Ion channels: novel biomarkers and therapeutic targets in cancer

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Department of Experimental and Clinical Medicine
University of Florence
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
Review

Ion channel expression as promising cancer biomarker

Elena Lastraioi, Jessica Iorio, Annarosa Arcangeli

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

Figure 1
Targeting Ion Channels in Cancer: A Novel Frontier in Antineoplastic Therapy

A. Arcangeli*,1, O. Crociani1, E. Lastraioli1, A. Masi1, S. Pillozzi1 and A. Becchetti2

1Department of Experimental Pathology and Oncology, University of Firenze, Italy; 2Department of Biotechnology and Biosciences, University of Milano-Bicocca, Italy
hERG1 (Kv 11.1)


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 Coronello†, 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
Complex functional interaction between integrin receptors and ion channels

Annarosa Arcangeli\textsuperscript{1} and Andrea Becchetti\textsuperscript{2}

\textsuperscript{1}Department of Experimental Pathology and Oncology, University of Firenze, Viale G.B. Morgagni 50, 50134 Firenze, Italy
\textsuperscript{2}Department of Biotechnology and Biosciences, University of Milano-Bicocca, Piazza della Scienza 2, 20126 Milano, Italy
 integrin

PLCγ

Src

Talin

Fyn

α-actinin

Paxillin

PI3K

PIP2

PIP3

PDK

PTEN

PI3K

Grb7

Graf

Rho

Tensin

P

Grb2

Sos

ILK

PKB/Akt

14-3-3

NF-κB

Foxo

Bad

TSC1/2

mTOR

4E-BP1

Apaf-1

Casp9

Casp3

eIF4E

nucleus

transcription

+ / -

Migration

Proliferation

Differentiation / Survival

Apoptosis

Protein synthesis

Actin stress fibers

FAK

p130Cas

C3G

Rac

ASK1

JNK

MEK1/2

ERK1/2

PAK

Ras

Raf1

Rho

Migration

Proliferation

Differentiation / Survival

Apoptosis

Protein synthesis

+ / -

Migration

Proliferation

Differentiation / Survival

Apoptosis

Protein synthesis

+ / -
Integrin-channel complex: hERG1/β1

Cherubini A. et al., Mol. Biol. Cell, 2005
VEGFR-1 (FLT-1), β1 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

MAPK

Proliferation

Migration

PI3K-pAKT

Trans Endothelial Migration

Angiogenesis

WB:

anti p-ERK

WB:

anti p-MAPK

WB:

anti ERK1

WB:

anti ERK2

WB:

anti AKT

WB:

anti p-AKT
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

β1/hERG1/CXCR4 complex

SURVIVAL (ILK, AKT)
The hERG1/β1 integrin complex in CRC

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

Olivia Crociani1, Francesca Zanieri1, Serena Pillozzi1, Elena Lstraoli1, Matteo Stefanini1, Antonella Fiore1, Angelo Fortunato1, Massimo D’Amico1, Marika Masselli1, Emanuele De Lorenzo1, Luca Gasparoli1, Martina Chiu2, Ovidio Bussolati2, Andrea Becchetti2 & Annarosa Arcangeli1
The hERG1/β1 integrin pathway in CRC
• Molecular data (RQ-PCR)
• Immunohistochemistry (IHC) data
• Flow cytometry data
• Functional data

hERG1: novel cancer biomarker
hERG1 positivity with Glut-1 negativity identifies a patient group with poor prognosis within stage I-II CRC.
hERG1 is an independent prognostic factor in PDAC (hERG1 positive patients have a worse prognosis)
Use of anti-hERG1 Mab in vivo
hERG1: novel therapeutic target in oncology
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)

<table>
<thead>
<tr>
<th>ORTOTHOPIC MODEL</th>
<th>Control</th>
<th>E4031</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local tumor growth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coecum</td>
<td>+++</td>
<td>-</td>
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<tr>
<td>Invasion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intestin</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peritoneum</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Diaphragm</td>
<td>++++</td>
<td>-</td>
</tr>
<tr>
<td>Liver</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Spleen</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Kidneys</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Complications</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Ascites</td>
<td>++</td>
<td>-</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>LIVER METASTASES MODEL</th>
<th>Control</th>
<th>E4031</th>
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<tbody>
<tr>
<td>Metastases</td>
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<td></td>
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<tr>
<td>Macrosopic metastases</td>
<td><strong>19.3 ± 3.50</strong></td>
<td><strong>9.85 ± 4.80</strong></td>
</tr>
<tr>
<td>Microscopic metastases (number/microscopic field)</td>
<td><strong>4.0 ± 0.70</strong></td>
<td><strong>1.2 ± 0.14</strong></td>
</tr>
<tr>
<td>% necrotic area/total metastases area</td>
<td><strong>2.1 ± 0.30</strong></td>
<td><strong>8.55 ± 0.36</strong></td>
</tr>
</tbody>
</table>
hERG1 is considered an antitarget!

hERG1 blockers can induce LQT syndrome and TdP
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/β1 complex occurs only in tumor cells NOT in the heart
- The hERG1/β1 complex triggers intracellular signaling
- Targeting the hERG1/β1 complex for cancer therapy?
Bi-functional antibody

PP9K

P. Pastoris
Strategies to target hERG1 in cancer and avoid cardiotoxicity

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

Differences between “cardiac” and “tumour” hERG1
hERG1B in cancer cells
hERG1B in leukemias vs heart

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

LETTER TO THE EDITOR
Differential expression of hERG1A and hERG1B genes in pediatric acute lymphoblastic leukemia identifies different prognostic subgroups

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

Merve Erdem,1,4 Tugce Ayca Tekiner,1,2 Arta Fejzullahu,1,2 Gokce Akan,4 Semra Anaku,2 Ebru Tugrul Sanibeyoglu,1 Ugur Ozbek,1 and Fatmahan Atalar1
Targeting hERG1B in leukemias

New Pyrimido-Indole Compound CD-160130 Preferentially Inhibits the Kv11.1B Isoform and Produces Antileukemic Effects without Cardiotoxicity

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

Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy (L.G., S.P., A.A.); Department of Chemistry “Ugo Schiff,” University of Florence, Florence, Italy (M.M., A.P.); DI.V.A.L. Toscana srl, Sesto Fiorentino, Italy (M.D.A., M.M.); Department of Cell Physiology and Pharmacology, University of Leicester, Leicester, United Kingdom (R.C., R.K., J.S.M.); BlackSwan Pharma GmbH, Leipzig, Germany (W.T., K.M.); Oncohematology Laboratory, Department of Woman and Child Health, University of Padova, Padova, Italy (G.B.); and Department of Biotechnologies and Biosciences, University of Milano-Bicocca, Milan, Italy (A.B.)

Received July 22, 2014; accepted November 19, 2014

B

![Chemical structures of CD-160130 and CD-140793]
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)

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

Lymphoid primary samples and cell lines

<table>
<thead>
<tr>
<th></th>
<th>L2 (early B) (CD34+, CD33+, CALLA+)</th>
<th>t(8;14)</th>
<th>6.68 (1A: 0.03)(^a)</th>
<th>5.6 ± 1.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-ALL-1</td>
<td>L2 (T) (aberrant expression of CD34, CD117, and CD13)</td>
<td>UNK</td>
<td>5.11 (1A: 0.76)(^b)</td>
<td>0.6 ± 0.2</td>
</tr>
<tr>
<td>T-ALL-1</td>
<td>pro-B-ALL (CD3−, CD10+, CD13−, CD19+, CD34−, CD37−, CD38+, cyCD79a+, CD80−, CD138+, HLA-DR+, sm/cyIgG−, sm/cyIgM−, sm/cykappa−, sm/cylambda−)</td>
<td>t(12; 21)(p13;q22)</td>
<td>120 (1A: 6.5)</td>
<td>6.66 ± 0.22</td>
</tr>
<tr>
<td>REH</td>
<td>697 pro-B-ALL (CD3−, CD10+, CD13−, CD19+, CD34−, CD37−, CD38+, CD80−, HLA-DR+, sm/cyIgG−, smIgM−, cyIgM+, sm/cykappa−, sm/cylambda−)</td>
<td>t(1;19)</td>
<td>1200 (1A:85)</td>
<td>3.78 ± 0.37</td>
</tr>
<tr>
<td>697</td>
<td>RS pro-B-ALL-L2 (HLA DR+, CD9+, CD24+)</td>
<td>t(4;11)(q21; q23) and i(7q)</td>
<td>0.16 (1A: 0.005)</td>
<td>7.0 ± 0.2</td>
</tr>
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</table>
CD 160130 is cytotoxic for leukemias (in vitro)

<table>
<thead>
<tr>
<th>Primary Sample/Cell Line</th>
<th>Binet Stage</th>
<th>Gender</th>
<th>Cytogenetics</th>
<th>Mean EC_{50} (± S.D.) of CD-160130 (μM)</th>
<th>Mean EC_{50} (± S.D.) of Fludarabine (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL-004</td>
<td>B</td>
<td>M</td>
<td>UNK</td>
<td>1.48 ± 0.55</td>
<td>0.56 ± 0.03</td>
</tr>
<tr>
<td>CLL-005</td>
<td>A</td>
<td>M</td>
<td>13q and 11q deletion</td>
<td>0.07 ± 0.03</td>
<td>0.49 ± 0.11</td>
</tr>
<tr>
<td>CLL-006</td>
<td>C</td>
<td>F</td>
<td>13q deletion</td>
<td>2.47 ± 0.39</td>
<td>0.49 ± 0.05</td>
</tr>
<tr>
<td>CLL-017</td>
<td>B</td>
<td>M</td>
<td>13q and 11q deletion</td>
<td>0.08 ± 0.02</td>
<td>0.17 ± 0.07</td>
</tr>
<tr>
<td>CLL-024</td>
<td>C</td>
<td>F</td>
<td>13q deletion</td>
<td>8.33 ± 0.29</td>
<td>ND</td>
</tr>
<tr>
<td>CLL-027</td>
<td>B</td>
<td>F</td>
<td>None</td>
<td>11.0 ± 1.50</td>
<td>4.55 ± 0.22</td>
</tr>
<tr>
<td>CLL-028</td>
<td>A</td>
<td>F</td>
<td>None</td>
<td>2.17 ± 0.02</td>
<td>ND</td>
</tr>
<tr>
<td>CLL-030</td>
<td>B</td>
<td>M</td>
<td>13q and 11q deletion</td>
<td>0.80 ± 0.05</td>
<td>ND</td>
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<tr>
<td>CLL-036</td>
<td>A</td>
<td>M</td>
<td>UNK</td>
<td>15.2 ± 3.74</td>
<td>ND</td>
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<tr>
<td>CLL-038</td>
<td>A</td>
<td>M</td>
<td>UNK</td>
<td>5.86 ± 0.53</td>
<td>5.63 ± 0.95</td>
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<td>MEC-1</td>
<td>—</td>
<td>—</td>
<td>Near-diploid karyotype with 10% polyploidy-46(44-47)&lt;2n&gt;XY, t(1;6)(q22-23;p21); add(7)(q11); del(17)(p11)</td>
<td>5.36 ± 0.94</td>
<td>0.22 ± 0.03</td>
</tr>
</tbody>
</table>

....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 donogenic 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.

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

BFU, burst forming unit.
CD 160130 interferes with signalling pathways (in vitro)
.....and overcomes chemoresistance (in vitro)

ALL

**A**

Lymphoid

<table>
<thead>
<tr>
<th></th>
<th>SusP</th>
<th>MSCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
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<tr>
<td>Doxo</td>
<td>0</td>
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</tr>
<tr>
<td>CD-160130</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CD + Doxo</td>
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697

<table>
<thead>
<tr>
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<tr>
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<tr>
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<td>0</td>
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<tr>
<td>CD-160130</td>
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<tr>
<td>CD + Doxo</td>
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**B**

BCP-ALL1

<table>
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<td>0</td>
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<tr>
<td>Doxo</td>
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<td>0</td>
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<tr>
<td>CD-160130</td>
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<tr>
<td>CD + Doxo</td>
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MFI 20

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<td>0</td>
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<tr>
<td>Doxo</td>
<td>0</td>
<td>0</td>
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<tr>
<td>CD-160130</td>
<td>0</td>
<td>0</td>
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<tr>
<td>CD + Doxo</td>
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BCP-ALL2

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<td>0</td>
</tr>
<tr>
<td>Doxo</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CD-160130</td>
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<td>0</td>
</tr>
<tr>
<td>CD + Doxo</td>
<td>0</td>
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</tbody>
</table>
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)

![Cardiac action potential](image)

<table>
<thead>
<tr>
<th>ECG parameters</th>
<th>CD-160130 (n=5) 10mg/kg</th>
<th>Sotalol (n=5) 3mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>QT ± SEM (ms)</td>
<td>129.0 ± 4.2</td>
<td>115.4 ± 3.6</td>
</tr>
<tr>
<td>HR ± SEM</td>
<td>237.1 ± 3.4</td>
<td>240.3 ± 3.7</td>
</tr>
<tr>
<td>Qtc ± SEM</td>
<td>305.1 ± 7.5</td>
<td>276.4 ± 6.8</td>
</tr>
<tr>
<td>ΔQtc (% vs Pre-drug)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

- 0 min:
  - CD-160130: 131.4 ± 5.4
  - Sotalol: 115.4 ± 3.8
- 5 min:
  - CD-160130: 127.5 ± 7.0
  - Sotalol: 131.3 ± 4.0
- 10 min:
  - CD-160130: 129.0 ± 5.8
  - Sotalol: 135.3 ± 4.2
- 15 min:
  - CD-160130: 128.0 ± 6.7
  - Sotalol: 133.0 ± 5.8
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.
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