« Women have a passion for Mathematics…

…They divide their age in half, double the price of their clothes, and always add at least five years to the age of their best friend »

Welcome to
METRONOMICS 3.0

Nicolas André MD, PhD
Metronomics Global Health Initiative
CRO2, Faculté de Pharmacie, Université de la Méditerranée
Hématologie & Oncologie Pédiatrique
Marseille, France

METRONOMICS 0.5

« Oral low dose chemotherapy »…

… « Continous Infusion »

Oral low dose chemotherapy

Pediatr Blood Cancer 2004;42:320–324

Oral Etoposide for Recurrent/Progressive Sarcomas of Childhood†

Rejin Kebudi, MD,* Ömer Görgün, MD, and İnci Ayan, MD

are uncommon tumors that constitute 1% to 2% of all pediatric brain tumors.[1-27] Because of the location of optic pathway gliomas, cytoreductive surgery is infrequently performed.[19,28] As a result, clinical management consists primarily of radiotherapy or chemotherapy.* Because the slow growth of these tumors may, in part, reflect the high incidence of low-grade tumor histologic findings, natural history is unpredictable; therefore, treatment is usually post-

mary therapy. Data that have established the efficacy of chemotherapy for the treatment of low-grade gliomas have been limited, although a number of preliminary studies that used a variety of chemotherapeutic agents have suggested high response rates.[2,4,6,8,11,20,26,29-31]

The present study, conducted at the University of California, San Diego, expands on this experience wherein a long-term, oral-dosing schedule of etoposide (VP-16) was utilized in treating 14 children with recurrent chiasmatic-hypo-

response of 8 months. In summary; oral VP-16 is a well tolerated and relatively non-toxic chemothera agent with apparent activity in this small cohort of patients with recurrent brainstem gliomas.

Introduction

Malignant gliomas involving the brainstem account for 10–20% of pediatric and 1–2% of adult brain tumors [1, 2]. These tumors produce disproportionate neurological dysfunction for their size. While these tumors vary from well differentiated

results when the surgeon operates on intr lesions of the brainstem. Radiation thera malignant gliomas of the brainstem is of p therapeutic value and the most effective t [8]. Reported series indicate that 5 year survi 20–30% are to be expected following rad therapy [8]. Radiation therapy improve sym

21 patients
50 mg/m2/day
D1-D21 D31-52
CR=1 +2; PR=4; SD=7+1
7 months (+2 alive years)

14 patients
50 mg/m2/day
D1-D21 D36-57
CR=1; PR=4; SD=3
8 months

12 patients
50 mg/m2/day
D1-D21 D36-57
CR=1; PR=3; SD=2
8 months

To overcome these problems, a study was designed to test the ability of a therapy to prolong the duration of a remission. A higher proportion of patients would be available early in the course of their illness for such a study. Moreover, the treatment of patients in whom the leukemic process is in remission would permit objective evaluation of pharmacologic and toxic properties of the agent. Finally, a study of remission maintenance uses a continuous variable, namely duration of remission compared to remission induction where a yes or no variable is used, and allows for the quantitative evaluation of an agent. Such a quantitative evaluation could be a basis for ranking of agents in man. This ranking could be of great aid to those concerned with the synthesis of new compounds and the testing of compounds in animal systems.

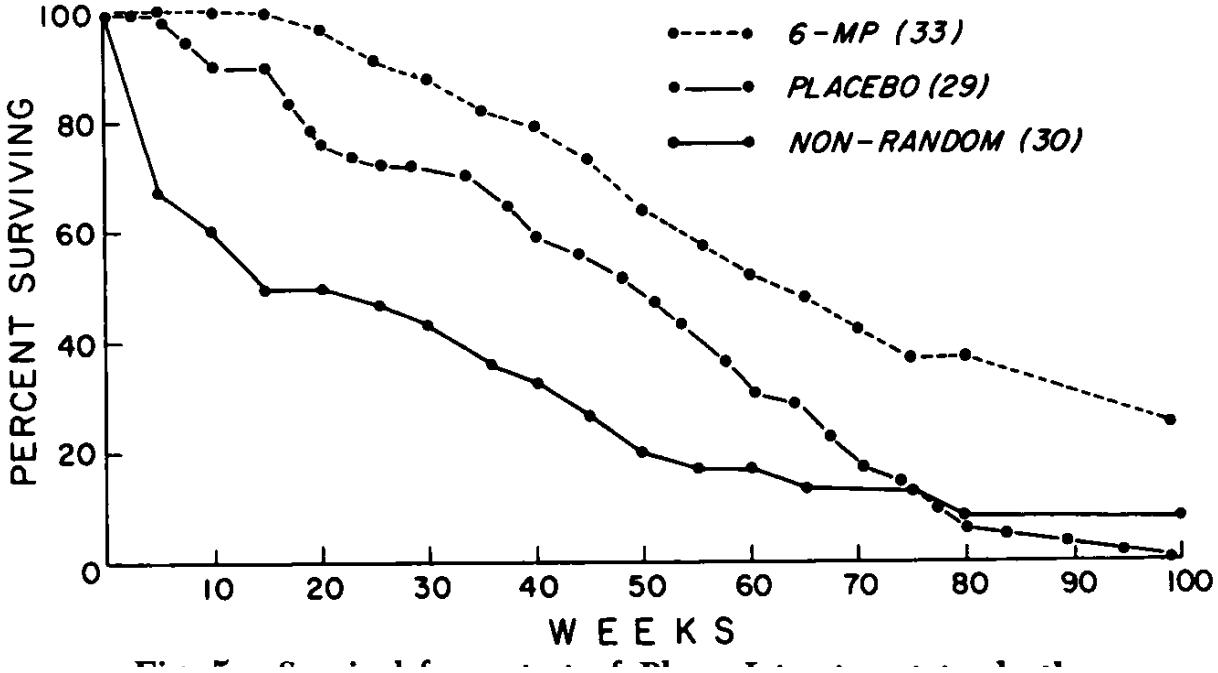
6-MP was selected as a known active agent to test such an experimental

blood 1963 21: 699-716

achieved (A-1)† or for a maximum of 28 days. Patients who
rovement (from A-3) after 28 days of corticosteroid therapy we
t course of therapy for remission induction (Phase III, NRS pa
row remission (A-1) before 28 days or marrow remission (A-1
were assigned randomly to 6-MP or placebo (given double-bl
ntenance phase of the study (Phase II). This part of the st
uential evaluation so that the study could be stopped as soon
t one treatment was superior to the other in the maintenan
uential design is explained in the Appendix.

ull dosage of 6-MP (3 mg./Kg./day) was used for maintenance
dified dose.[9] Placebo was given at the same dose. Maintenance
Phase II until bone marrow relapse occurred (A-3). At this
ned and those patients who had received placebo maintenar
IP for remission induction and maintenance (Phase III. RS pat

Fig. 4.—Survival from start of Phase II treatment to death.



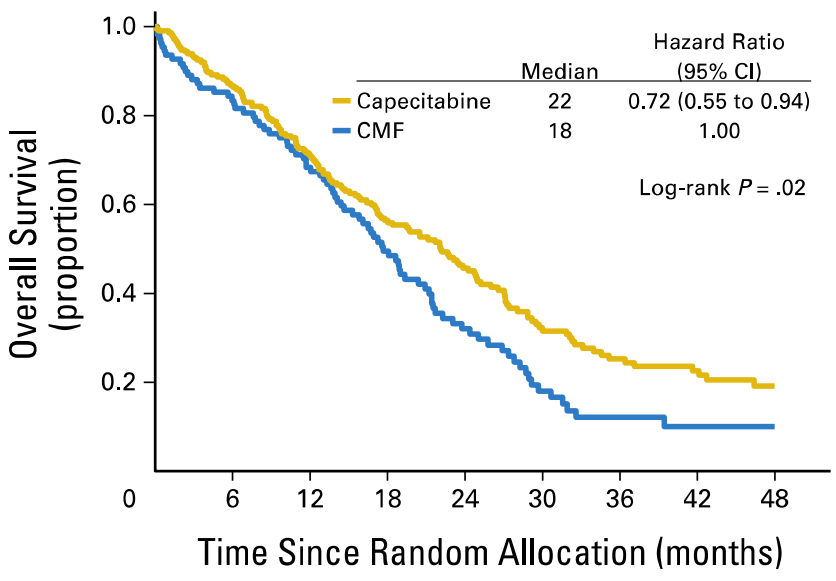
« Low dose purinethol » is active un first line treatment of children ALL and increases the lengh of CR

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Capecitabine Versus Classical Cyclophosphamide, Methotrexate, and Fluorouracil As First-Line Chemotherapy for Advanced Breast Cancer

Martin R. Stockler, Vernon J. Harvey, Prudence A. Francis, Michael J. Byrne, Stephen P. Ackland, Bernie Fitzharris, Guy Van Hazel, Nicholas R.C. Wilcken, Peter S. Grimison, Anna K. Nowak, M. Corona Gainford, Akiko Fong, Lisa Paksec, Tatiana Sourjina, Diana Zannino, Val Gebski, R. John Simes, John F. Forbes, and Alan S. Coates

B

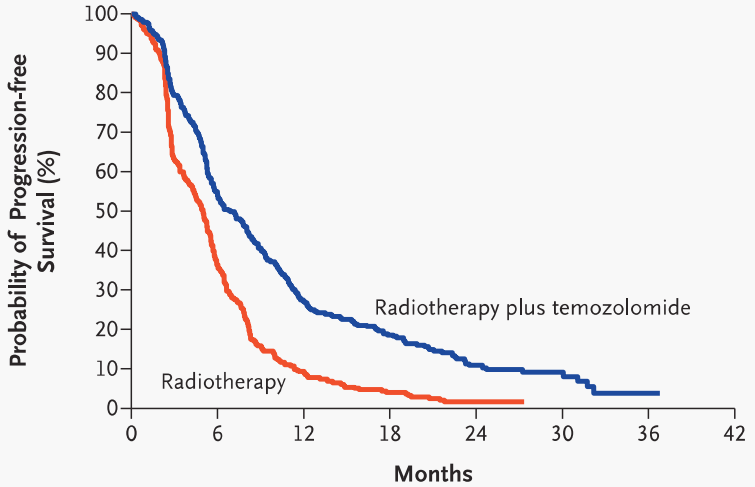


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D., Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D., Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D., Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Robert C. Janzer, M.D., Samuel K. Ludwin, M.D., Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D., Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D., and René O. Mirimanoff, M.D., for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group*



No. at Risk							
Radiotherapy	286	104	26	11	4	0	0
Radiotherapy plus temozolomide	287	154	77	51	24	8	1

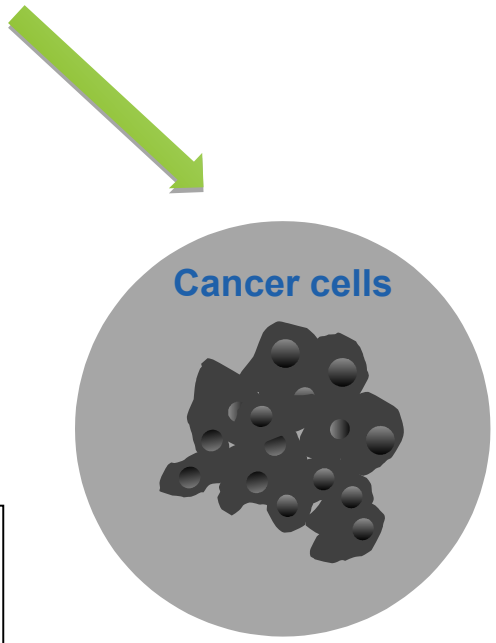
METRONOMICS 0.5

Journal of Neuro-Oncology **15**: 133–139, 1993.

Clinical Study

Recurrent brainstem gliomas treated with oral VP-16*

Marc C. Chamberlain
University of California, San Diego, Department of Neurosciences, USA

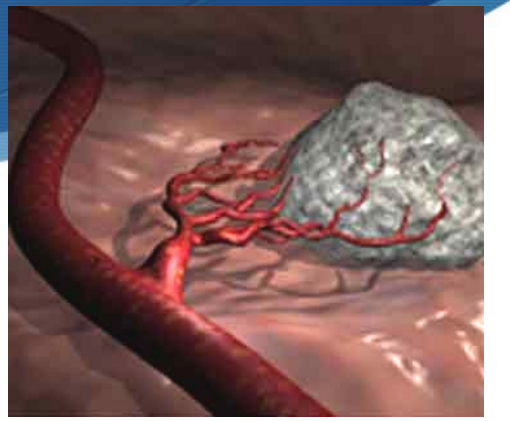


Clinical Cancer Research

Clinical pharmacology of chronic oral etoposide in patients with small cell and non-small cell lung cancer.

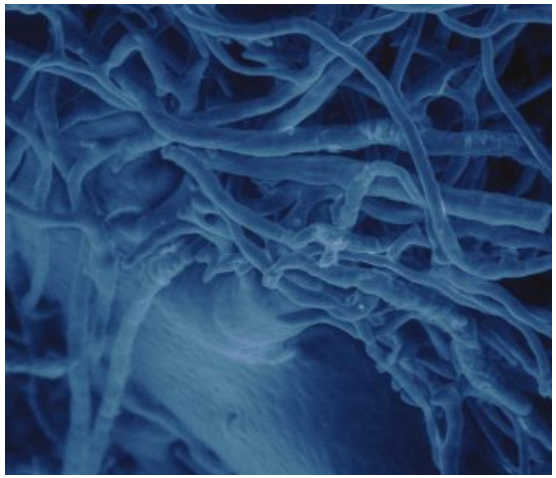
M Zucchetti, O Pagani, V Torri, et al.

Clin Cancer Res 1995;1:1517-1524.



METRONOMICS 1.0

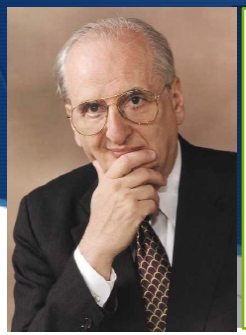
Metronomic Chemotherapy : an anti-angiogenic chemotherapy



THE ANTI-ANGIOGENIC BASIS OF METRONOMIC CHEMOTHERAPY

Robert S. Kerbel and Barton A. Kamen‡*

NATURE REVIEWS | CANCER VOLUME 4 | JUNE 2004 | 423



[CANCER RESEARCH 60, 1878–1886, April 1, 2000]

Antiangiogenic Scheduling of Chemotherapy Improves Efficacy against Experimental Drug-resistant Cancer[1]

Timothy Browder, Catherine E. Butterfield, Birgit M. Kräling, Bin Shi, Blair Marshall, Michael S. O'Reilly, and Judah Folkman[2]

Laboratory of Surgical Research [T. B., C. E. B., B. M. K., B. S., B. M., M. S. O., J. F.] and Division of Hematology/Oncology [T. B.], Children's Hospital; Departments of Surgery and Cell Biology, Harvard Medical School [J. F.]; Department of Pediatric Oncology, Dana-Farber Cancer Institute [T. B.]; and the Joint Center for Radiation Therapy [M. S. O.], Boston, Massachusetts 02115

Continuous low-dose therapy with vinblastine and VEGF receptor-2 antibody induces sustained tumor regression without overt toxicity

Giannoula Klement,[1] Sylvain Baruchel,[2] Janusz Rak,[1] Shan Man,[1] Katherine Clark,[1] Daniel J. Hicklin,[3] Peter Bohlen,[3] and Robert S. Kerbel[1]

[1]Sunnybrook and Women's College Health Sciences Centre, Biological Sciences Program, Division of Cancer Biology Research, and Toronto-Sunnybrook Regional Cancer Centre, Toronto, Ontario M4N 3M5, Canada; Department of Medical Biophysics, University of Toronto, Ontario, Canada
[2]Hospital for Sick Children, Department of Pediatrics, Division of Hematology/Oncology, New Agent and Innovative Therapy Program, Toronto, Ontario M5G 1X8, Canada
[3]ImClone Systems Inc., New York, New York 10014, USA

The Journal of Clinical Investigation | April 2000 | Volume 105 | Number 8

Less is more, regularly: metronomic dosing of cytotoxic drugs can target tumor angiogenesis in mice

Commentary

See related article, pages R15–R24.

Douglas Hanahan,[1,2] Gabriele Bergers,[1,2] and Emily Bergsland[2,3]

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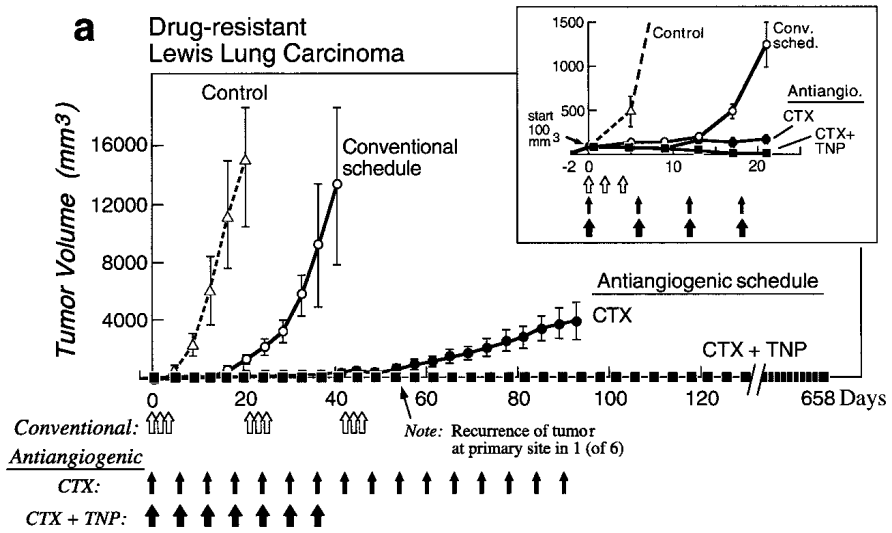

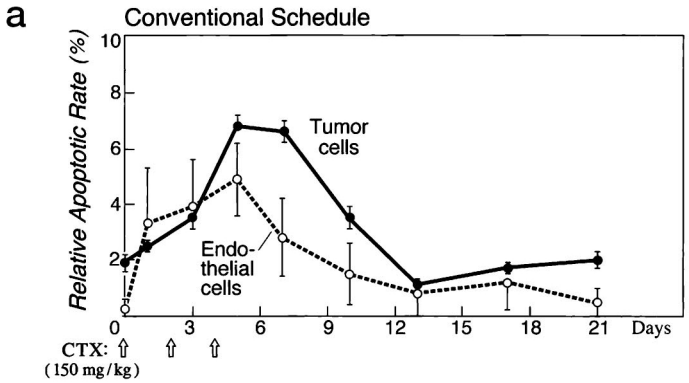

« Low dose : anti-angiogenic scheduling »

- activity in S&R cell lines
- Cyclophosphamide, 5FU, purinethol

- Good tolerance

- Lung cancer
- Breast cancer
- Leukemias

-- Target the endothelium AND NOT CANCER CELLS

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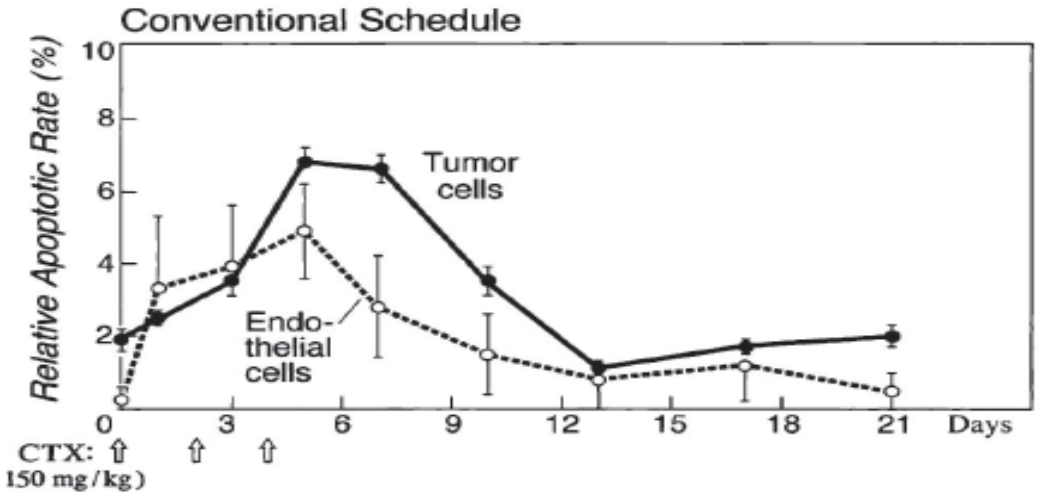
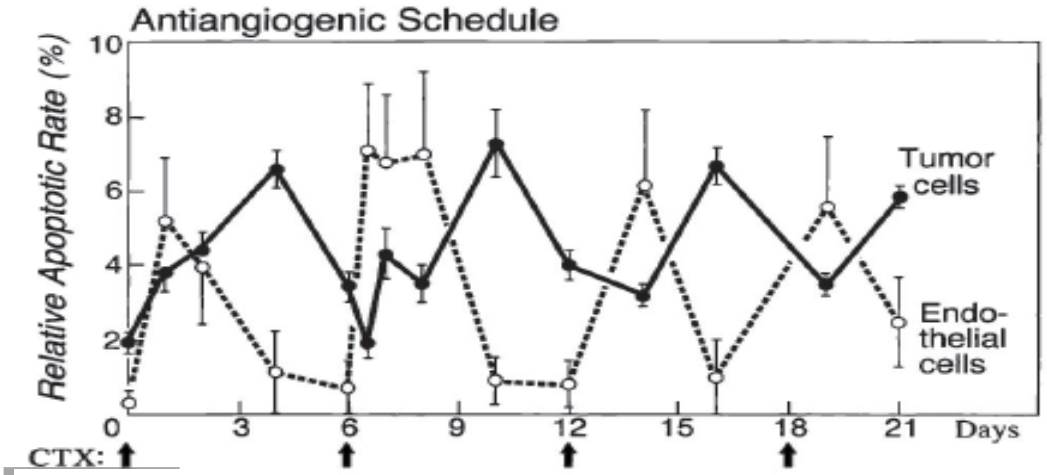
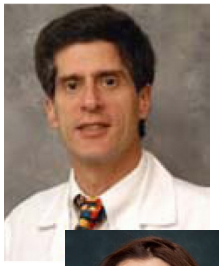




METRONOMICS 1.0

- **Metronomic Chemotherapy**
  - Frequent administration & low dose chemotherapy without long breaks (Kerbel *Nat Rev Cancer* 2004)
  - « Less is more, regularly »
  - Overcomes resistance, CHANGES THE TARGET !!!
  - The minimum biologically effective dose of a chemotherapeutic agent, which, when given at a continuous dosing regimen with no prolonged drug-free breaks leads to anti-tumor activity.”
    (Klement & Kamen JPHO 2011)



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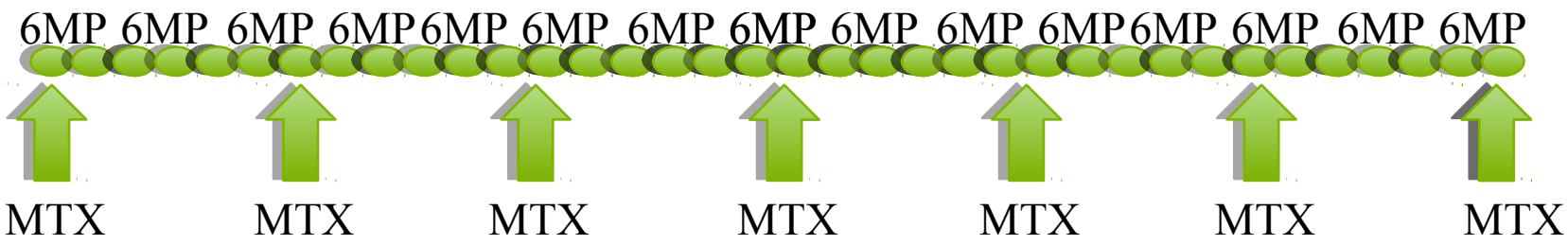
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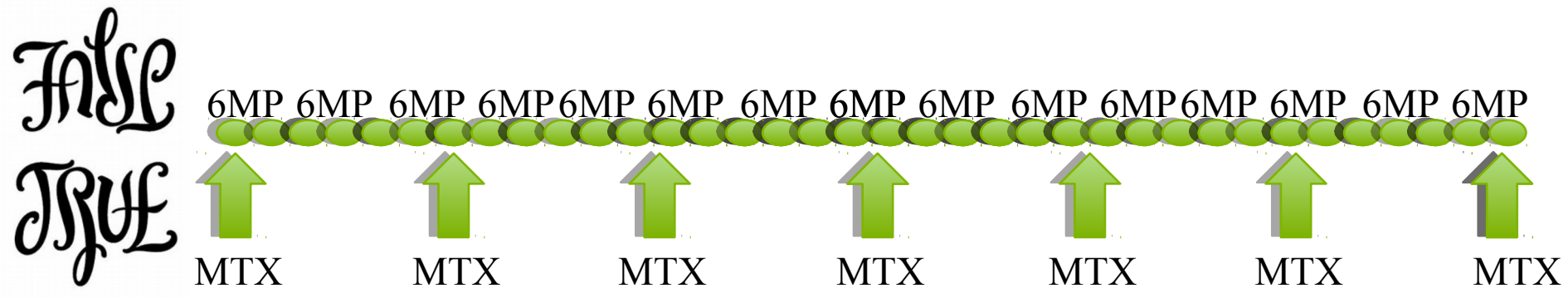
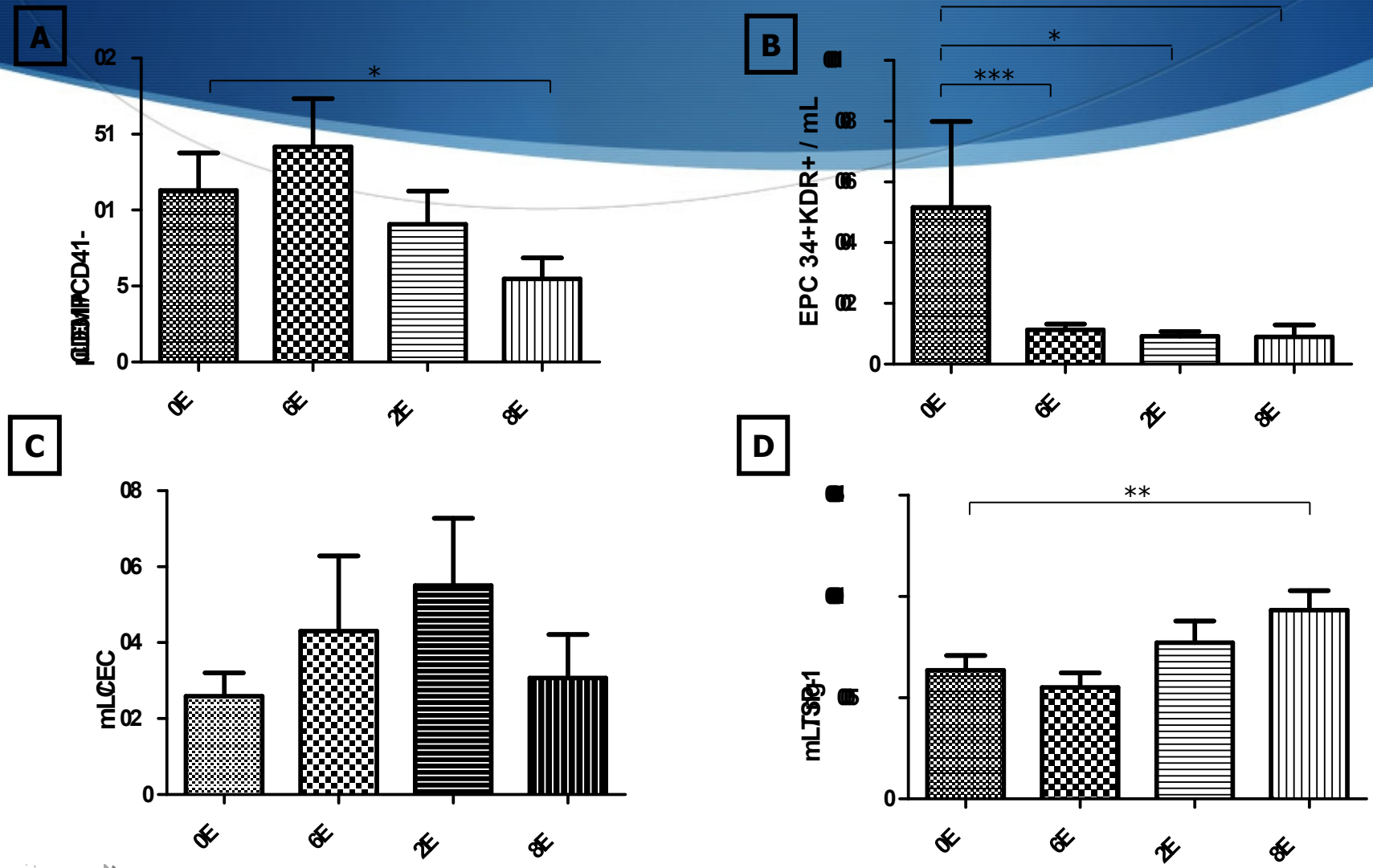
MTX MTX MTX MTX MTX MTX MTX

Maintenance for ALL ????



Metronomic Chemotherapy ????



Maintenance

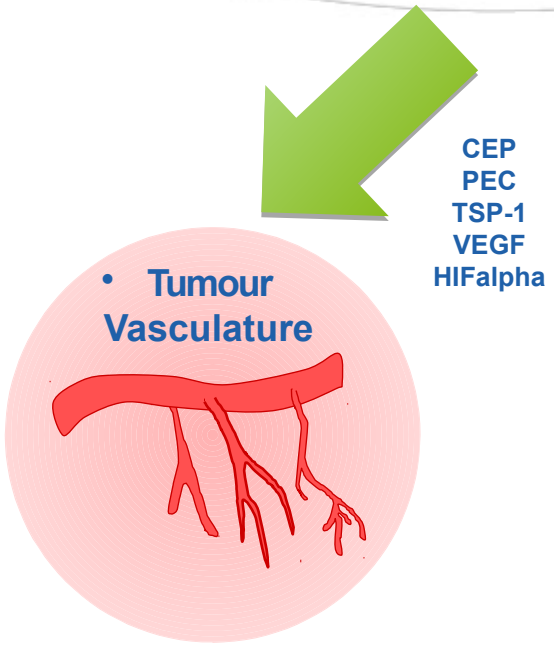
- puts the endothelium to rest:
- decreases its activation and mobilization of EPC
- associated with an increase in TSP-1

André Oncotarget 2015

Palliative Chemotherapy ????

Metronomic Chemotherapy ????

Metronomic Chemotherapy 1.0



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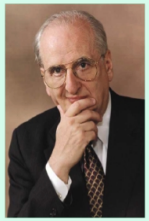
[1]Department of Biochemistry and Biophysics,
[2]Hormone Research Institute, and
[3]Department of Medicine, University of California San Francisco, San Francisco, California, USA



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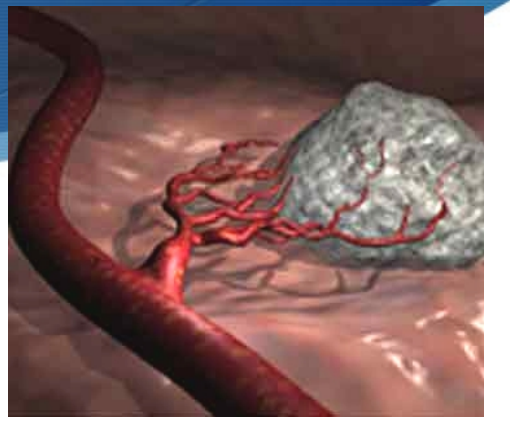
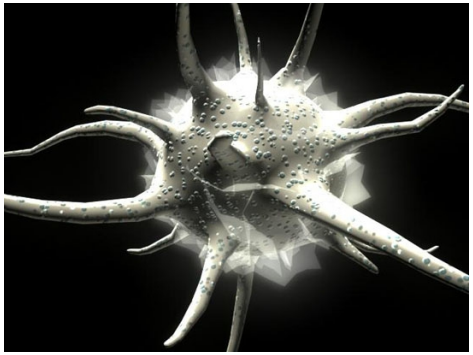


METRONOMICS 2.0

The Multi-target nature of Metronomic Chemotherapy

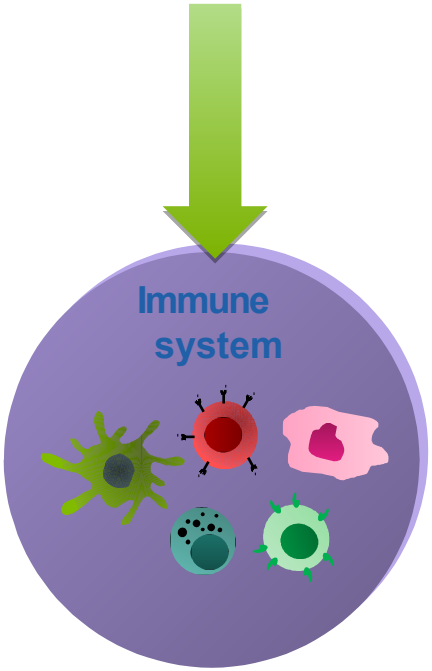


Metronomic chemotherapy: new rationale for new directions

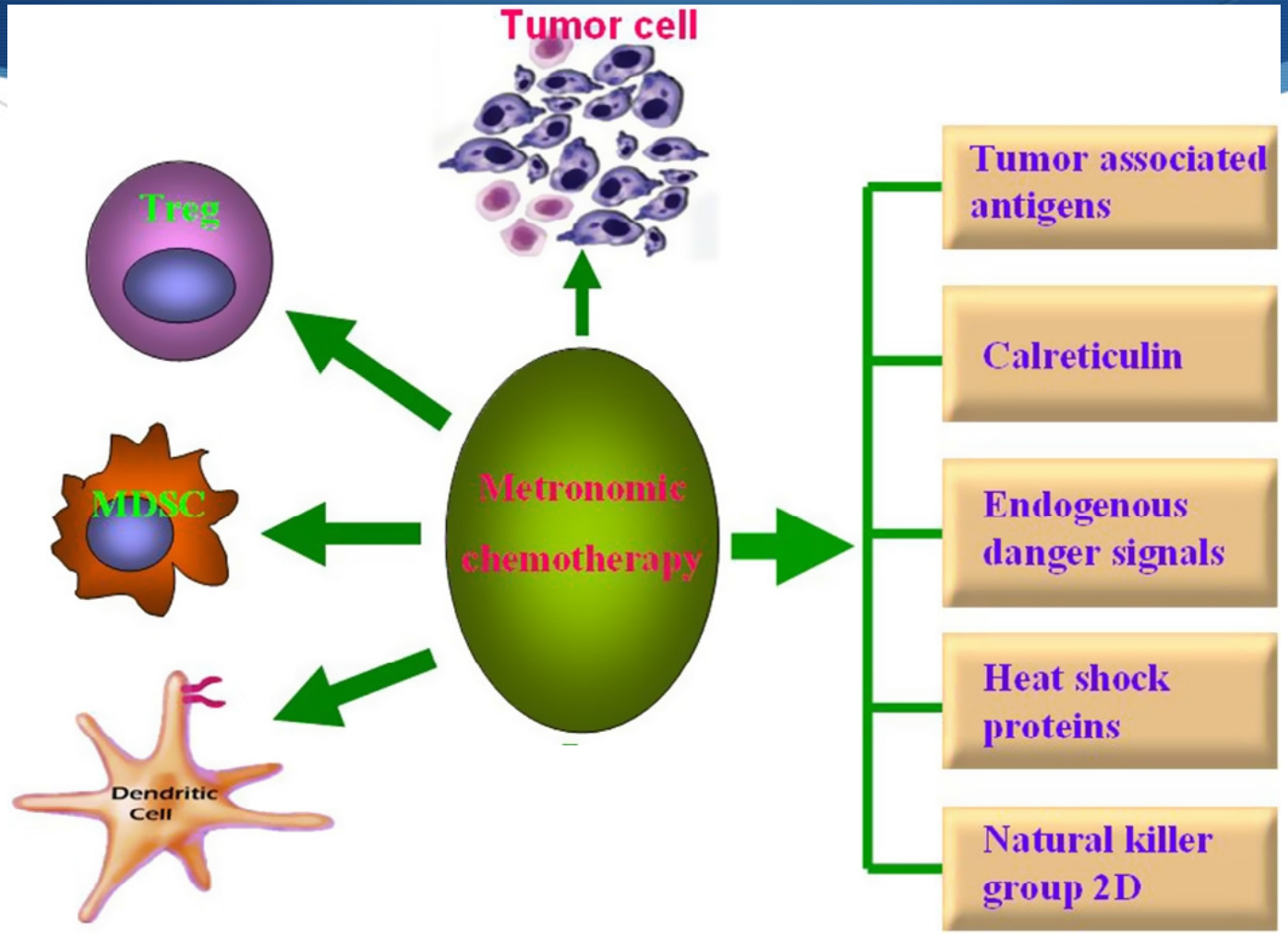
Eddy Pasquier, Maria Kavallaris and Nicolas André

NATURE REVIEWS | CLINICAL ONCOLOGY

Metronomic Chemotherapy



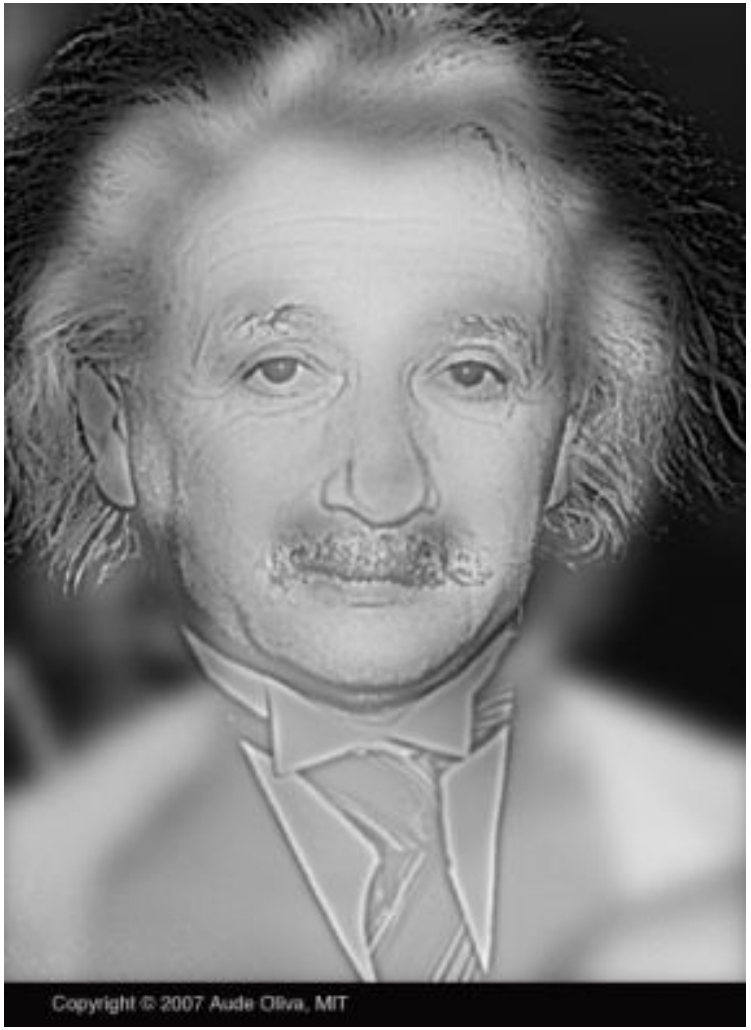
Metronomic & Immunity



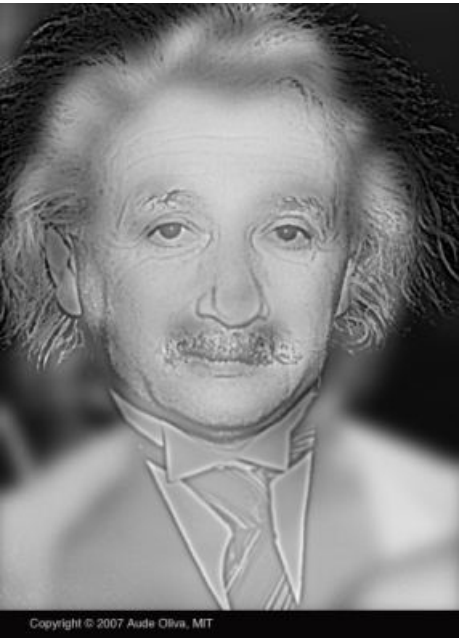
Yi-Bin Hao Cancer Letters 2014

MC tilts the immune system from immuno-suppression to immuno-stimulation.

1) Induces immunogenic cell death
2) Increases immunogenicity of cancer cells
3) Increases Ag presentation via Dendritic cells activation
3) Induces Treg Depletion
4) Modulates myeloidderived suppressor cells (MDSC)
5) Increaess the cytotoxic activity of T cells


Copyright © 2007 Aude Oliva, MIT

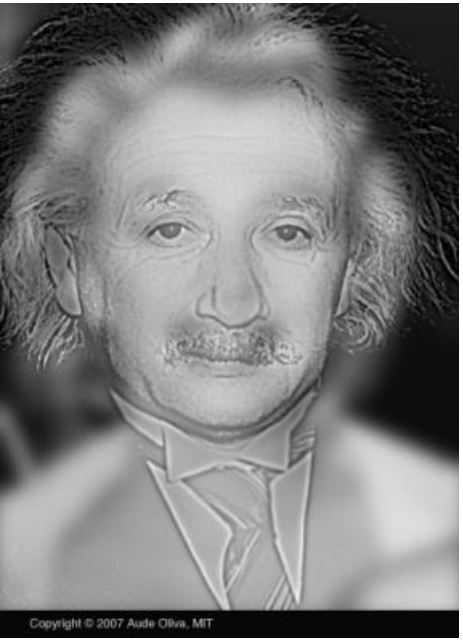
Metronomic temozolomide (cyclophosphamide)



TMZ TMZ TMZ TMZ TMZ TMZ TMZ TMZ
TMZ TMZ TMZ TMZ TMZ TMZ TMZ TMZ

Metronomic Treg Depletor ????
Antiangiogenic treatment ????

[Shevchenko IJC 2013], [Rozados Oncol Res 2010] [Ghirighelli CCI 2007] [Vincent CR 2010].

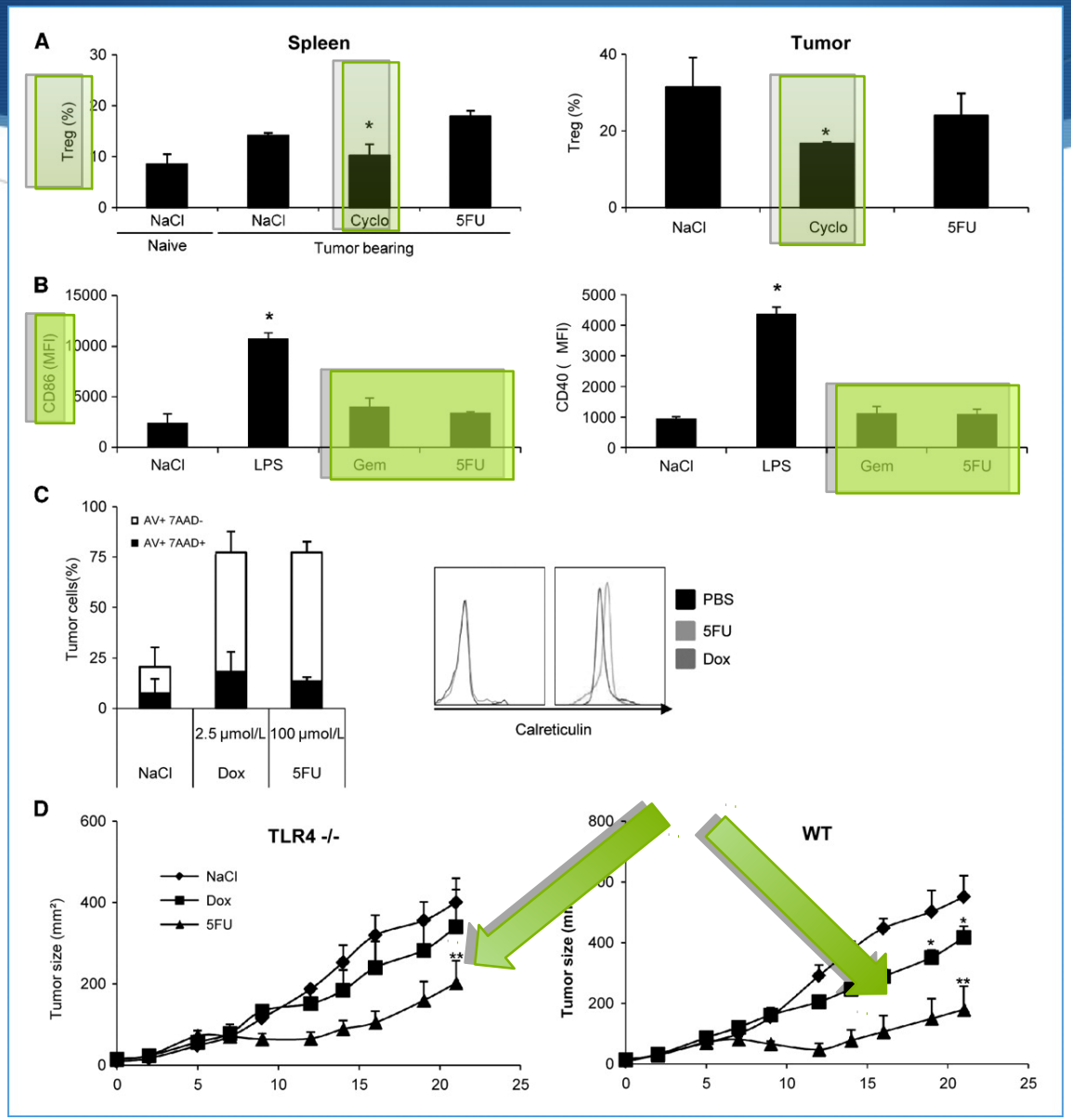


(Metronomic low) dose vinblastine

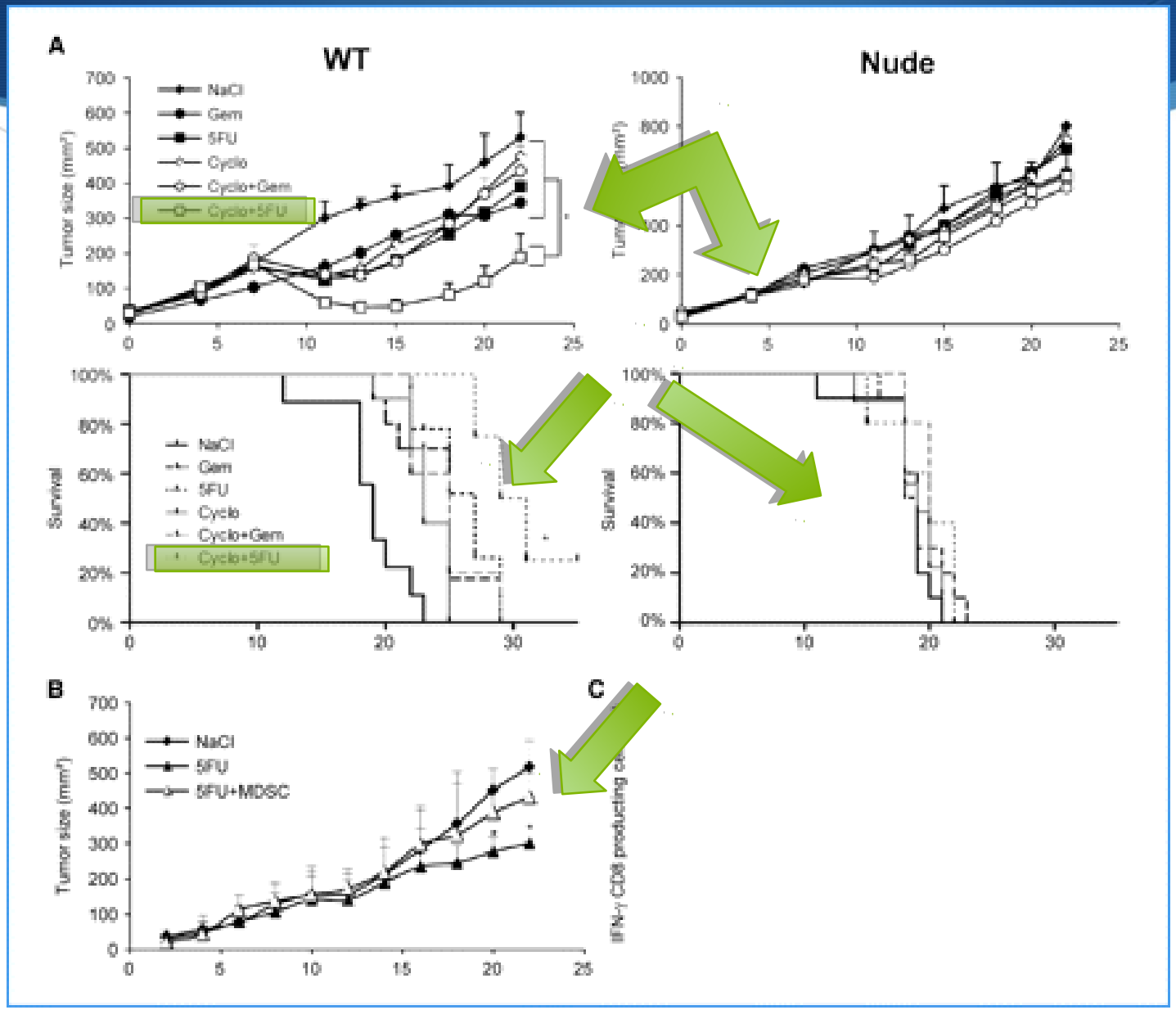
VBL VBL VBL VBL VBL VBL

Dendritic Cell Activator ????

Zitvogel Nat Rev Immunol 2008, [Mainetti Ann Oncol 210], [Fioravanti Eur J P 2009], [Vincent CR 2010], [Moes EJBP 2013], [Hodge IJC 2013], [Cerullo Mol Ther 2012], [Tongu CII 2013]



Vincent and al. ***5FU selectively kills tumor-associated myeloid-derived suppressor cells resulting in enhanced T cell-dependent antitumor immunity*** **Cancer Research 2010**



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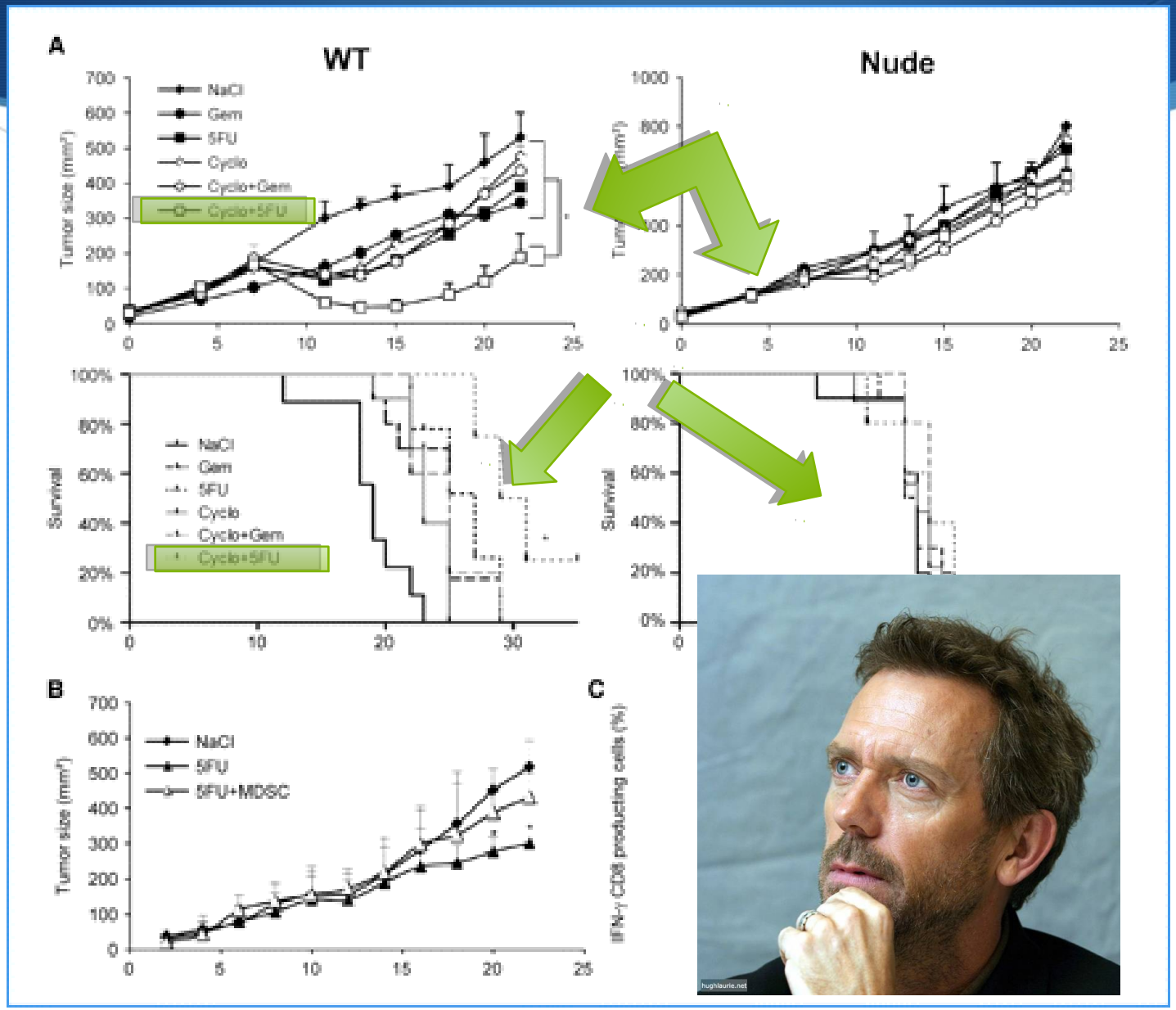

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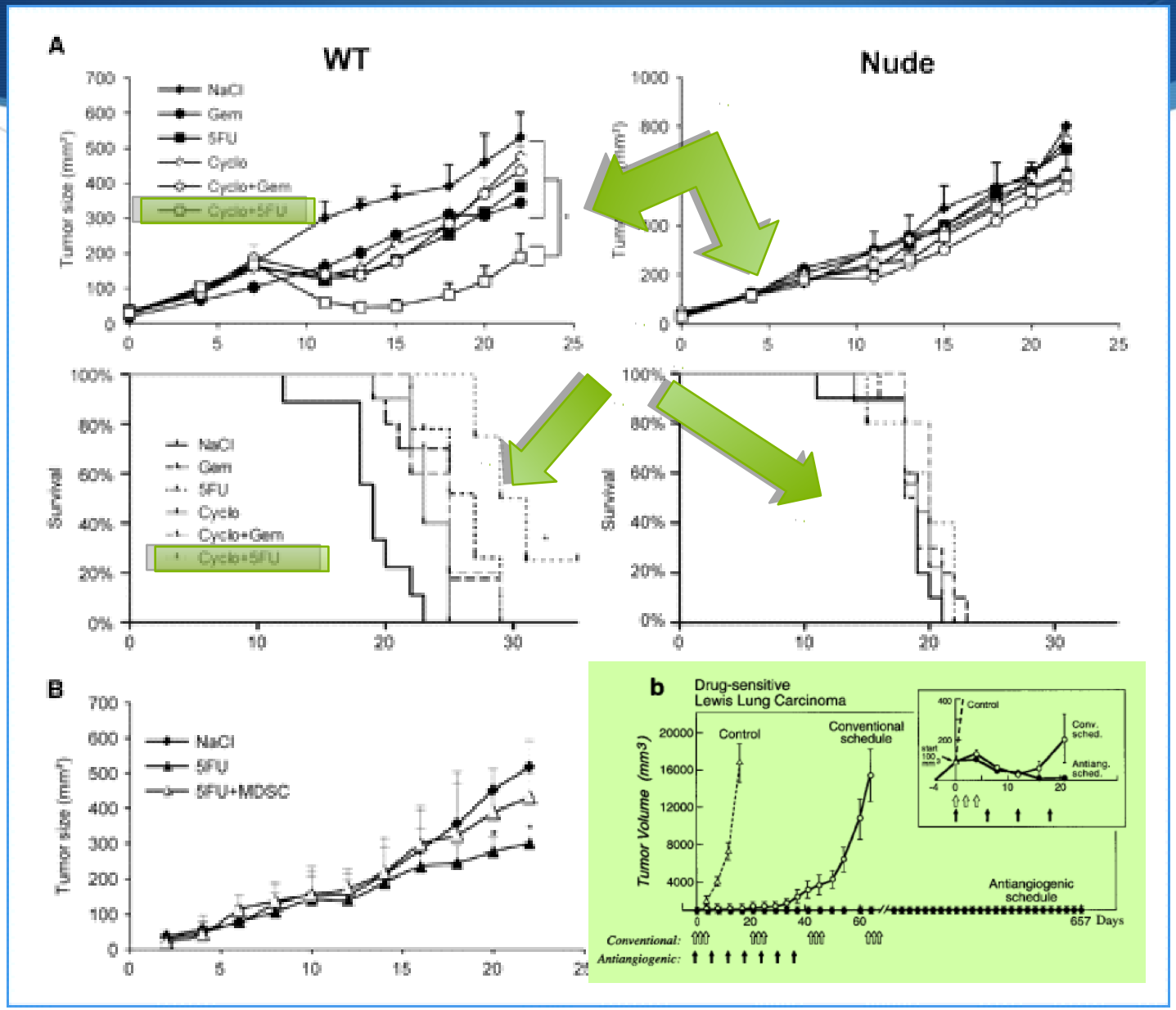

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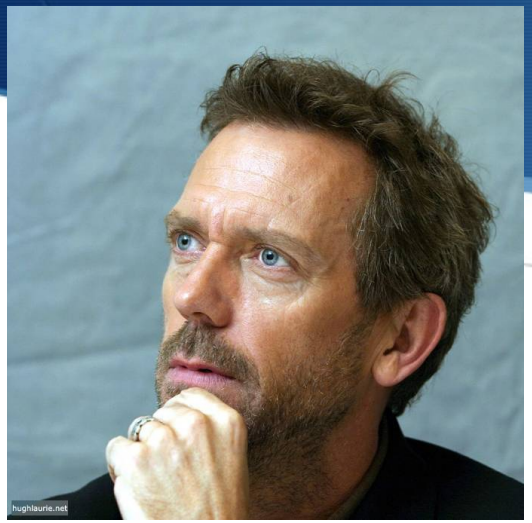
hughlaurie.net

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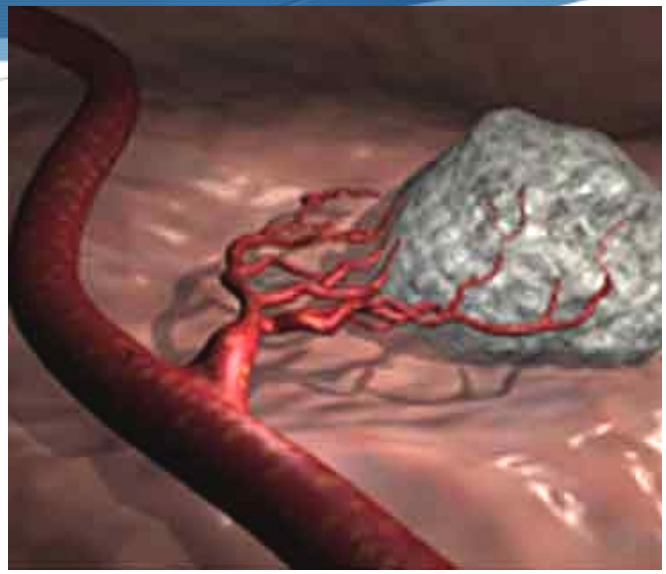
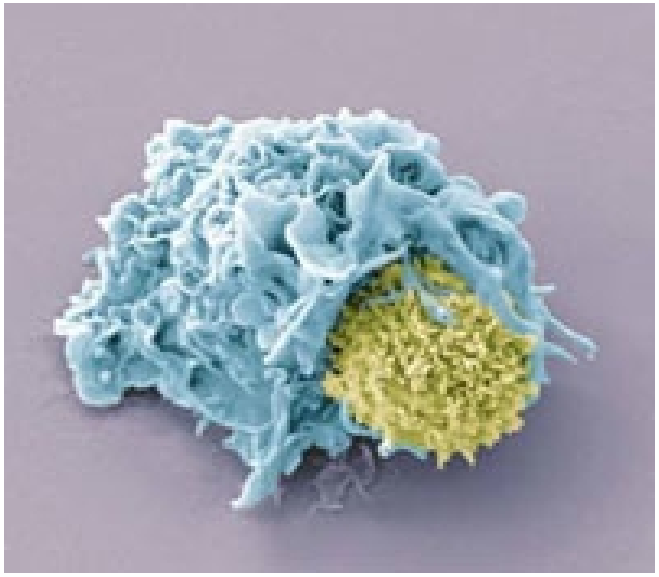




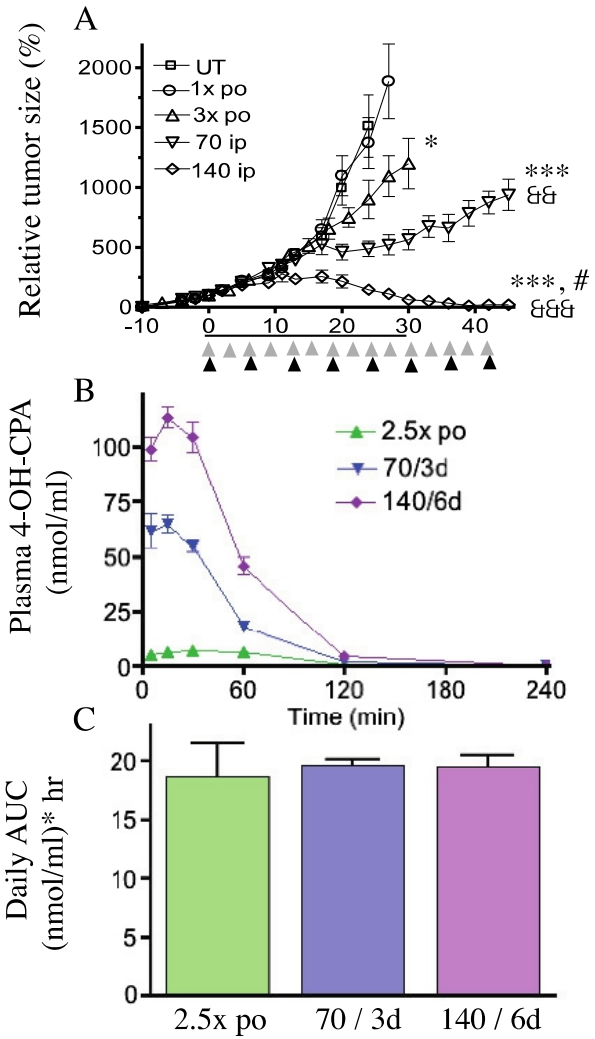
Volume 16 Number 1 January 2014 pp. 84–96 84

Intermittent Metronomic Drug Schedule Is Essential for Activating Antitumor Innate Immunity and Tumor Xenograft Regression[1,2]

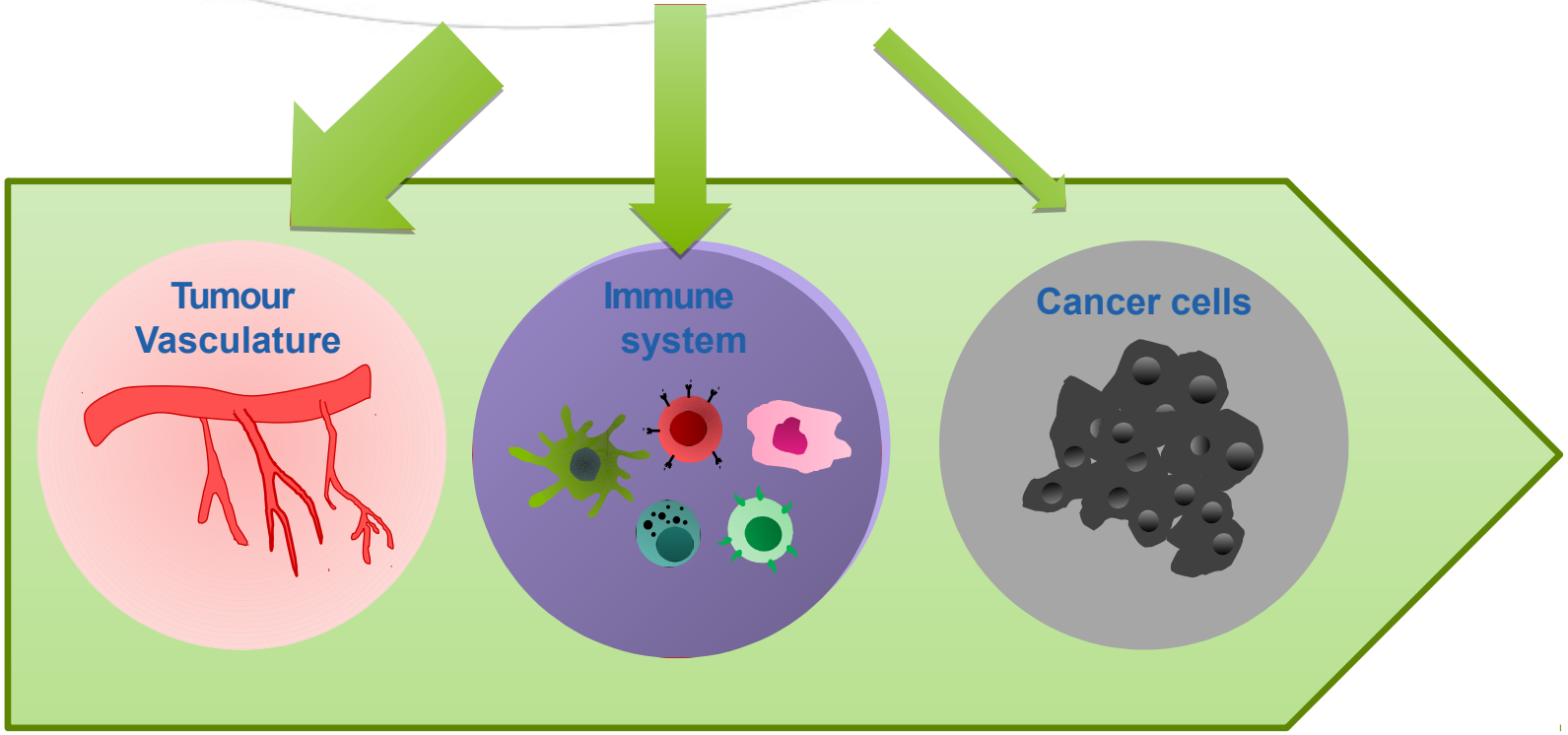
Chong-Sheng Chen[3], Joshua C. Doloff[3] and David J. Waxman

Division of Cell and Molecular Biology, Department of Biology, Boston University, Boston, MA

NEOPLASIA
www.neoplasia.com



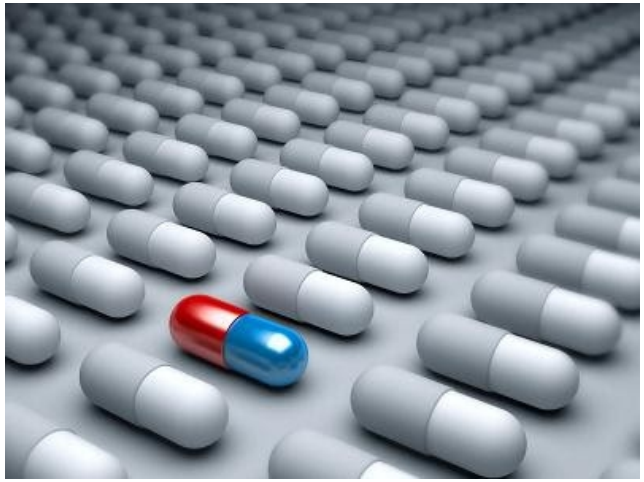
Metronomic Chemotherapy 2.0



Eddy Pasquier, Maria Kavallaris and Nicolas André

NATURE REVIEWS | CLINICAL ONCOLOGY

METRONOMICS 3.0



Metronomics: towards personalized

?y

NATURE REVIEWS CLINICAL ONCOLOGY
VOLUME 11 JULY 2014 34

METRONOMICS 3.0

New mechanisms of actions

Combination with modern therapies

- **drug repositioning**
- **target therapies**
- **immunotherapies**

Computational metronomics

Metronomics for low incomes coutries

METRONOMICS 3.0

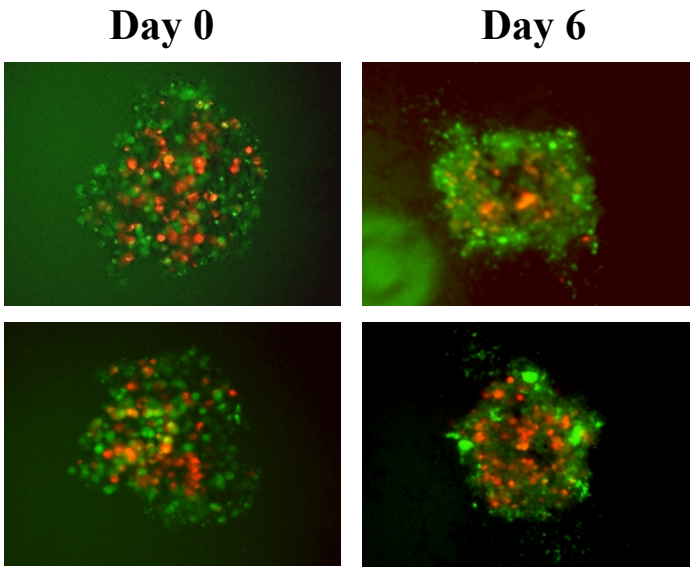
New mechanisms of actions

- **Action on clonal heterogenity**

  maintain biodiversity & avoid R-clone proliferation

  2D & 3D model of heterogenous lung cancer

Communication : Cecile Carrère
Optimal treatment for an heterogeneous in vitro tumor composed of resistant and sensitive cells.



- **Anti-metastatic effect**

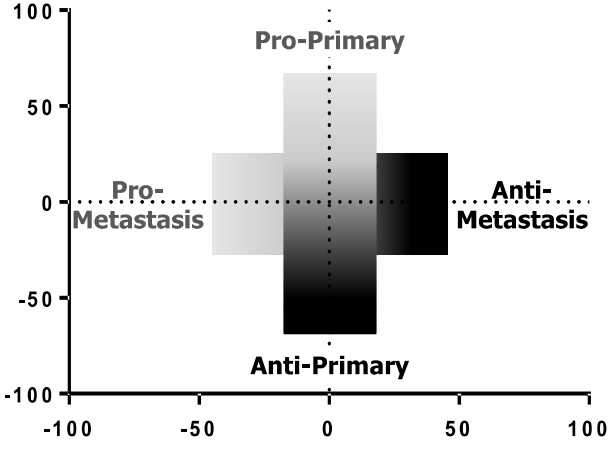
METRONOMICS 3.0

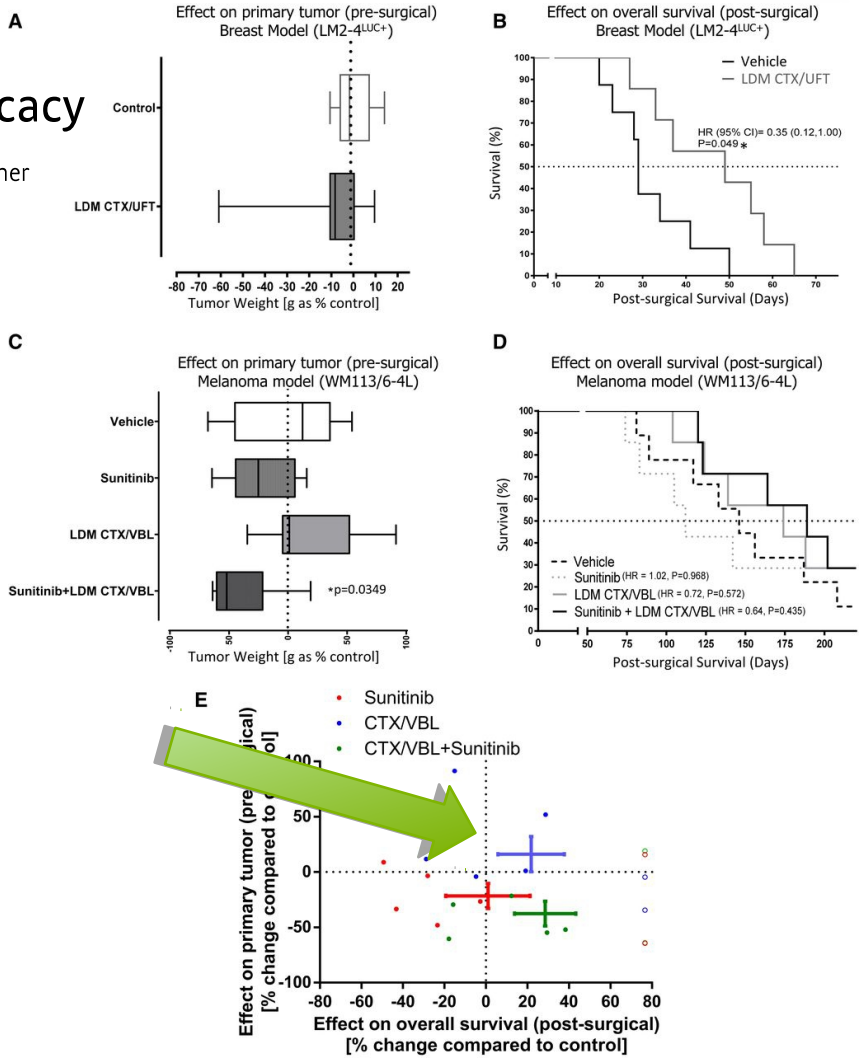
Neoadjuvant antiangiogenic therapy reveals contrasts in primary and metastatic tumor efficacy

John ML Ebos[1,*], Michalis Mastri[1], Christina R Lee[2], Amanda Tracz[1], John M Hudson[2], Kristopher Attwood[3], William R Cruz-Munoz[2], Christopher Jedeszko[2], Peter Burns[2,4] & Robert S Kerbel[2,4]

EMBO Molecular Medicine Vol 6 | No 12 | 2014

EMBO Molecular Medicine





METRONOMICS 3.0

aT ble 3|M etronomic hemotherapy nd mmunotherapy tudies n adults

aP tient population/ disease	Type of	n	rT eatment regimen		Best
y s[4]		71	virOncolytic su +	76% R:	1/17 PR:
y s[4]		8 12 7 7	virOncolytic su cyclophosphamide MC cyclophosphamide MTD virOncolytic virus oncolytic su + MTD cyclophosphamide MC	22% R: 61% R: 55% R: 77% R:	AN AN AN AN
crent varian [1]		6	+ + cyclophosphamide	C 33% R: %66	2/6 PR:
Unresectable prostate [2]	Randomized	A1: chemotherapy Standard A2: chemotherapy Standard	y y + + + GFS + antigen tumour	AN AN	AN AN
Metastatic [3]	II	82	vaccine DC + + cyclophosphamide +	57% R:	16/28 SD:
Metastatic breast [4]		12	‡ + cyclophosphamide + methotrexate	62% R:	2/21 CR: 3/21 PR:
Metastatic renal cell [5]	II	54	+ + +	76% R:	4/45 CR: 12/45 PR:

*Autologous -pulsed dendritic cell vaccination and adoptive transfer of -primed ex vivo co-stimulated T cells. ‡1E10 anti-idiotype. Abbreviations: CB, clinical benefit; CR, complete response; DC, dendritic cell; GSF, granulocyte colony-stimulating factor; IFN, interferon; IL, interleukin; MC, metronomic chemotherapy; MTD, maximum tolerated dose; NA, not available; PD, progressive disease; PR, partial response; RR, response rate; SD, stable disease.

André *Nature Reviews Clinical Oncology* 2014

METRONOMICS 3.0

MC :

-decreases “Treg”
- decreases immunosuppressive cytokines (TGF-β, IL-10 and IL-2)
- triggers T cell and INF-γ producing NK cell effector functions
- induces maturation of dendritic cells

MC : synergy anti- PD1 antibody in a pre-clinical model

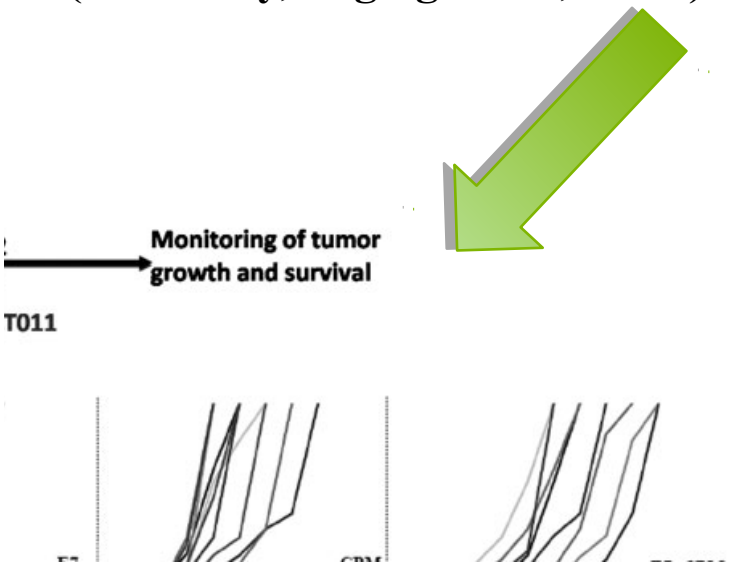
Well tolerated broad spectrum activity combination (immunity, angiogenesis, ect…)

European Journal of Immunology

Anti-PD-1 synergizes with cyclophosphamide to induce potent anti-tumor vaccine effects through novel mechanisms

Mikayel Mkrtichyan[1], Yana G. Najjar[1], Estella C. Raulfs[1], Maher Y. Abdalla[1], Raed Samara[1], Rinat Rotem-Yehudar[2], Larry Cook[3] and Samir N. Khleif[1]

Eur. J. Immunol. 2011. 41: 2977–2986



METRONOMICS 3.0

Combination with modern therapies

- **drug repositioning**

- **target therapies**
  - **intrinsic activity**
  - **well tolerated**
  - **potential synergies**
  - **limits monoclonal R emergence**

- **immunotherapies**

Propranolol for Severe Hemangiomas of Infancy

The NEW ENGLAND JOURNAL of MEDICINE

June 2008, 358 (24): 2649-51

Christine Léauté-Labrèze, M.D.
Eric Dumas de la Roque, M.D.
Thomas Hubiche, M.D.
Franck Boralevi, M.D., Ph.D.
Jean-Benoît Thambo, M.D.
Alain Taïeb, M.D.

Could β-blockers be used in cancer treatment ?

→HYPOTHESIS

β-blockers may be able to increase the efficacy of chemotherapy through direct effects on cancer cells or *via* anti-angiogenic mechanisms

Oncotarget, Nov 2010, 1 (7): 628-68

Beta-Blocker Drug Therapy Reduces Secondary Cancer Formation in Breast Cancer and Improves Cancer Specific Survival

Desmond G. Powe[1], Melanie J. Voss[2], Kurt S. Zänker[2], Hany O. Habashy[3], Andrew R. Green[3], Ian O. Ellis[3] & Frank Entschladen[2]

J Clin Oncol, July 2011, 29 (19): 2635-62

Beta Blockers and Breast Cancer Mortality: A Population-Based Study

Thomas I. Barron, Roisin M. Connolly, Linda Sharp, Kathleen Bennett, and Kala Visvanathan

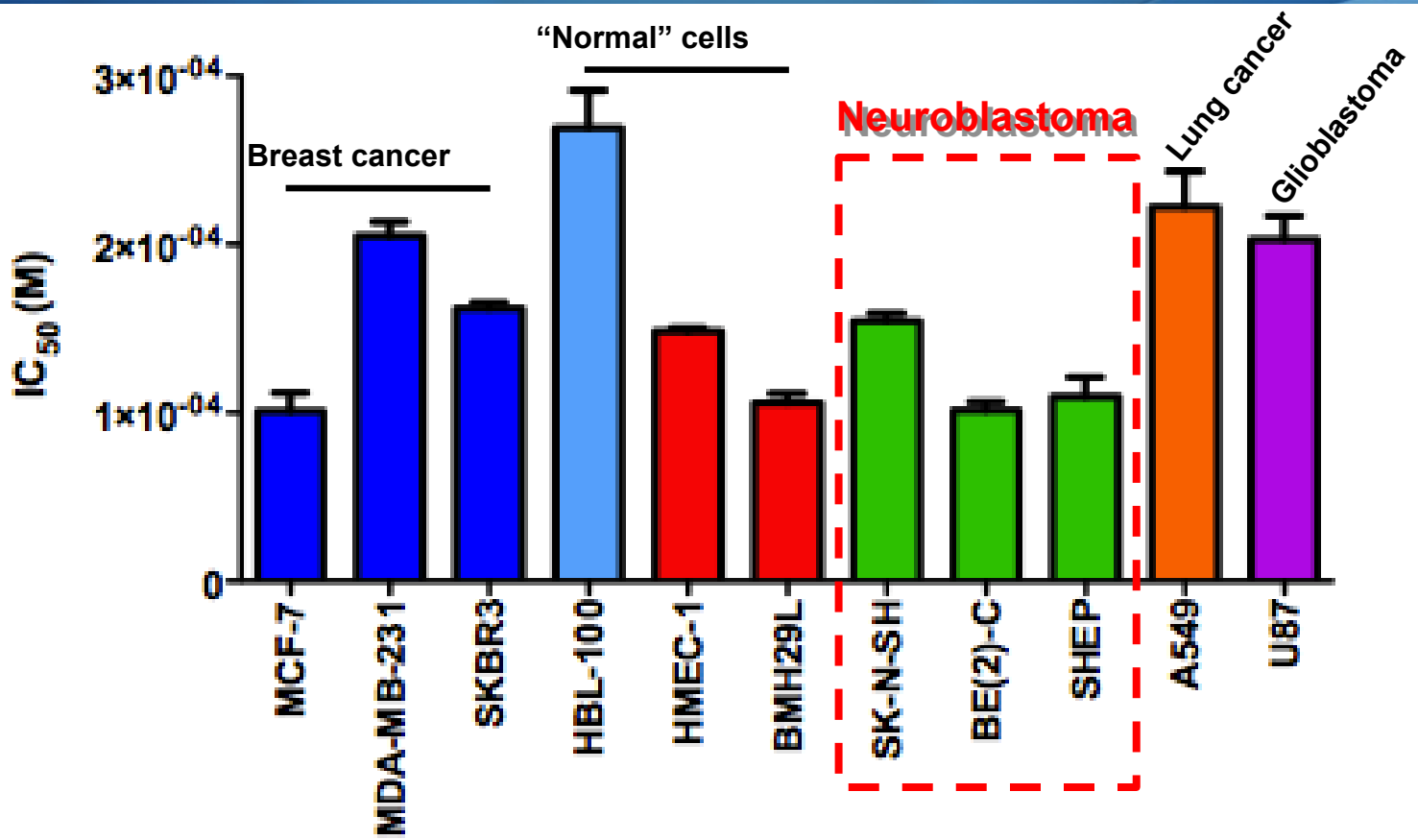
Beta-Blocker Use Is Associated With Improved Relapse-Free Survival in Patients With Triple-Negative Breast Cancer

Amal Melhem-Bertrandt, Mariana Chavez-MacGregor, Xiudong Lei, Erika N. Brown, Richard T. Lee, Funda Meric-Bernstam, Anil K. Sood, Suzanne D. Conzen, Gabriel N. Hortobagyi, and Ana-Maria Gonzalez-Angulo

Expanding Our Therapeutic Options: Beta Blockers for Breast Cancer?

Patricia A. Ganz, *University of California, Los Angeles (UCLA) School of Public Health; Jonsson Comprehensive Cancer Center at UCLA; David Geffen School of Medicine at UCLA, Los Angeles, CA*
Steven W. Cole, *Jonsson Comprehensive Cancer Center at UCLA; David Geffen School of Medicine at UCLA; Norman Cousins Center for Psychoneuroimmunology at UCLA; and UCLA Molecular Biology Institute, Los Angeles, CA*

Anti-proliferative properties of propranolol



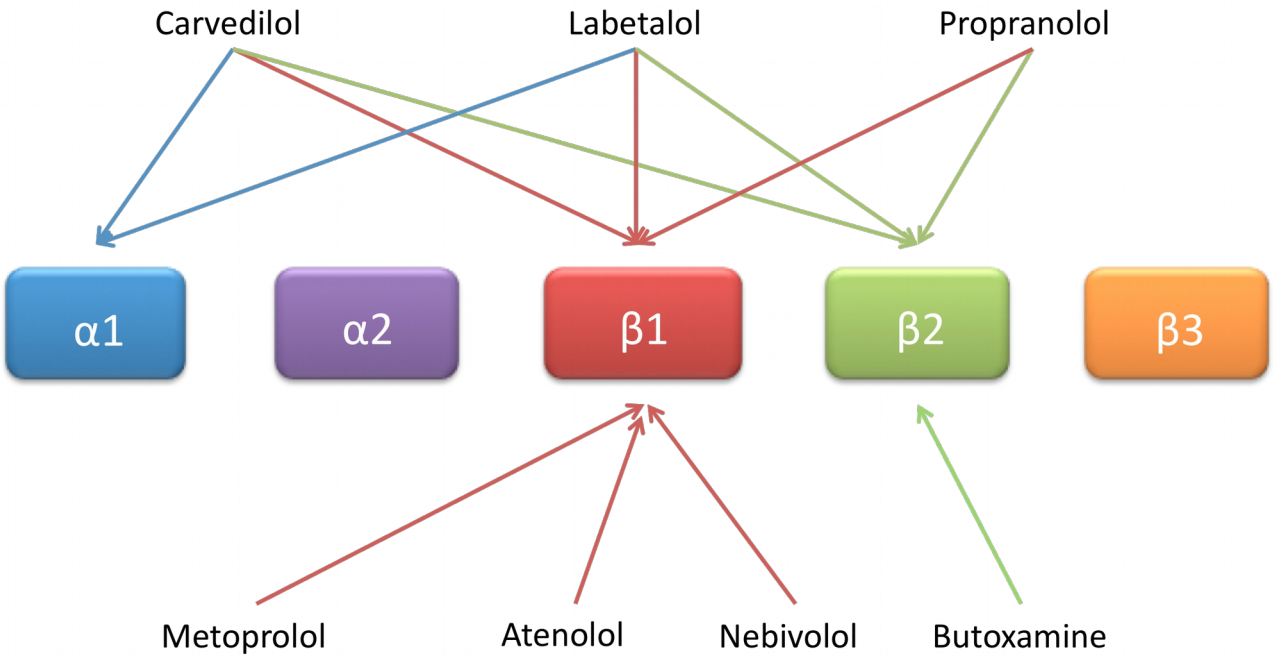
Growth inhibition assay, 72h drug incubation

STUDY DESIGN

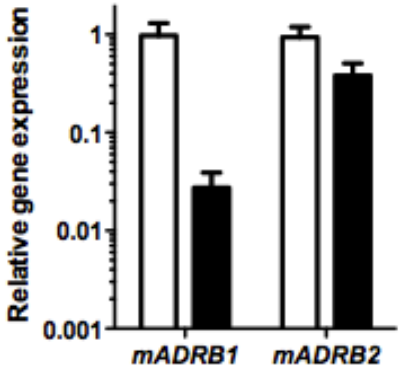
7 β-blockers with different selectivity for the β-adrenergic receptors

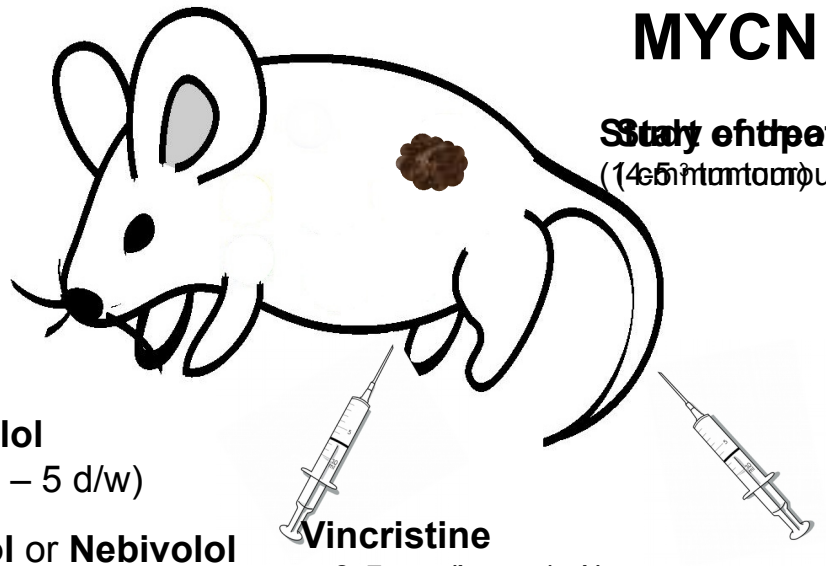
Anti-proliferative & anti-angiogenic properties

Combination with 7 chemotherapy agents *in vitro*



In vivo drug combination studies
TH-MYCN model of neuroblastoma





Propranolol
(50 mg/kg – 5 d/w)

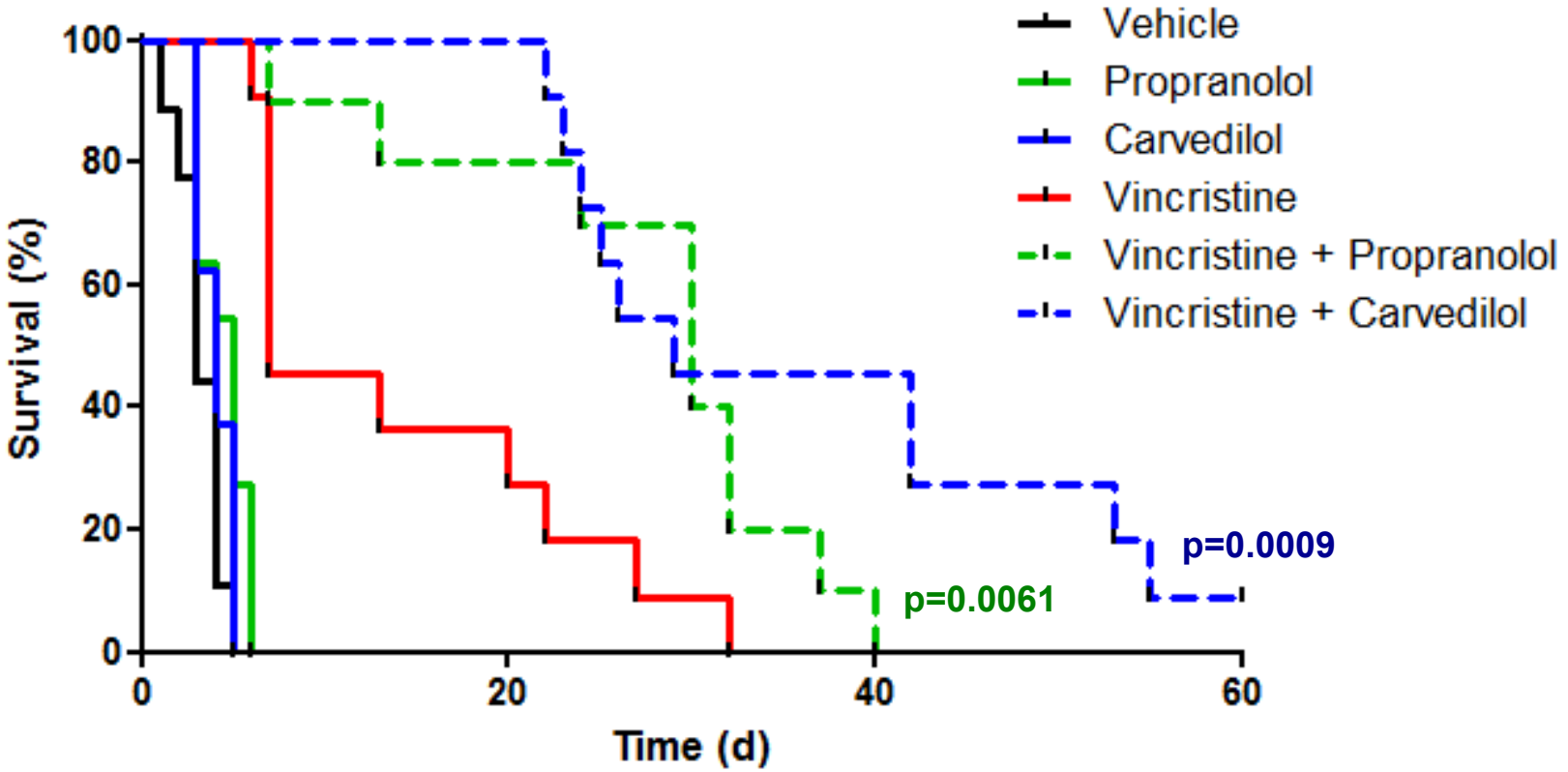
Carvedilol or **Nebivolol**
(10 mg/kg – 5 d/w)

Vincristine
0.5 mg/kg – 1 d/w

METRONOMICS
Global Health Initiative

In vivo drug combination studies

TH-MYCN model of neuroblastoma



β-blockers in combination with vincristine prolong median survival in TH-MYCN mice

Neuroblastoma study

BJC

British Journal of Cancer (2013), 1–10 | doi: 10.1038/bjc.2013.205

Keywords: neuroblastoma; β-blockers; chemotherapy; angiogenesis; vincristine; mitochondria

β-blockers increase response to chemotherapy via direct antitumour and anti-angiogenic mechanisms in neuroblastoma

E Pasquier*[,1,2], J Street[1], C Pouchy[1,8], M Carre[3], A J Gifford[1,4], J Murray[1], M D Norris[1], T Trahair[1,5], N Andre[2,3,6,9] and M Kavallaris[1,7,9]

www.impactjournals.com/oncotarget/ Oncotarget, January, Vol. 5, No. 1

Anti-tumor activity of the beta-adrenergic receptor antagonist propranolol in neuroblastoma

Jennifer K Wolter[1,2], Nikolaus E Wolter[3], Alvaro Blanch[2], Teresa Partridge[2], Lynn Cheng[2], Daniel A. Morgenstern[1,2], Monika Podkowa[2], David R. Kaplan[2,4], Meredith S. Irwin[1,2]

« Previous Journal of Pediatric Surgery Next »
Volume 48, Issue 12 , Pages 2460-2465, December 2013

Antiangiogenic effect of propranolol on the growth of the neuroblastoma xenografts in nude mice☆

Ting Xu, Xianmin Xiao✉, Shan Zheng, Jicui Zheng, Haitao Zhu, Yi Ji, Shaobo Yang

METRONOMICS 3.0

aT ble 2|M etronomic hemotherapy nd argeted herapies in adults

Patient population/ disease [illegible]	Type of study	n	Treatment regimen	[illegible]	Best [illegible]
[illegible] Relapsed [illegible]	[illegible] II	34	[illegible] + [illegible]	53[illegible] RR:	5/43 PR:
[illegible] stoma rent [illegible]	[illegible] II	32	[illegible] + etoposide ro [illegible]	52[illegible] RR:	12/23 SD:
[illegible] Advanced y [illegible] carcinomatical [illegible]	[illegible] II	01	[illegible] + [illegible]	0[illegible] RR:	9/9 PD:
[illegible] recurresistant rent cervarian [illegible]	[illegible]	66	[illegible] + [illegible]	65[illegible] RR:	7/66–CR: 21/66 PR:
[illegible] orent cervarian [illegible]	[illegible]	83	[illegible] + [illegible]	49[illegible] RR:	3/37–CR: 12/37 PR:
[illegible] Metastatic [illegible]	[illegible] I	32	[illegible] + [illegible]	+25[illegible] RR:	2/20 PR:
Metastatic HER2 breast [illegible]	[illegible] II	42	[illegible] + [illegible] + [illegible]	83[illegible] RR:	1/24–CR: 14/24 PR:
[illegible] Metastatic [illegible]	[illegible] II	31	[illegible] + [illegible]	54[illegible] RR:	1/13 PR:
Advanced colorectal [illegible]	[illegible] I	53	[illegible] + [illegible] + [illegible]	20[illegible] RR:	7/35 SD:
[illegible] Advanced [illegible]	[illegible] II	54	[illegible] + [illegible] + [illegible]	87[illegible] RR:	31/45 PR:
Refractory/ relapsing [illegible]	Randomized [illegible] II	[illegible]	[illegible] + [illegible]	66[illegible] RR: 75[illegible] RR:	20/58 PR: 21/57 PR:
Advanced hepatocellular [illegible]	[illegible] II	35	[illegible] + [illegible]	57[illegible] RR:	4/53 PR:
[illegible] y solid tumour [illegible]	[illegible] I	53	[illegible] + [illegible]	40[illegible] RR:	7/35 PR:
Advanced neuroendocrine [illegible]	study Pilot	51	[illegible] + [illegible] +	80[illegible] RR:	1/15–CR: 8/15 PR:
[illegible] Gynaecological [illegible]	study PK	12	[illegible] + [illegible]	AN	AN

[illegible] viations: [illegible] clinical benefit; [illegible] not available; NSCLC [illegible] -cell lung cancer; PD, progressive disease; PR, partial response; RR, response rate; DS , stable [illegible]

André, Carré, Pasquier *Nature Reviews Clinical Oncology* 2014

METRONOMICS 3.0

Computational metronomics

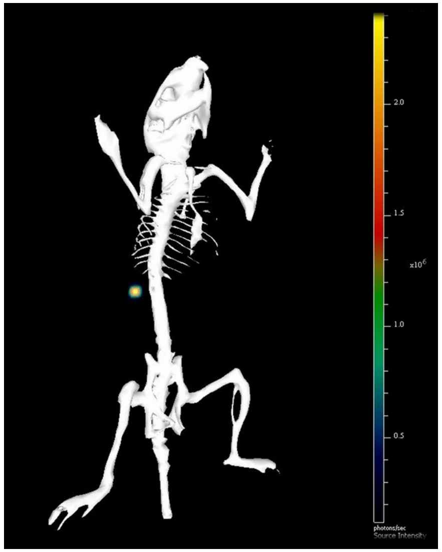
- use of modelisation to optimize
  - Dose & Schedule
  - Sequence of treatments
  - Biological effect

Urzula Ledzewicz
Modelling and Optimization
Of Metronomic chemotherapy : More questions than answers

Aurelie Lombard: Revisiting metronomics: model-driven gemcitabine in mice with resistant neuroblastoma.

Computational Metronomic

$$\dot{y}_1 = -k_a y_1 + u(t)$$
$$\dot{y}_2 = -k_e y_2 + \frac{k_a}{V} y_1$$
$$\dot{y}_3 = -a_1 \exp(-b_1 y_3) y_3 + (y_2 - c_1) H(y_2 - c_1)$$
$$\dot{y}_4 = -a_2 \exp(-b_2 y_4) y_4 + (y_2 - c_2) H(y_2 - c_2)$$
$$\dot{y}_5 = \lambda y_6 \log\left(\frac{K}{y_5}\right) y_5 - N_1 y_5$$
$$\dot{y}_6 = R - (R + N_2) y_6$$
$$\dot{y}_7 = (y_2 - c_1) H(y_2 - c_1)$$



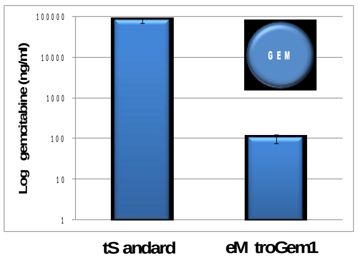
D3 LD Tlm igtion of tumorrgwo th using
vl isufS mtceclo (Pgeyk imE re)

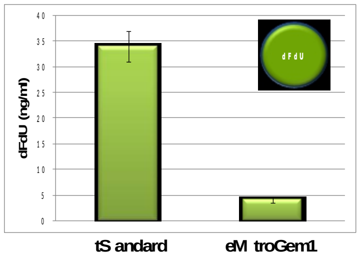
- y1, y2 :hp racan ko ri ite codn leri gR) fo eg trio ba ri e.
- y3, y4 : feef t fo eg trio ba ri e no me ec sll y(3)oda no ne od te ai lec sll y(4).
- y5 rot rrghtw .
- y6 :na it ra iggo ne ci feef t fo eg trio ba ri e.eT ab es ril eav ul e 1si of on na it ra iggo ne ci feef t.nA na it - na iggo ne ci feef tsi tp rew y6)(< 1.
- y7 :ea rd et uc vr e fo lpsa am oc on ne at ot n y2htw al ht se oh d AC) .

Computational Metronomic

100 mg/kg QW - 4 weeks
0.5 and 1 mg/kg/d - 4 weeks

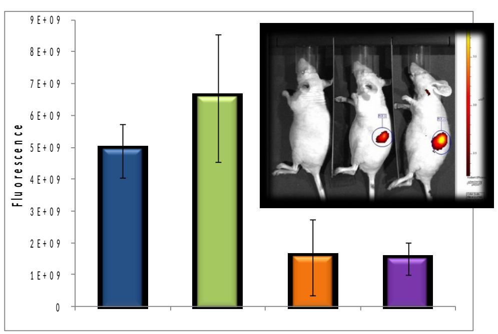
Gemcitabine Drug Monitoring

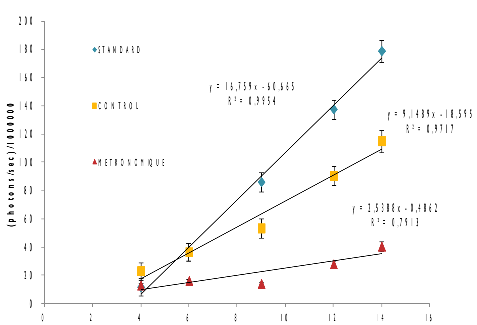




s in plasma re
50 l0 ower with Met -1

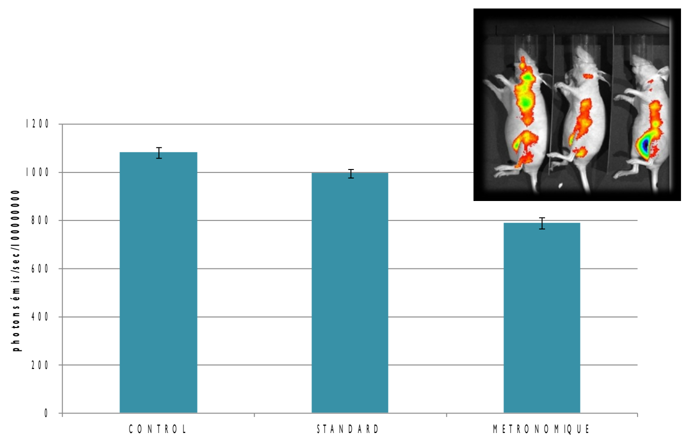
Vascular Density & Blood Flow





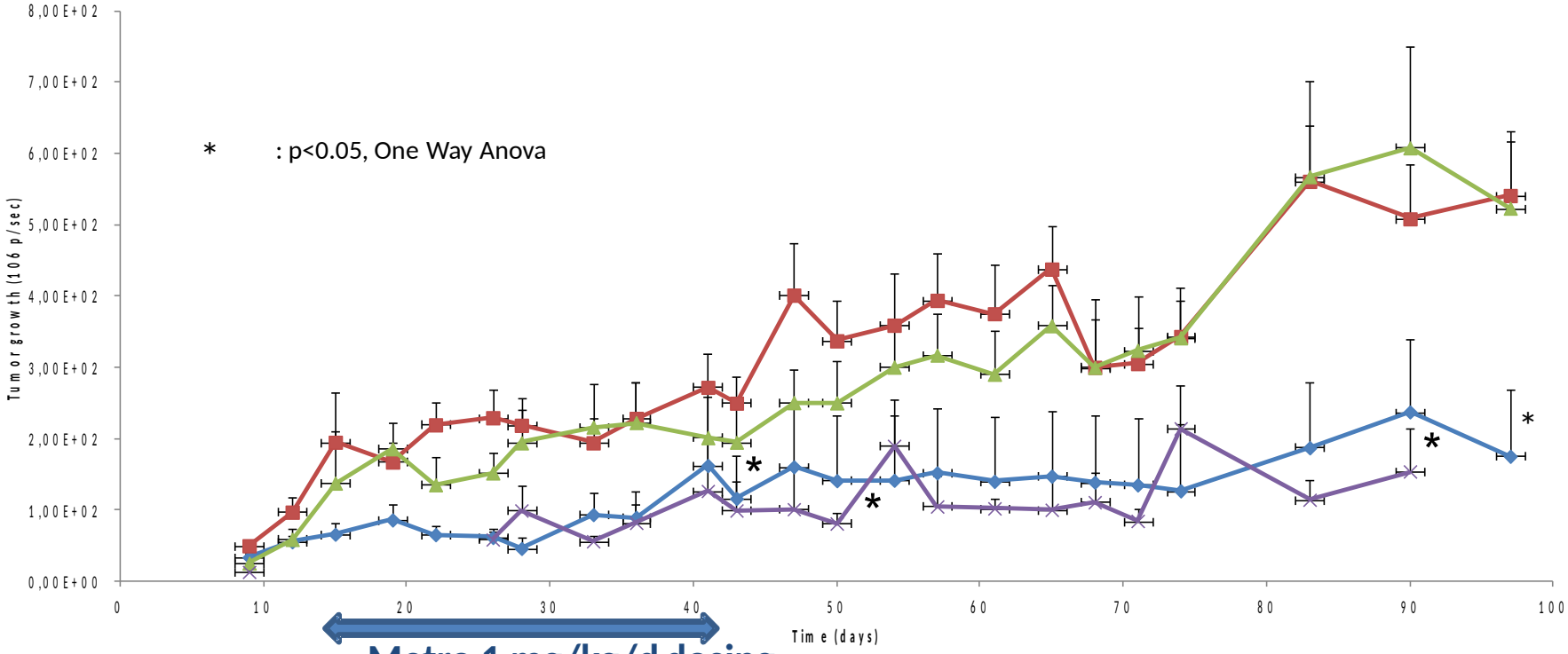
nsity red
w was observed in Met .n

Tumor Inflammation



observed with Met -1

Computational Metronomic

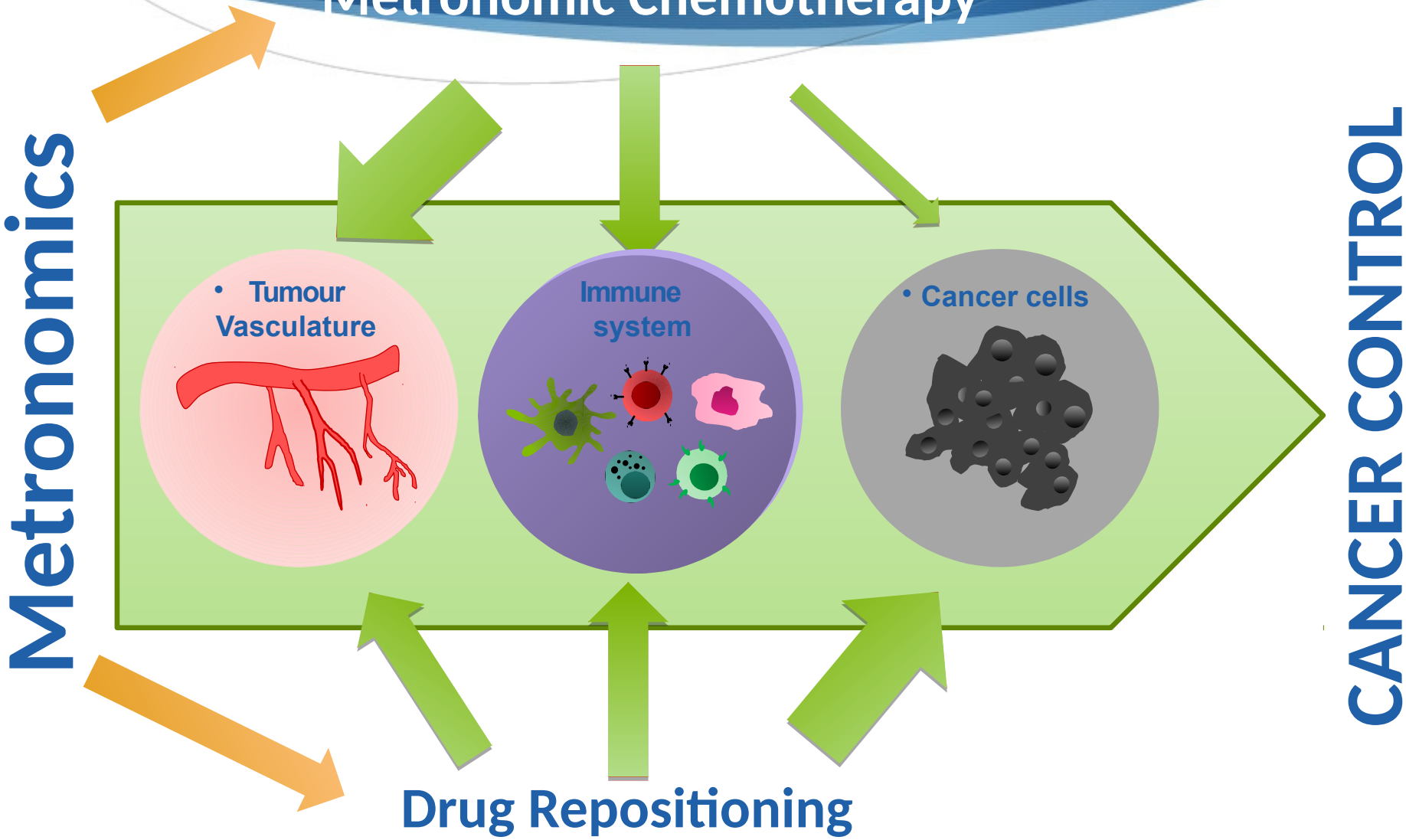


Metro 1 mg/kg/d dosing

Metro 0.5 mg/kg/d dosing

Injection 100 mg/kg

Metronomic Chemotherapy



André et al. *Lancet Oncol 2013*

METRONOMICS 3.0

- **LOW COST, ORAL, NON TOXIC,**
- **CLINICAL ACTIVITY**
- **MULTITARGET**
  - **Angiogenesis**
  - **Immune system**
  - **Stroma**
  - **Cancer cells & stems cells**
- **COMBINATION (sequential / associated)**
  - **drug repositioning**
  - **Chemotherapy**
  - **Immunotherapy +++**
  - **Target therapy**
- **COMPUTATIONAL METRONOMIC**

  PK, biomarkers, molecular biology

Orion 4 1/2 years old boy

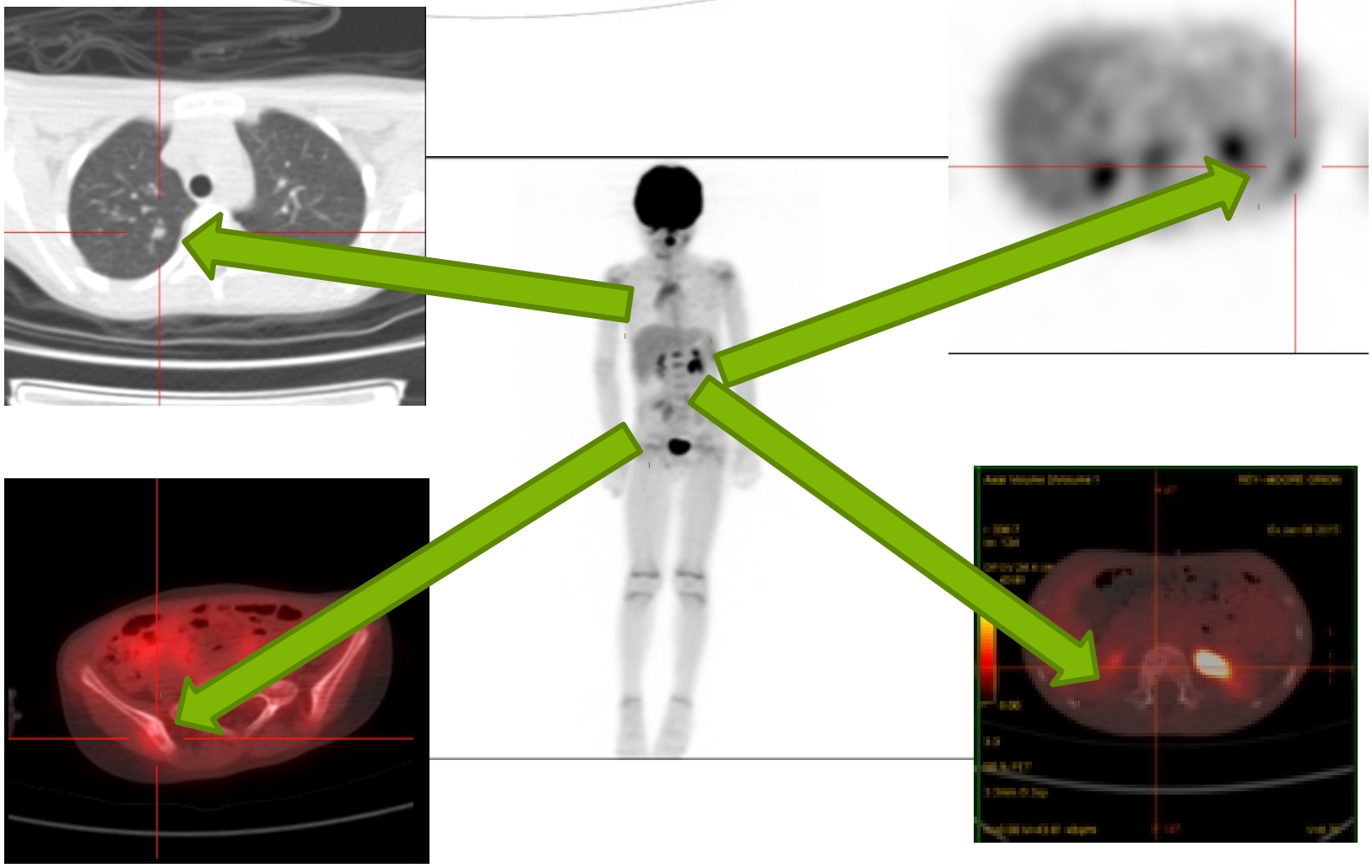
Retroparotid mass + lymph nodes

Myoepithelial carcinoma

- Ifosphamide-vcr-actD- doxo x 2: SD
- Gemcitabine-docetaxel x2: SD
- 5FU-cisplatinum x2: SD
- Surgery
- Radiotherapy

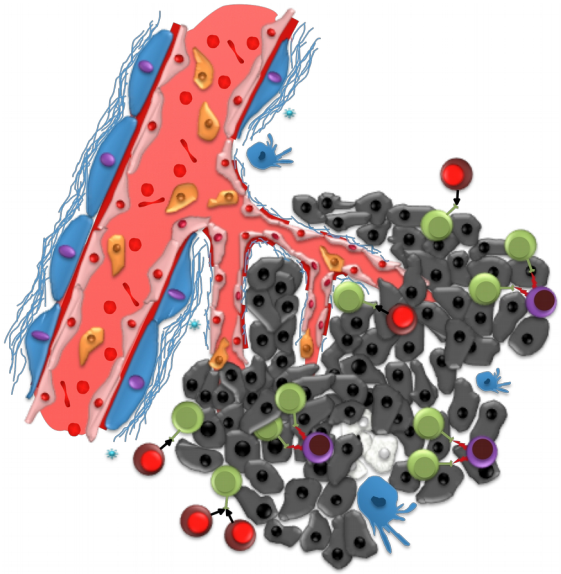
-> CR

One year later…



METRO-SFCE01

1. Metronomic regimen for children with refractory disease
2. Multi-drug
3. Low toxicities
   (no temo- no eto)
4. Mainly Oral
5. Pro-immune and antiangiogenic
   - Treg
   - Activate Dendritic cells

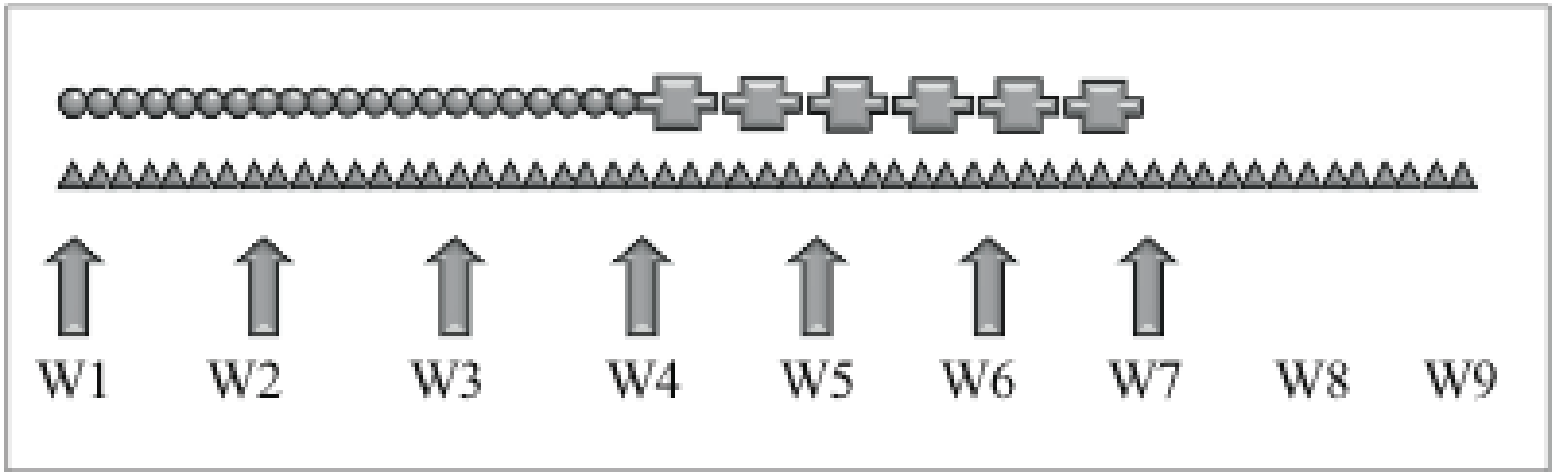


Pasquier, André NRCO 2010

Pilot study of a pediatric metronomic 4-drug regimen

Nicolas André[1,2], Sylvie Abed[1], Daniel Orbach[3], Corinne Armari Alla[4], Laetitia Padovani[5], Eddy Pasquier[2,6], Jean Claude Gentet[1], Arnauld Verschuur[1,2]

Oncotarget, December, Vol.2, No 12

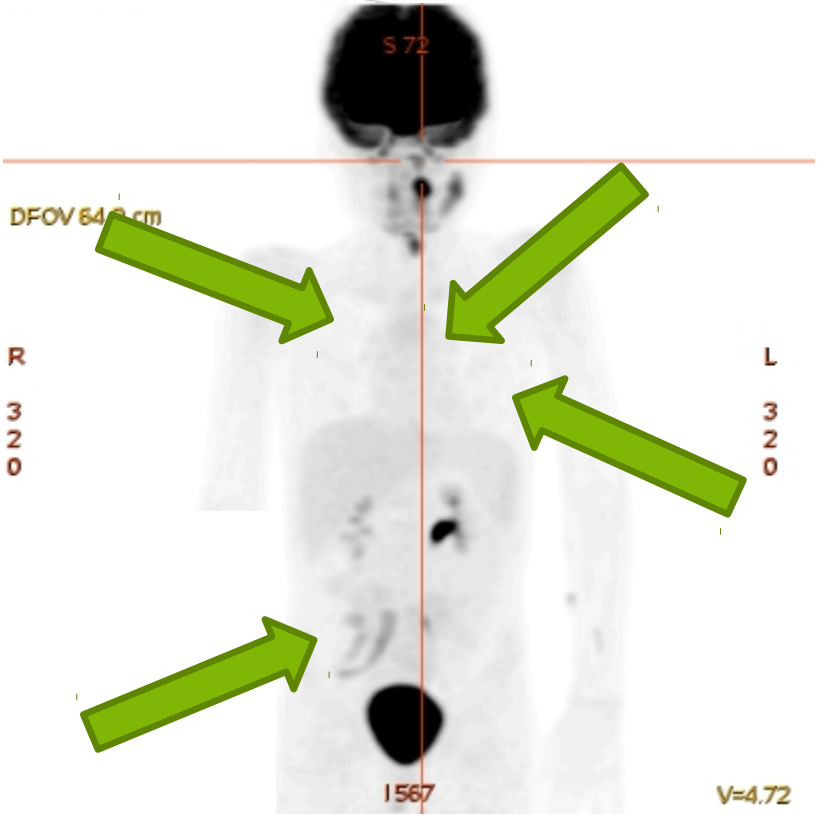


Cyclophophamide 30 mg/m2/day PO for 3 weeks

Celecoxib 100-200-400 mg/x2/day PO for 8 weeks (<20 kg BW, 20-50 kg, > 50 kg, respectively)

Methotrexate 10mg/m² 2X/week PO for 3 weeks

Vinblastine 3 mg/m²/week IV 7 weeks



CR : 3 months of treatment
SD : 6 months of on going treatment

Have the courage to follow
your heart and intuition.
They somehow already know
what you truly want to become

Steve Jobs
1955 - 2011

Scientific & Medical Innovation

Must be shared

Low and Middle Income Ccountries

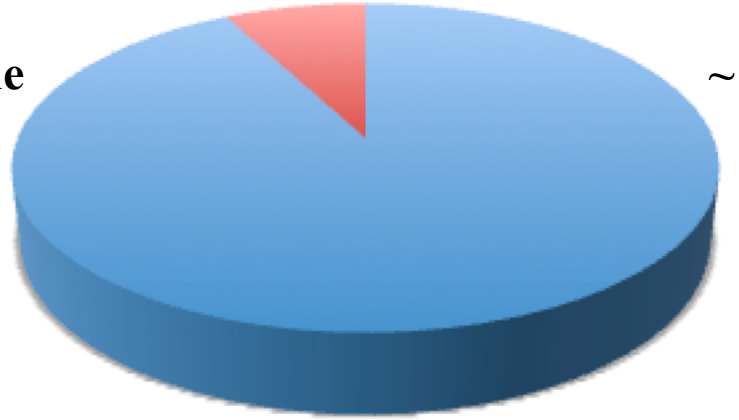
Social innovation Mandatory

CHILDHOOD CANCER

Each year ~250,000 children are affected by cancer worldwide

~ 50,000 in high-income countries

>75% survival rate



~ 200,000 in low- & middle-income countries

<25% survival rate

Advantages of Metronomics in LMICs

- **Off-patent drugs = low cost**
- **Oral formulations = no hospitalization required**
- **Low toxicity = less II^R infections**

Cheap, non-toxic and easy to administer

METRONOMICS 3.0

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Has the time come for metronomics in low-income and middle-income countries?

Nicolas André, Shripad Banavali, Yuliya Snihur, Eddy Pasquier

	Patient population	Metronomic protocol	Response (%)	Other outcomes (median)	Clinical benefit
Paediatric studies					
Banavali et al (2002)[47]	Residual or recurrent Ewing's sarcoma or rhabdomyosarcoma (n=7)	Oral tamoxifen once daily, oral etoposide once daily for 3 weeks, and cyclophosphamide once daily for 3 weeks	CR 28·5%, PR 42·8%, SD 28·5%,	EFS 5 months, OS 14 months	..
Banavali et al (2004)[48]	Children and young adults with acute myeloid leukaemia (n=26)	Oral prednisolone for 21 days, oral etoposide for 21 days, and oral tioguanine for 21 days	RR 89%, CR 62%, PR 27%	OS 13 months (range 3–30)	..
Banavali et al (2005)[49]	Children and young adults with acute promyelocytic leukaemia (n=23)	Oral prednisolone for 21 days, oral etoposide for 21 days, and oral tioguanine for 21 days with all-trans retinoic acid	CR 91·3%,	Two induction deaths, OS 84% at 2 years	..
Fousseyni et al (2011)[50]	Refractory or relapsing solid tumours (n=12)	Oral cyclophosphamide once daily for 3 weeks alternating with oral methotrexate twice a week for 3 weeks and intravenous vincristine once a week every 8 weeks	RR 0%	..	Mean 58% at 20 weeks
Banavali et al (2011)[51]	Maintenance after standard acute therapy in children with acute myeloid leukaemia (n=87)	Oral etoposide once daily for 3 weeks and oral tioguanine for 21 days	Relapse rate decreased to 23·7%	EFS 67% and OS 64% at 28 months	..

METRONOMICS GLOBAL HEALTH INITIATIVE

Network
Website
Meetings
Preclinical work
Clinical studies
Publications

Metronomics.newethicalbusiness.org

SOCIÉTÉ INTERNATIONALE D'ONCOLOGIE PÉDIATRIQUE
SIOP
INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

SIOP 2015
CAPE TOWN

47th Congress of the International Society of Paediatric Oncology

October 8 -11, 2015
Cape Town, South Africa

Math & Cancer Workshop

CIRM 7-11 dec 2015
Marseille, France

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