Antibody-Drug Conjugates: Current Status and Future Directions

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AD Cs: Current Status & Future Directions

- Introduction – the vision for ADCs, and its challenges
- Where are we now? (success, failure, enthusiasm, disappointment & resurrection)
- What have we learned – addressing the challenges
- Future directions
“We must search for magic bullets. We must strike the parasites (cancer cells), and the parasites only, if possible, and to do this, we must learn to aim with chemical substances!”

– Paul Ehrlich
Requirements for Effective Cancer Therapy

- > $10^{12}$ Cancer cells (1 kg tumor) in disseminated disease
- > 99% Cell kill required to induce a complete response
- Further cell kill needed for disease eradication

*Former Physician in Chief, Dana Farber Cancer Institute, Boston. Deceased 2013
Increasing Potency:

- **Combination Chemotherapy**: Combining two or more cancer drugs with non-overlapping mechanisms/toxicity
  - Some improvement in potency
  - Increased toxicity

- **More potent agents**: 100 to 10,000-fold more cytotoxic than standard anti-cancer drugs evaluated in the clinic
  - **Tubulin interacting agents**:
    - Maytansine (1978)
    - Dolastatin 10 (1997)
  - **DNA interacting agents**:
    - Adozelesin (1994)
    - Bizelesin (2002)

**High systemic toxicity**: Low clinical doses
  = Insufficient activity
Increasing the Therapeutic Window: the Aim of an ADC

**Cytotoxic Chemotherapy**
- MTD (Maximum Tolerated Dose)
- MED (Minimum Effective Dose)

**Antibody-Drug Conjugate Therapy**
- Increase MTD (increase selectivity)
  - Decreased systemic toxicity via altered distribution
- Decrease MED (increase potency)
  - Specific delivery to tumor via antibody binding

**Therapeutic index**
Antibody-Drug Conjugates (ADCs)

ADCs can be viewed as:

- Conferring therapeutic potency to antibodies
- Conferring tumor-specificity to cytotoxic agents

Cytotoxic molecule
ADCs – The Challenge and the Opportunity
Using Antibodies to Provide Specificity to Cytotoxic Compounds

- Tumor penetration
- Binding & internalization
- Non-lysosomal activation
- Lysosomal activation
- Metabolites – profiles, fates
- Bystander killing
- Effect on tumor microenvironment
Critical Challenge: The Properties of the Payload Requirements for use in ADCs

- High Potency: IC$_{50}$ $\sim$ 10$^{-10}$ to 10$^{-11}$ M range
  - Low tumor localization of antibodies in patients: dosimetry studies with radiolabeled MAbs$^1$ (24 h after injection)

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>% Injected Dose / g Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>0.005 – 0.01</td>
</tr>
<tr>
<td>Ovarian</td>
<td>0.006 – 0.009</td>
</tr>
<tr>
<td>Melanoma</td>
<td>0.003 – 0.01</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>0.08</td>
</tr>
<tr>
<td>Breast</td>
<td>0.06</td>
</tr>
<tr>
<td>Median</td>
<td>$\sim$ 0.01% ID/g</td>
</tr>
</tbody>
</table>

- Synthetically accessible
- Retains potency when modified for linkage
- Reasonably soluble in aqueous solution: unique requirement for use in ADCs
- Stable in aqueous solution

Many Challenges Overcome to Achieve Success in ADCs

Knife Edge on Katahdin, Maine. September 2014
Gemtuzumab Ozogamicin (Mylotarg®)
The First ADC approved for the treatment of cancer

- Conditional approval for Acute Myeloid Leukemia (AML) in 2000 (1)
  - Dosing: 9 mg/m² x 2 (day 1, day 15)
  - Side Effects: neutropenia and hepatic veno-occlusive disease (2)

- Withdrawn in 2010 (negative phase 3 trial)

(1) Bross et al. Clin Cancer Res 2001; 7:490-496
ADCs of Highly Potent Tubulin Agents: Clinical Success Achieved in Hematopoietic cancer!

Auristatin ADC: Adcetris® (brentuximab vedotin)

Received accelerated approval by FDA in 2011 for Hodgkin lymphoma and ALCL (Full approval in 2015)
ADCs of Highly Potent Tubulin Agents: Clinical Success Achieved in Solid Tumors!

Maytansinoid ADC: Kadcyla® (ado-trastuzumab emtansine)

Received full approval by FDA in 2013 for HER2-positive metastatic breast cancer after Herceptin + a taxane
The Success of Adcetris ® & Kadcyla ® Spawned Renewed Enthusiasm for ADCs

- Number of new ADCs entering into clinical testing each year (to 2015)

Chari ACS Med Chem Lett 2015
Early 2013 – mid 2017

- No more ADCs approved
  - Discontinuation of several ADC development programs leads to disappointment in the field
  - Perhaps expectations of development timelines have not been realistic?
    - Only 4 – 5 years since approvals of Adcetris and Kadcyla
First approval was a 13-year process (8 years of clinical development) from start of preclinical research to approval.
Aug/Sept 2017 - Two Calicheamicin ADCs Approved by FDA!

- Inotuzumab ozogamicin (targeting CD22)
  - Approved for B cell acute lymphoblastic leukemia (B-ALL)

- Gemtuzumab ozogamicin (targeting CD33)
  - (re) Approved for acute myeloid leukemia (AML)
    - Phase 1 published in 1999 Sievers et al Blood 93:3678
    - ~20 years in clinical development
    - Lower dose and different schedule versus 2000 approval
# ADCs That Have Entered Clinical Trials

(1) Beck et al., *Nature Reviews Drug Discovery* 17th March 2017; (updated Sept. 2017; jml)

(2) calicheamicin.  (3) PBD  (4) 60 different targets.

<table>
<thead>
<tr>
<th>PAYLOAD CLASS</th>
<th>Approved ADCs</th>
<th>ADCs in Pivotal trials</th>
<th>ADCs in Clinical Trials (non-pivotal)</th>
<th>ADCs Discontinued</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auristatins (vcMMAE/mcMMAF)</td>
<td>1</td>
<td>2</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Maytansinoids (DM1/DM4)</td>
<td>1</td>
<td>2</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>DNA-targeting (calicheamicin/duocarmicin/PBD/IGN/dox)</td>
<td>2 (2)</td>
<td>1 (3)</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Other tubulin-targeting (auristatins/tubulysin)</td>
<td>-</td>
<td>0</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Miscellaneous (SN38-deriv. / other)</td>
<td>-</td>
<td>1</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td><strong>TOTAL (95)</strong> (4)</td>
<td>4</td>
<td>6</td>
<td>54</td>
<td>31</td>
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</table>
ADCs – The Challenge and the Opportunity

- Non-lysosomal activation
- Lysosomal activation
- Binding & internalization
- Tumor penetration
- Bystander killing
- Metabolites – profiles, fates
- Effect on tumor microenvironment

Effect on tumor microenvironment
Delivery of ADC into the tumor

- Potential limiting factors
  - **Size of IgG molecule**
  - **Pharmacokinetics**
    - Intrinsic antibody PK properties
    - Effect of payload (hydrophobic) on antibody PK
    - Stability of linker
  - **Influence of target on penetration**
Distribution of IgG into tumor tissue is relatively slow.

- Maximum concentration achieved in 24 – 48 h (distribution phase)

Erickson Mol Cancer Ther 2012
Distribution of IgG into tumor tissue

- IgG does accumulate into tumor tissue due to prolonged PK
  - Any compromise to mAb PK compromises amount that can be delivered
  - Antibodies do penetrate tumors
    eg. trastuzumab is active
    BUT dosing not limited by toxicity

- High target density may compromise distribution
  - “binding site barrier”

Schmidt & Wittrup Mol Cancer Ther 2009
Distribution of ADC into tissues – Future Directions

- Improving PK properties of antibody
  - Alter binding to FcRn
- Minimizing effect of normal tissue antigen “sink”
  - Identify selective tumor targets (role for bispecificity?)
  - Mask binding to normal tissue (e.g., CytomX technology)
- Improving PK properties of ADC
  - Improved linker stability
  - Site specific technologies to minimize payload effects on PK (alter location and/or number of hydrophobic payloads)
- Minimizing size
  - Small protein domains +/- albumin-binding (e.g., Ablynx, Crescendo)
  - Very small – e.g., Bicycle Therapeutics
EXAMPLE: Increasing the half life in plasma may increase therapeutic window of ADCs

Hamblett et al Mol Pharmaceutics 2016
FDA: Correlation between Kadcyla Exposure and Response Rate

Model predicts 60%-80% response rate for patients in highest quartile

Cycle 1 $C_{\text{min}}$
ADC Catabolism: Safety Considerations

Uptake/catabolism:
- Target mediated
- Non-target mediated

Potential toxicity

Plasma cleavage

Normal Tissue

Blood Pool

CANCER CELL

Normal Tissue

metabolism & clearance

Potential toxicity
ADC Catabolism: Safety Considerations

Potential toxicity

Uptake/catabolism: Target mediated Non-target mediated

Normal Tissue

metabolism & clearance

Potential toxicity
Delivery of ADC to tumors: Influence of target density

Trastuzumab Delivery *In Vivo* — IgG1 Retention + HER2 Binding

Associations between the uptake of $^{111}$In-DTPA-trastuzumab, HER2 density and response to trastuzumab (Herceptin) in athymic mice bearing subcutaneous human tumour xenografts

Kristin McLarty - Bart Cornelissen - Deborah A. Scolar - Susan J. Done - Kathy Chun - Raymond M. Reilly


Trastuzumab Delivery vs. HER2 Levels
(3 d post administration)

BT474EEI cell line
Trastuzumab — 9% ID/g
Non-specific IgG1 — 4% ID/g

Specific Uptake Ratio (SUR)

HER2 Receptor Density (receptors/cell)
Kaplan-Meier plot of PFS based on HER2 mRNA Levels in T-DM1 Phase II Trial (Burris et al 2011).

Of 112 total subjects, 74/95 confirmed HER2+ by IHC

50/74 HER2+ mRNA by qRT-PCR

ADCs – The Challenge and the Opportunity

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Delivery of Payload into Cancer Cells

- A reason for poor activity
  - The ADC get to the tumor, but not enough active payload accumulates **within** cells
  - More potent payload?
  - ADC chemical tools to optimize uptake and release of payload
Delivery of Payload into Cancer Cells

- **Uptake & intracellular trafficking**
  - Efficiency of internalization upon binding target
    - Net transport into cancer cell is a function of target antigen density and turnover rate to/from plasma membrane
  - Is ADC recycled to cell surface or routed to lysosomes?
    - Alter transport/trafficking by bispecific mAbs (eg MEDI4276)?

- **Release of cytotoxic metabolites**
  - Peptide linkers cleaved by proteases (cell surface to lysosome)
  - Total mAb protein degradation by lysosomal proteases
  - Increased rate of hydrolytic release at low pH (endosome/lysosome)
  - Reductive cleavage of disulfide linkers

- **Chemical nature of released intermediate and final metabolites**
  - Hydrophilic (charged) or hydrophobic (uncharged)
    - Affects cell retention, potential for bystander killing
Future Directions: Utilizing the Growing ADC Toolbox to Address the Challenge of Improving Therapeutic Index

**Targeting Vehicles**
- MAbs
- Probodies
- Novel protein and chemical binders

**Linkers**
- Thioether
- Peptide
- Hindered disulfides
- Others in development

**Payloads**
- TUBULIN-acting agents (Maytansinoids, auristatins, tubulysin, others)
- DNA-acting (PBDs, IGNs, duocarmicins, others)
- OTHERS (amanitin, SN38-analogs, others)

**Conjugate Chemistry and Screening**
- Lysine, cysteine and site-specific conjugation
- Microscale synthesis and screening methods
- Proprietary conjugate CMC capabilities
Anti-FRα – Maytansinoid ADC (mirevetuximab soravtansine) Arriving at an Optimized Linker through *In Vivo* Studies

Activity in Mice Bearing FRα-Expressing OVCAR3 Xenografts

![Graph showing tumor volume over days post inoculation](image)

- **Vehicle control**
- **Anti-FRα-maytansinoid DM4 conjugate**

2.5 mg/kg X single dose

n ~ 3.4 per antibody

Ab O, et al. Mol Cancer Ther. 2015; 14:1605
ImmunoGen’s Hydrophilic Linker for ADCs

- Activity against multidrug resistant (mdr) cells

**In Vitro Cytotoxicity**

- **Ab-sulfo-SPDB-DM4**

**In Vivo Efficacy**

- **Ab-SPDB-DM4**

- **Ab-sulfo-SPDB-DM4 Conjugate is more activity in vitro and in vivo towards mdr+ cells**

Peptide-cleavable Maytansinoid ADC with High Bystander Killing

Widdeson  AACR 2017 Abstr 2186
Qui  AACR 2017 Abstr 71
Improved Efficacy with Similar Tolerability

Anti-CanAg AMC Efficacy: Highly Heterogeneous CanAg+ HT-29 Xenografts

Mouse tolerability: MTD ~ 1250 g/kg (DM dose) for both mAb-LDL-Imm-DM and mAb-sSPDB-DM4

Widdison AACR 2017 Abstr 2186; Qui AACR 2017 Abstr 71
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**Conjugate Chemistry and Screening**

- Lysine and site-specific conjugation
- Microscale synthesis and screening methods
- Proprietary conjugate CMC capabilities
IGNs: New Class of DNA-Acting Agents
Designed for Efficacy and Tolerability

ImmunoGen IGNs (indolinobenzodiazepines)

- Alkylate DNA without crosslinking it
- Highly potent anti-tumor activity without the sustained toxicity that limits re-dosing (preclinical)

ImmunoGen IGN ADCs

- **CD33-targeting IMGN779**
  - First ADC with IGN payload
  - Phase 1 in AML began 1H 2016

- **CD123-targeting IMGN632**
  - Peptide-linked IGN; site-specific
  - Phase 1 1H 2017
Comparison of Alkylator and Crosslinker of an anti-FRα-IGN

MTD = 5.60 mg/kg (antibody dose)

MTD = 1.96 mg/kg (antibody dose)

Miller et al
AACR 2017
Abstr 53
Clinical Development – Challenges and Future Directions

- **Patient selection**
  - Development of T-DM1
    - selection of HER+ patients critical to success
  - High bar for patient inclusion, low bar for the level of target antigen expression (per cell, and proportion of cells positive) is a recipe for failed development.
  - Example: selection of patients with high FRα expression for the phase 3 development of mirvetuximab soravtansine
Patients with FRα-positive, platinum resistant ovarian cancer

FRα ≥ 50% ≥2+ ≤ 3 prior Tx

Primary endpoint: PFS [all patients (med + high), or high-FRα-expressers only]

AIWB = adjusted ideal body weight; PLD: pegylated liposomal doxorubicin
Clinical Development – challenges and future directions

- **Patient selection**
  - Development of T-DM1
    - Selection of HER+ patients critical to success
  - High bar for patient inclusion, low bar for the level of target antigen expression (per cell, and proportion positive) is a recipe for failed development.
  - The future is “Precision Medicine”
  - Example: selection of patients with high FRα expression for the phase 3 development of mirvetuximab soravtansine

- **Combinations of ADCs with chemotherapy, biologic and immunologic agents**
  - Single agent development is possible in some disease settings (eg., platinum-resistant ovarian cancer)
  - However, most cancers treated with combinations of agents
  - ADCs well suited to combinations – good tolerability profiles
Mirvetuximab Soravtansine Combination Options

Patients with previously treated FRα-positive ovarian cancer

FRα-positive 2+/3+ on at least 25% tumor cells

Dose Escalation

- MS + PLD
- MS + bevacizumab
- MS + carboplatin
- MS + pembrolizumab


Preclinical data Ponte et al., AACR-NCI-EORTC 2015 Abstr C170. Ponte, Neoplasia 2016; 18:775-784

MS = mirvetuximab soravtansine
PLD = pegylated liposomal doxorubicin
ADCs – The Challenge and the Opportunity

- Tumor penetration
- Binding & internalization
- Non-lysosomal activation
- Lysosomal activation
- Bystander killing
- Metabolites – profiles, fates

Effect on tumor Microenvironment
- Neovasculature
- Immunosuppressive
Looking into the Future – Meeting the Challenges of Developing ADCs for Treating Cancer

- Improved target selection
- Diversified linkers and cytotoxics
- Improved conjugation technology
- Diversified mAbs, small domains, bispecifics, etc.
- Companion Dx for pt. selection
- Combinations, especially I-O