Application of Novel Therapeutic Approaches in Melanoma

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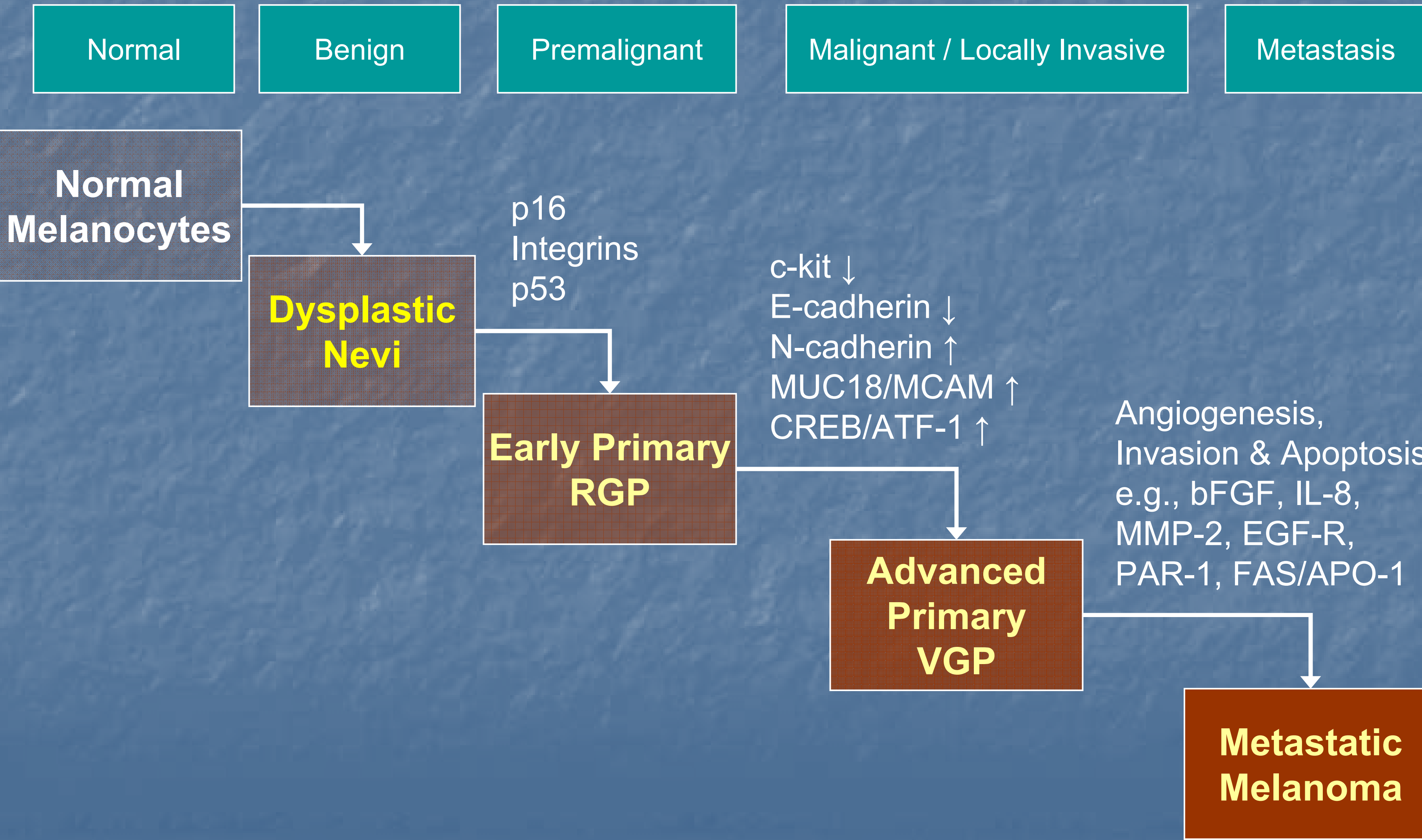
Melanoma Statistics

- Median age at presentation – 45-55 years
- Incidence: 2003 – 54,200 cases
- 2006 (projected) 62,190
  - 5th among men
  - 7th among women
- Increasing in incidence in men and women
- Mortality (2003) – 7600 patients, (2006) – 8100 projected deaths
- 1 in 17 white Australians

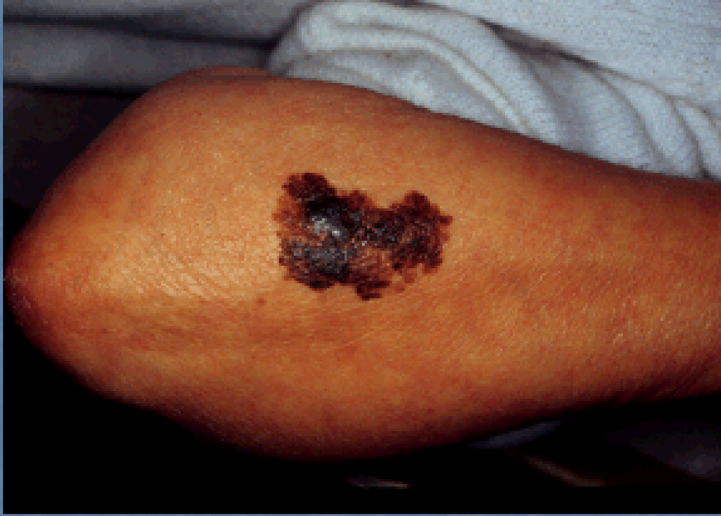
Tumorigenesis in Melanoma

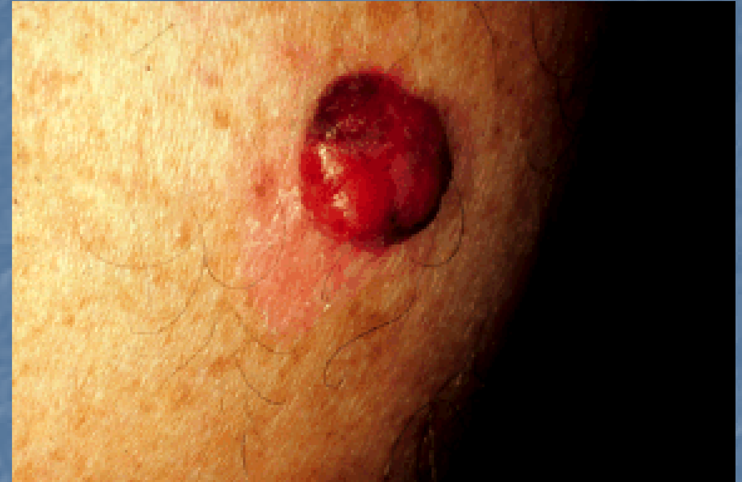


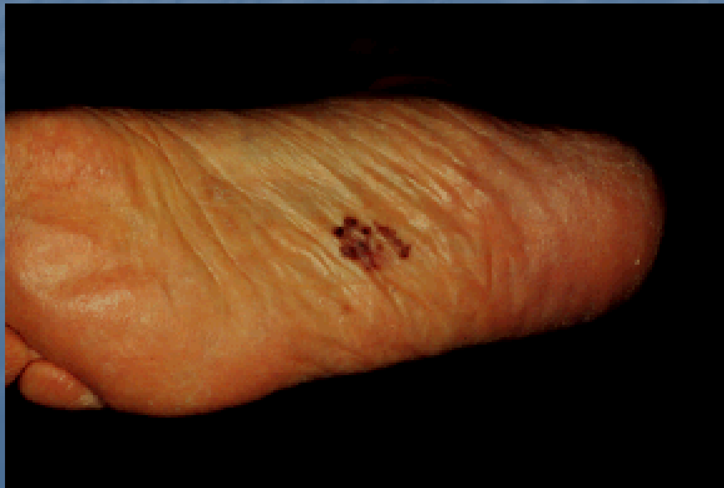
Risk Factors for Melanoma

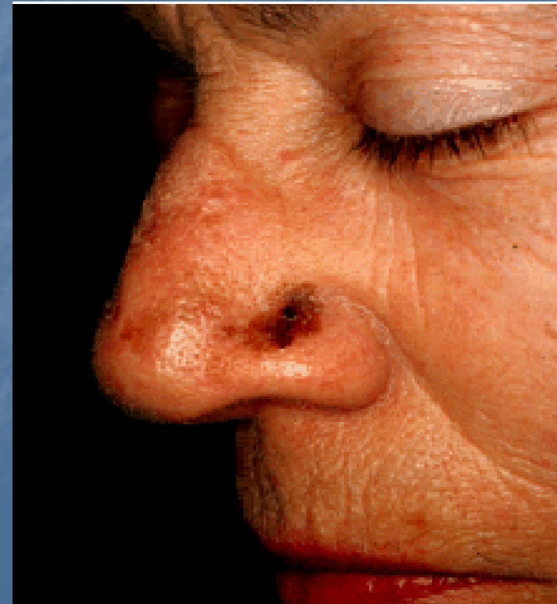
- Genetics & Environment
  - Race (Caucasians 5-20 fold increased risk over Africans, East Asians, Hispanics)
  - Geographic location (proximity to equator)
- Genetic Factors & Risk
  - Skin pigmentation
  - Family history of melanoma
  - Density and type of nevi (common, ‘atypical’)
  - Propensity to sunburn
  - p16 and CDK4 mutated in up to 50%
- Environmental Factors
  - Occupation (white collar greater risk than blue collar) → “intermittent sun exposure” hypothesis
  - Recreational sun exposure
  - Ozone depletion

Melanoma Subtypes









Relationship between the Stage of Melanoma and Survival

Probability of Survival

1.0

0.5

0.0

Stage I

Stage II

Stage III

Stage IV

0 1 5 10 15

Years after Diagnosis

Tsao, H. et al. N Engl J Med 2004;351:998-1012

The NEW ENGLAND JOURNAL of MEDICINE

Primary therapy

- Suspicous lesions: Biopsy. If positive, wide local excision
- Margins: *in situ:* 0.5cm

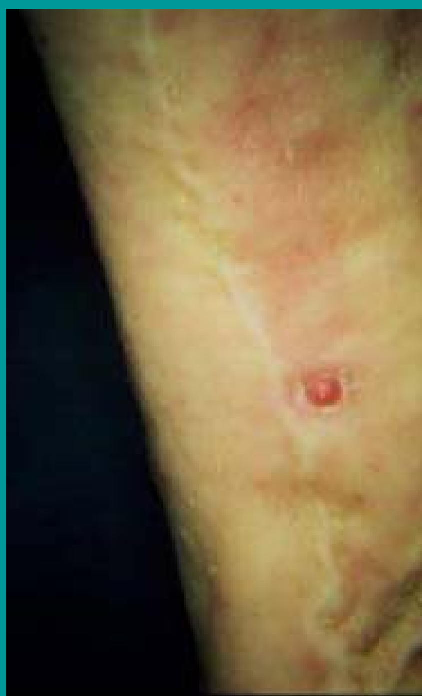
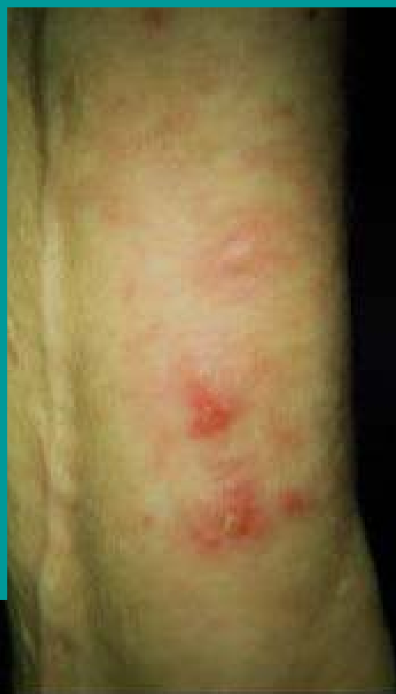
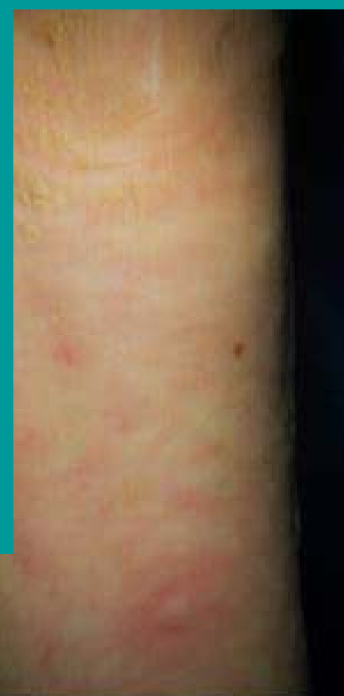
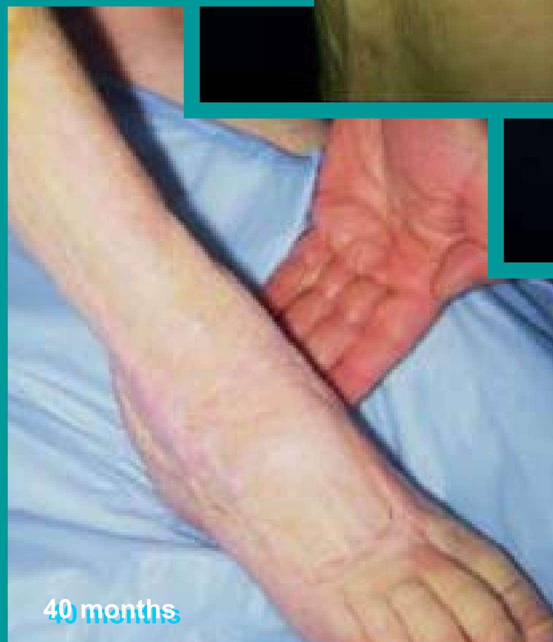
  <1mm – 1cm margins

  >=1mm – 2cm margins (based on a randomized trial looking at tumors over 4mm)

Thicker lesions – lymph node biopsy and removal

In-transit metastases

- In the limb: isolated limb perfusion with chemo, cytokines with/without hyperthermia
- High response rates in phase II studies, up to 60%
- Agents used: thiotepa, DTIC, melphalan, CDDP, carbo and mustard. Cytokines: IFN, TNF alpha





40 months

Standard Systemic Treatment for Metastatic Melanoma

- Chemotherapy
  - Alkylating agents (dacarbazine, temozolomide, BCNU)
  - Cisplatin
  - Microtubule toxins (vinblastine, paclitaxel)
- Interferon-alfa
- Interleukin-2 (high-dose)

Table 4. Key Randomized Trials for Stage IV Melanoma.*

Study	Trial Regimen	No. of Patients	Response Rate	Median Survival
			%	*mo*
Costanzi et al.	Carmustine, hydroxyurea, and dacarbazine with or without BCG	256	29	With BCG, 6.7; without BCG, 6
	versus			
	Dacarbazine and BCG	130	18	6.9
Buzaid et al.	Cisplatin, vinblastine, and dacarbazine	46	24	6
	versus			
	Dacarbazine	45	11	5
Chapman et al.	Cisplatin, dacarbazine, carmustine, and tamoxifen	108	18	7
	versus			
	Dacarbazine	118	10	7
Cocconi et al.	Dacarbazine and tamoxifen	60	28†	10.7‡
	versus			
	Dacarbazine	52	12	6.4
Rusthoven et al.	Cisplatin, dacarbazine, carmustine, and tamoxifen	98	30	Men, 6.4; women, 6.9
	versus			
	Cisplatin, dacarbazine, and carmustine	97	21	Men, 6.4; women, 7.1
Falkson et al.	Dacarbazine and interferon alfa	30	53	17.6§
	versus			
	Dacarbazine	30	18	9.6
Falkson et al.	Dacarbazine, interferon alfa with or without tamoxifen	126	16	With tamoxifen, 9.5; without tamoxifen, 9.3
	versus			
	Dacarbazine with or without tamoxifen	129	21	With tamoxifen, 8; without tamoxifen, 10
Keilholz et al.	Interleukin-2 (decrescendo regimen) and interferon alfa	66	18	9
	versus			
	Cisplatin, interleukin-2, and interferon alfa	60	35; overall survival same	9
Rosenberg et al.	Cisplatin, dacarbazine, and tamoxifen	52	27	15.8
	versus			
	Cisplatin, dacarbazine, tamoxifen, high-dose interleukin-2, and interferon alfa	50	44; overall survival worse	10.7
Eton et al.	Cisplatin, vinblastine, and dacarbazine	92	25	9.5
	versus			
	Cisplatin, vinblastine, dacarbazine, interleukin-2, and interferon alfa (sequential)	91	48	11.8
Keilholz et al.	Cisplatin, dacarbazine, and interferon alfa	180	23	9.0
	versus			
	Cisplatin, dacarbazine, interferon alfa, and interleukin-2	183	21	9.0
Atkins et al.	Cisplatin, vinblastine, and dacarbazine	201	11	8.7
	versus			
	Cisplatin, vinblastine, dacarbazine, interleukin-2, and interferon alfa (concurrent)	204	17	8.4

* All study data are taken from Atkins et al.[86] BCG denotes bacille Calmette–Guérin.
† P=0.03.
‡ P=0.02.
§ P<0.01.

Conclusions

Standard of care

- Early stage disease:

Local therapy is a wide excision and sentinel lymph node biopsy. Radiation has no role in adjuvant treatment. Adjuvant interferon is controversial, but FDA approved.

Metastatic disease:

Standard of care is a clinical trial.

High dose IL-2 is standard for a subset of patients with an excellent performance status.

Melanoma research activity at Yale

- New disease unit head
- Recent recipients of SPORE grant, as well as other melanoma-specific NIH funding
- Volume has increased 50% over past 2 years
- Number of patients enrolled in clinical trials has quadrupled in 2 years
- Dedicated pathologists, scientists, clinical oncologists and surgeons

Carboplatin Resistance and XIAP Over-expression in Melanoma are Reduced by Phenoxodiol *in Vitro*

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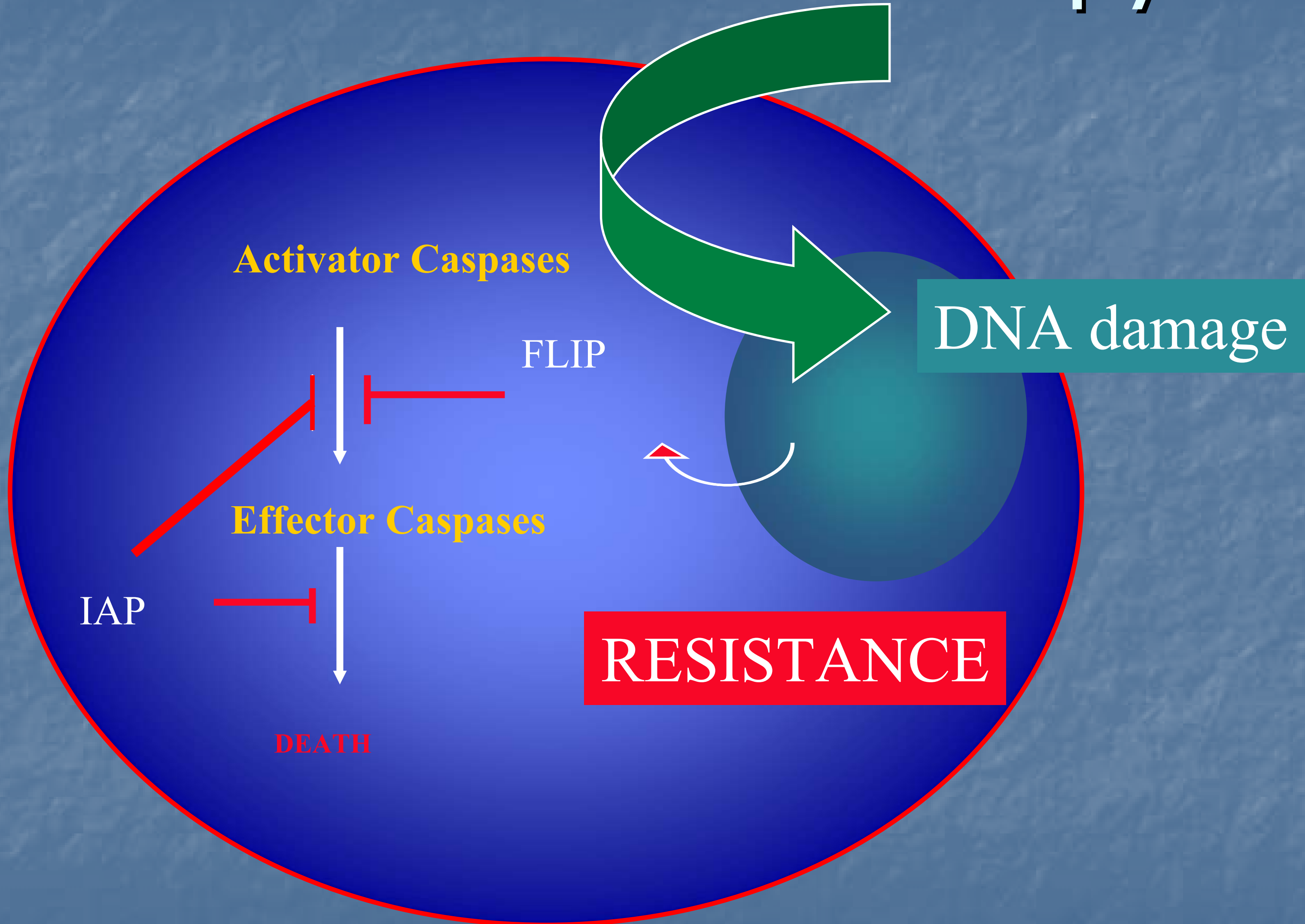
Rationale

- Melanoma is relatively resistant to chemotherapy
- Response rates to single agent chemotherapy or polychemotherapy range from 7%-25%
- Platinum drugs are among the commonly used agents, response rates of 10-16% for cisplatin or carboplatin
- New strategies are needed to improve response to chemotherapy

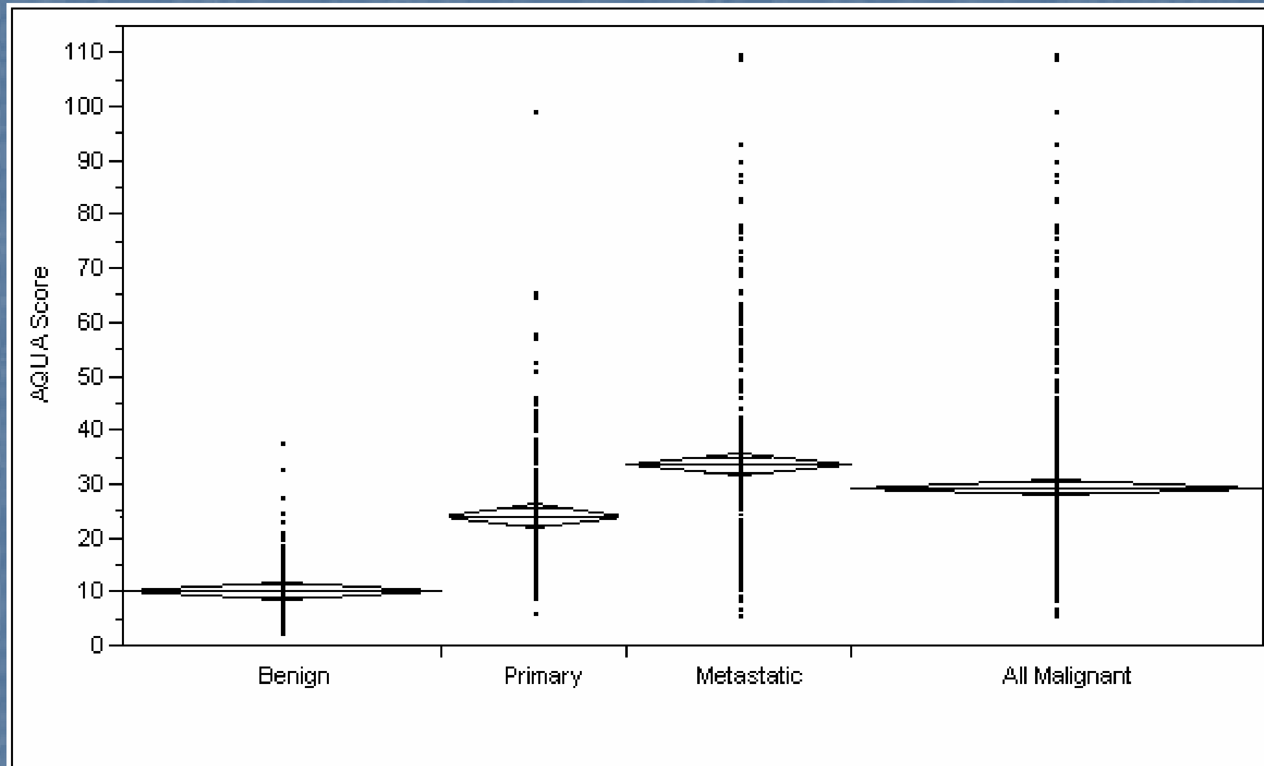
Chemotherapy



Hypothesis

- Chemoresistance in melanoma is due to up-regulation of XIAP
- Resistance might be reversed with drugs that target XIAP.

AQUA analysis of 436 melanomas and 336 nevi

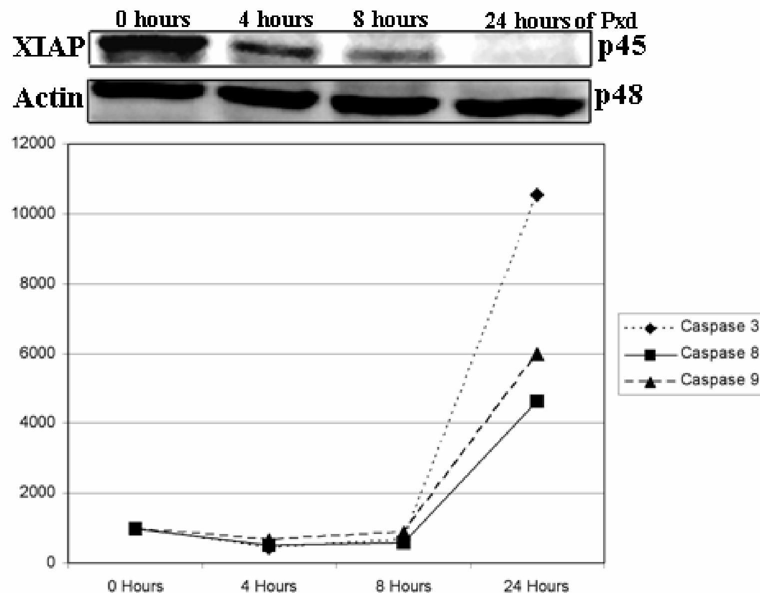


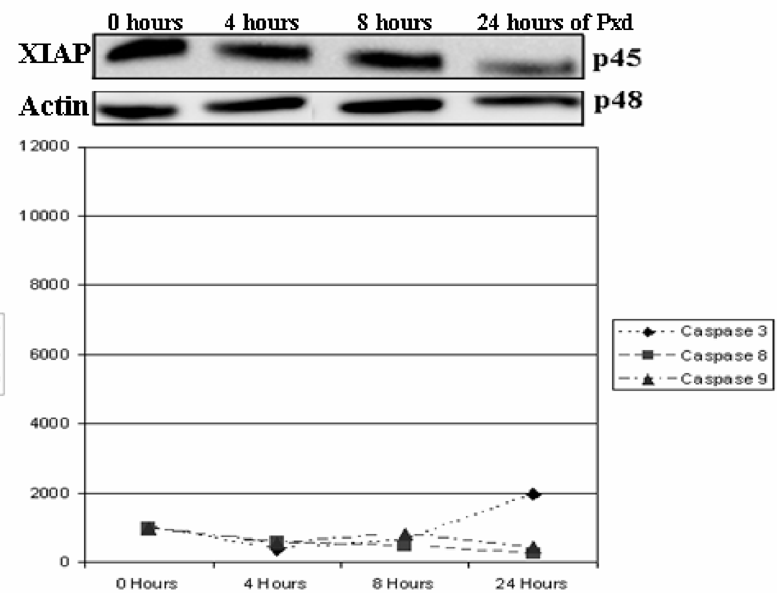
XIAP expression is significantly higher in melanomas than in nevi (P<0.0001), and higher in metastatic than in primary specimens (P<0.0001).

Prior experience with Phenoxodiol in Ovarian Cancer Cells

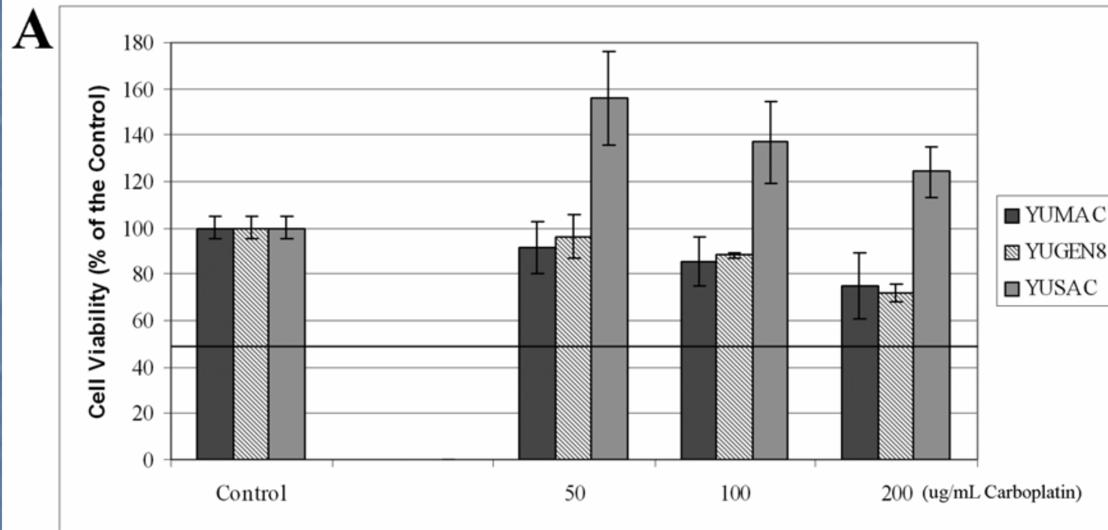
- XIAP levels increase in ovarian cancer cells as they acquire platinum resistance
- Platinum resistance in cancer cells can be reversed with Phenoxodiol
- Precise mechanism of action of Phenoxodiol is unknown, but it causes XIAP degradation.
- Phenoxodiol is currently in clinical trials for ovarian cancer patients resistant to platinum
- No significant drug related adverse events with Phenoxodiol alone
- Toxicities on combination therapy similar to that seen with Cisplatin alone
- Response is associated with decreases in XIAP levels

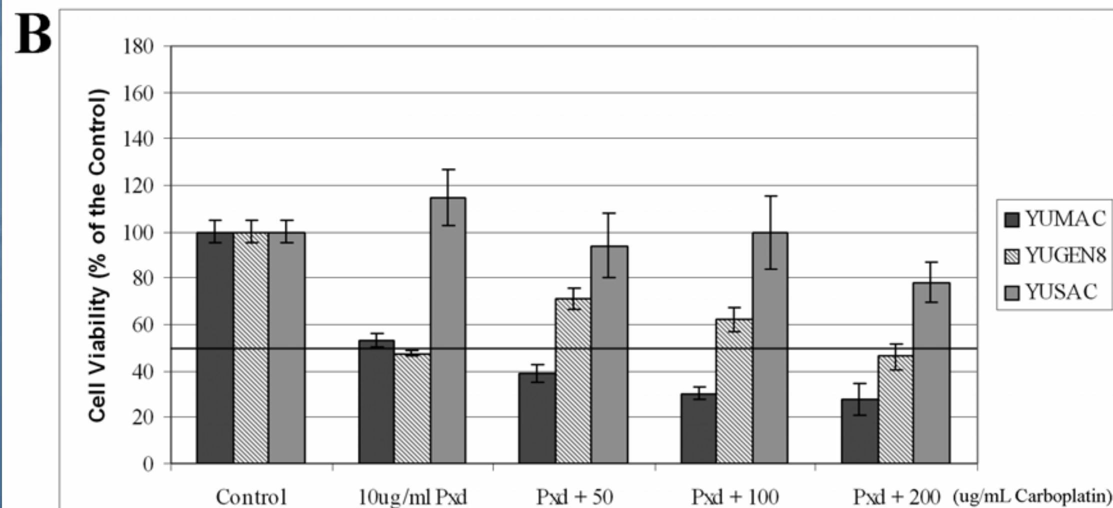
XIAP degradation and Caspase activation in Pxd sensitive and Pxd resistant melanoma cells





Phenoxodiol sensitizes melanoma cells to Carboplatin





Conclusions

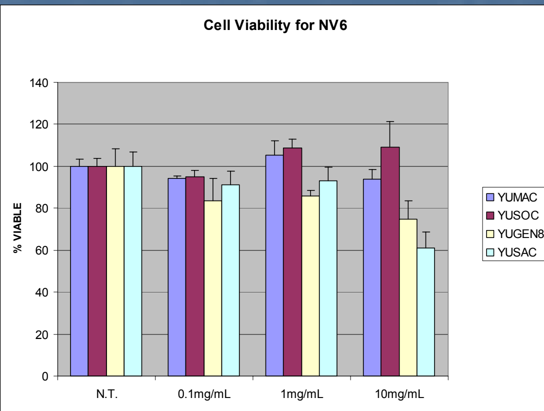
- XIAP expression is higher in melanoma specimens than in nevi, and expression is associated with disease aggression
- Treatment of melanoma cell strains with Phenoxodiol can result in XIAP degradation and sensitization of cells to Carboplatin

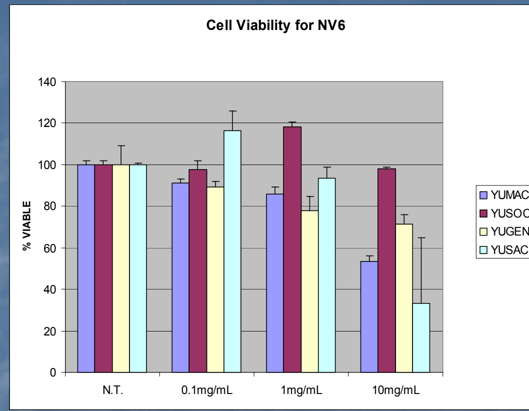
Ongoing Studies

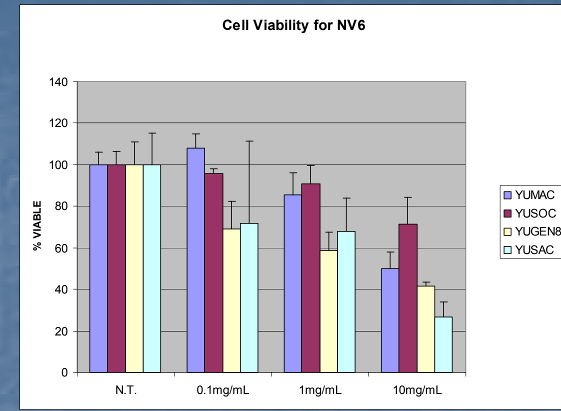
- NV-196, another investigational isoflavone analogue, currently in Phase I studies in Australia.
- NV-143, a metabolite of NV-196, still undergoing pre-clinical evaluation.

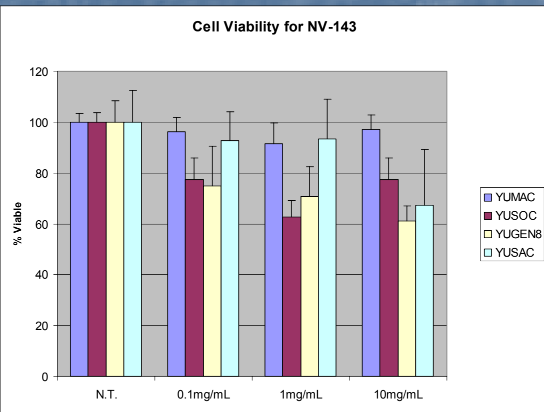
3 Day Drug Treatment: NV-6,NV-143, NV-196 Cell Viability Assay

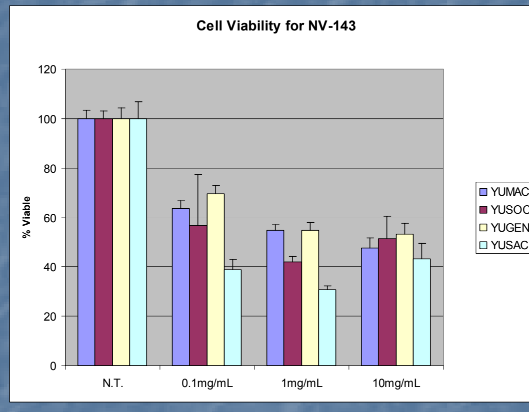
DAY 1 | DAY 2 | DAY 3

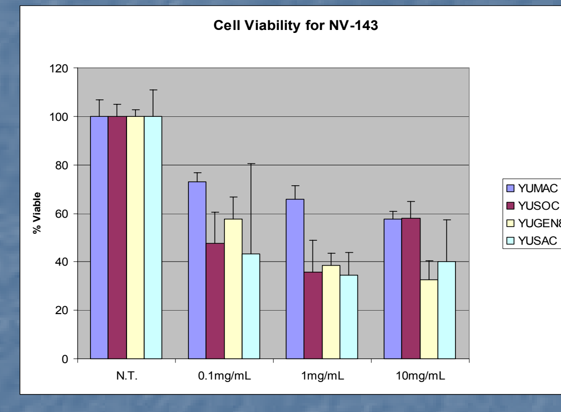


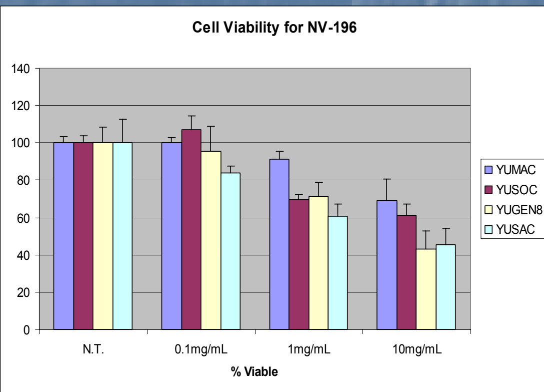


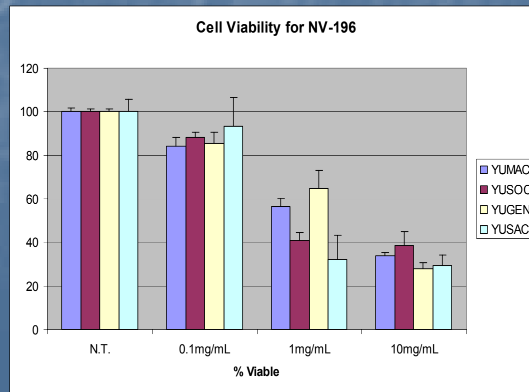


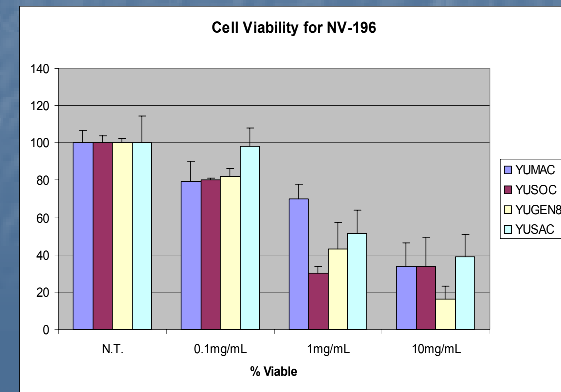




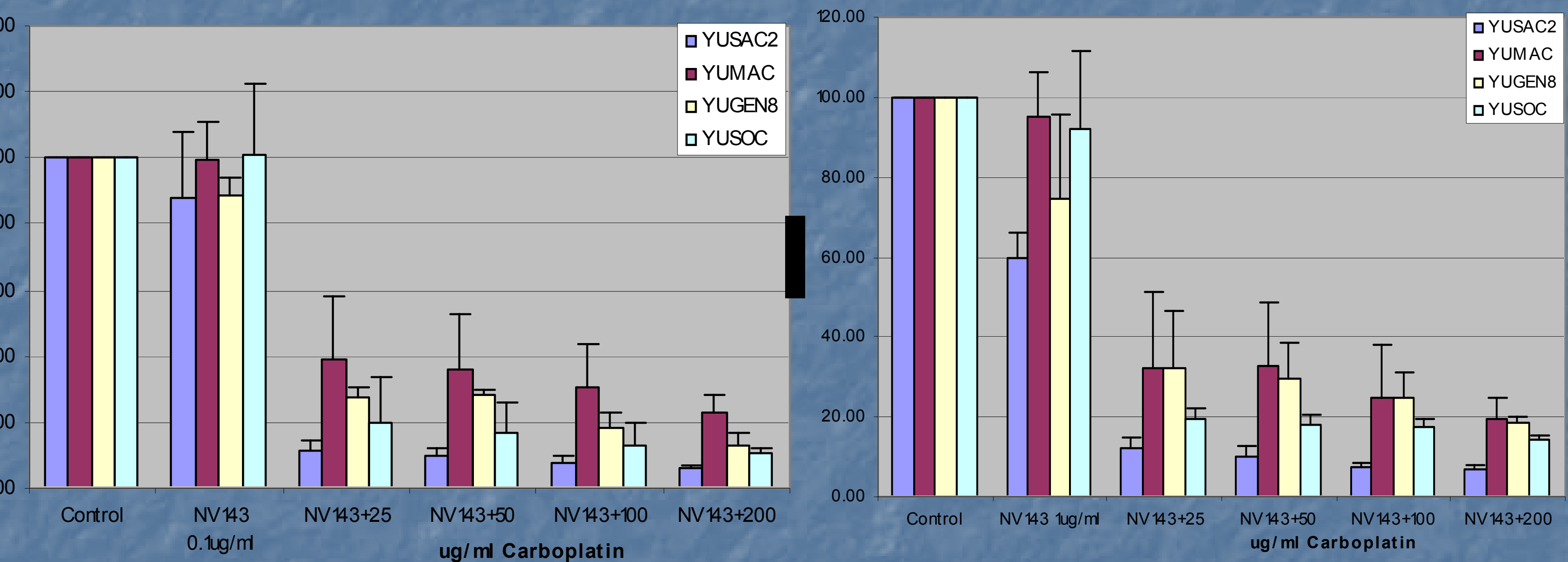




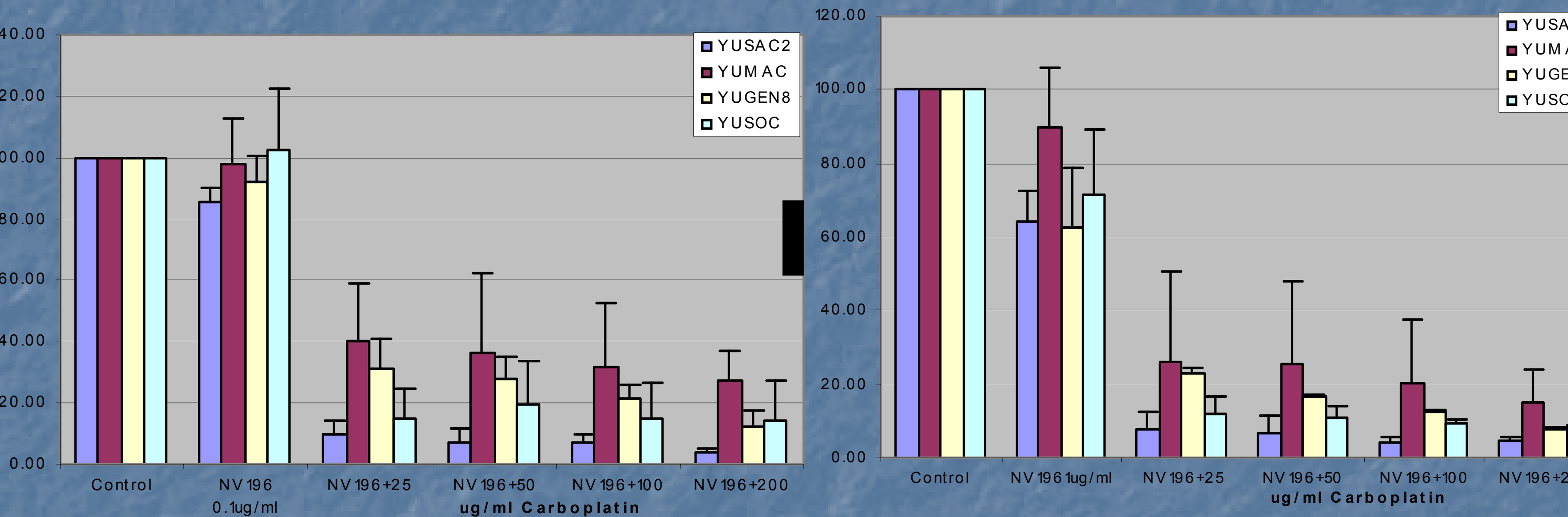




NV-143 as a sensitizer to Carboplatin in melanoma cells



NV-196 as a sensitizer to Carboplatin in melanoma cells



Ongoing and future studies

- Determination of mechanism of action of NV-143 and NV-196 as chemotherapy sensitizers
- Verification of synergism of NV-143 and NV-196 with Carboplatin in mice – David Brown
- Clinical trial with combination of NV-143 OR NV-196 and Carboplatin in humans – metastatic disease and/or patients with in-transit metastases prior to surgery.

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