Nuovi bersagli terapeutici nella leucemia mieloide acuta

Moderatori: **S. Amadori, M. Krampera**

Sabato **20 Novembre**

09:30

Targettare il microambiente midollare:

- L'adrenomedullina *M. Gottardi*
- Le vescicole extracellulari *I. Tanasi*

Targettare i pathways metabolici
G. Martinelli

I.O.V.
Istituto Oncologico Veneto I.R.C.C.S.
OECI COMPREHENSIVE Cancer Centre

Michele Gottardi
Oncoematologia, Dipartimento di Oncologia
Istituto Oncologico Veneto (IOV)-IRCCS

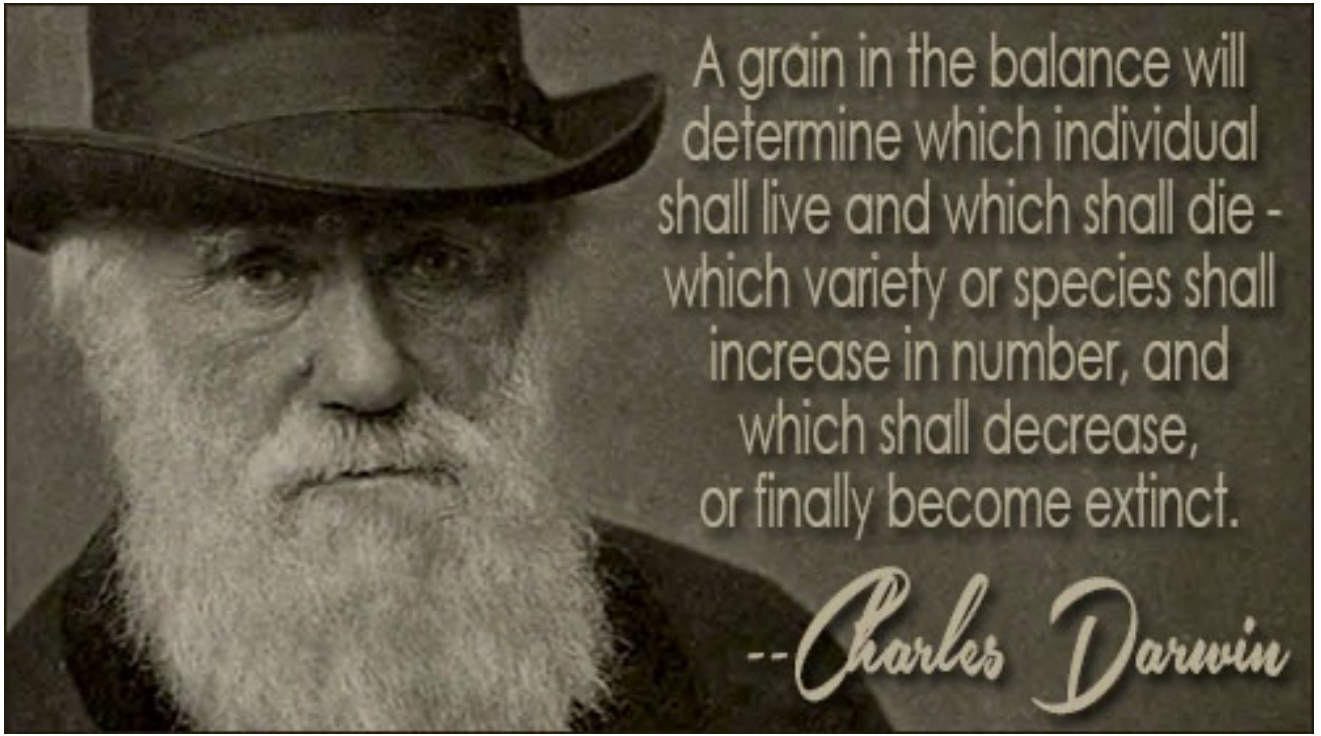
20 ANNI DI EMATOLOGIA A TREVISO
Treviso, Auditorium Fondazione Cassamarca
18-20 Novembre 2021

DICHIARAZIONE

Relatore: NOME COGNOME

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- Partecipazione ad Advisory Board **(ASTELLAS, JANSSEN CILAG, JAZZ HEALTHCARE)**
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- Altro


A grain in the balance will
determine which individual
shall live and which shall die -
which variety or species shall
increase in number, and
which shall decrease,
or finally become extinct.
--Charles Darwin

Stem cells, cancer, and cancer stem cells

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

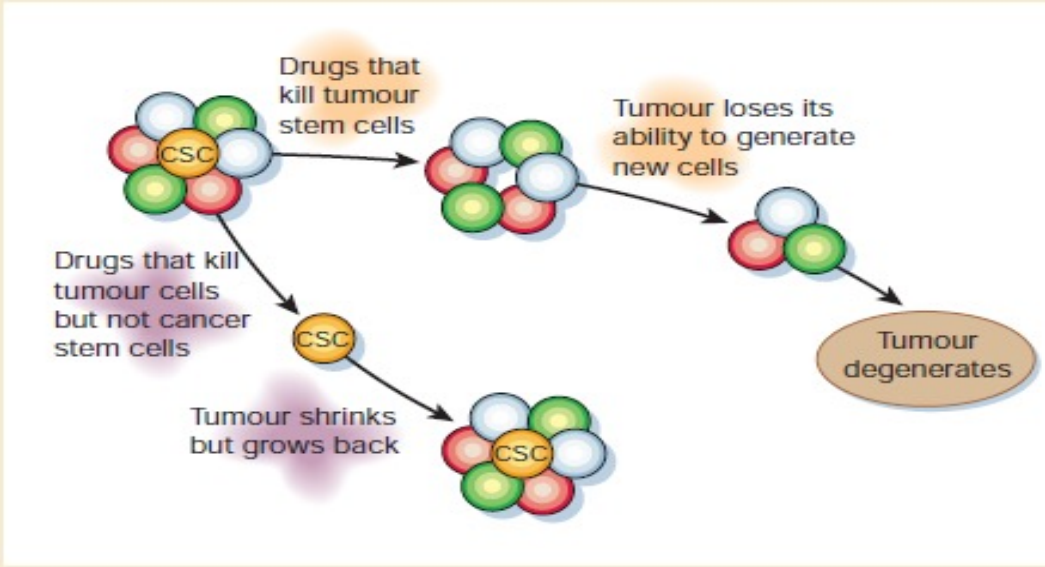
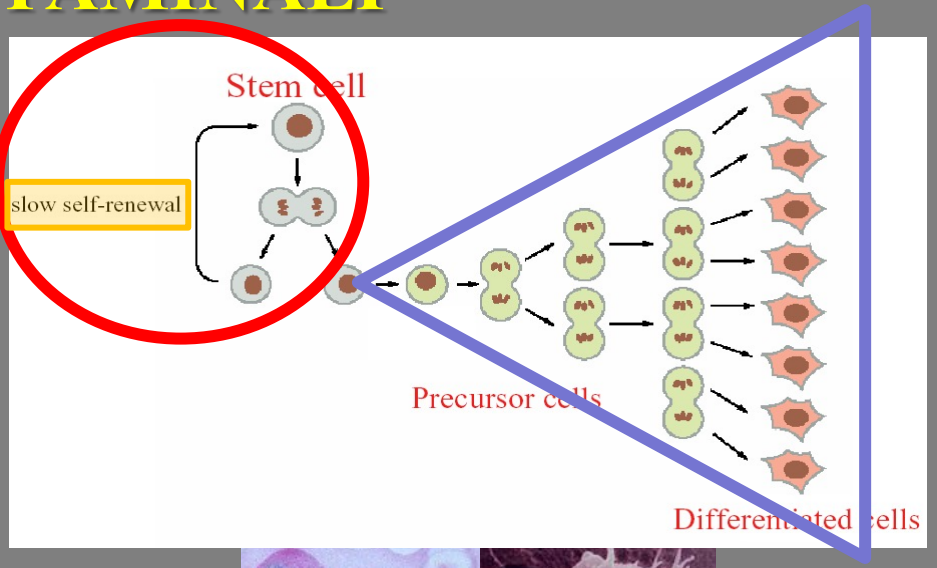
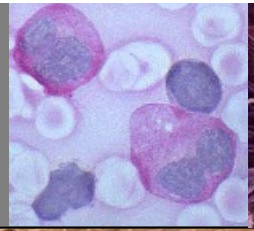


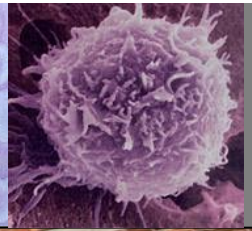
Figure 5 Conventional therapies may shrink tumours by killing mainly cells with limited proliferative potential. If the putative cancer stem cells are less sensitive to these therapies, then they will remain viable after therapy and re-establish the tumour. By contrast, if therapies can be targeted against 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

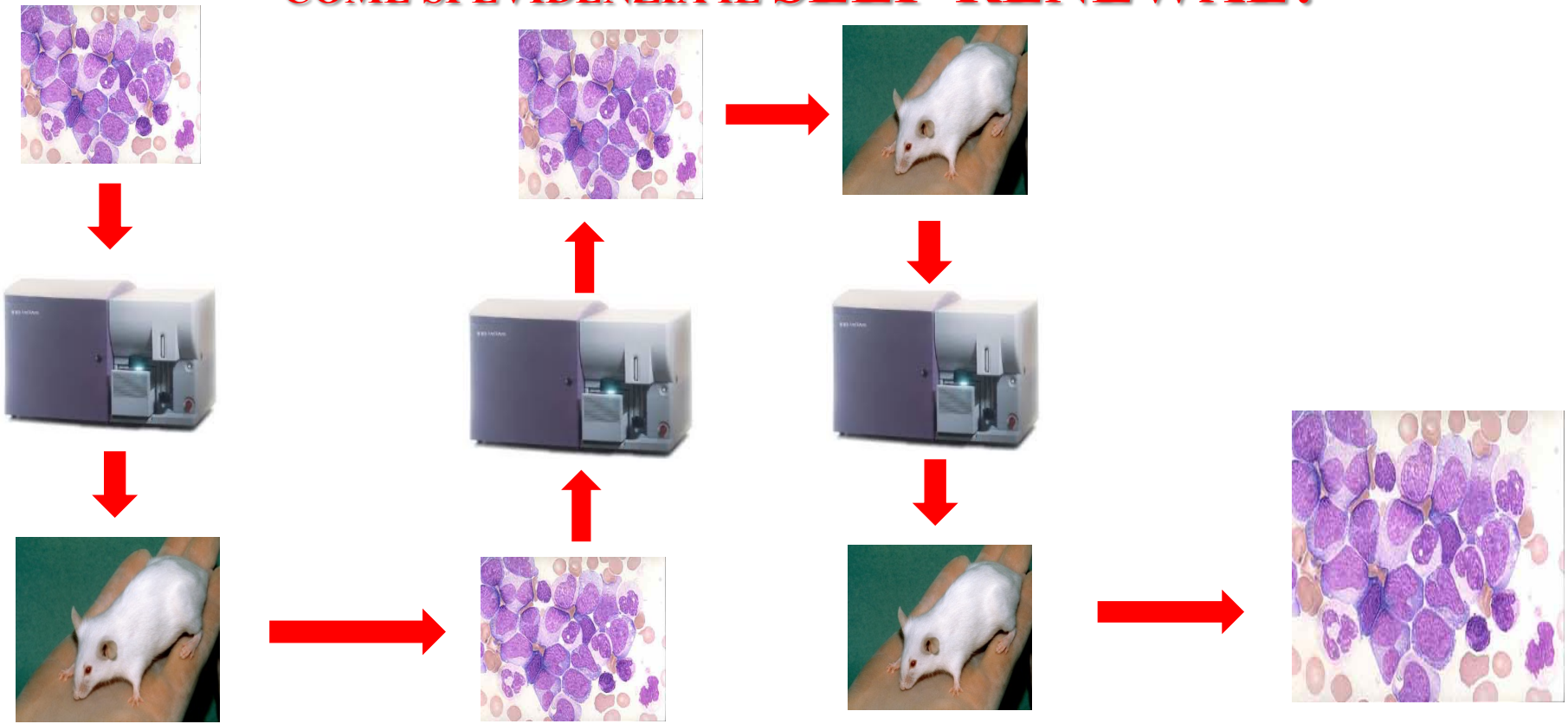
- Autorinnovamento
- Automantenimento
- Potenziale differenziativo
- Scarsa attività replicativa
- Immortalità replicativa







COME SI EVIDENZIA IL SELF-RENEWAL?



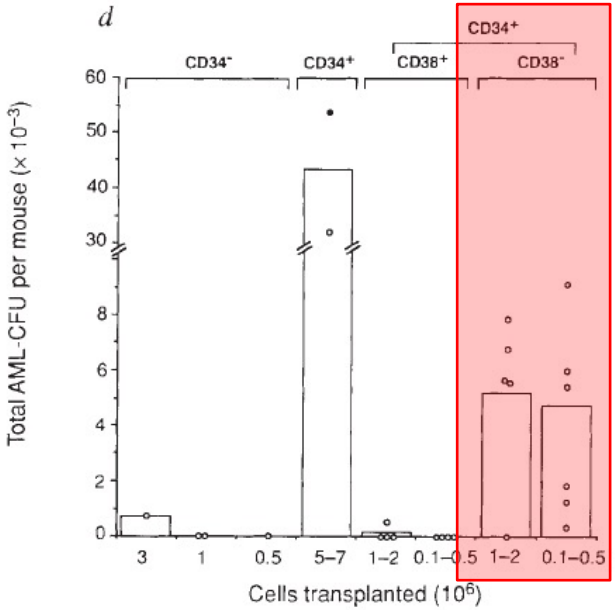
A cell initiating human acute myeloid leukaemia after transplantation into SCID mice

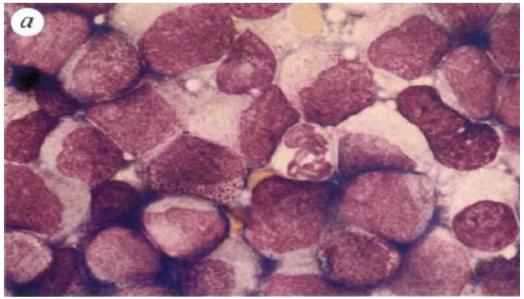
Tsvee Lapidot, Christian Sirard, Josef Vormoor, Barbara Murdoch, Trang Hoang*, Julio Caceres-Cortes*, Mark Minden†, Bruce Paterson‡, Michael A. Caligiuri§ & John E. Dick‖

Department of Genetics, Research Institute, Hospital for Sick Children and Department of Molecular and Medical Genetics, University of Toronto, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada
* 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.

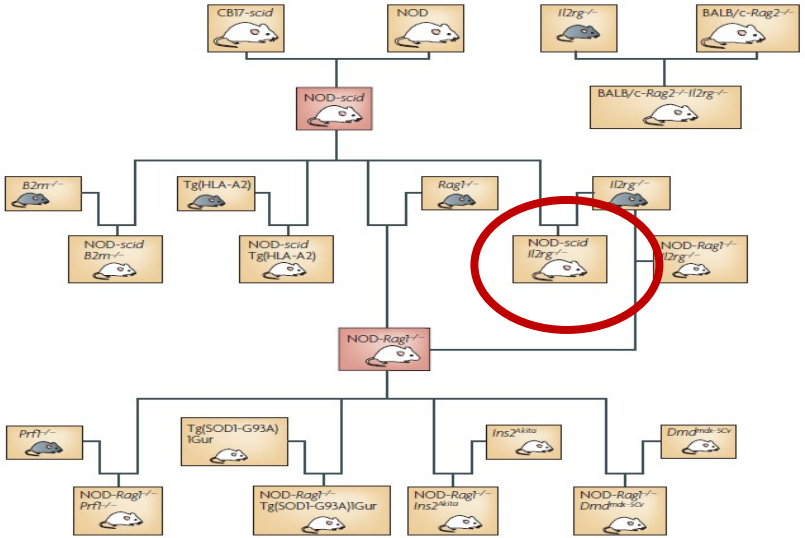
NATURE · VOL 367 · 17 FEBRUARY 1994





CONTROVERSIE

NATURE REVIEWS | IMMUNOLOGY
122 | FEBRUARY 2007 | VOLUME 7



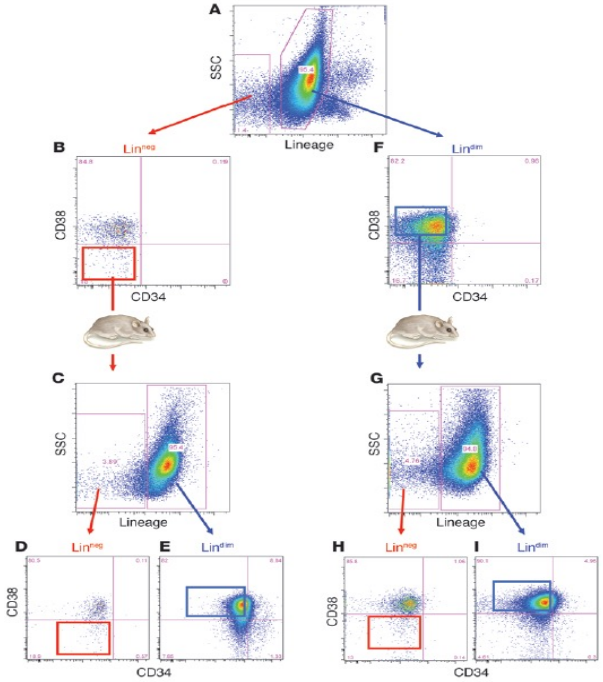
Humanized mice in translational biomedical research

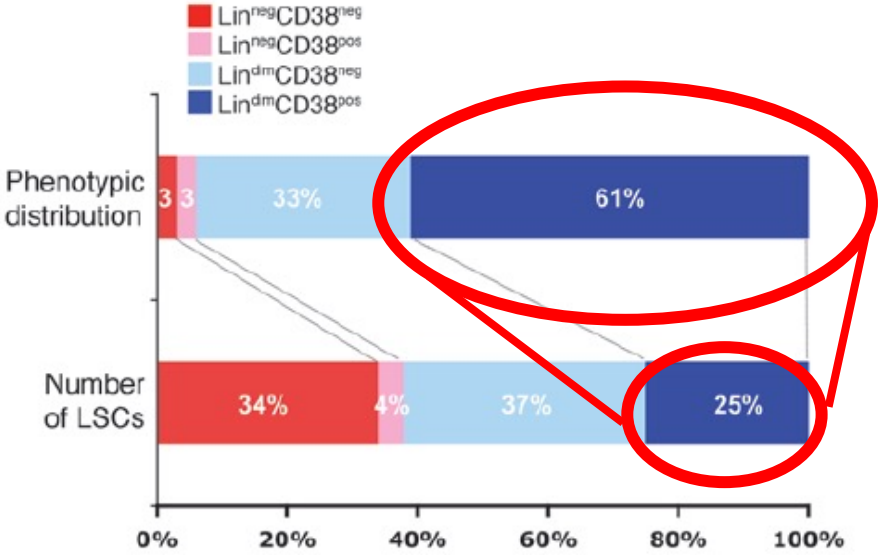
Leonard D. Shultz, Fumihiko Ishikawa‡ and Dale L. Greiner§*

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]

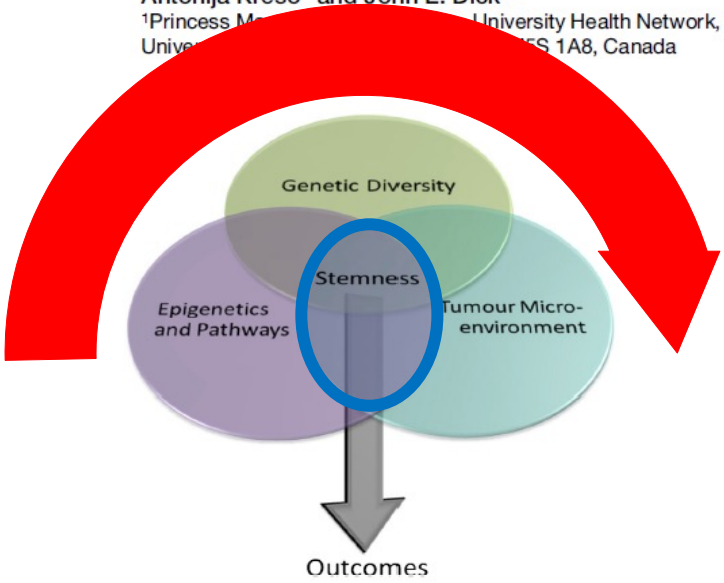




The Journal of Clinical Investigation

Evolution of the Cancer Stem Cell Model

Antonija Kreso[1] and John E. Dick[1,*]
[1]Princess M... University Health Network, Toronto, Ontar
Unive... 5S 1A8, Canada



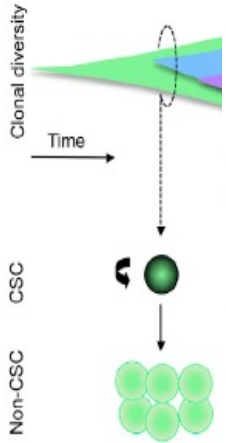


Figure 2. Unified Mo

Figure 1. Stemness as a Guiding Princ... Response
Three fields in biology—cancer genetics, ...ment—are coming together to provide incre... determine stemness and in turn influence cli... can influence stemness simultaneously, but ... over time. Through evolutionary time, diff... stemness properties and thereby shape tu... response.

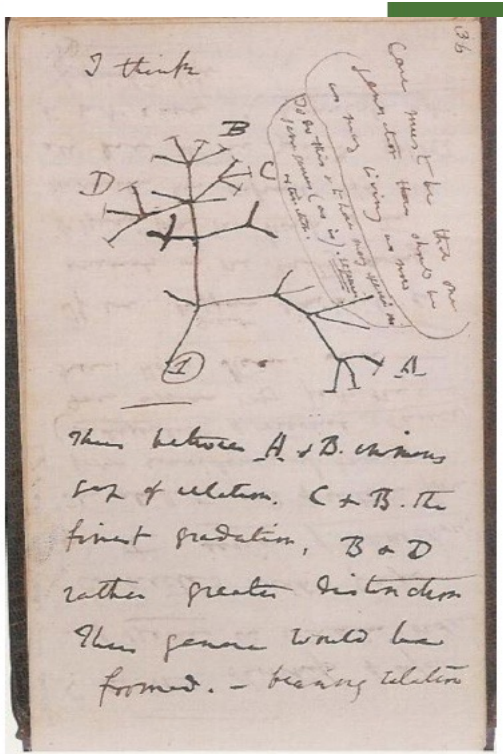


Fig. 5. Evolutionary speciation or ancestral tree, from Charles Darwin's 1837 Transmutation notebook B [62]. Ancestor ① gives rise, via non-linear, branching descent to progeny types A, B, C and D.

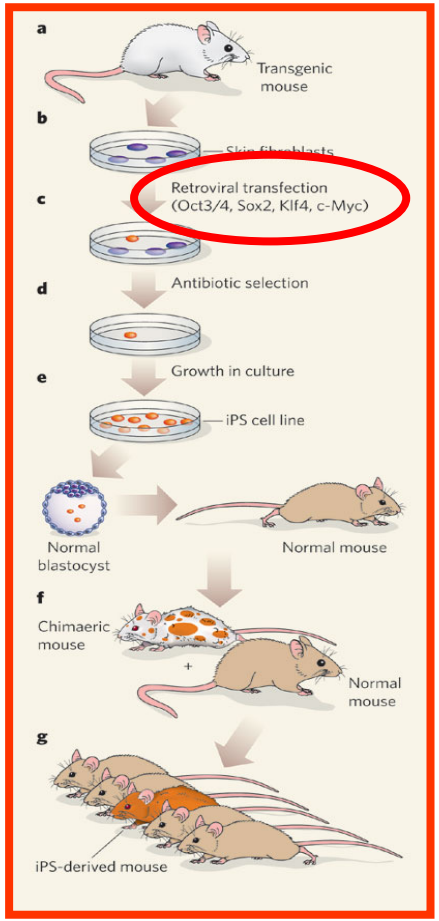
Review

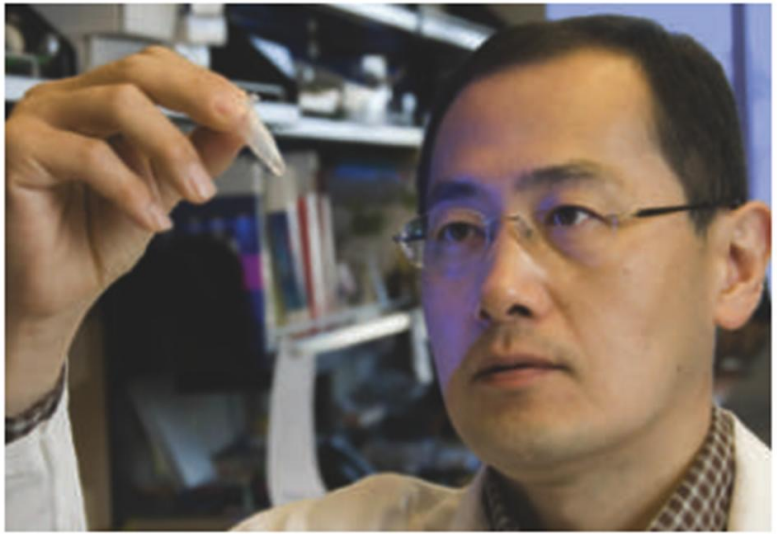
Cancer stem cells: Back to Darwin?

Mel Greaves*

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

Cell Stem Cell
Review





Shinya Yamanaka made mouse iPS cells in 2006.

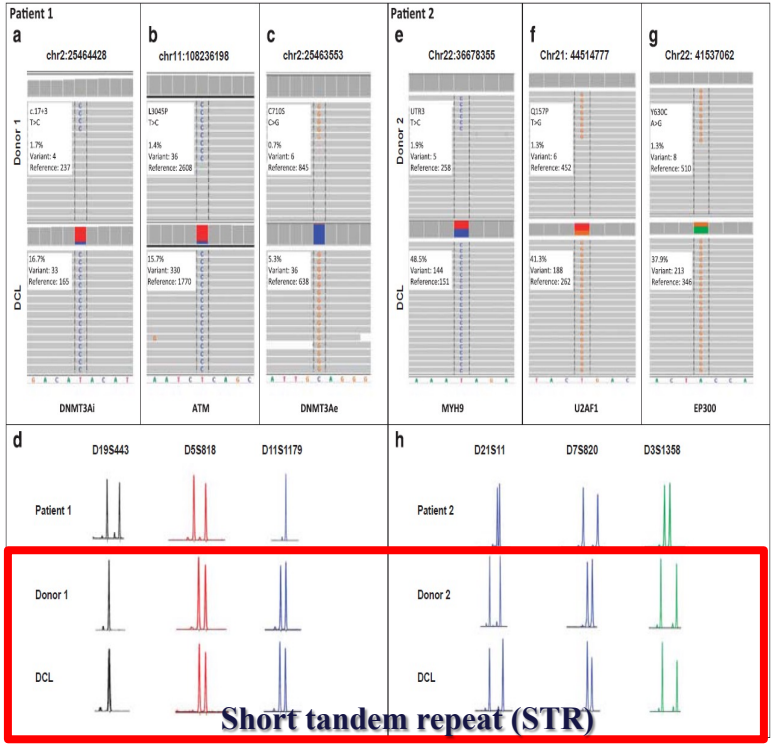
la cellula staminale non esiste:

esiste la funzione staminale.

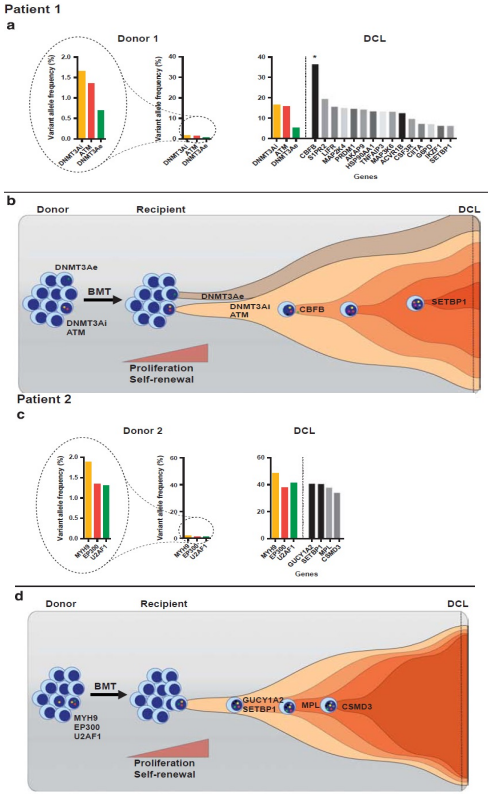
ALCUNI INDIZI

(che si prestano a molte interpretazioni)

Donor cell leukemia arising from clonal hematopoiesis after bone marrow transplantation

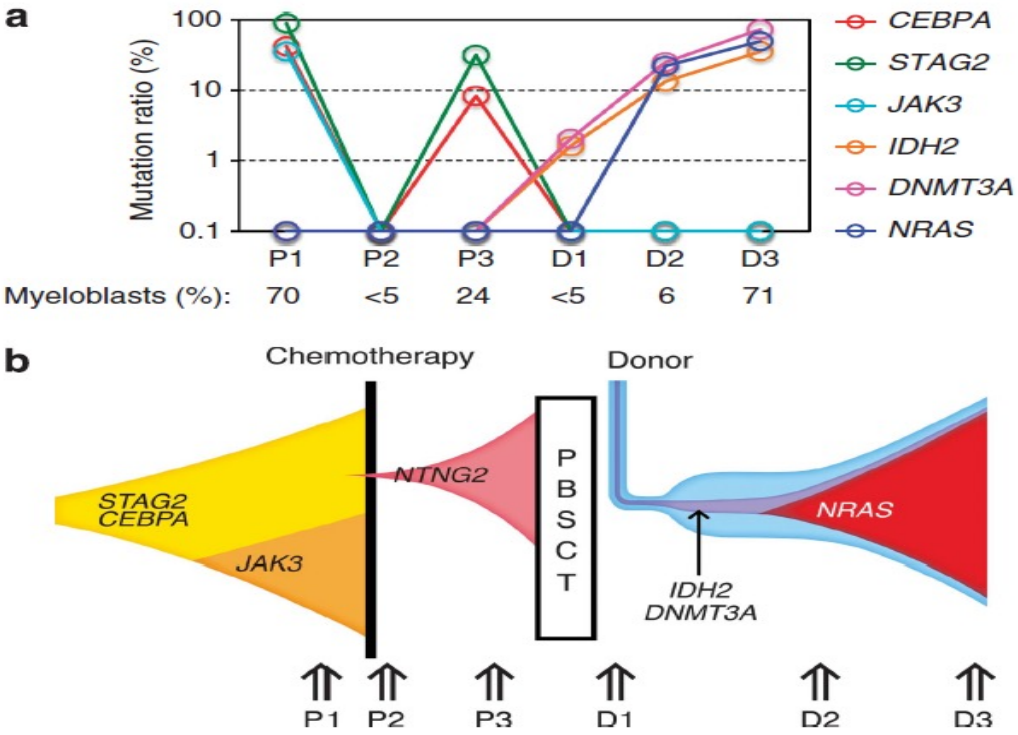


Short tandem repeat (STR)



Leukemia (2016) 1909 – 1962

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



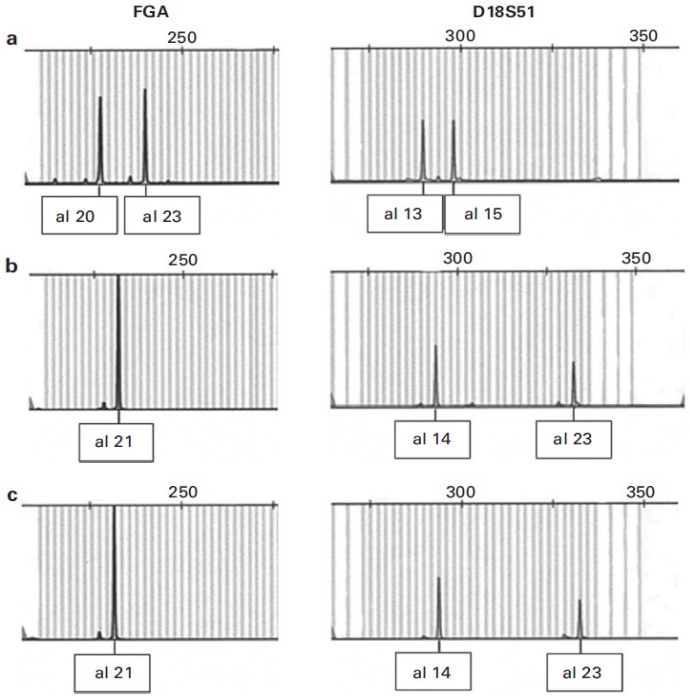
Leukemia (2014) 404 – 463

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

Bone Marrow Transplantation (2014) 102 – 109



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 progenitor dysfunction induces myelodysplasia and secondary leukaemia

NATURE|Vol 464|8 April 2010

Marc H. G. P. Raaijmakers[1,6,7]*, Siddhartha Mukherjee[1,2,6,7]*†, Shangqin Guo[1,6,7], Siyi Zhang[1,6,7], Tatsuya Kobayashi[3], Jesse A. Schoonmaker[1,6,7], Benjamin L. Ebert[8,9], Fatima Al-Shahrour[8,9], Robert P. Hasserjian[4], Edward O. Scadden[1,6,7], Zinmar Aung[1,6,7], Marc Matza[1,6,7], Matthias Merkenschlager[10], Charles Lin[5], Johanna M. Rommens[11] & David. T. Scadden[1,2,6,7]

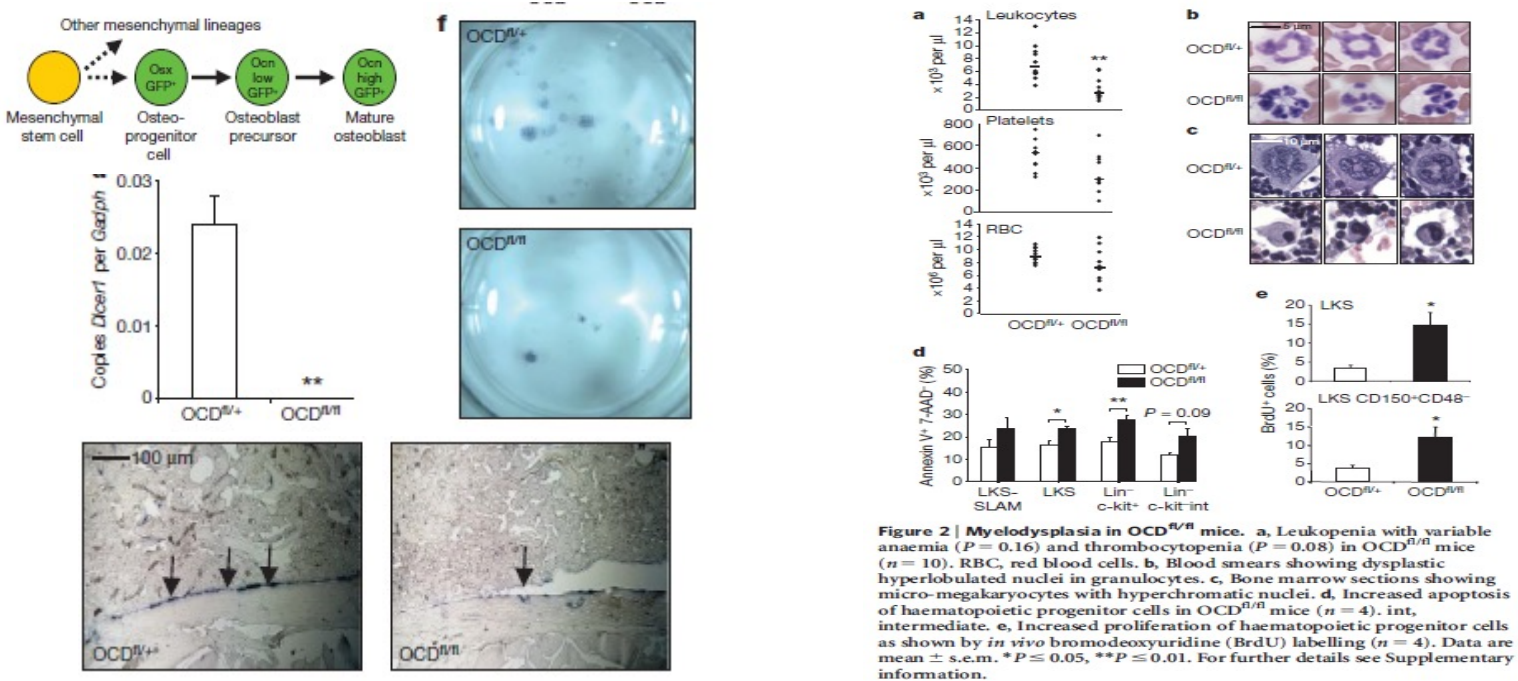
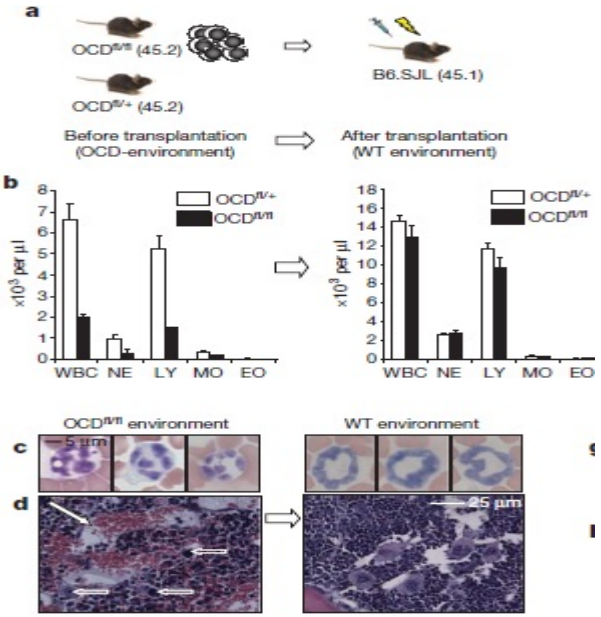


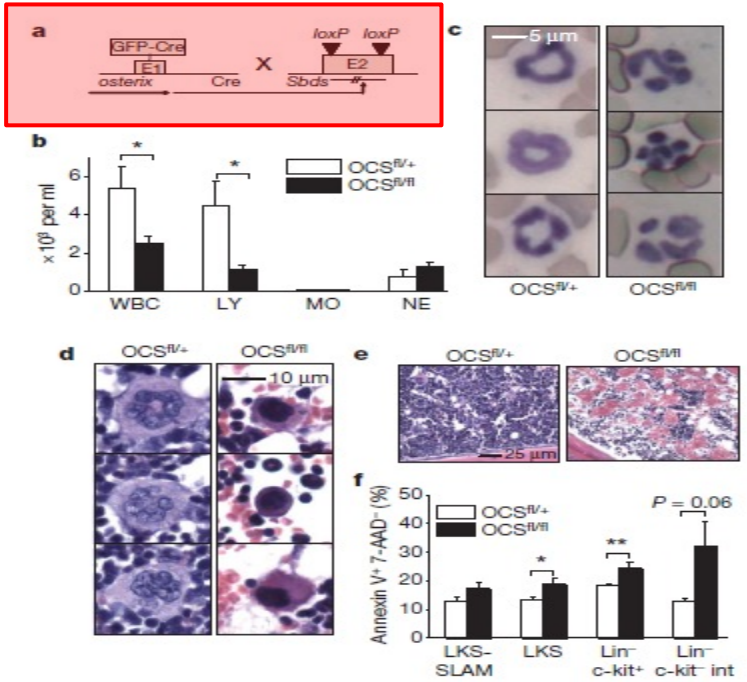
Figure 2 | Myelodysplasia in OCD$^{fl/fl}$ mice. a, Leukopenia with variable anaemia ($P = 0.16$) and thrombocytopenia ($P = 0.08$) in OCD$^{fl/fl}$ mice ($n = 10$). RBC, red blood cells. b, Blood smears showing dysplastic hyperlobulated nuclei in granulocytes. c, Bone marrow sections showing micro-megakaryocytes with hyperchromatic nuclei. d, Increased apoptosis of haematopoietic progenitor cells in OCD$^{fl/fl}$ mice ($n = 4$). int, intermediate. e, Increased proliferation of haematopoietic progenitor cells as shown by *in vivo* bromodeoxyuridine (BrdU) labelling ($n = 4$). Data are mean ± s.e.m. *$P \leq 0.05$, **$P \leq 0.01$. For further details see Supplementary information.

Bone progenitor dysfunction induces myelodysplasia and secondary leukaemia

NATURE|Vol 464|8 April 2010

Marc H. G. P. Raaijmakers[1,6,7]*, Siddhartha Mukherjee[1,2,6,7]*†, Shangqin Guo[1,6,7], Siyi Zhang[1,6,7], Tatsuya Kobayashi[3], Jesse A. Schoonmaker[1,6,7], Benjamin L. Ebert[8,9], Fatima Al-Shahrour[8,9], Robert P. Hasserjian[4], Edward O. Scadden[1,6,7], Zinmar Aung[1,6,7], Marc Matza[1,6,7], Matthias Merkenschlager[10], Charles Lin[5], Johanna M. Rommens[11] & David. T. Scadden[1,2,6,7]





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Marc H. G. P. Raaijmakers[1,6,7]*, Siddhartha Mukherjee[1,2,6,7]*†, Shangqin Guo[1,6,7], Siyi Zhang[1,6,7], Tatsuya Kobayashi[3], Jesse A. Schoonmaker[1,6,7], Benjamin L. Ebert[8,9], Fatima Al-Shahrour[8,9], Robert P. Hasserjian[4], Edward O. Scadden[1,6,7], Zinmar Aung[1,6,7], Marc Matza[1,6,7], Matthias Merkenschlager[10], Charles Lin[5], Johanna M. Rommens[11] & David. T. Scadden[1,2,6,7]

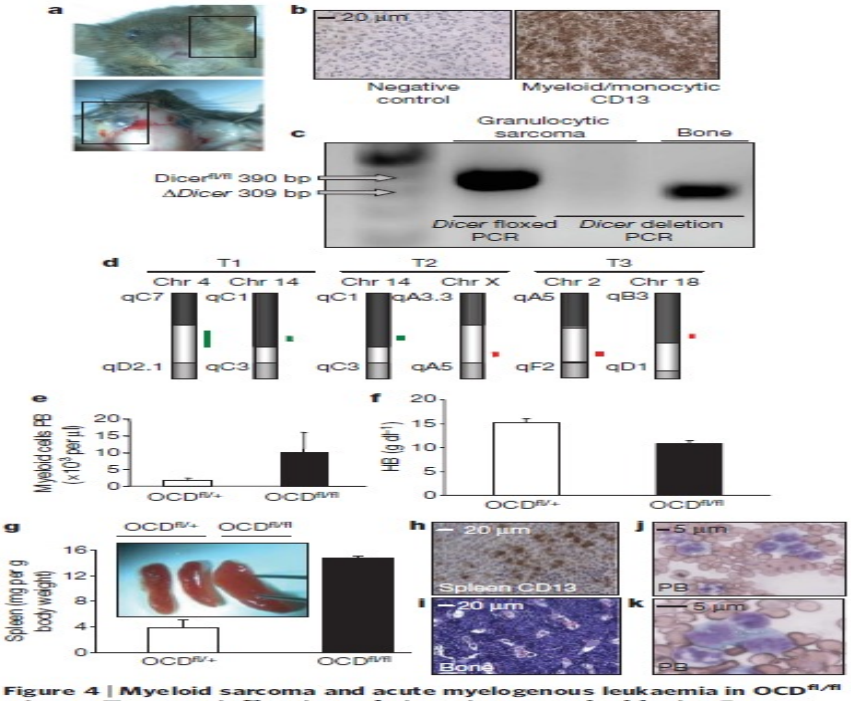
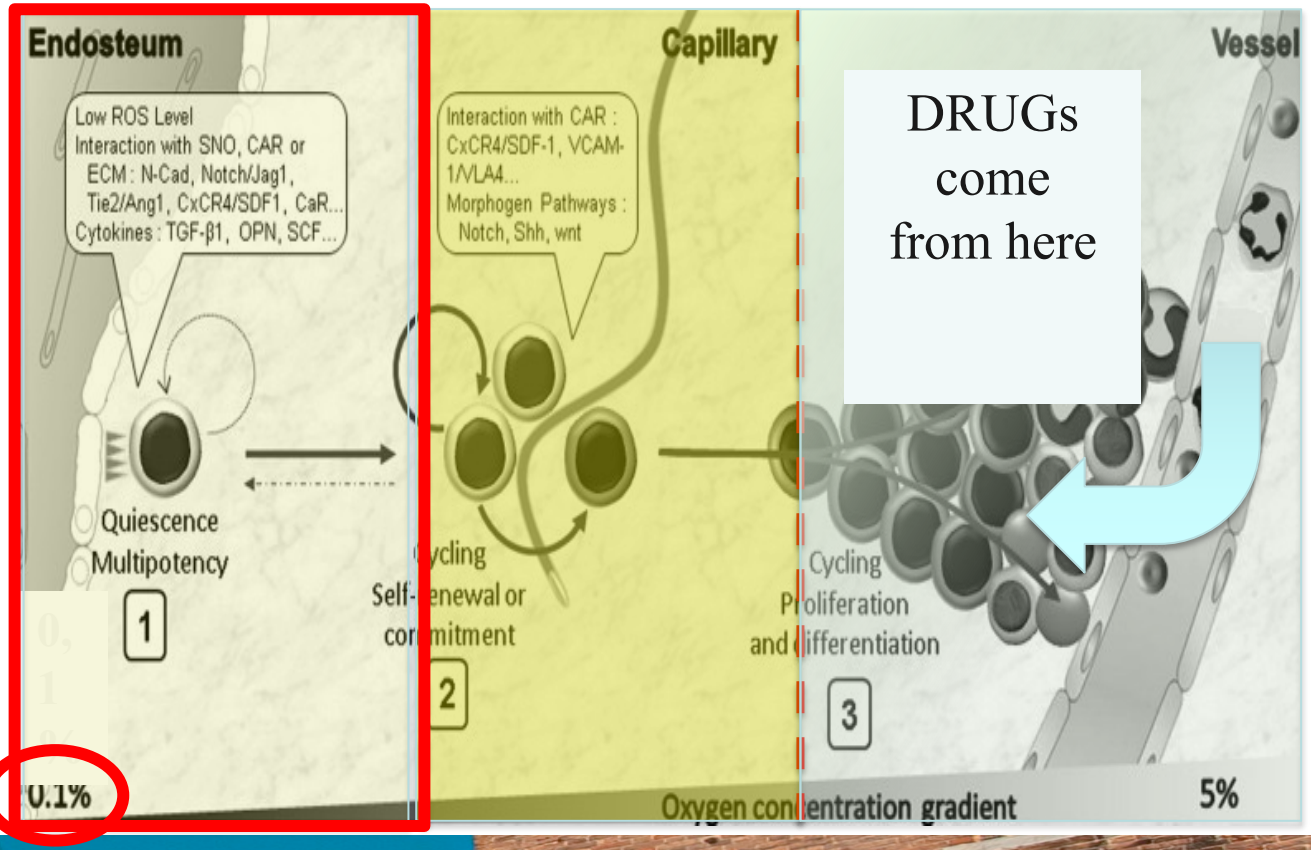


Figure 4 | Myeloid sarcoma and acute myelogenous leukaemia in OCD$^{fl/fl}$

EVIDENZE SPERIMENTALI

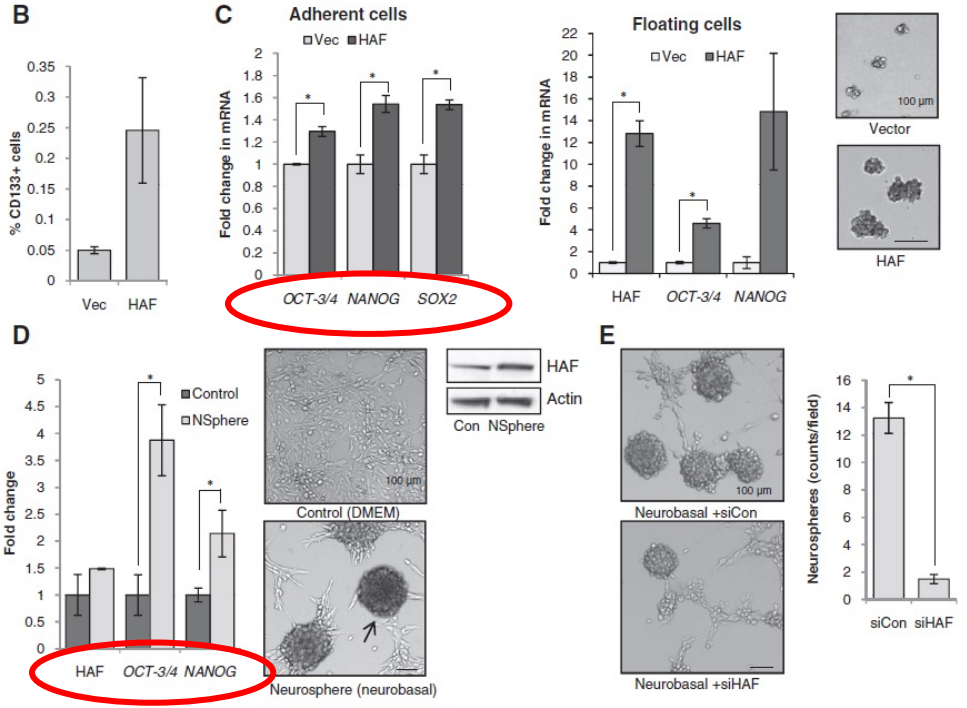
LE NICCHIE


Endosteum
Low ROS Level
Interaction with SNO, CAR or
ECM : N-Cad, Notch/Jag1,
Tie2/Ang1, CxCR4/SDF1, CaR...
Cytokines : TGF-β1, OPN, SCF...
Quiescence
Multipotency
1
0.1%
Capillary
Interaction with CAR :
CxCR4/SDF-1, VCAM-
1/VLA4...
Morphogen Pathways :
Notch, Shh, wnt
ycling
Self-enewal or
commitment
2
Vessel
DRUGs
come
from here
Cycling
Proliferation
and differentiation
3
Oxygen concentration gradient
5%

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

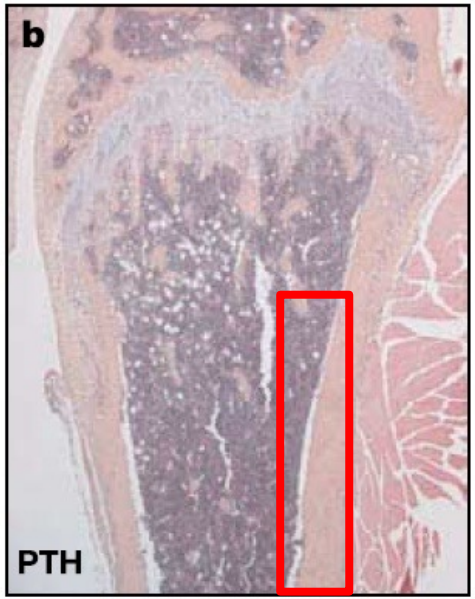
Cancer Research

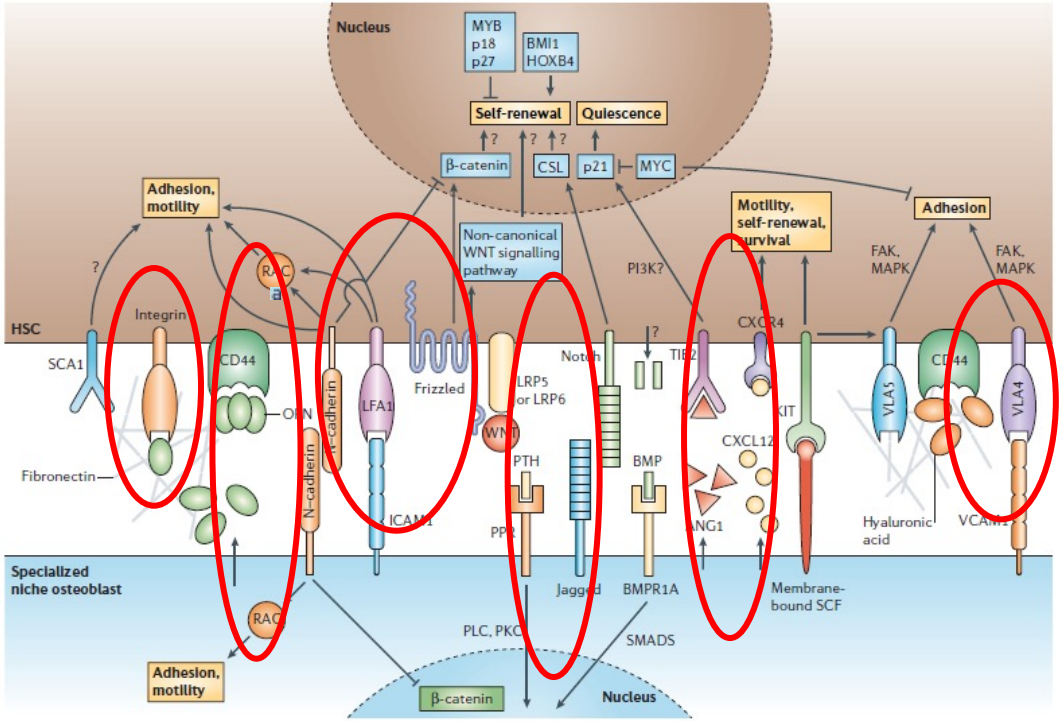
Mei Yee Koh, Robert Lemos Jr, Xiuping Liu, and Garth Powis



Bone-marrow haematopoietic-stem-cell niches

Anne Wilson and Andreas Trumpp‡*

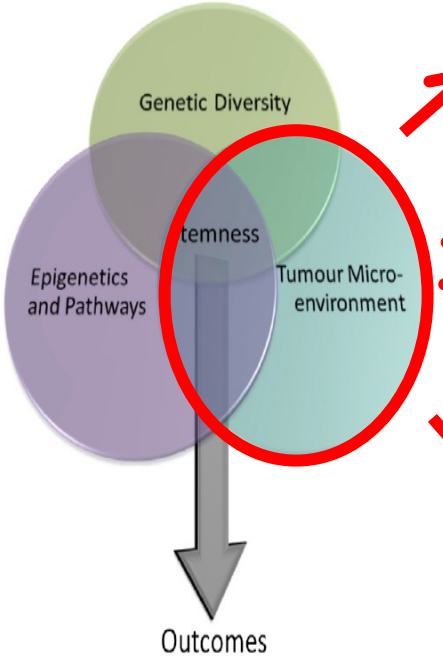




Evolution of the Cancer Stem Cell Model

Antonija Kreso[1] and John E. Dick[1,*]
[1]Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario M5G 1L7, Canada and Department of Molecular Genetics, University of Toronto, Toronto, Ontario M5S 1A8, Canada

Cell Stem Cell
Review



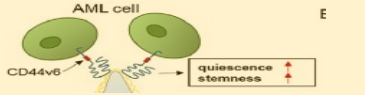
CD44: More than a mere stem cell marker

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



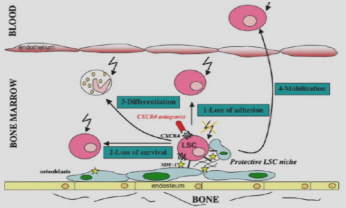
Review

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

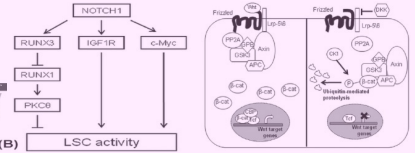
1. Leukemic stem cells: the reason for relapse

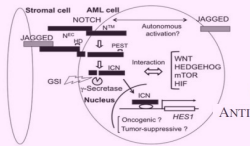


Targeting leukemia stem cells: which pathways drive self-renewal activity in T-cell acute lymphoblastic leukemia?

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)

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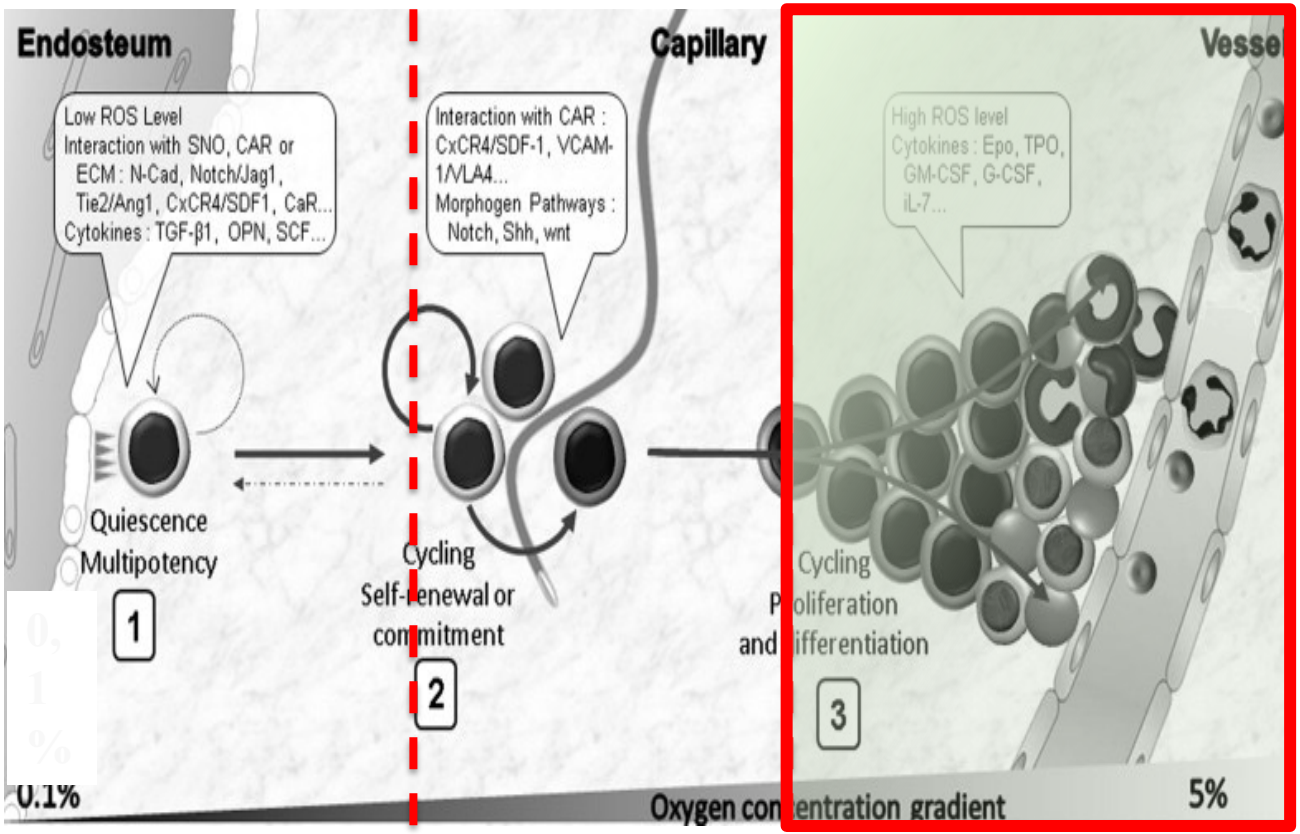

Endosteum
Capillary
Vesse
Low ROS Level
Interaction with SNO, CAR or ECM : N-Cad, Notch/Jag1, Tie2/Ang1, CxCR4/SDF1, CaR...
Cytokines : TGF-β1, OPN, SCF...
Interaction with CAR : CxCR4/SDF-1, VCAM-1/VLA4...
Morphogen Pathways : Notch, Shh, wnt
High ROS level
Cytokines : Epo, TPO, GM-CSF, G-CSF, iL-7...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

BLOOD, 2 APRIL 2009 • VOLUME 113, NUMBER 14

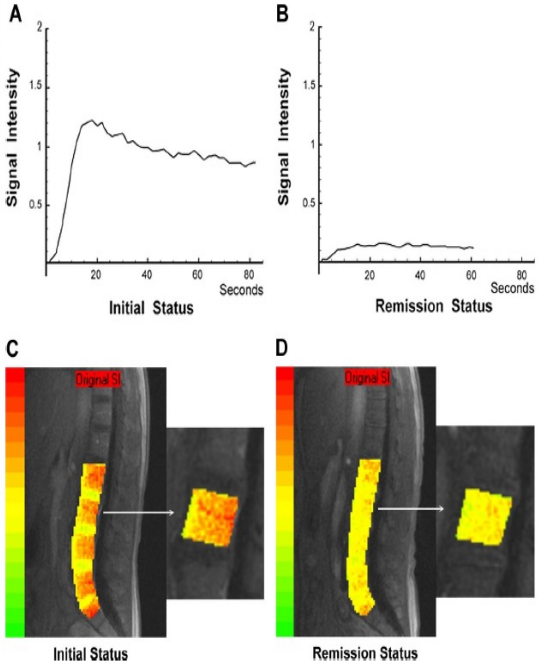
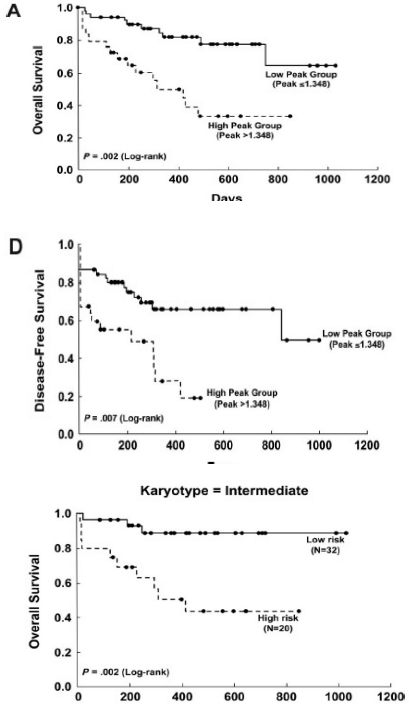


Figure 1. The time-intensity curves derived from DCE-MRI and color-coded angiogenesis maps of vertebral bone marrow in a 54-year-old female patient with de novo AML are shown. She achieved complete remission after induction chemotherapy. Her remission duration until the end of August 2007 was 1002 days. 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.

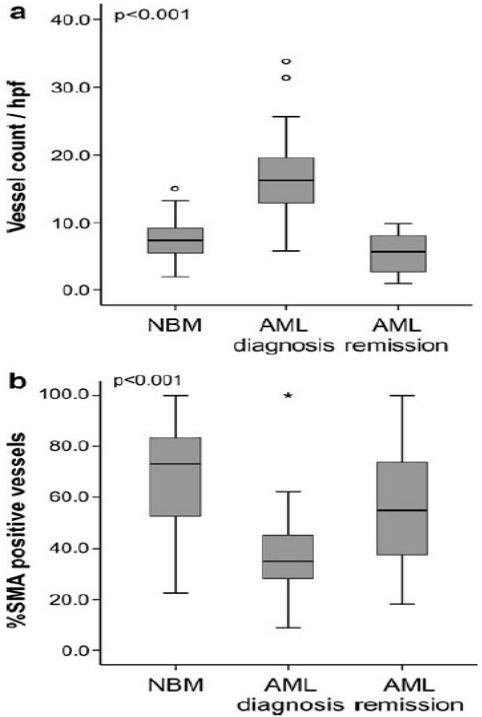


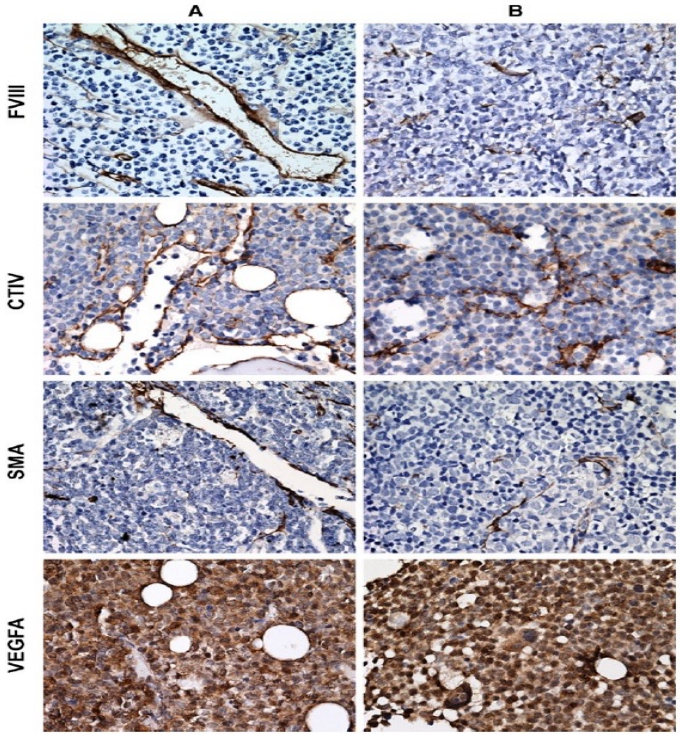
High Acute Myeloid Leukemia derived VEGFA levels are associated with a specific vascular morphology in the leukemic bone marrow

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

ORIGINAL PAPER

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





ADRENOMEDULLIN

l. 192, No. 2, 1993 BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS Pages 553-560
ril 30, 1993

ADRENOMEDULLIN: A NOVEL HYPOTENSIVE PEPTIDE ISOLATED FROM HUMAN PHEOCHROMOCYTOMA

Kazuo Kitamura, Kenji Kangawa §, Mari Kawamoto, Yoshinari Ichiki, Shigeru Nakamura, Hisayuki Matsuo* and Tanenao Eto

Departments of First Internal Medicine and §Biochemistry, Miyazaki Medical College, Kihara, Kiyotake, Miyazaki 889-16, Japan

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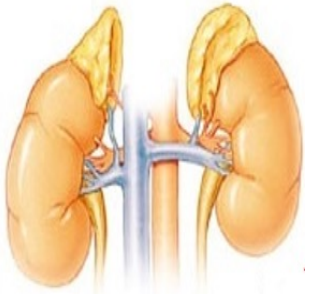
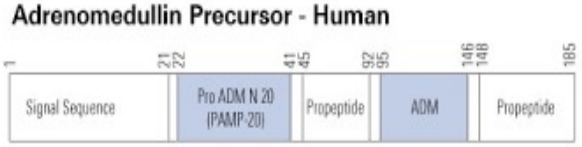
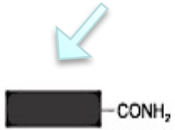
Received March 15, 1993

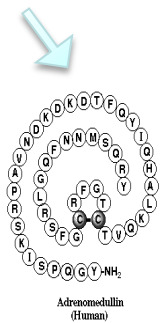






proadrenomedullin N-terminal 20-peptide PAMP

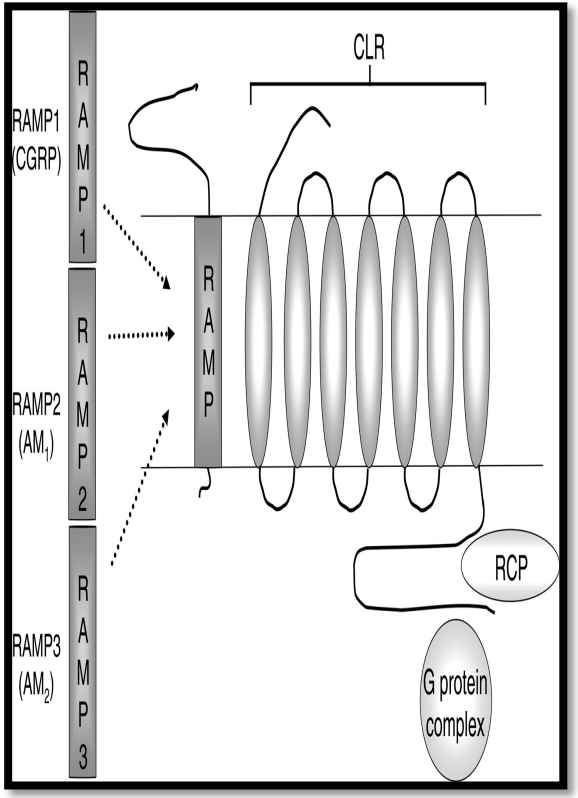
Transient hypotensive activitye

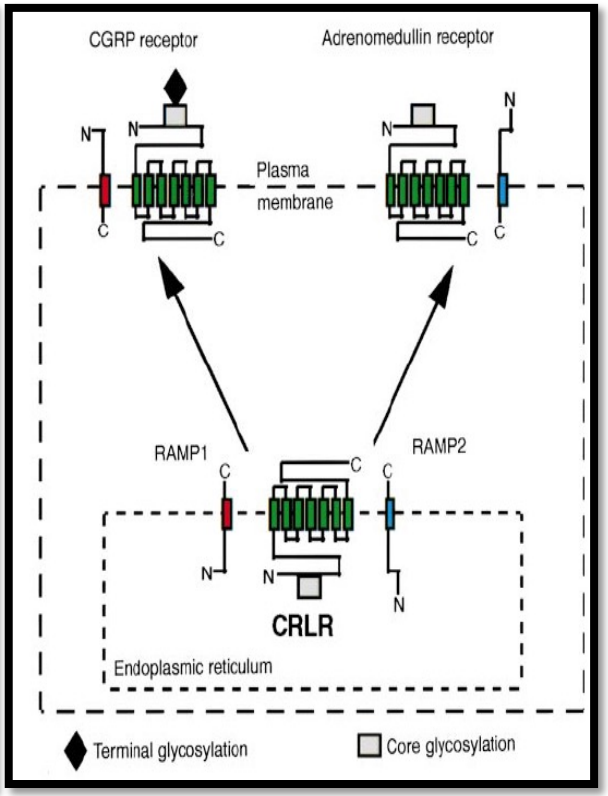


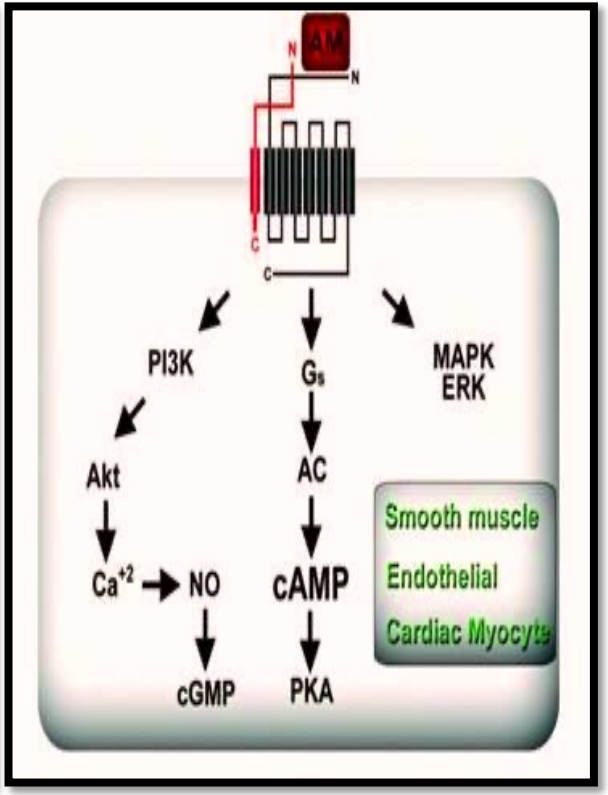
Enzymatic amidation by peptidylglycine alpha-amidating monooxygenase (PAM)

Long-lasting hypotensive activitye

ADRENOMEDULLIN







Minireview

Adrenomedullin and tumour angiogenesis

British Journal of Cancer (2006) 94, 1–7

www.bjcancer.com

LL Nikitenko*[,1,3], SB Fox[2], S Kehoe[1], MCP Rees[1] and R Bicknell[3,4]

[1]Nuffield Department of Obstetrics and Gynaecology, The University of Oxford, John Radcliffe Hospital, Oxford, OX3 9DU, United Kingdom; [2]Nuffield Department of Clinical Laboratory Sciences, The University of Oxford, John Radcliffe Hospital, Oxford, OX3 9DU, United Kingdom; [3]Molecular Angiogenesis Laboratory, Cancer Research UK, Weatherall Institute of Molecular Medicine, The University of Oxford, John Radcliffe Hospital, Oxford, OX3 9DU, United Kingdom; [4]Institute for Biomedical Research, Birmingham University Medical School, Edgbaston, Birmingham B15 2TT, United Kingdom

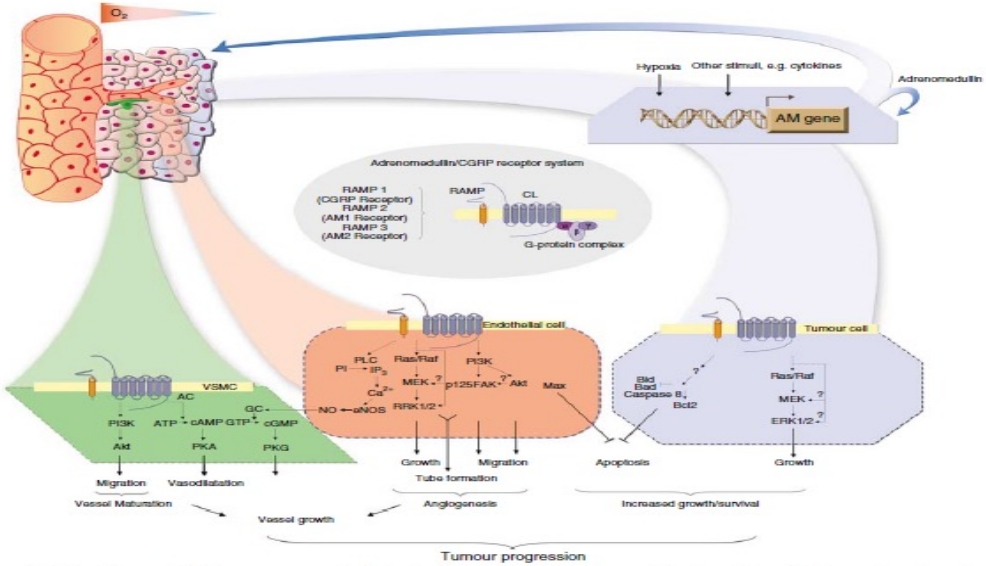


Figure 1 Role of adrenomedullin in tumour progression. The role of hypoxia and inflammatory cytokines in regulation of AM expression and secretion by tumour cells *in vivo* has been suggested. Adrenomedullin promotes formation of xenografted tumours by stimulation of autocrine growth and survival of tumour cells, and through paracrine effects on surrounding vessels. Possible intracellular signalling mechanisms underlying effects of AM in tumour microenvironment (in endothelial, vascular smooth muscle (VSMC) and tumour cells) suggest its potential role in tumorigenesis, resistance to chemotherapy and tumour progression. Based on McLatchie *et al* (1998), Shichiri *et al* (1999), Hinson *et al* (2000), Oehler *et al* (2001), Martinez *et al* (2002), Poyner *et al* (2002), Kim *et al* (2003) and Iwase *et al* (2005). AC = adenylate cyclase, GC = guanylate cyclase; PKA = protein kinase A, PKG = protein kinase G, PLC = phospholipase C, MEK = mitogen-activated protein kinase kinase; ERK = extracellular signal-regulated kinase (also termed MAPK).

Adrenomedullin in the growth modulation and differentiation of acute myeloid leukemia cells

ROSA DI LIDDO[1], DEBORAH BRIDI[1], MICHELE GOTTARDI[2], SERGIO DE ANGELI[3], CLAUDIO GRANDI[1], ALESSIA TASSO[1], THOMAS BERTALOT[1], GIOVANNI MARTINELLI[4], FILIPPO GHERLINZONI[2] and MARIA TERESA CONCONI[1]

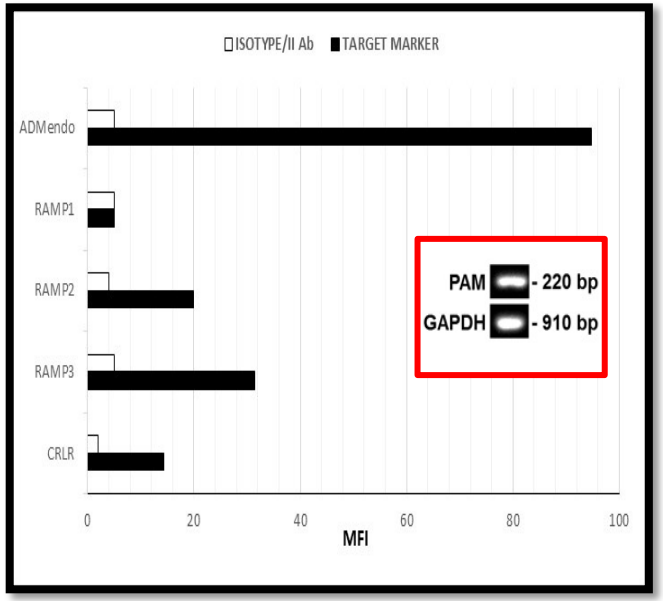


Figure 2. (A) The immunophenotypic analysis was performed by FCM to detect the expression of endogenous ADM (ADM_{endo}), ADM receptors (RAMP1/2/3, CRLR) using specific primary antibodies and Alexa Fluor 488- and PE-conjugated secondary antibody. In parallel, secondary antibody-matched controls were used as reference. For each marker, the percentage (%) ± SD of positive cells (grey peak) was detected by the substraction statistical tool of Summit 4.3 software using as reference II Ab-matched control (black peak). (B) Analysis by RT-PCR of PAM gene in HL60 cells cultured at basal conditions. In parallel, the expression of *GAPDH* housekeeping gene was considered. The amplification products were electrophoresed on 2% agarose gel and stained by GelRed™.

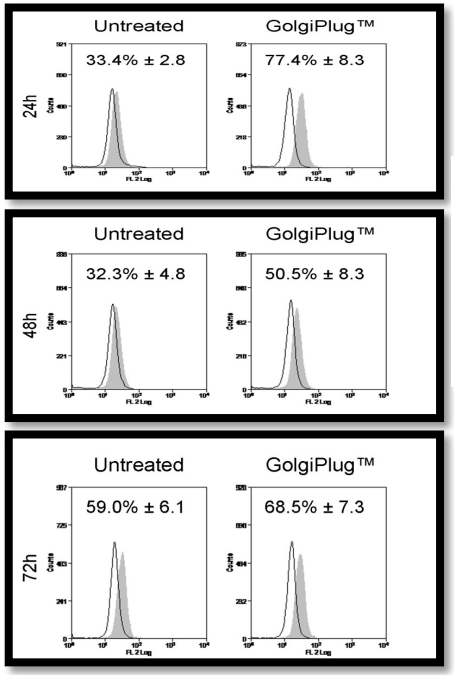


Figure 3. ADM secretion in HL60 cells was demonstrated using protein transport inhibition. Cells were cultured for 12, 36 and 60 h in proliferation medium before incubation for 12 h with Brefeldin A/GolgiPlug™. Thus, the samples were collected at 24, 48 and 72 h from plating and analyzed by intracellular ADM staining followed by flow cytometric analysis. In this analysis, cultures untreated with GolgiPlug™ were used as positive control of ADM secretion. The acquired data were expressed as a percentage (%) ± SD of ADM positive cells (grey filled peak) compared to II Ab-matched control (black profile).

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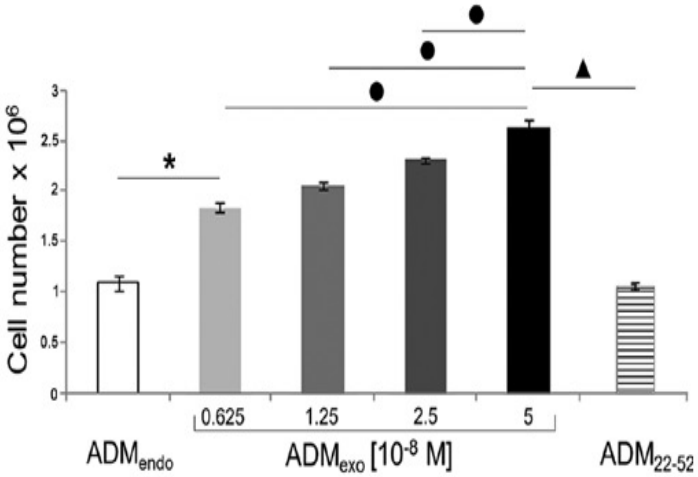

Figure 4. Proliferative effect of exogenous ADM solutions (from 0.625×10^{-8} M to 5×10^{-8} M) and 5×10^{-7} M ADM_{22-52} on HL60 cells cultured for 72 h. Untreated cultures (ADM_{endo}) were used as reference. Bars are means ± SD (n=10). *P<0.05 using the Student's t-test. *P<0.05 vs. ADM_{endo} reference group; •P<0.05 and ▲P<0.05 vs. 5×10^{-8} M ADM_{exo}.

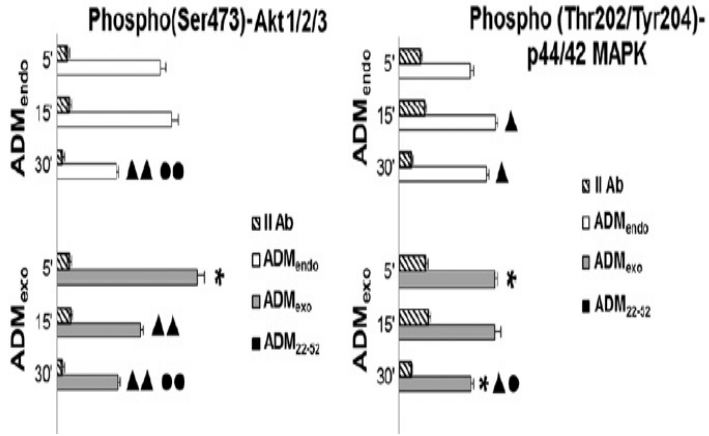

Figure 6. Changes in the activation state of Akt and MAPK upon treatment with 5×10^{-8} M ADM_{exo} and 5×10^{-7} M ADM_{22-52}. The samples were collected at 5, 15 and 30 min from stimulation and analyzed by intracellular detection of phospho(Ser473)-Akt1/2/3 and phospho(Thr202/Tyr204)-p44/42 MAPK followed by flow cytometric analysis. In parallel, untreated cultures (ADM_{endo}) were used as reference. Hatched bars, II Ab-matched control; white bars, untreated samples (ADM_{endo}); grey bars, ADM_{exo}-treated samples; black bars, ADM_{22-52}-samples. Bars are means ± SD (n=3). *P<0.05 vs. relative value of ADM_{endo} reference group; ▲P<0.05 and ▲▲P<0.01 vs. relative value detected at 5 min in each experimental group; •P<0.05 and ••P<0.01 vs. relative value detected at 15 min in each experimental group.

Adrenomedullin in the growth modulation and differentiation of acute myeloid leukemia cells

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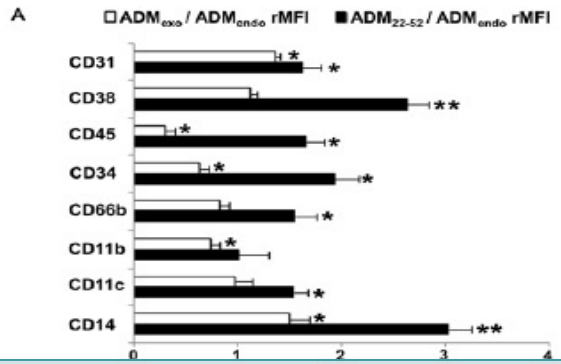

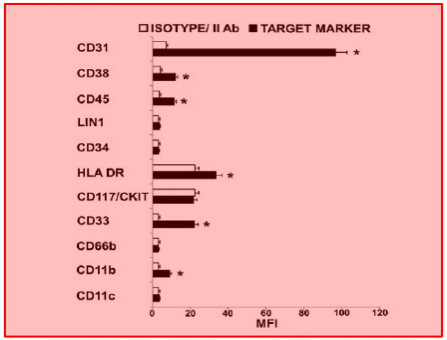

Figure 1. Characterization by flow cytometry of HL60 cells. Data were expressed as mean fluorescence intensity (MFI) ± SD. White bars, isotype- or secondary (II) Ab-matched control; black bars, target marker-matched samples.

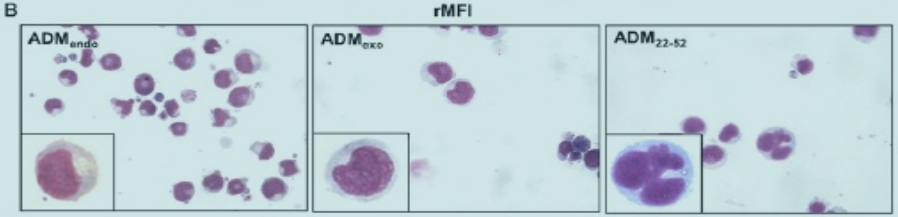

Figure 8. (A) Expression of differentiation markers in HL60 cells stimulated with $5x10^{-6}$ M ADM_{exo} or $5x10^{-7}$ M ADM_{22-52} for 72 h. The analysis was performed by flow cytometry and data are reported as the ratio of geometric mean fluorescence intensity (rMFI) obtained for samples treated with ADM_{exo} or ADM_{22-52} and untreated (ADM_{endo}) cultures. White bars, ADM_{exo}/ADM_{endo} rMFI; black bars, ADM_{22-52}/ADM_{endo} rMFI. *P<0.05 and **P<0.01 vs. rMFI value=1. (B) Morphological analysis by May Grunwald-Giemsa staining of untreated (ADM_{endo}) and treated cells with ADM_{exo} or ADM_{22-52}. Low magnification, x400; high magnification, x1,000.

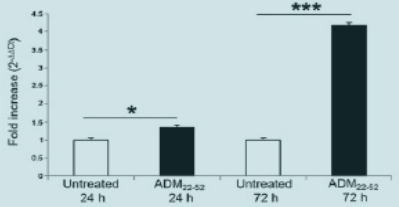

Figure 7. Quantitative RT-PCR analysis of Cul5 expression in HL60 cells treated with $5x10^{-7}$ M ADM_{22-52} or untreated (ADM_{endo}) for 24 and 72 h. In parallel, the expression of HPRT housekeeping gene was evaluated. The relative expression of Cul5 mRNA was determined using the ΔΔCT method. Data are reported as the fold difference calculated from the equation $2^{-\Delta\Delta CT}$ ± SD. *P<0.05 and ***P<0.01 vs. ADM_{endo} reference group.

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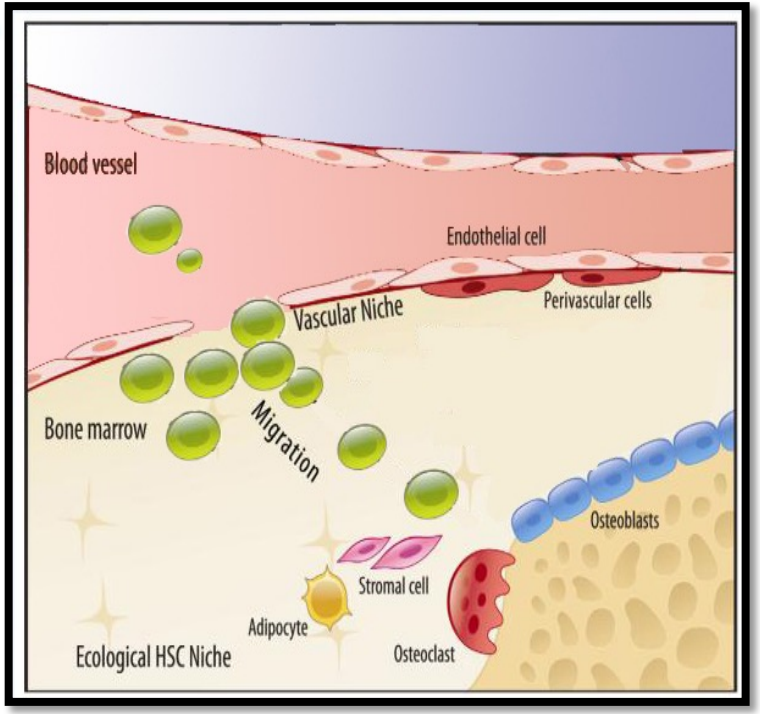
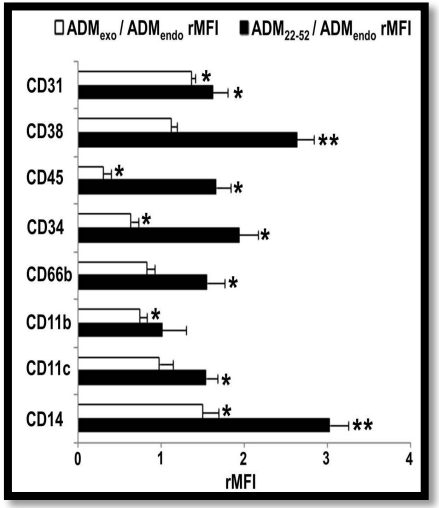
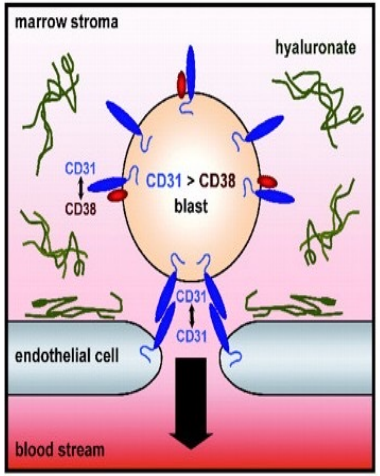


Ratio MFI : ADMexo: $5x10^{-8}$M; ADM22-52: $5x10^{-7}$



CD31/CD38 > 1



*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*

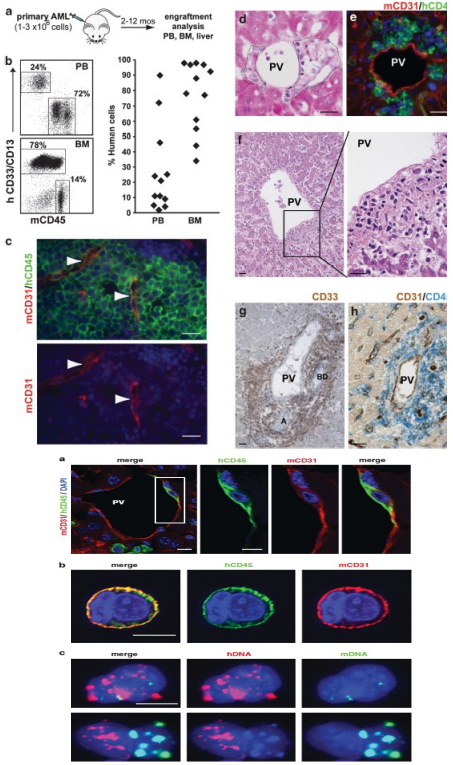
ORIGINAL ARTICLE

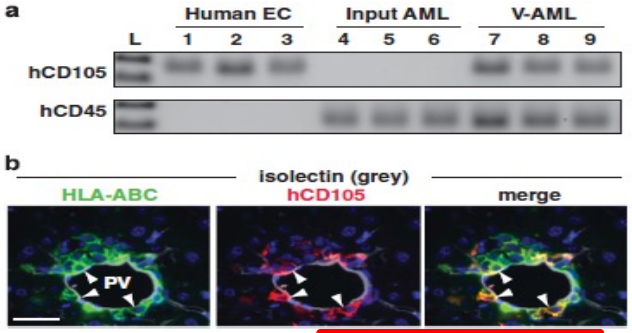
Functional integration of acute myeloid leukemia into the vascular niche

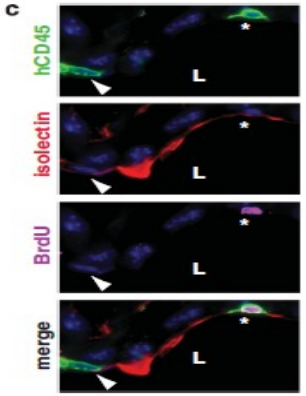
Leukemia (2014) 28, 1978–1987

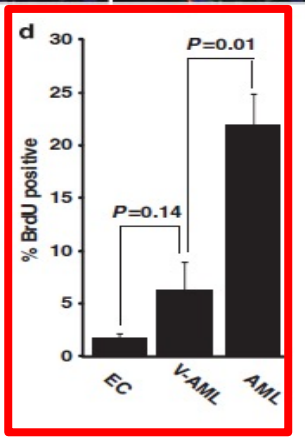
www.nature.com/leu

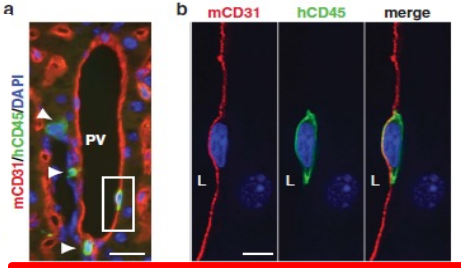
CR Cogle[1,6], DC Goldman[2,3,6], GJ Madlambayan[1,6,7], RP Leon[2,3], A Al Masri[2,3], HA Clark[2,3], SA Asbaghi[2,3], JW Tyner[3], J Dunlap[3,4], G Fan[3,4], T Kovacsovics[2,3], Q Liu[2,3], A Meacham[1], KL Hamlin[2,3], RA Hromas[1], EW Scott[5] and WH Fleming[2,3]

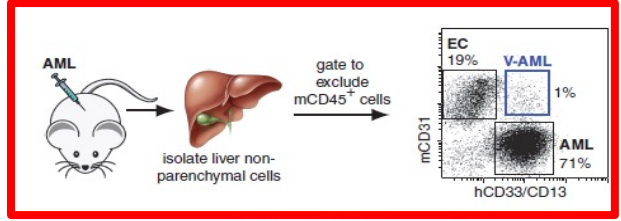


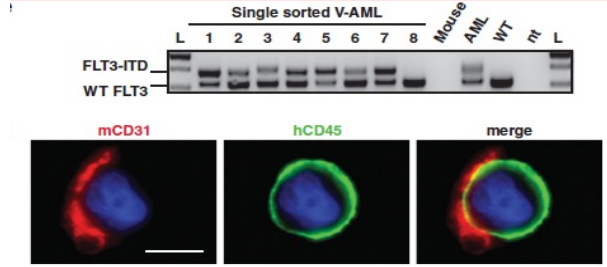












Special Article - Acute and Chronic Myeloid Leukemia

Journal of Blood Disorders

Some Reasons to Deeper Investigate the Vascular Niche in Acute Myeloid Leukemia

Gottardi M[1*], Conconi MT[2], Gherlinzoni F[1] and Di Liddo R[2]

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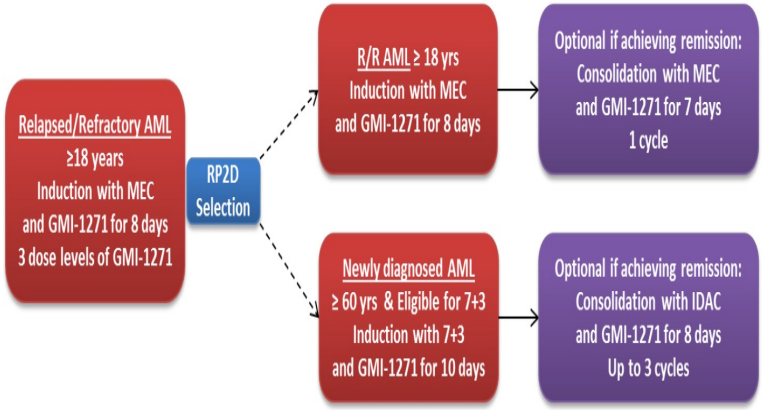
microenvironmental influences. HSC niche is generally divided into two compartments: a hypoxic endosteal bone marrow niche, that is developed within cancellous/trabecular bone and a vascular niche characterized by higher oxygen tension. The former is believed to maintain the HSCs in a quiescent state, especially during bone marrow repair. Hypoxia, that has been demonstrated to preserve the stemness of HSCs through the stabilization of the master transcriptional regulator of hypoxia response (HIF-1α), is a prominent feature of BM microenvironment in different hematological malignancies, such as leukemia [6]. A growing body of evidence suggests that HIF-1α promotes the quiescence of leukemic cells residing in the endosteal niches, thus contributing to the persistence of a minimal residual disease [7]. Finally, it has been demonstrated that hypoxia is able to activate a stemness genomic signature in cancer cells through the up-regulation of some genes such us *OCT-3/4*, *NANOG*, and *SOX2* [8], two of which were used by Takahashi and Yamanaka to generate induced Pluripotent Stem cells (iPS) from fibroblasts [9]. Based on numerous studies reporting the functional role of the endosteal niche as L-IC supportive microenvironment, therapies interfering with the endosteal localization of blasts have been proposed as a valid strategy for AML treatment. Unlike the endosteal niche, the vascular

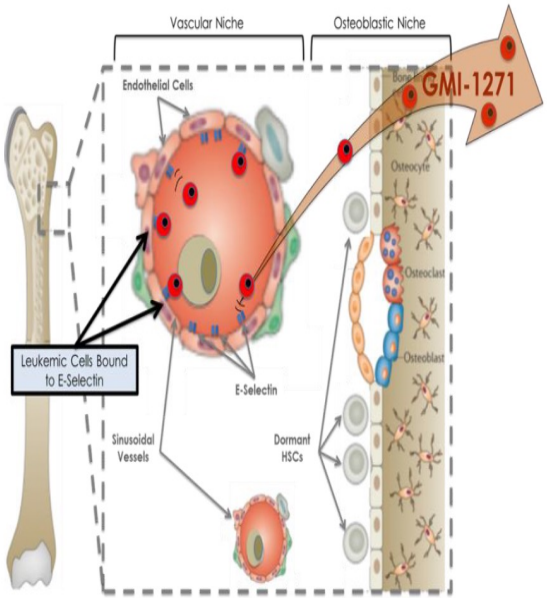
In conclusion, the vascular niche can behave as an L-IC supportive microenvironment and consequently may represent an attractive target for selective therapies. To our opinion this is the main, among other, reason to deeper investigate the vascular niche in AML.

GMI-1271 improves efficacy and safety of chemotherapy in R/R and newly diagnosed older patients with AML: results of a Phase 1/2 study

Daniel J. DeAngelo, Brian A. Jonas, Jane L. Liesveld, Dale L. Bixby, Anjali S. Advani, Paula Marlton, Michael E. O'Dwyer, John L. Magnani, Helen M. Thackray, Pamela S. Becker



GMI-1271, an E-selectin Antagonist, Disrupts the Relationship Between Tumor Cells and Bone Marrow Microenvironment



E-selectin –

- Constitutively expressed in the bone marrow microvasculature
- Binds to the E-selectin ligand on AML cells
- Promotes cell-adhesion-mediated drug resistance (CAMDR) of leukemic cell

GMI-1271, an E-selectin antagonist –

- Inhibits activation of cancer survival pathways (e.g. NF-KB), disrupting CAMDR within bone marrow micro-environment
- Protects normal HSCs by enhancing quiescence and ability for self-renewal
- Reduces chemotherapy-associated mucositis

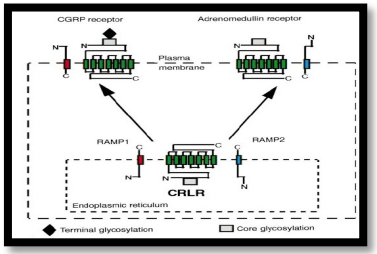


Table 1 (continued)

Variables	*CALCRL*			
	Low	Intermediate	High	*P* value
NPM1, *n* (%)				0.51[b]
Mutated	35 (29.9)	65 (27.5)	28 (23.3)	
Wild type	82 (70.1)	171 (72.5)	92 (76.7)	
NPM1/*FLT3*-ITD, *n* (%)				0.0070[b]
NPM1^{mut}/*FLT3*-ITD^{negative}	28 (23.9)	40 (17.0)	9 (7.5)	
NPM1^{mut}/*FLT3*-ITD^{high}	7 (6.0)	25 (10.6)	19 (15.8)	
NPM1^{wt}/*FLT3*-ITD^{negative}	79 (67.5)	157 (66.5)	87 (72.5)	
NPM1^{wt}/*FLT3*-ITD^{high}	3 (2.6)	14 (5.9)	5 (4.2)	
CEBPA, *n* (%)				0.0029[d]
Double mutated	10 (9.9)	3 (1.5)	4 (4.0)	
Wild type or single mutated	91 (90.1)	201 (98.5)	95 (96.0)	
RUNX1, *n* (%)				<0.0001[b]
Mutated	12 (10.3)	27 (11.4)	33 (27.5)	
Wild type	105 (89.7)	209 (88.6)	87 (72.5)	
ASXL1, *n* (%)				0.57[b]
Mutated	10 (8.6)	29 (12.3)	14 (11.7)	
Wild type	107 (91.4)	207 (87.7)	106 (88.3)	
TP53, *n* (%)				0.0017[b]
Mutated	7 (6.0)	23 (9.8)	24 (20.0)	
Wild type	110 (94.0)	213 (90.2)	96 (80.0)	
Cytogenetic and molecular risk[c], *n* (%)				<0.0001[b]
Favorable	65 (54.6)	78 (32.2)	16 (13.3)	
Intermediate	26 (21.9)	67 (27.7)	28 (23.3)	
Adverse	28 (23.5)	97 (40.1)	76 (63.3)	

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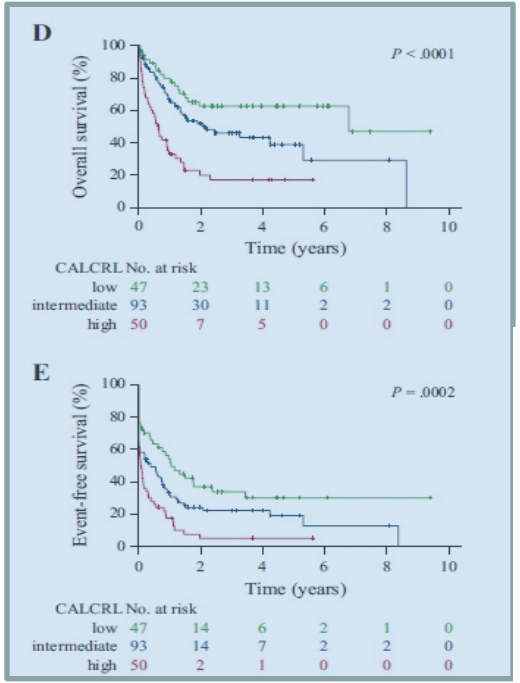
https://doi.org/10.1038/s41375-019-0505-x

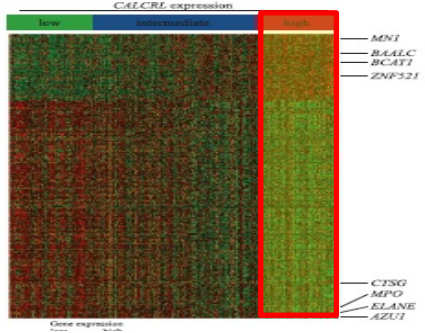
ARTICLE

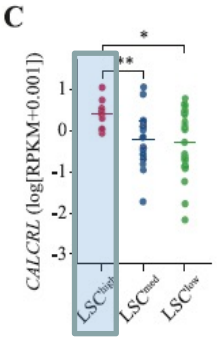
Acute myeloid leukemia

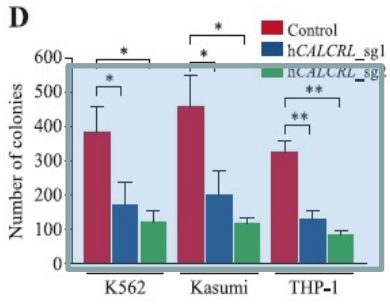
The neuropeptide receptor calcitonin receptor-like (CALCRL) is a potential therapeutic target in acute myeloid leukemia

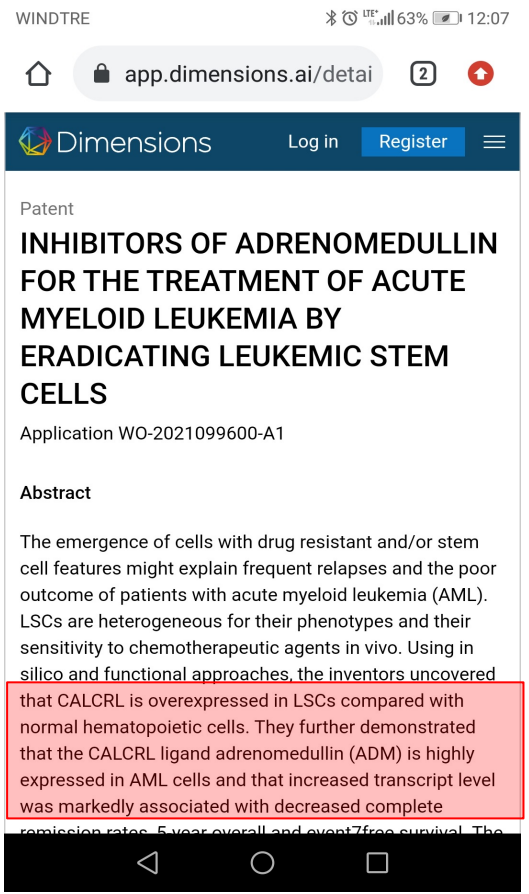
Linus Angenendt[1] · Eike Bormann[2] · Caroline Pabst[3] · Vijay Alla[1] · Dennis Görlich[2] · Leonie Braun[1] · Kim Dohlich[1] · Christian Schwöppe[1] · Stefan K. Bohlander[4] · Maria Francisca Arteaga[1] · Klaus Wethmar[1] · Wolfgang Hartmann[5] · Adrian Angenendt[6] · Torsten Kessler[1] · Rolf M. Mesters[1] · Matthias Stelljes[1] · Maja Rothenberg-Thurley[7] · Karsten Spiekermann[7] · Josée Hébert[8,9,10,11] · Guy Sauvageau[8,9,10,11] · Peter J. M. Valk[12] · Bob Löwenberg[12] · Hubert Serve[13] · Carsten Müller-Tidow[3] · Georg Lenz[1] · Bernhard J. Wörmann[14] · M. Christina Sauerland[2] · Wolfgang Hiddemann[7] · Wolfgang E. Berdel[1] · Utz Krug[15] · Klaus H. Metzeler[7] · Jan-Henrik Mikesch[1] · Tobias Herold[7,16] · Christoph Schliemann[1]







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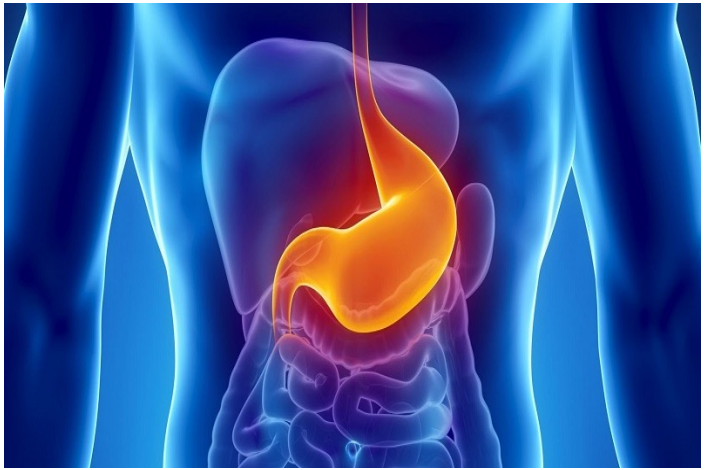
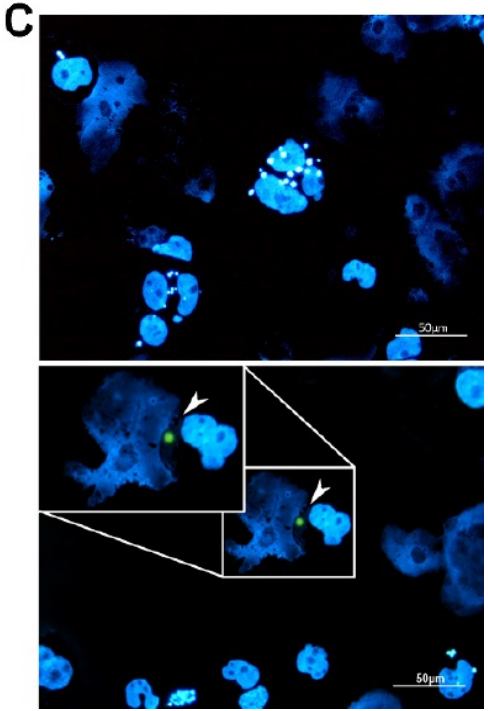
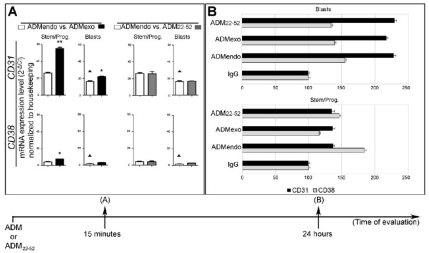
Patent
INHIBITORS OF ADRENOMEDULLIN FOR THE TREATMENT OF ACUTE MYELOID LEUKEMIA BY ERADICATING LEUKEMIC STEM CELLS
Application WO-2021099600-A1
Abstract
The emergence of cells with drug resistant and/or stem cell features might explain frequent relapses and the poor outcome of patients with acute myeloid leukemia (AML). LSCs are heterogeneous for their phenotypes and their sensitivity to chemotherapeutic agents in vivo. Using in silico and functional approaches, the inventors uncovered that CALCRL is overexpressed in LSCs compared with normal hematopoietic cells. They further demonstrated that the CALCRL ligand adrenomedullin (ADM) is highly expressed in AML cells and that increased transcript level was markedly associated with decreased complete

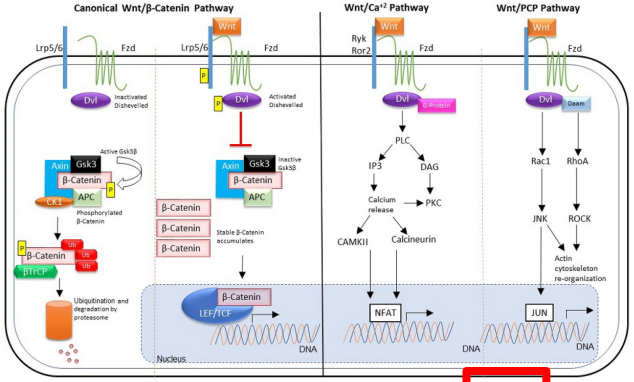


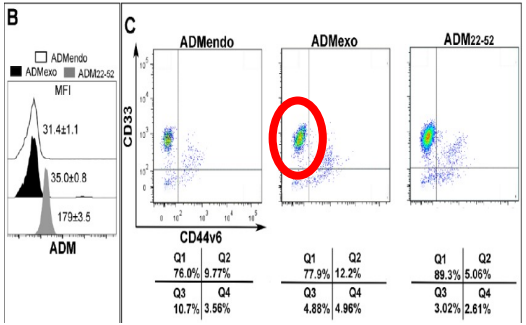
Title: *In vitro* cell-based approach to explore the regulatory activity of Adrenomedullin in AML epigenetics.

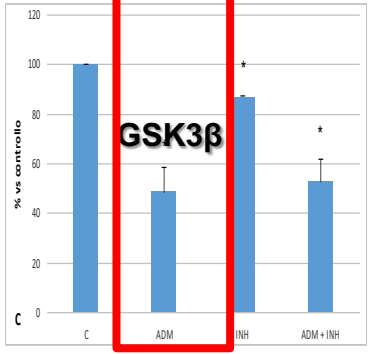
Authors
[3§]Michele Gottardi, [1§]Alessia Tasso, [1§]Monica Piccione, [1]Giulio Sturaro, [1]Enrico Rossi Sirena, [1]Francesca Franzolin, [2]Giorgia Simonetti, [2]Giovanni Martinelli, [3]Filippo Gherlinzoni, [1,#]Maria Teresa Conconi, [1,*,#]Rosa Di Liddo

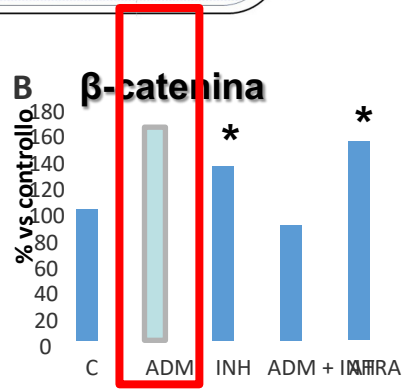












Adrenomedullin Expression Characterizes Leukemia Stem Cells and Associates With an Inflammatory Signature in Acute Myeloid Leukemia

Giorgia Simonetti[1*], Davide Angeli[2], Elisabetta Petracci[2], Eugenio Fonzi[2], Susanna Vedovato[3], Alessandra Sperotto[4], Antonella Padella[1], Martina Ghetti[1], Anna Ferrari[1], Valentina Robustelli[5,6], Rosa Di Liddo[7], Maria Teresa Conconi[7], Cristina Papayannidis[5], Claudio Cerchione[8], Michela Rondoni[9], Annalisa Astolfi[10,11], Emanuela Ottaviani[5], Giovanni Martinelli[12] and Michele Gottardi[13]

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published: 02 June 2021

Gene Expression Datasets

Gene expression data were obtained from the BLUEPRINT consortium (http://dcc.blueprint-epigenome.eu/#/home) (24) and the Gene Expression Omnibus (GEO) repository [https://www.ncbi.nlm.nih.gov/gds, GSE98791 (25), GSE24759 (26), GSE24006 (27), GSE63270 (28), GSE158596 (29), GSE117090 (30), GSE14924 (31), GSE14468 (32), GSE6891 (33), GSE13159 (34)]. Array data from 61 AML bone marrow samples (blasts ≥80%) and 29 Philadelphia-negative (Ph−) B-ALL have been generated by the Next Generation Sequencing platform for targeted Personalized Therapy of Leukemia (NGS-PTL) project, as previously described (35, 36). The Beat AML (37) and The Cancer Genome Atlas (TCGA) project on AML (38) transcriptomic cohorts were obtained from https://portal.gdc.cancer.gov (projects BEATAML1.0-COHORT and TCGA-LAML), respectively. The datasets used in the manuscript are described in **Supplementary Table 1**.

24. Stunnenberg HG, Abrignani S, Adams D, de Almeida M, Altucci L, Amin V, et al. The International Human Epigenome Consortium: A Blueprint for Scientific Collaboration and Discovery. *Cell* (2016) 167:1145–9. doi: 10.1016/j.cell.2016.11.007

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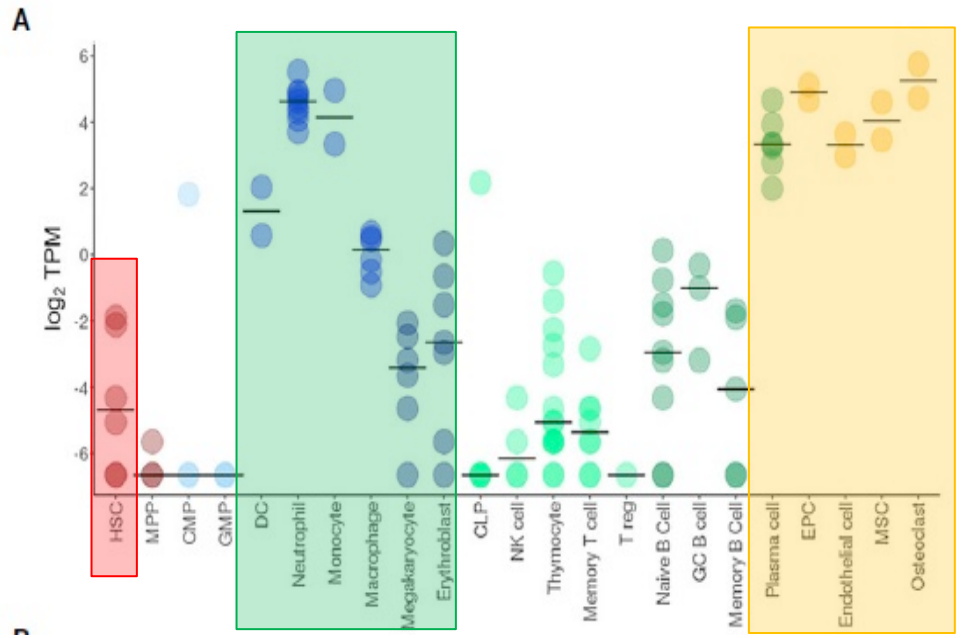

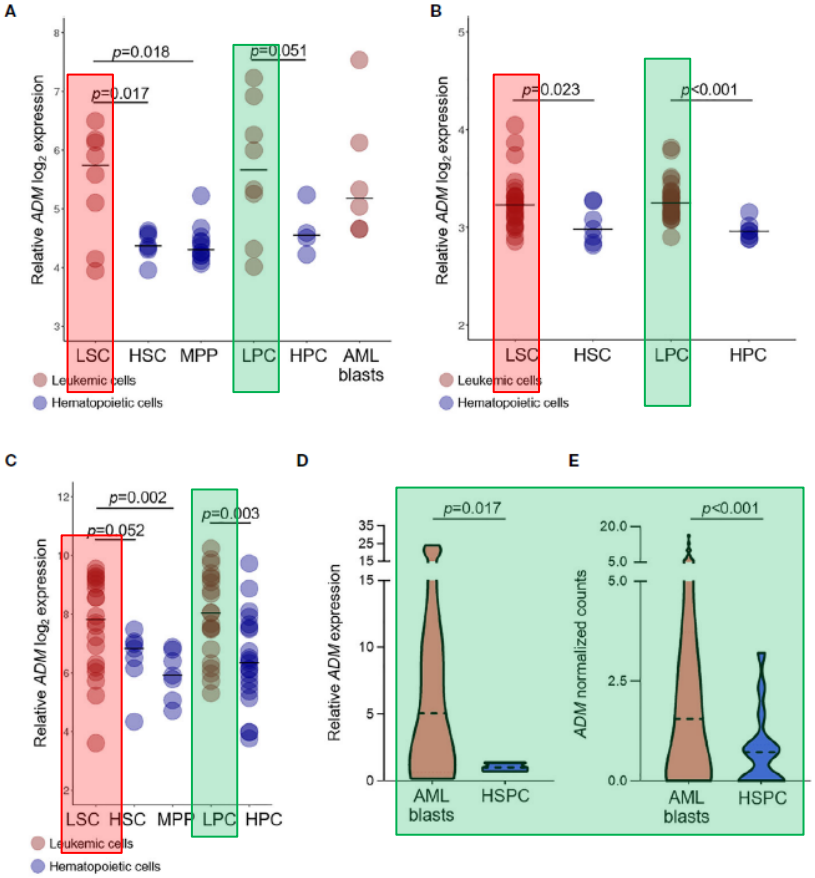

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FIGURE 2 | *ADM* expression is elevated in leukemic compared with hematopoietic stem and progenitor cells and in AML compared with ALL. **(A–C)** Comparison of *ADM* levels between leukemic cells subpopulations and normal stem and progenitor cells in the GSE24006 **(A)**, the GSE117090 **(B)** and the GSE63270 **(C)** datasets. Subpopulations according to their surface phenotype: leukemia stem cells (LSC): (Lin^-)$CD34^+CD38^-(CD90^-)$, hematopoietic stem cells (HSC): $Lin^-CD34^+CD38^-CD90^+(CD45RA^{+/-})$, hematopoietic multipotent progenitor cells (MPP): $Lin^-CD34^+CD38^-CD90^-CD45RA^-$, leukemia progenitor cells (LPC): (Lin^-) $CD34^+CD38^+(CD90^-)$, hematopoietic progenitor cells (HPC): $Lin^-CD34^+CD38^+(CD90^+)$, AML blasts: Lin^-CD34^-. Scatter plots were generated with the R package ggplot2 (48) (version 3.3.1). Each dot indicates one sample and the bar represents the median value. **(D)** Comparison of *ADM* levels between AML blasts (n = 12) and healthy $CD34^+$ bone marrow cells (n = 3, hematopoietic stem-progenitor cells, HSPC, qRT-PCR) and **(E)** between AML blasts (n = 60) and healthy G-CSF mobilized HSPC (n = 16) from the GSE158596 dataset. **(F)** *ADM* transcript levels in AML (n = 505) and ALL (n = 784, GSE13159), **(G)** separated in T-ALL (n = 173) and B-ALL (n = 441) and **(H)** in AML (n = 61) *versus* Ph–B-ALL (n = 29, NGS-PTL). Violin plots were generated with GraphPad Prims (version 8.4.3). The plots represent the frequency distribution of *ADM* levels (from minimum to maximum) and the dotted line indicates the median value.

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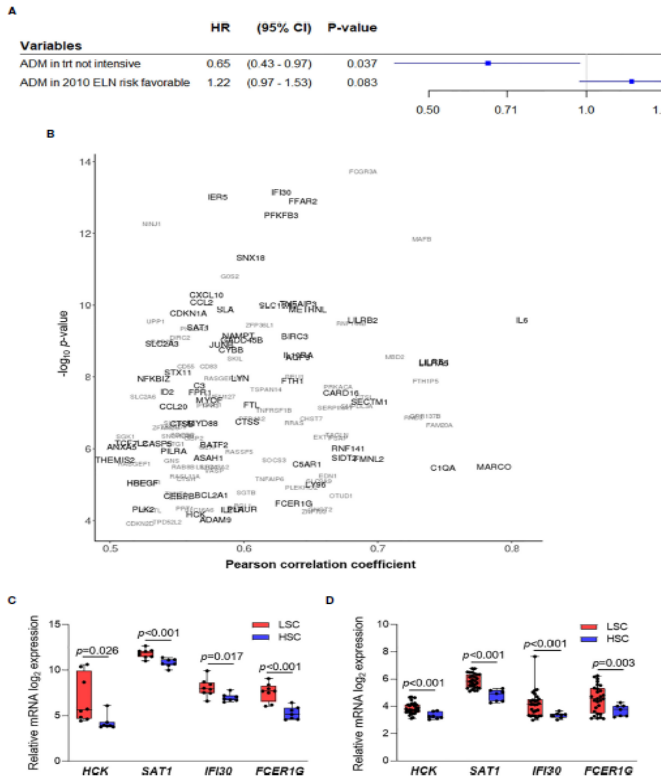

FIGURE 3 | *ADM* prognostic role and co-expressed genes in AML. **(A)** Results from two separate Cox regression models within the subgroup with 2010 ELN favorable risk (adjusting for age, n = 214) and within the subgroup receiving a not-intensive treatment (n = 64, HR, Hazard ratio, CI, confidence interval, trt, treatment). **(B)** Correlation analysis between *ADM* expression and the AML transcriptome across bone marrow samples from five AML datasets (GSE6891, GSE13159, Beat AML, TCGA-LAML, NGS-PTL). Genes showing an absolute value of Pearson correlation coefficient ≥0.50 and a *p* value ≤0.05 in at least two cohorts were reported. Genes are represented according to the weighted arithmetic mean of the correlation coefficient and *p* value across the datasets. The scatter plot was generated with the R package ggplot2 (48) (version 3.3.1). **(C)** Transcriptional analysis of *ADM* co-expressed genes in LSC compared with HSC in the GSE24006 and **(D)** in the GSE117090 datasets (fold change ≥1.5 and *p* ≤0.05 were set as cut off). The boxes extend from minimum to maximum values, each individual value is plotted and the line represents the median value.

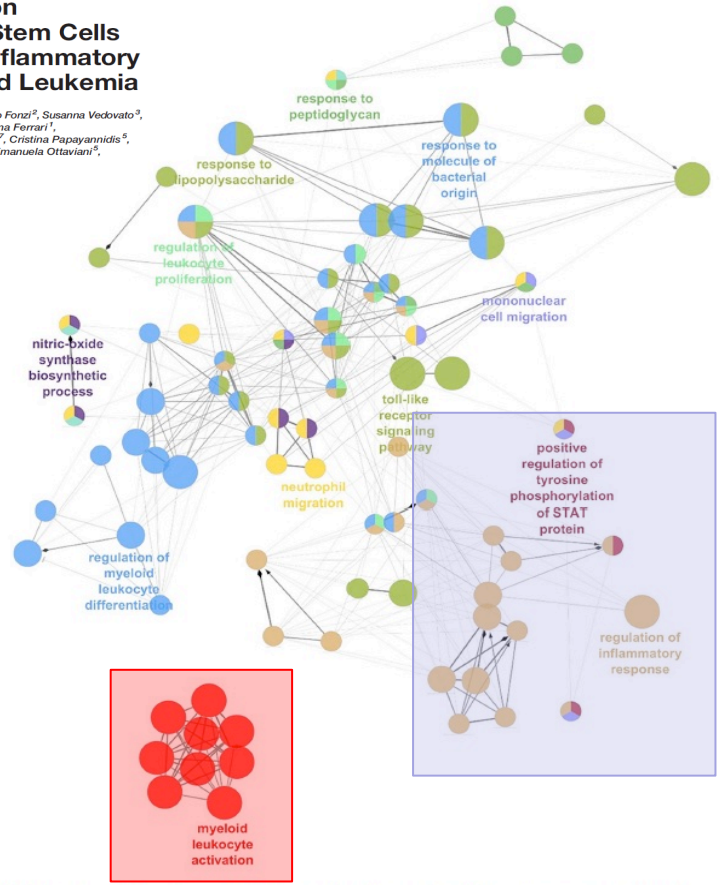

FIGURE 4 | The network of *ADM* co-expressed genes in AML. Network analysis of the Gene Ontology Biological Processes pathways enriched by *ADM* co-expressed genes in AML (ClueGO). Colors indicate functionally-related pathways; one representative pathway for each subnetwork is specified.

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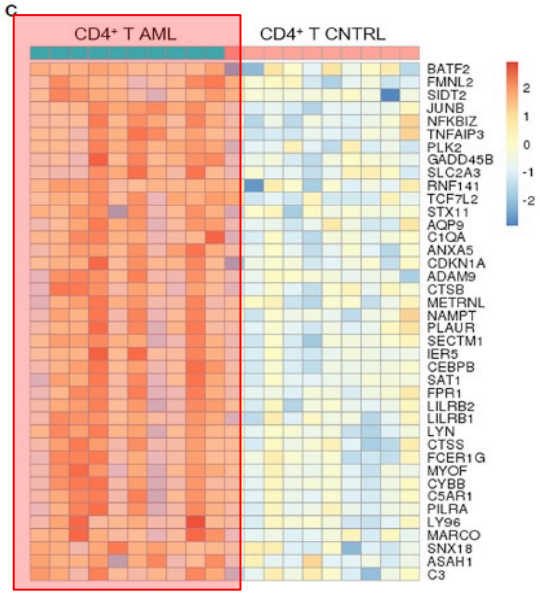
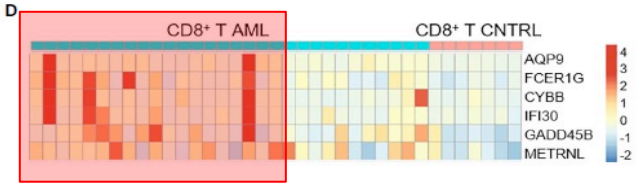
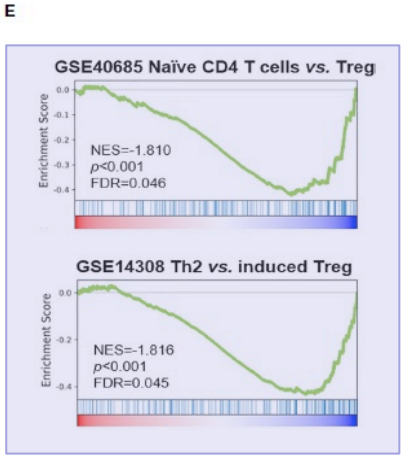
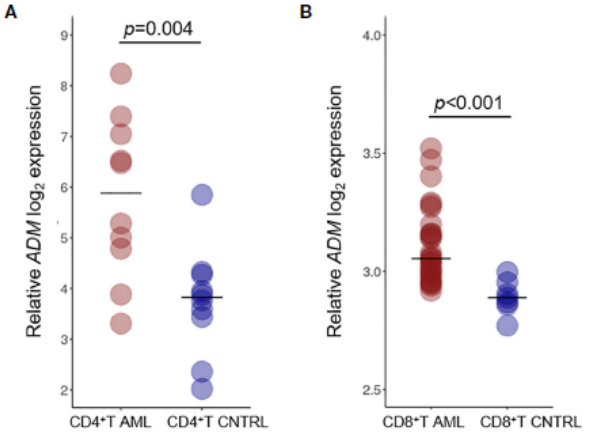
Giorgia Simonetti[1], Davide Angeli[2], Elisabetta Petracci[2], Eugenio Fonzi[2], Susanna Vedovato[3], Alessandra Sperotto[4], Antonella Padella[1], Martina Ghetti[1], Anna Ferrari[1], Valentina Robustelli[5,6], Rosa Di Liddo[7], Maria Teresa Conconi[7], Cristina Papayannidis[5], Claudio Cerchione[8], Michela Rondoni[9], Annalisa Astolfi[10,11], Emanuela Ottaviani[5], Giovanni Martinelli[12] and Michele Gottardi[13]*





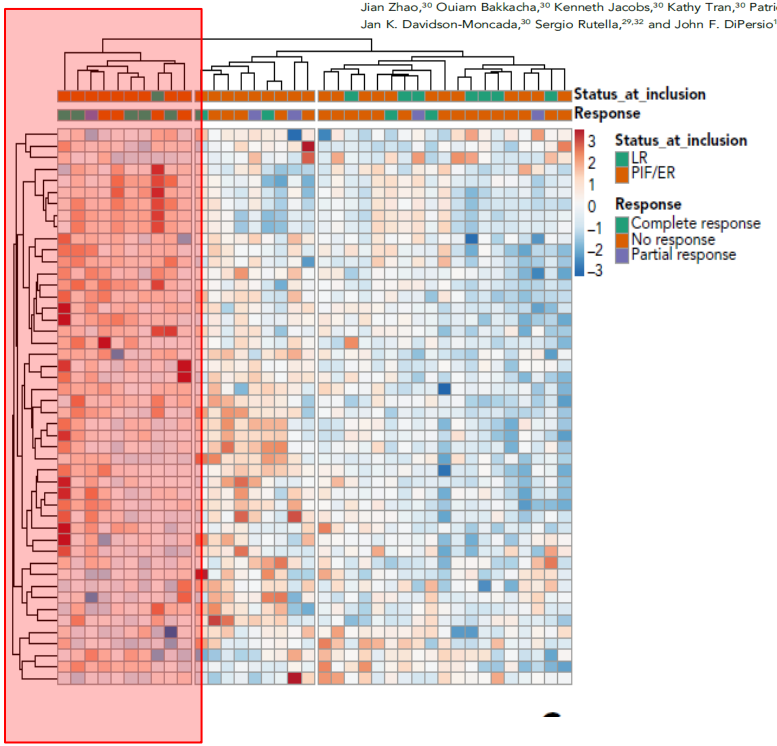


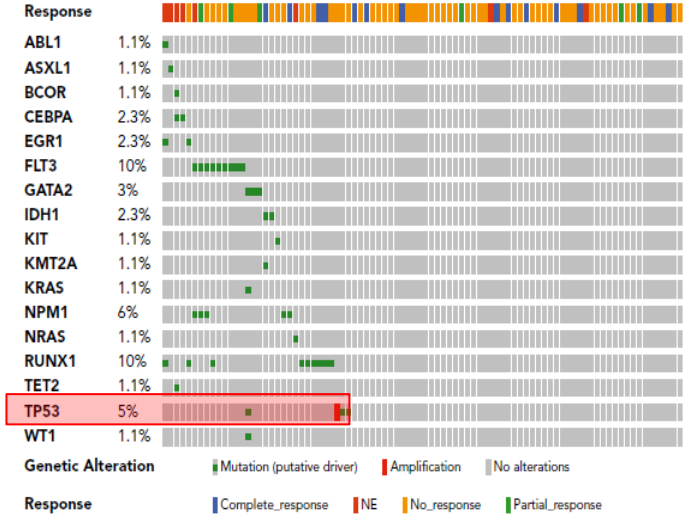


CLINICAL TRIALS AND OBSERVATIONS

Flotetuzumab as salvage immunotherapy for refractory acute myeloid leukemia

Geoffrey L. Uy,[1] Ibrahim Aldoss,[2] Matthew C. Foster,[3] Peter H. Sayre,[4] Matthew J. Wieduwilt,[5] Anjali S. Advani,[6] John E. Godwin,[7] Martha L. Arellano,[8] Kendra L. Sweet,[9] Ashkan Emadi,[10] Farhad Ravandi,[11] Harry P. Erba,[12] Michael Byrne,[13] Laura Michaelis,[14] Max S. Topp,[15] Norbert Vey,[16] Fabio Ciceri,[17] Matteo Giovanni Carrabba,[17] Stefania Paolini,[18] Gerwin A. Huls,[19] Mojca Jongen-Lavrencic,[20] Martin Wermke,[21] Patrice Chevallier,[22] Emmanuel Gyan,[23] Christian Récher,[24] Patrick J. Stiff,[25] Kristen M. Pettit,[26] Bob Löwenberg,[20] Sarah E. Church,[27] Erica Anderson,[28] Jayakumar Vadakekolathu,[29] Marianne Santaguida,[28] Michael P. Rettig,[1] John Muth,[30] Teia Curtis,[30] Erin Fehr,[30] Kuo Guo,[30] Jian Zhao,[30] Ouiam Bakkacha,[30] Kenneth Jacobs,[30] Kathy Tran,[30] Patrick Kaminker,[30] Maya Kostova,[30] Ezio Bonvini,[30] Roland B. Walter,[31] Jan K. Davidson-Moncada,[30] Sergio Rutella,[29,32] and John F. DiPersio[1]





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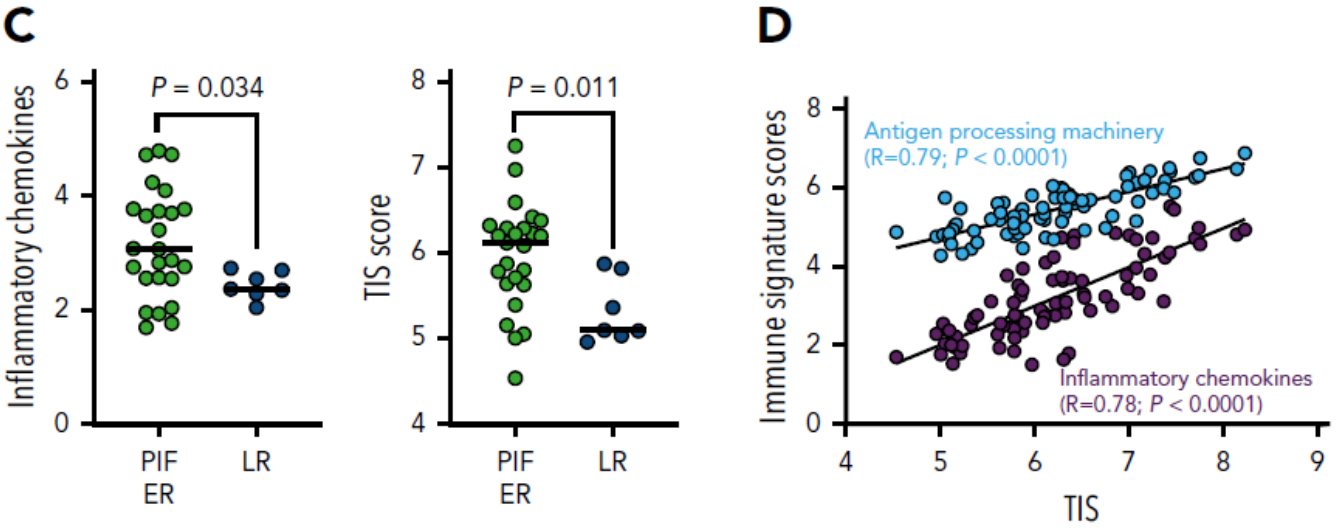


REGULAR ARTICLE

blood advances

TP53 abnormalities correlate with immune infiltration and associate with response to flotetuzumab immunotherapy in AML

Jayakumar Vadakekolathu,[1,*] Catherine Lai,[2,*] Stephen Reeder,[1] Sarah E. Church,[3] Tressa Hood,[3] Anbarasu Lourdusamy,[4] Michael P. Rettig,[5] Ibrahim Aldoss,[6] Anjali S. Advani,[7] John Godwin,[8] Matthew J. Wieduwilt,[9] Martha Arellano,[10] John Muth,[11] Tung On Yau,[1] Farhad Ravandi,[12] Kendra Sweet,[13] Heidi Altmann,[14] Gemma A. Foulds,[1] Friedrich Stölzel,[14] Jan Moritz Middeke,[14] Marilena Ciciarello,[15] Antonio Curti,[15] Peter J. M. Valk,[16] Bob Löwenberg,[16] Ivana Gojo,[17] Martin Bornhäuser,[14] John F. DiPersio,[5] Jan K. Davidson-Moncada,[11] and Sergio Rutella[1,18]

[1]John van Geest Cancer Research Centre, School of Science and Technology, Nottingham Trent University, Nottingham, United Kingdom; [2]MedStar Georgetown University Hospital's Lombardi Comprehensive Cancer Center, Washington, DC; [3]NanoString Technologies, Inc., Seattle, WA; [4]School of Medicine, Biodiscovery Institute, University of Nottingham, Nottingham, United Kingdom; [5]Division of Oncology, Department of Internal Medicine, Washington University in St. Louis, St. Louis, MO; [6]Department of Hematology and Hematopoietic Cell Transplantation, Gehr Family Center for Leukemia Research, City of Hope, Duarte, CA; [7]Leukemia Program, Department of Hematology and Medical Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH; [8]Earle A. Chiles Research Institute, Providence Cancer Centre, Portland, OR; [9]Moores Cancer Center, University of California San Diego, La Jolla, CA; [10]Winship Cancer Institute of Emory University, Atlanta, GA; [11]MacroGenics, Inc., Rockville, MD; [12]Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX; [13]Moffitt Cancer Center, Tampa, FL; [14]Department of Internal Medicine I, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany; [15]Institute of Hematology "L. and A. Seràgnoli," Department of Hematology and Oncology, University Hospital S. Orsola-Malpighi, Bologna, Italy, [16]Department of Hematology, Erasmus Medical Centre, Rotterdam, The Netherlands; [17]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD; and [18]Centre for Health, Ageing and Understanding Disease, Nottingham Trent University, Nottingham, United Kingdom

fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

Role of Adrenomedullin in Leukemic Endosteal/Vascular Niches

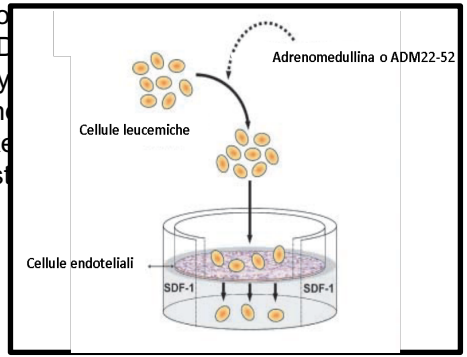
GIMEMA AML2220

ClinicalTrials.gov Identifier NCT04460963

STUDY DESIGN

The present study will be divided into 5 phases:

1. Collection of bone marrow and peripheral blood (PB) samples from AML patients at diagnosis, at CR, at the end of treatment and at relapse;
2. Measurement of Midregional Proadrenomedullin (MR-proADM) plasma concentrations with an Immunoluminometric Assay of newly diagnosed AML patients not affected by concomitant cardiovascular disease or sepsis.
3. Analysis of exosomes and microvesicles derived from PB and bone marrow samples of AML patients and culture media collected from AML samples stimulated with ADM and/or ADM (22-52)
4. Study of adrenomedullin system in leukemic stem cells (CD44+/CD38-/CD31+/Lin-) in order to define a correlated expression of ADM and ADM receptors (RAMPs, PAM) with adhesion molecules (CD31, CD38, CD44s, CD44v6), cell cycle regulatory proteins (p21, p27) and genes or molecules involved in the hemato
CD11b, CD11c, CD66, CD14, CD
5. *In vitro* evaluation of ADM activity
endothelial migration of blasts an
endothelial cells. To do this, leuke
by using *in vitro* models of endost



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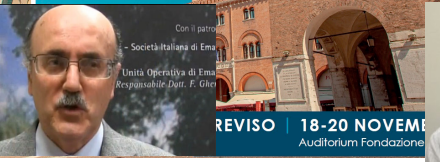
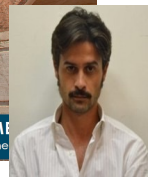
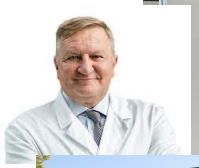
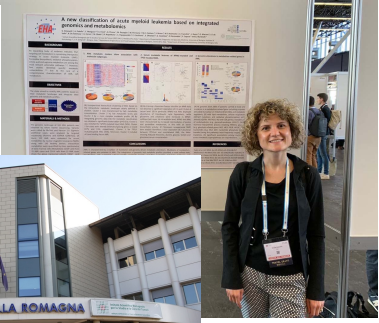




Prof. Sergio Amadori
Prof Adriano Venditti
Dr. Enrico Crea
Dr. Alfonso Piciocchi
Dr.ssa Veleria Sargentini



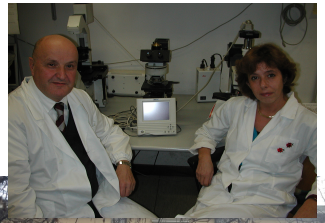


Prof. Giovanni Martinelli
Dr.ssa Giorgia Simonetti

GRAZIE

AIL Treviso
ASSOCIAZIONE ITALIANA CONTRO LEUCEMIE LINFOMI E MIELOMA

Dr. Sergio De Angeli



Prof.ssa Maria Teresa Conconi
Prof.ssa Rosa Diliddo

Dr.ssa Roberta De Marchi
Dr.ssa Nilla Maschio
Dr.ssa Alessandra Sperotto
Dr.ssa Angelica Spolzino
Dr. Paolo Radossi
Dr. Roberto Sartori

Farmacista di reparto:
Dr. Marco Basso