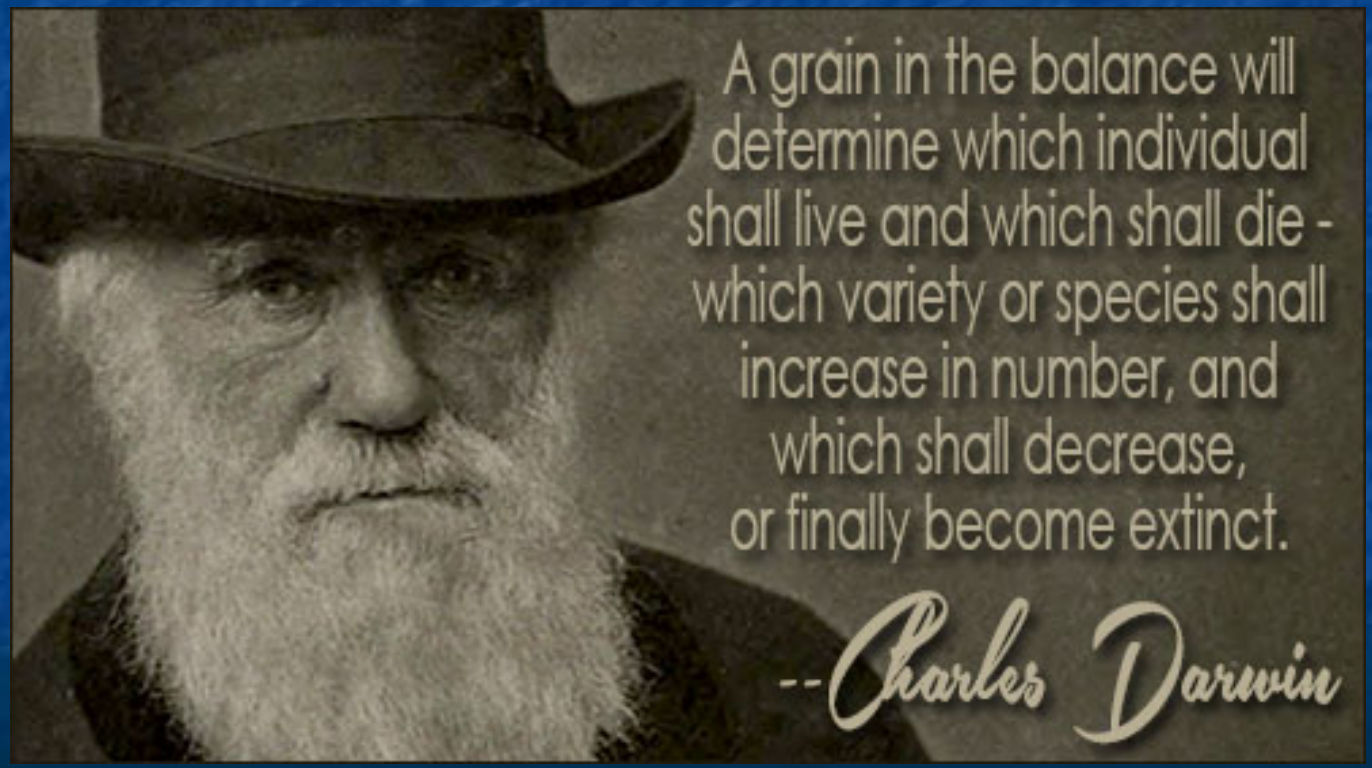
TARGETTARE IL MICROAMBIENTE NELLE LEUCEMIE ACUTE

Dr. Michele Gottardi
U.O. Ematologia
Ospedale Ca' Foncello Treviso

Treviso 26 Novembre 2016

1  OSSERVANDO LE COSE DA LONTANO: CONCETTI



Stem cells, cancer, and cancer stem cells

Tannishtha Reya*§||, Sean J. Morrison†||, Michael F. Clarke‡ & Irving L. Weissman*

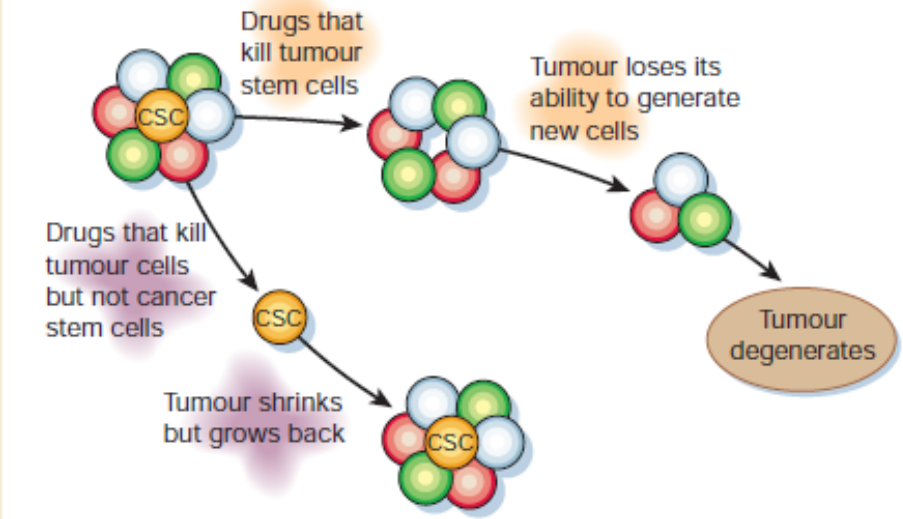
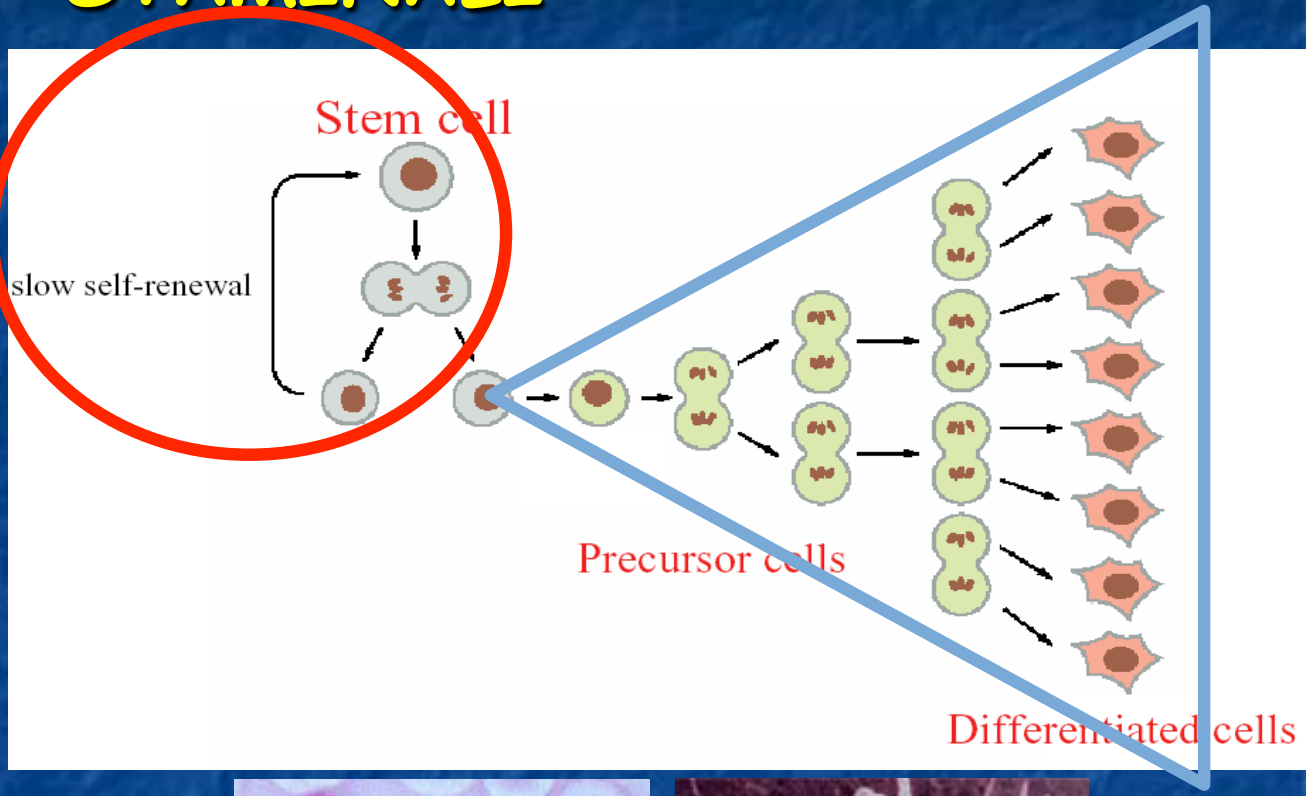
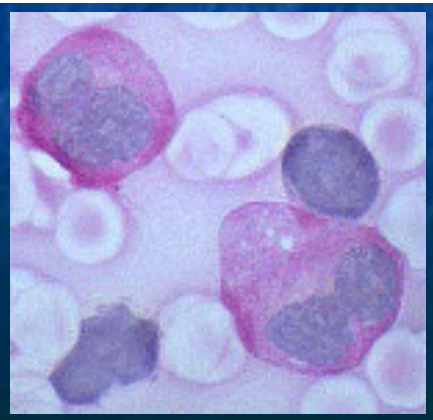


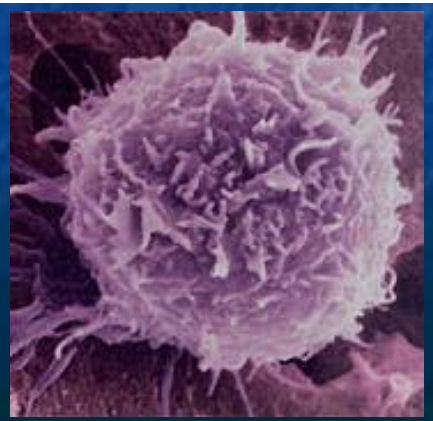
Figure 5 Conventional therapies may shrink tumours by killing mainly cells with limited proliferative potential. If the putative cancer stem cells are less sensitive to these therapies, then they will remain viable after therapy and re-establish the tumour. By contrast, if therapies can be targeted against cancer stem cells, then they might more effectively kill the cancer stem cells, rendering the tumours unable to maintain themselves or grow. Thus, even if cancer stem cell-directed therapies do not shrink tumours initially, they may eventually lead to cures.

LE CARATTERISTICHE DELLE CELLULE STAMINALI

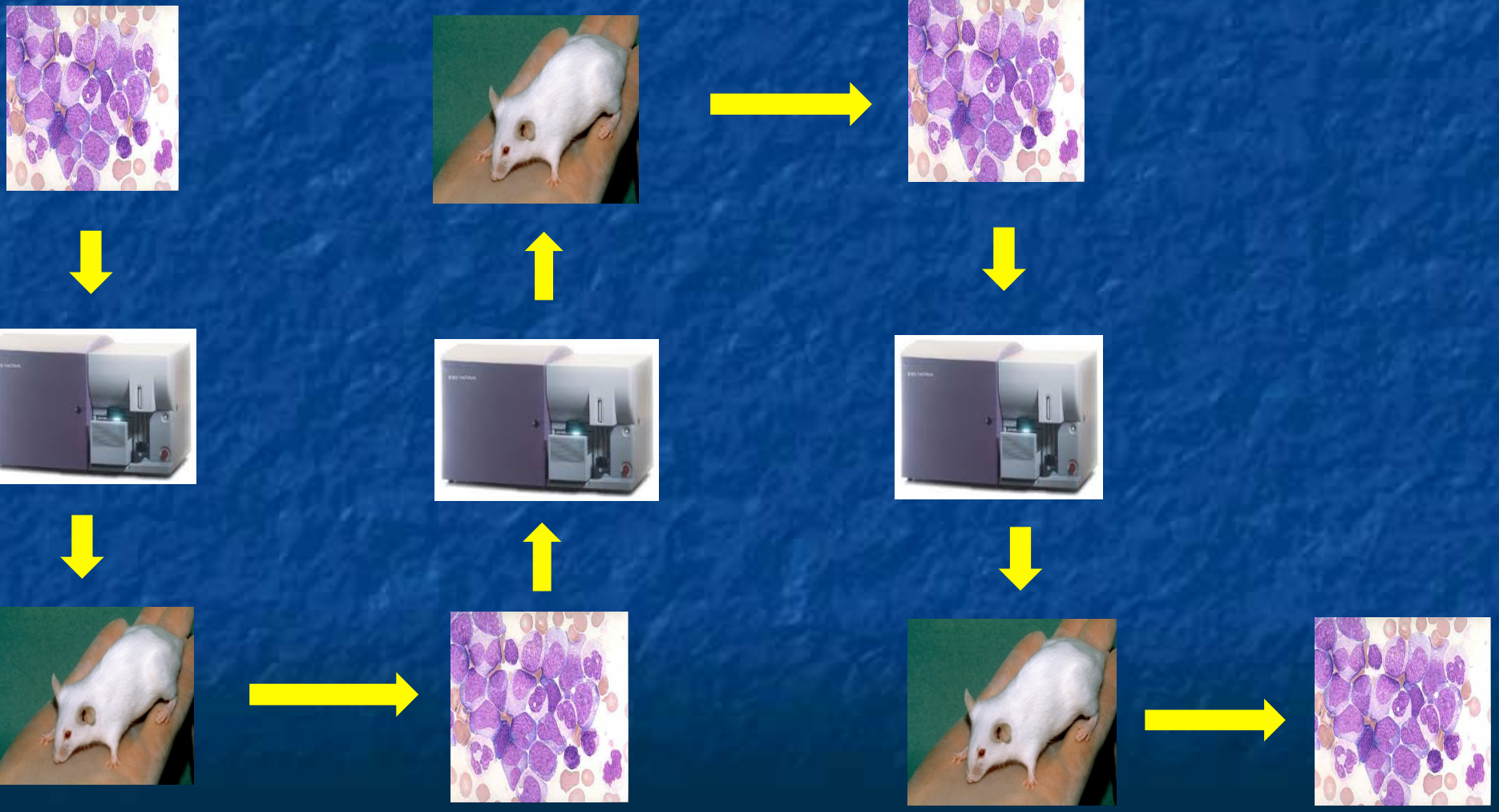
- Autorinnovamento
- Automantenimento
- Potenziale differenziativo
- Scarsa attività replicativa
- Immortalità replicativa







COME SI EVIDENZIA IL SELF-RENEWAL?



A cell initiating human acute myeloid leukaemia after transplantation into SCID mice

Tsvee Lapidot, Christian Sirard, Josef Vormoor, Barbara Murdoch, Trang Hoang*, Julio Caceres-Cortes*, Mark Minden†, Bruce Paterson‡, Michael A. Caligiuri§ & John E. Dick‖

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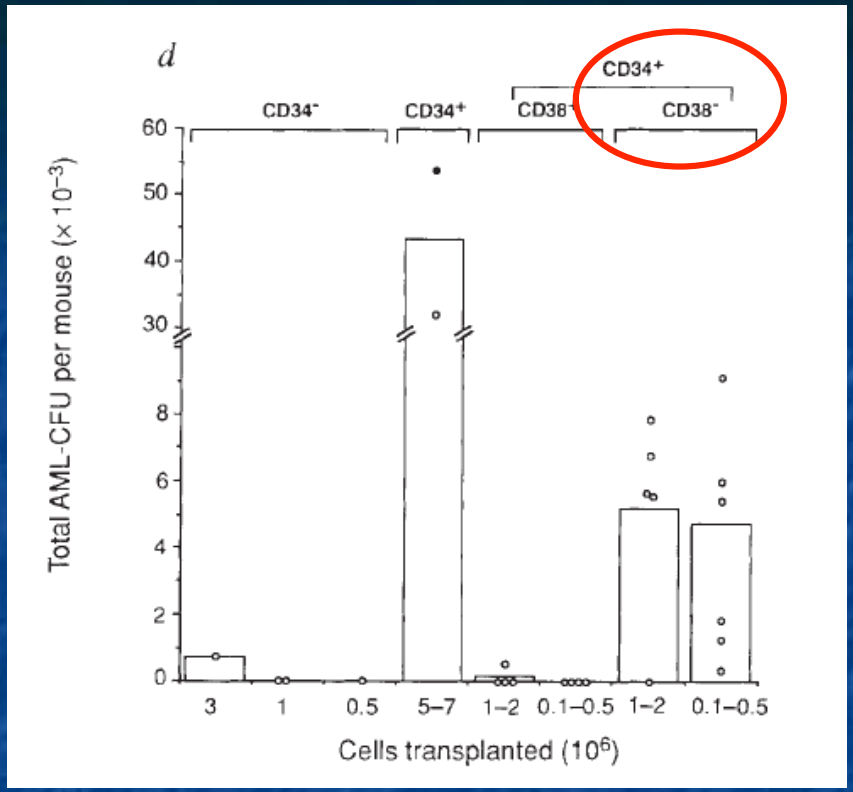
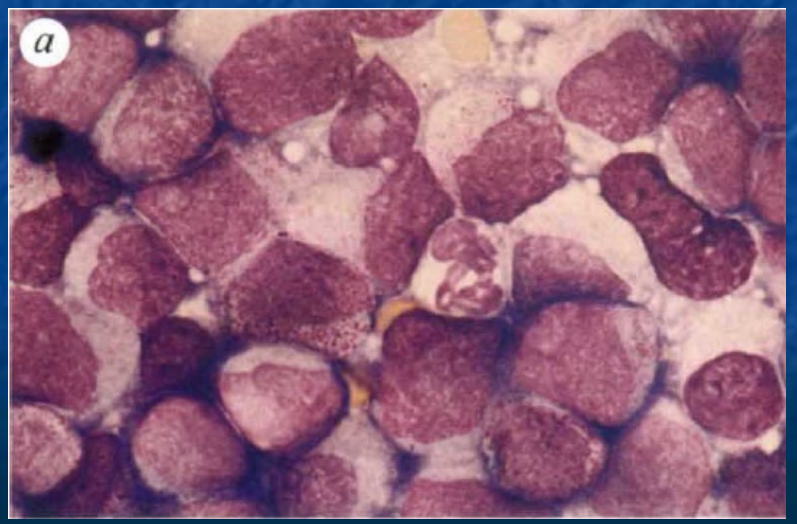
* Clinical Research Institute, Montreal, Quebec H2W 1R7, Canada
† Department of Medicine and ‡ Department of Oncologic Pathology, Princess Margaret Hospital, Toronto, Ontario M4X 1K9, Canada
§ Department of Medicine, Roswell Park Cancer Institute, Buffalo, New York 14263-0001, USA



unit in 250,000 cells. We fractionated AML cells on the basis of cell-surface-marker expression and found that the leukaemia-initiating cells that could engraft SCID mice to produce large numbers of colony-forming progenitors were $CD34^+CD38^-$; however, the $CD34^+CD38^+$ and $CD34^-$ fractions contained no cells with these properties. This *in vivo* model replicates many aspects of human AML and defines a new leukaemia-initiating cell which is less mature than colony-forming cells.

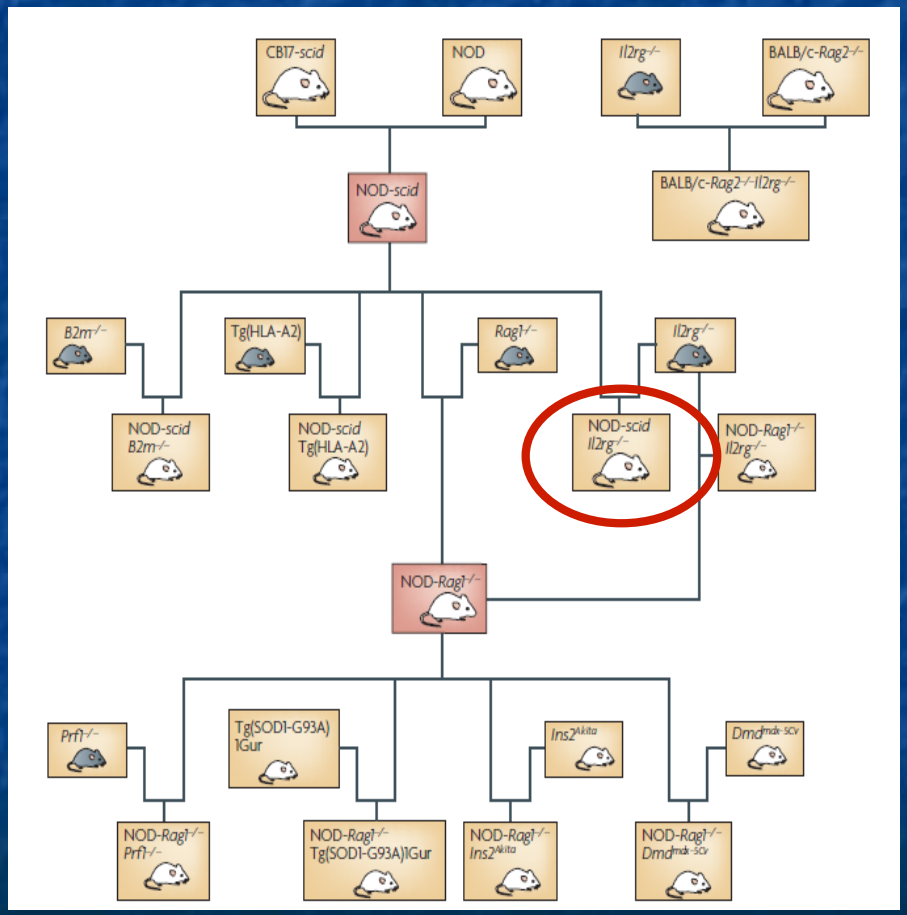


NATURE · VOL 367 · 17 FEBRUARY 1994

CONTROVERSIE

Humanized mice in translational biomedical research

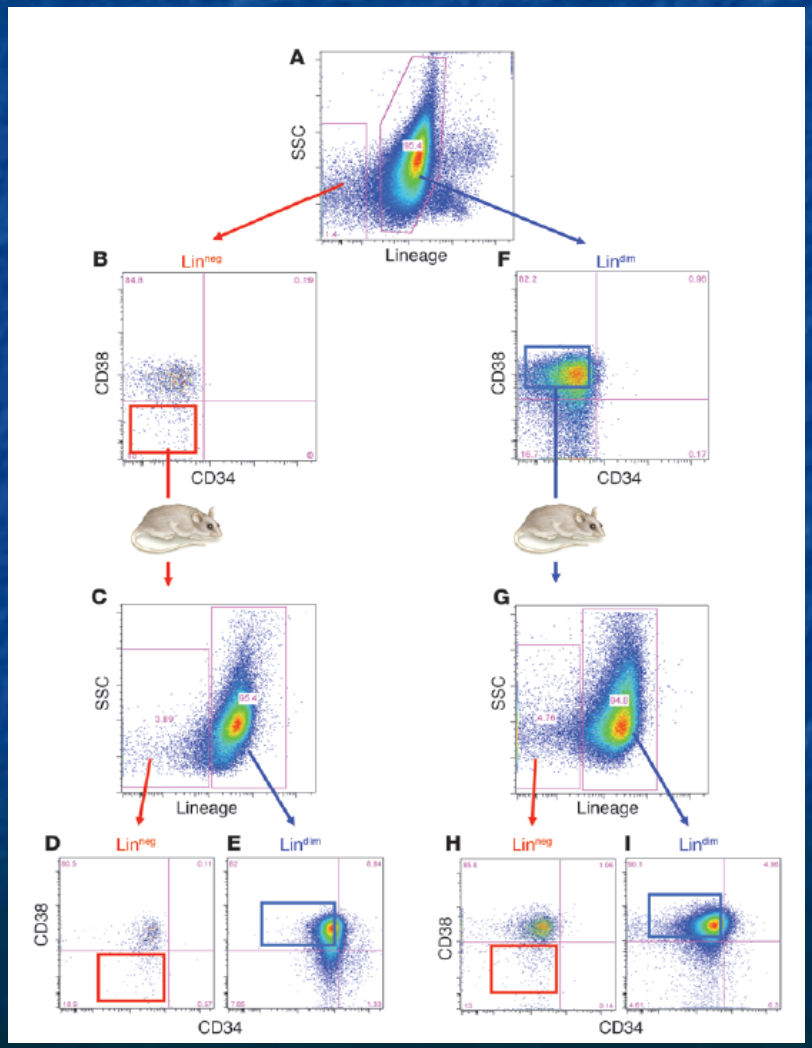
Leonard D. Shultz, Fumihiko Ishikawa‡ and Dale L. Greiner§*

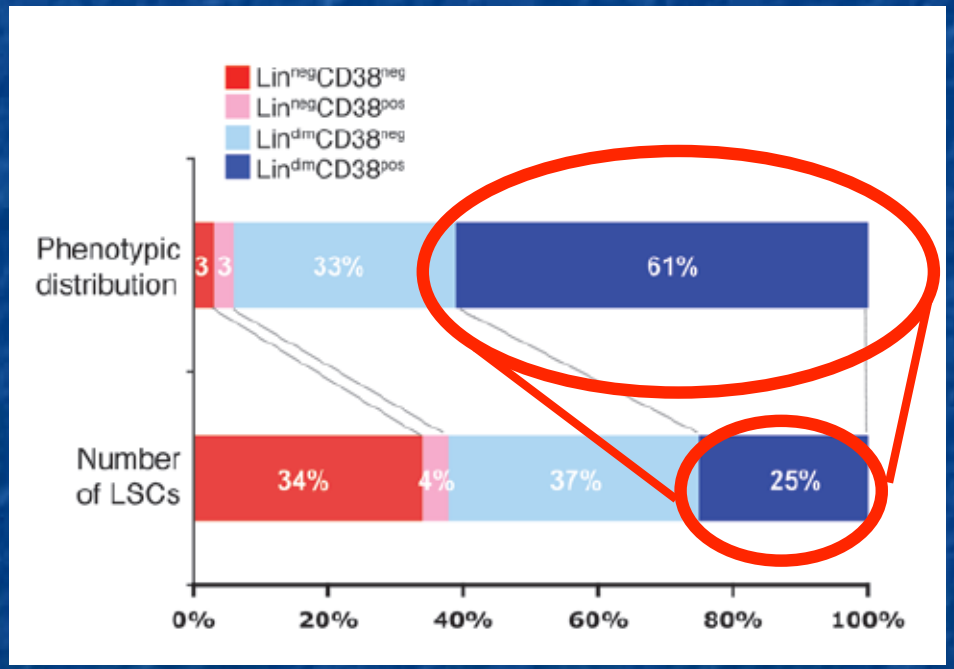


Prkdc^{scid}	CB17-*scid*	C.BKa*Igh*^{b}-*Prkdc*^{scid}/IcrSmn	• No mature T and B cells • Radiation sensitive (DNA-repair defect, cannot survive high doses of radiation)	• Lacks mature T and B cells	• High level of innate immunity and NK-cell function • Leaky • Very low level of engraftment of human cells	1
Prkdc^{scid}	NOD-*scid*	NOD.CB17-*Prkdc*^{scid}	• No mature T and B cells • Radiation sensitive • Decreased innate immunity	• Low level of innate immunity • Low NK-cell function • Increased engraftment of human HSCs and PBMCs	• Residual innate immunity • Low but present NK-cell activity • Decreased lifespan owing to thymic lymphomas	9
Prkdc^{scid} *Il2rg*^{tm1Wjl}	NOD/LtSz-*scid* *Il2rg*$^{-/-}$	NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm1Wjl}/SzJ	• No mature T and B cells • Radiation sensitive • IL-2R γ-chain deficiency; no high-affinity signalling through multiple cytokine receptors leading to many innate-immune defects	• Long lifespan • Further reduction in innate immunity • NK cells absent • Higher level of engraftment of human cells • Develop functional human immune system • Complete absence of *Il2rg* gene	• Lack appropriate MHC molecules for T-cell selection in the mouse thymus • Seem to lack some human-specific cytokines required for human cell development and survival • Low and variable level of T-cell-dependent antibody responses	16,17

Human acute myelogenous leukemia stem cells are rare and heterogeneous when assayed in NOD/SCID/IL2Rγc-deficient mice

Jean-Emmanuel Sarry,[1] Kathleen Murphy,[1] Robin Perry,[1] Patricia V. Sanchez,[1] Anthony Secreto,[1] Cathy Keefer,[1] Cezary R. Swider,[1] Anne-Claire Strzelecki,[2] Cindy Cavelier,[3] Christian Récher,[2,3,4] Véronique Mansat-De Mas,[2,3,4] Eric Delabesse,[2,3,4] G. Danet-Desnoyers,[1] and Martin Carroll[1]





The Journal of Clinical Investigation

Evolution of the Cancer Stem Cell Model

Antonija Kreso[1]
[1]Princess Mar ork, Toronto, Ontario M5G 1L7, Canada and Department of Molecular Genetics
University

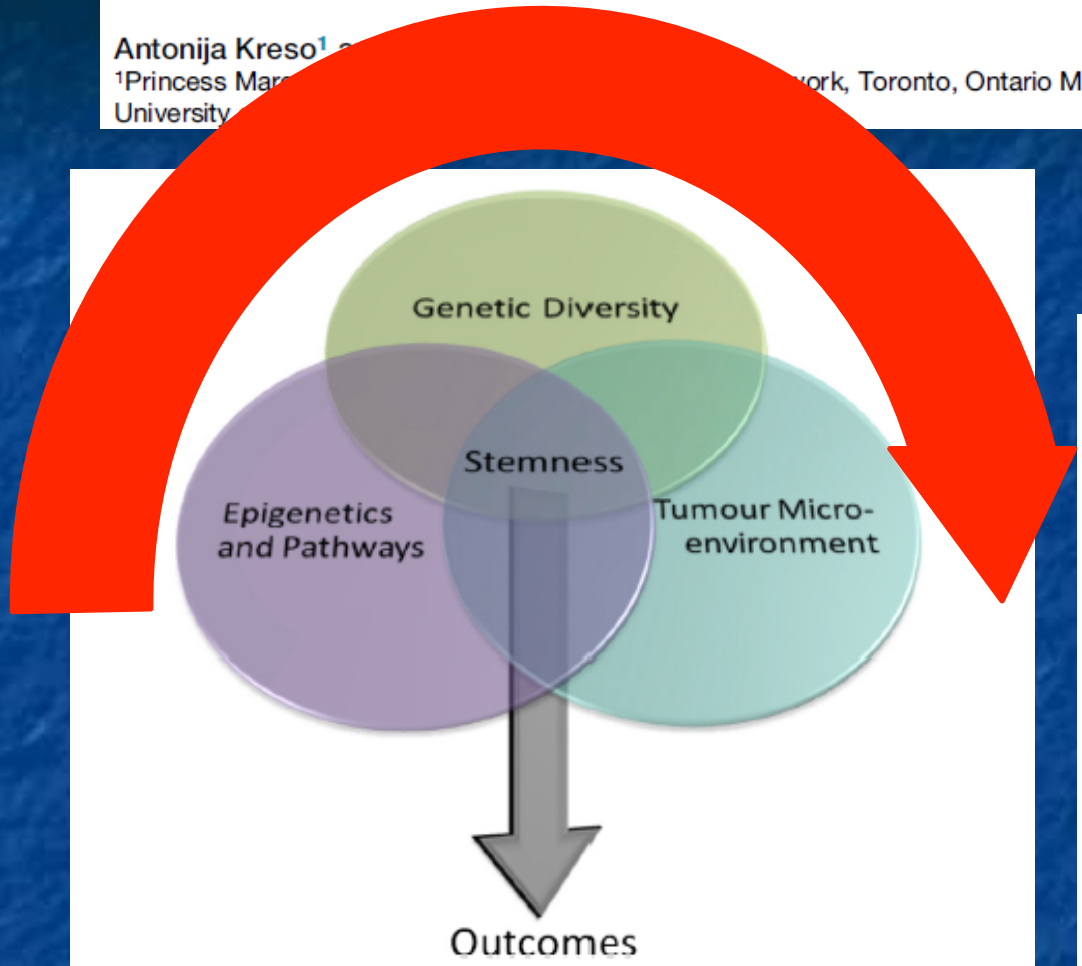


Figure 1. Stemness as a Guiding Principle that Governs Therapeutic Response

Three fields in biology—cancer genetics, epigenetics, and microenvironment—are coming together to provide increasing clarity to the processes that determine stemness and in turn influence clinical outcome. These three factors can influence stemness simultaneously, but they can also act independently over time. Through evolutionary time, different forces can impact a cell's stemness properties and thereby shape tumor progression and therapeutic response.

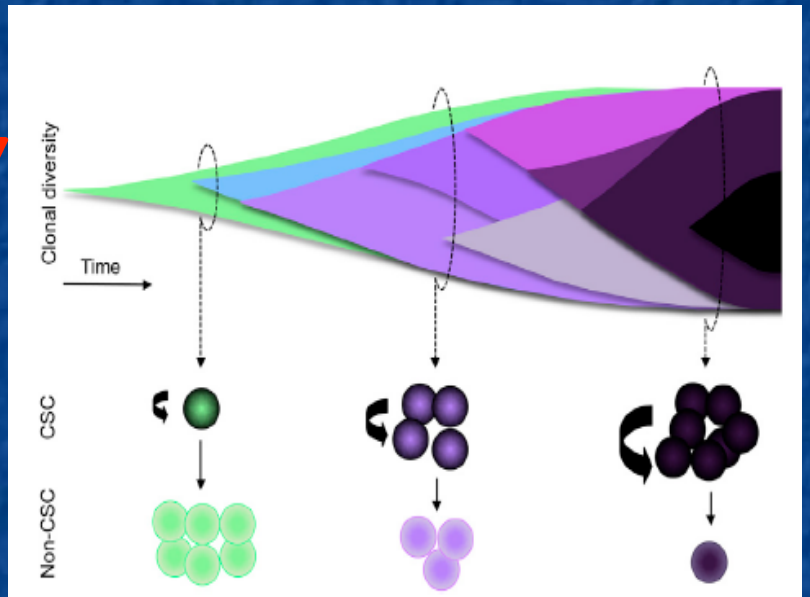


Figure 2. Unified Model of Clonal Evolution and Cancer Stem Cells

Cell Stem Cell
Review

Review

Cancer stem cells: Back to Darwin?

Mel Greaves*

Section of Haemato-Oncology, The Institute of Cancer Research, Brookes Lawley Building, 15 Cotswold Road, Sutton, Surrey SM2 5NG, United Kingdom

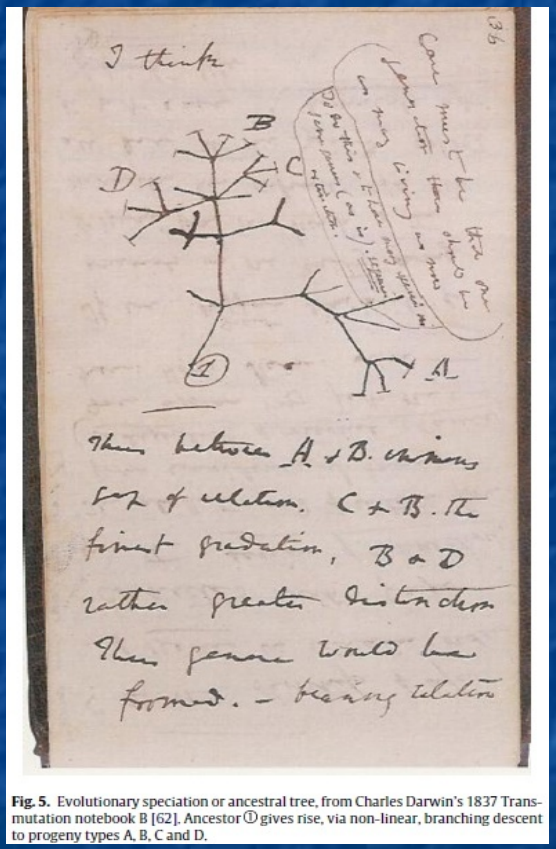
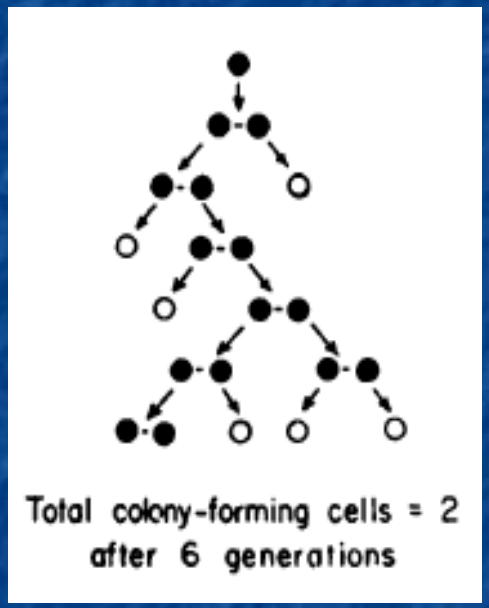
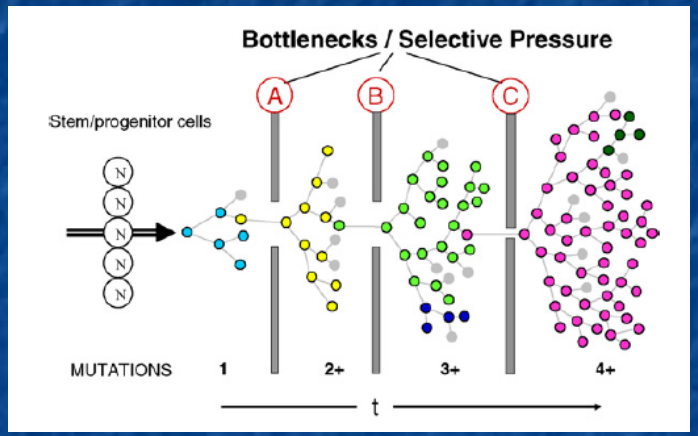


Fig. 5. Evolutionary speciation or ancestral tree, from Charles Darwin's 1837 Transmutation notebook B [62]. Ancestor ① gives rise, via non-linear, branching descent to progeny types A, B, C and D.





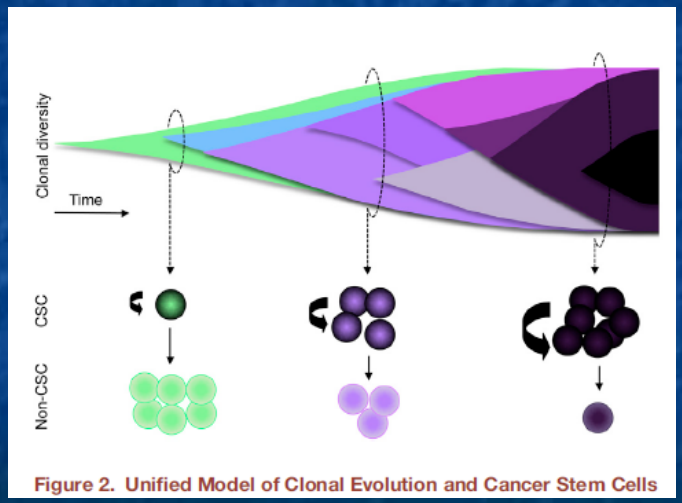
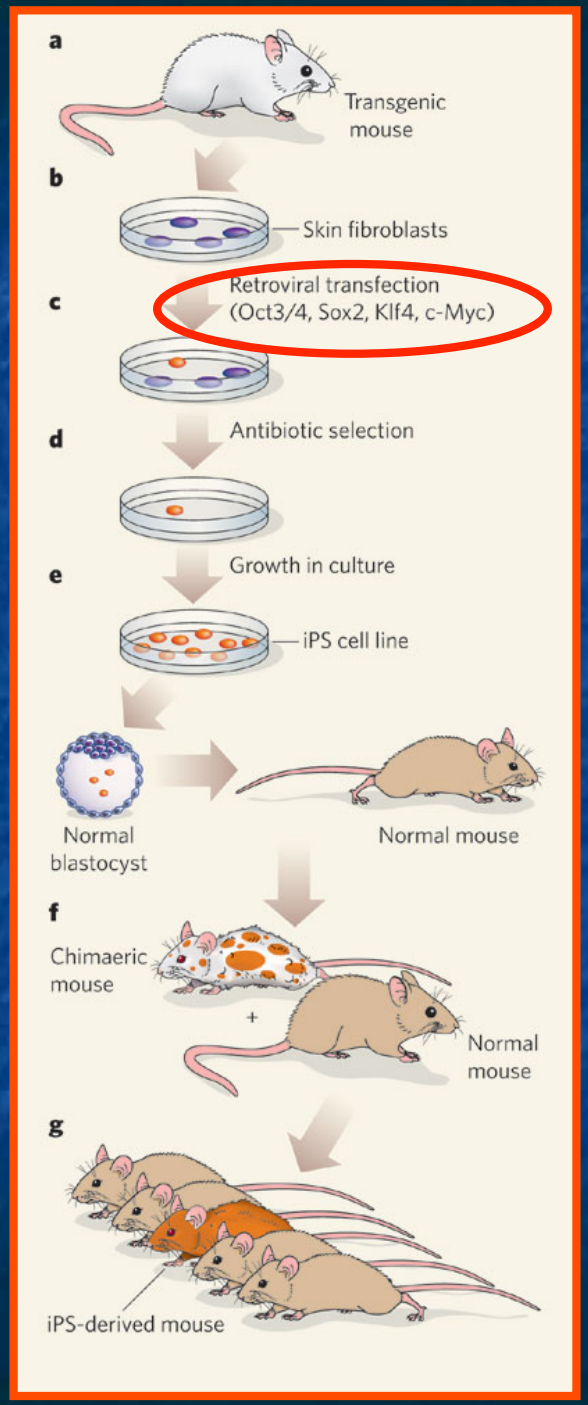


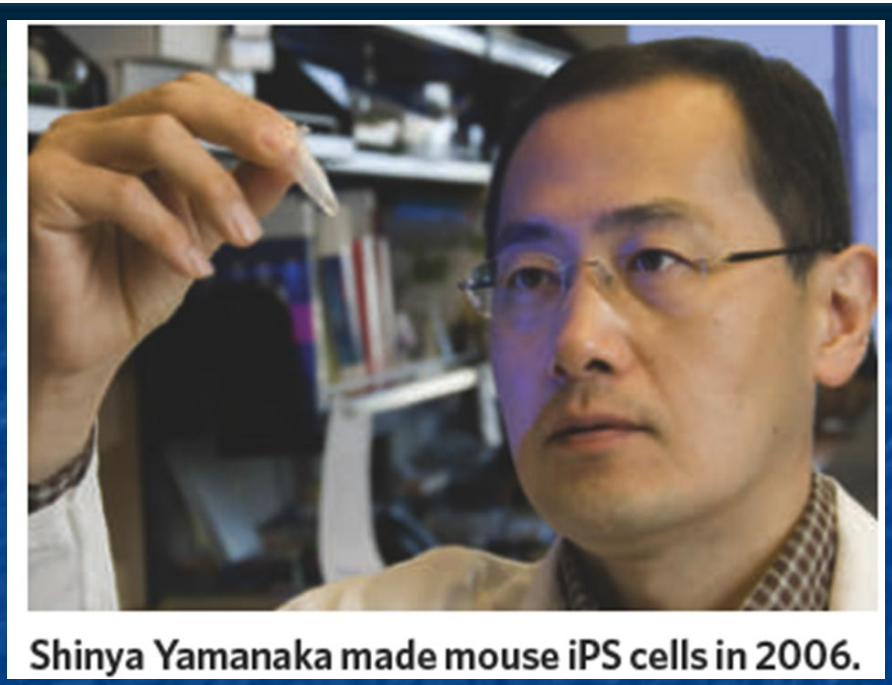
Figure 2. Unified Model of Clonal Evolution and Cancer Stem Cells

Contents lists available at ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer





Shinya Yamanaka made mouse iPS cells in 2006.

- Le Cellule Staminali Somatiche (adulte) se opportunamente manipolate possono ringiovanire trasformandosi in cellule embrionali;
- tutte le cellule embrionali e le cellule somatiche (adulte) hanno uguale capacità rigenerativa;

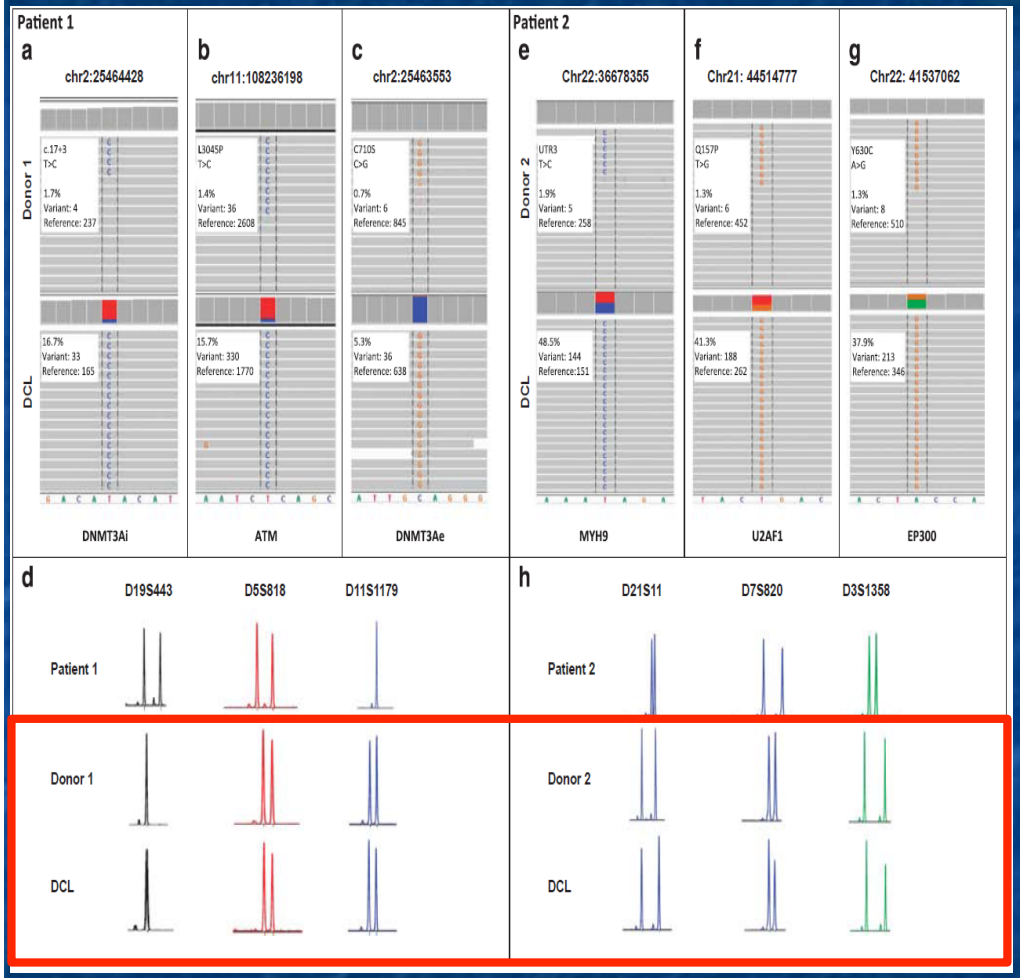
la cellula staminale non esiste:

esiste la funzione staminale.

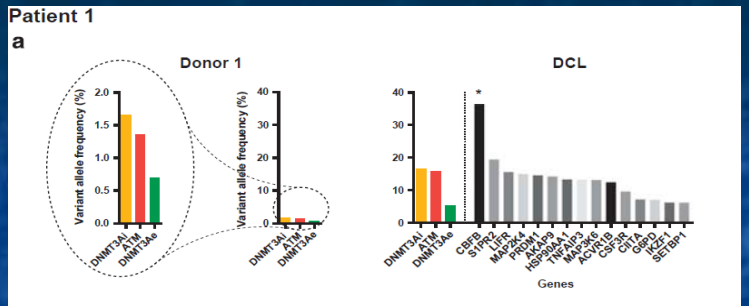
2  ALCUNI INDIZI

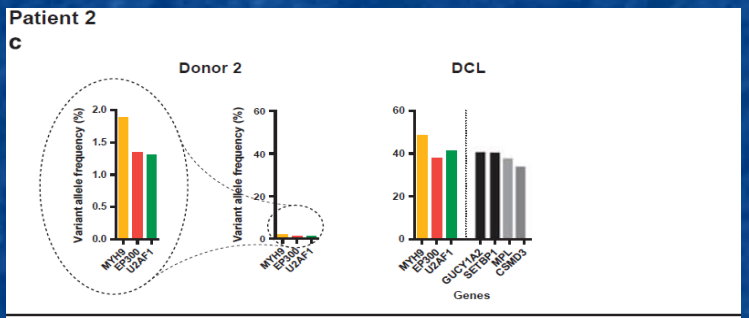
(che si prestano a molte, forse troppe, interpretazioni)

Donor cell leukemia arising from clonal hematopoiesis after bone marrow transplantation

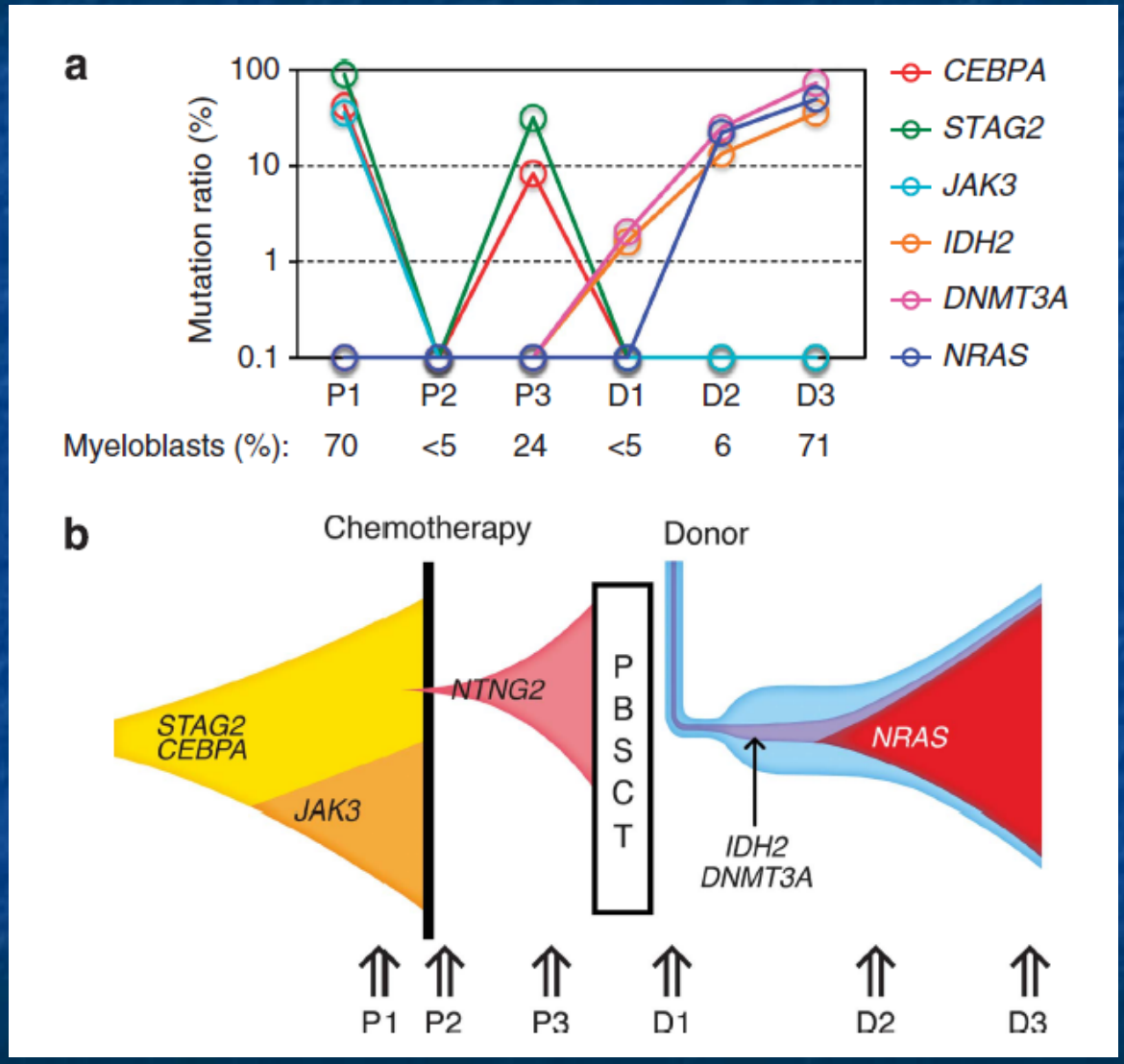


Leukemia (2016) 1909 – 1962





Leukemic evolution of donor-derived cells harboring *IDH2* and *DNMT3A* mutations after allogeneic stem cell transplantation

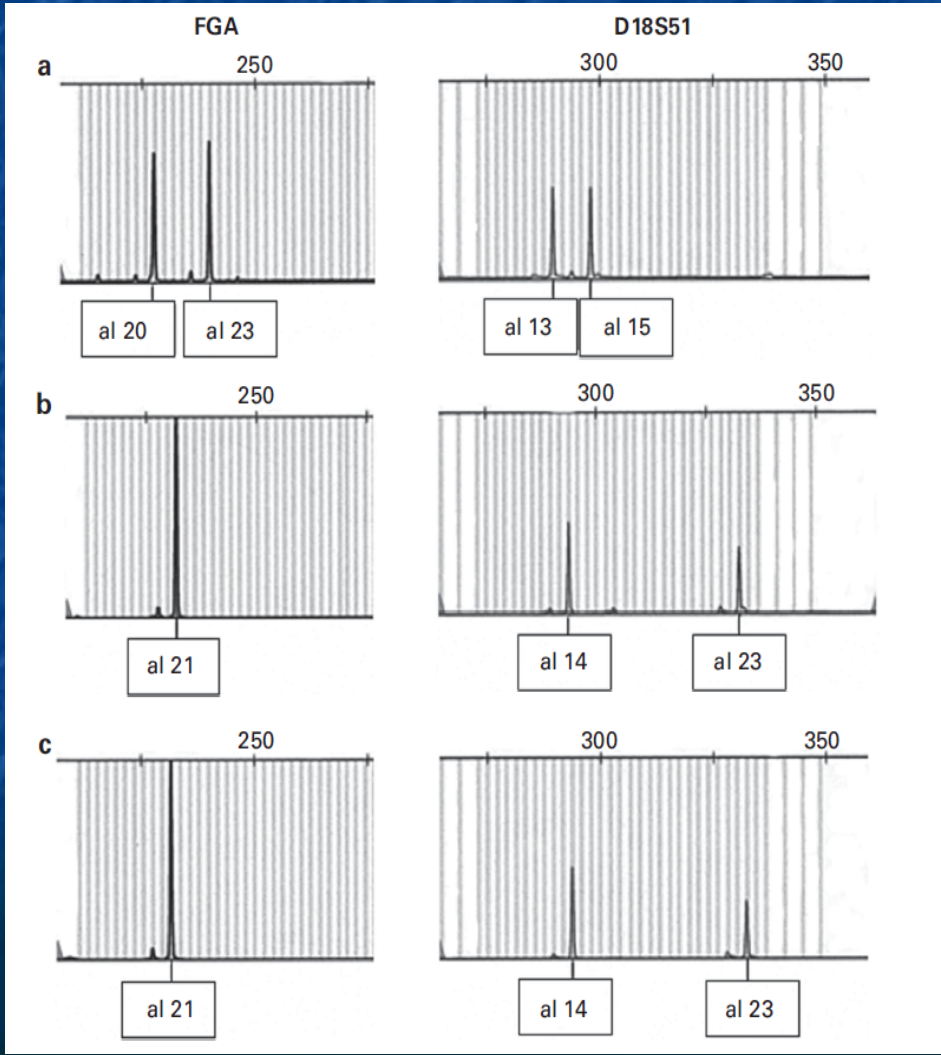


Leukemia (2014) 404 – 463

ORIGINAL ARTICLE

Donor cell-derived leukemia after cord blood transplantation and a review of the literature: differences between cord blood and BM as the transplant source

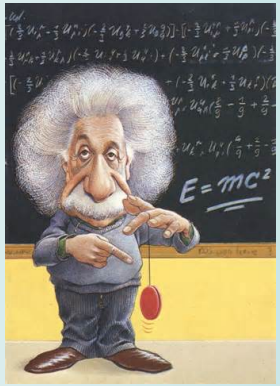
H Shiozaki, K Yoshinaga, T Kondo, Y Imai, M Shiseki, N Mori, M Teramura and T Motoji



Several mechanisms for the development of DCL after CBT have been proposed. One possibility is that the donor cord blood itself may contain leukemic clones at the time of transplantation. Mori *et al.*[69] reported the presence of the *TEL–AML1* fusion gene in 6 of 567 cases of unselected umbilical cord blood cells and the *AML1–ETO* fusion gene in 1 of 496 cases. The presence of the *AML1–ETO* fusion gene sequence was also reported in the neonatal blood spots of children who developed AML later.[70] A transferred leukemic clone would be 'the first hit' of leukemogenesis after CBT, and then additional hits could lead to leukemia. From the data showing a shorter period for the occurrence of DCL following CBT and the high frequency of monosomy 7 in DCL, it is natural enough to consider that an umbilical leukemia clone could have been transplanted into the recipient, which could cause DCL. Another possibility that may explain the development of DCL after CBT is that even if the transplanted cord blood cells are intact, the environment of the recipients may permit the occurrence of leukemia. This mechanism might be also applicable to DCL following BMT. The microenvironments in recipients, including stem cell niches or stromal cells, have been reported to be changed by irradiation or chemical agents,[71] which may lead to impaired immune surveillance or dysregulation of cytokines or homeostasis for hematopoiesis. Indeed, deficiencies in antigen-specific cellular immunity within the first 100 days after CBT have been demonstrated.[72] Further, a high proliferation of cord blood cells may be sufficient for inducing replication errors or mutations in the DNA.[73]

Bone Marrow Transplantation (2014) 102 – 109

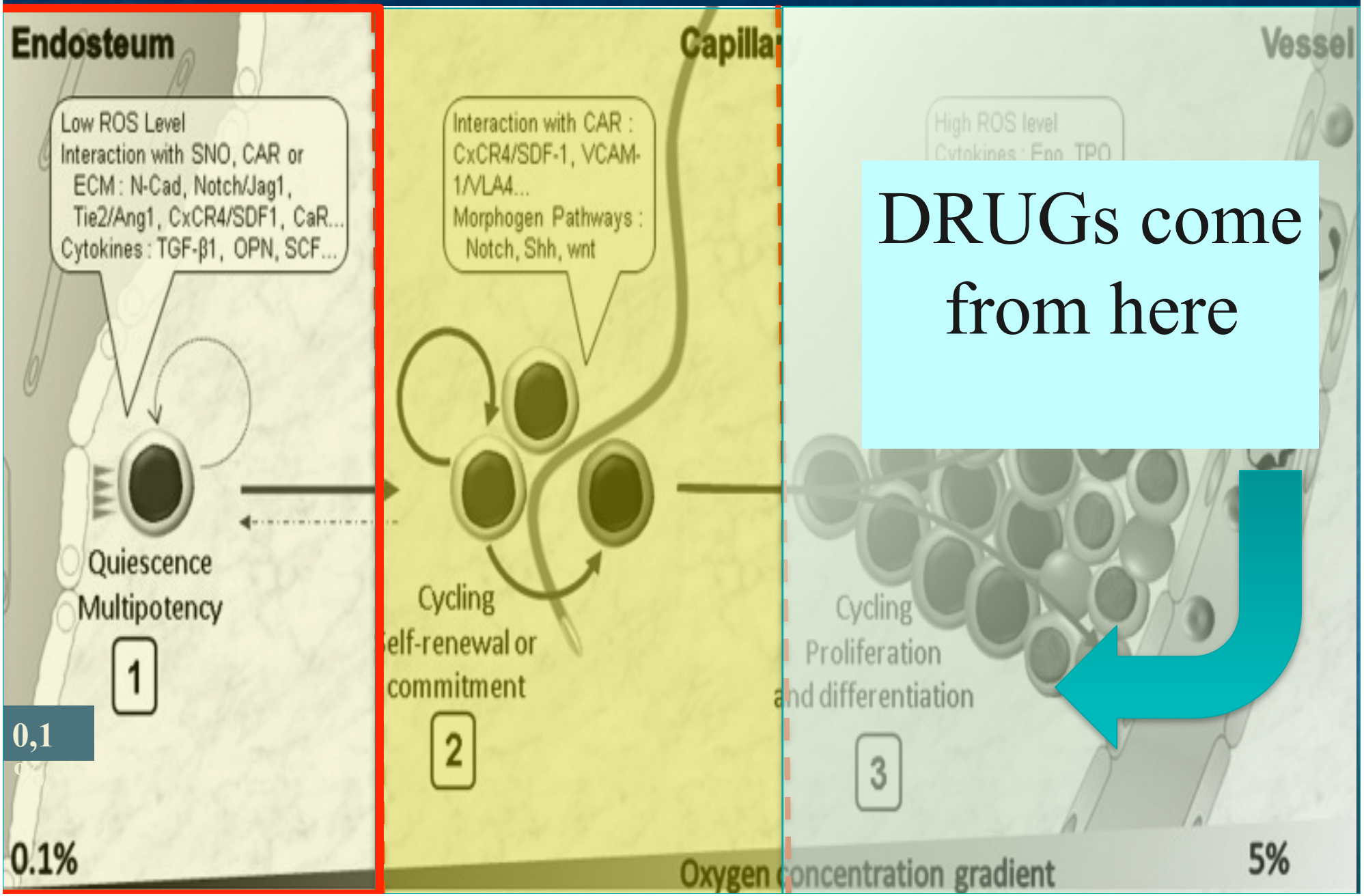
3



EVIDENZE SPERIMENTALI

"It's a lemon tree, my dear Watson."

LE NICCHIE



DRUGs come from here

IL RISIEDERE (FISICAMENTE)
NELLA
NICCHIA SUB ENDOSTALE
PUO' DI PER SE'
MODIFICARE LE
CARATTERISTICHE FUNZIONALI
DELLA CELLULA LEUCEMICA?

ELSEVIER

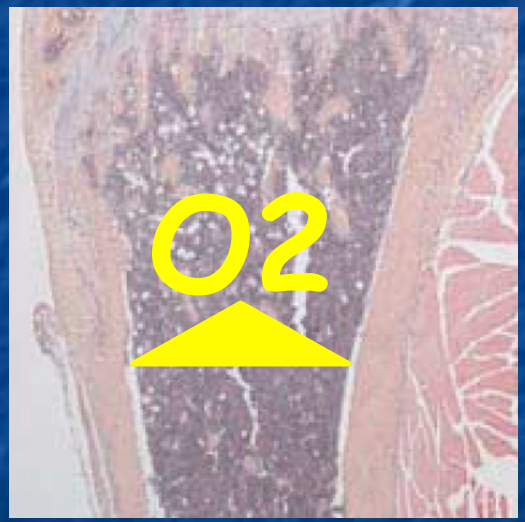
Experimental Hematology 2010;38:847–851

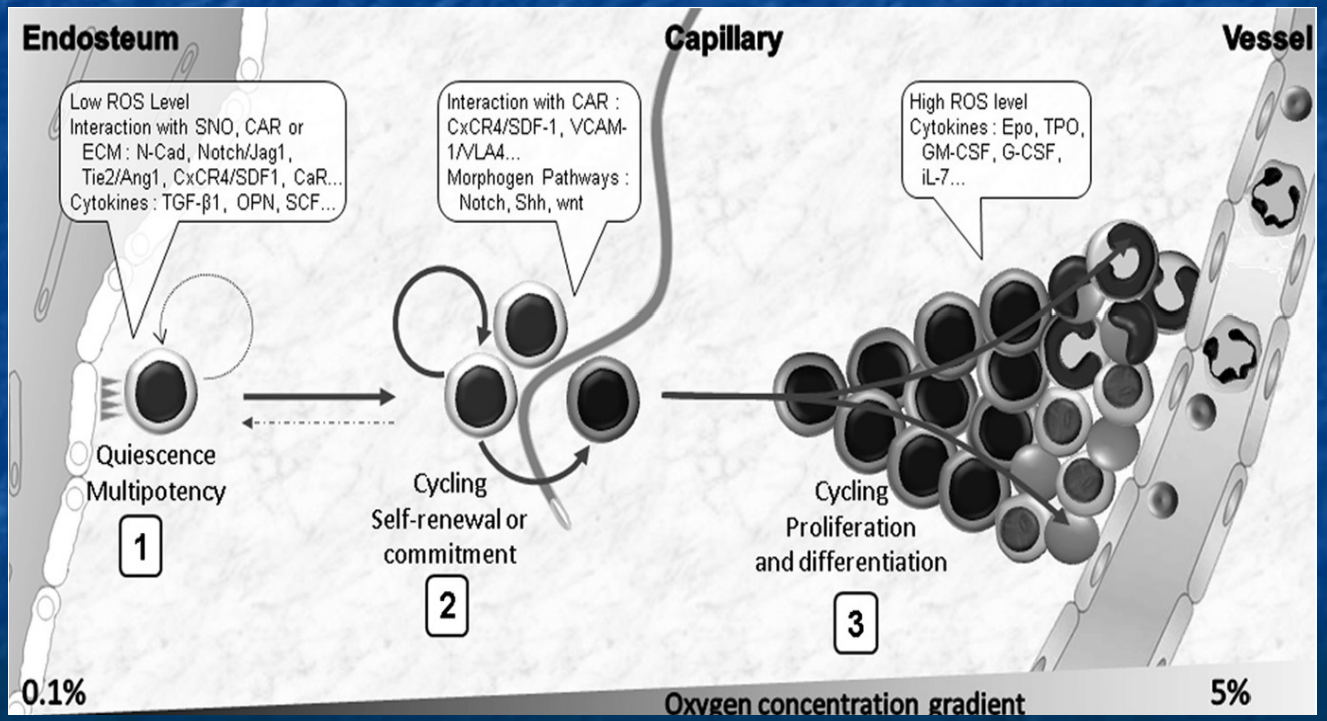
Slow-cycling/quiescence balance of hematopoietic stem cells is related to physiological gradient of oxygen

Amélie V. Guitart[a,b,c], Mohammad Hammoud[d,e], Persio Dello Sbarba[f], Zoran Ivanovic[d], and Vincent Praloran[a,b,c]

[a]*Bordeaux University, Bordeaux, France;* [b]*CNRS UMR 5164-CIRID, Bordeaux, France;* [c]*IFR66, Bordeaux, France;* [d]*Aquitaine-Limousin Branch of French Blood Institute, Bordeaux, France;* [e]*Franche-Comté University, Besançon, France;* [f]*Department of Experimental Pathology and Oncology, University of Firenze, Firenze, Italy*

(Received 12 March 2010; revised 12 March 2010; accepted 7 June 2010)

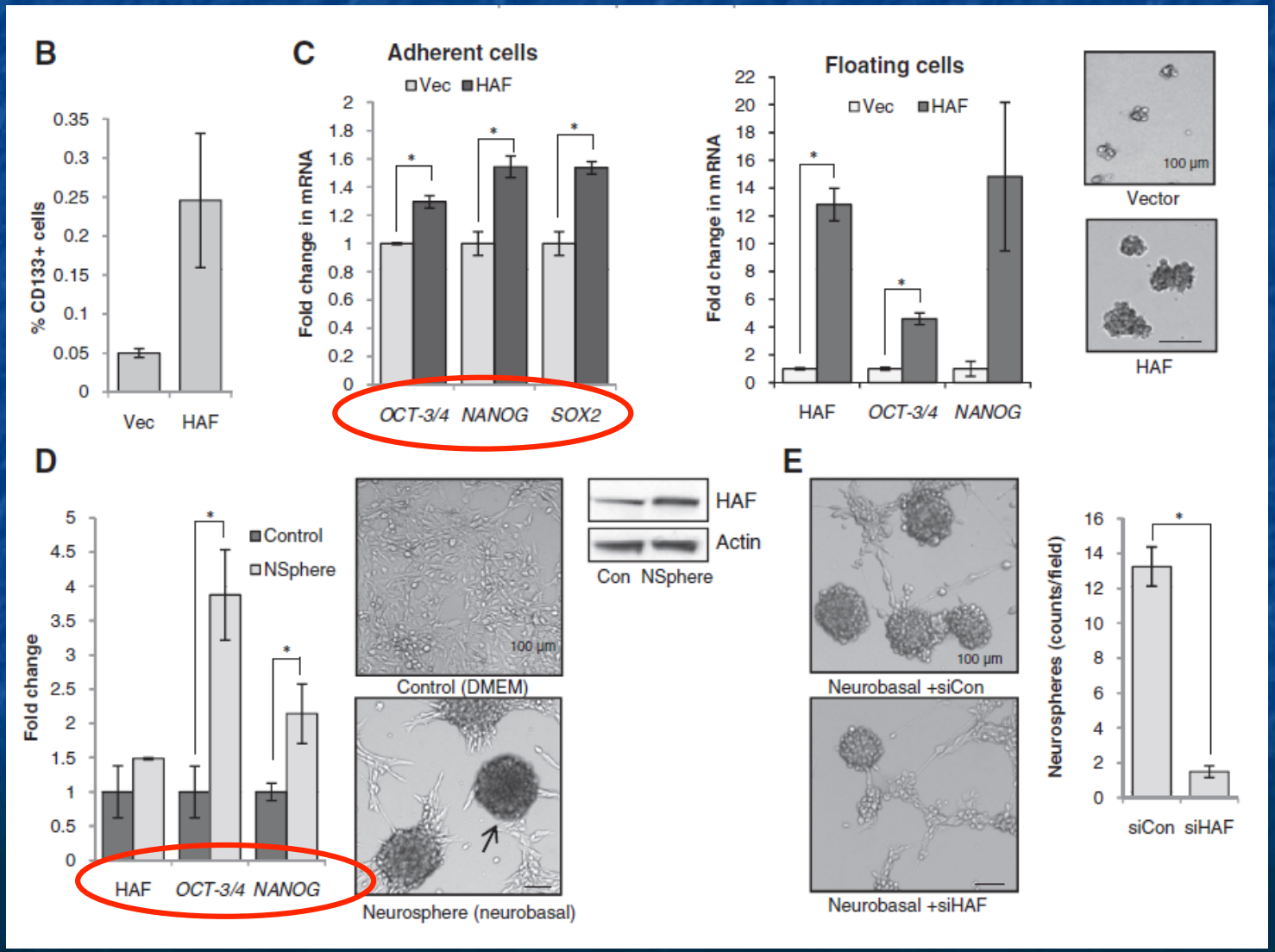




The Hypoxia-Associated Factor Switches Cells from HIF-1α– to HIF-2α–Dependent Signaling Promoting Stem Cell Characteristics, Aggressive Tumor Growth and Invasion

Mei Yee Koh, Robert Lemos Jr, Xiuping Liu, and Garth Powis

Cancer Research



Article Series: Thirty years of p53

p53 and stem cells: new developments and new concerns

Tongbiao Zhao and Yang Xu

Section of Molecular Biology, Division of Biological Sciences, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0322, USA

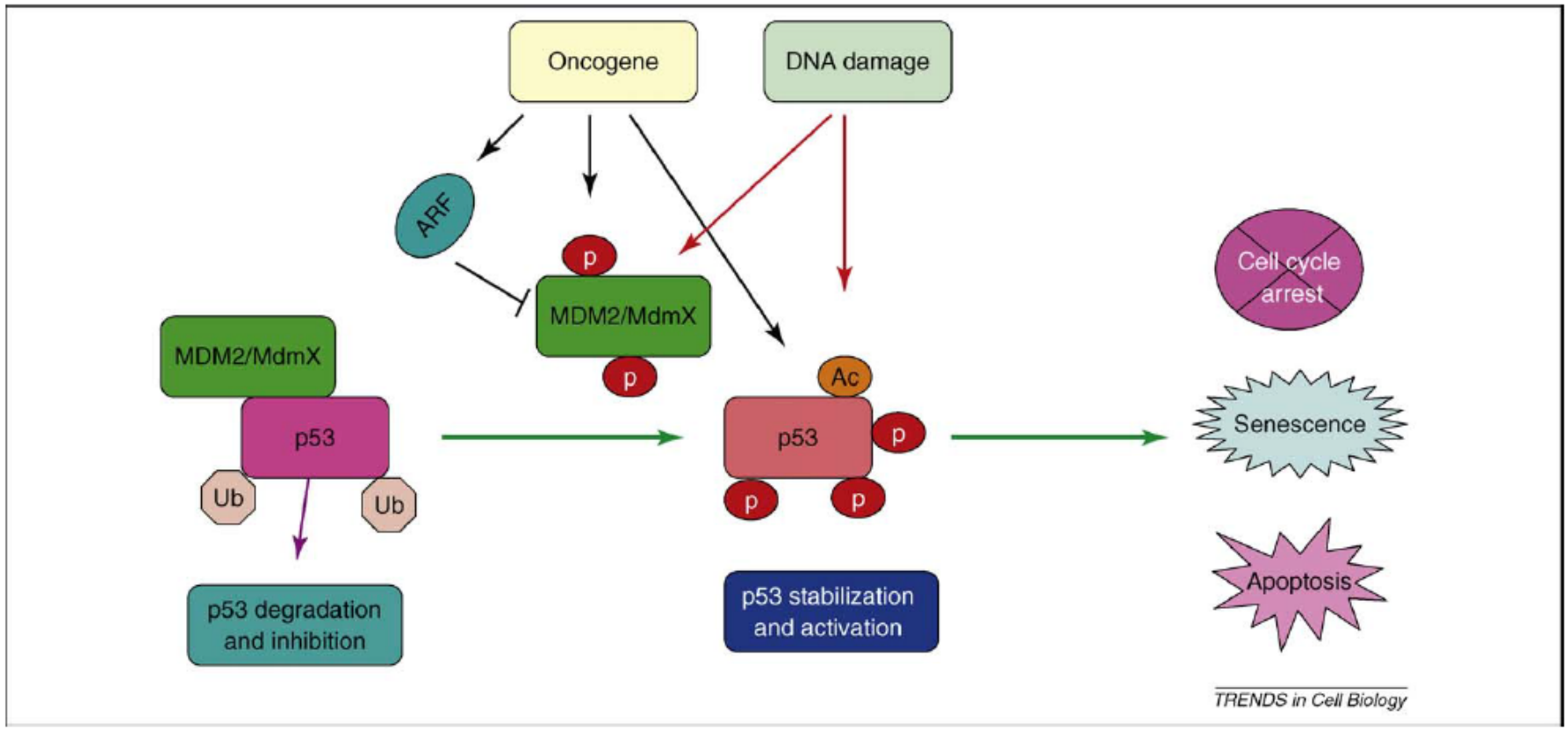


Figure 1. Activation of p53 by genotoxic and oncogenic stresses. In the absence of stresses, the stability and activity of p53 is negatively regulated by MDM2/MDMX. In responses to stresses, posttranslational modifications of p53 and its negative regulators such as phosphorylation and acetylation disrupt the interaction between p53 and MDM2/MDMX, leading to p53 stabilization and activation. In responses to oncogenic stresses, ARF is induced to inactivate MDM2 and plays a crucial role in p53 activation after oncogenic stresses.

Article Series: Thirty years of p53

p53 and stem cells: new developments and new concerns

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Section of Molecular Biology, Division of Biological Sciences, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0322, USA

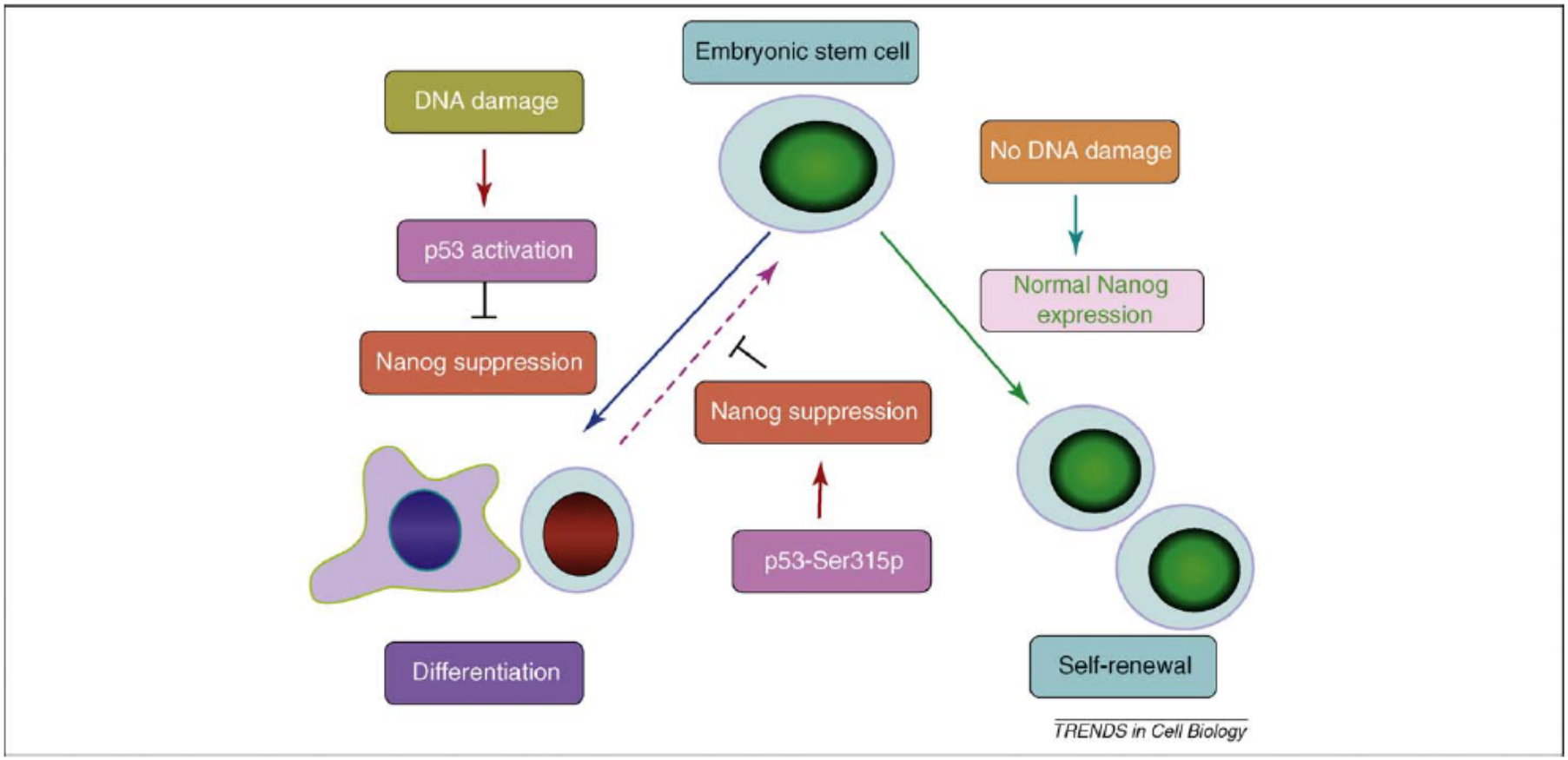


Figure 2. The roles of p53 in coordinating self-renewal and DNA damage responses in ESCs. Activation of p53 post DNA damage or the initiation of differentiation suppresses Nanog expression, leading to the inhibition of self-renewal and dedifferentiation.

Article Series: Thirty years of p53

p53 and stem cells: new developments and new concerns

Tongbiao Zhao and Yang Xu

Section of Molecular Biology, Division of Biological Sciences, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0322, USA

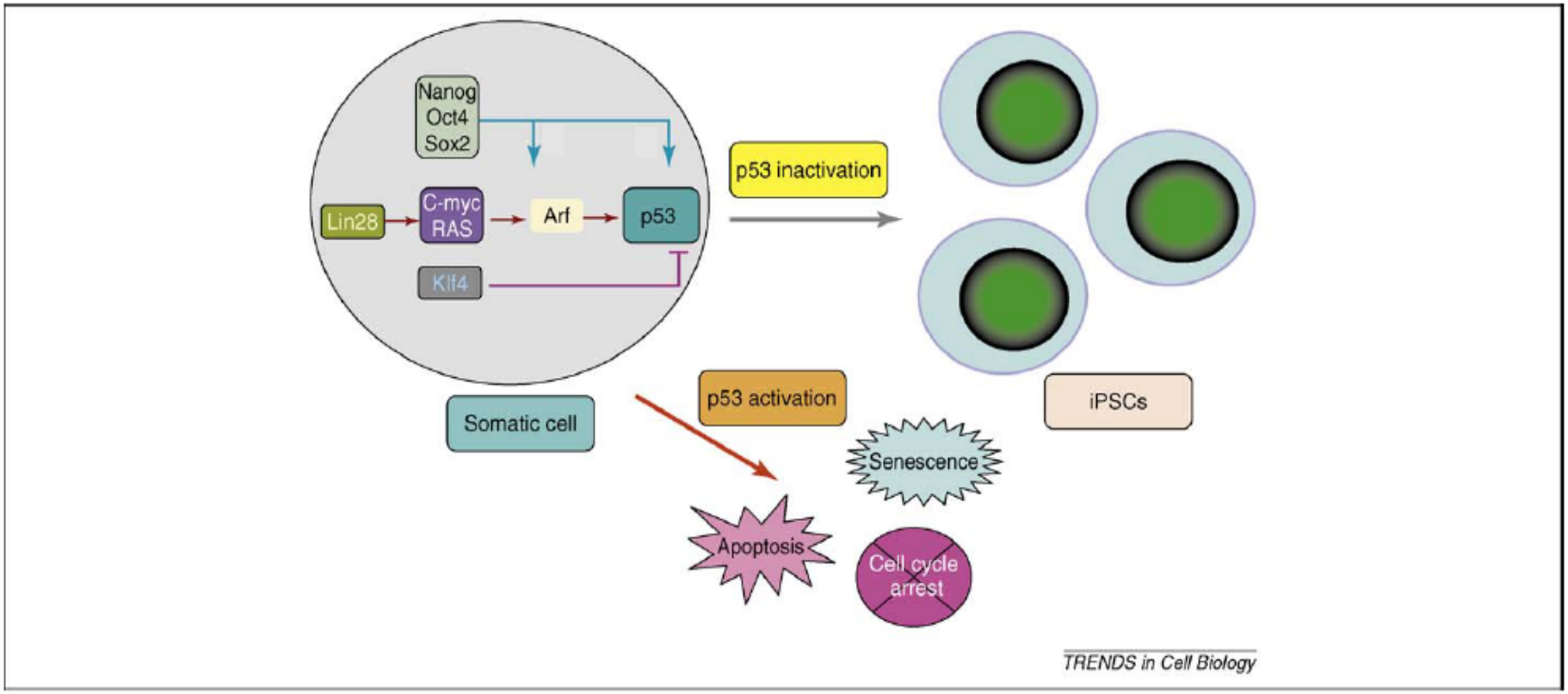


Figure 3. ARF-p53 pathways in suppressing reprogramming of somatic cells into induced pluripotent stem cells, Overexpression of oncogenic reprogramming factors activates ARF/p53 pathways in somatic cells, leading to cell cycle arrest or elimination of these cells. Inactivation of ARF/p53 pathways allows the successful reprogramming.

AMPK Protects Leukemia-Initiating Cells in Myeloid Leukemias from Metabolic Stress in the Bone Marrow

Yusuke Saito,[1] Richard H. Chapple,[1] Angelique Lin,[1] Ayumi Kitano,[1] and Daisuke Nakada[1,*]
[1]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX 77030, USA
*Correspondence: nakada@bcm.edu

CellPress

Restrizione dietetica
Microamb. Ipoglicemico
Microam. Ipossico

Aumento AMP:ATP ratio

Attivazione Tumor supp. Kinase Lkb-1

AMP-activated Protein Kinase (AMPK)

NOTCH mutations

L-IC

GLUCOSIO

GLUT 1/4

ACIDI GRASSI

POTENZIAMENTO VIA GLICOLITICA

POTENZIAMENTO VIA PENTOSO FOSFATI

NADPH / NADP

GSH / GSSG

ROS↓↓↓

MECCANISMO NON ATTIVO NELLE HSC

Cell Metabolism 23, 649–662, April 12, 2016

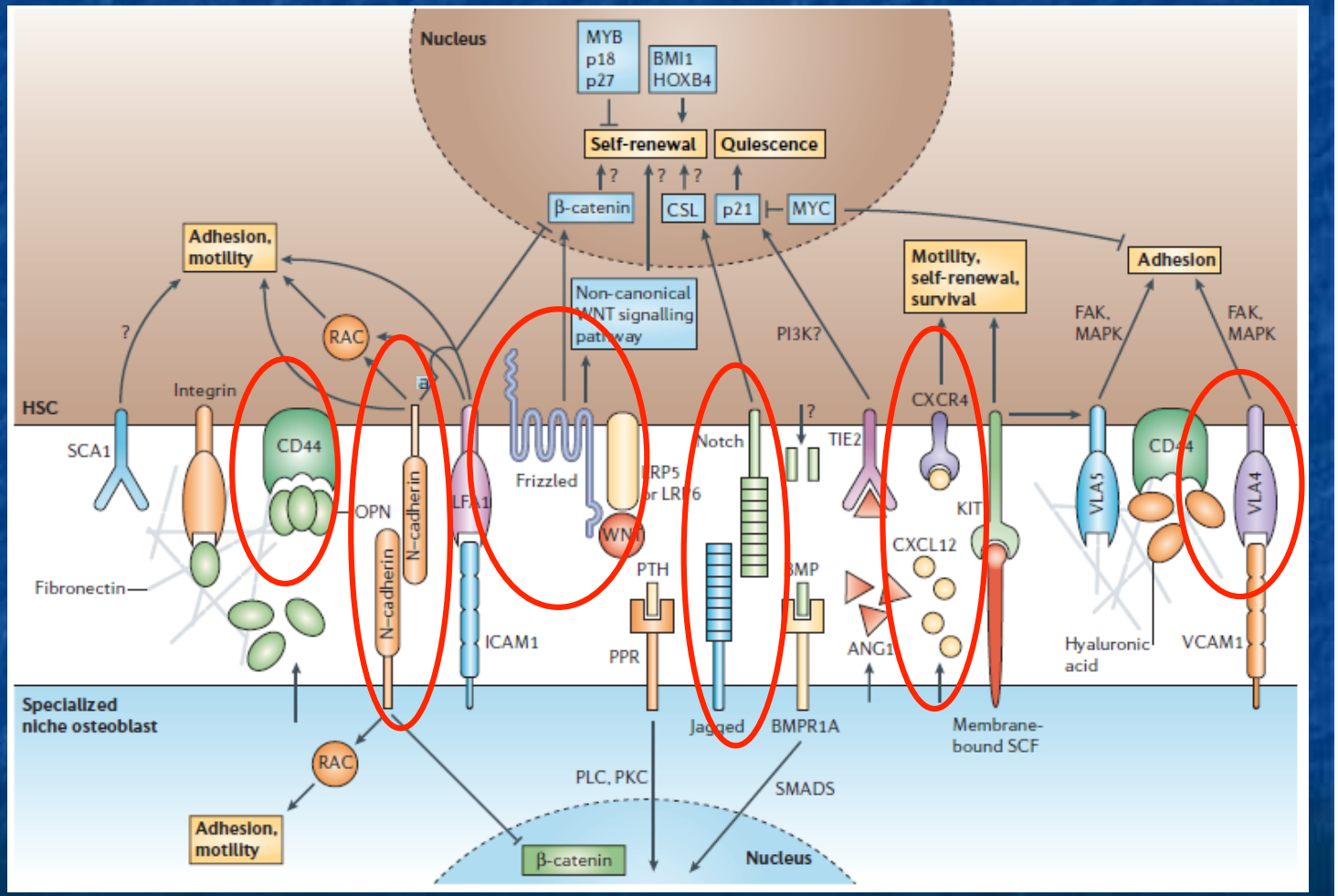
AMPK Is Essential to Balance Glycolysis and Mitochondrial Metabolism to Control T-ALL Cell Stress and Survival

Rigel J. Kishton,[1,2,3] Carson E. Barnes,[1] Amanda G. Nichols,[1,2,3] Sivan Cohen,[1,2,3] Valerie A. Gerriets,[1] Peter J. Siska,[1,2,3,4] Andrew N. Macintyre,[1] Pankuri Goraksha-Hicks,[1] Aguirre A. de Cubas,[5] Tingyu Liu,[1] Marc O. Warmoes,[6] E. Dale Abel,[7] Allen Eng Juh Yeoh,[8,9] Timothy R. Gershon,[10] W. Kimryn Rathmell,[5] Kristy L. Richards,[10] Jason W. Locasale,[1,6] and Jeffrey C. Rathmell[1,2,3,4,*]

Cell Stem Cell *17*, 585–596, November 5, 2015

Bone-marrow haematopoietic-stem-cell niches

Anne Wilson and Andreas Trumpp‡*



NATURE REVIEWS | IMMUNOLOGY

Evolution of the Cancer Stem Cell Model

Antonija Kreso[1] and John E. Dick[1,*]
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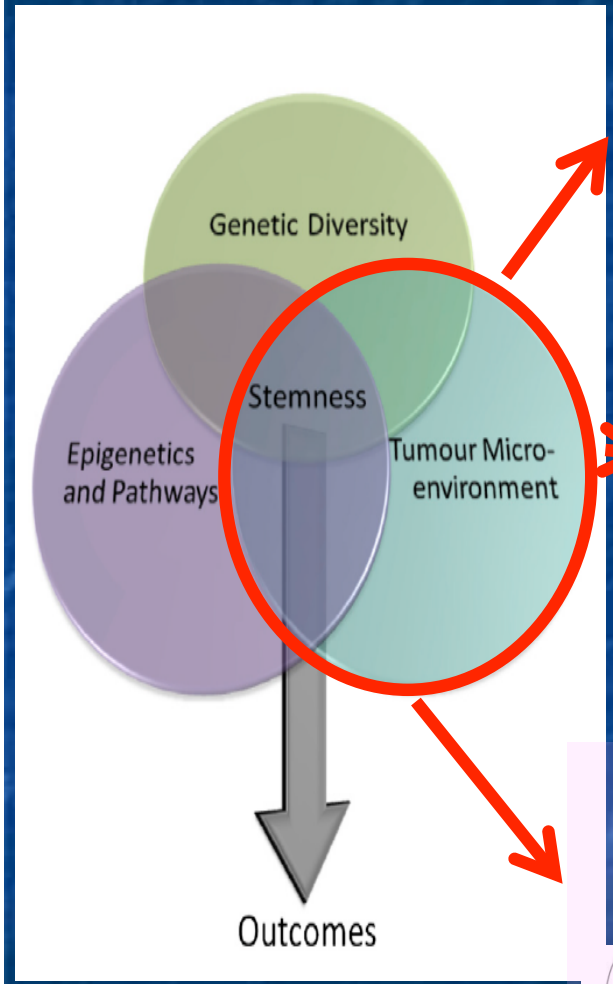
Cell Stem Cell
Review

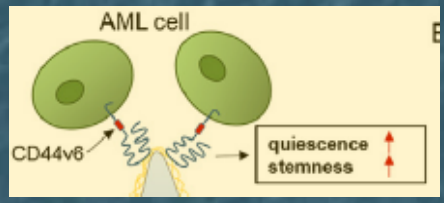


CD44: More than a mere stem cell marker

I. Morath[a], T.N. Hartmann[b], V. Orian-Rousseau[a,*]
[a] Karlsruhe Institute of Technology, Institute of Toxicology and Genetics, Karlsruhe, Germany
[b] Laboratory for Immunological and Molecular Cancer Research, Third Medical Department with Hematology, Medical Oncology, Hemostaseology, Infectious Diseases, and Rheumatology, Oncologic Center, Paracelsus Medical University, Salzburg, Austria

3. CD44 and the cancer stem cell concept

4. Contribution of CD44 to the cancer stem cell state of myeloid leukemia

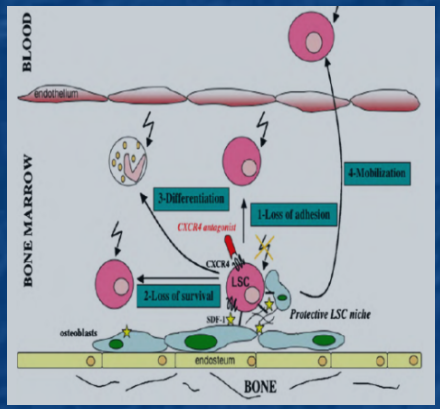


Review

Can inhibition of the SDF-1/CXCR4 axis eradicate acute leukemia?

Sigal Tavor[a,*], Isabelle Petit[b]
[a] Institute of Hematology and Bone Marrow Transplantation, Sourasky Medical Center, Tel Aviv, Israel
[b] INSERM U898, Faculty of Medicine, Av. Valombrose, Nice 06107, France

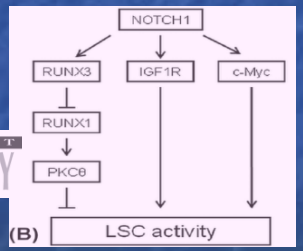
1. Leukemic stem cells: the reason for relapse

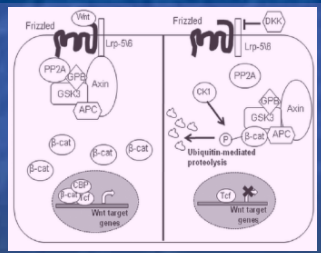


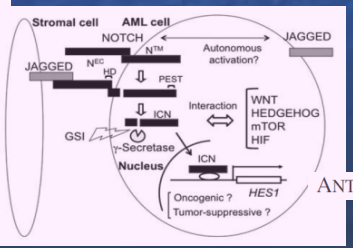
Targeting leukemia stem cells: which pathways drive self-renewal activity in T-cell acute lymphoblastic leukemia?

M. Belmonte BSc,* C. Hoofd PhD,* A.P. Weng MD PhD,* and V. G

CURRENT ONCOLOGY







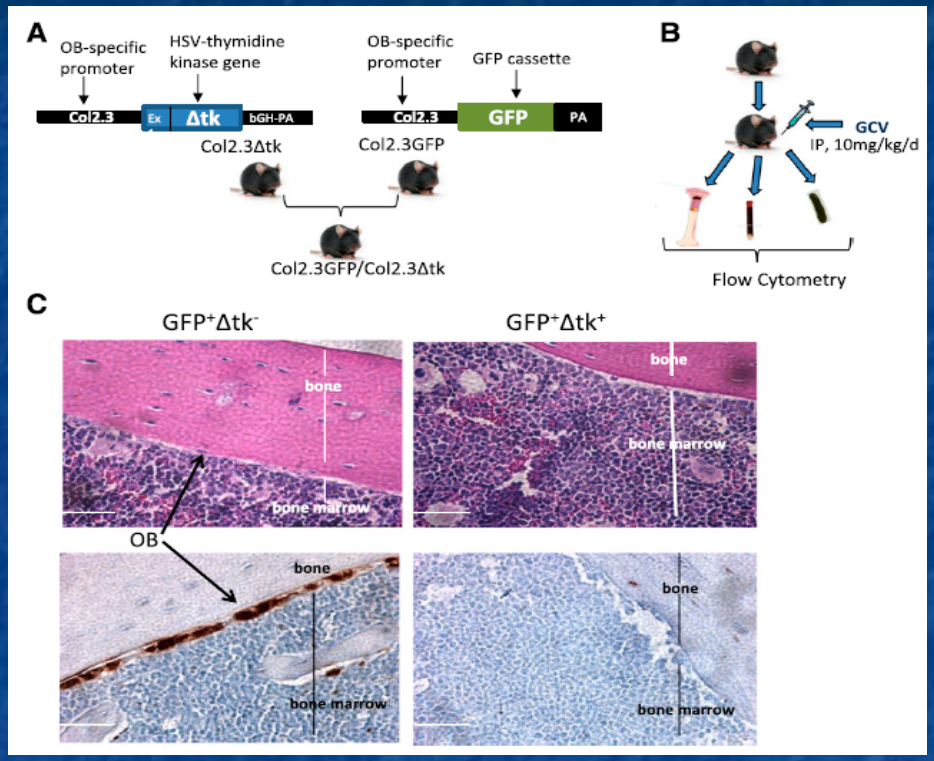
NOTCH Signaling Roles in Acute Myeloid Leukemia Cell Growth and Interaction with other Stemness-related Signals

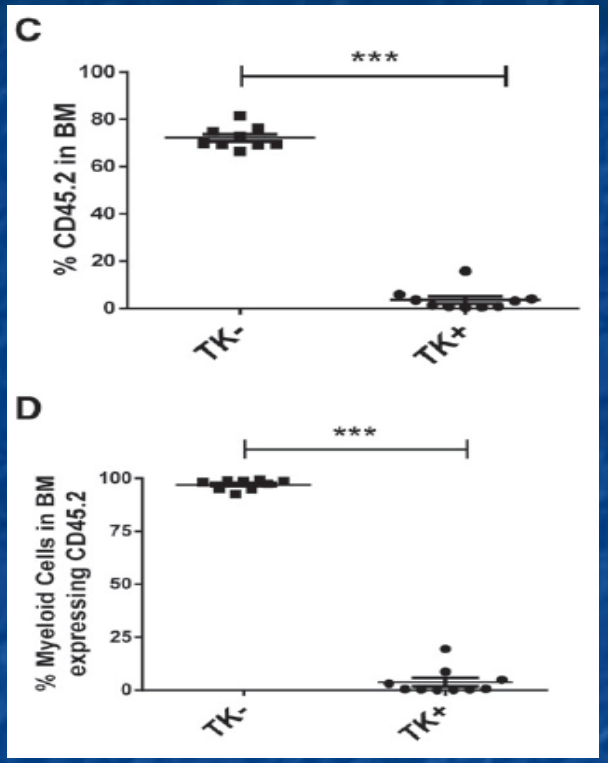
ANTICANCER RESEARCH *34*: 6259-6264 (2014)

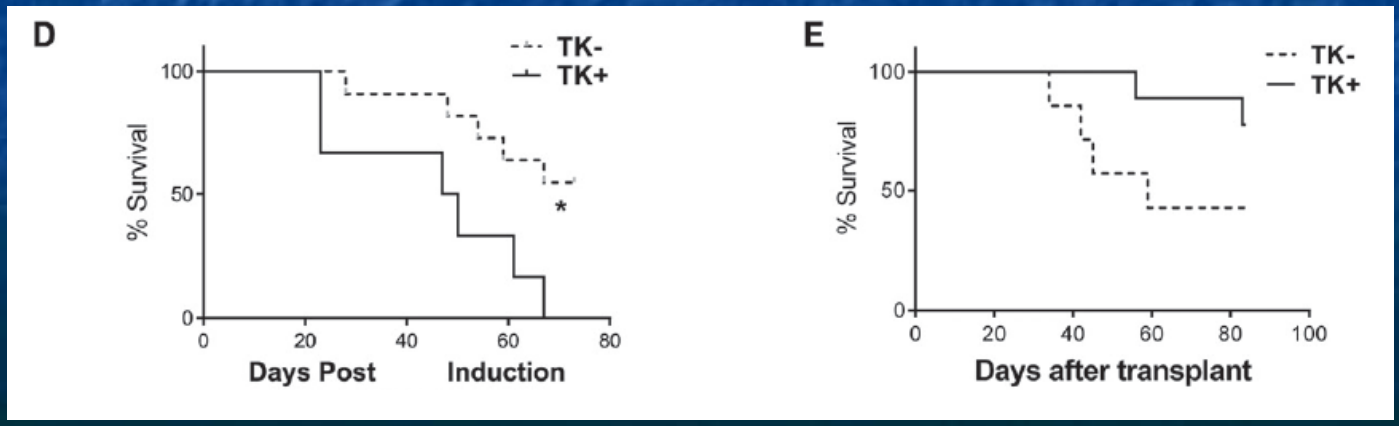
Osteoblast ablation reduces normal long-term hematopoietic stem cell self-renewal but accelerates leukemia development

Marisa Bowers,[1] Bin Zhang,[1] Yinwei Ho,[1] Puneet Agarwal,[2] Ching-Cheng Chen,[1] and Ravi Bhatia[2]

[1]Division of Hematopoietic Stem Cell and Leukemia Research, City of Hope National Medical Center, Duarte, CA; and [2]Division of Hematology-Oncology, Department of Medicine, University of Alabama Birmingham, Birmingham, AL







Targeting of CD44 eradicates human acute myeloid leukemic stem cells

Liqing Jin[1,3], Kristin J Hope[1,3], Qiongli Zhai[2], Florence Smadja-Joffe[2] & John E Dick[1]

nature medicine

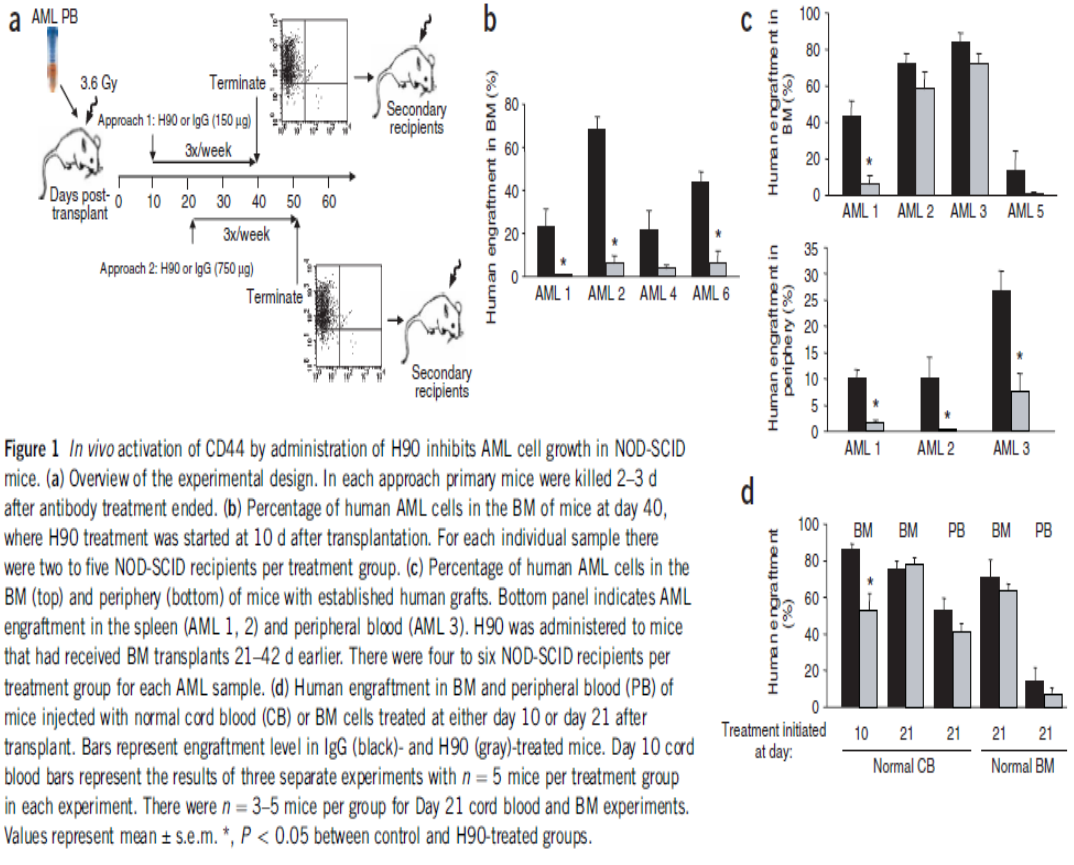
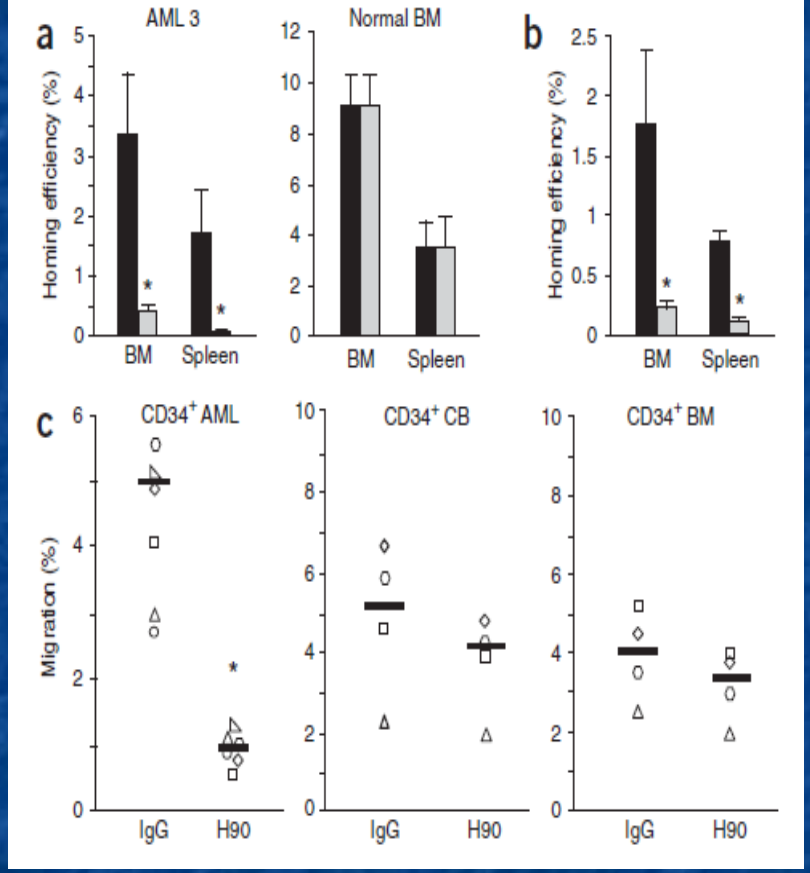


Figure 1 *In vivo* activation of CD44 by administration of H90 inhibits AML cell growth in NOD-SCID mice. (**a**) Overview of the experimental design. In each approach primary mice were killed 2–3 d after antibody treatment ended. (**b**) Percentage of human AML cells in the BM of mice at day 40, where H90 treatment was started at 10 d after transplantation. For each individual sample there were two to five NOD-SCID recipients per treatment group. (**c**) Percentage of human AML cells in the BM (top) and periphery (bottom) of mice with established human grafts. Bottom panel indicates AML engraftment in the spleen (AML 1, 2) and peripheral blood (AML 3). H90 was administered to mice that had received BM transplants 21–42 d earlier. There were four to six NOD-SCID recipients per treatment group for each AML sample. (**d**) Human engraftment in BM and peripheral blood (PB) of mice injected with normal cord blood (CB) or BM cells treated at either day 10 or day 21 after transplant. Bars represent engraftment level in IgG (black)- and H90 (gray)-treated mice. Day 10 cord blood bars represent the results of three separate experiments with $n = 5$ mice per treatment group in each experiment. There were $n = 3$–5 mice per group for Day 21 cord blood and BM experiments. Values represent mean ± s.e.m. *, $P < 0.05$ between control and H90-treated groups.



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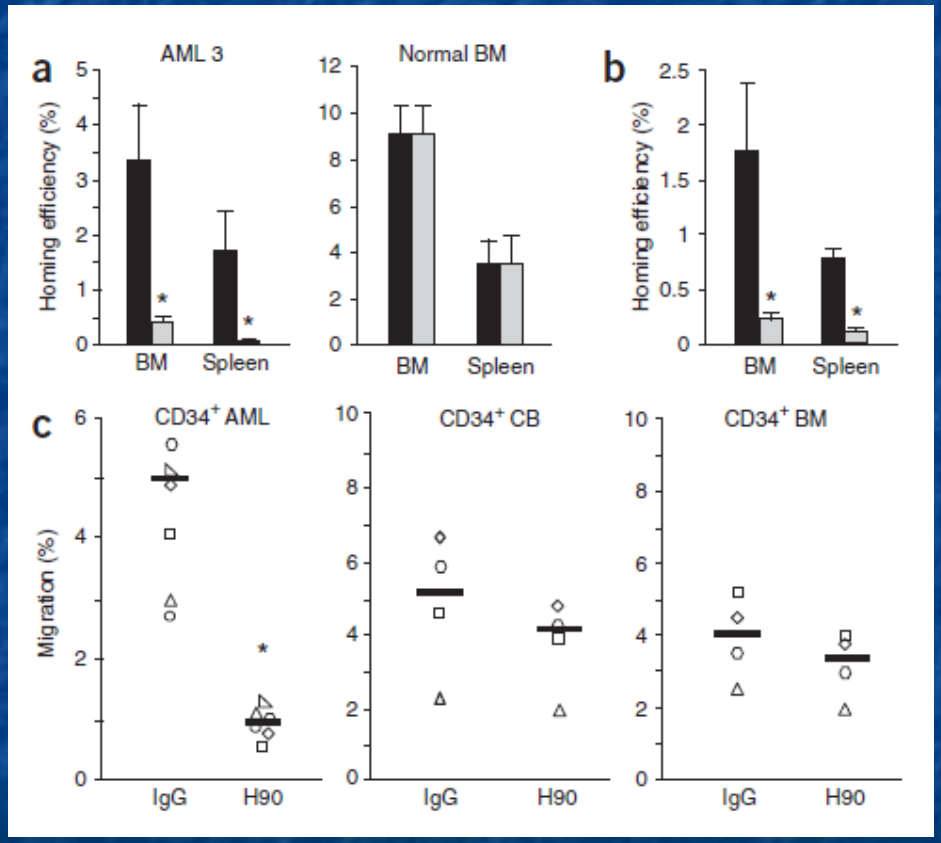
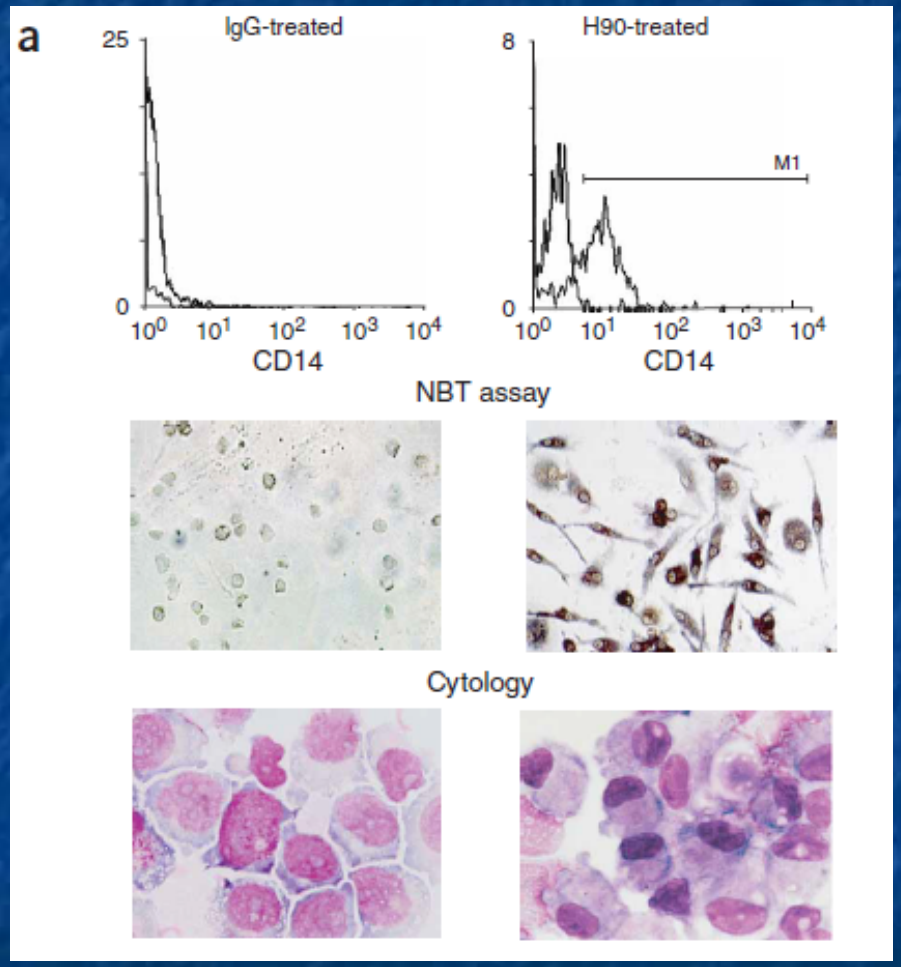
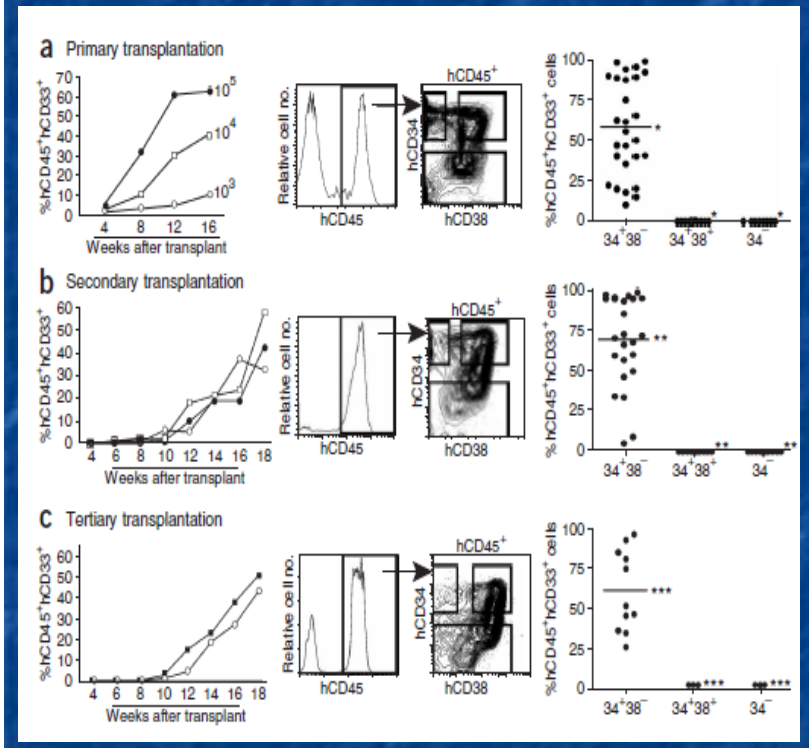
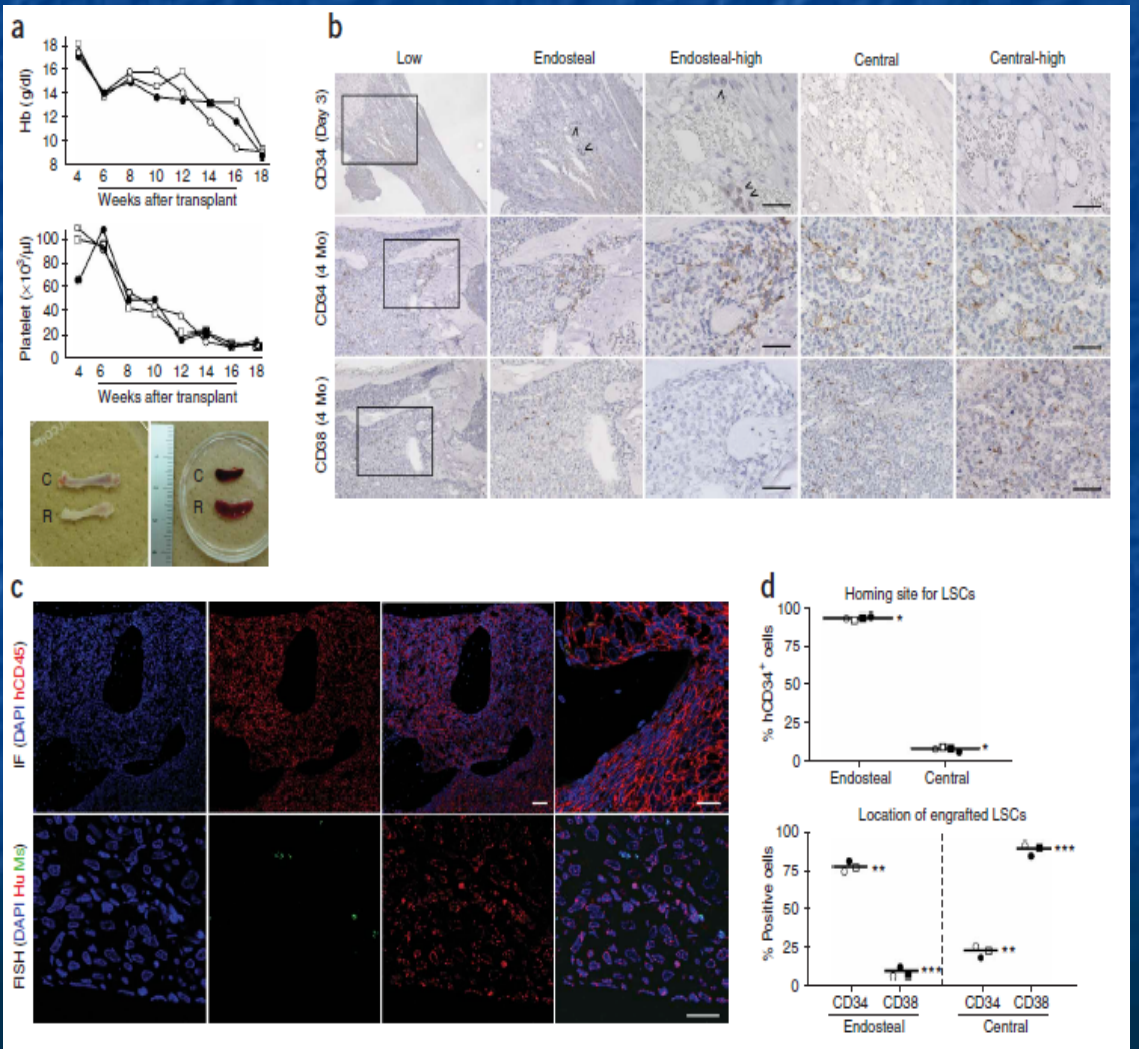




Chemotherapy-resistant human AML stem cells home to and engraft within the bone-marrow endosteal region

Fumihiko Ishikawa[1,3], Shuro Yoshida[1,3], Yoriko Saito[1,5], Atsushi Hijikata[2], Hiroshi Kitamura[2], Satoshi Tanaka[6], Ryu Nakamura[7], Toru Tanaka[7], Hiroko Tomiyama[6], Noriyuki Saito[3], Mitsuhiro Fukata[3], Toshihiro Miyamoto[4], Bonnie Lyons[8], Koichi Ohshima[9], Naoyuki Uchida[10], Shuichi Taniguchi[10], Osamu Ohara[2,11], Koichi Akashi[4,12], Mine Harada[3] & Leonard D Shultz[8]





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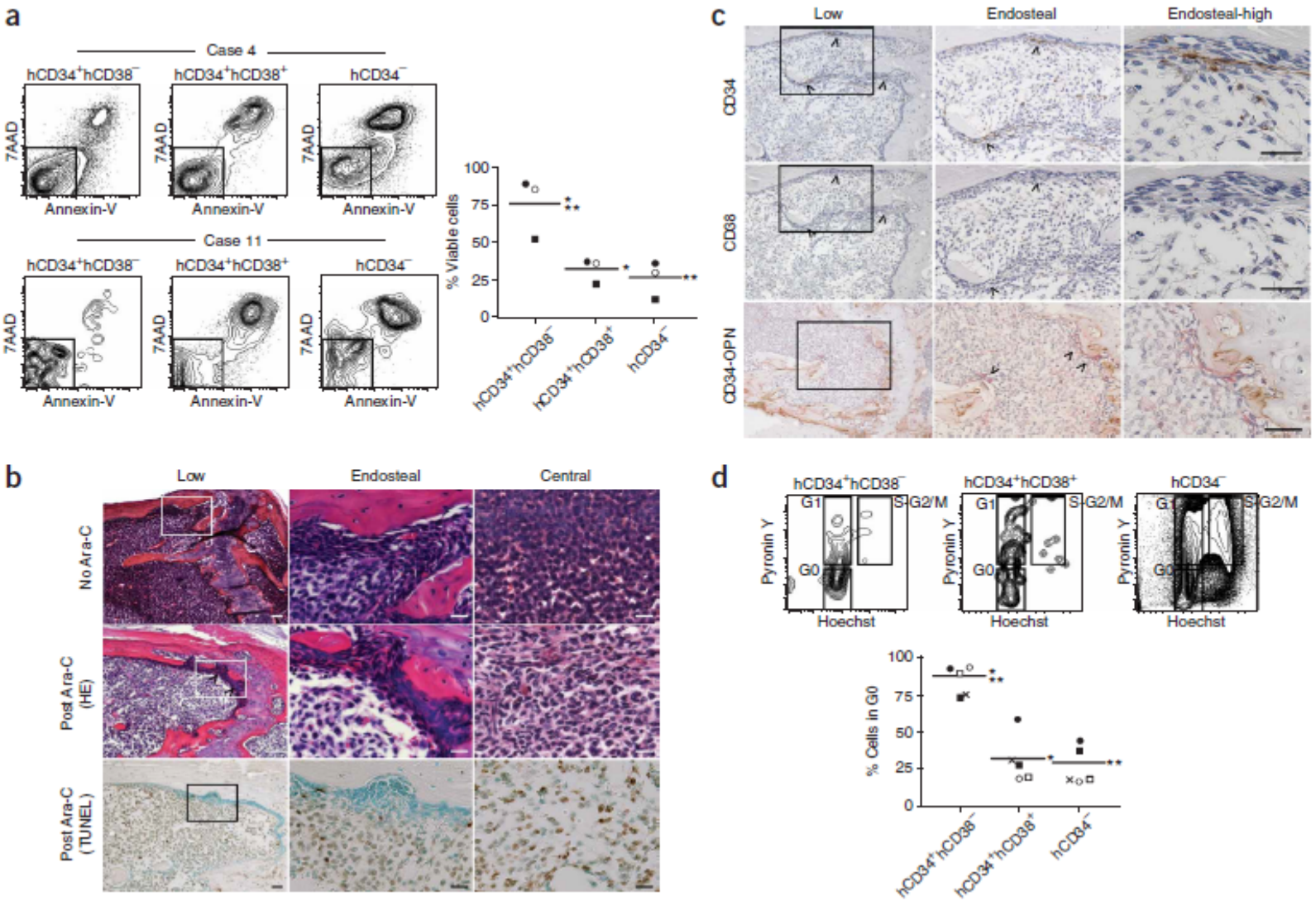

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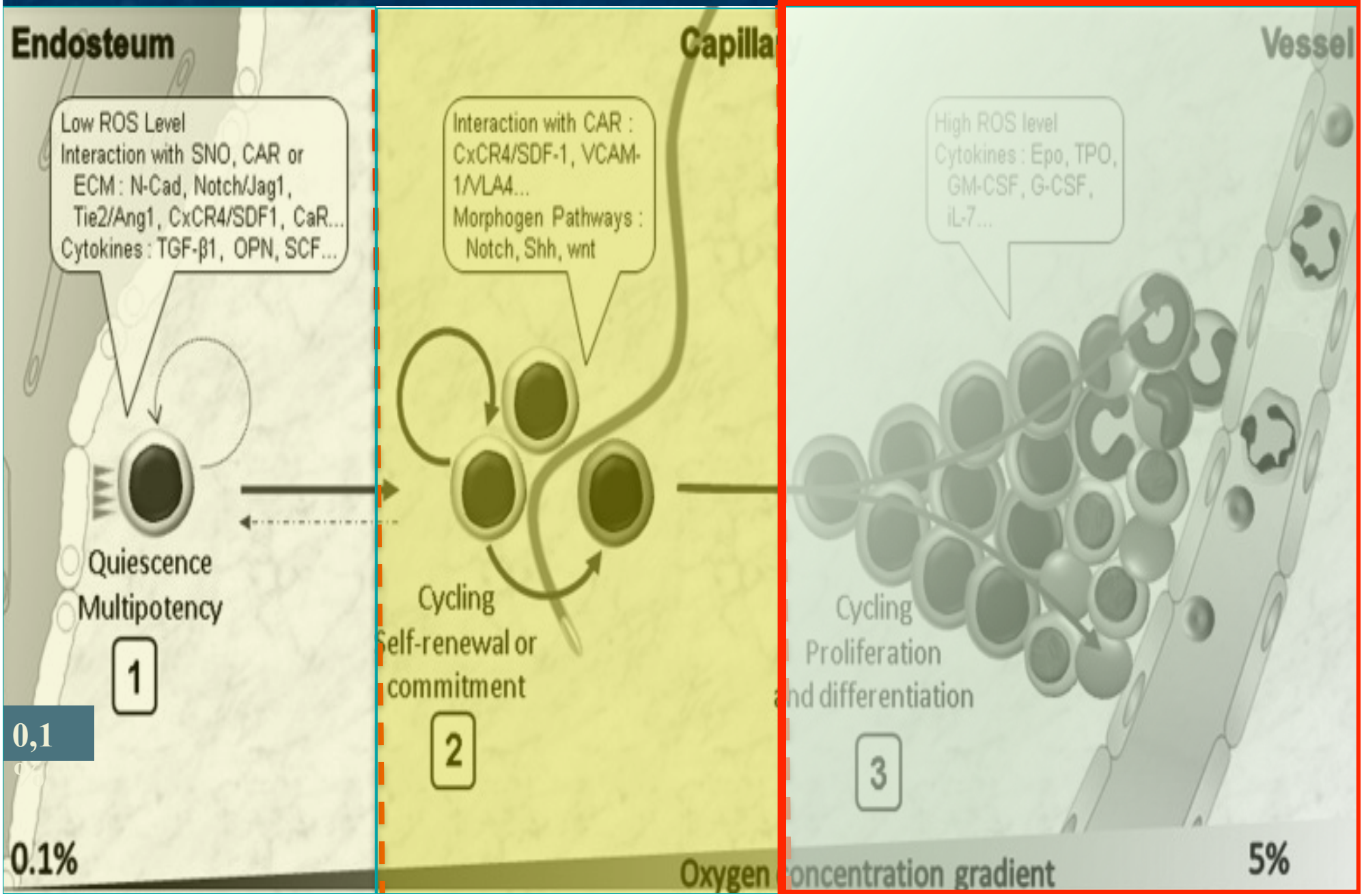

Endosteum
Capilla
Vessel
Low ROS Level
Interaction with SNO, CAR or ECM : N-Cad, Notch/Jag1, Tie2/Ang1, CxCR4/SDF1, CaR...
Cytokines : TGF-β1, OPN, SCF...
Interaction with CAR : CxCR4/SDF-1, VCAM-1/VLA4...
Morphogen Pathways : Notch, Shh, wnt
High ROS level
Cytokines : Epo, TPO, GM-CSF, G-CSF, iL-7...
Quiescence
Multipotency
1
Cycling
Self-renewal or commitment
2
Cycling
Proliferation
nd differentiation
3
0,1
0.1%
Oxygen
oncentration gradient
5%

Bone marrow angiogenesis magnetic resonance imaging in patients with acute myeloid leukemia: peak enhancement ratio is an independent predictor for overall survival

Tiffany Ting-Fang Shih,[1] Hsin-An Hou,[2,3] Chieh-Yu Liu,[4] Bang-Bin Chen,[1] Jih-Luh Tang,[2] Hsuan-Yu Chen,[5] Shwu-Yuan Wei,[1] Ming Yao,[2] Shang-Yi Huang,[2] Wen-Chien Chou,[6] Szu-Chun Hsu,[6] Woei Tsay,[2] Chih-Wei Yu,[1] Chao-Yu Hsu,[1] *Hwei-Fang Tien,[2] and *Pan-Chyr Yang[2]

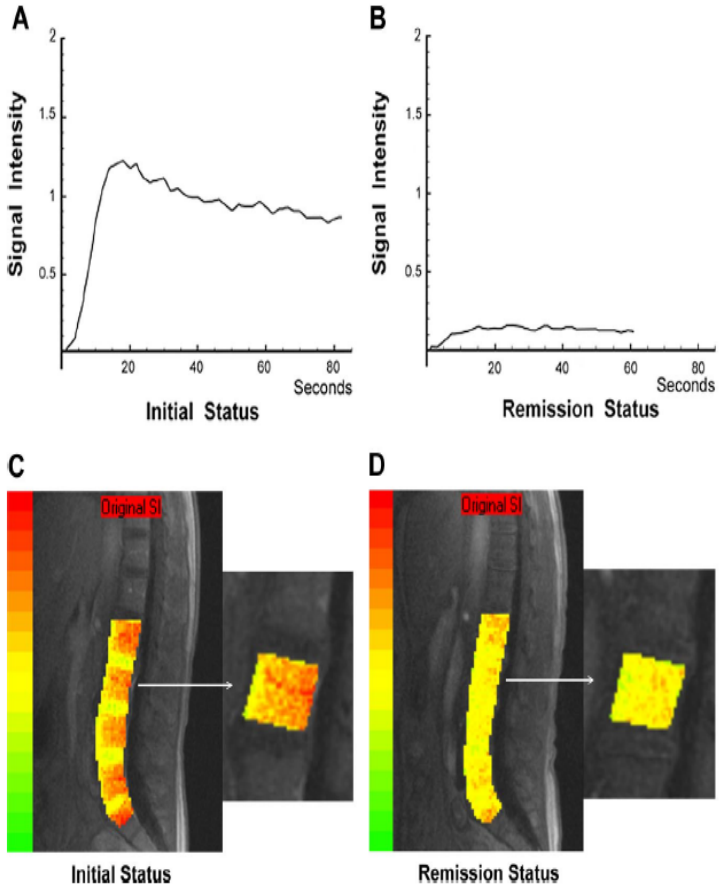
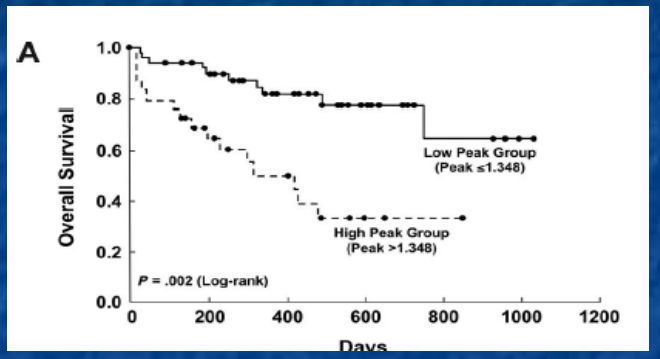
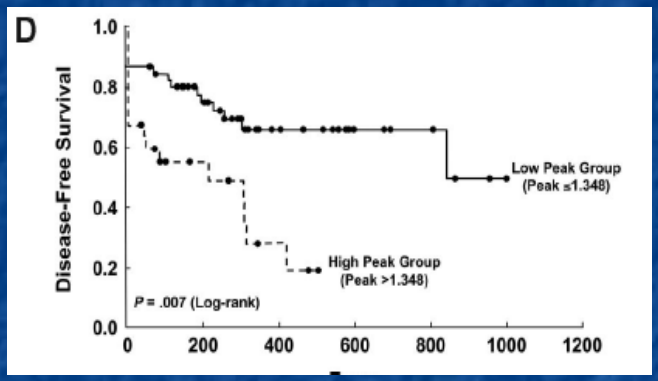
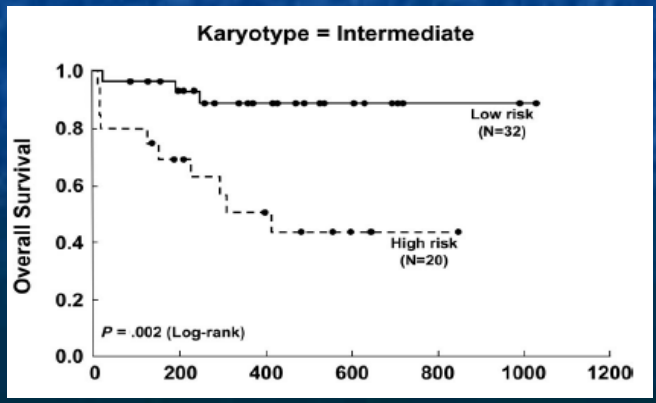


Figure 1. The time-intensity curves derived from DCE-MRI and color-coded angiogenesis maps of vertebral bone marrow in a 54-year-old female patient with de novo AML are shown. She achieved complete remission after induction chemotherapy. Her remission duration until the end of August 2007 was 1002 days. The time-intensity curve (A) and color-coded angiogenesis map (C) at initial diagnosis are shown; those in complete remission are shown (B,D), respectively.





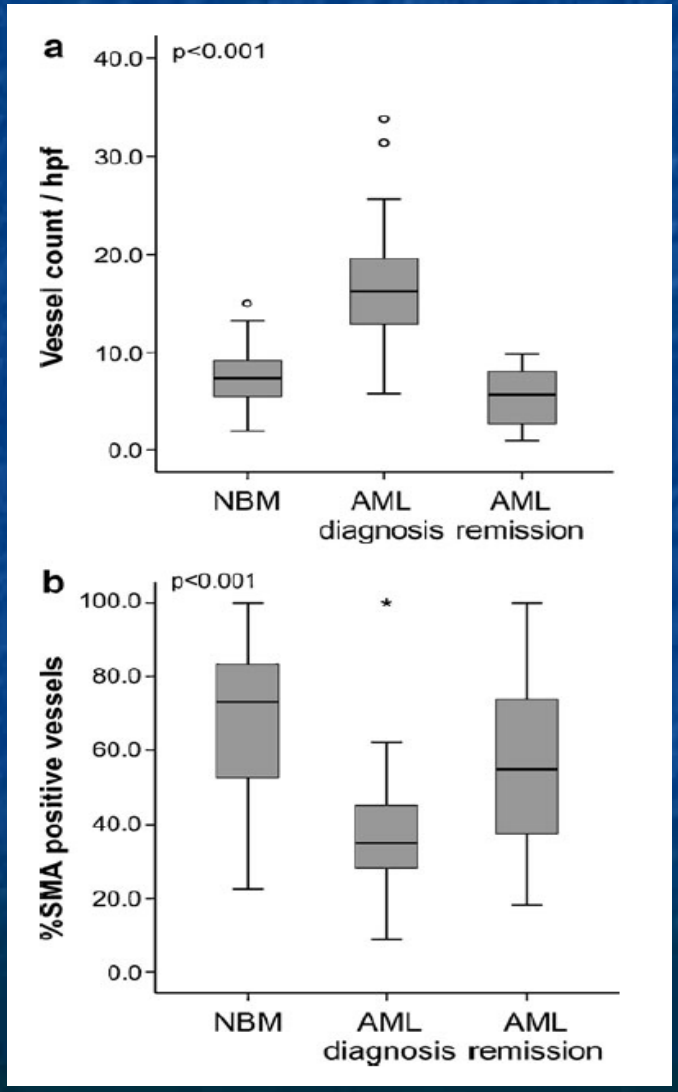


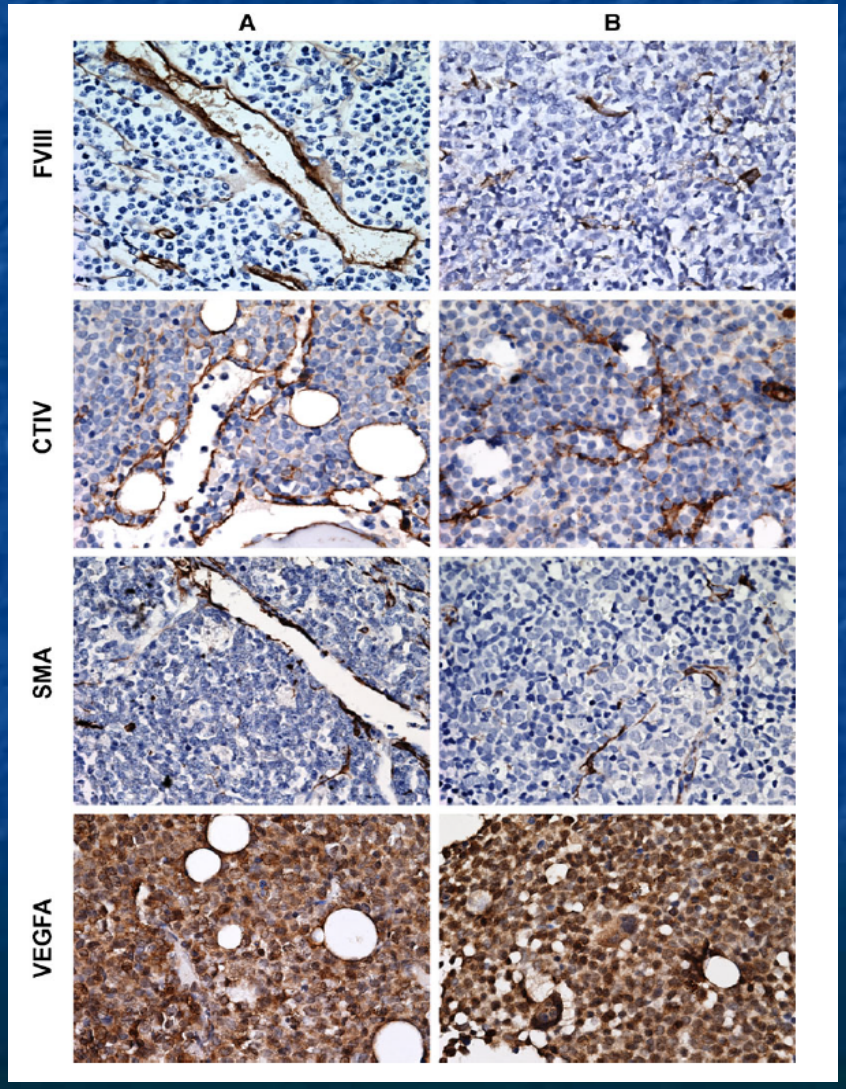
High Acute Myeloid Leukemia derived VEGFA levels are associated with a specific vascular morphology in the leukemic bone marrow

Alida C. Weidenaar · Arja ter Elst · Gineke Koopmans-Klein · Stefano Rosati · Wilfred F. A. den Dunnen · Tiny Meeuwsen-de Boer · Willem A. Kamps · Edo Vellenga · Eveline S. J. M. de Bont

Cell Oncol. (2011) 34:289–296
DOI 10.1007/s13402-011-0017-9

ORIGINAL PAPER





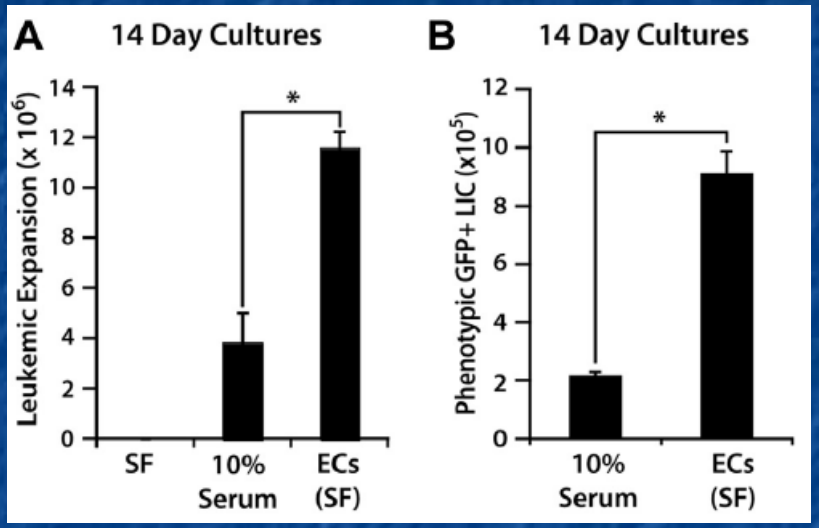
Activation of the vascular niche supports leukemic progression and resistance to chemotherapy

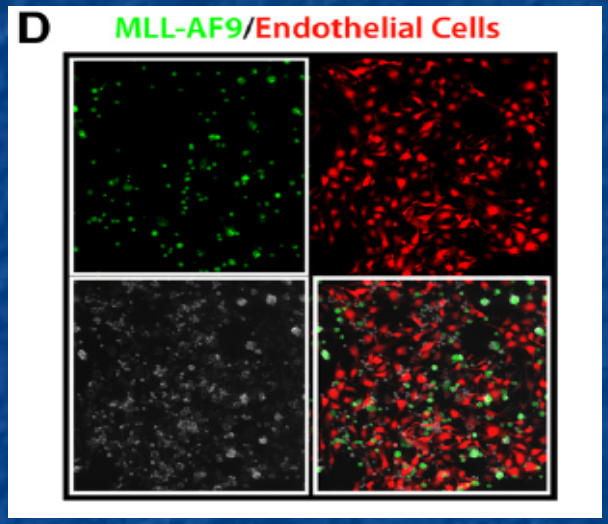
Michael G. Poulos[a], Eric J. Gars[a], Michael C. Gutkin[a], Christopher C. Kloss[a], Michael Ginsberg[b], Joseph M. Scandura[c], Shahin Rafii[a], and Jason M. Butler[a]

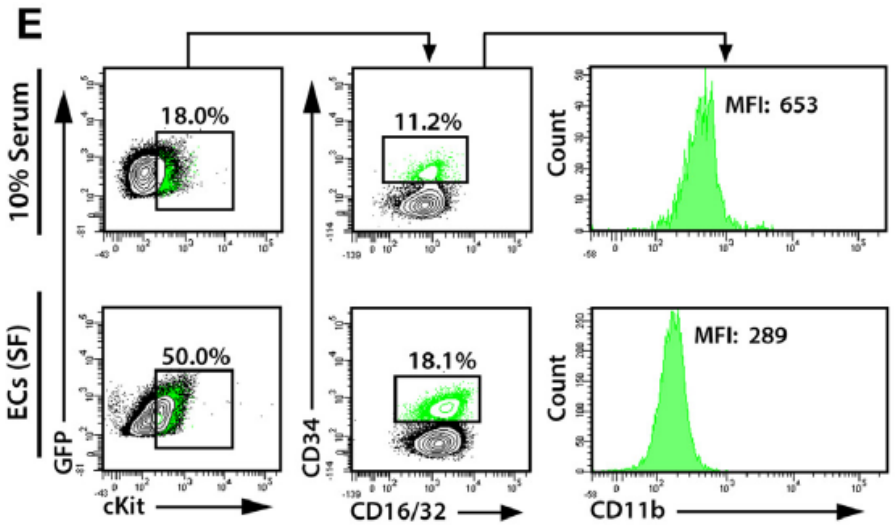
[a]*Department of Genetic Medicine, Weill Cornell Medical College, New York, NY, USA;* [b]*Angiocrine Bioscience, New York, NY, USA;* [c]*Division of Hematology and Medical Oncology, Leukemia and Bone Marrow Failure Program, Weill Cornell Medical College, New York, NY, USA*

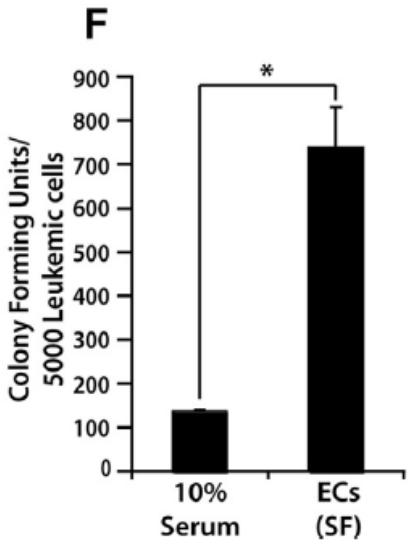
(Received 15 April 2014; revised 3 July 2014; accepted 22 August 2014)

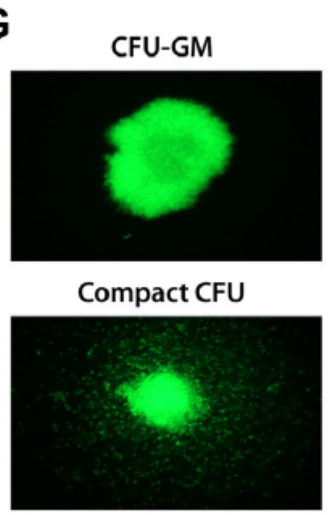
Experimental Hematology











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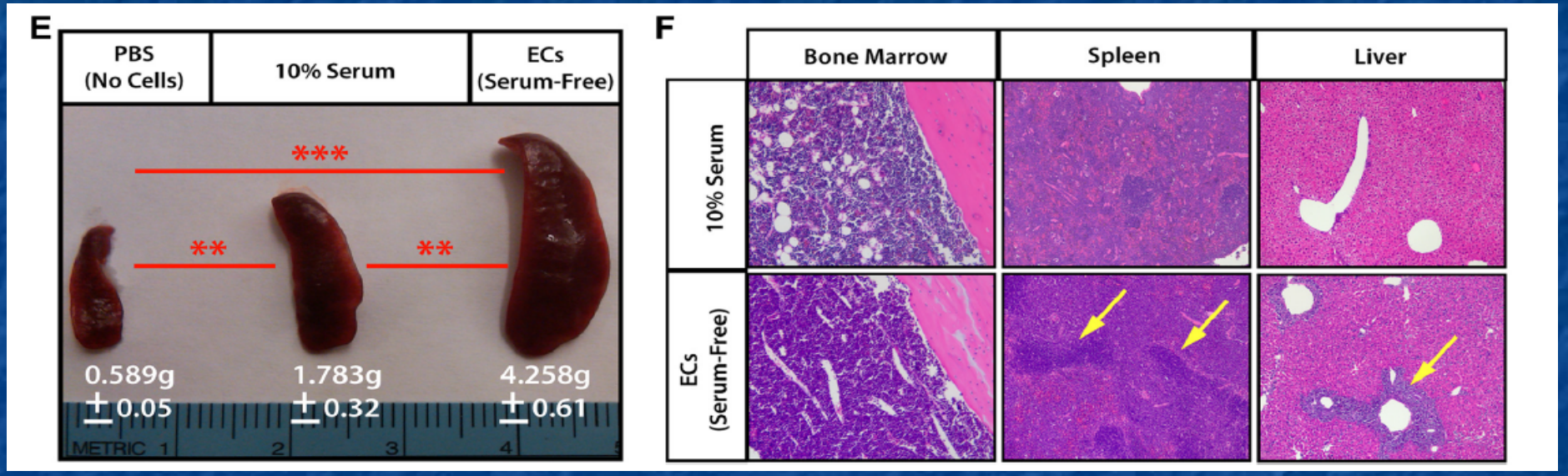

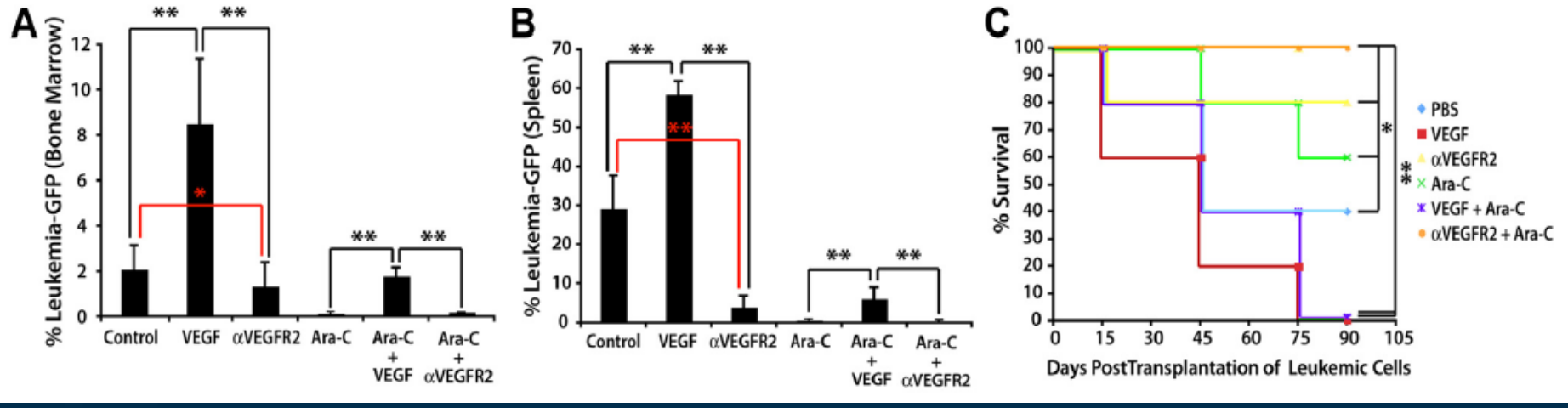

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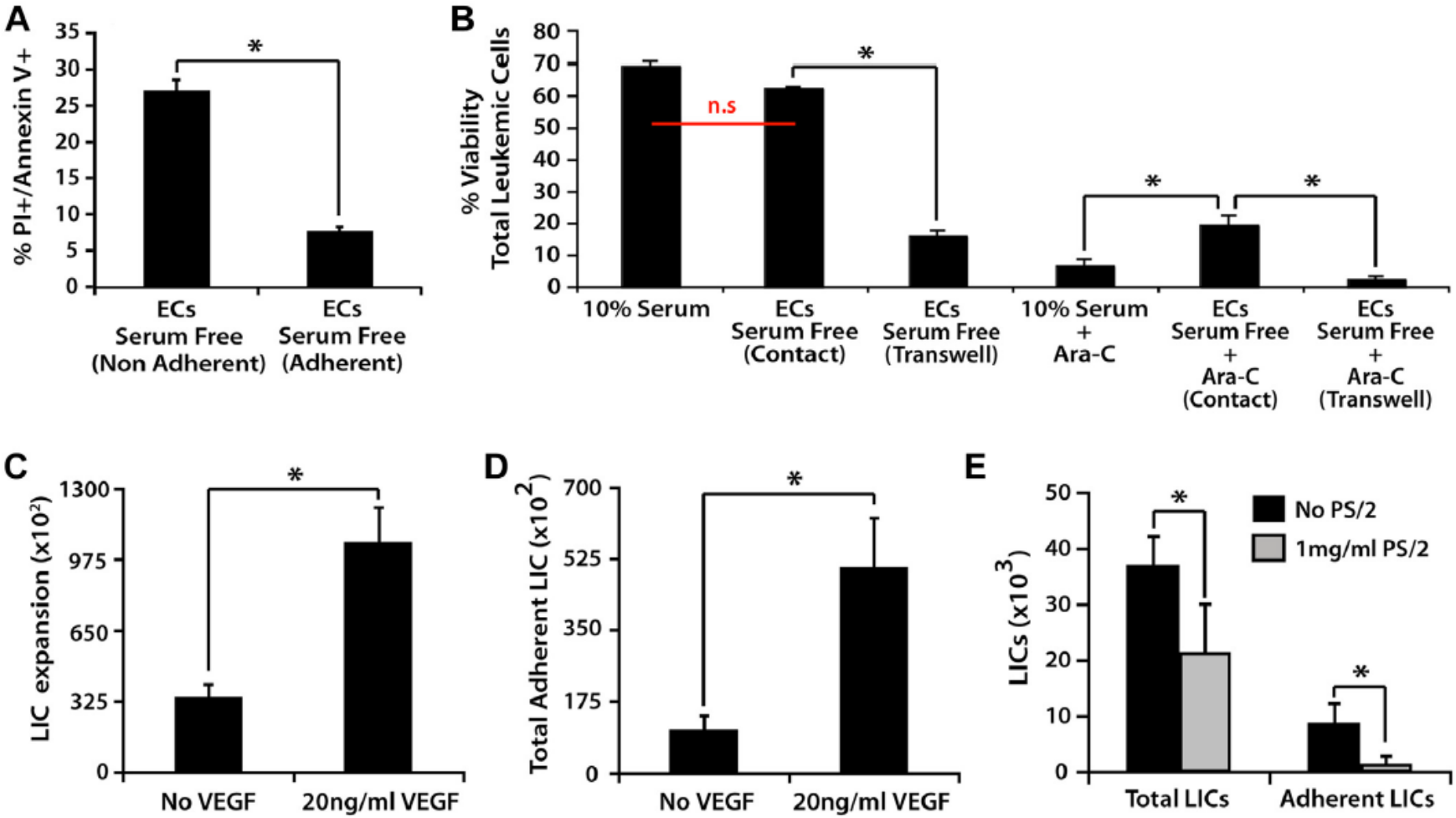

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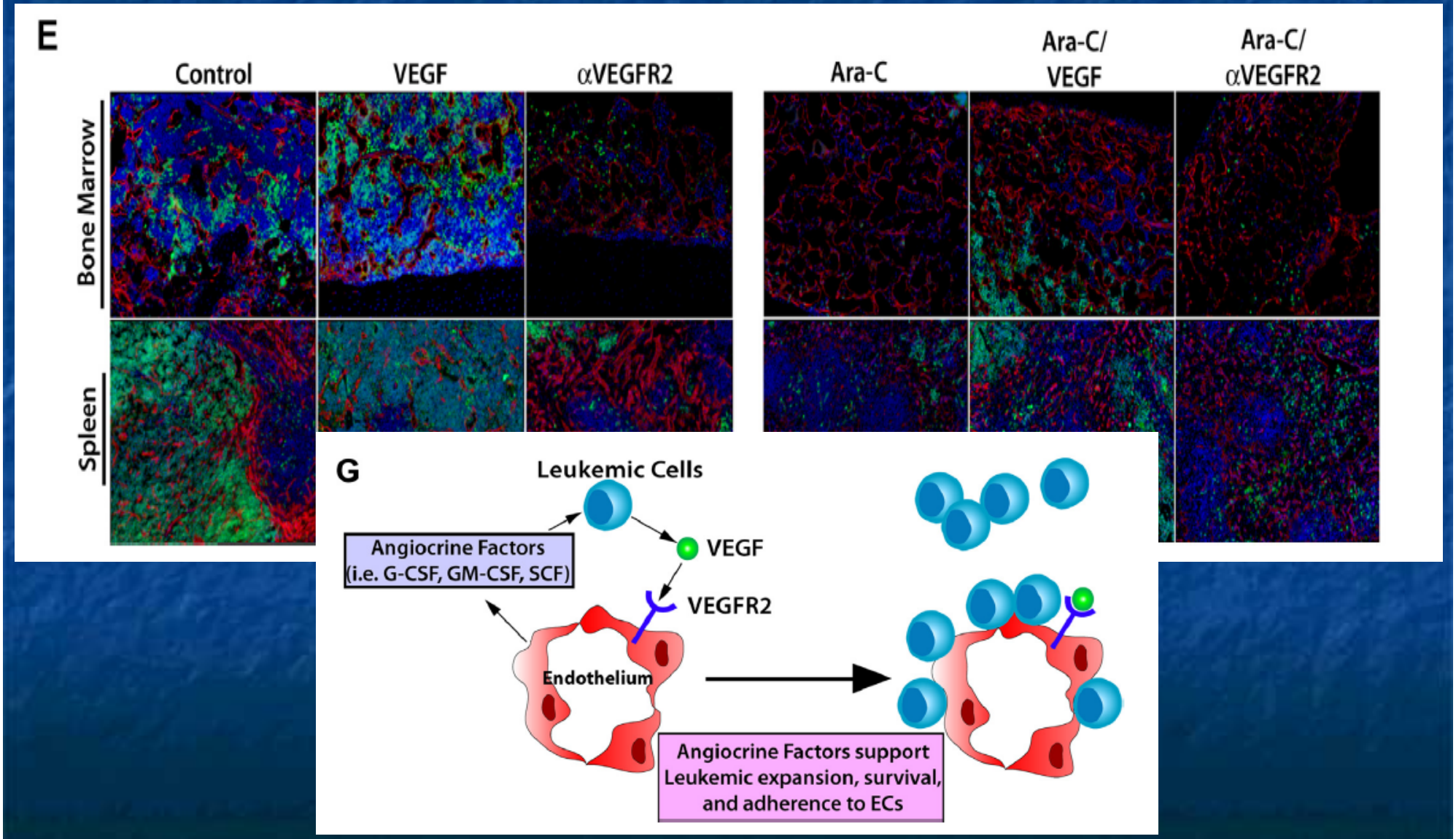
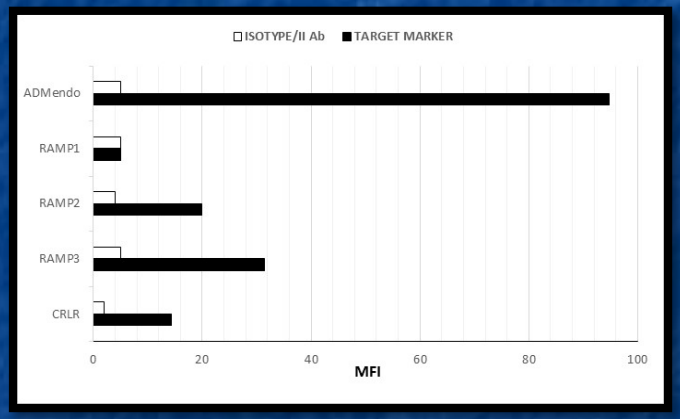
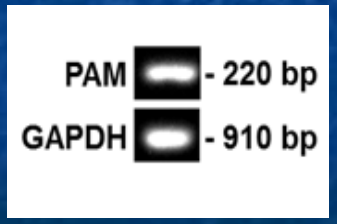


Adrenomedullin in the growth modulation and differentiation of acute myeloid leukemia cells: preliminary studies in HL60 cell line

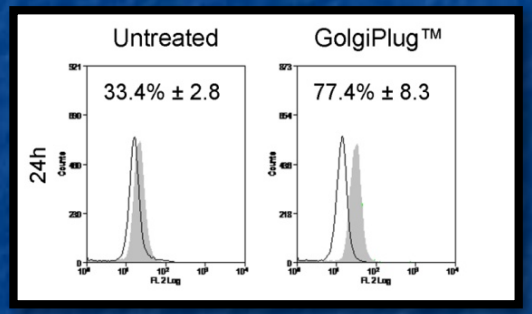
Rosa Di Liddo[a], Deborah Bridi[a], Michele Gottardi[b], Sergio De Angeli[c], Claudio Grandi[a], Alessia Tasso[a], Thomas Bertalot[a], Giovanni Martinelli[d], Filippo Gherlinzoni[b], Maria Teresa Conconi[a]

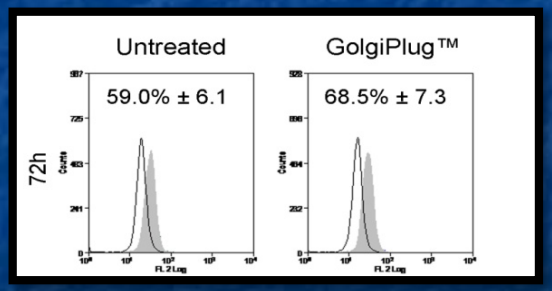
Le cellule HL60 esprimono ADM e il suo sistema recettoriale ed enzimatico





Le cellule HL60 producono adrenomedullina





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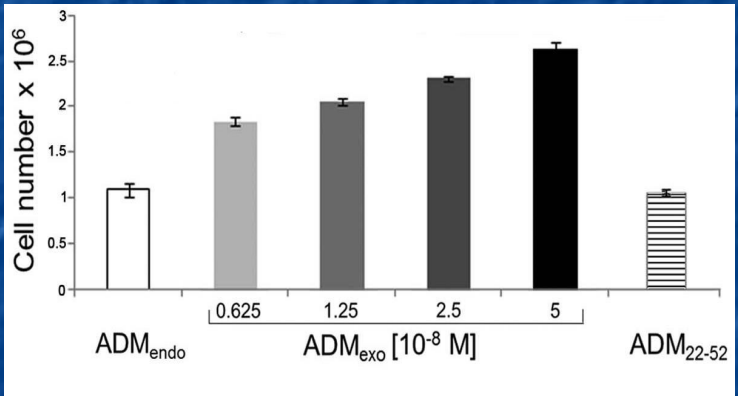
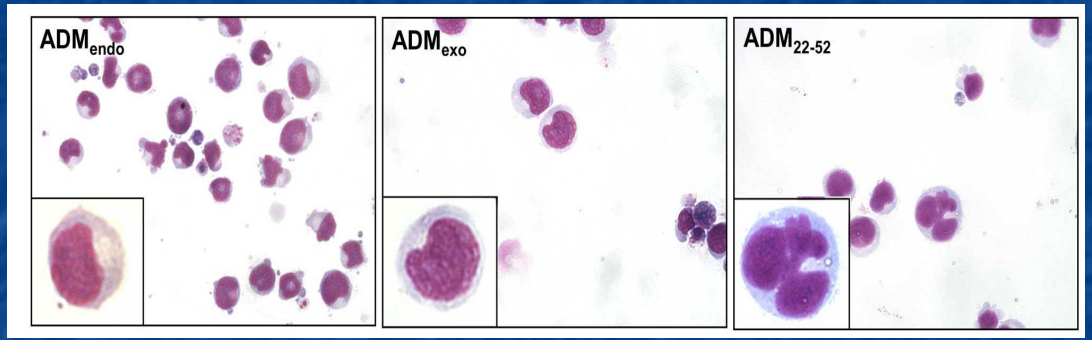
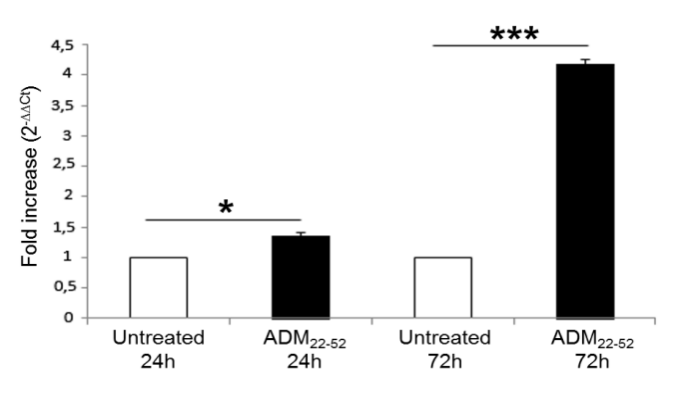
Adrenomedullina induce proliferazione cellulare



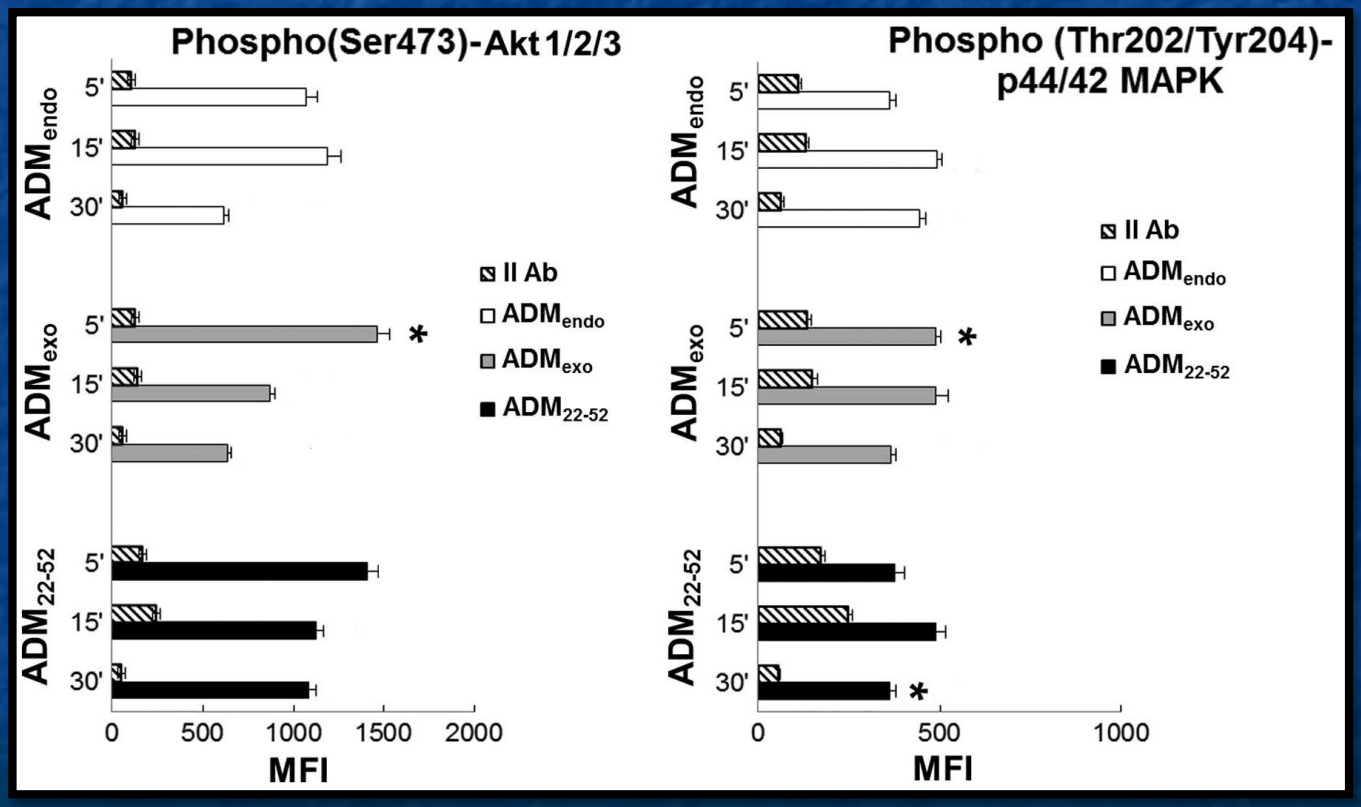
Adrenomedullina inibisce la differenziazione cellulare



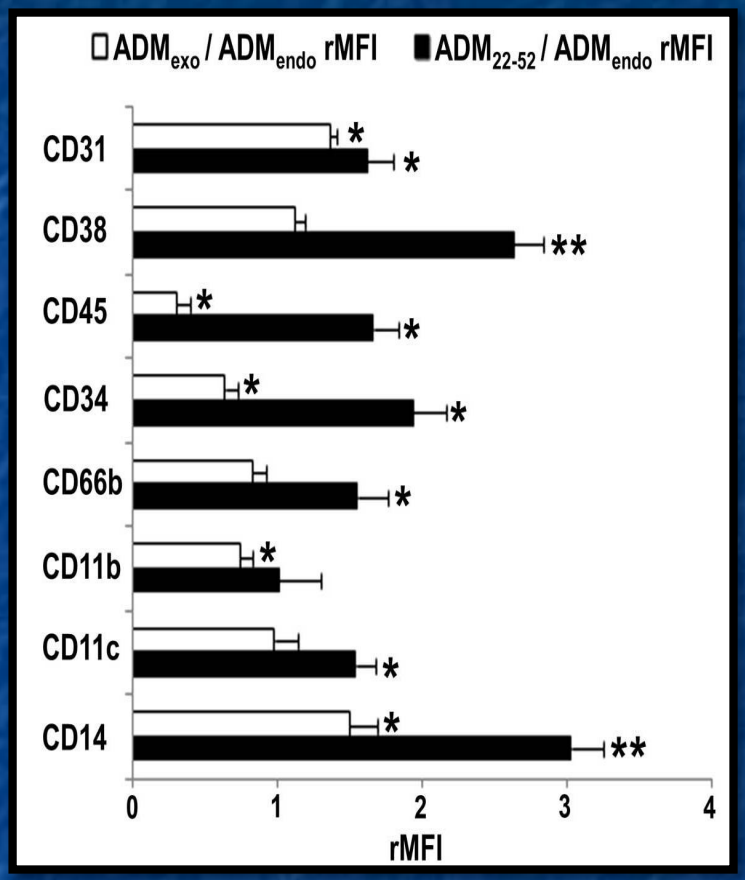


Adrenomedullin in the growth modulation and differentiation of acute myeloid leukemia cells: preliminary studies in HL60 cell line

Rosa Di Liddo[a], Deborah Bridi[a], Michele Gottardi[b], Sergio De Angeli[c], Claudio Grandi[a], Alessia Tasso[a], Thomas Bertalot[a], Giovanni Martinelli[d], Filippo Gherlinzoni[b], Maria Teresa Conconi[a]

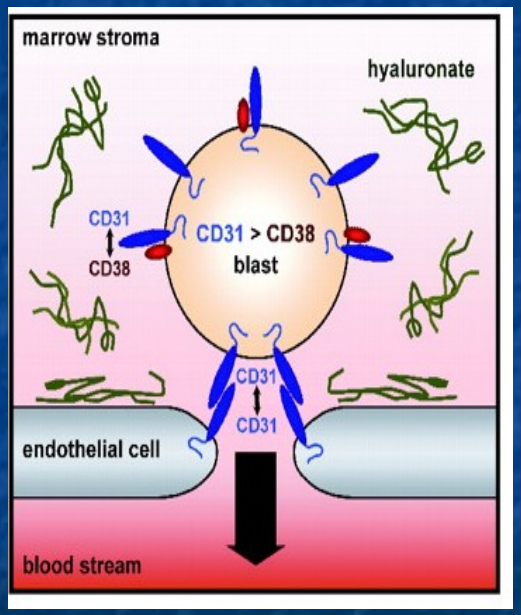


Adrenomedullina inibisce la differenziazione cellulare

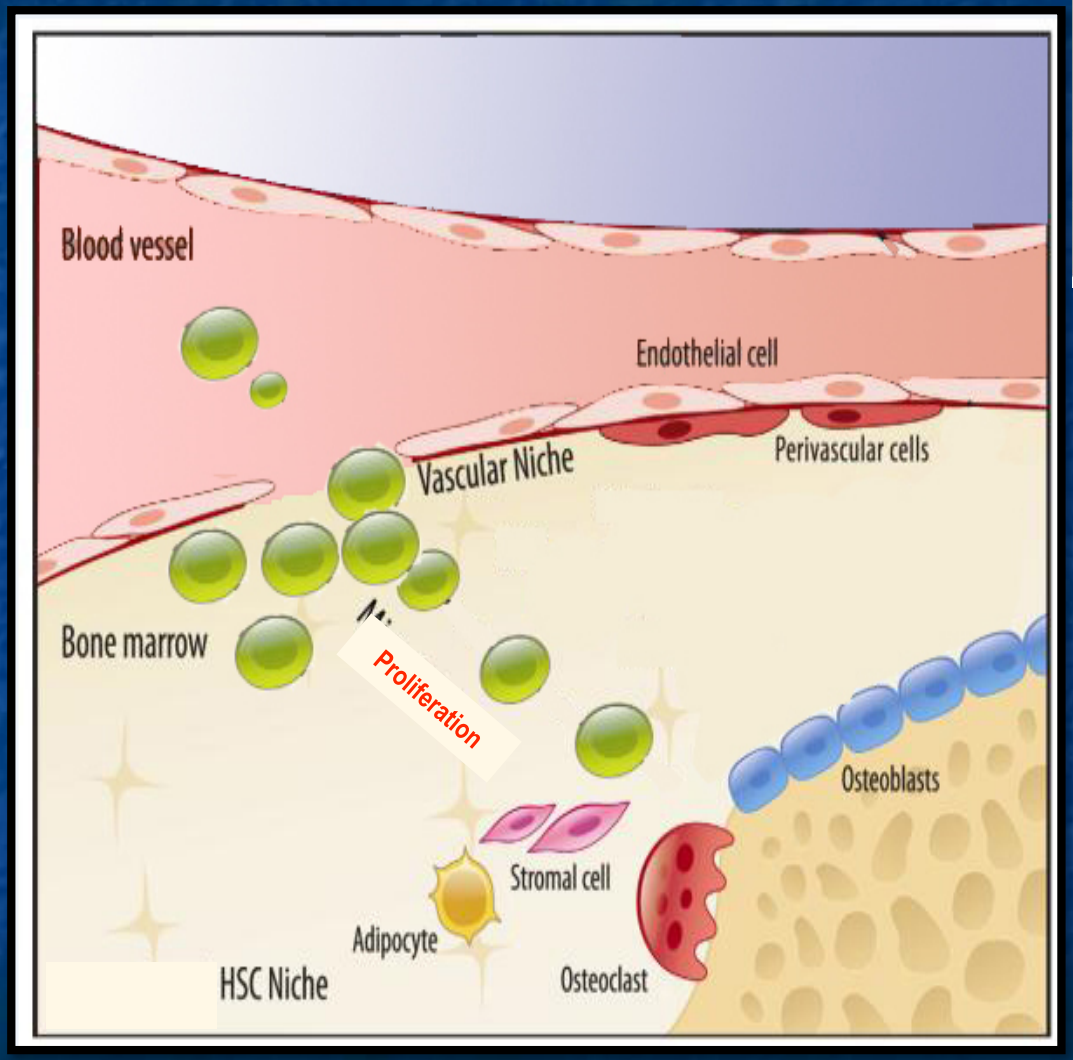


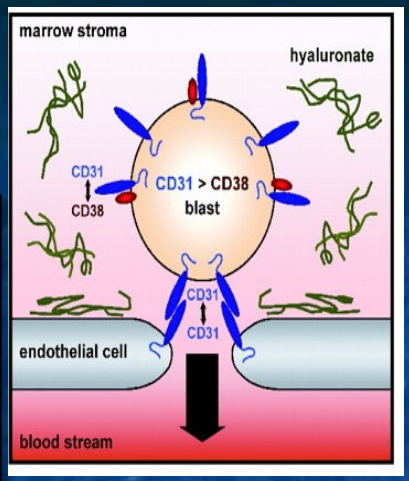
rMFI: rapporto di immunofluorescenza media
ADMexo: $5x10^{-8}$M; ADM22-52: $5x10^{-7}$

interazioni con microambiente CD31/CD38 > 1 potenziale di migrazione transendoteliale*



*Gallay N, "The role of Platelet/Endothelial Cell Adhesion Molecule-1 (CD31) CD38 Antigens in Marrow Microenvitonmental Retention of Acute Myelogenous Leukemia Cells" *Cancer Res, 2007*


Blood vessel
Endothelial cell
Vascular Niche
Perivascular cells
Bone marrow
Proliferation
Osteoblasts
Stromal cell
Adipocyte
HSC Niche
Osteoclast


marrow stroma
hyaluronate
CD31
CD38
CD31 > CD38
blast
CD31
CD31
endothelial cell
blood stream

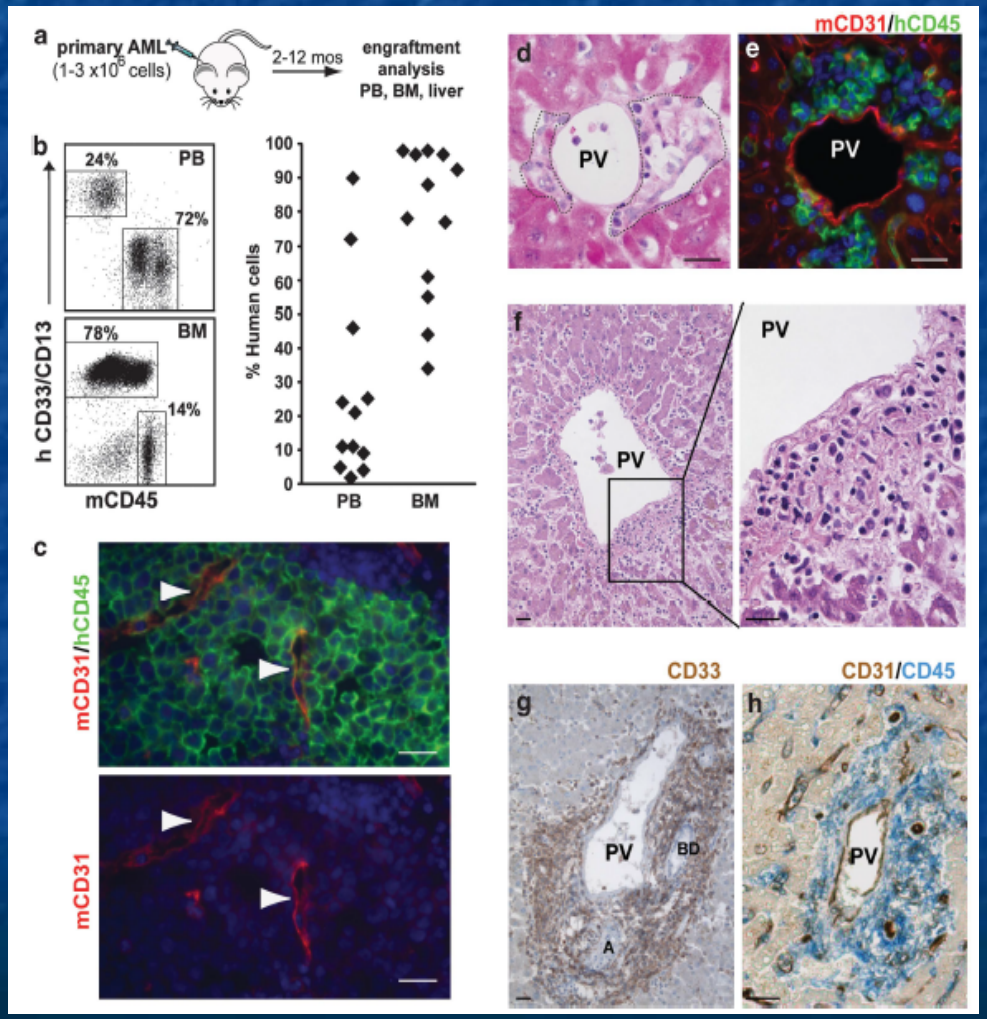
ORIGINAL ARTICLE

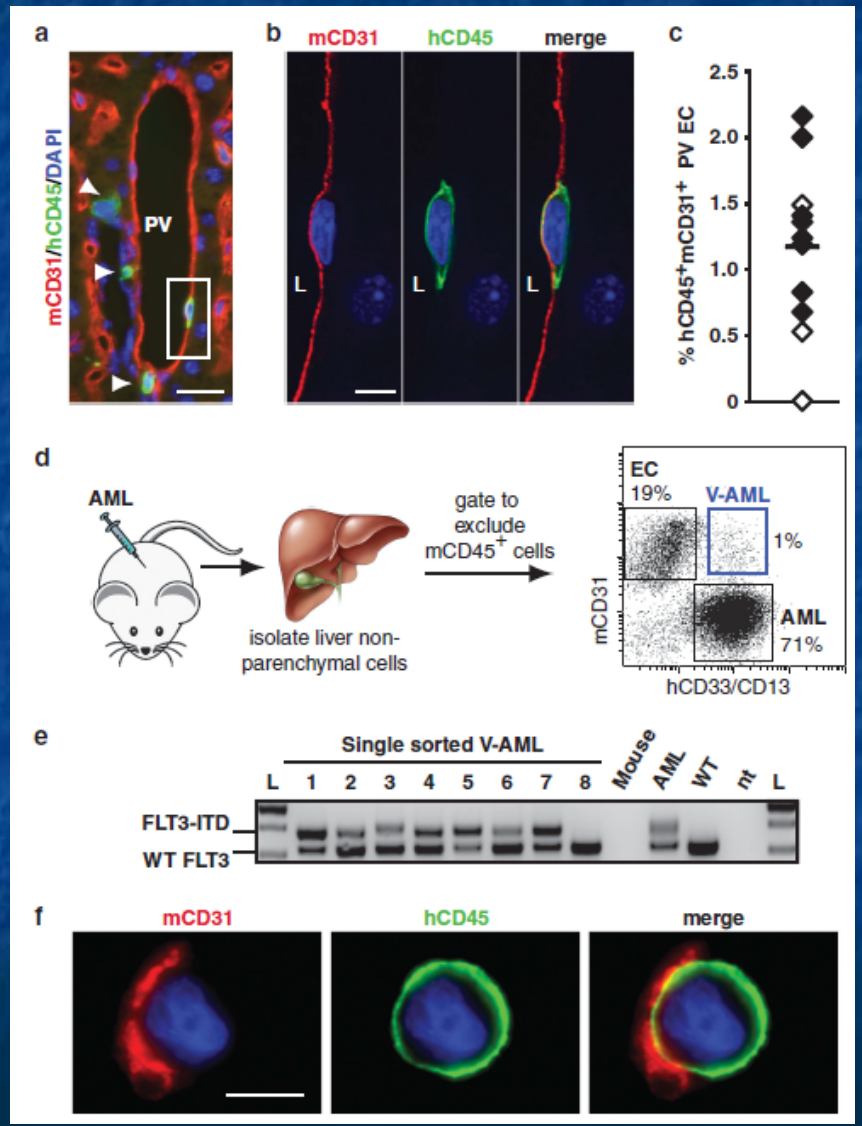
Functional integration of acute myeloid leukemia into the vascular niche

CR Cogle[1,6], DC Goldman[2,3,6], GJ Madlambayan[1,6,7], RP Leon[2,3], A Al Masri[2,3], HA Clark[2,3], SA Asbaghi[2,3], JW Tyner[3], J Dunlap[3,4], G Fan[3,4], T Kovacsovics[2,3], Q Liu[2,3], A Meacham[1], KL Hamlin[2,3], RA Hromas[1], EW Scott[5] and WH Fleming[2,3]

Leukemia (2014) **28**, 1978–1987

www.nature.com/leu





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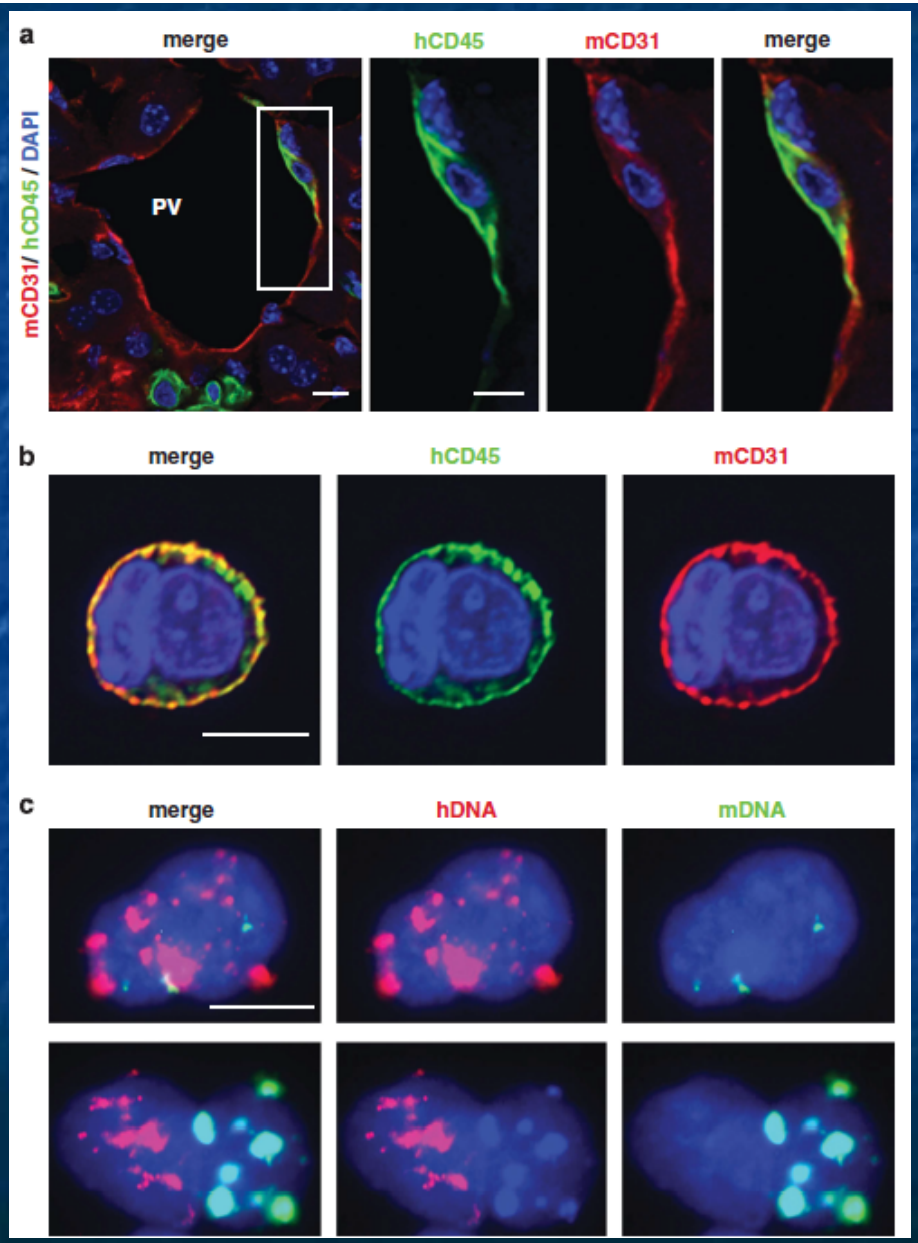

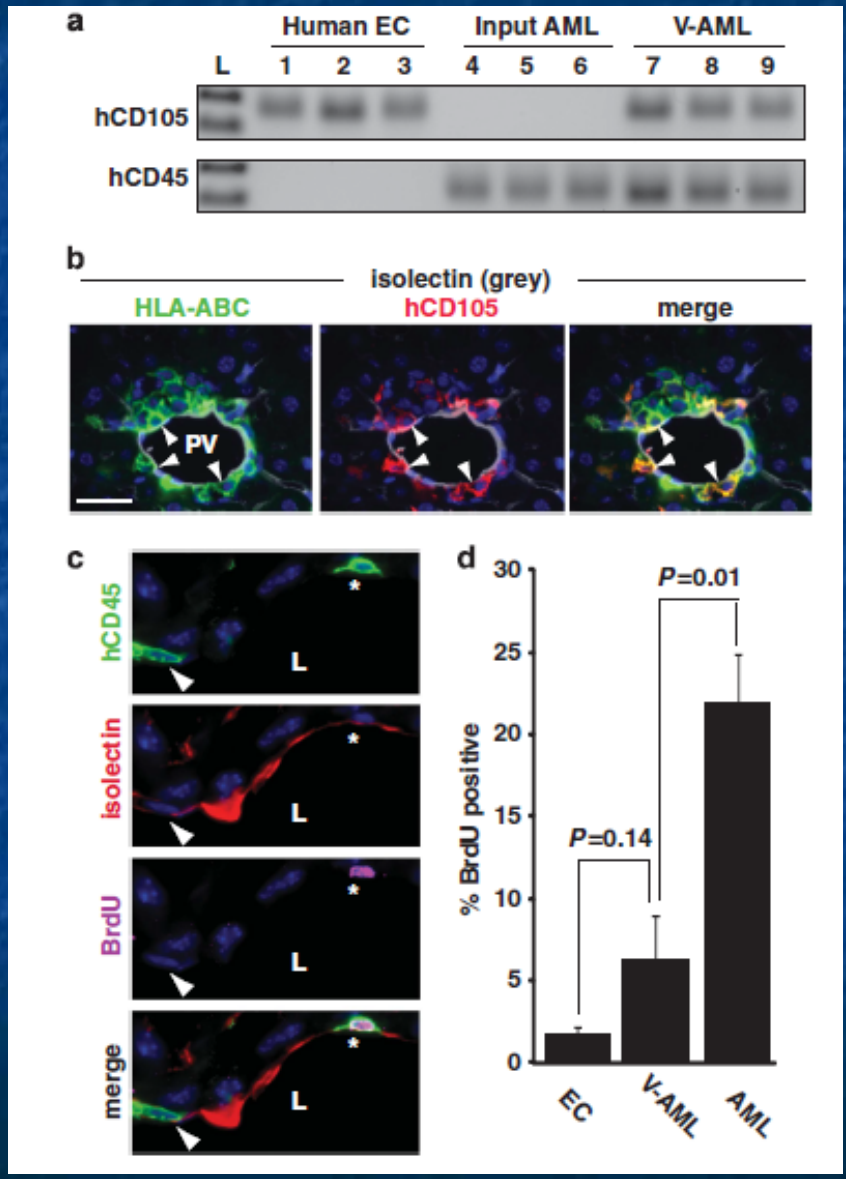

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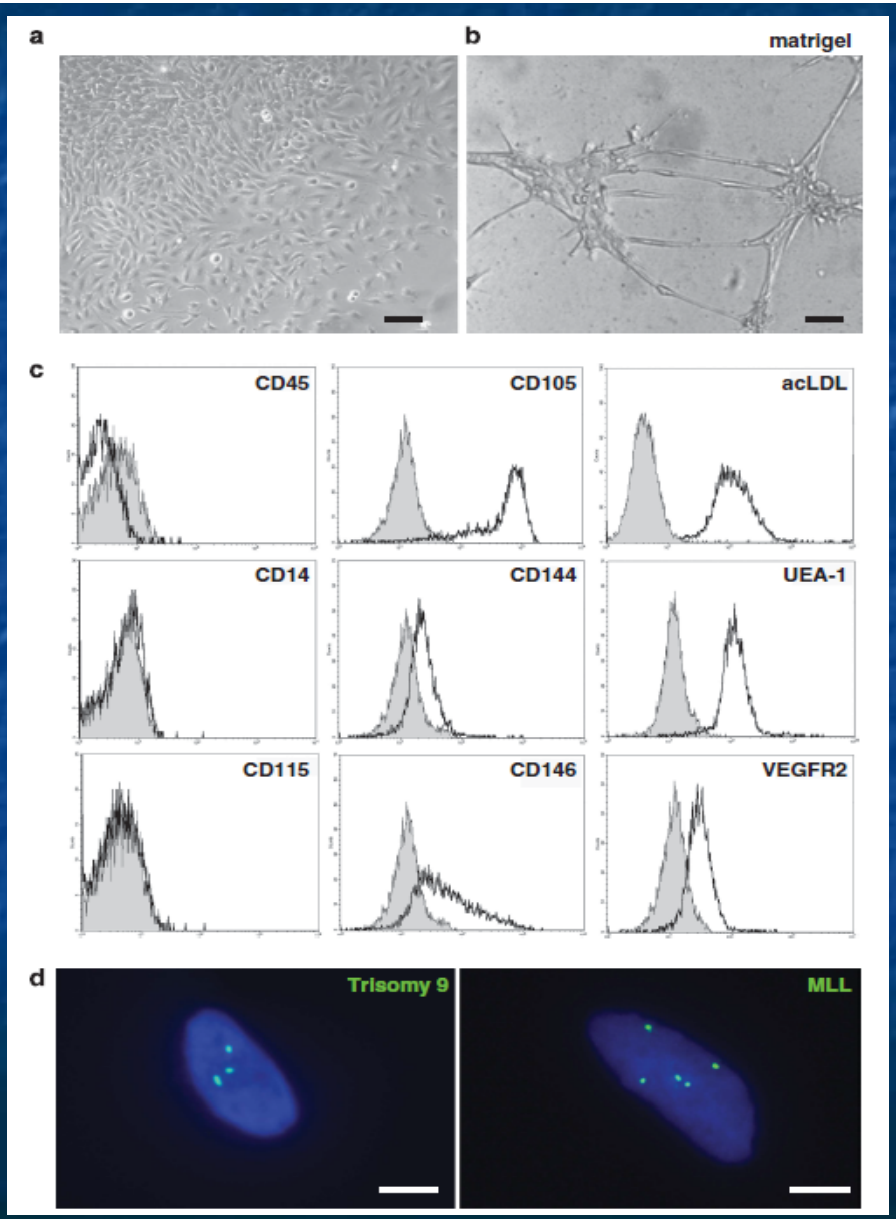
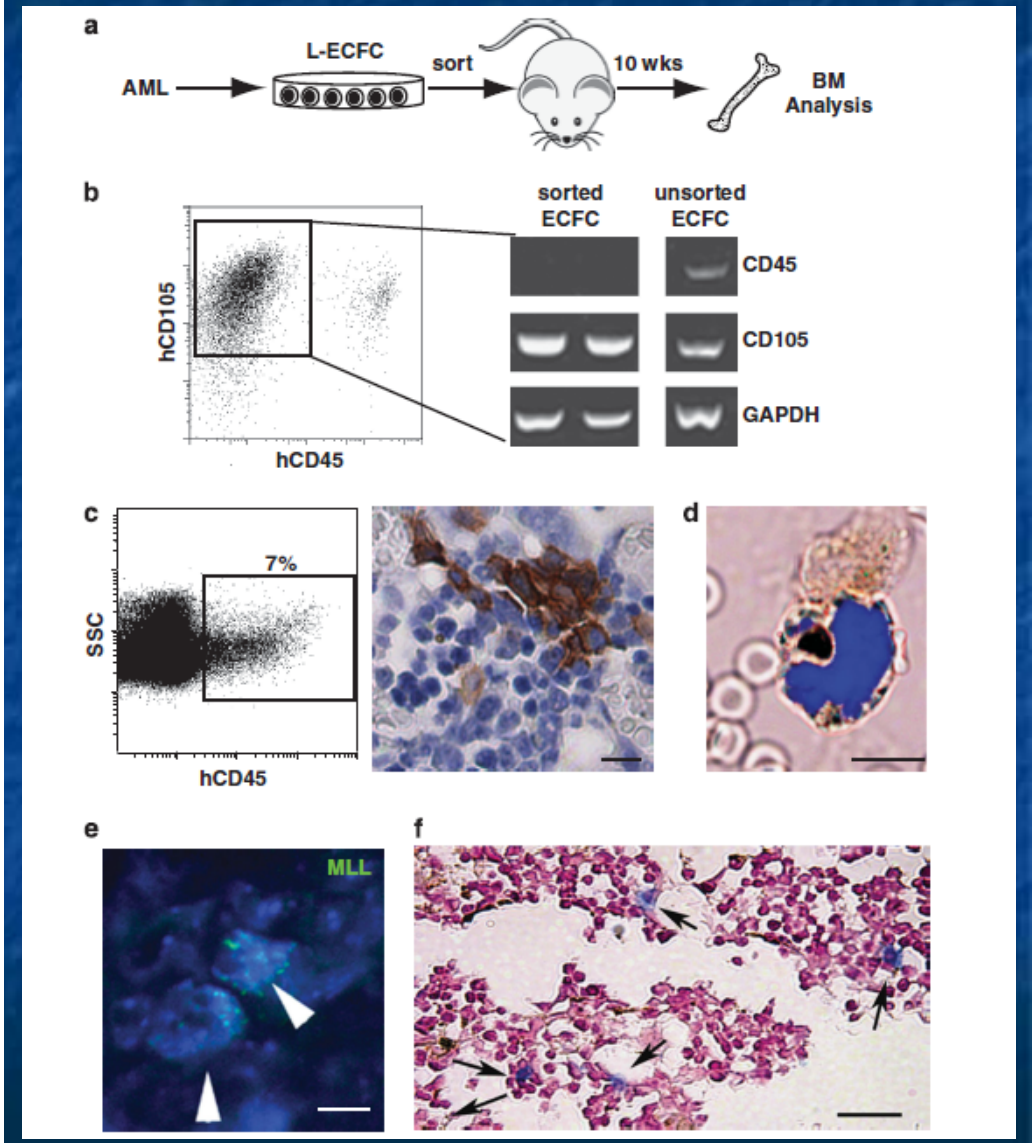




4 INIZIALI ESPERIENZE CLINICHE

CLINICAL TRIALS AND OBSERVATIONS

A phase 1/2 study of chemosensitization with the CXCR4 antagonist plerixafor in relapsed or refractory acute myeloid leukemia

*Geoffrey L. Uy,[1] *Michael P. Rettig,[1] Ibraheem H. Motabi,[1] Kyle McFarland,[1] Kathryn M. Trinkaus,[2] Lindsay M. Hladnik,[1] Shashikant Kulkarni,[3] Camille N. Abboud,[1] Amanda F. Cashen,[1] Keith E. Stockerl-Goldstein,[1] Ravi Vij,[1] Peter Westervelt,[1] and John F. DiPersio[1]

[1]Division of Oncology, [2]Department of Biostatistics, and [3]Department of Pathology and Immunology, Washington University School of Medicine, St Louis, MO

Plerixafor+ mitoxantrone, etoposide and cytarabine	I/II	Relapsed/refractory	Washington University	NCT00512252	CR + CRi: 46%
Plerixafor + daunorubicin/cytarabine	I	Untreated, Age 18-70	Genzyme/Sanofi	NCT00990054	CR: 67%
Plerixafor + daunorubicin/clofarabine and daunorubicin/cytarabine	I	Untreated, Age ≥ 60	Cardiff University	NCT01236144	
Plerixafor + clofarabine	I/II	Untreated, Age ≥ 60	MD Anderson	NCT01160354	ORR: 43%
Plerixafor + G-CSF, mitoxantrone, etoposide, cytarabine	I	Relapsed/refractory, Age ≥ 18	Washington University	NCT00906945	
Plerixafor + decitabine	I	Untreated, Age ≥ 60	Weill/Cornell University	NCT01352650	
Plerixafor + cytarabine, etoposide	I	Relapsed/refractory, Age 3-30	Emory University	NCT01319864	
Plerixafor + FLAG (Fludarabine, idarubicin, cyarabine, G-CSF)	I/II	Second line induction, Age ≤ 65	PETHEMA	NCT01435343	
Plerixafor + Busulfan/Fludarabine and Thymoglobulin	I/II	Allogeneic hematopoietic cell transplant, Age 18-65	MD Anderson	NCT00822770	
Plerixafor + sorafenib + G-CSF		Relapsed/refractory, FLT3-ITD, Age ≥ 18	MD Anderson	NCT00943943	ORR: 77%
Ulocuplumab + mitoxantrone, etoposide and cytarabine	I	Relapsed/refractory, Age ≥ 18	Bristol-Myers Squibb	NCT01120457	
BL-8040 + cytarabine	IIa	Relapsed/refractory, Age 18-75	BioLineRx	NCT01838395	
E-Selectin Inhibitor					
GMI-1271 + mitoxantrone, etoposide and cytarabine	I/II	Relapsed/Refractory or untreated Age ≥ 60	GlycoMimetics	NCT02306291	
VLA-4 inhibitor					
AS101 + chemotherapy				NCT01010373	
Hypoxia inducible drugs					
TH-302			naceutic als	NCT001149915	

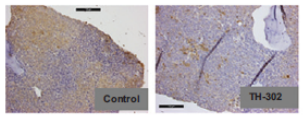
AML: acute myeloid leukemia; CR: compl… ocyte colony stimulating factor; ORR: overall response rate

Cancer Therapy: Preclinical

Clinical Cancer Research

Hypoxia-Activated Prodrug TH-302 Targets Hypoxic Bone Marrow Niches in Preclinical Leukemia Models

C

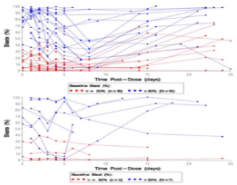


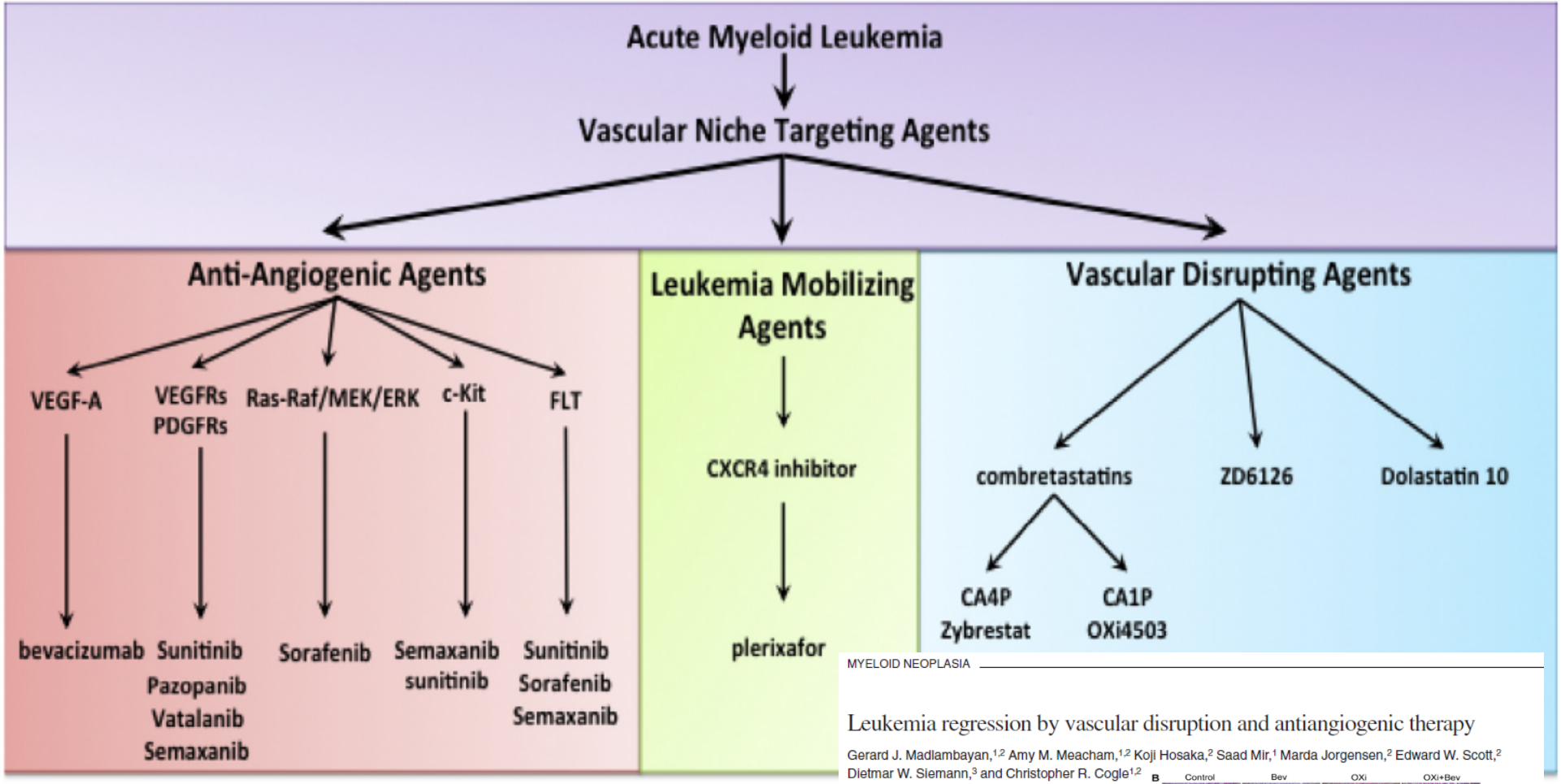
RESEARCH ARTICLE

AJH

Phase I study of evofosfamide, an investigational hypoxia-activated prodrug, in patients with advanced leukemia

Talha Badar,[1] Damian R. Handisides,[2] Juliana M. Benito,[1] Mary Ann Richie,[1] Gautam Borthakur,[1] Elias Jabbour,[1] Karine Harutyunyan,[1] Sergej Konoplev,[3] Stefan Faderl,[1] Stew Kroll,[2] Michael Andreeff,[1,4] Tillman Pearce,[2] Hagop M. Kantarjian,[1] Jorge E. Cortes,[1] Deborah A. Thomas,[1]* and Marina Konopleva[1,4]*





MYELOID NEOPLASIA

Leukemia regression by vascular disruption and antiangiogenic therapy

Gerard J. Madlambayan,[1,2] Amy M. Meacham,[1,2] Koji Hosaka,[2] Saad Mir,[1] Marda Jorgensen,[2] Edward W. Scott,[2] Dietmar W. Siemann,[3] and Christopher R. Cogle[1,2]

[1]Department of Medicine, Division of Hematology/Oncology, [2]Prog Oncology, University of Florida, Gainesville

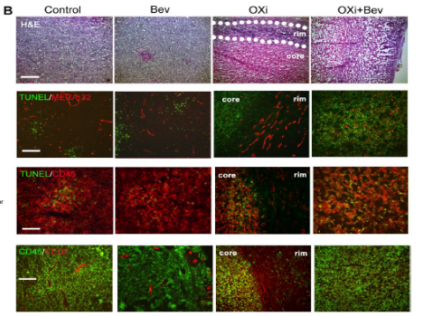


Fig. 4. Vascular niche targeting agents for AML. The three categories of vascular niche targeting agents include anti-angiog ıts, and vascular disrupting agents (VDAs). The VDAs operate by binding tubulin in endothelial cells and causing microtubule scaffold

www.impactjournals.com/oncotarget/ Oncotarget, Vol. 7, No. 22

Phase I clinical study of RG7356, an anti-CD44 humanized antibody, in patients with acute myeloid leukemia

Norbert Vey[1,2], Jacques Delaunay[3], Giovanni Martinelli[4], Walter Fiedler[5], Emmanuel Raffoux[6], Thomas Prebet[1], Carlos Gomez-Roca[7,8], Cristina Papayannidis[4], Maxim Kebenko[5], Peter Paschka[9], Randolph Christen[10], Ernesto Guarin[11], Ann-Marie Bröske[12], Monika Baehner[12], Michael Brewster[13], Antje-Christine Walz[11], Francesca Michielin[11], Valeria Runza[12], Valerie Meresse[11], Christian Recher[7,14]

Status	
Relapsed/refractory after ≥ 2 lines	5 (11)
Relapsed/refractory after 1 line	21 (48)
Post-transplant relapse	11 (25)
Previously untreated elderly	7 (16)
Median interval from diagnosis to study enrollment (range), months	13 (0.9–130)

Table 2: Dose escalation, dose-limiting toxicities, and response

Dose	Schedule	Number of patients	Number of DLT-evaluable patients[a]	DLTs	Response
300 mg	q2w	4	3	0	0
600 mg	q2w	5	3	0	0
1200 mg	q2w	7	4	0	1 CRp, 1 PR
2400 mg	q2w	5	5	0	0
1200 mg	Weekly	9	3	0	0
600 mg	Twice weekly	4	3	0	1 HI
1200 mg[b]	Twice weekly	10	5	1	0


TARGETTARE IL MICROAMBIENTE
NELLE
LEUCEMIE ACUTE
GRAZIE DELL' ATTENZIONE
Treviso 26 Novembre 2016