13th Annual ION CHANNEL RETREAT 2015
Share Knowledge. Exchange Ideas. Establish Partnerships.

Ion channels: novel biomarkers and therapeutic targets in cancer

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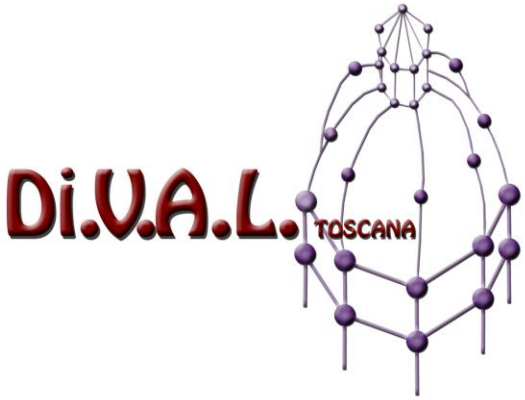
UNIVERSITÀ DEGLI STUDI FIRENZE

Di.V.A.L. TOSCANA

Disclosures

- Scientific coordinator of Dival Toscana Srl (Laboratory for Drug Validation and Antibody Production), Firenze, Italy



Outline

- Expression and role of ion channels in cancer
- hERG1 potassium channels in cancer
- hERG1 channels: novel biomarkers in cancer
- hERG1 channels: novel therapeutic targets in cancer
- Strategies to avoid cardiac side effects when targeting hERG1 in cancer

Contents lists available at ScienceDirect

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

Review

Ion channel expression as promising cancer biomarker☆

Elena Lastraioli, Jessica Iorio, Annarosa Arcangeli *

Department of Experimental and Clinical Medicine, Section of Internal Medicine University of Florence, Florence, Italy

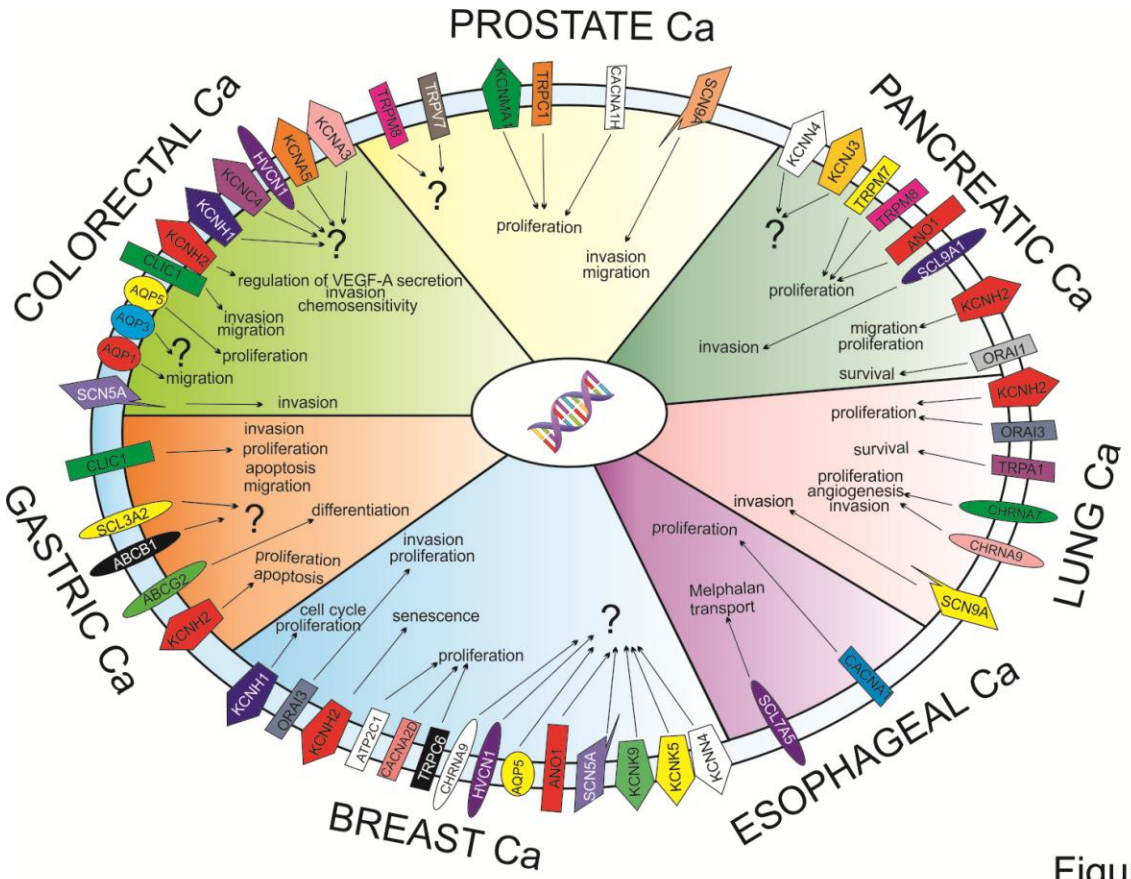
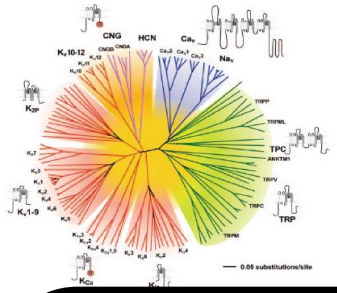


Figure 1



66 *Current Medicinal Chemistry*, 2009, *16*, 66-93

Targeting Ion Channels in Cancer: A Novel Frontier in Antineoplastic Therapy

A. Arcangeli*[,1], O. Crociani[1], E. Lastraioli[1], A. Masi[1], S. Pillozzi[1] and A. Becchetti[2]

[1]*Department of Experimental Pathology and Oncology, University of Firenze, Italy;* [2]*Department of Biotechnology and Biosciences, University of Milano-Bicocca, Italy*

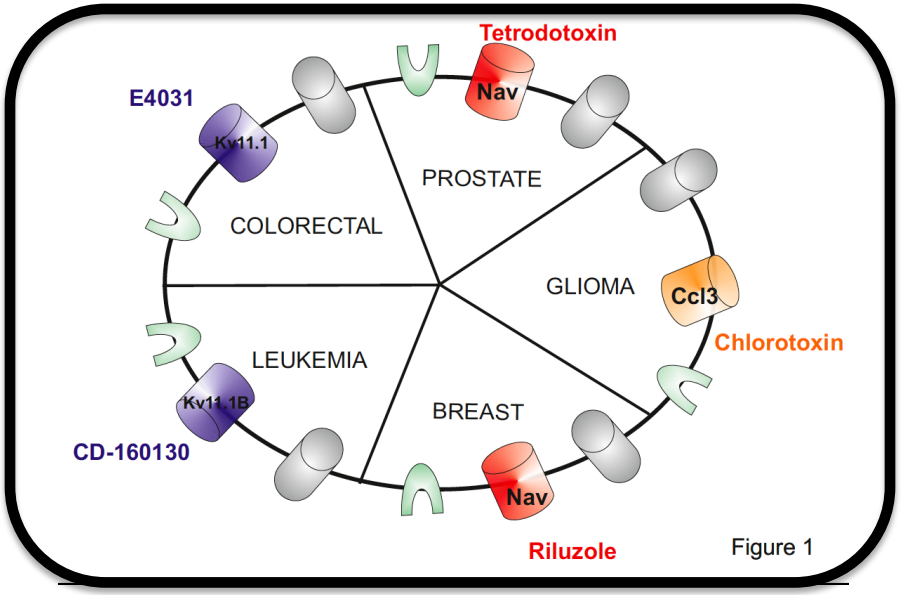


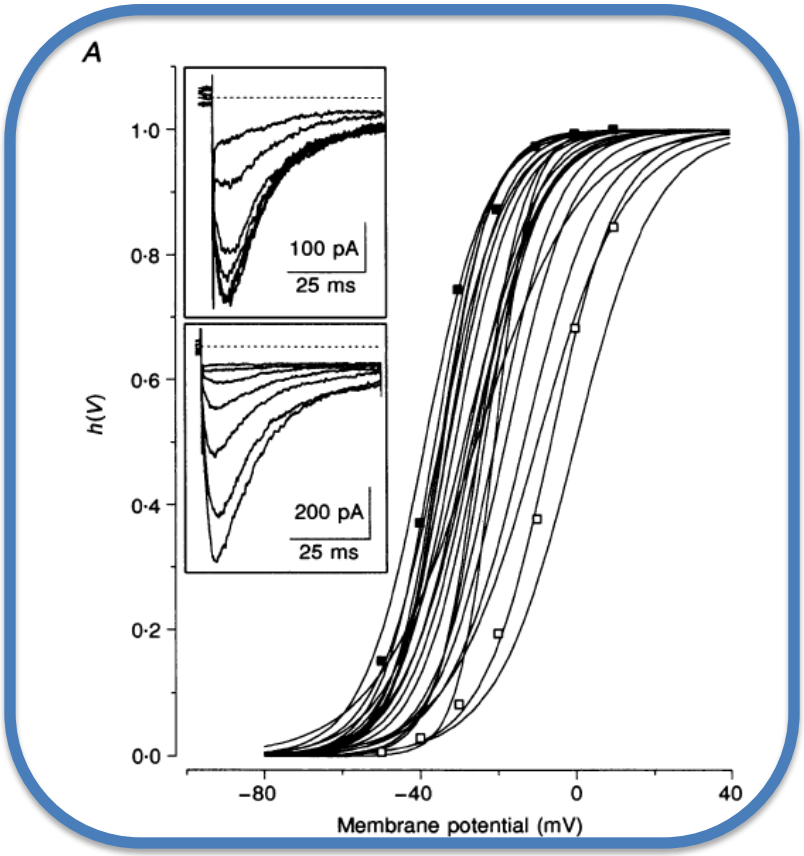
Figure 1

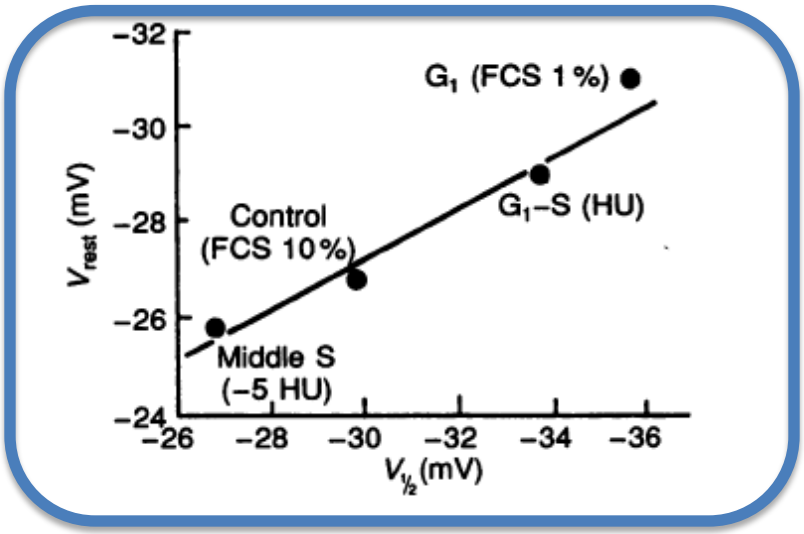
hERG1 (Kv 11.1)

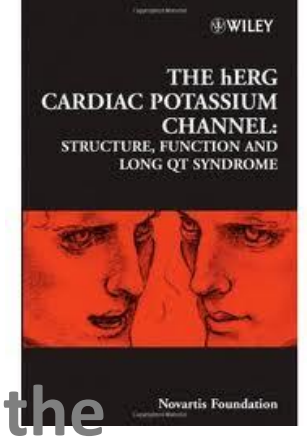
Journal of Physiology (1995), **489.2**, *pp.*455–471

A novel inward-rectifying K^+ current with a cell-cycle dependence governs the resting potential of mammalian neuroblastoma cells

Annarosa Arcangeli*, Laura Bianchi, Andrea Becchetti, Laura Faravelli, Marcella Coronnello†, Enrico Mini†, Massimo Olivotto* and Enzo Wanke‡







- hERG1 is expressed in the human heart (Ikr)
- Point mutations of the hERG1 gene account for the inherited LQT syndrome

- **hERG1 is mis- and over-expressed in several types of human cancers where it regulates different aspect of cancer cell behaviour (proliferation, resistance to apoptosis, chemoresistance, angiogenesis, cell migration, cell invasiveness)**

INTRACELLULAR SIGNALLING

Review TRENDS in Cell Biology Vol.16 No.12

Complex functional interaction between integrin receptors and ion channels

Annarosa Arcangeli[1] and Andrea Becchetti[2]

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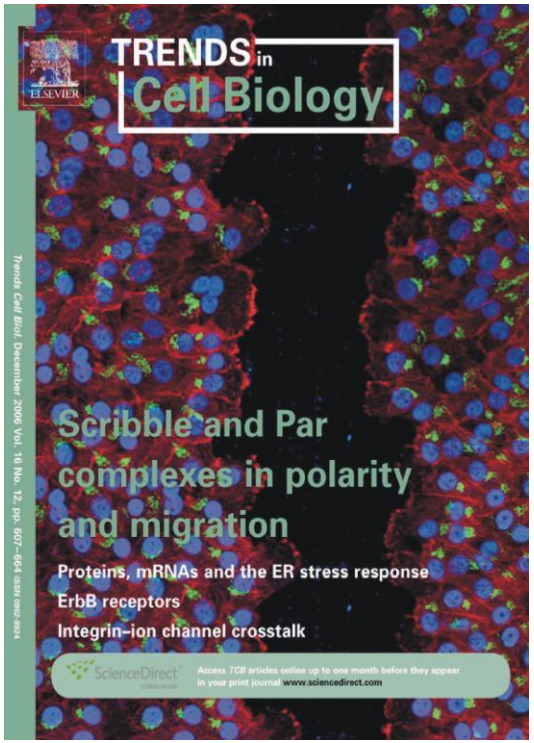
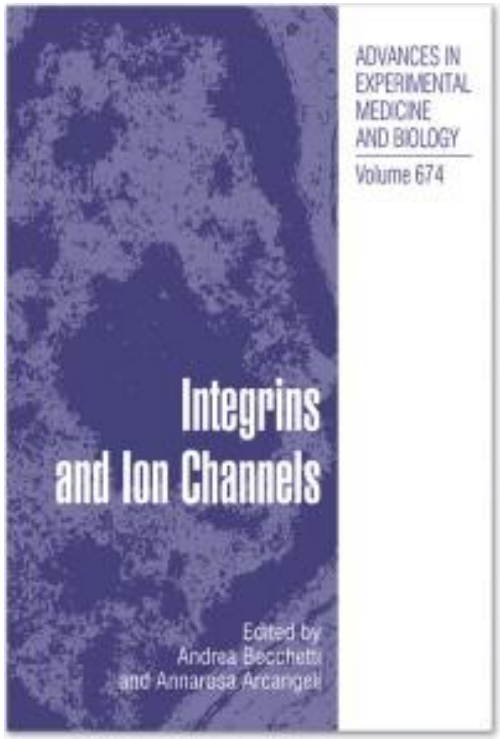
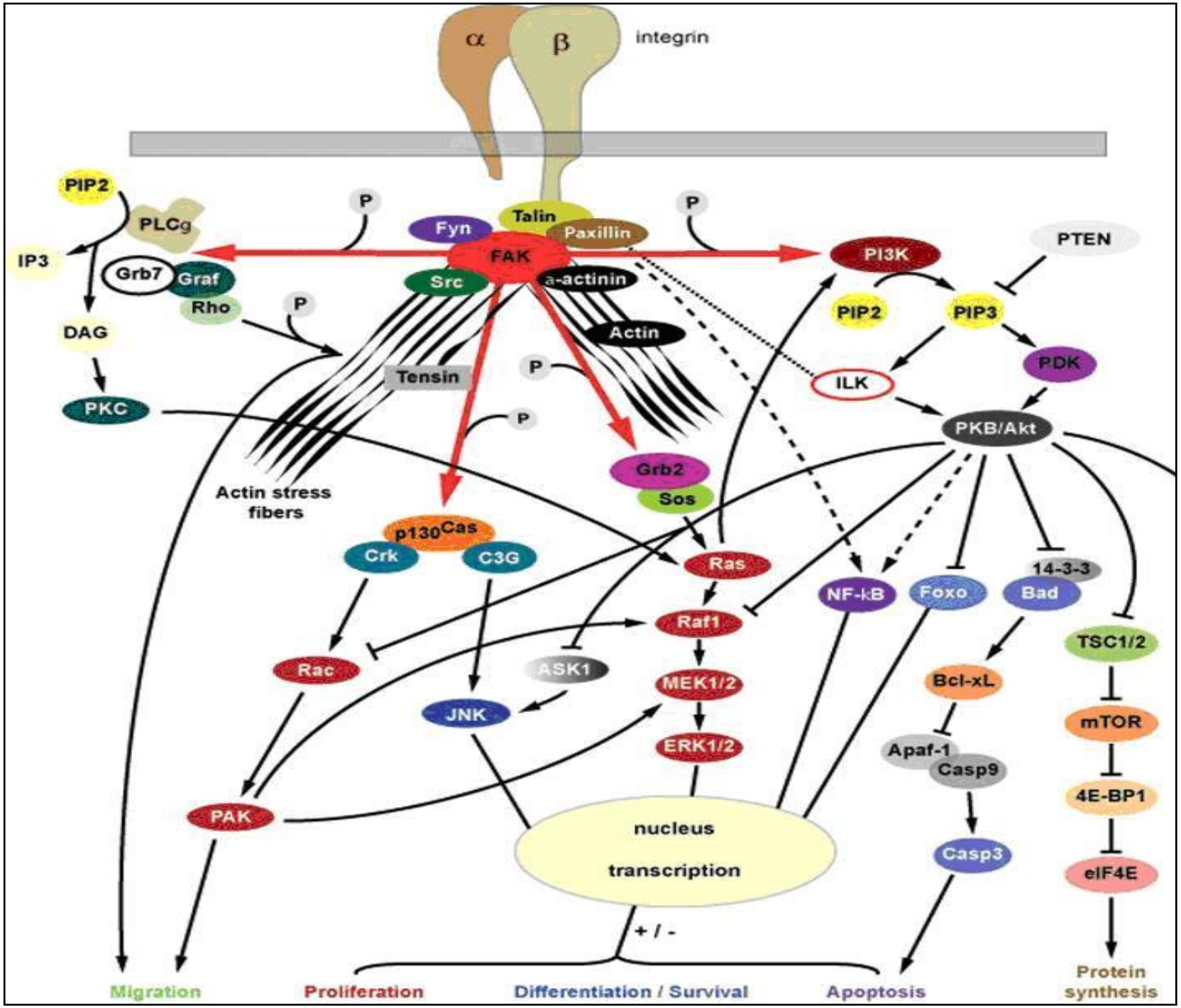
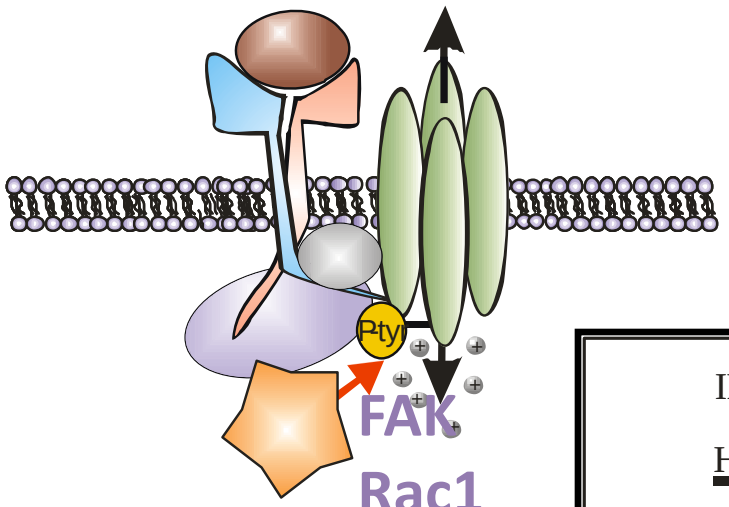
[2] Department of Biotechnology and Biosciences, University of Milano-Bicocca, Piazza della Scienza 2, 20126 Milano, Italy

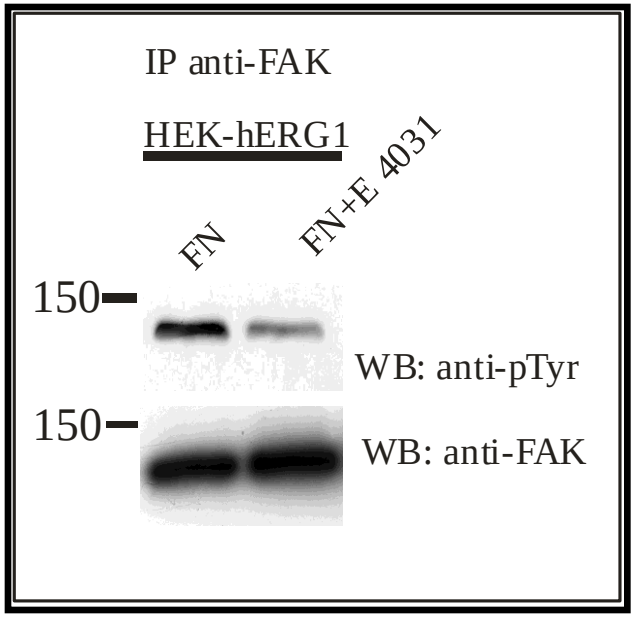


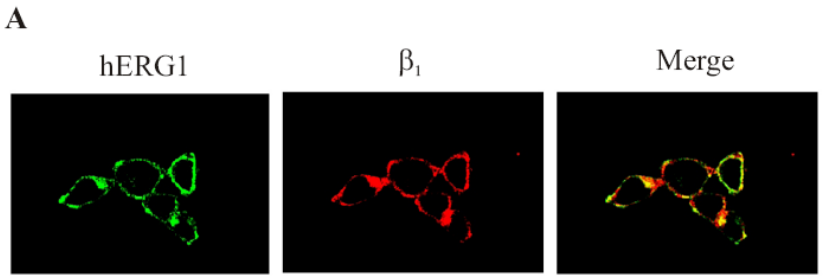


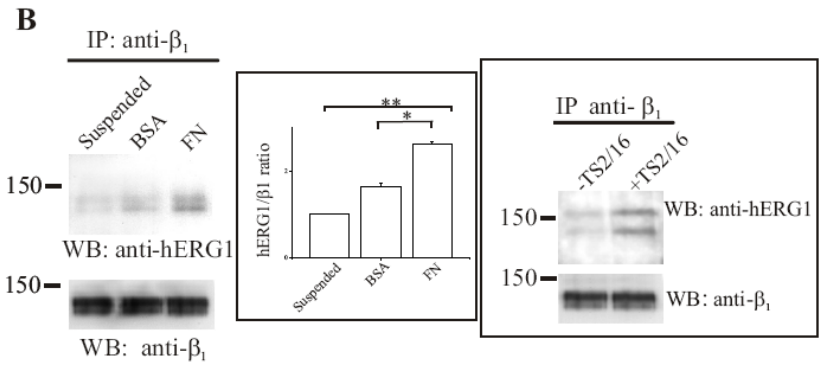

α
β
integrin
PIP2
PLCg
IP3
DAG
PKC
Grb7
Graf
Rho
P
Fyn
Talin
Paxillin
FAK
Src
a-actinin
Actin
Tensin
Actin stress fibers
PI3K
PTEN
PIP2
PIP3
PDK
ILK
PKB/Akt
Grb2
Sos
Ras
p130Cas
Crk
C3G
Raf1
Rac
ASK1
MEK1/2
JNK
ERK1/2
PAK
NF-kB
Foxo
14-3-3
Bad
Bcl-xL
Apaf-1
Casp9
Casp3
TSC1/2
mTOR
4E-BP1
eIF4E
Protein synthesis
nucleus
transcription
+ / -
Migration
Proliferation
Differentiation / Survival
Apoptosis

Integrin-channel complex: hERG1/β1









Cherubini A. et al., Mol.Biol.Cell, 2005

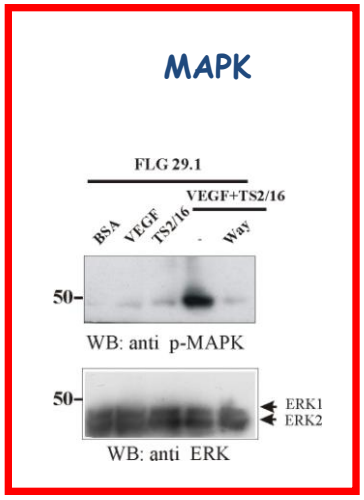
blood

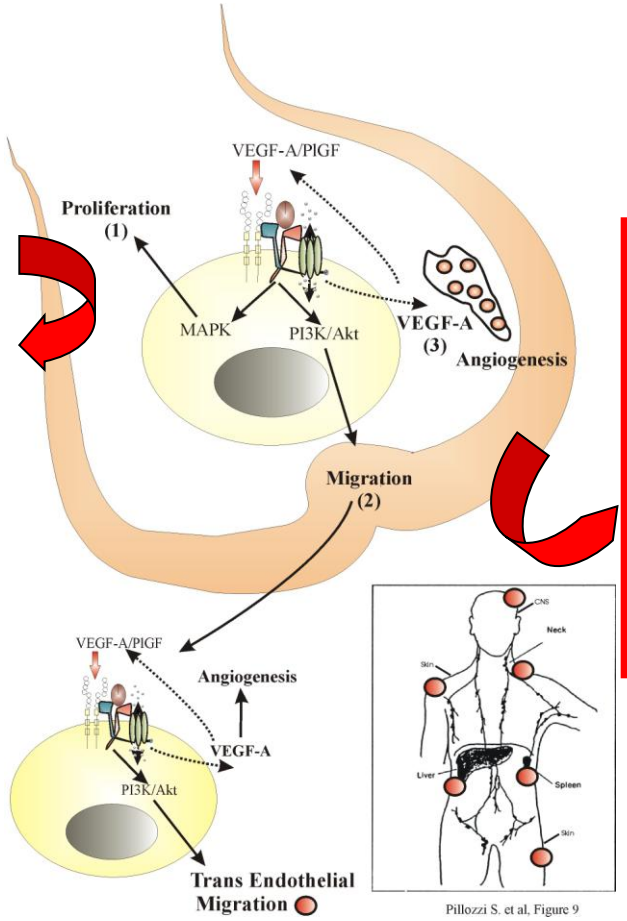
2007 110: 1238-1250
Prepublished online Apr 9, 2007;
doi:10.1182/blood-2006-02-003772

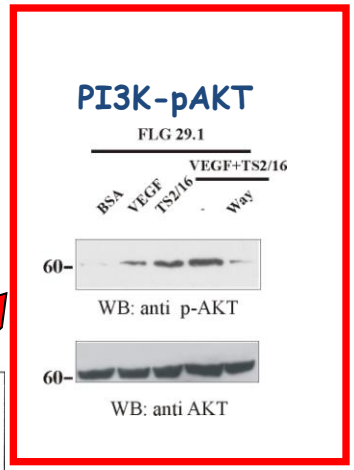
VEGFR-1 (FLT-1), ß1 integrin, and hERG K+ channel for a macromolecular signaling complex in acute myeloid leukemia: role in cell migration and clinical outcome

Serena Pillozzi, Maria Felice Brizzi, Pietro Antonio Bernabei, Benedetta Bartolozzi, Roberto Caporale, Venere Basile, Vieri Boddi, Luigi Pegoraro, Andrea Becchetti and Annarosa Arcangeli

Serena Pillozzi







blood

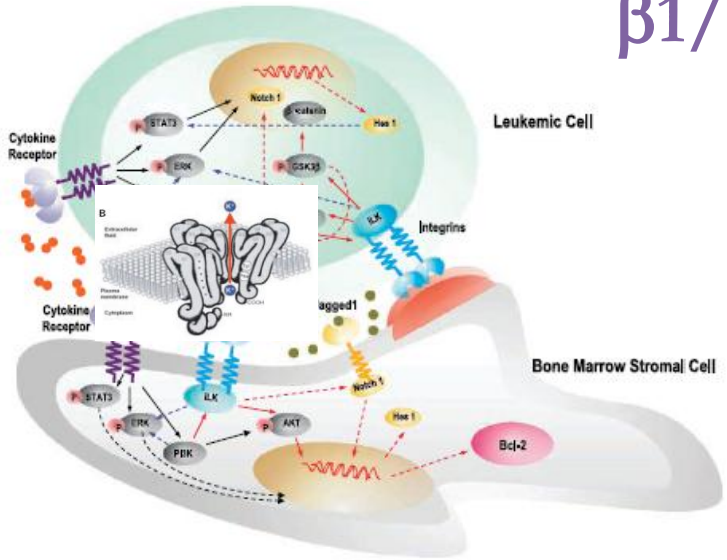
2011 117: 902-914
Prepublished online November 3, 2010;
doi:10.1182/blood-2010-01-262691

Chemotherapy resistance in acute lymphoblastic leukemia requires hERG1 channels and is overcome by hERG1 blockers

Serena Pillozzi, Marika Masselli, Emanuele De Lorenzo, Benedetta Accordi, Emanuele Cilia, Olivia Crociani, Amedeo Amedei, Marinella Veltroni, Massimo D'Amico, Giuseppe Basso, Andrea Becchetti, Dario Campana and Annarosa Arcangeli

Serena Pillozzi

β1/hERG1/CXCR4 complex



SURVIVAL (ILK, AKT)

The hERG1/β1 integrin complex in CRC

SCIENTIFIC REPORTS

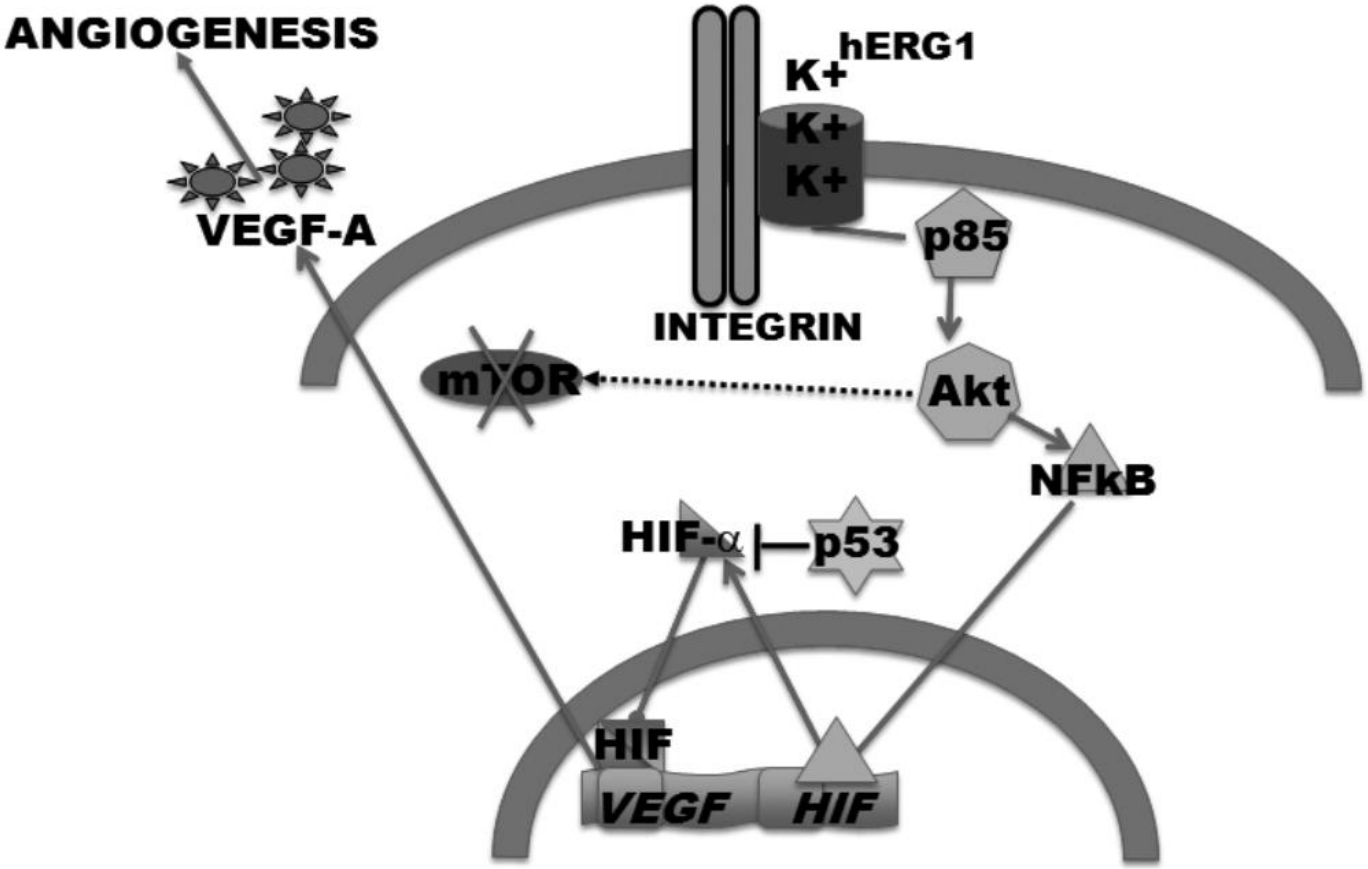
OPEN

SUBJECT AREAS:
COLORECTAL CANCER
INTEGRIN SIGNALLING
TUMOUR ANGIOGENESIS
ION CHANNEL SIGNALLING

hERG1 channels modulate integrin signaling to trigger angiogenesis and tumor progression in colorectal cancer

Olivia Crociani[1], Francesca Zanieri[1], Serena Pillozzi[1], Elena Lastraioli[1], Matteo Stefanini[1], Antonella Fiore[1], Angelo Fortunato[1], Massimo D'Amico[1], Marika Masselli[1], Emanuele De Lorenzo[1], Luca Gasparoli[1], Martina Chiu[2], Ovidio Bussolati[2], Andrea Becchetti[3] & Annarosa Arcangeli[1]

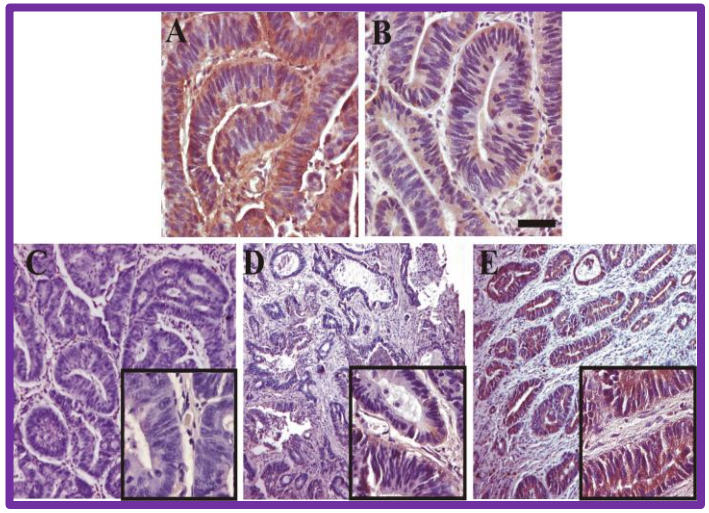
The hERG1/β1 integrin pathway in CRC



- Molecular data (RQ-PCR)
- Immunohistochemistry (IHC) data
- Flow cytometry data
- Functional data

hERG1: novel cancer biomarker

COLORECTAL CANCER

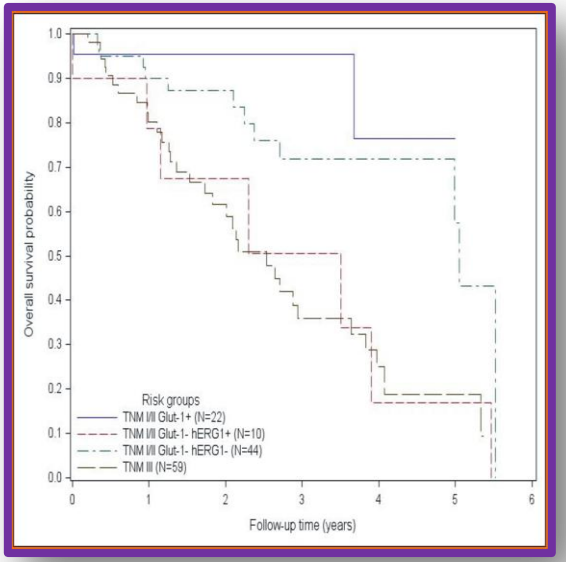


Translational Oncology
www.transonc.com
Volume 5 Number 2 April 2012 pp. 105–112

hERG1 Channels and Glut-1 as Independent Prognostic Indicators of Worse Outcome in Stage I and II Colorectal Cancer: A Pilot Study[1]

Elena Lastraioli*, Lapo Bencini†, Elisa Bianchini‡, Maria Raffaella Romoli*, Olivia Crociani*, Elisa Giommoni§, Luca Messerini¶, Silvia Gasperoni§, Renato Moretti†, Francesco Di Costanzo§, Luca Boni‡,2 and Annarosa Arcangeli*,2

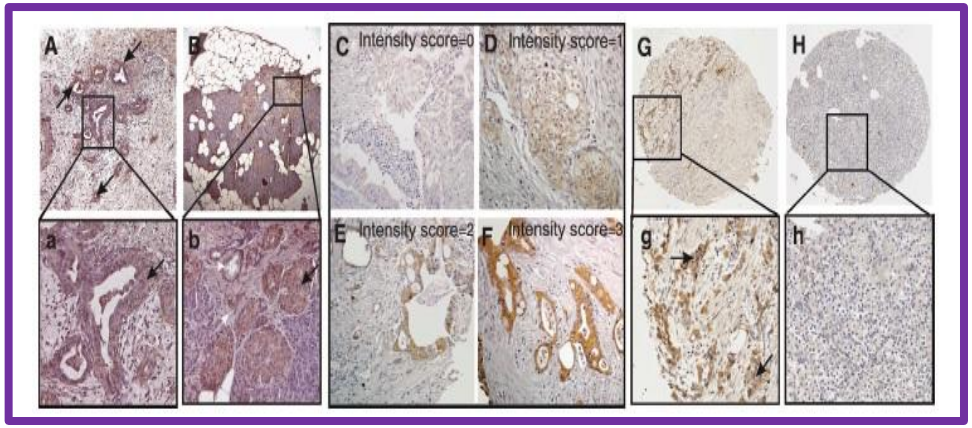
*Department of Experimental Pathology and Oncology, University of Florence, Istituto Toscano Tumori, Florence, Italy; †General Surgery and Surgical Oncology, Azienda Ospedaliero-Universitaria, Careggi, Florence, Italy; ‡Clinical Trials Coordinating Center, Azienda Ospedaliero-Universitaria, Careggi, Florence, Italy; §Medical Oncology, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy; ¶Department of Human Pathology and Oncology, University of Florence, Florence, Italy



hERG1 positivity with Glut-1 negativity identifies a patient group with poor prognosis within stage I-II CRC.

PANCREATIC CANCER (PDAC)

- ✓ **hERG1 is an independent prognostic factor in PDAC (hERG1 positive patients have a worse prognosis)**



BJC

FULL PAPER

British Journal of Cancer (2015), 1–12 | doi: 10.1038/bjc.2015.28

Keywords: pancreatic ductal adenocarcinoma (PDAC); hERG1 potassium channels; EGF-R; prognosis; molecular-imaging

hERG1 channels drive tumour malignancy and may serve as prognostic factor in pancreatic ductal adenocarcinoma

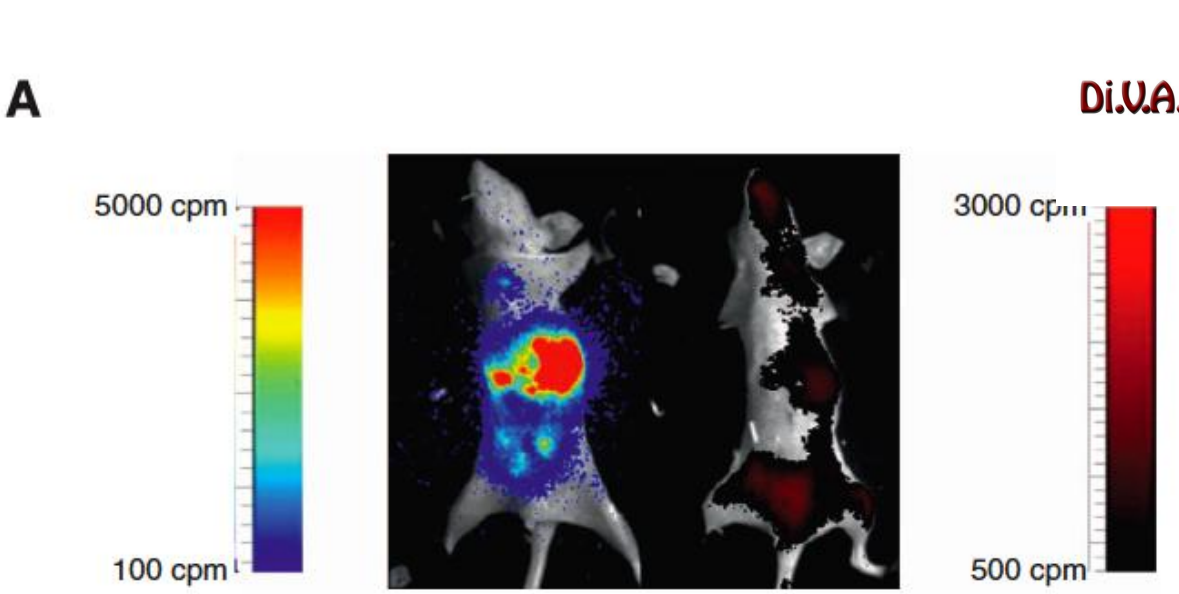
E Lastraioli[1,10], G Perrone[2,10], A Sette[1], A Fiore[1], O Crociani[1], S Manoli[1,11], M D'Amico[1], M Masselli[1], J Iorio[1], M Callea[2], D Borzomati[3], G Nappo[3], F Bartolozzi[4], D Santini[5], L Bencini[6], M Farsi[6], L Boni[7], F Di Costanzo[8], A Schwab[9], A O Muda[2], R Coppola[3,10] and A Arcangeli*[,1,10]

Table 2. Univariate and multivariate overall survival analyses and cumulative 1-year overall survival in stage I and II patients

			Univariate analysis			Final multivariate model	
Variable	*n*	*n* failed	Cumulative proportion 1-year survival	Hazard ratio (95% CI)	LR test (*P* value)	Hazard ratio (95% CI)	LR test (*P* value)
Category							
Gender							
Female	19	15	0.684	1 (ref.)	0.869		
Male	20	16	0.700	0.94 (0.46–1.92)			
hERG1 test							
Negative	17	12	0.882	1 (ref.)	**0.029***	1 (ref.)	**0.049***
Positive	22	19	0.545	2.23 (1.07–4.66)		2.12 (1.01–4.48)	
EGF-R test							
Negative	14	8	0.677	1 (ref.)	0.195		
Positive	25	16	0.45	1.75 (0.74–4.14)			
hERG1 and EGF-R test							
Both negative	9	6	0.889	1 (ref.)	0.067		
Both positive	17	15	0.529	2.85 (1.09–7.49)			
One positive	13	10	0.769	1.47 (0.53–4.07)			
TNM stage							
I	16	10	0.75	1 (ref.)	**0.049***	1 (ref.)	0.085
II	23	21	0.652	2.11 (0.98–4.56)		2.00 (0.91–4.41)	
Grading							
Grade 1	3	2	0.667	1 (ref.)	0.461		
Grade 2	22	17	0.682	1.59 (0.36–6.92)			
Grade 3	14	12	0.714	2.24 (0.49–10.18)			
Ki67							
<20%	22	16	0.727	1 (ref.)	0.346		
≥20%	9	8	0.667	1.53 (0.65–3.63)			

Abbreviations: CI = confidence interval; EGF-R = Epidermal Growth Factor Receptor; hERG1 = human ether a go-go related gene 1; LR = log rank test. Significant associations ($P<0.05$) are indicated in bold and marked with *.

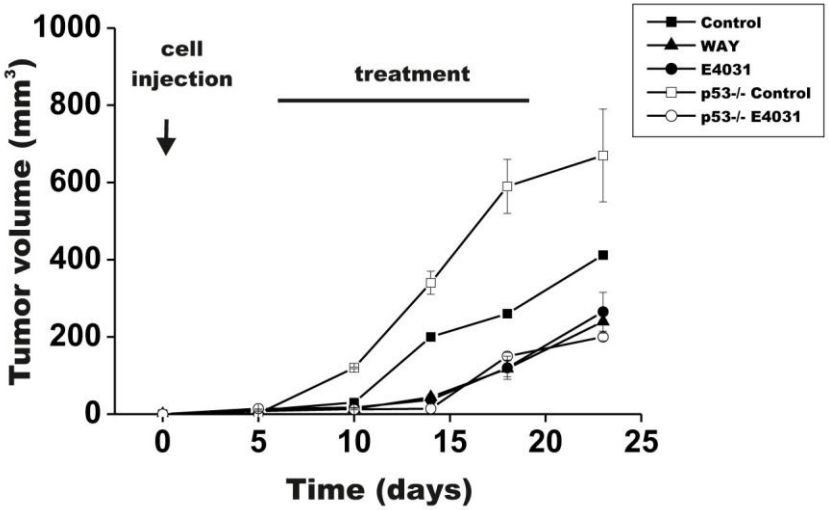
Use of anti-hERG1 Mab in vivo

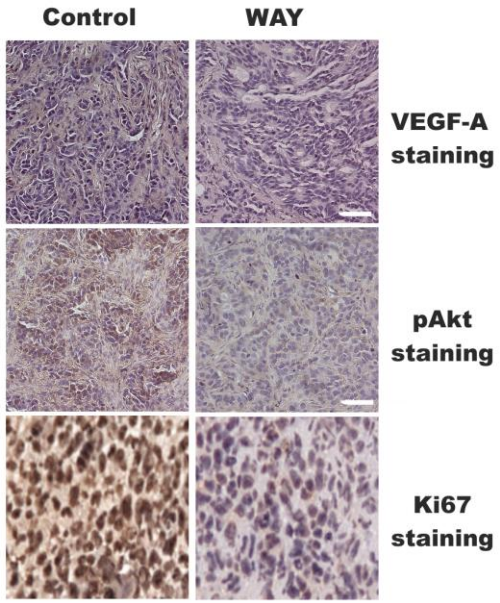


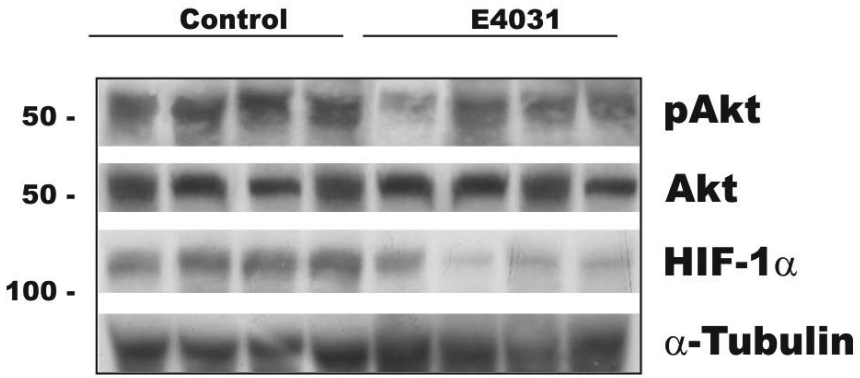
hERG1: novel therapeutic target in oncology

Di.V.A.L. TOSCANA

Targeting hERG1 in CRC: in vivo studies (s.c.)







hERG1 targeting: orthotopic CRC model

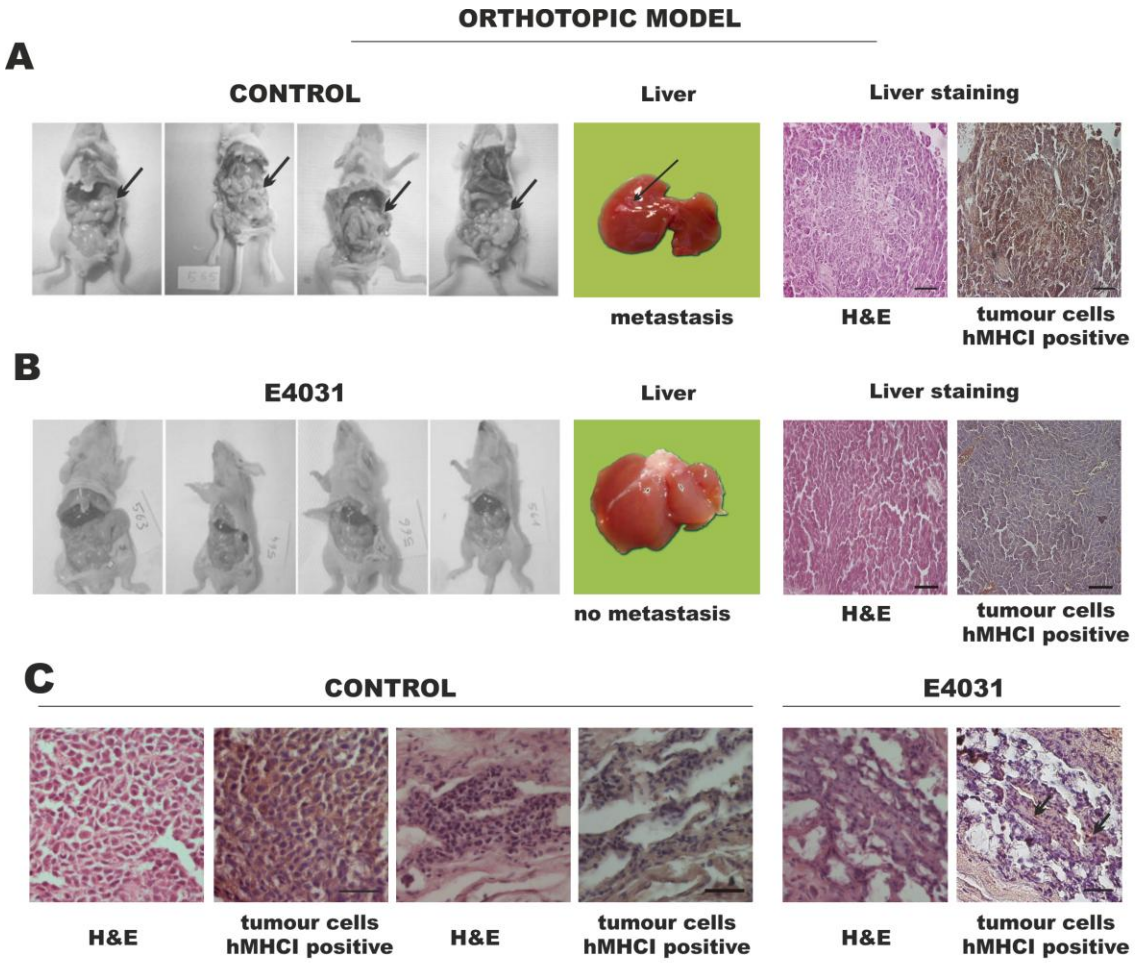


Table 1 | Quantitative evaluation of local tumor growth, invasion, distant metastases and complications in control and E4031-treated mice (20 mg/Kg). (+++ = high number of neoplastic masses, ++ = several neoplastic masses, + = few neoplastic masses)

ORTOTHOPIC MODEL		
Local tumor growth	Control	E4031
Coecum	+++	-
Invasion		
Intestin	++	-
Metastasis		
Peritoneum	++	-
Diaphragm	+++	-
Liver	++	-
Spleen	++	-
Kidneys	+	-
Complications		
Ascites	++	-

hERG1 targeting: CRC metastasis model

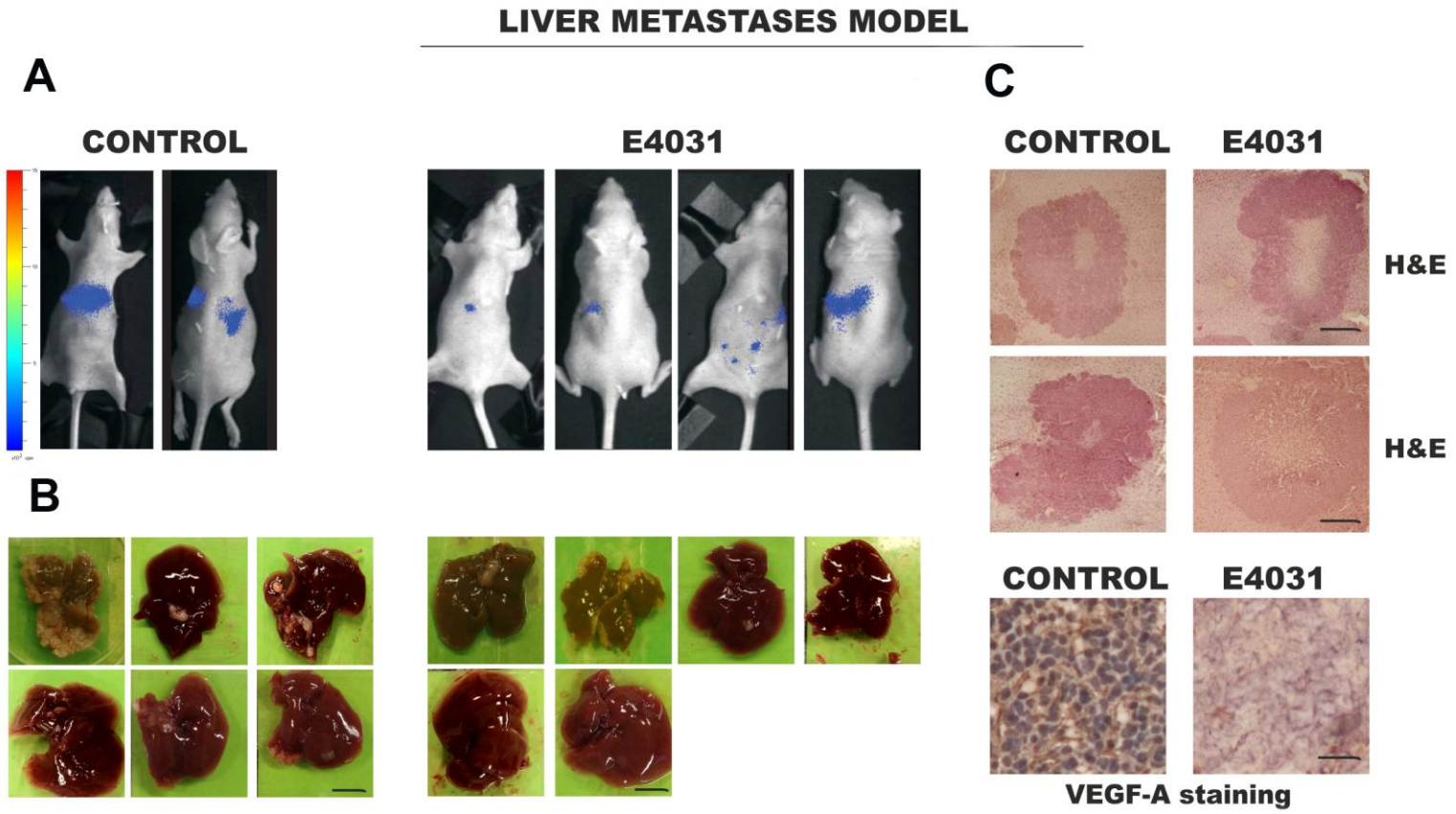
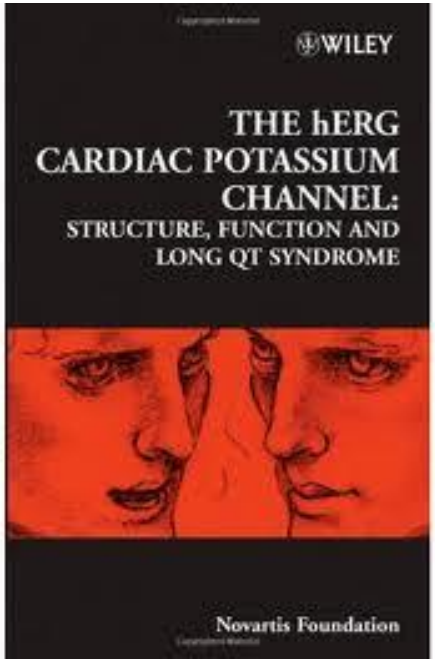
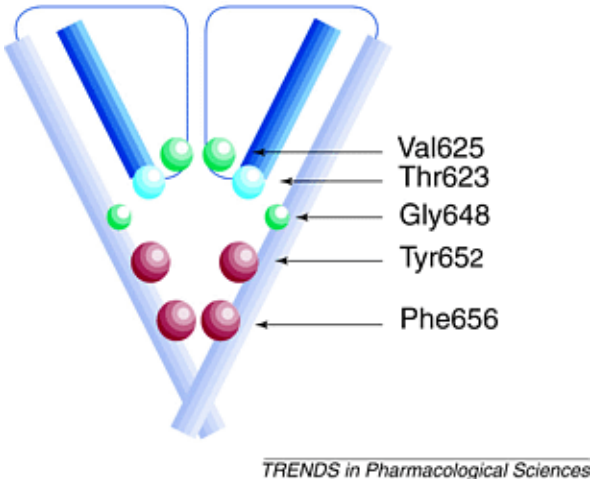


Table 2 | Number of hepatic macroscopic and microscopic lesions as well as % of necrotic area of livers reported in Fig. 7E–F. Further descriptions are reported in Supplementary Information

LIVER METASTASES MODEL		
Metastases	Control	E4031
Macroscopic metastases	**19.3 ± 3.50**	**9.85 ± 4.80**
Microscopic metastases (number/ microscopic field)	**4.0 ± 0.70**	**1.2 ± 0.14**
% necrotic area/total metastases area	**2.1 ± 0.30**	**8.55 ± 0.36**

hERG1 is considered an antitarget!
hERG1 blockers can induce LQT syndrome and TdP





TRENDS in Pharmacological Sciences

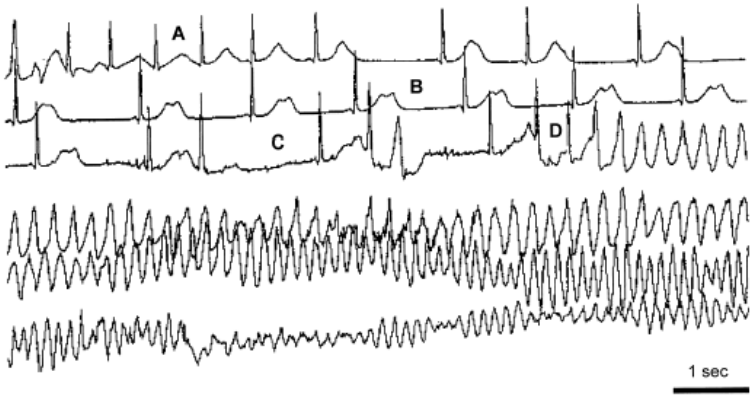
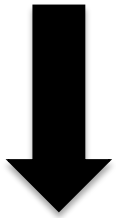


Fig. 2 Part of a continuous single-channel Holter recording from a patient with long QT syndrome. In this record, the characteristic prolonged QT interval (A), followed by giant late-repolarization 'T-wave humps' (B), led to premature beats with a bigeminal pattern with short-long-short sequences of R–R intervals (C) before onset of *torsade de pointes* (D). The episode progressed into ventricular fibrillation before spontaneously resolving into sinus rhythm; the patient was later treated successfully with pacing and beta-blockers (Reproduced with permission from Benhorin and Medina.[39])

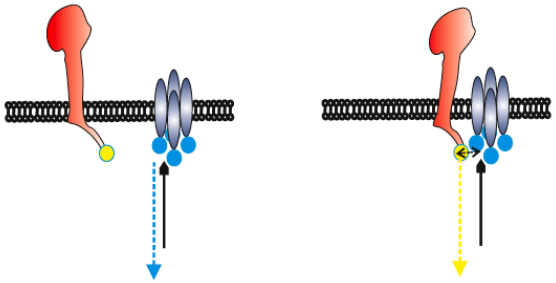
Strategies to target hERG1 in cancer and avoid cardiotoxicity

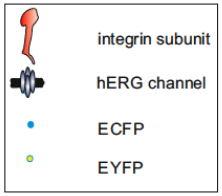


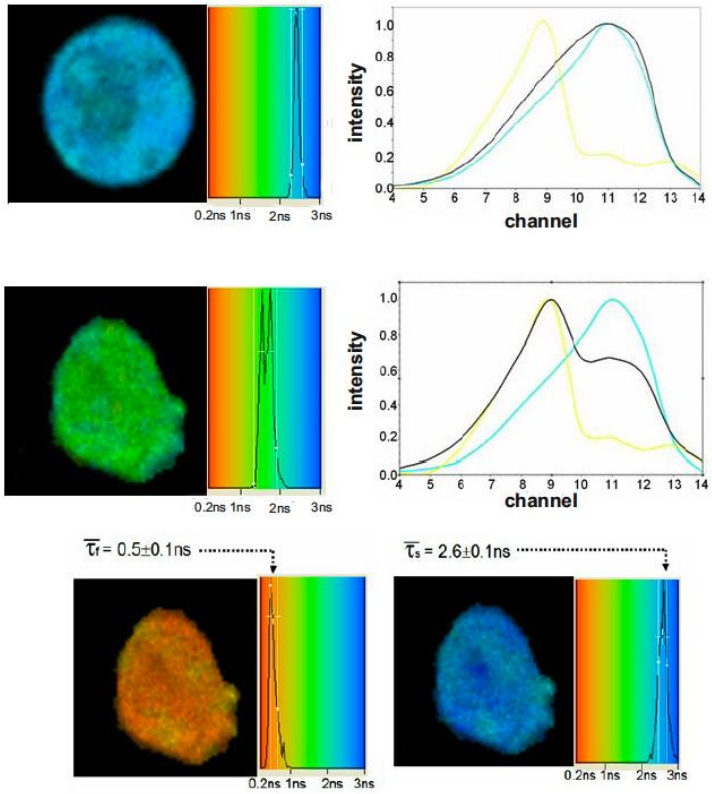
Differences between “cardiac” and “tumour” hERG1

- interaction with adhesion receptors of the integrin family
- prevalence of hERG1B isoform in tumors (leukemias)

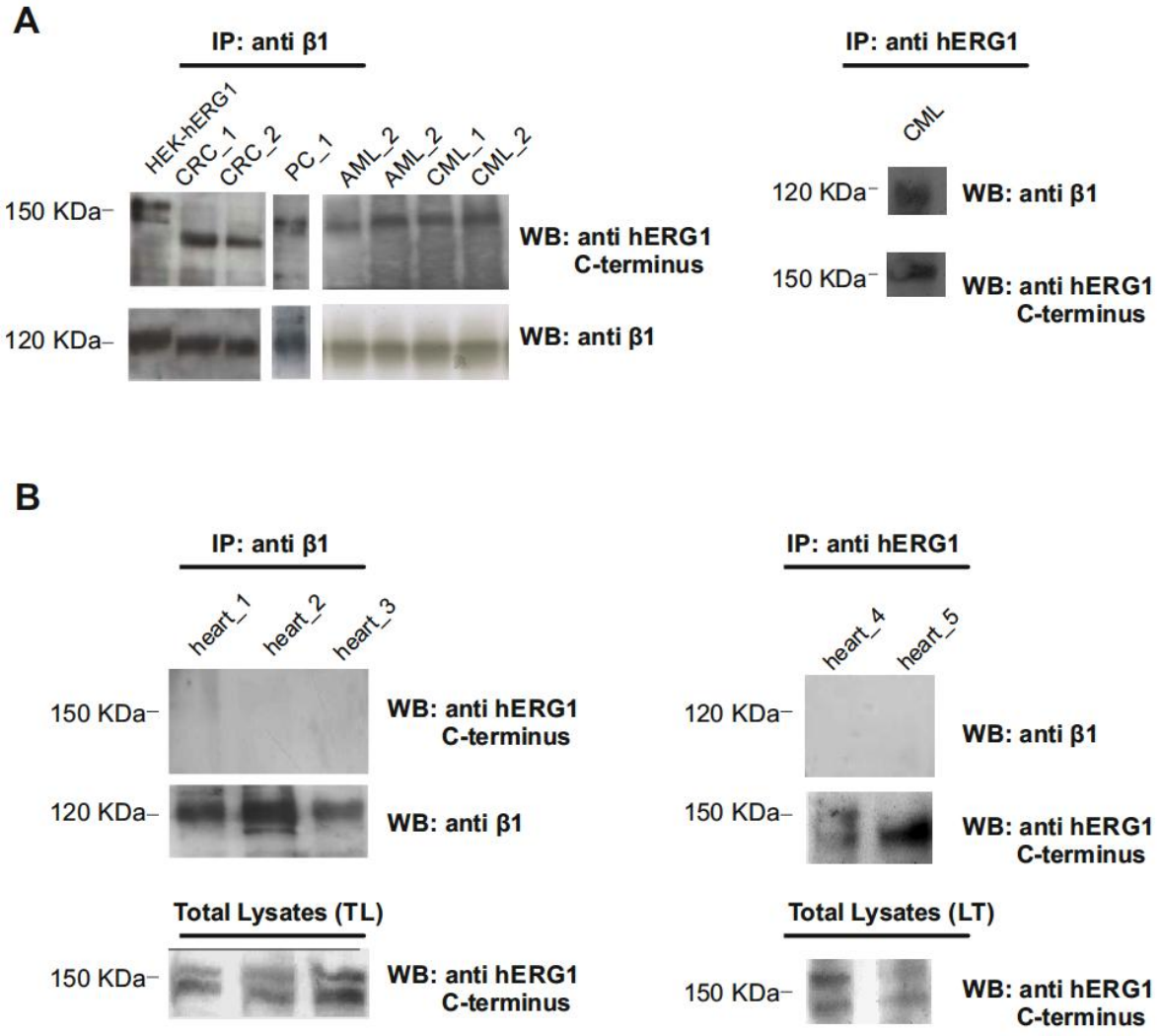
hERG1 and β1 integrin interact directly: intermolecular distance < 1nm (FRET experiments)







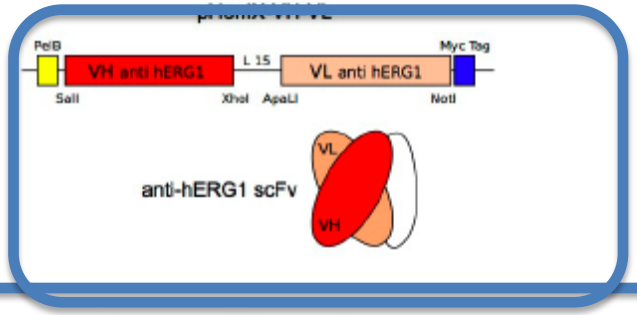
The hERG1/β1 complex occurs in cancers but NOT in the heart

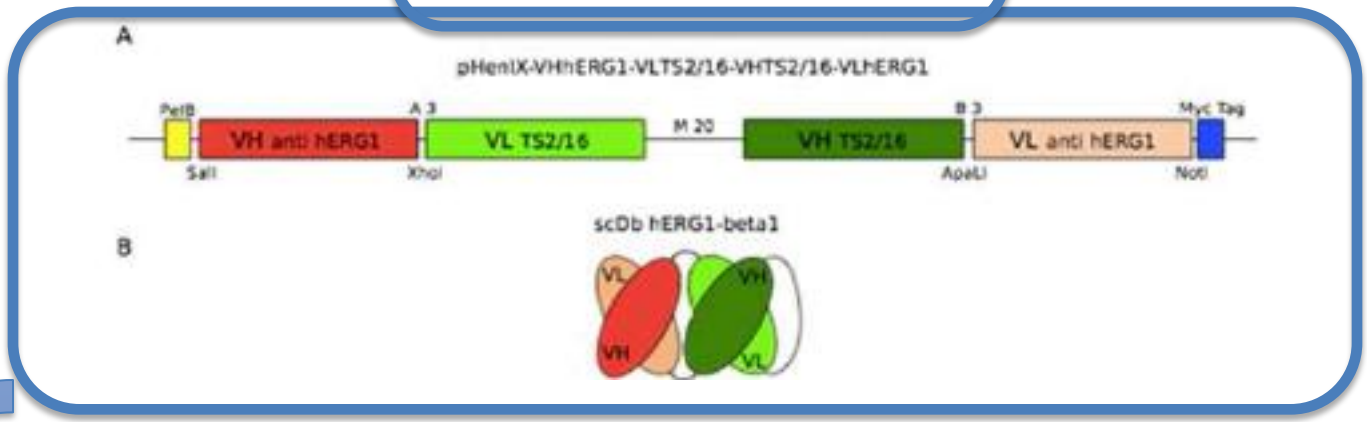


Conclusions

- hERG1 directly complexes with integrins (β1 subunit)
- The hERG1/β1complex occurs only in tumor cells NOT in the heart
- The hERG1/β1complex triggers intracellular signaling
- **Targeting the hERG1/β1complex for cancer therapy?**

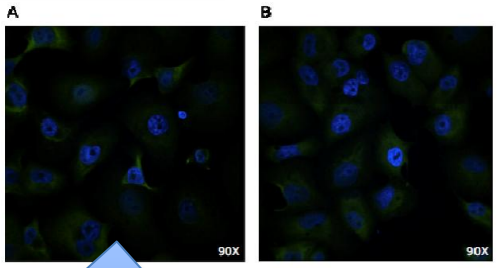
Bi-functional antibody



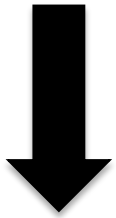


PP9K

P. Pastoris



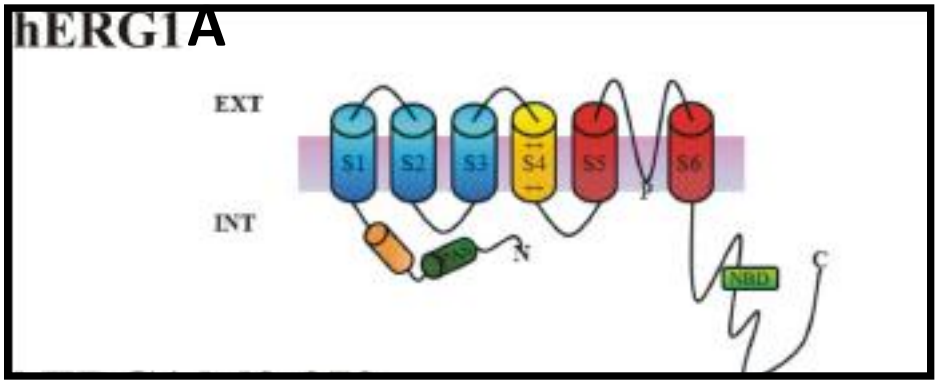
Strategies to target hERG1 in cancer and avoid cardiotoxicity

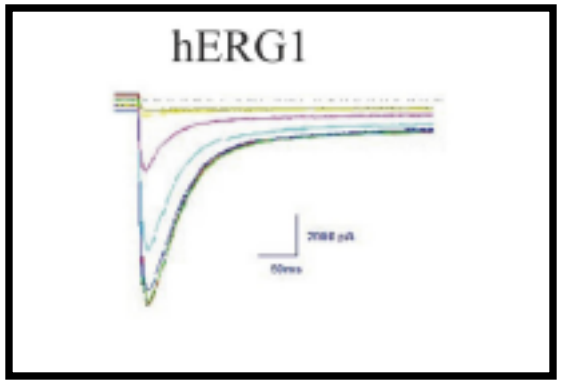


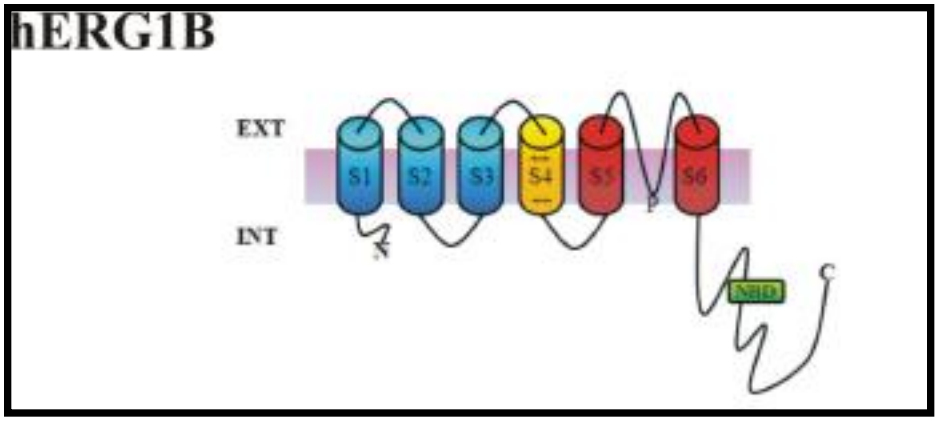
Differences between “cardiac” and “tumour” hERG1

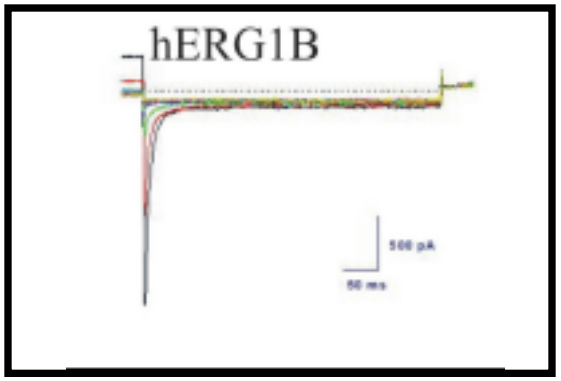
- interaction with integrin receptors (cell adhesion)
- **prevalence of hERG1B isoform in tumors (leukemias)**

hERG1B in cancer cells









hERG1B in leukemias vs heart

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Cell Cycle-dependent Expression of HERG1 and HERG1B Isoforms in Tumor Cells*

Received for publication, October 22, 2002, and in revised form, November 12, 2002
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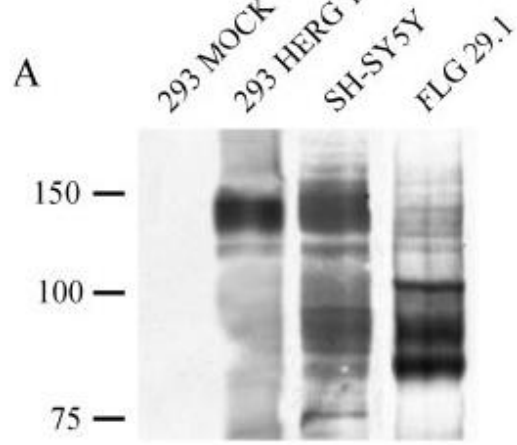

OPEN

Leukemia (2014), 1–4

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LETTER TO THE EDITOR

Differential expression of *hERG1A* and *hERG1B* genes in pediatric acute lymphoblastic leukemia identifies different prognostic subgroups

Pediatric Hematology and Oncology, 32:182–192, 2015

ISSN: 0888-0018 print / 1521-0669 online
DOI: 10.3109/08880018.2014.949941

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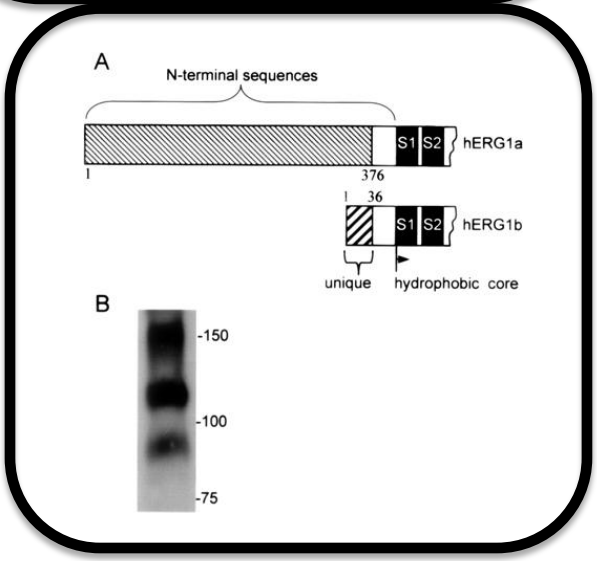
ORIGINAL ARTICLE

herg1b Expression as a Potential Specific Marker in Pediatric Acute Myeloid Leukemia Patients with HERG 897K/K Genotype

Merve Erdem,[1,*] Tugce Ayca Tekiner,[1,2] Arta Fejzullahu,[1,3] Gokce Akan,[4] Sema Anak,[5] Ebru Tugrul Saribeyoglu,[5] Ugur Ozbek,[6] and Fatmahan Atalar[1]

heart



Targeting hERG1B in leukemias

1521-0111/87/2/183–196$25.00
MOLECULAR PHARMACOLOGY

http://dx.doi.org/10.1124/mol.114.094920
Mol Pharmacol 87:183–196, February 2015

New Pyrimido-Indole Compound CD-160130 Preferentially Inhibits the K_V11.1B Isoform and Produces Antileukemic Effects without Cardiotoxicity

Luca Gasparoli, Massimo D'Amico, Marika Masselli, Serena Pillozzi, Rachel Caves, Rawan Khuwaileh, Wolfgang Tiedke, Kenneth Mugridge, Alessandro Pratesi, John S. Mitcheson, Giuseppe Basso, Andrea Becchetti, and Annarosa Arcangeli

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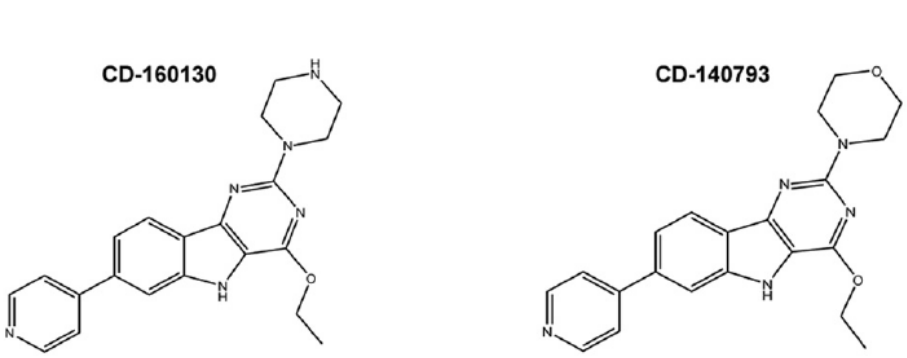
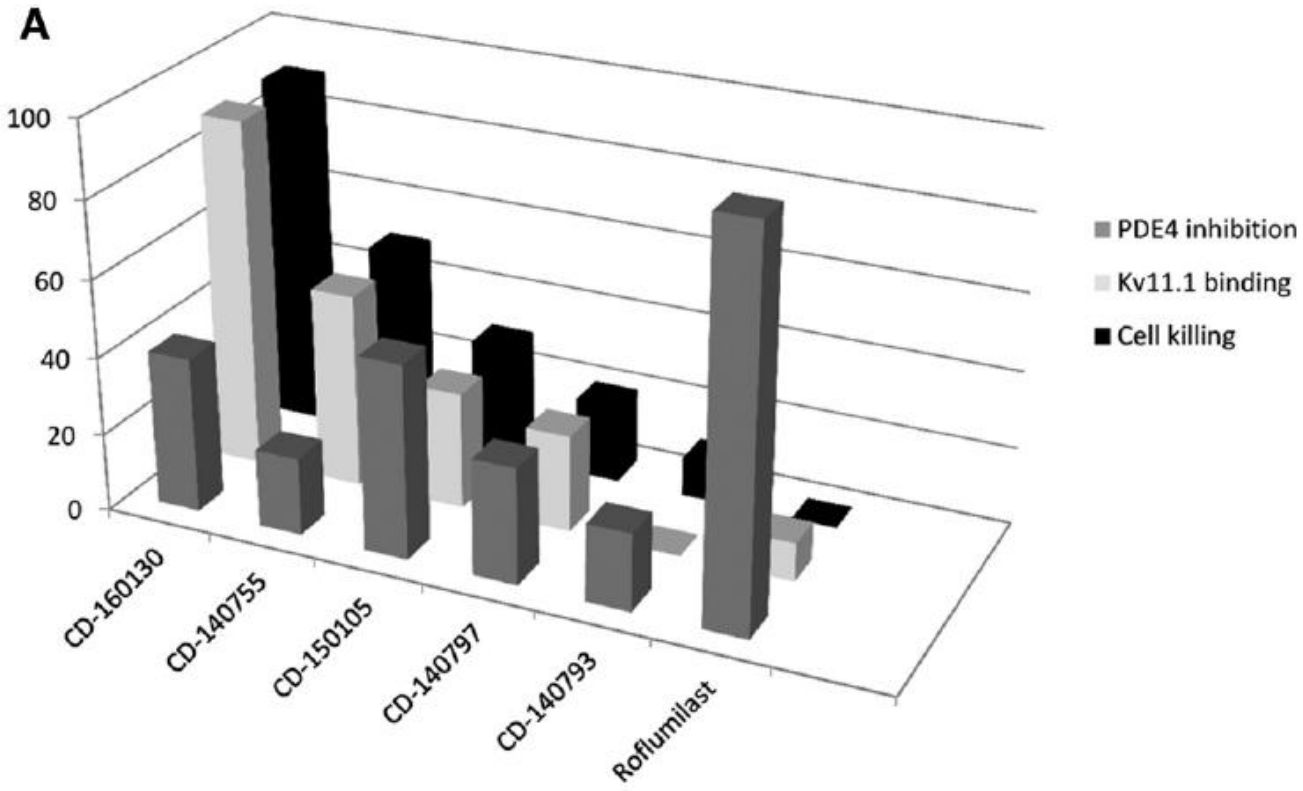
Received July 22, 2014; accepted November 19, 2014

BlackSwan Pharma

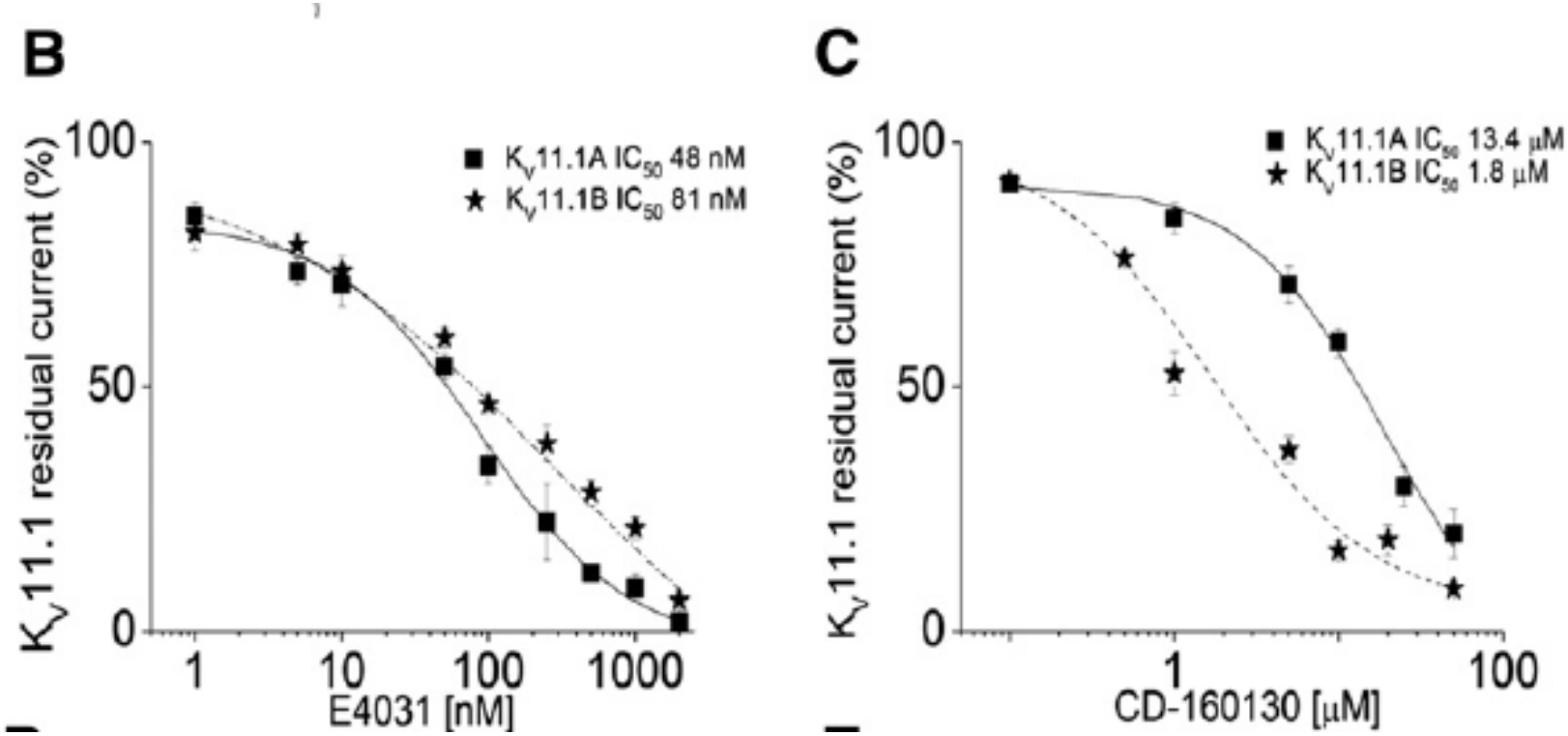
B



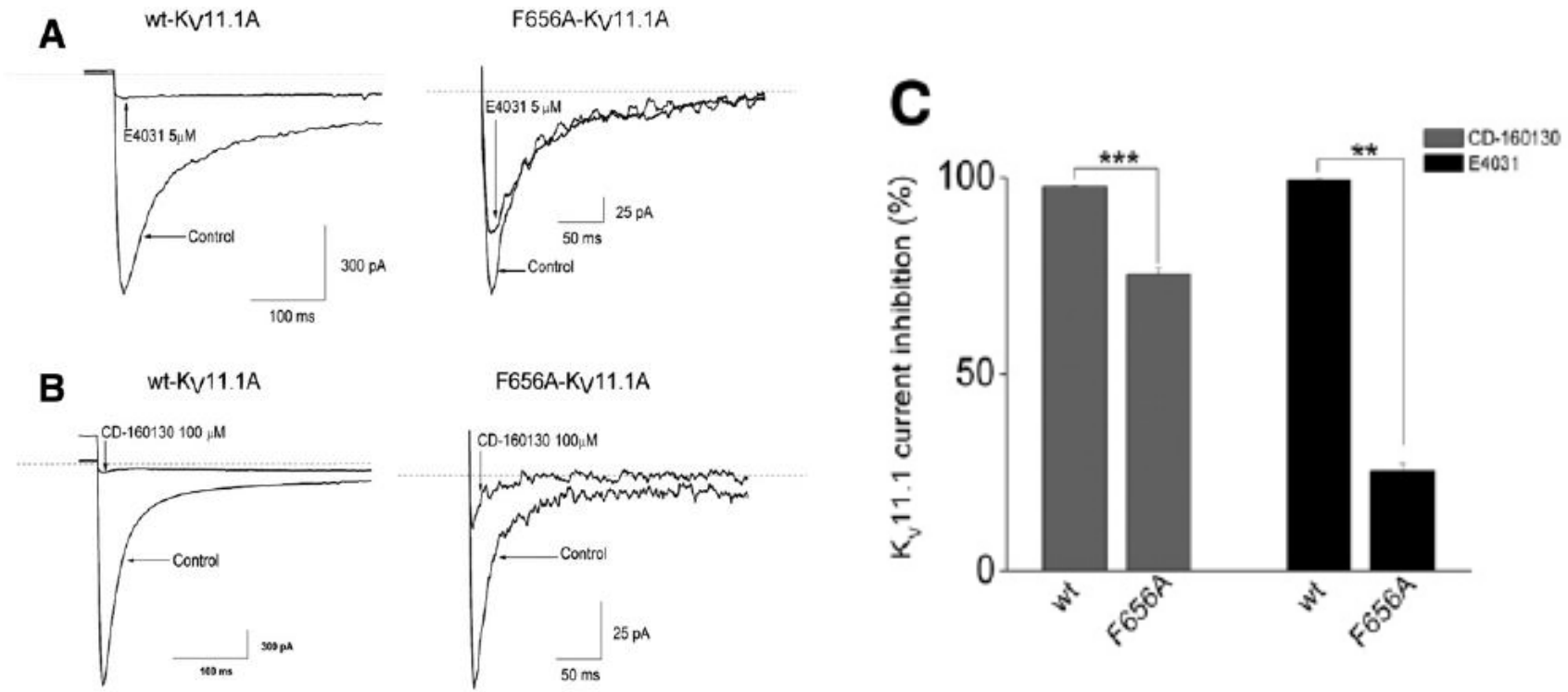
CD 160130 blocks hERG1



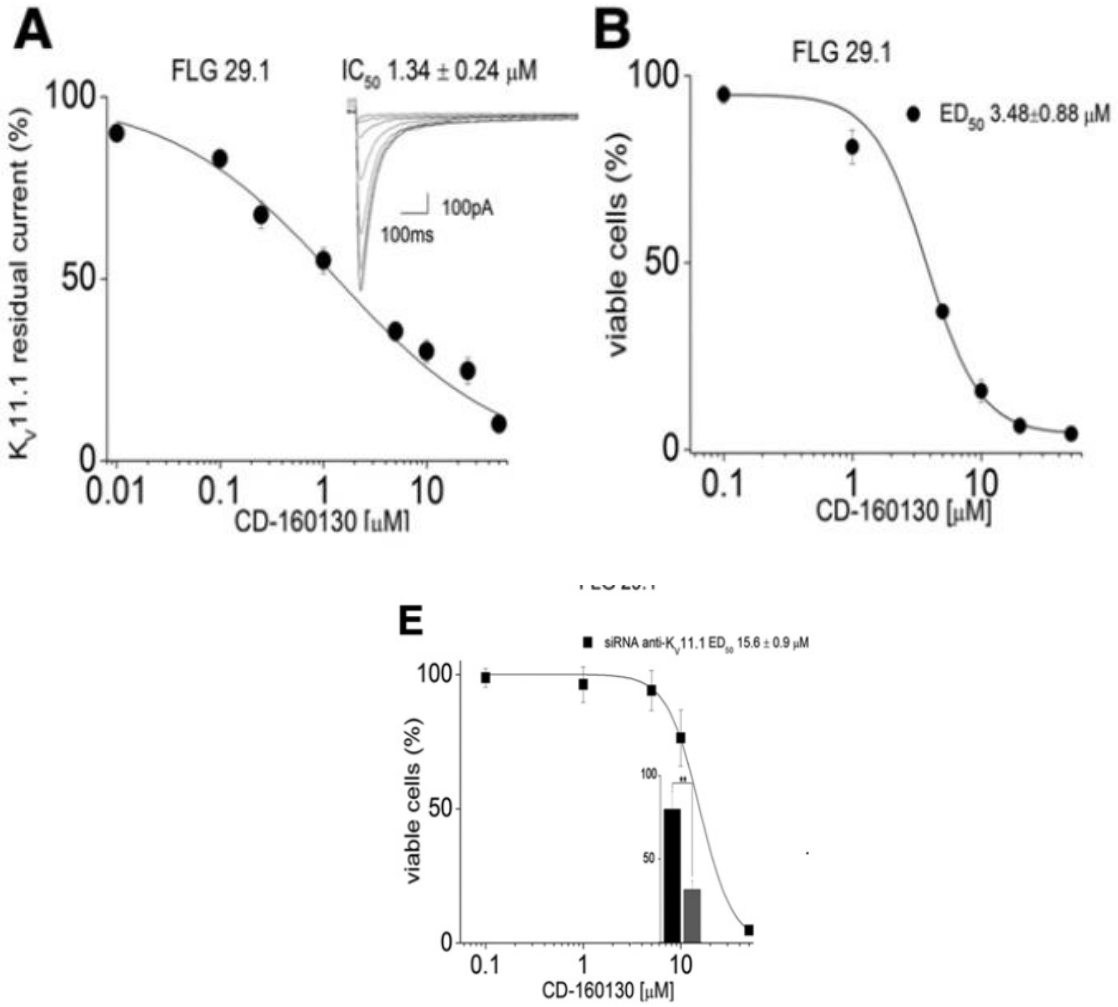
CD 160130 preferentially blocks hERG1B



CD-160130 does not bind the F656 “canonical” hERG1 binding site



CD-160130 blocks hERG1B in leukemias and has antileukemic effect (in vitro)



CD 160130 is cytotoxic for leukemias (in vitro)

PS/Cell Line	FAB (Immunophenotype)	Cytogenetics	*1B* Gene Expression	Mean ED_{50} (± S.E.M.) of CD-160130
			Arbitrary Units	μM
Myeloid primary samples and cell lines				
AML-1 (Pillozzi et al., 2007)	AML-M4 (CD13+, CD33+, CD14+, CD11b+, CD34+)	UNK	0.92 (1A: 12.20)	20% maximum killing at 50
AML-2 (Pillozzi et al., 2007)	AML-M1 (CD13+, CD34+, HLDRA+)	Complex	68.10 (1A: 18)	40.4 ± 11.2
KG-1	AML-M6 (CD34+, CD15+, Cd13+, HLA A30+, A31+, B35+)	Complex (Pelliccia et al., 2012)	0.62 (1A: 24.76)	7.6 ± 0.55
FLG 29.1	AML-M5 (CD9+, CD13+, CD32+, CD42b+, CD51+, CD54+, CD44+, CD61+, CD45+, CD31+)	polyploidy, 3p+	3413 (1A: 1086)	3.48 ± 0.88
HL60	AML-M2 (Dalton et al., 1988) (CD3−, CD13+, CD14−, CD15+, CD19−, CD33+, HLA-DR−)	Pseudodiploid	94.70 (1A: 13.70)	6.65 ± 0.26
NB4	AML-M3 (CD3−, CD4+, CD11b−, CD13+, CD14-, CD15+, CD19-, CD33+, CD34−, CD38+, HLA-DR−)	t(15;17)(q22;q11-12)	196.72 (1A: 80.44)	7.02 ± 0.31

CD 160130 is cytotoxic for leukemias (in vitro)

Lymphoid primary samples and cell lines				
B-ALL-1	L2 (early B) (CD34+, CD33+, CALLA+)	t(8;14)	6.68 (1A: 0.03)[a]	5.6 ± 1.5
T-ALL-1	L2 (T) (aberrant expression of CD34, CD117, and CD13)	UNK	5.11 (1A: 0.76)[b]	0.6 ± 0.2
REH	pro-B-ALL (CD3−, CD10+, CD13−, CD19+, CD34−, CD37−, CD38+, cyCD79a+, CD80−, CD138+, HLA-DR+, sm/cyIgG−, sm/cyIgM−, sm/cykappa−, sm/cylambda−)	t(12; 21)(p13;q22)	120 (1A: 6.5)	6.66 ± 0.22
697	pre-B-ALL (CD3−, CD10+, CD13−, CD19+, CD34−, CD37−, CD38+, CD80−, HLA-DR+, sm/cyIgG−, smIgM−, cyIgM+, sm/cykappa−, sm/cylambda−)	t(1;19)	1200 (1A:85)	3.78 ± 0.37
RS	pre-B-ALL-L2 (HLA DR+, CD9+, CD24+)	t(4;11)(q21; q23) and i(7q)	0.16 (1A: 0.005)	7.0 ± 0.2

CD 160130 is cytotoxic for leukemias (in vitro)

Primary Sample/Cell Line	Binet Stage	Gender	Cytogenetics	Mean EC_{50} (± S.D.) of CD-160130	Mean EC_{50} (± S.D.) of Fludarabine
				μM	μM
CLL-004	B	M	UNK	1.48 ± 0.55	0.56 ± 0.03
CLL-005	A	M	13q and 11q deletion	0.07 ± 0.03	0.49 ± 0.11
CLL-006	C	F	13q deletion	2.47 ± 0.39	0.49 ± 0.05
CLL-017	B	M	13q and 11q deletion	0.08 ± 0.02	0.17 ± 0.07
CLL-024	C	F	13q deletion	8.33 ± 0.29	ND
CLL-027	B	F	None	11.0 ± 1.50	4.55 ± 0.22
CLL-028	A	F	None	2.17 ± 0.02	ND
CLL-030	B	M	13q and 11q deletion	0.80 ± 0.05	ND
CLL-036	A	M	UNK	15.2 ± 3.74	ND
CLL-038	A	M	UNK	5.86 ± 0.58	5.63 ± 0.95
MEC-1	—	—	Near-diploid karyotype with 10% polyploidy-46(44-47)<2n>XY. t(1;6)(q22-23;p21); add(7)(q11); del(17)(p11)	5.36 ± 0.94	0.22 ± 0.03

….but not for normal human bone marrow cells

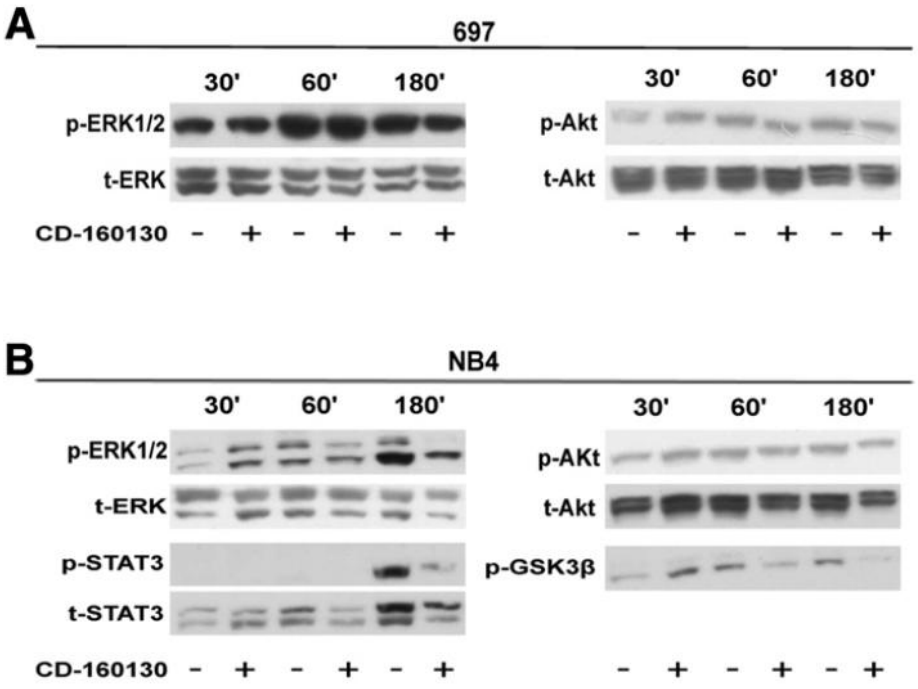
Evaluation of CD-160130 toxicity in healthy human bone marrow colonies.

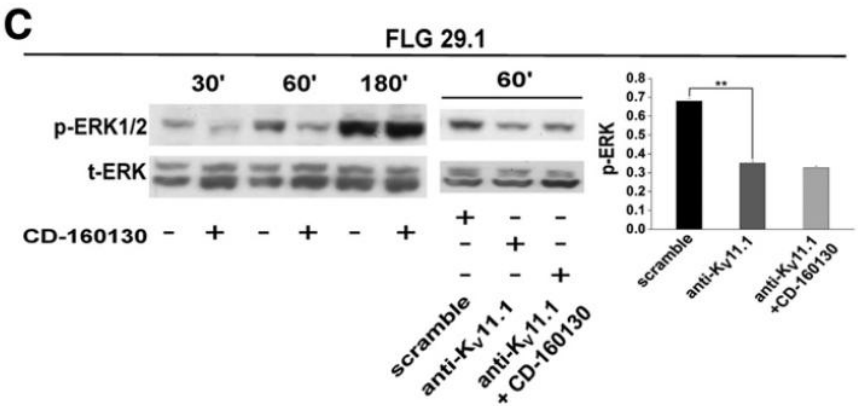
Results of the overall colony numbers obtained with clonogenic assay of three samples of healthy bone marrow treated with two different concentrations of CD-160130 (5 and 10 μM) are reported. The different colony fractions (CFU-GEMM, CFU-GM, CFU-G, CFU-M, CFU-E and BFU-E) for each group are reported. All the data were average ± S.E.M.

	Total CFU Number	CFU-GEMM Fraction	CFU-GM Fraction	CFU-G Fraction	CFU-M Fraction	BFU-E Fraction	CFU-E Fraction
	%	%	%	%	%	%	%
Control	100	5 ± 1	19.5 ± 2.5	15 ± 3	31 ± 3	7 ± 1	22.5 ± 1.5
CD-160130 (5 μM)	97 ± 5.2	5.5 ± 1.5	21.5 ± 2.5	14 ± 3	28.5 ± 2.5	6.5 ± 0.5	24 ± 2
CD-160130 (10 μM)	75 ± 8.8	4 ± 1	18 ± 1	13 ± 3	25 ± 1	9 ± 0	31 ± 1

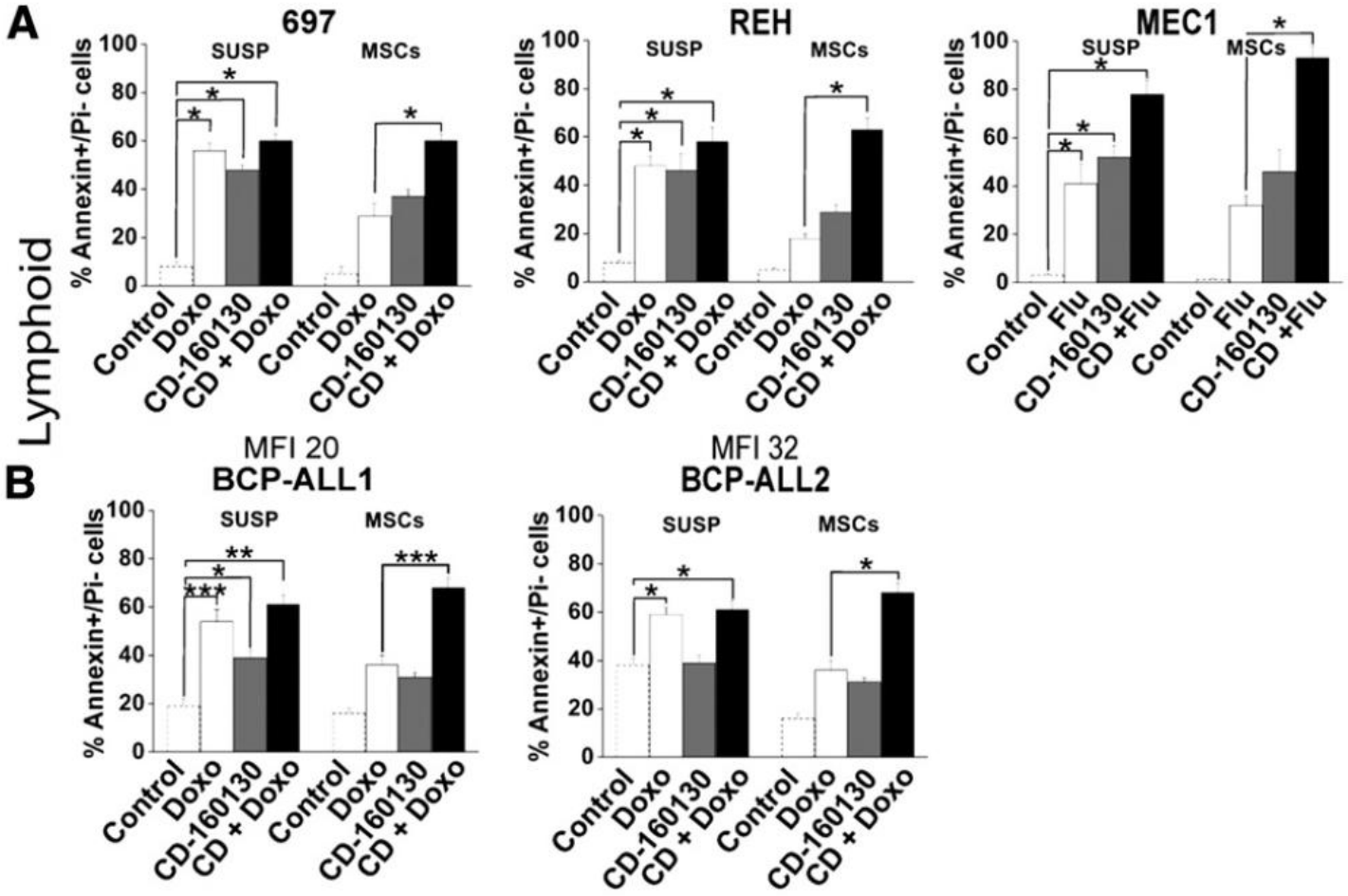
BFU, burst forming unit.

CD 160130 interpheres with signalling pathways (in vitro)

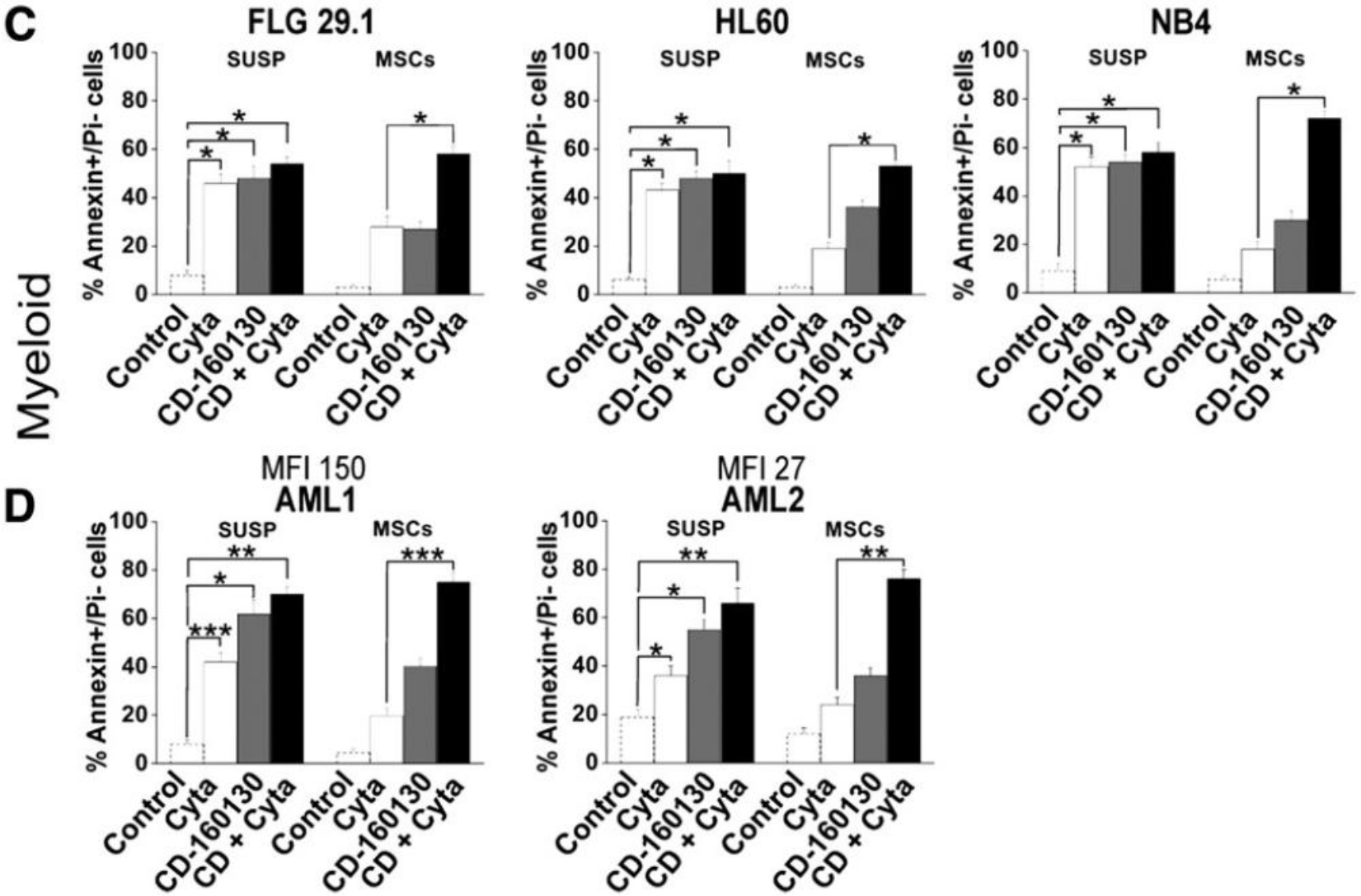




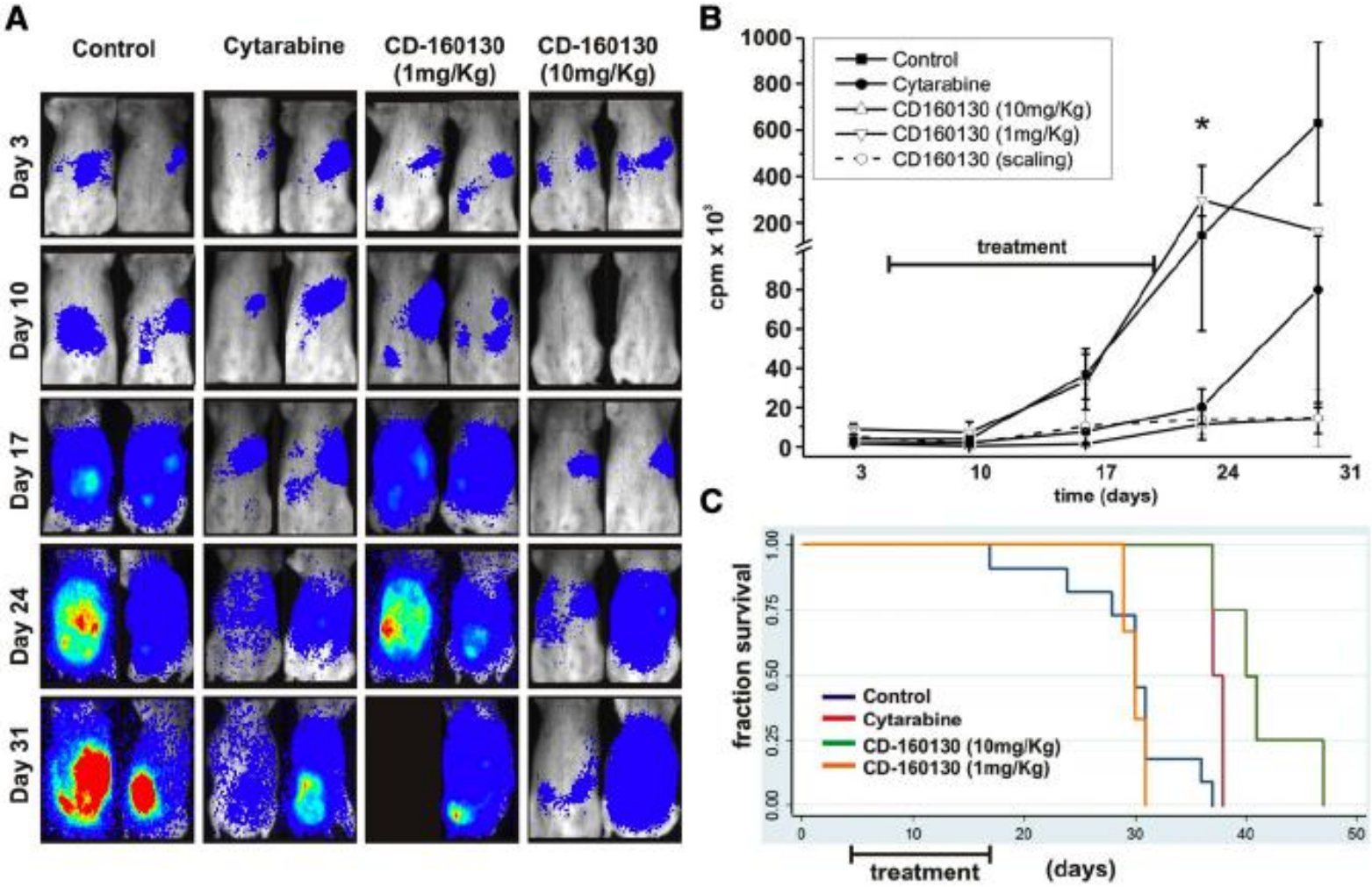
…..and overcomes chemoresistance (in vitro)
ALL



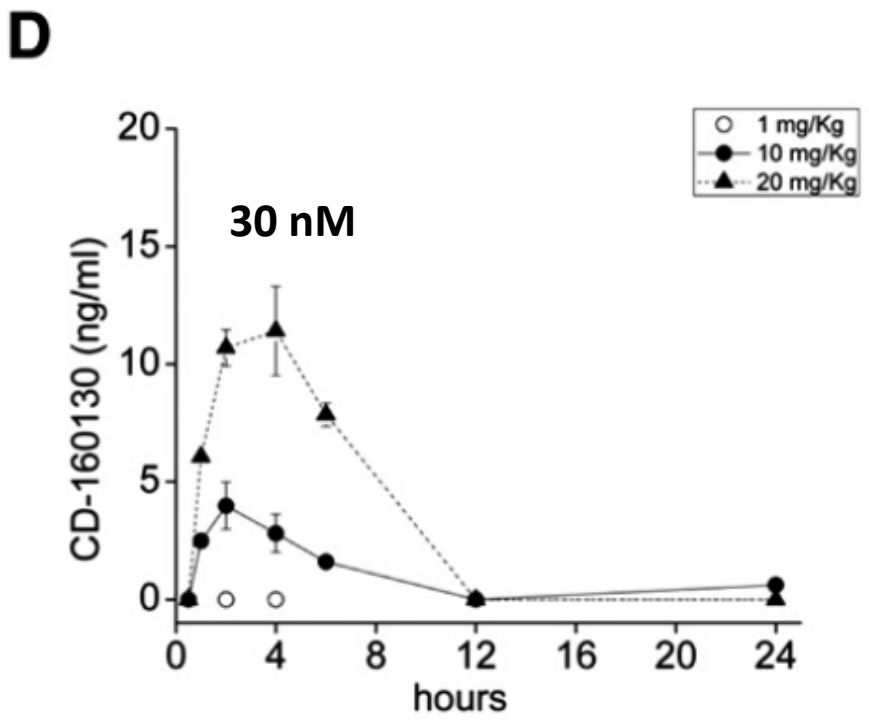
AML

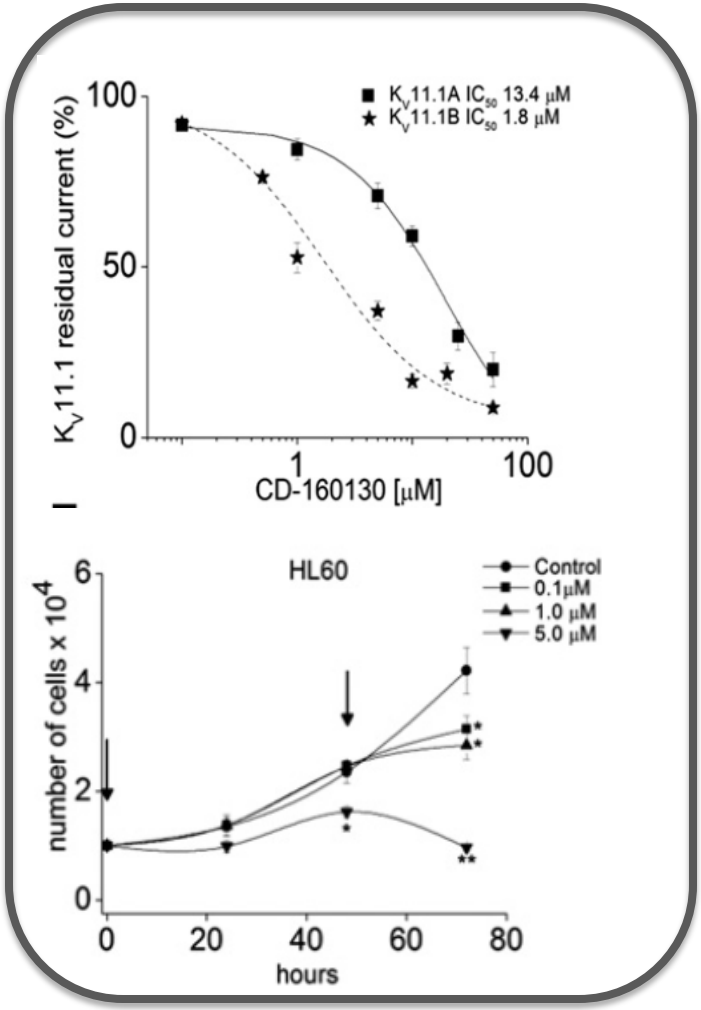

C
Myeloid
FLG 29.1
HL60
NB4
SUSP
MSCs
% Annexin+/Pi- cells
Control
Cyta
CD-160130
CD + Cyta
D
MFI 150
AML1
MFI 27
AML2

CD 160130 is cytotoxic for leukemias (in vivo)



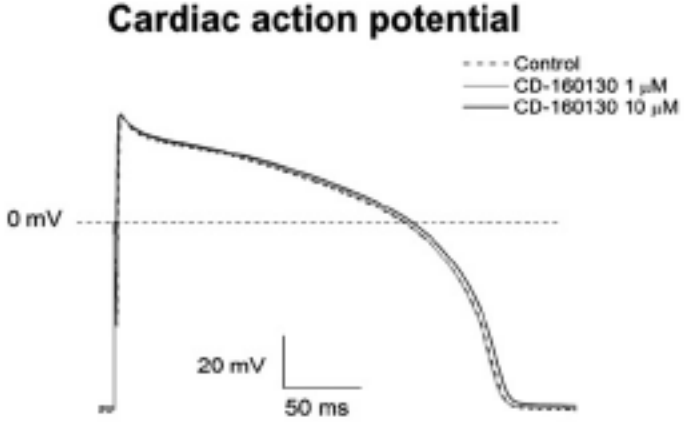
CD 160130 is orally available biodistribution (in vivo)





CD 160130 does not induce cardiac side effects (in guinea pigs)

A



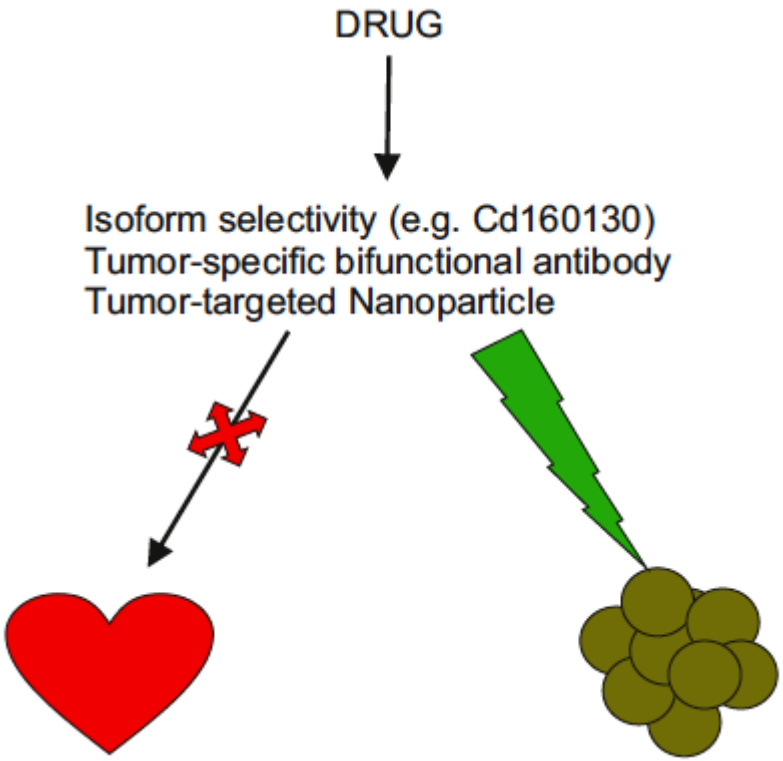
B

ECG parameters

CD-160130 (n=5) 10mg/kg	QT ± SEM (ms)	HR ± SEM (beat/min)	QTc ± SEM	ΔQTc (% vs Pre-drug)
Pre-drug	129.0 ± 4.2	237.1 ± 3.4	305.1 ± 7.5	-
0 min	131.4 ± 5.4	241.1 ± 5.2	308.4 ± 7.4	1.1 ± 3.5
5 min	127.5 ± 7.0	249.1 ± 1.1	298.8 ± 12.9	-2.1 ± 4.9
10 min	129.0 ± 5.8	240.5 ± 3.4	300.9 ± 11.2	-1.4 ± 4.4
15 min	128.0 ± 6.7	240.5 ± 2.8	298.6 ± 11.8	-2.2 ± 4.6
Sotalol (n=5) 3mg/kg	QT ± SEM (ms)	HR ± SEM (beat/min)	QTc ± SEM	ΔQTc (% vs Pre-drug)
Pre-drug	115.4 ± 3.6	240.3 ± 3.7	276.4 ± 6.8	-
0 min	115.4 ± 3.8	240.4 ± 5.1	273.7 ± 6.7	-1.0 ± 3.4
5 min	132.7 ± 4.0	240.4 ± 1.2	301.1 ± 6.2	8.9 ± 3.5
10 min	135.3 ± 4.2	235.0 ± 3.1	304.3 ± 6.1	10.1 ± 3.5
15 min	133.0 ± 5.8	232.2 ± 4.5	299.5 ± 8.0	8.4 ± 3.9

CD-160130

The characterization of CD-160130 opens the way to the development of compounds with a higher selectivity for the different Kv 11.1 isoforms, accompanied by inhibitory action on the chemotherapy resistant leukemia forms and negligible QT liability



Arcangeli A. and Becchetti A. Drug Resistance Updates, 2015

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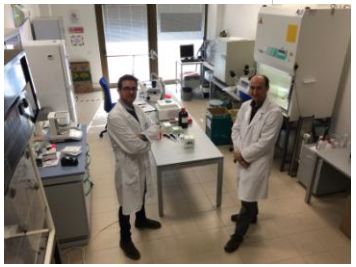
Prof.Andrea Becchetti and Prof.E.Wanke
University of Milano Bicocca, Italy



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