Antiangiogenesis Effects of Chemotherapy

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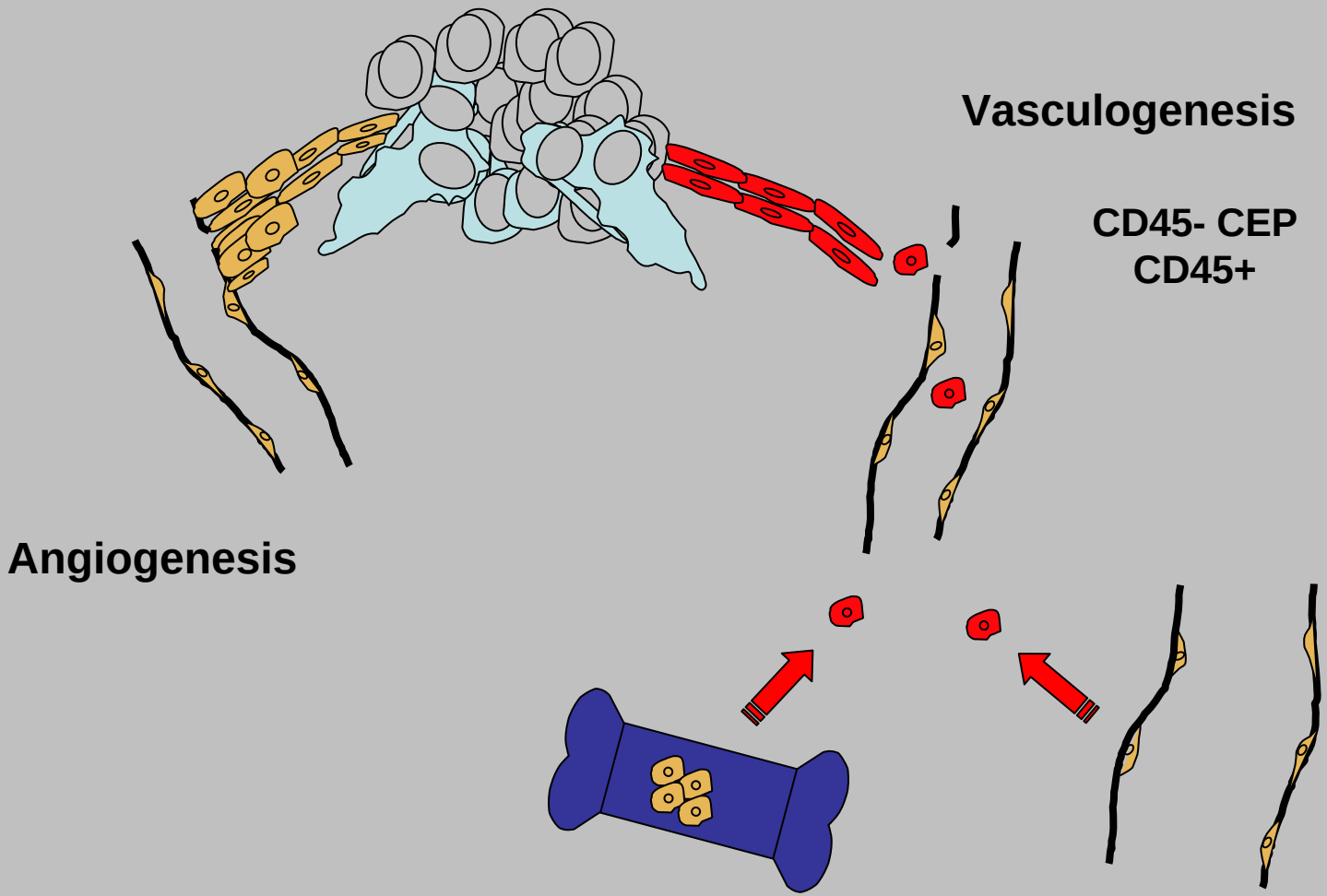
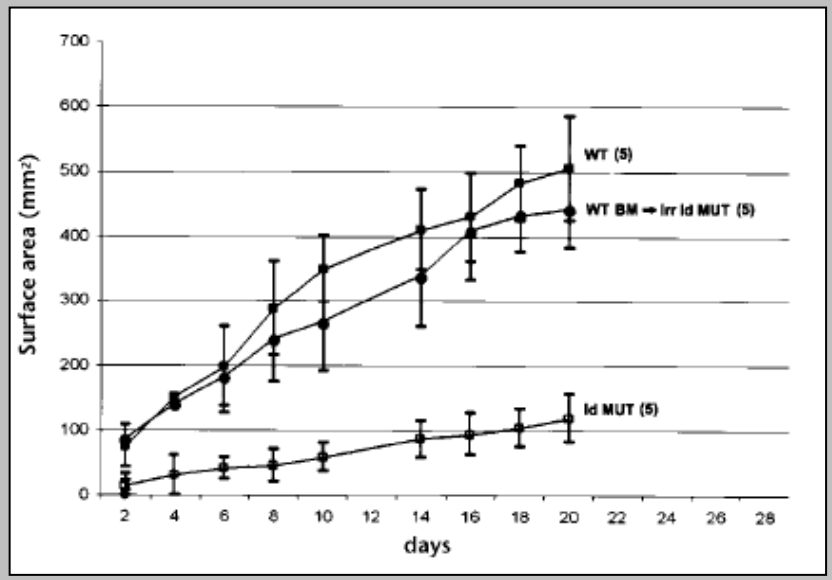
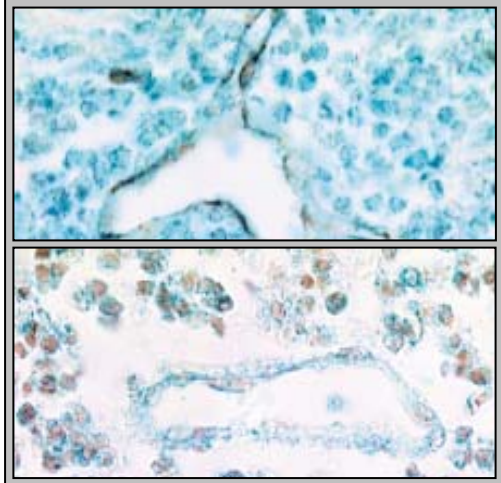
Mechanisms of Tumor Vascular Development

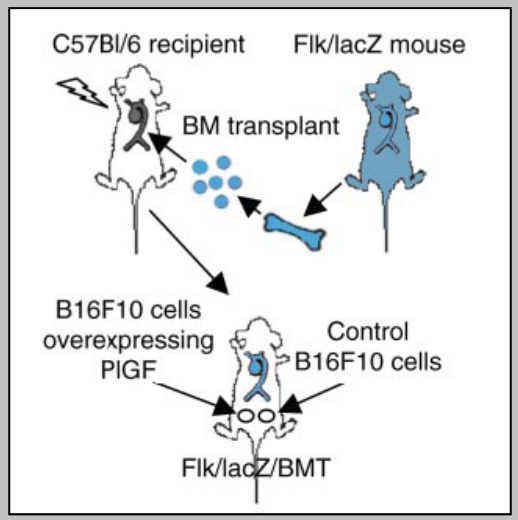


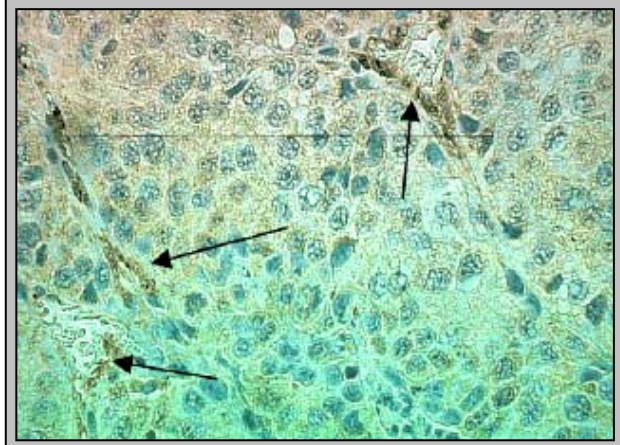
Myeloid Progenitor Cells Promote Vasculogenesis





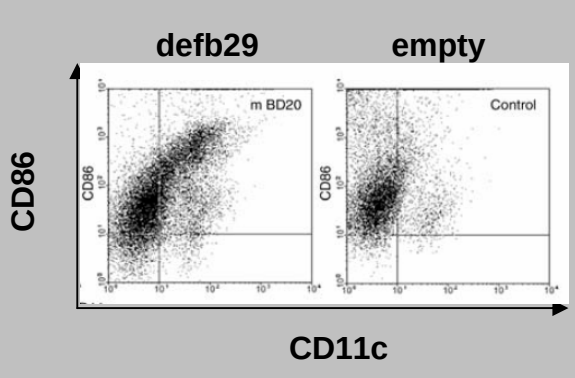
Lyden et al, *Nature Med* 2001

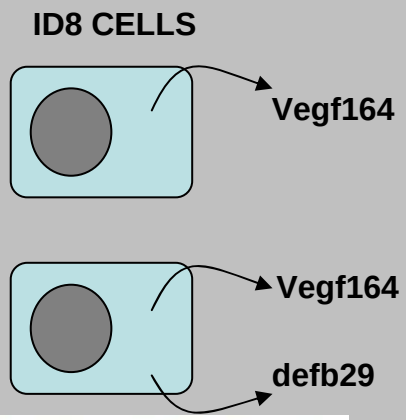


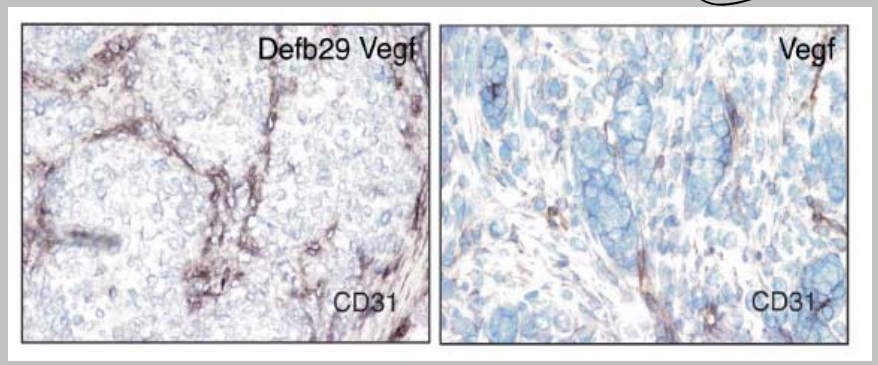


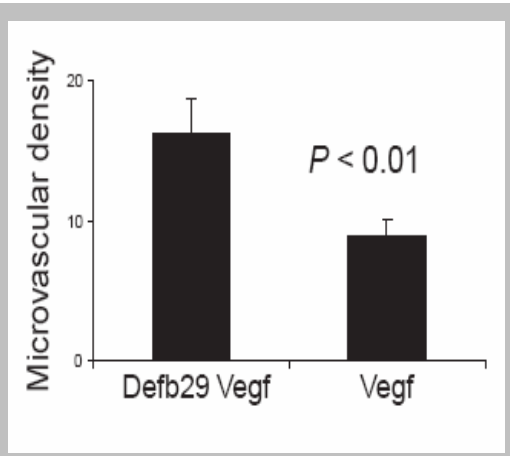
Li et al, *FASEB J* 2006

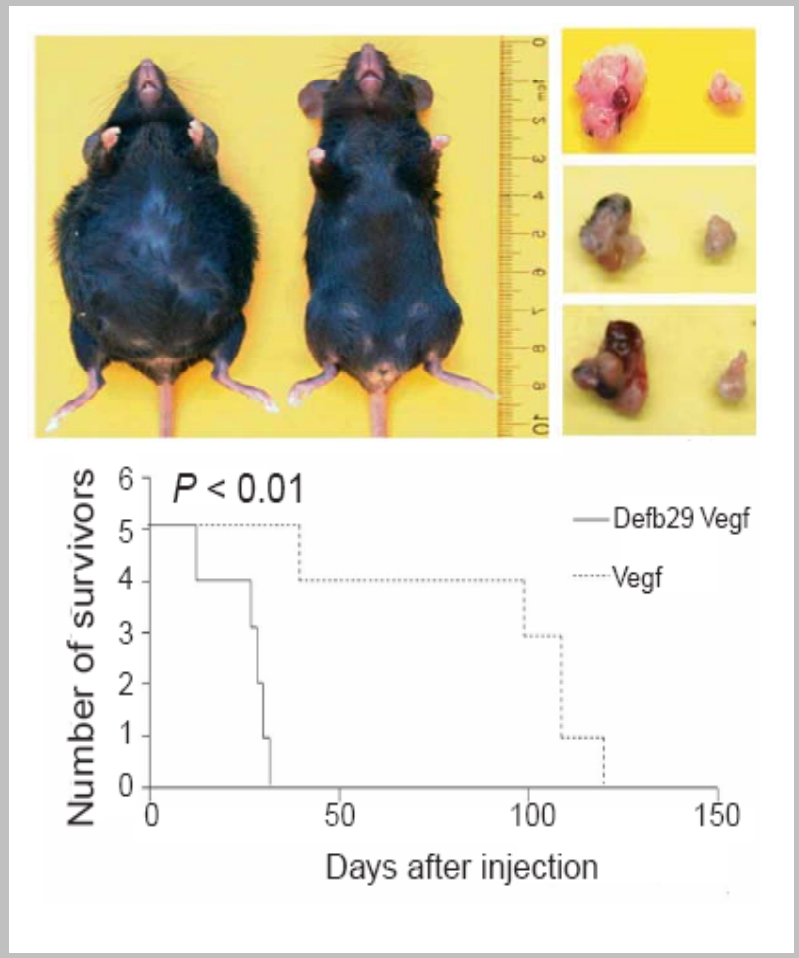
Recruitment of myeloid DC progenitors promotes tumor vascularization and growth





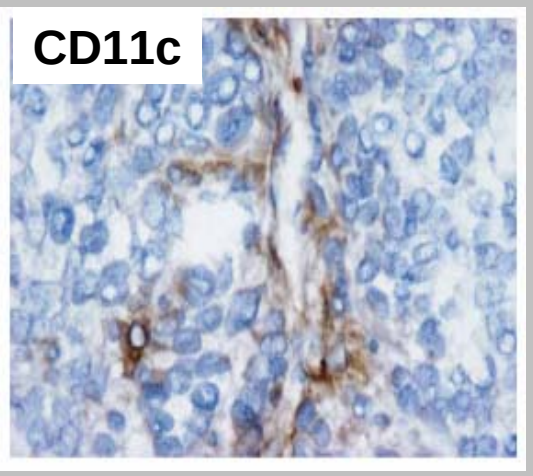


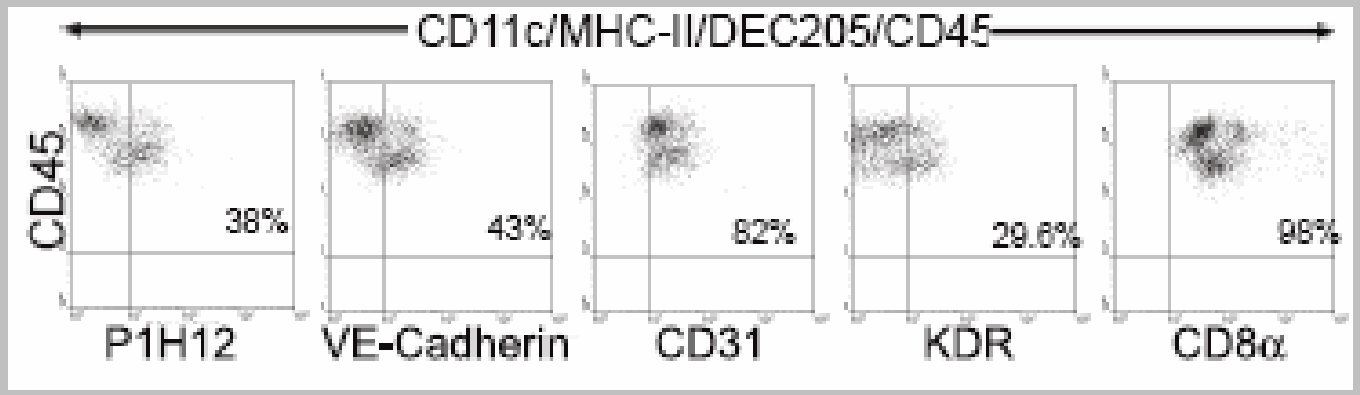


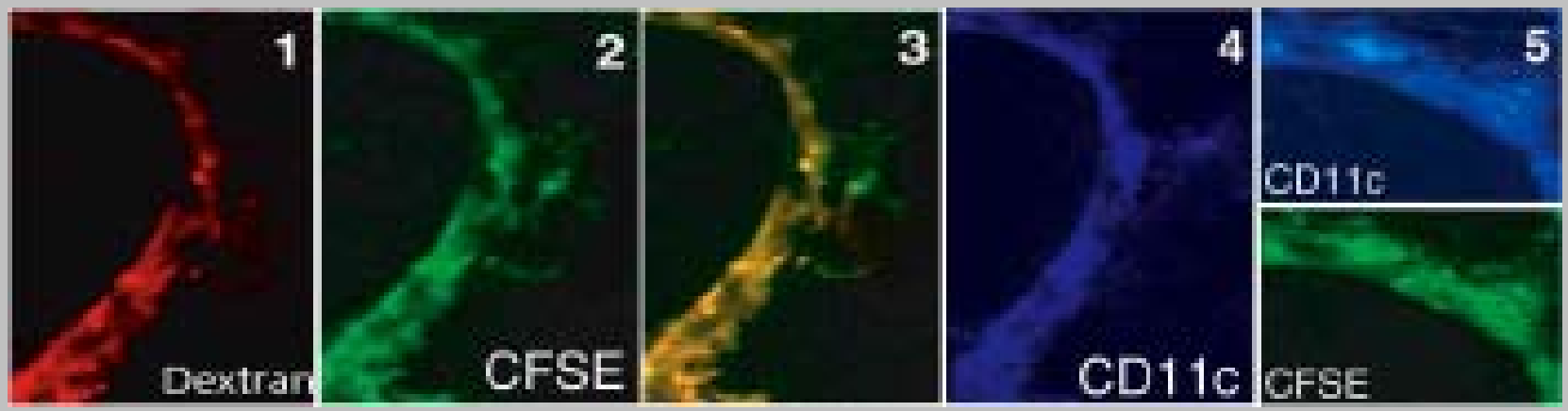


Conejo-Garcia et al, *Nature Med* 2004

Discovery of mouse vascular DCs



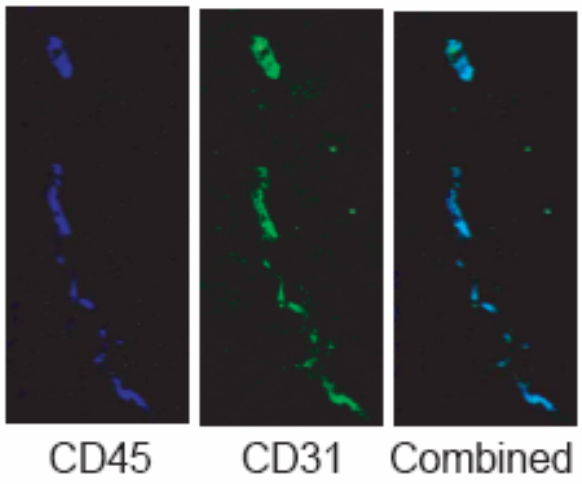


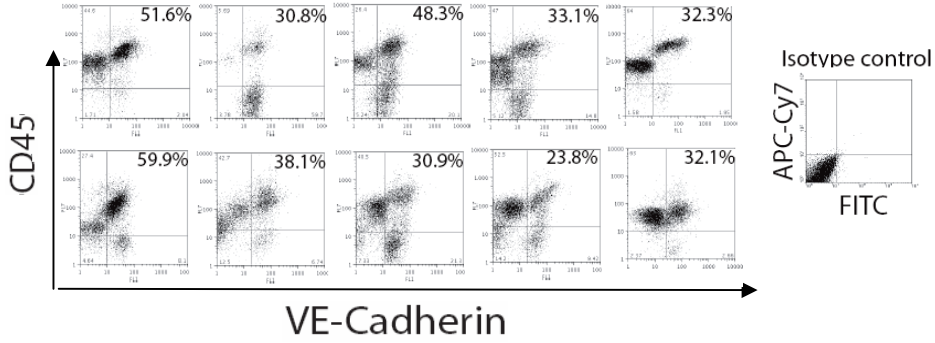


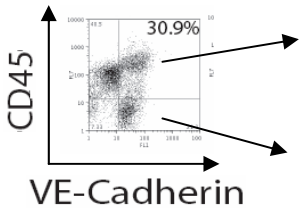
Matrigel

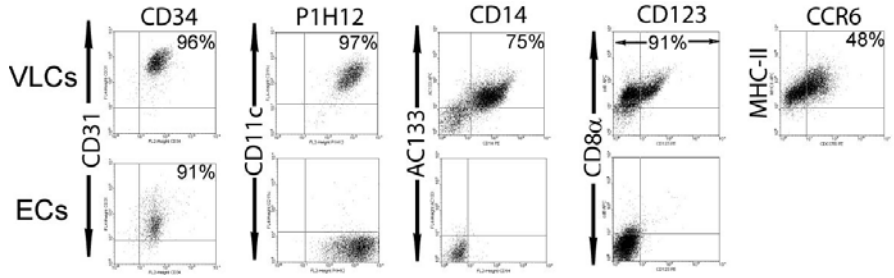
Conejo-Garcia et al, *Nature Med* 2004

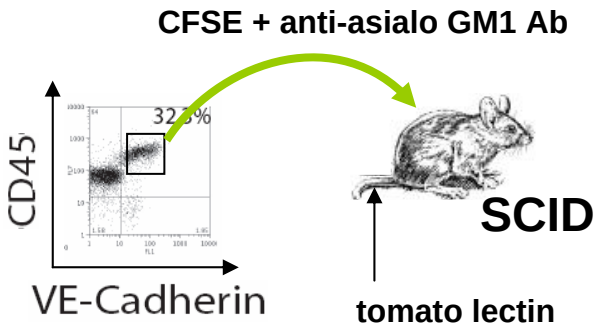
Discovery of Human Vascular DCs

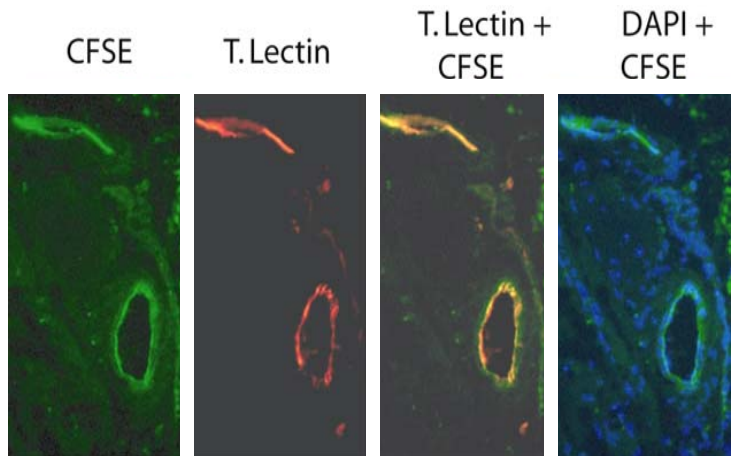










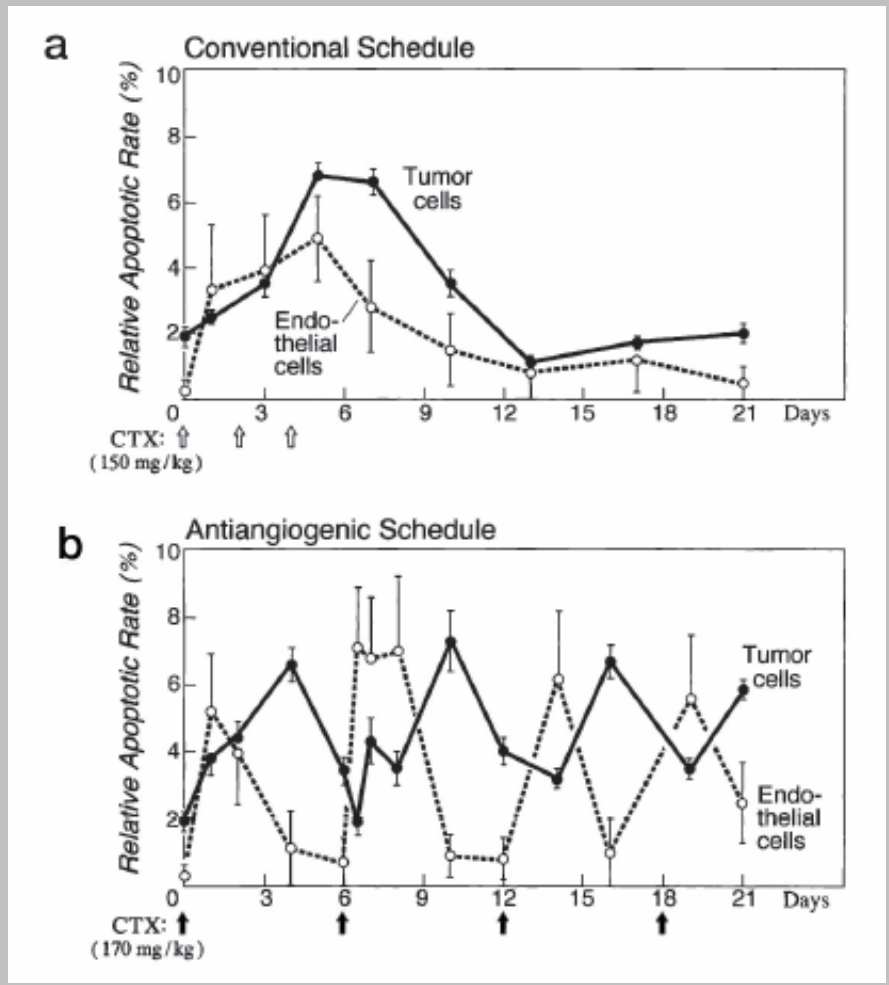


Conejo-Garcia et al, *Blood* 2005

Chemotherapy Targets Tumor Endothelium

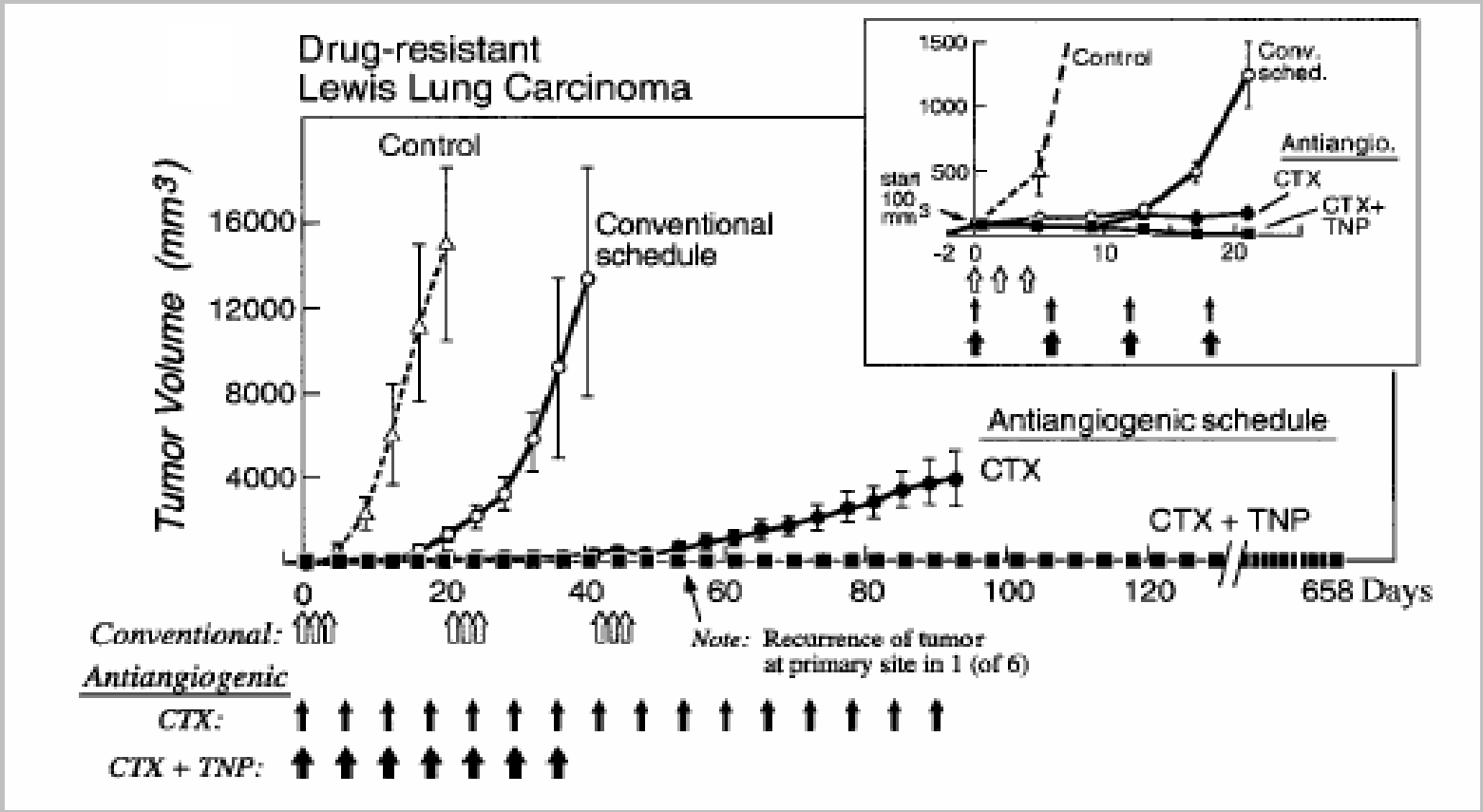
Maximal Tolerated Dose ➔

Low Dose Metronomic ➔



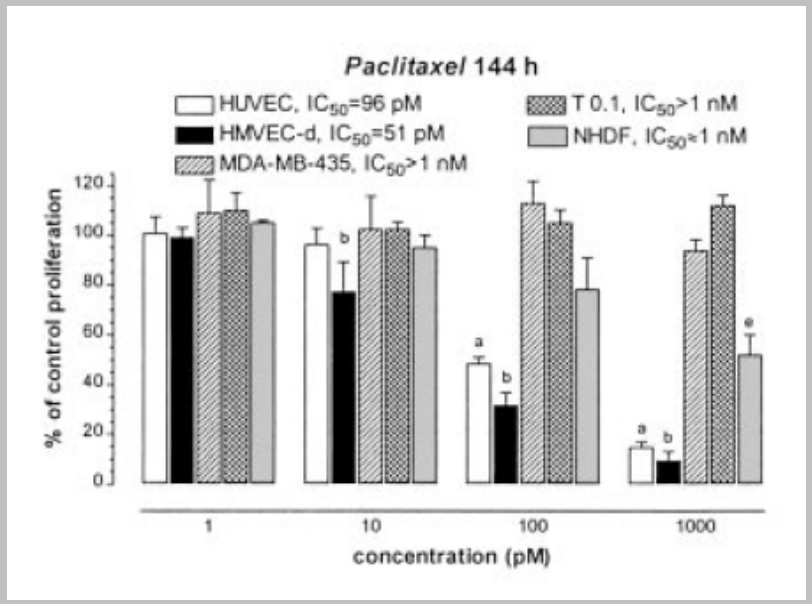
Browder et al, *Cancer Res* 2000

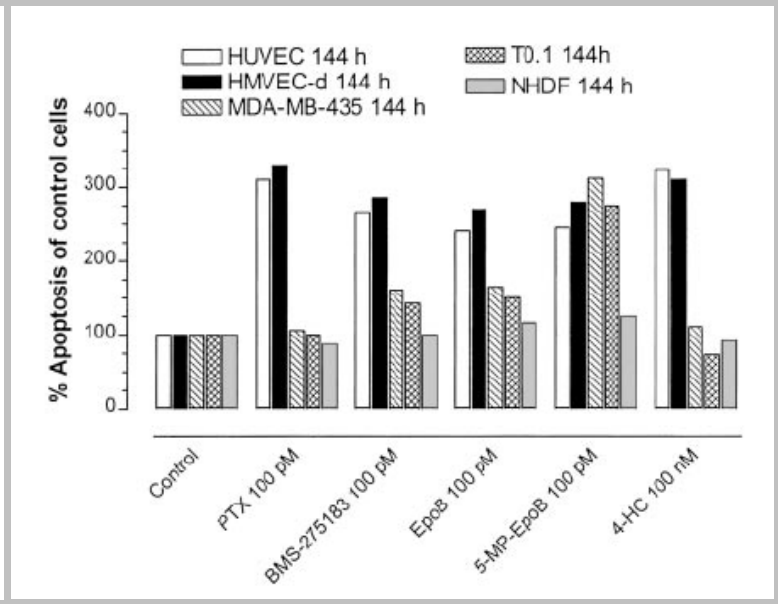
LDM Chemotherapy Overcomes Tumor Resistance



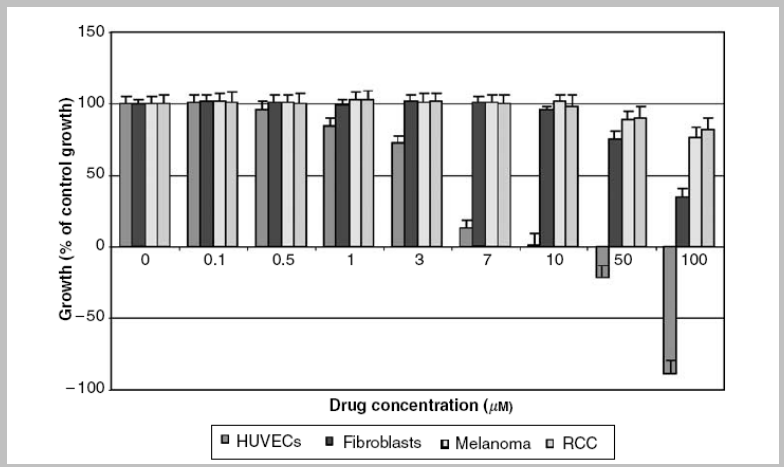
Browder et al, *Cancer Res* 2000

LDM Chemotherapy Targets Tumor Angiogenesis





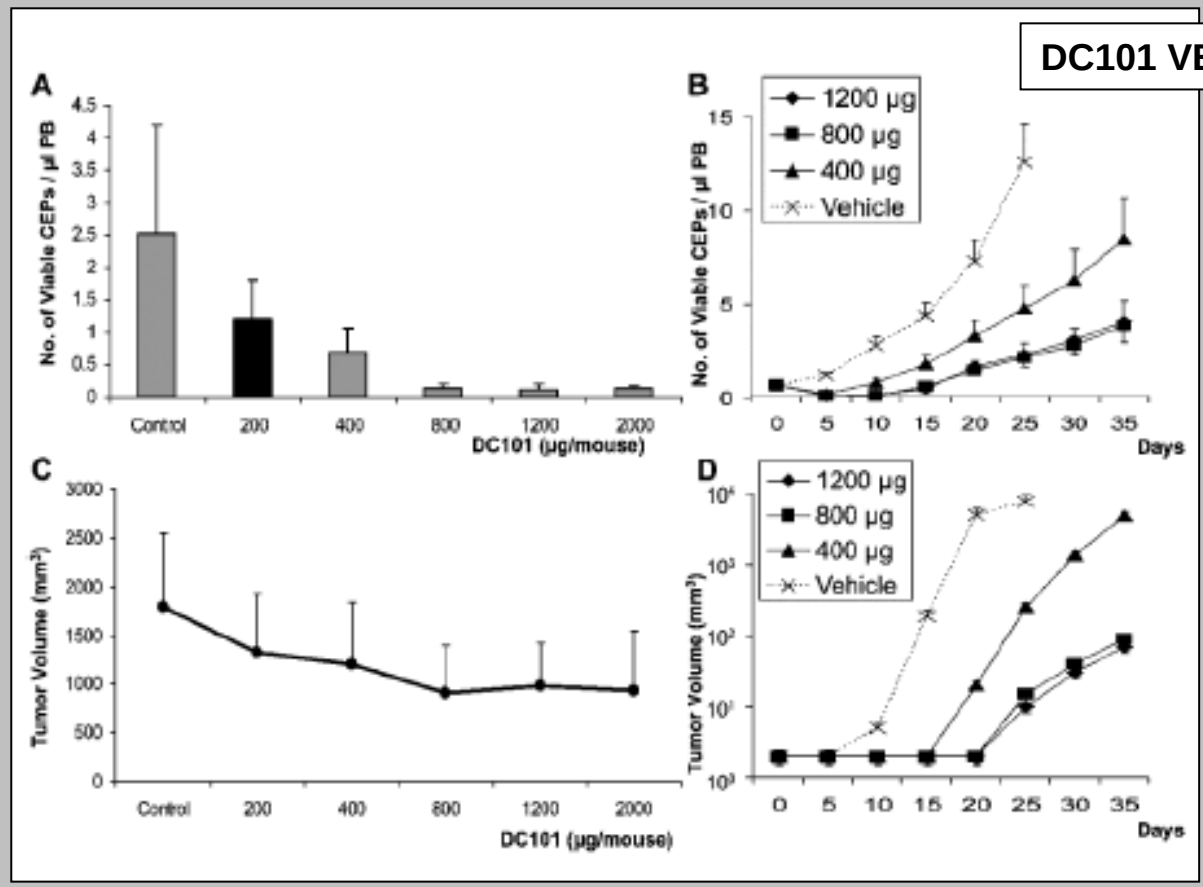
Bocci et al, *Cancer Res* 2002



Maraveyas et al, *Br J Ca* 2005

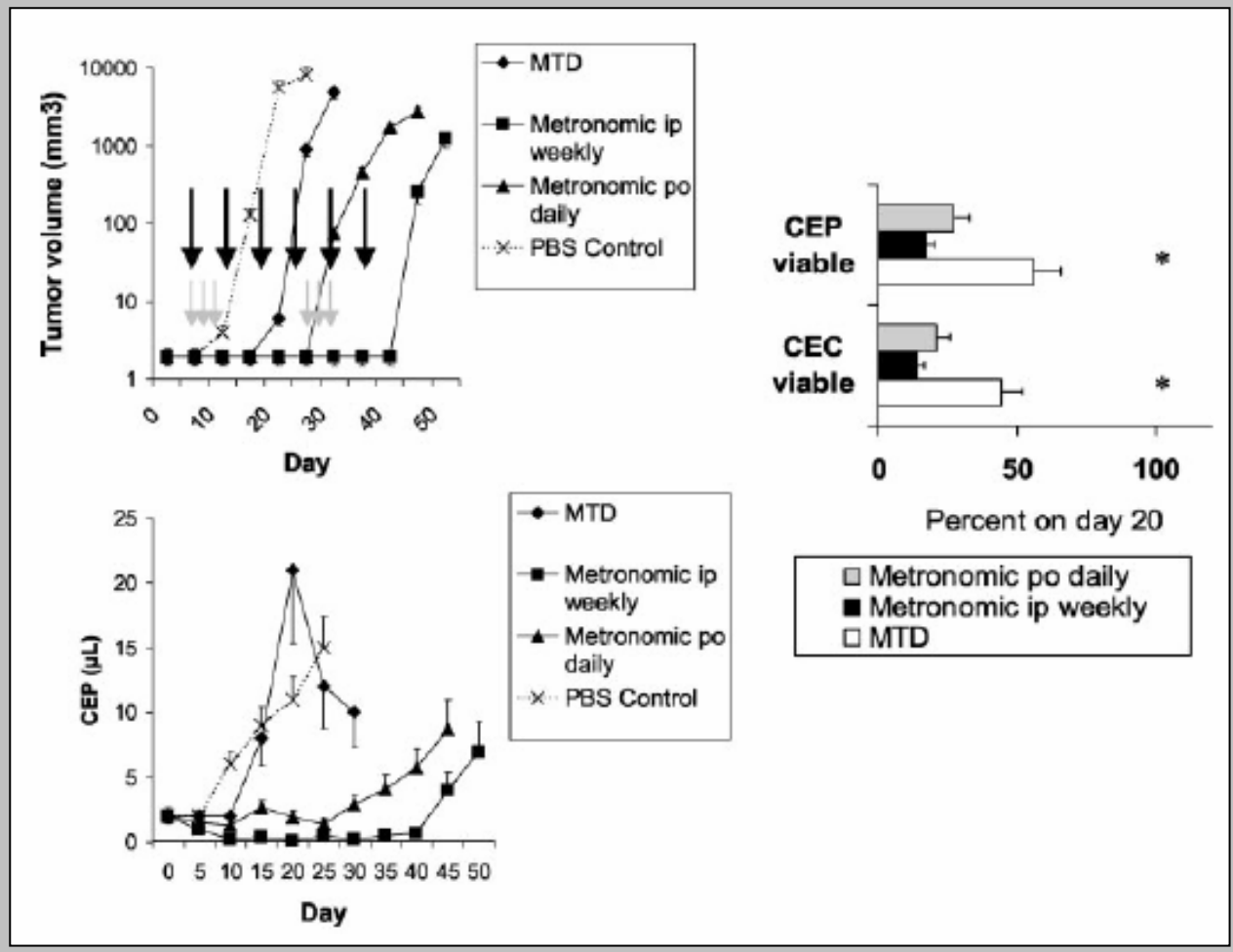
CEP Predict Response to Antiangiogenesis Therapy

CD13+/VEGFR-2+/CD45-/c-kit (CD117)+



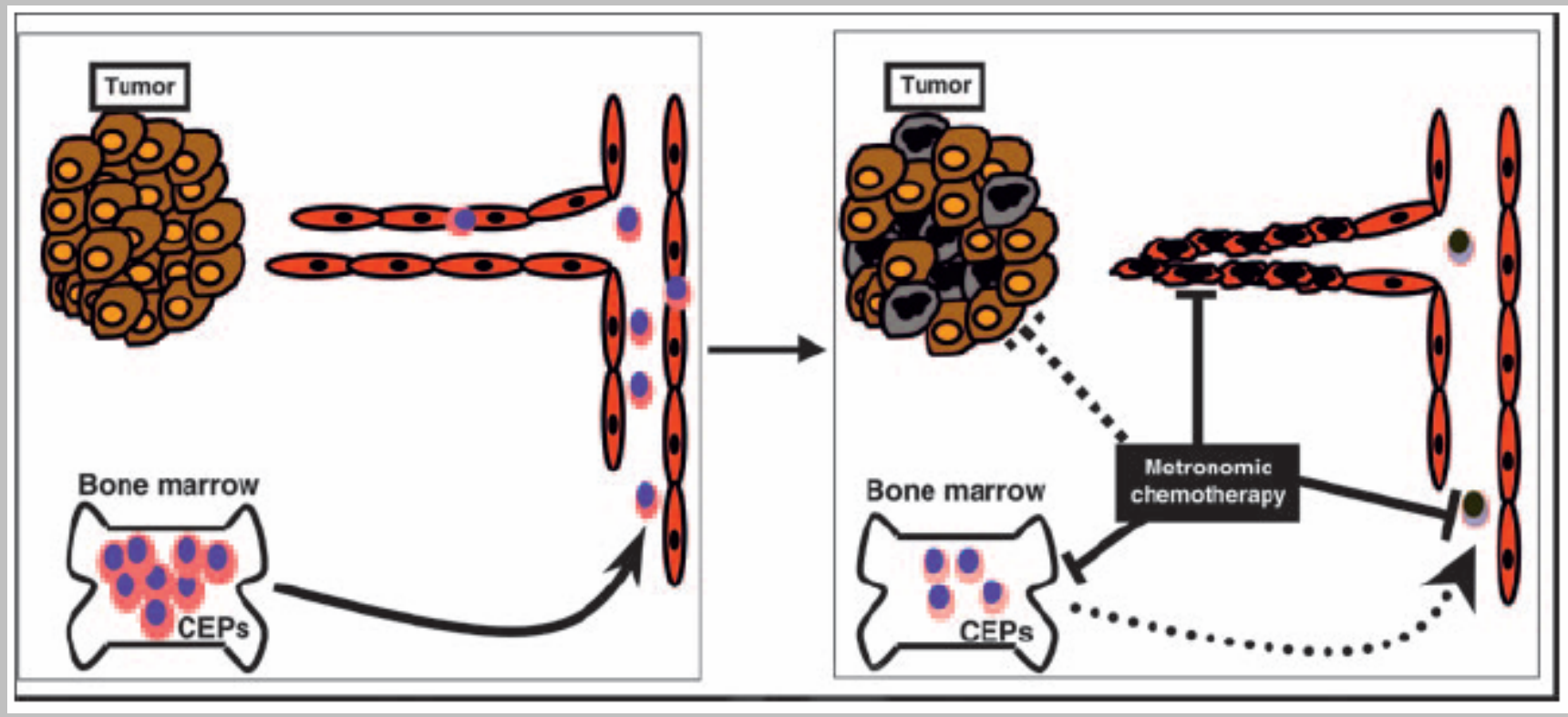
Shaked, et al *Cancer Cell* 2005

LDM Chemotherapy Targets Tumor Vasculogenesis



Bertolini et al, *Cancer Res* 2003

LDM Chemotherapy Suppresses Multiple Pathways



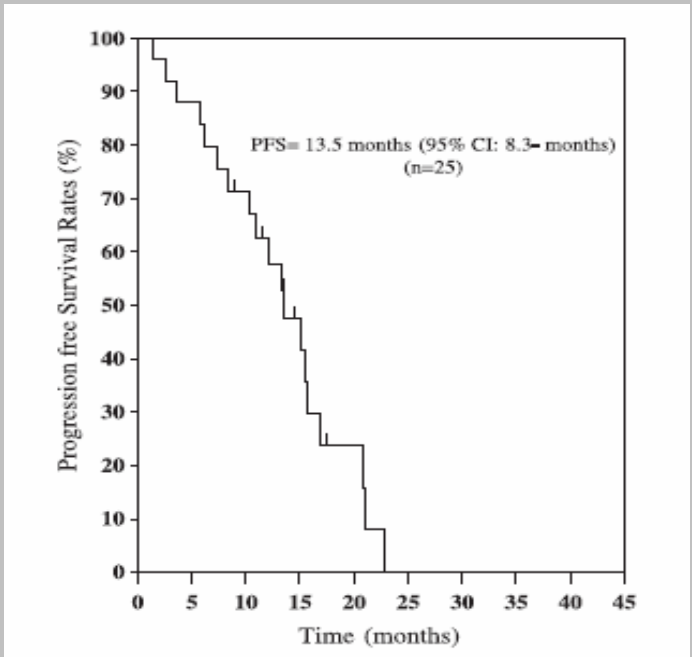
Shaked et al, *Blood* 2005

Metronomic chemotherapy acts through multiple mechanisms

- Reduction of tumor/systemic VEGF-A levels
- Increase in endogenous antiangiogenic factors
- Direct inhibition of angiogenic sprouting
- Direct killing of tumor endothelial cells
- Suppression of circulating endothelial progenitor cells (CEP)
- Suppression of circulating endothelial cells (CEC)
- Suppression of recruitment and function of CEP and/or CEC in tumors.

LDM Chemotherapy Moves to the Clinic

Cisplatin, paclitaxel, topotecan, etoposide, vincristine, vinblastine, doxorubicin, mitoxantrone, 6-mercaptopurine, 9-amino-20(S)-camptothecin, camptosar,combrestatin A-4



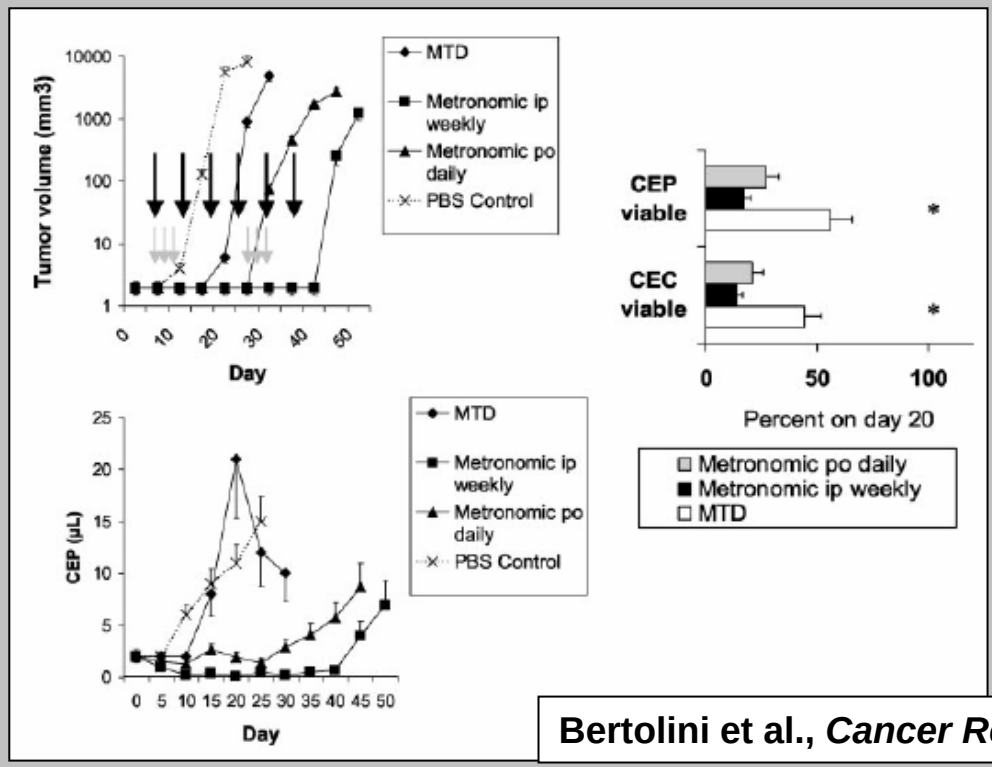
Paclitaxel at 60 mg/m^2 + carboplatin (AUC = 2) q 3 weeks / 4 weeks

Watanabe et al, *Gyn Oncol* 2005

Challenges with LDM Chemotherapy

- Identify the optimal biological dose of LDM (in the clinic LDM chemotherapy doses arbitrarily chosen as 10-40% of MTD).
- Identify metrics of efficacy
- Identify optimal combinations
- Identify tumor/patient variables that affect response

What is the optimal LDM CMT dose?



Bertolini et al., *Cancer Res* 2003

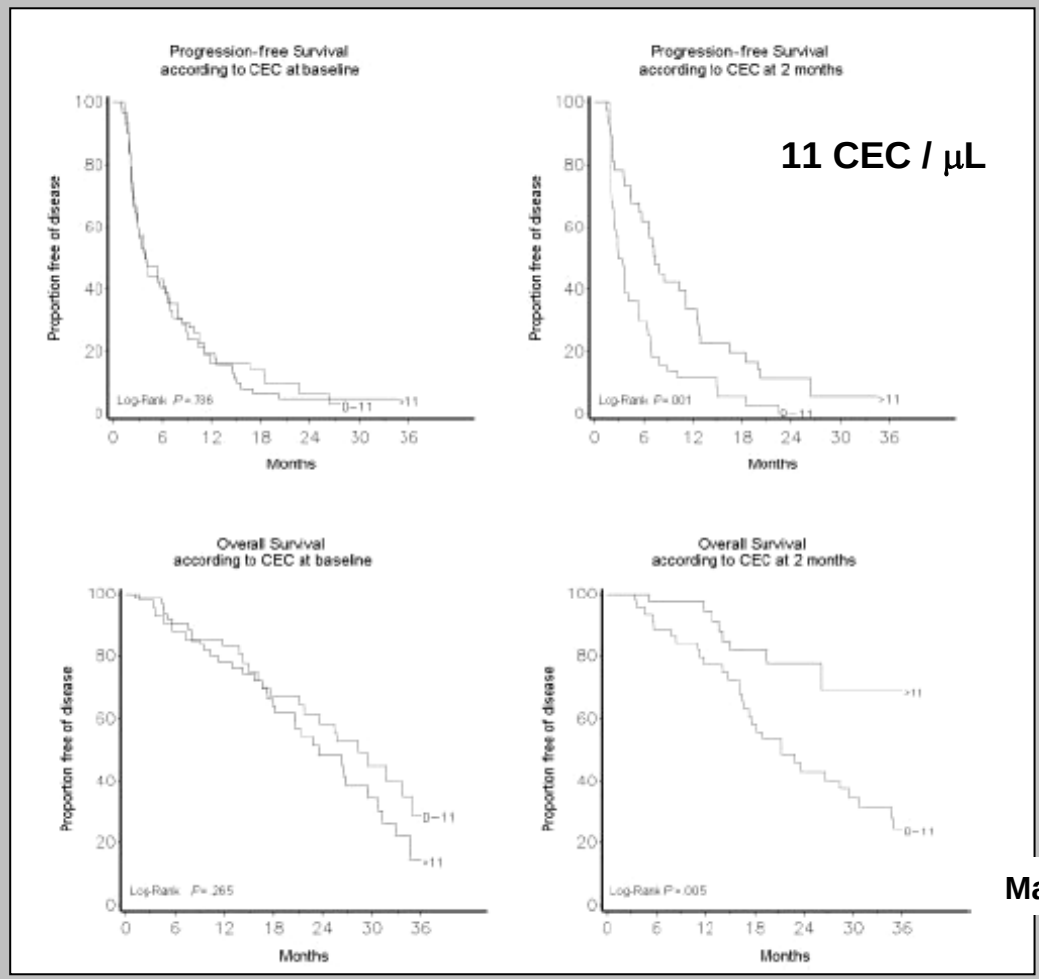
The highest dose that that can be delivered metronomically without causing bone marrow disruption (or other major toxicity) (Maraveyas et al, *Br J Cancer* 2005; Shaked, *Blood* 2005).

Rapid Screening Requires Reliable Pharmacodynamic Markers

Biomarker	Disadvantages	Advantages
Microvascular Density	Invasive, Inter-observer variability	
Tumor VEGF-A	Invasive, Inter-observer variability	Predictive of rsponse
Tumor Response (RECIST)	Not predictive of time to progression	Standardized
Tumor Blood Flow (DCE-MRI)	Expensive	Potentially reliable
Circulating VEGF-A	Not predictive of response to therapy	Cheap, non invasive
Circulating Endothelial Cells	Stnadardization needed	Cheap, non invasive
Circualting Endothelial Progenitors	Stnadardization needed	Cheap, non invasive

CEC Predict Response to LDM Chemotherapy and Outcome

CD45-/CD31+/P1H12+/CD133-



Mancuso et al, *Blood* 2006

MTX PO 2.5 mg BID 2X/wk + CY PO 50 mg QD +/- THL PO 200 mg/dQD

Metrics

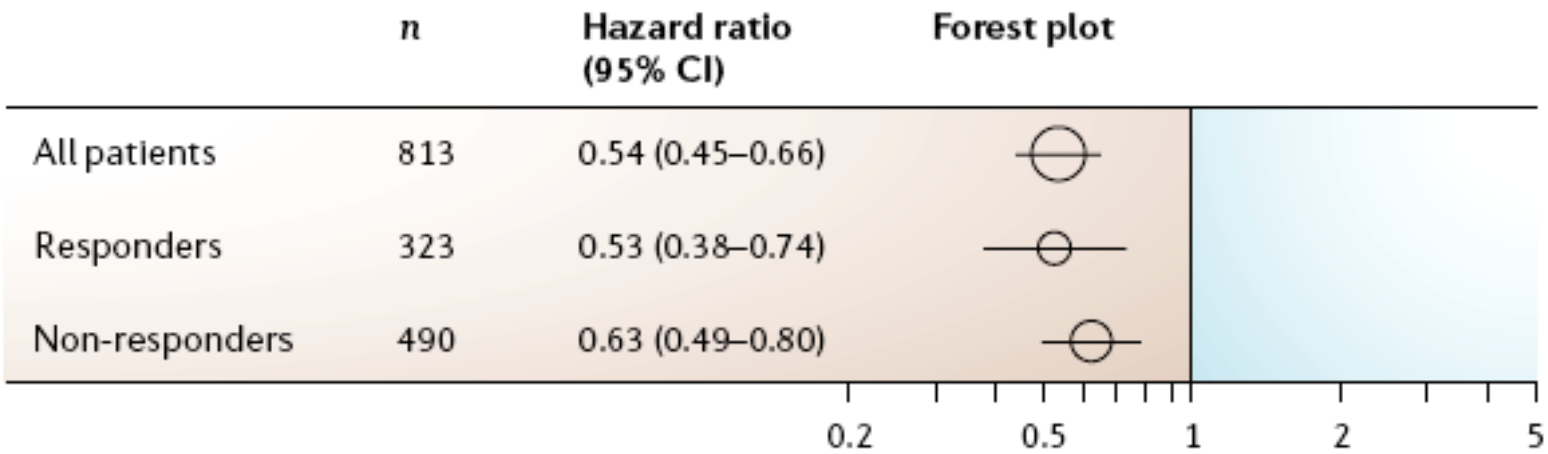
Unlike cytotoxic therapies, antiangiogenic therapies may not result in a measurable decrease in tumor size.

The clinical endpoints to define therapeutic success of LDM chemotherapy may be quite different than for MTD chemotherapy.

Objective response rates may markedly underestimate the clinical benefit resulting from disease stabilization, increased progression-free or overall survival, and increased quality of life or palliation

Bevacizumab + Cytotoxic Chemotherapy in Metastatic Colorectal Cancer:

Survival benefit irrespectively of objective response



Jubb et al, *Nature Reviews Cancer* 2006

Identification of combinations

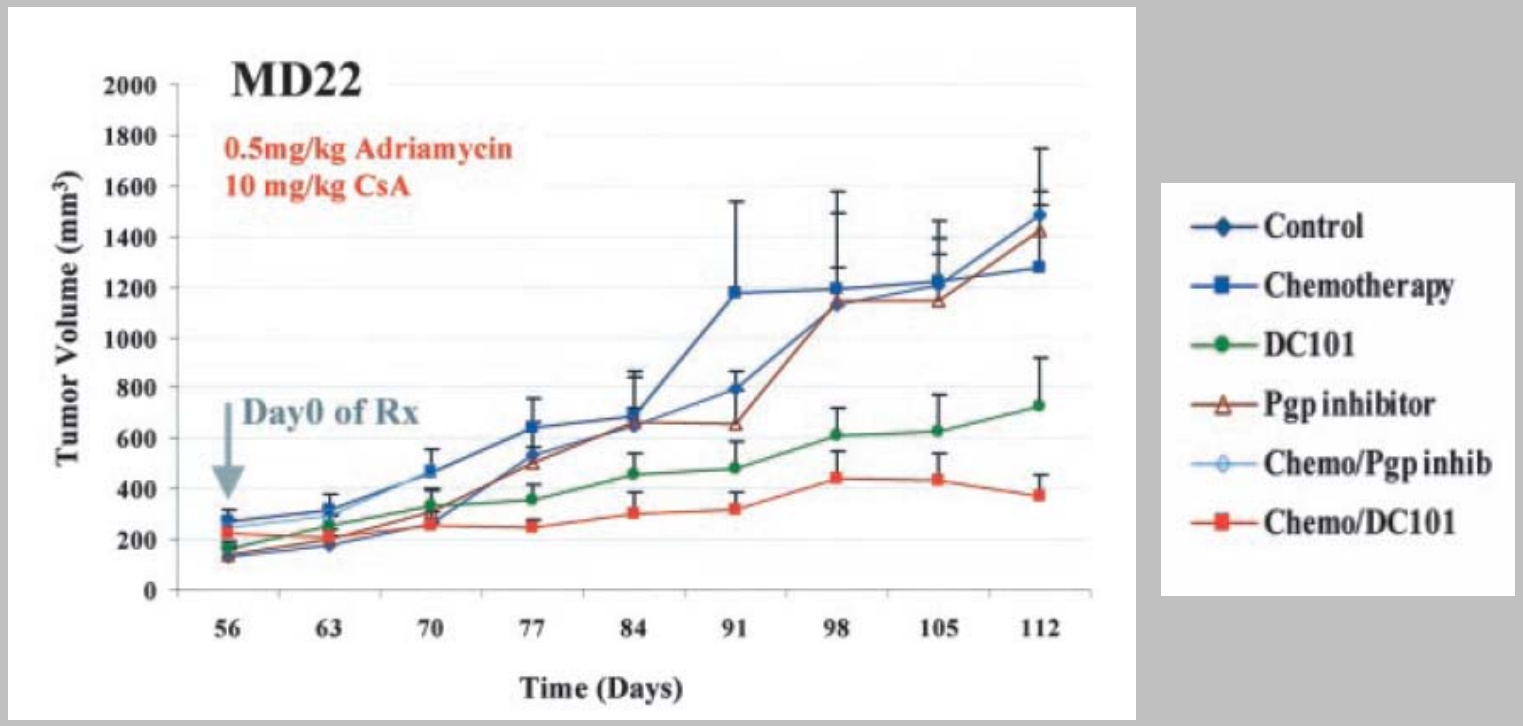
Because of its low toxicity, metronomic chemotherapy is ideally suited for long-term combination with other drugs.

Antiangiogenic drugs, vascular disrupting agents and immunotherapy are attractive candidates.

How to triage drugs?

How to screen combinations / schedules?

LDM + Antiangiogenesis Therapy



Klement et al, *Clin Cancer Res* 2002

LDM + Antiangiogenesis Therapy

cisplatin 20 mg/m^2 weekly on d 1 +
SU-5416 145 mg/m^2 q 2 weeks, on d 1 and 3

Gasparini, *Lancet Oncol* 2001

The Promise of LDM Chemotherapy

- Optimize biological dose of LDM
- Validate metrics of efficacy
- Optimize combinations – antiangiogenesis, VDA, immunotherapy, targeted therapy
- Identify tumor/patient variables that affect response