Targeting Cancer Stem Cells

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Outline

- Historical perspective of SC and CSC
- Definition and properties of CSC
- Evolution of CSC hypothesis
- Earlier studies targeting CSCs in clinical practice, focus on hematological malignancies
- Future directions and remaining questions
Historical perspective of SC and CSC

- 1874: Durante hypothesized tumors derive from a rare cell population with properties similar to what we now know as stem cell

- Around same time, Conheim (Virchow’s student) speculated cancer results from embryonic-tissue remnants (embryonal rest theory)

- Late 19th, dedifferentiation theory: SC from dedifferentiation of differentiated adult cells

Embryonal rest vs. Dedifferentiation theory of CSC

Fulawka L et al, BR, 2014
Historical perspective (cont.)

- The term “stem cell” first used by Russian research Alexander Maximov in 1909
- 1950: Makino et al found cancer cells from rat peritoneal fluid contains cells with specific karyotype, can be serially grafted
- 1960: Pierce et al isolated cell from teratocarcinoma, able to differentiate into mature tissues
- 1961: Till and McCulloch grafted BM cells into host mouse after radiation, found these cells gave rise to HSCs in the spleen, then differentiate to mature blood cells
- 1994: Landmark study by Lapidot et al showed CD34+CD38- cells of AML form derivative leukemia after serial transplantation into NOD/SCID mice, termed L-ICs

CSCs exist in most cancers

- CSCs were first identified in AML
- Breast cancer
- Brain tumor
- Lung cancer
- Colon cancer
- Prostate cancer
- Pancreatic cancer
- Ovarian cancer
- Liver cancer
- Melanoma
- CML
- MM
- Lymphomas
- ......
Definition of CSC

- Workshop on CSCs by AACR in 2006

- “A cell within a tumor that possesses the capacity to self-renew and to cause the heterogeneous lineages of cancer cells that comprise the tumor”
Normal stem cells

Rare cells within organs with the ability to self-renew and give rise to all types of cells within the organ to drive organogenesis

Cancer stem cells

Rare cells within tumors with the ability to self-renew and give rise to the phenotypically diverse tumor cell population to drive tumorigenesis
Cancer Stem Cell Hypothesis

- Cancers are driven by cells with stem cell properties
  - Self-renewing and long lived, relatively quiescent
  - Immune privileged, not eliminated by immune cells
  - Multipotent, able to contribute to tumor cell heterogeneity
  - Antiapoptotic
  - Drug effluxion

- Cancer stem cells arise from
  - Normal stem cells with acquired mutations that promote deregulated self-renewal
  - Dedifferentiation of differentiated cells

- Cancer stem cells contribute to tumor development, recurrence, and metastases
  - Less sensitive to chemotherapy, radiation and biologic agents
  - Tumor recurrence and metastasis even in patients who had complete response

Tie-mediated signal from apoptotic cells protects SCs in Drosophila Melanogaster from radiation damage

- Adult SCs are resistant to radiation or chemically induced apoptosis
- Dying “daughter” cells send survival signal to protect their “mother” SCs for future population of the tissue
- If conserved in CSCs, may provide therapeutic options for the eradication of cancer

*Xing and Ruohloa-Baker et al, Nature Communications, 2015 in press*
Wnt, Shh, and Notch pathways have been shown to contribute to the self-renewal of stem cells and/or progenitors in a variety of organs, including the haematopoietic and nervous systems. When dysregulated, these pathways can contribute to oncogenesis. Mutations of these pathways have been associated with a number of human tumours, including colon carcinoma and epidermal tumours (Wnt), medulloblastoma and basal cell carcinoma (Shh), and T-cell leukaemias (Notch).
Some tissue types give rise to cancers millions of times more often than other tissue types.

Life time risk of cancer is 6.9% for lung, 1.08% for thyroid, 0.6% for brain, 0.003% for pelvic bone and 0.00072% for laryngeal cartilage.

Only 1/3 of the variation in cancer risk is related to environmental or genetic risk factor.

Majority is due to “bad luck”, random mutations arising during DNA replication of normal, noncancerous stem cells.

Lifetime risk of cancer for many different tissues is strongly correlated (0.81) with the total number of divisions of normal self-renewing SCs to maintain that tissue’s homeostasis.

Variations in cancer risk among tissues can be explained by the number of stem cell divisions

Hierarchy of hematopoietic system
Serial transplantation assay to study HSCs or LSCs
CSCs are resistant to conventional chemotherapy
Challenges in CSCs research

- How to characterize CSCs at the single cell level

- Understand the genetic, epigenetic and biochemical mechanisms that control the self-renewal phenotype, asymmetric subdivision, and the role of the stem cell niche in regulating the biological properties of both normal and cancer SCs

- How to characterize the response of CSCs to chemotherapeutic regimens: use of circulating tumor cells or monitor for MRD

- Develop therapeutic strategies to target CSCs to prevent tumor recurrence, while minimizing the toxicities to normal SCs
## Tumor-Specific CSC Markers

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>CSC Surface Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid tumors</td>
<td></td>
</tr>
<tr>
<td>Brain(^{[26]})</td>
<td>CD133+ CD49f+ CD90+</td>
</tr>
<tr>
<td>Breast(^{[27]})</td>
<td>ALDH+ ESA+ CD44+ CD24-/low</td>
</tr>
<tr>
<td>Colon(^{[28]})</td>
<td>CD133+ CD44+ CD166+ EpCAM+ CD24+</td>
</tr>
<tr>
<td>Lung(^{[29]})</td>
<td>CD133+ ABCG2++</td>
</tr>
<tr>
<td>Melanoma(^{[30]})</td>
<td>CD20+</td>
</tr>
<tr>
<td>Pancreatic(^{[31]})</td>
<td>CD133+ CD44+ EpCAM+ CD24+</td>
</tr>
<tr>
<td>Prostate(^{[32]})</td>
<td>CD133+ CD44+ CD24-</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
</tr>
<tr>
<td>AML(^{[33]})</td>
<td>CD34+ CD38-</td>
</tr>
<tr>
<td>Leukemia(^{[34]})</td>
<td>CD34+ CD38- HLA-DR- CD71- CD90- CD117- CD123+</td>
</tr>
</tbody>
</table>

Potential targets for CSC

Chen K et al, Act Pharma Sinica 2013
Therapeutic Agents Targeting CSC Survival and Self-Renewal


Cancer stem cell

- DLL/JAG
- NOTCH
- β-CAT
- WNT
- LPR/FZD
- β-CAT, STAT3, Nanog
- TARGET DNA
- IL-8
- CXCR1
- FAK
- Reparixin
- Defactinib
- Self-renewal
drug resistance
metastasis

- Tarextumab (OMP-59R5)
- Demcizumab (anti-DLL4)
- Ipafricept (OMP-54F28)
- Vantictumab (anti-FZD)
- BBI608
- β-CAT, STAT3, Nanog
## CSC-Targeted Therapies: Phase I Trials (abstracts from ASCO 2014)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Tumor</th>
<th>Key Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tarextumab + etoposide/platinum$^{[38]}$</td>
<td>SCLC</td>
<td>MTD not reached; DLT: 1 nausea; tumor reduction in 9/10 pts</td>
</tr>
<tr>
<td>Demcizumab + carbo/pem$^{[39]}$</td>
<td>NSCLC</td>
<td>DLT: 1 reversible pulmonary HTN/heart failure; ORR: 13/28; SD: 11/28</td>
</tr>
<tr>
<td>Ipafricept$^{[40]}$</td>
<td>Multiple</td>
<td>No grade ≥ 3 AEs; SD: 9/26</td>
</tr>
<tr>
<td>BBI608 + paclitaxel$^{[41]}$</td>
<td>Multiple</td>
<td>MTD not reached; DCR: 10/15</td>
</tr>
<tr>
<td>BBI608$^{[42]}$</td>
<td>Multiple</td>
<td>DCR: 4/6</td>
</tr>
<tr>
<td>BBI503$^{[43]}$</td>
<td>Multiple</td>
<td>MTD not reached; SD: 11/20</td>
</tr>
</tbody>
</table>

## CSC-Targeted Therapies: Ongoing Randomized Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Disease</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO23</td>
<td>III</td>
<td>mCRC</td>
<td>BBI608 vs BSC</td>
</tr>
<tr>
<td>BRIGHTER[45]</td>
<td>III</td>
<td>Gastric/GEJ</td>
<td>BBI608 + Pac vs Pac + Placebo</td>
</tr>
<tr>
<td>COMMAND</td>
<td>II</td>
<td>Pleural mesothelioma</td>
<td>Defactinib vs placebo</td>
</tr>
<tr>
<td>DENALI[48]</td>
<td>II</td>
<td>NSCLC</td>
<td>Demcizumab + Carbo/Pem vs Carbo/Pem + placebo</td>
</tr>
<tr>
<td>YOSEMITE</td>
<td>II</td>
<td>Pancreatic</td>
<td>Demcizumab + Gem/nab-P vs Gem/nab-P + placebo</td>
</tr>
<tr>
<td>ALPINE[50]</td>
<td>Ib/Ii</td>
<td>Pancreatic</td>
<td>Tarextumab + Gem/nab-P vs Gem/nab-P + placebo</td>
</tr>
<tr>
<td>PINNACLE</td>
<td>Ib/Ii</td>
<td>SCLC</td>
<td>Tarextumab + E/Plt vs E/Plt + placebo</td>
</tr>
</tbody>
</table>

*ClinicalTrials.gov*
“I’ve been in this business for better or worse for 40 years. Many of the things we’ve worked on have proved to be relatively useless in the clinic. This is really the first time where I’m positioned to help effect the development of an agent or agents that actually will benefit cancer patients”

----- Robert Weinberg from MIT, founder of Verastem, Inc

“I think the onus is on all of us in the community that is developing CSC therapies to show beyond a doubt that these therapies really work”

----- Max Wicha from U. of Michigan
> 60 ongoing or planned CSC clinical trials

$200 million invested in Verastem

### A cancer hypothesis on trial

Some efficacy trials of drugs aimed at cancer stem cells, often combined with conventional tumor treatments.

<table>
<thead>
<tr>
<th>COMPANY</th>
<th>DRUG</th>
<th>TARGET</th>
<th>CANCER</th>
<th>STAGE</th>
<th>COMBINATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>OncoMed</td>
<td>Tarextumab</td>
<td>Notch 2,3 receptors DLL4</td>
<td>Pancreatic, lung, Ovarian</td>
<td>Phase II</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Demcizumab</td>
<td>(Notch ligand)</td>
<td></td>
<td>Phase II,</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>mid-2015</td>
<td></td>
</tr>
<tr>
<td>Verastem</td>
<td>VS-6063</td>
<td>Focal adhesion kinase</td>
<td>Mesothelioma, lung</td>
<td>Phase II</td>
<td>No</td>
</tr>
<tr>
<td>Boston Biomedical (Sumitomo Dainippon)</td>
<td>BBI608</td>
<td>STAT3, β-catenin, Nanog</td>
<td>Colon, Gastric, esophageal</td>
<td>Phase III halted*</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Colon, other cancers</td>
<td>Phase III</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Solid tumors</td>
<td>Phase III</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Phase II</td>
<td>No</td>
</tr>
<tr>
<td>Stemline Therapeutics</td>
<td>SL-401</td>
<td>Interleukin-3 receptor</td>
<td>Leukemia</td>
<td>Phase I/II</td>
<td>No</td>
</tr>
<tr>
<td>Dompé</td>
<td>Reparixin</td>
<td>Chemokine receptors 1 and 2</td>
<td>Breast</td>
<td>Phase II</td>
<td>No</td>
</tr>
</tbody>
</table>

*Failed to meet efficacy endpoint
Targeting CSCs in hematological malignancies

- The LSCs are the critical target in AML therapy
- Further understanding of the biology of both LSC and the normal HSC is required
  - Share many similar signaling pathways
  - Features distinguishing LSCs from normal HSCs
- Target pathways preferentially utilized by LSC, while sparing normal HSC
SC origin of CML was confirmed 20 years ago by several groups. Identified and isolated CML cells capable of expansion ex vivo using characteristics known to define normal HSCs. Dick et al showed primitive HSCs purified from CML patients generate leukemia in vivo when injected into NOD/SCID mice. Expression patterns of CML stem cells closely resemble those of normal HSCs.

• CML stem cells are insensitive to TKIs
  ○ Overexpression of ABC transporters block update of TKIs
  ○ Decreased BCR-ABL expression in SC compartment
  ○ Lack of dependence for BCR-ABL for SC survival

• INF-a more toxic to CML progenitors, results in slower but more durable response

• Successful d/c of imatinib in selected patients suggests LSC eradication may not be absolutely necessary for long term control
Pathways involved in CML stem cells

Hamad A et al, Stem Cells International, 2013; Cogle C, JNCI 2013
CSCs and minimal residual disease

- The CSC concept potentially explains
  - Only a minority of cells from most malignancies are clonogenic in vitro and in vivo
  - Why complete treatment responses rarely translate into cures for most cancer patients
  - Initial responses represent the therapeutic effectiveness against the bulk cancer cells, while rarer and more resistant CSCs are responsible for relapse
CSCs and minimal residual disease

- If CSCs indeed are resistant to therapy and responsible for relapse, then MRD after treatment should be enriched for these cells
  - Breast cancer (Creighton et al, PNAS, 2009)
  - Patients with 5q- MDS had MDS SCs (CD34+CD38lowCD90+) even in complete clinical and cyto remission (Tehranchi et al, NEJM 2010)
  - Association between myeloma SCs number and PFS after treatment with rituximab, rituximab found on surface of circulating myeloma SCs at progression (Huff CA, AACR, 2008)
  - MRD in AML has SC phenotype, and presence of AML CSCs correlate with PFS, elimination of LSCs will reduce MRD and improve patient outcome (Gerber JM, Blood, 2011)
CSCs in AML

- AML was the first model in which CSCs (L-ICs) were identified
- These AML SCs not only reproduced disease in NOD/SCID mice, but also possess self-renewal and HSC phenotype
- Thus, HSC markers, such as CD34, absence of CD38, Lin, CD133, and expression of ALDH have been used to isolate putative AML SCs

Lapidol et al, Nature 1994
Markers expressed in AML LSCs

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Function/Characteristics</th>
<th>Expression</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD123</td>
<td>High affinity IL-3 receptor (IL-3α)</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>CD47</td>
<td>Ligand for SIRPa, inhibits phagocytosis</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>CD96</td>
<td>Activation of Antibody dependent cell-mediated toxicity</td>
<td>++*</td>
<td>+</td>
</tr>
<tr>
<td>CD32</td>
<td>Fc-g receptor 2 (FCGR2)</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>CD25</td>
<td>High-affinity IL-2 receptor (IL2Rα)</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>CD44</td>
<td>Facilitates adhesive interactions, key regulator of AML-LSCs homing to microenvironmental niches</td>
<td>++*</td>
<td>+</td>
</tr>
<tr>
<td>CXCR4</td>
<td>Cell membrane receptor, contributes to SDF-1α/CXCR4 interactions</td>
<td>++*</td>
<td>+</td>
</tr>
<tr>
<td>AurA</td>
<td>Mitotic serine/threonine kinases that play a role in cytokinesis during mitosis and cell division</td>
<td>++*</td>
<td>+</td>
</tr>
<tr>
<td>Mcl-1</td>
<td>Plays a critical role in maintenance and survival of LSCs</td>
<td>++*</td>
<td>+</td>
</tr>
<tr>
<td>TIM-3</td>
<td>Regulator of macrophage activation, role with complement-dependent and antibody dependent cell-mediated cellular cytotoxic activities</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>NF-κB</td>
<td>Transcription factor, responsible for LSC antiapoptotic activity</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: IL, interleukin; SIRPa, signal regulatory protein α; SDF, stromal cell-derived factor; LSCs, leukemic stem cells; HSCs, haematopoietic stem cells; CXCR4, C-X-C chemokine receptor type 4; AurA, Aurora A kinase; Mcl-1, myeloid cell leukemia-1; TIM-3, T cell immunoglobulin mucin-3; NF-κB, nuclear factor-κB. *Increased expression

Table 1: Significant cell surface and intracellular targets in AML-LSCs.

## Phenotypes of AML CSCs

### Table 1. Phenotype of AML CSC

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Xenograft model</th>
<th>Comments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD34+CD38−</td>
<td>NOD/SCID</td>
<td></td>
<td>Lapidot et al. [13]</td>
</tr>
<tr>
<td>CD34+CD38+</td>
<td>NOD/SCID, NOD/SCID/β2m−/−, NOD/SCID/IL2Rγ−/−</td>
<td></td>
<td>Taussig et al. [14]</td>
</tr>
<tr>
<td>CD34+CD123+</td>
<td>NOD/SCID</td>
<td></td>
<td>Jordan et al. [15]</td>
</tr>
<tr>
<td>CD44+</td>
<td>NOD/SCID</td>
<td>Neutralizing antibodies reduces AML CSC</td>
<td>Jin et al. [16]</td>
</tr>
<tr>
<td>CD96+</td>
<td>Newborn Rag2−/−γc−/−</td>
<td>Neutralizing antibodies reduces AML CSC</td>
<td>Jin et al. [17]</td>
</tr>
<tr>
<td>CD34+CD38−−CLL1+</td>
<td>NOD/SCID</td>
<td></td>
<td>Hosen et al. [18]</td>
</tr>
<tr>
<td>CD34−</td>
<td>NOD/SCID/β2m−/−, NOD/SCID/IL2Rγ−/−</td>
<td>Only NPM1+AML</td>
<td>van Rhenen et al. [19]</td>
</tr>
<tr>
<td>Lin−CD38−</td>
<td>NOD/SCID/IL2Rγ−/−</td>
<td>Lin−CD38− fraction had the highest AML CSC frequency but all populations showed some AML CSC activity</td>
<td>Sarry et al. [21]</td>
</tr>
</tbody>
</table>

Abbreviations: AML, acute myeloid leukemia; CD, cluster of differentiation; CLL1, C lectin like molecule 1; CSC, cancer stem cell; IL2Rγ−/−, interleukin 2 receptor gamma knock out; NOD/SCID: nonobese diabetes/severe combined immunodeficiency; NPM1, nucleophosmin; Rag2−/−, recombination activating gene 2 knock out; β2m−/−, beta-2 microglobulin knock out.
Krause and Van Etten, Trends in Molecular Medicine, 2007
<table>
<thead>
<tr>
<th>Putative LSC target</th>
<th>Potential intervention(s)</th>
<th>Active and recruiting trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hedgehog signaling pathway</td>
<td>Small molecule inhibitors of pathway regulators (e.g. Smoothened)</td>
<td>NCT01841333, NCT01546038, NCT01842646</td>
</tr>
<tr>
<td>NfkB Signaling/induction of oxidative stress</td>
<td>Parthenolide, bortezomib&lt;sup&gt;3,4,7,20&lt;/sup&gt;</td>
<td>NCT01174888, NCT01863114, NCT01127009, NCT01534260, NCT01371981, NCT01736943, NCT01075425, NCT00410423</td>
</tr>
<tr>
<td>MLL</td>
<td>EPZ-5676 (inhibitor of DOT1-L)&lt;sup&gt;45&lt;/sup&gt;</td>
<td>NCT01684150</td>
</tr>
<tr>
<td>CLL-1 Have monoclonal antibody&lt;sup&gt;45&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD44</td>
<td>Monoclonal antibody&lt;sup&gt;45&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>CD47</td>
<td>Monoclonal antibody&lt;sup&gt;45&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>CD33</td>
<td>Antibody-based (gemtuzumab ozogamicin, SGNCD33A, actinium-225, labeled HuM195), chimeric antigen receptor (CART33), others in development&lt;sup&gt;43,44&lt;/sup&gt;</td>
<td>NCT01902339, NCT01864902, NCT00672165, NCT01869803</td>
</tr>
<tr>
<td>CD96</td>
<td>Monoclonal antibody&lt;sup&gt;45&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>IL3 Receptor-α (CD123)</td>
<td>Diptheria toxin-IL3 fusion protein; CSL362 (monoclonal antibody)&lt;sup&gt;4,7,20&lt;/sup&gt;</td>
<td>NCT00397579, NCT01632852</td>
</tr>
<tr>
<td>c-KIT, SRC Family Kinases</td>
<td>Dasatinib&lt;sup&gt;45&lt;/sup&gt;, RK-20449 (HCK inhibitor)&lt;sup&gt;45&lt;/sup&gt;</td>
<td>NCT00892190, NCT01876963,</td>
</tr>
<tr>
<td>BCL-2</td>
<td>ABT-199, oblimersen sodium (inhibitors of BCL-2)&lt;sup&gt;4,8,9&lt;/sup&gt;</td>
<td>NCT01994837</td>
</tr>
</tbody>
</table>
AML stem cells can be made susceptible to chemotherapy by inducing them to divide

- Mouse model of human AML
- Treatment with G-CSF induced mobilization and cell cycle entry of LSCs, more susceptible to cytarabine
- No increase in apoptosis of HSCs, whether HSC and LSC respond differently to G-CSF?

*Saito et al, Nature biotechnol 2010*
Targeting CXCR4

- Membrane receptor found on SCs
- Interaction between SDF-1a and CXCR4 contributes to resistance of LSCs to apoptosis
- CXCR4 expression is associated with poor prognosis in AML and is marker of more aggressive disease
- Targeting CXCR4 eliminates LSCs protected by the BM microenvironment

Burger JA, Leukemia 2008; Konopleva M, Drug Resist Updat 2009
NFkB

- NFkB is constitutively expressed in the blasts in most AML patients
- NFkB activity is detectable in the quiescent LSCs where normal HSCs don’t express
- Eradicate LSCs by direct targeting NFkB pathway is a potential strategy

Aurora kinase

Aurora A kinase (AurA) is a family of mitotic serine/threonine kinases important in mitosis and cell division.

- AurA higher level of expression in AML LSCs than HSCs.
- Reduction in LSCs could be enhanced by stimulation with G-CSF and AurA inhibitors.
- AurA inhibitors inhibit proliferation, impair self-renewal and induce apoptosis in LSCs, when AurA inhibitor was used during engraftment of CD34+CD38- AML cells in immunocompromised mice.
- Alisertib (MLN8237) is being studied in patients with PTCL and other solid tumors.

Targeting Bcl-2 and ROS

- LSCs from primary AML samples have low level of ROS
- ROS-low LSCs aberrantly overexpress Bcl-2
- Bcl-2 inhibition reduced oxidative phosphorylation and selectively eradicated quiescent LSCs, this could explain why targeting Bcl-2 is effective in AML
- Several Bcl-2 inhibitors are in clinical trial in patients with AML
  - ABT-199
  - Venetoclax

Lagadinou et al, Cell Stem Cell 2013; Konopleva et al, ASH 2014;
Targeting other cell surface antigens

- **CD33:**
  - Highly expressed in LSCs and its progeny
  - Gemtuzumab ozogamicin (Myelotarg) has been used previously in AML patients
  - Several new anti-CD33 abs are in development

- **CD123 (IL-3 receptor):**
  - Overexpressed in LSCs and leukemia blasts
  - Prevent engraftment in NOD/SCID mice and reduced leukemic cell burden in mice with established disease
  - SL-401 is being developed in myeloid neoplasms

- **CD44 and CD47:**
  - Also effective in AML xenograft model

Future direction

- Clinical trials to target both CSC and mature tumor cells for curative intent
- Identifications of markers and pathways that are unique to CSC
- Reduce the potential toxicities to normal SCs from agents intended to be CSC-directed
- How to sequence conventional therapy and CSC-targeted therapy for maximal benefit
Questions and comments?