Targeting Tumors and Their Vasculature with Antibody-Drug Conjugates (ADCs)

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University of Pittsburgh Medical School
Targeting Tumors and Their Vasculature with Antibody-Drug Conjugates (ADCs)

- Anti-cancer therapeutic antibodies and our research - an update
- CD276 as a target – expressed on cancer cells and tumor microvasculature
- ADCs targeting CD276
- Efficacy in animal models
- ADCs against GPC2 and other cancer-related targets
- Summary and conclusions
Monoclonal Antibody (mAb) Therapeutics Approved for Clinical Use in 2016
2 IgG1s against Cancer

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<thead>
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<th>International non-proprietary name</th>
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*Data as of December 1, 2016; a comprehensive table of approved antibody therapeutics and those in regulatory review in the EU or US is maintained on The Antibody Society’s website (www.antibodiesociety.org).

Abbreviations: CD, cluster of differentiation; EC, European Commission; IL, interleukin; NA, not approved or in review in the EU; PDGFR, platelet-derived growth factor receptor; PD-L1, programmed death ligand 1.
mAb-based Therapeutics Approved for Clinical Use in 2017 – Five against Cancer Compared to Two in 2016, One ADC

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Identification of mAbs by Phage/Yeast Display

- **Library**
  - DNA encoding displayed Fabs, scFvs
- **Display**
  - Displayed Fabs, scFvs
- **Panning/sorting**
  - Selected Fabs, scFvs
- **Production and conversion**
  - Production and conversion to IgG1 or other formats

- **Antigen**
- **IgG1, chimeric antigen receptor (CAR), bispecific mAb, antibody-drug conjugate (ADC)**

Generation of Libraries of Engineered Antibody Domains (eAds)

Libraries of eAds

Grafting CDRs

Mutations

Engineered mAb-based Composite Molecules

- Antibody-drug conjugates (ADCs)
- Chimeric Antigen Receptors (CARs)
- Bispecific mAbs (BsmAbs)
- Bispecific T cell engagers (BiTEs)
- Bispecific killers cell engagers (BiKEs)
- mAb-based fusion proteins (mAbFPs)
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Site-Specific Conjugation through Native N-Glycans for Generation of Antibody-Drug Conjugates (ADCs)

Zhu Z et al mAbs 2014
An ADC Model

Prabakaran P et al, unpublished
CD276 Overexpression BOTH in Cancer Cells and Tumor Vasculature but NOT in Normal Cells

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**Kidney**

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Sieman S et al, Cancer Cell 2017
CD276 Overexpression BOTH in Tumor Cells and Tumor Vasculature but NOT in Normal Cells

TC-tumor cells, SC-stromal cells

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Sieman S et al, Cancer Cell 2017
m276

- Identified from a human scFv yeast display library by sequential selection against human and mouse CD276

- Cross-reactive to human, monkey, mouse and rat CD276

- High affinity: $K_d$ human, mouse, monkey, rat $= 29, 24, 33, 3.3$ nM

- High specificity

- High internalization – generated ADCs with MMAE and PBD dimers
ADC m276-PBD

- Site-specific conjugation through glycans
- DAR = 2
- Low IC50 (pM to nM)
- PBD is a poor substrate for P-glycoprotein
- PBD binds the DNA minor groove thus avoiding repair enzymes
- PBD can kill non-dividing cells

Sieman S et al, Cancer Cell 2017
m276-PBD Is Highly Effective and Specific in Vitro and its Cytotoxicity Correlates with the CD276 Surface Concentration

Sieman S et al, Cancer Cell 2017
ADC m276-MMAE

- Site-specific conjugation through glycans
- DAR ~ 4
- Low IC50 (pM to nM)
- MMAE is a substrate for P-glycoprotein
- MMAE binds tubulin
- MMAE kills dividing cells

Sieman S et al, Cancer Cell 2017
m276-MMAE Kills Efficiently (pM IC50) and Specifically CD276-Expressing Cells

Sieman S et al, Cancer Cell 2017
m276-PBD but Not m276-MMAE Eradicates DMS-273 Human Lung Tumor Xenografts in Athymic Nude Mice

DMS-273 tumors: both tumor cells and tumor vasculature - CD276 positive

Sieman S et al, Cancer Cell 2017
m276-PBD Ablates P-gp/CD276/CD31 Triple-positive Tumor Vessels in MC38 Tumors

Sieman S et al, Cancer Cell 2017
m276-PBD Induces Apoptosis of MC38 Tumor Vessels from CD276 Wild Type Mice

Sieman S et al, Cancer Cell 2017
m276-MMAE Induces Apoptosis - CD276-positive KM12 Tumor Cells but Not Tumor Vessels

Sieman S et al, Cancer Cell 2017
Cell Killing by free MMAE Is Sensitive to the P-glycoprotein Inhibitor Zosuquidar, by PBD Is Not

Sieman S et al, Cancer Cell 2017
Better Killing Efficacy when Both Tumor Cells and Vasculature Are Targeted

Sieman S et al, Cancer Cell 2017
M276-PBD Blocks the Growth of Experimental Colon Liver Metastasis

Sieman S et al, Cancer Cell 2017
m276-PBD Treatment Prolongs Survival of Mice with 4T1 Experimental Breast Cancer Lung Metastasis

Sieman S et al, Cancer Cell 2017
Eradication of CD276-positive Tumors by PBD-ADC; Impaired Tumor Growth by MMAE-ADC

Sieman S et al, Cancer Cell 2017
GPC2 is a Predicted Cell Surface Heparan Sulfate Proteoglycan

- Glypicans (1 - 6) are cell surface signaling co-receptors
- GPC2 may bind ?SHH, ?midkine, ?WNT
- GPC2 on chromosome 7q
- Chromosome 7/7q gained in ~1/3 of primary neuroblastomas
- Other glypicans are candidate immunotherapy targets/oncogenes

Kurosawa, N et al. 2001, Mythreye, K et al. 2009, Melo, SA et al. 2015, Grobe, K et al. 2015

Courtesy of Kris Bosse
GPC2 as a Candidate Target - Overexpression in Neuroblastoma but not in Normal Tissues

Bosse KR et al, Cancer Cell 2017
D3-GPC2-IgG1 ADC

- Fab D3 - identified from a human antibody library
- Cross-reactive to human and mouse GPC2
- High (pM) affinity and specificity
- ADC D3-GPC2-PBD – generated by site-specific conjugation through glycans

Bosse KR et al, Cancer Cell 2017
IgG1-GPC2-D3 Is Specific for GPC2

Bosse KR et al, Cancer Cell 2017
Potent Inhibition of GPC2-expressing Neuroblastoma Cells by D3-GPC2-PBD

Bosse KR et al, Cancer Cell 2017
D3-GPC2-PBD Regresses Tumors and Prolongs Survival of a Neuroblastoma NB-1643 PDX Model

Bosse KR et al, Cancer Cell 2017
Summary and Conclusions

- New high-affinity fully human mAbs to CD276 and GPC2 identified and characterized
- New ADCs with MMAE (m276-MMAE) or PBD dimers (m276-PBD) generated and characterized
- CD276 is overexpressed by both tumor cells and tumor vasculature but the m276-MMAE primarily targets tumor cells while m276-PBD targets both
- m276-PBD – more effective than m276-MMAE in animal models
- m276-PBD may be a better drug choice in cases where CD276 is overexpressed in tumor vasculature
- Targeting the tumor microenvironment with ADCs is an effective anti-cancer strategy
- ADCs-PBD targeting CD276 and GPC2 are promising candidate therapeutics against cancer
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Jonathan Keller
Chris Szot
Steven Seaman
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Karen Morris
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Dimiter Dimitrov (former)
Brad St. Croix

Ilya Lyakhov
Dontcho Jelev
Wei Li
Dimiter Dimitrov

Center for Antibody Therapeutics
University of Pittsburgh Medical School
Positions available!!!

Kristopher Bosse
Pichai Raman
Robyn Sussman
John Maris

Children Hospital of Philadelphia

John Mellors
University of Pittsburgh

Michelle Zhang
Saurabh Saha
Dean Welsch
Gary DeCrescenzo

BioMed Valley Discoveries
CRADA partner

Sabine Heitzeneder
Crystal Mackcall
Stanford University

Nathan Li
Antibodies Journal

National Cancer Institute
NIH
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<th>INN or code name</th>
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<th>Target(s)</th>
<th>Most advanced phase</th>
<th>Pivotal Phase 2, Phase 2/3 or 3 indications</th>
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<td>Actinium Pharmaceuticals</td>
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<td>Murine IgG1, radio-labeled</td>
<td>CD45</td>
<td>Phase 3</td>
<td>Ablation of bone marrow prior to hematopoietic cell transplantation in AML patients</td>
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<tr>
<td>Janssen</td>
<td>JNJ-56022473, CSL362</td>
<td>Humanized mAb</td>
<td>IL-3Rα (CD123)</td>
<td>Phase 2/3</td>
<td>Acute myeloid leukemia</td>
</tr>
<tr>
<td>Seattle Genetics</td>
<td>Vadastuximab talirine</td>
<td>IgG1 ADC</td>
<td>CD33</td>
<td>Phase 3</td>
<td>Acute myeloid leukemia</td>
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<tr>
<td>TG Therapeutics</td>
<td>Ubiliximab</td>
<td>Chimeric IgG1</td>
<td>CD20</td>
<td>Phase 3</td>
<td>Chronic lymphocytic leukemia</td>
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<tr>
<td>AstraZeneca/ MedImmune LLC</td>
<td>Moxetumomab pasudotox</td>
<td>Murine IgG1 dsFv immunotoxin</td>
<td>CD22</td>
<td>Phase 3</td>
<td>Hairy cell leukemia</td>
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<tr>
<td>Xencor</td>
<td>XMAB-5574, MOR208</td>
<td>Humanized IgG1</td>
<td>CD19</td>
<td>Phase 2/3</td>
<td>Diffuse large B-cell lymphoma</td>
</tr>
<tr>
<td>Viventia Bio</td>
<td>Oportuzumab monax</td>
<td>Humanized scFv</td>
<td>EpCAM</td>
<td>Phase 3</td>
<td>Bladder cancer</td>
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<tr>
<td>MacroGenics</td>
<td>Margertuximab</td>
<td>Chimeric Ig1</td>
<td>HER2</td>
<td>Phase 3</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>Merrimack Pharmaceuticals</td>
<td>MM-302</td>
<td>scFv-targeted liposome containing doxorubicin</td>
<td>HER2</td>
<td>Phase 2/3</td>
<td>Breast cancer</td>
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<tr>
<td>Immunomedics, Inc.</td>
<td>Sacituzumab govitecan</td>
<td>IgG1 ADC</td>
<td>TROP-2 (epithelial glycoprotein-1)</td>
<td>Phase 3</td>
<td>Triple-neg. breast cancer</td>
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<tr>
<td>Cellnex Therapeutics</td>
<td>Glembatumumab vedotin</td>
<td>Human IgG2 ADC</td>
<td>Glyco-protein NMB</td>
<td>Pivotal Phase 2</td>
<td>Gastric cancer or gastroesophageal junction adenocarcinoma</td>
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<td>Gilead Sciences</td>
<td>Andecaliximab</td>
<td>Humanized IgG4</td>
<td>MMP9</td>
<td>Phase 3</td>
<td>Glioblastoma</td>
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<tr>
<td>AbbVie</td>
<td>Depatuxizumab mafodotin</td>
<td>IgG1 ADC</td>
<td>EGFR</td>
<td>Phase 2/3</td>
<td>Non-small cell lung, head and neck, bladder, triple-neg. breast, urothelial cancers</td>
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<tr>
<td>AstraZeneca/ MedImmune LLC</td>
<td>Durvalumab</td>
<td>Human IgG1</td>
<td>PD-L1 (CD274)</td>
<td>Phase 3</td>
<td>Non-small cell lung, head and neck, urothelial cancer</td>
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<tr>
<td>AstraZeneca/ MedImmune LLC</td>
<td>Tremelimumab</td>
<td>Human IgG2</td>
<td>CTLA4</td>
<td>Phase 3</td>
<td>Non-small cell lung cancer</td>
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<td>Recombio SL</td>
<td>Racotumomab</td>
<td>Murine IgG1</td>
<td>GM3</td>
<td>Phase 3</td>
<td>Non-small cell lung cancer</td>
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<tr>
<td>Bayer</td>
<td>Anetumab ravninesine</td>
<td>Human IgG1 ADC</td>
<td>Mesothelin</td>
<td>Pivotal Phase 2</td>
<td>Mesothelioma</td>
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<td>ImmunoGen</td>
<td>Mirvetuximab soravantines</td>
<td>IgG1 ADC</td>
<td>Folate receptor 1</td>
<td>Phase 3</td>
<td>Ovarian cancer</td>
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<td>Philogen SpA</td>
<td>L19IL2 + L19TNF</td>
<td>scFv conjugates</td>
<td>Fibronectin extra-domain B Endoglin</td>
<td>Phase 3</td>
<td>Melanoma</td>
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<td>Tracan</td>
<td>Carotuximab</td>
<td>Chimeric Ig1</td>
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<td>Phase 3</td>
<td>Angiosarcoma</td>
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Note: Data updated as of December 1, 2016.

Abbreviations: ADC, antibody-drug conjugate; CD, cluster of differentiation; CTLA, cytotoxic T-lymphocyte-associated protein 4; dsFv, disulfide-stabilized variable fragment; EGFR, epidermal growth factor receptor; EpCAM, epithelial cell adhesion molecule; IL, interleukin; MMP, matrix metalloproteinase; PD, programmed death; PD-L1, programmed death ligand 1; scFv, single-chain variable fragment.
Optimization of mAbs: Full Size IgG1s, Engineered Antibody Domains (eAds, VH, CH2 and mCH3) and Fragments (Fab, scFv, Fc and mFc)

- Identification of small-size binders - long half-lives and enhanced penetration in solid tumors
- Development of monomeric Fc fusion proteins including cytokine-mFc – smaller size and lack of ADCC, bivalency