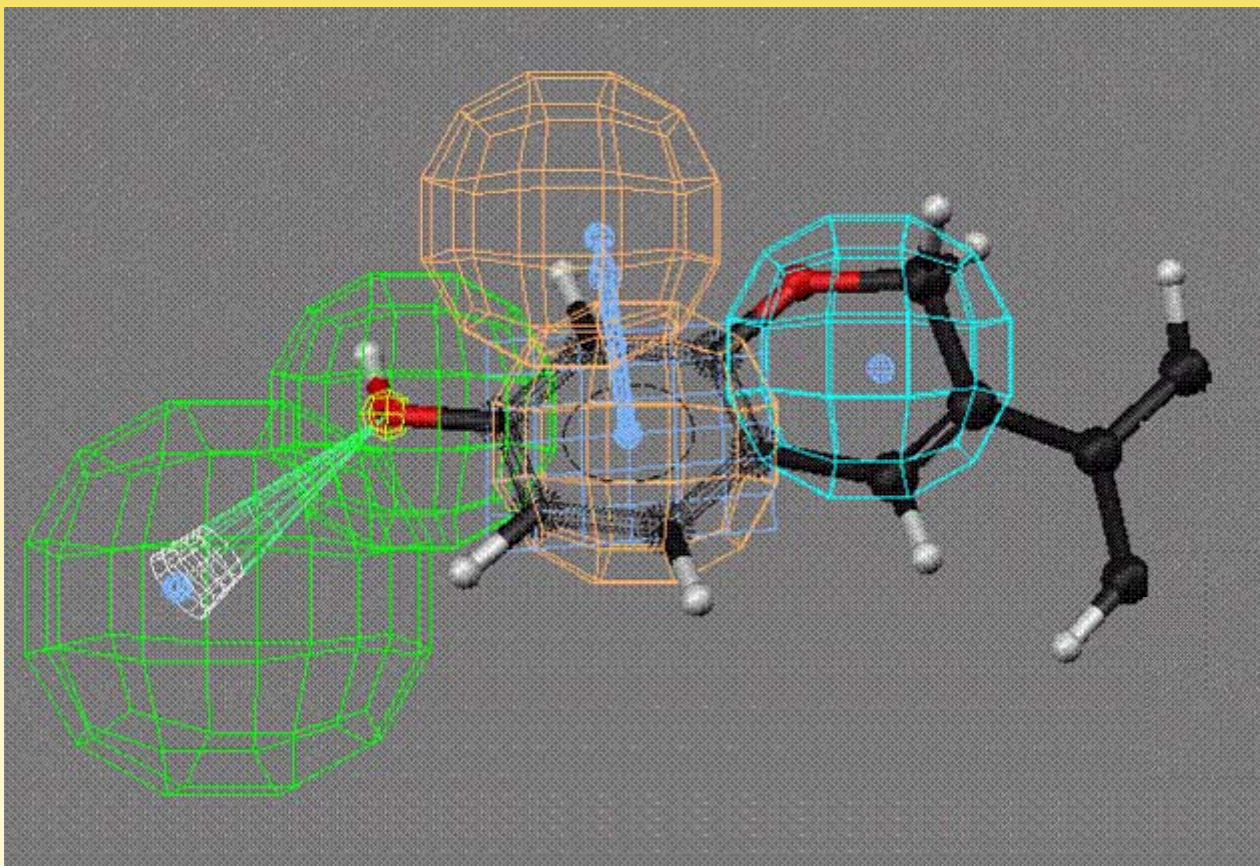


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## Using QSAR to identify the anti-cancer active sites



## Current Drug Candidates

- Phenoxodiol
- NV-196
- NV-143

## Phenoxodiol: potential benefits...

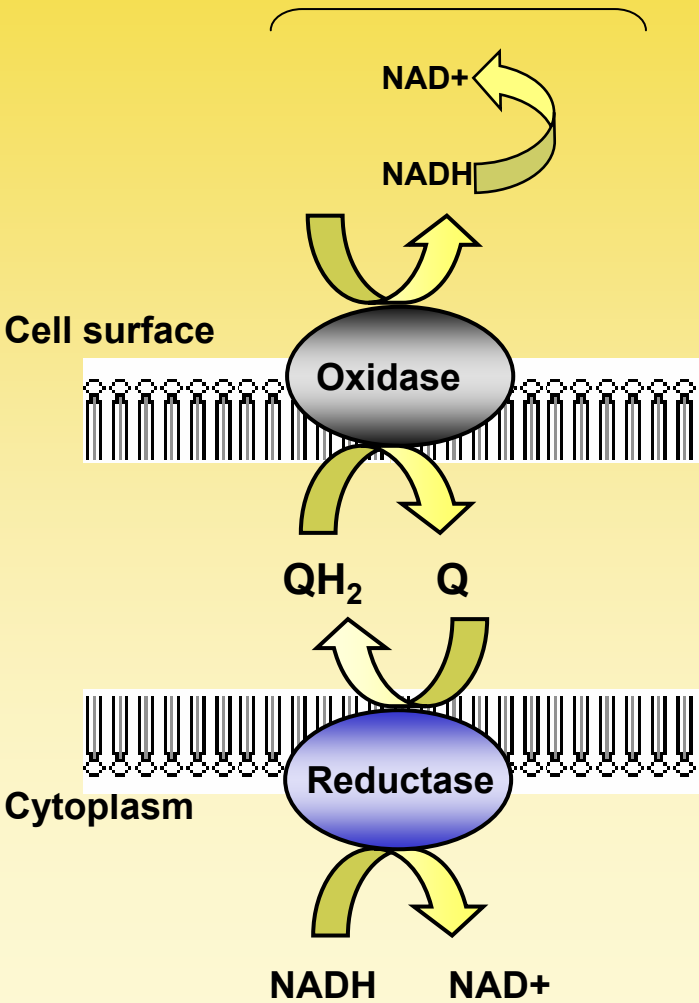
- Safe but effective – no significant drug-related adverse events observed
- Active in broad range of cancers
- Current targets: ovarian, prostate and cervical



## Mechanism of action

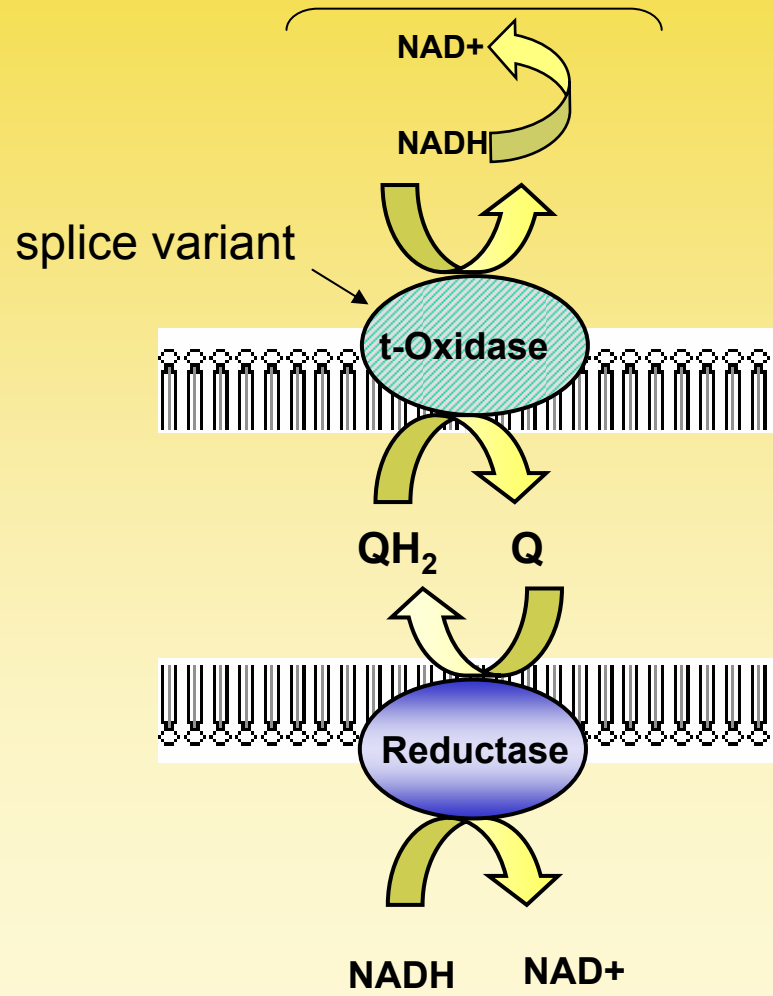
- Phenoxodiol is a pan kinase inhibitor with specific activity for tumor cells as a result of inhibition of a trans-membrane redox pump specific for cancer cells.
- The resulting acidotic effect has been shown to reverse chemo-resistance in tumor cells
- It does this in a highly-selective manner because it only targets the redox pump in cancer cells
- Expected common mechanism of action for the pipeline compounds

NADH oxidase (NOX)

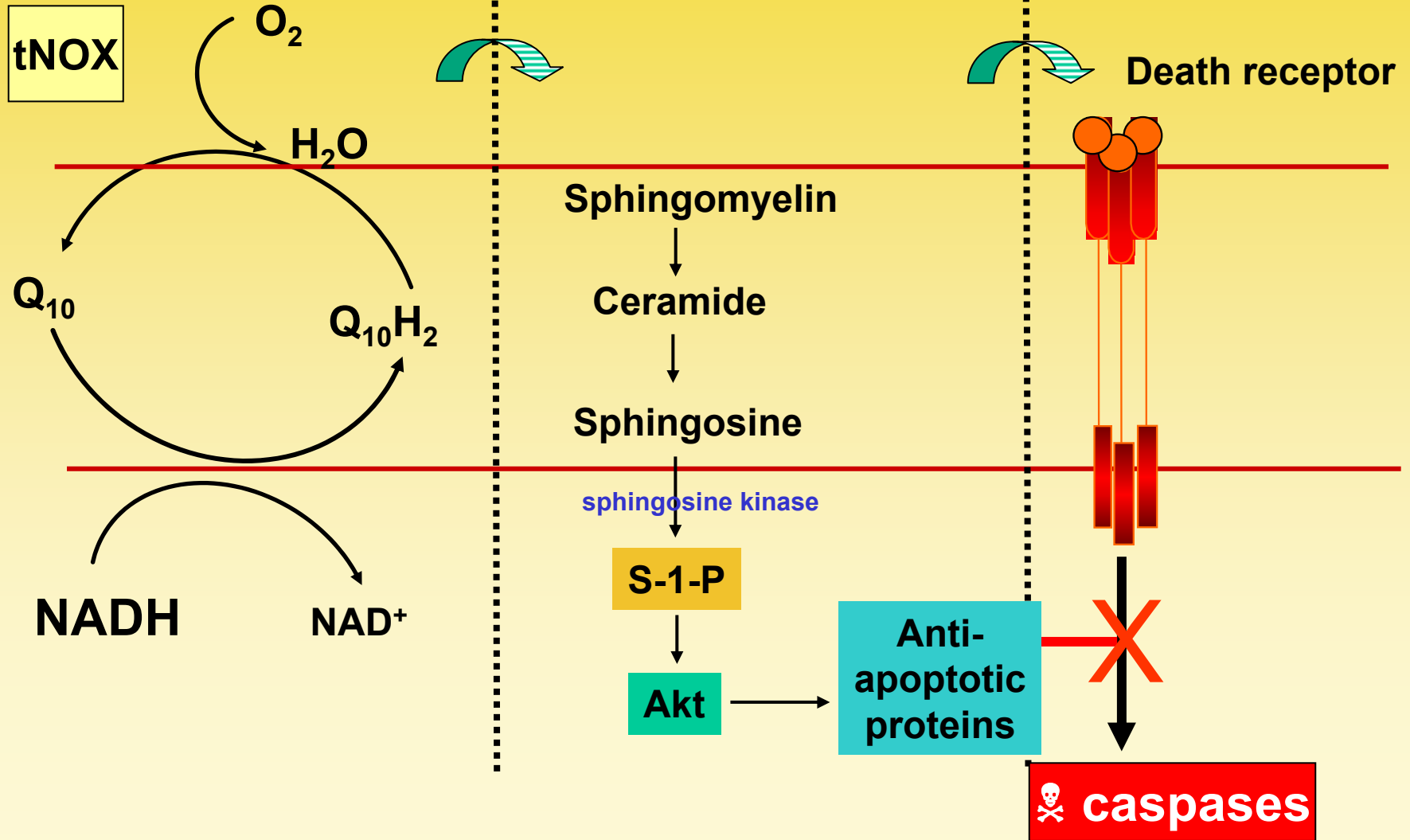


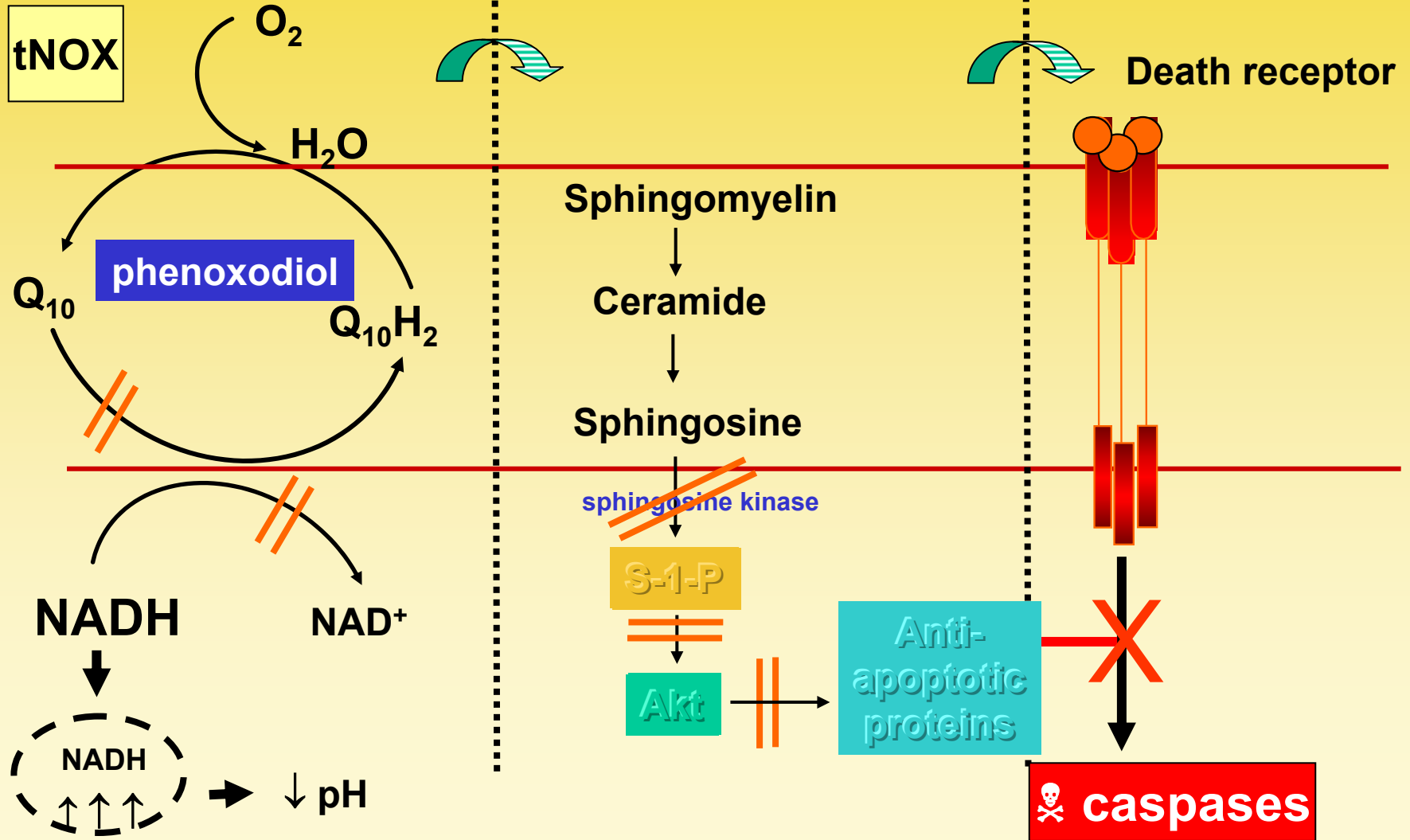
NORMAL CELL

tumor-specific NOX (tNOX)



CANCER CELL





# Phenoxodiol

- On basis of current trial data, FDA granted Fast Track Status for
  - ovarian cancer refractory to chemotherapy
  - hormone refractory prostate cancer
- For ovarian cancer, Phase III OVATURE study, CRO appointed, trial site selection in progress, agreement on protocol reached with FDA under SPA process
- Joint study with Sanofi-Aventis in combination therapy for chemoresistant ovarian cancer at Yale (recruitment at 25% of target)

**Phase II: NV06-0037 Ovarian Cancer Combination Therapy**  
**Preliminary Results Announced 24 March 2006, SGO Meeting**

<b>Best Response (RECIST)</b>	<b>Cisplatin + PXD</b>
No. patients	21
Complete Response	0
Partial Response	6
<b>Objective Response Rate</b>	<b>29%</b>
Stable Disease	9
Progressive Disease	6
<b>Disease Control Rate</b>	<b>71%</b>

## **Phase II: Ovarian Cancer Combination Therapy**

### **Preliminary Results Announced 24 Oct. 2005:**

- Median survival:
  - PXD+cisplatin arm = 62 weeks
  - Compares with median survival reported for patients on standard therapy of only 28 to 40 weeks (*Ann. Oncol.* 15:100-103, 2004)
  
- The PXD/cisplatin combinations were well tolerated, with no unexpected toxicities encountered

## **Phase III Pivotal Study: OVATURE**

Patients with Platinum-Resistant or Platinum-Refractory Late-Stage Epithelial Ovarian, Fallopian or Primary Peritoneal Cancer Following at Least Second Line Therapy

Treatment Group: PXD oral 400mg tid + weekly carboplatin (10xIC<sub>50</sub>)

Control Group: Placebo + weekly carboplatin

- Responded to platinum previously; <6 months since progression following last platinum therapy
- Treatment cycle = 4 wks; CT scan at commencement, then at 8 wk intervals; if response, confirmed by follow-up CT within 4 wks
- N = 235 per group
- Primary endpoint: Progression free survival
- Secondary endpoint: Overall survival
- Interim analysis when all patients recruited and 95 events recorded
- Enrolment commenced

## Phase III Pivotal Study: OVATURE

### Australian Sites:

- 5 sites Sydney (2), Melbourne (1), Brisbane (1), Adelaide (1)
- All sites have been initiated and recruitment commenced
- Drs Michael Friedlander (Prince of Wales, Sydney) and Geraldine Goss (Royal Women's, Melbourne) appointed as co-lead investigators for Aust.

### EU/UK Sites:

	<b>Total contacted</b>	<b>Accepted</b>	<b>Patient No's</b>
Belgium	8	3	28
Netherlands	7	1	10
Poland	7	7	59
Spain	14	5	27
UK	20	4	42
Italy	11	0	6
	<b>67</b>	<b>20</b>	<b>172</b>

- Dr Hani Gabra appointed as lead investigator for UK/EU

### US sites:

- 9 sites confirmed (incl. Yale and US Oncology Research, Inc., network listed as 2 sites but comprising 10-15 hospitals)
- Expected first site start up February 07 with the majority starting in March 07.
- Drs Thomas Rutherford (Yale) and Deborah Armstrong (Johns Hopkins) appointed as co-lead investigators for US.

**Phase II: Prostate Cancer Oral Dose Form**

**Monash Medical Centre, Sir Charles Gairdner Hospital, Aust.:** Oral Phenoxodiol in patients with late stage hormone-refractory prostate cancer (data presented at AACR 18/11/05):

<b>Dose</b>	<b>n</b>	<b>PSA Response</b>	<b>PSA Doubling Time (wks)</b>	<b>Time to Progression (wks)</b>
<b>20</b>	<b>6</b>	<b>0</b>	<b>14</b>	<b>13</b>
<b>80</b>	<b>6</b>	<b>0</b>	<b>22</b>	<b>17</b>
<b>200</b>	<b>5</b>	<b>1</b>	<b>66*</b>	<b>57*</b>
<b>400</b>	<b>9</b>	<b>2</b>	<b>39**</b>	<b>44**</b>

\*One patient remaining on PXD as at Nov 06

\*\* Two patients remaining on PXD therapy as at Nov 06

## **Prostate Cancer: Phase II Studies Planned**

Strategy to be pursued as Phase II study:

PXD as first-line drug therapy in men who have “biochemical recurrence” (rising PSA levels) following prostatectomy or irradiation

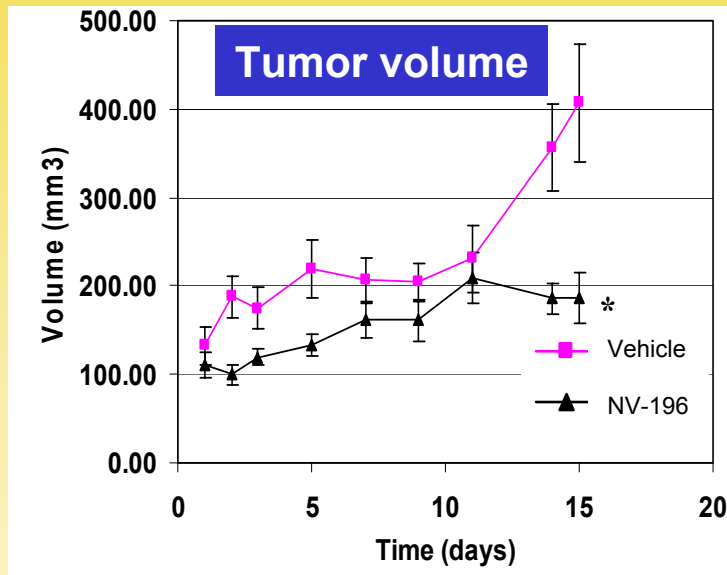
**Phase I: Cervical Cancer Oral Monotherapy (Yale University)**

Patient Number	Dose	% Change in Tumor Size (RECIST)	Classification
01	50	8.89%	SD
02	50	7.78%	SD
03	50	34.18%	DP
04	50	13.43%	SD
05	50	-4.76%	SD
06	50	0.00%	SD
11	200	15.48%	SD
13	200	-16.67%	SD
14	200	0.66%	SD
15	200	-7.55%	SD
16	200	-4.35%	SD
18	200	-17.65%	SD
19	200	10.81%	SD
20	200	11.94%	SD
21	400	5.19%	SD
22	400	36.51%	DP

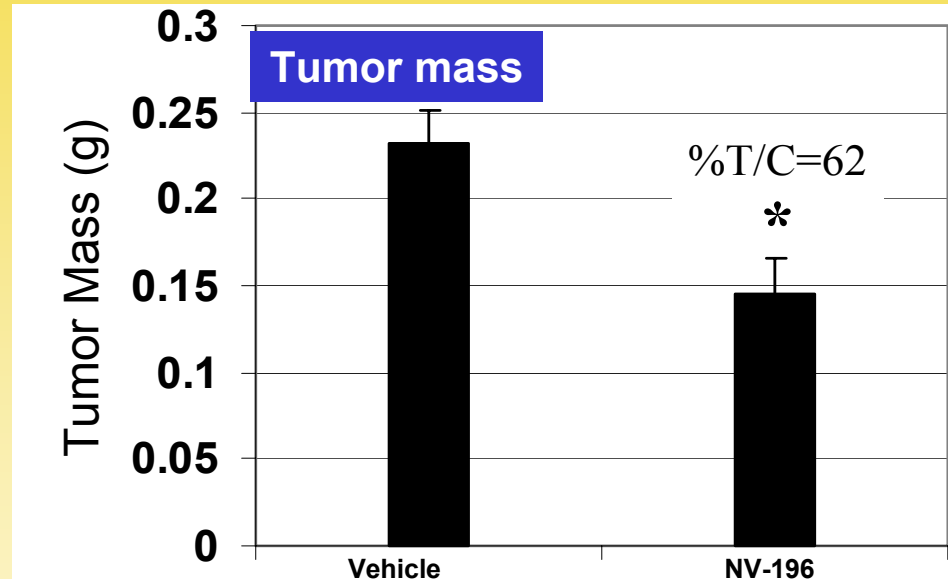
- 14/16 SD despite relatively short treatment time (28-day)
- No phenoxodiol-related toxicity was observed in any patients
- Study continues at 400 mg per dose

**NV-196** : Targets: pancreatic cancer, cholangiocarcinoma

NV-196 in vivo Efficacy in HPAC tumor bearing mice



100 mg/kg, p.o.Qdx15

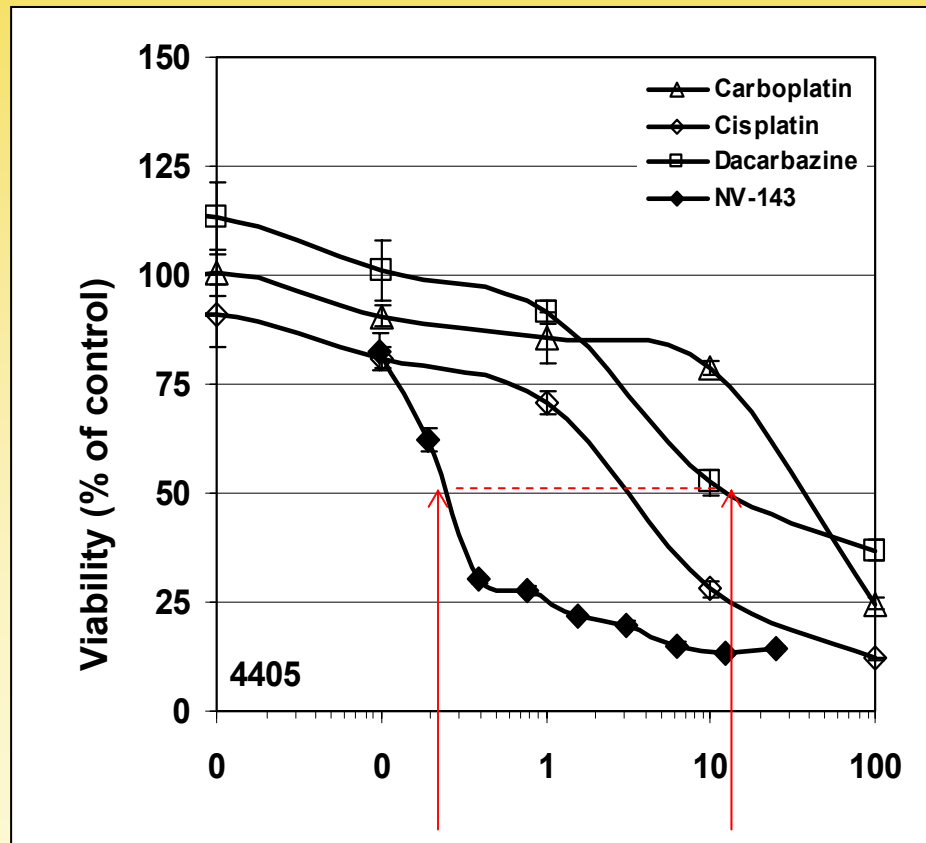
**NV196.001: Phase Ib - Bio-availability, Pharmacokinetic and Acute Safety**

Oral NV-196 in Patients with Solid Tumors, Brisbane Mater, Hospital

Day 1, 100 mg single oral dose; Day 3-8 100 mg 8-hourly (300mg/day total dose)  
 Target 12 patients.

## NV-143 : Targets: malignant melanoma

NV-143 in vitro efficacy against the melanoma cell line 4405 compared to other cytotoxic drugs



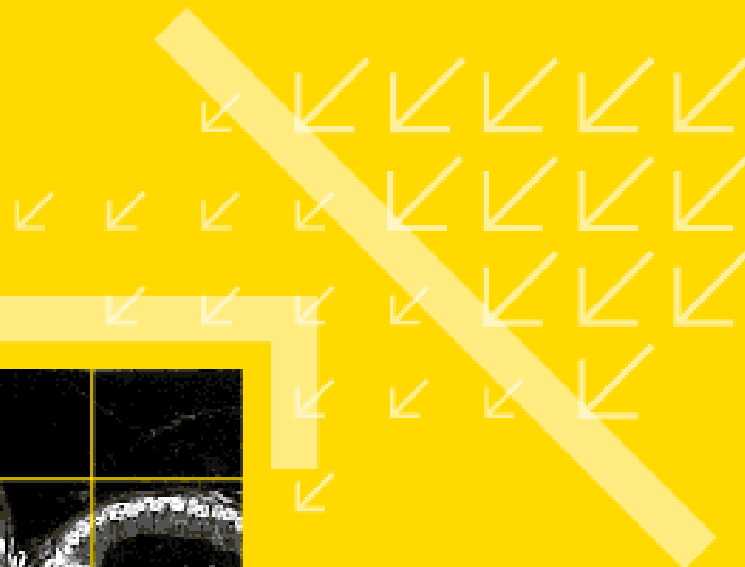
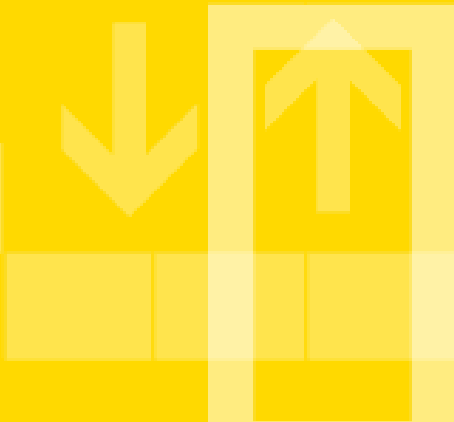
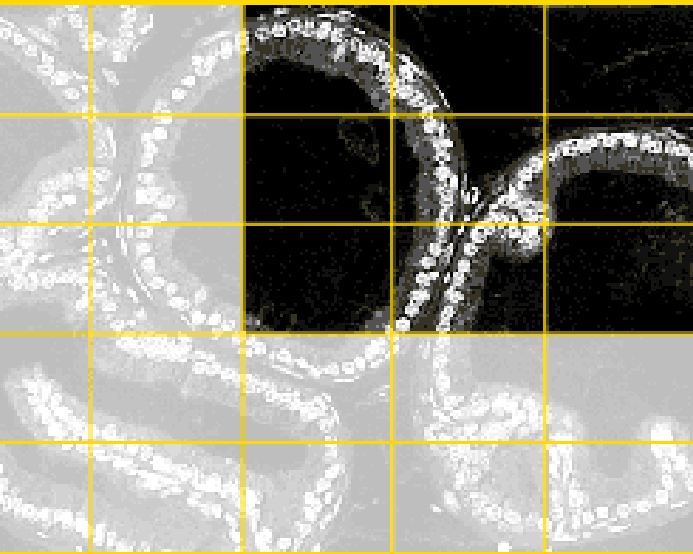
NV-143 is ~100-fold more effective than dacarbazine (standard of care in melanoma)

# Clinical Progress Summary

		Preclinical	Phase I	Phase II	Phase III	Target	
MSHL	<b>Phenoxodiol:</b>					Ovarian, prostate, cervical cancers	
	Ovarian Cancer						
	Prostate Cancer						
	Cervical Cancer						
	<b>NV-196</b>					Pancreatic cancer, cholangiocarcinoma	
	<b>NV-143</b>					Melanoma	
NOVOGEN	<b>NV-128</b>					NSCLC, breast	

MSHL has first and last refusal rights over any Novogen oncology compound at entry to clinical phase development

Novogen synthetic chemistry program has produced over 220 novel isoflavonoid compounds



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