The Advent of Antibody-Drug Conjugates

MacMillan Group Meeting
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Tracy Liu
Anti-cancer treatments should be as aggressive as possible to fully eradicate the tumor...

...but it is precisely this aggressiveness that often causes severe side effects

Common Chemotherapeutic Agents

- 5-fluorouracil
  - thymidylate synthase inhibitor
- methotrexate
  - anti-folate
- cisplatin
  - DNA crosslinking agent

- lack of tumor selectivity - killing of proliferating normal cells
- requires administration at near the maximum tolerated dosage
  - 99% of cells in a tumor must be killed to achieve complete remission
Limited clinical efficacy of chemotherapeutics is due to an insufficient therapeutic window - lack of ability to kill enough cancer cells without causing toxicity to normal cells.

Current most critical need: Maximization of the Therapeutic Window

$$\text{increase } MTD = \text{increase selectivity}$$

$$\text{decrease } MED = \text{increase potency}$$
Targeted Cancer Therapy

Direct Approaches

Targeting tumor-associated or specific proteins to directly alter their signaling by:

- direct binding of monoclonal antibody to antigen expressed on tumor cell surface to induce immune responses
- binding of small molecule drugs to active site of a protein to disrupt normal function

Targeted Cancer Therapy

Indirect Approaches

Reliance on proteins specifically expressed or overexpressed on tumor cell surfaces that function as a targeting platform for fusion proteins bearing different effector molecules

- antibody-directed enzyme prodrug therapy
  - selective activation of a mildly toxic prodrug to a toxic drug at the tumor site through conjugation of an enzyme to a tumor-specific antibody

**Targeted Cancer Therapy**  
*Indirect Approaches*

*Reliance on proteins specifically expressed or overexpressed on tumor cell surfaces that function as a targeting platform for fusion proteins bearing different effector molecules*

- monoclonal antibody (fusion protein)
- effector molecule
- antigen (overexpressed protein)
- tumor cell

**Effector molecule**
- small molecule drug (antibody-drug conjugate)
- toxin (immunotoxins)
- radionucleotides (radioimmuno conjugate)
- immunoregulatory cytokines (antibody-cytokine fusion protein)

Antibody-Drug Conjugates
A Brief Introduction and History

Anatomy of an Antibody-Drug Conjugate

A. Antibody
B. Linker
C. Small-molecule drug warhead

Number of Publications in Antibody-Drug Conjugate Research
1900 - present day
Antibody-Drug Conjugates
A Brief Introduction and History

1970 - advent of murine mAB
1975 - advent of murine mAB
1980 - first chimeric mAB
1987 - first chimeric mAB
1987 - first therapeutic mAB (unconjugated) - Rituxan
1990 - first therapeutic mAB (unconjugated) - Rituxan
Genentech/Biogen
Genentech/Biogen

Part I.
First Generation Antibody-Drug Conjugates and Lessons Learned

Part II.
Second Generation Antibody-Drug Conjugates and Their Improvements

Part III.
Current Challenges and Overview of Clinical Performance

mAB = monoclonal antibody
ADC = antibody-drug conjugate

2000 - first FDA approved ADC - Mylotarg
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Wyeth (Pfizer)
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2010 - FDA approves Adcetris
2010 - FDA approves Adcetris
Seattle Genetics
Seattle Genetics

2010 - Pfizer withdraws Mylotarg
2011 - FDA approves Kadcyla
2010 - FDA approval of Kadcyla
Genentech/Immunogen
Genentech/Immunogen

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1970

1975 - advent of murine mAB

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1987 - first chimeric mAB

1990

1997 - first therapeutic mAB (unconjugated) - Rituxan Genentech/Biogen

2000

2000 - first FDA approved ADC - Mylotarg Wyeth (Pfizer)

2006

2010 - FDA approves Adcetris Seattle Genetics

2011 - FDA approves Kadcyla Genentech/Immunogen

2010 - Pfizer withdraws Mylotarg

Deconstruction of Antibody-Drug Conjugates
Key Domains of the Immunoglobulin G Antibody Scaffold

The majority of antibody-drug conjugates are built upon the immunoglobulin G (IgG) scaffold

- represents 75% of serum antibodies in humans
- protein complex of 4 peptide chains in a Y shape
  - 2 identical heavy chains (light purple)
  - 2 identical light chains (dark purple)
- **F_{ab}** = Fragment antigen-binding domain
  - Consists of variable (V) and constant (C) domains
  - Antigen binding CDR domains found at termini
- **F_{c}** = Fragment crystallizable/constant domain
  - Ideal location for drug conjugation - far from CDR
  - Consists of a CH\(_2\) domain and a CH\(_3\) domain

Domains of a Typical IgG Antibody

Deconstruction of Antibody-Drug Conjugates
Key Domains of the Immunoglobulin G Antibody Scaffold Relevant to Drug Conjugation

Nature of the chemistry between antibody and linker is primarily determined by the naturally occurring functional groups present on the surface of the antibody.

Domains of a Typical IgG Antibody

Bioconj. Chem. 2015, 26, 176.
Deconstruction of Antibody-Drug Conjugates
Traditional Methods of Linker Conjugation to Antibody

Linking through native Cysteine residues

Pros

- High nucleophilicity of sulfur - naturally high reactivity for conjugation chemistry
- Low abundance of cysteine in primary sequence - easier control of drug to antibody ratio (DAR)

  4 interchain disulfide bridges - easier to reduce
  12 intrachain disulfide bridges - harder to reduce

Cons

- No free thiols naturally present - partial reduction required
- Selective reduction of the 4 interchain disulfide bridges is most common, but this partial reduction can result in a destabilized antibody

Bioconj. Chem. 2015, 26, 176.
Deconstruction of Antibody-Drug Conjugates

Traditional Methods of Linker Conjugation to Antibody

**Linking through native Cysteine residues**

**Common disulfide bridge reducing agents**

- dithiothreitol (DTT)
- tris(2-carboxyethyl)phosphine (TCEP)
- 2-mercaptoethanol

**Corresponding oxidized byproducts**
**Deconstruction of Antibody-Drug Conjugates**

**Key Domains of the Immunoglobulin G Antibody Scaffold Relevant to Drug Conjugation**

*Nature of the chemistry between antibody and linker is primarily determined by the naturally occurring functional groups present on the surface of the antibody.*

- **Linking through native cysteine residues**
  - Requires reduction to access free thiol
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- Linking through native **lysine** residues

Domains of a Typical IgG Antibody

Deconstruction of Antibody-Drug Conjugates
Traditional Methods of Linker Conjugation to Antibody

Linking through native Lysine residues

Pros

- Naturally nucleophilic functional handle
- No requirement for pre-functionalization prior to conjugation with linker

Cons

- Greater natural abundance of lysine - control of drug to antibody ratio significantly more difficult
  - ~86 lysine residues total spanning all domains
  - ~20 accessible for functionalization
- Low levels of competitive cysteine and tyrosine conjugation observed in some cases

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- Linking through conserved glycans in CH2 domain

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Linking through native Glycan residues

Pros

■ Post-translational glycosylation of N297 (Asparagine) residue provides facile site-specific conjugation
■ Glycosylation site is in CH$_2$ domain - well removed from antigen binding domain

Cons

■ Glycosylation is a heterogenous post-translational modification - difficult to control drug to antibody ratio
■ Requires pre-oxidation of vicinal diol moiety on glycan to access the bioorthogonal aldehyde handle

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- **Linking through conserved glycans in CH\(_2\) domain**
  - Post translational modification glycosylates N297
  - Oxidation of terminal sugar furnishes aldehyde

Domains of a Typical IgG Antibody

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Deconstruction of Antibody-Drug Conjugates

More on the Antibody

Advances in recombinant DNA technology have enabled the generation of engineered antibodies

murine mAB

chimeric mAB

humanized mAB

human mAB

replacement of protein sequences of a mouse antibody with naturally occurring sequences in humans significantly reduces undesired immune responses

First Generation Antibody-Drug Conjugates
Transition from Chemotherapeutics

In an attempt to achieve greater selectivity for chemotherapy drugs, first generation antibody-drug conjugates took clinically established cancer drugs as warheads.

methotrexate
anti-folate

vinca alkaloids
anti-mitotic/microtubule agent

doxorubicin
antibiotic

Survey of 4 clinically evaluated first generation antibody-drug conjugates

KS1/4 - methotrexate
KS1/4 - DAVLB
KS1/4 - DAVLBHYD
BR96 - doxorubicin

First Generation Antibody-Drug Conjugates

KS1/4S2 - Methotrexate Conjugate

methotrexate

KS1/4S2 murine mAB

KS1/4-methotrexate

- non-cleavable amide linker formed through non-selective EDC coupling
- significant localization to tumor
- Phase I clinical trials revealed little therapeutic benefit potentially due to non-cleavable linker
- murine mAB elicited a human anti-murine antibody (HAMA) response in patients

First Generation Antibody-Drug Conjugates

KS1/4 – 4-Desacetylvinblastine Conjugates

4-desacetylvinblastine

succinic anhydride

KS1/4S2 murine mAB

KS1/4-DAVLB

- esterase-labile hemisuccinate linker
- highly potent in vivo activity with greater efficacy than unconjugated drug
- Phase I clinical trials using radiolabeled conjugate indicates localization of drug to tumor cells
- no increased therapeutic effect
- patients developed immune responses to both the antibody and vinca alkaloid

**First Generation Antibody-Drug Conjugates**

**KS1/4 – 4-Desacetylvinblastine Conjugates**

- *4-desacetylvinblastine derivative*

- **KS1/4-DAVLBHYD**

- **KS1/4S2 murine mAB treated with NaIO₄**

- □ cleavable acid-labile hydrazone linker
- □ highly potent *in vivo* activity with greater efficacy than unconjugated drug
- □ Phase I clinical trials indicates localization drug to tumor cells
- □ no increased therapeutic effect - premature cleavage of hydrazone
- □ patients developed immune responses to both the antibody and vinca alkaloid

First Generation Antibody-Drug Conjugates

BR96 - Doxorubicin Conjugate

- BR96 - doxorubicin
- linker with hydrazide and maleimide
- BR96 chimeric mAB

- acid-labile hydrazone linker
- highly potent \textit{in vivo} activity with greater efficacy than unconjugated drug
- advanced to Phase II clinical trials
- significant gastrointestinal toxicity - target antigen expression on normal tissue cells
- 50\% of patients developed immune responses despite chimeric mAB

First Generation Antibody-Drug Conjugates
Universal Shortcomings and Lessons Learned

All four case studies successfully demonstrated localization of drug payload to tumor sites, but in all cases no significant improvement in therapeutic activity was observed...

I. Low in vitro potency - conjugation results in decreased cytotoxicity compared to free drug
   ■ Different mechanisms of cellular uptake
     ■ Free drugs can diffuse through cell membrane
     ■ Conjugated drugs require efficient internalization after binding to antigen
   ■ Need 10^6 molecules/cell of a moderately potent cytotoxic drug to effect cell kill
   ■ Limited expression of antigen - tumor cells typically express 1 x 10^5 receptors/cell

II. Stability of the linker was inadequately tuned
   ■ Hydrazone linkers were too labile - prone to cleavage prior to cellular uptake
   ■ Amide linker not labile enough - no cleavage to release drug after internalization

III. Antibodies of murine or chimeric origin illicited undesired immune response
   ■ Generation of human anti-murine antibodies
   ■ Rapid clearance of antibody-drug conjugate upon repeat dosing

Improving Antibody-Drug Conjugates
Ideal Characteristics of an Antibody-Drug Conjugate

A. Antibody
B. Linker
C. Small-molecule drug

- selective for antigens with high copy numbers (>10⁵/cell) on target cell
- selective for antigens uniquely expressed on tumor cell
- homogeneous expression of antigen on tumor cell
- induces minimal immunogenic response
- Stable to circulation in vivo
- Selectively cleaved only once internalized inside target cell
  - disulfide linkers
  - protease labile linkers
- Designed to release drug in its active form (without linkers)
  - self immolative linkers
- Stable to long-term storage in aqueous environments
- highly potent in vitro - potency in picomolar range required
- sensitive to the ideal mechanism of action for specific tumor types
- amenable to introduction of functional groups for linking
- water soluble

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Second Generation Antibody-Drug Conjugates
Most Commonly Used Drug Payloads

maytansanoids
anti-mitotic agent

auristatins
anti-mitotic agent

calicheamicins
DNA damaging agent

Second Generation Antibody-Drug Conjugates

Maytansanoid Antibody-Drug Conjugates

- 1000 fold more cytotoxic than first generation payloads
- Binds tubulin to suppress microtubule dynamics, resulting in cell arrest in G2/M phase
- Good aqueous solubility
- SAR activity indicates that the ester at C_3 can be derivatized for linker conjugation without impacting drug activity

maytansine
anti-mitotic agent

maytansinol

1. DTT reduction

Second Generation Antibody-Drug Conjugates
Maytansanoid Antibody-Drug Conjugates

Second Generation Antibody-Drug Conjugates

Maytansanoid Antibody-Drug Conjugates

Improved mechanism of selective drug release

- glutathione naturally present in high concentration inside tumor cells (millimolar range), but exceptionally low (micromolar range) in blood stream - selective cleavage upon internalization

- disulfide linkage is stable under physiological pH

- stability of the antibody-drug conjugate can be tuned by varying the steric of the R groups flanking the disulfide bond

Second Generation Antibody-Drug Conjugates
Maytansanoid Antibody-Drug Conjugates

Study on effect of linker stability to therapeutic efficacy

HuC242-DM1

HuC242-DM3

HuC242-DM4

Extreme case - synthesis of a non-cleavable conjugate?

Second Generation Antibody-Drug Conjugates

Maytansanoid Antibody-Drug Conjugates

maytansine
SMCC (non-cleavable) linker
succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate
humanized C242 mAB

\( \text{HuC242-MCC-DM1} \)

Second Generation Antibody-Drug Conjugates
Maytansanoid Antibody-Drug Conjugates

HuC242-MCC-DM1 shows greatest stability  
(*in vivo* half life of 134 hrs)  

HuC242-DM4 shows greatest cytotoxicity

What is the mechanism of action of these maytansanoid antibody-drug conjugates?
Second Generation Antibody-Drug Conjugates

Maytansanoid Antibody-Drug Conjugates

Cellular Processing of Disulfide Linked Maytansanoids

Second Generation Antibody-Drug Conjugates
Maytansanoid Antibody-Drug Conjugates

Enhanced Therapeutic Efficacy of Cleavable Disulfide Linkers is Due to Bystander Cell Killing

Second Generation Antibody-Drug Conjugates

Auristatin Antibody-Drug Conjugates

- inhibits tubulin-dependent GTP binding and microtubule dynamics
- fully synthetic series of highly potent anti-mitotic agents based on SAR studies on dolastatin 10
- SAR indicates terminal 3° amine can be derivatized for conjugation AND terminal phenethyl amine can be changed without loss of efficacy

**dolastatin 10**  
*anti-mitotic agent*

**monomethyl auristatin E (MMAE)**  
(R₁ = Me, R₂ = OH)

**monomethyl auristatin F (MMAF)**  
(R₁ = CO₂H, R₂ = H)

Second Generation Antibody-Drug Conjugates

Auristatin Antibody-Drug Conjugates

chimeric cAC10 mAB
mal-caproyl-val-cit-PAB linker
monomethyl auristatin

\[ \text{Mal-caproyl-val-cit-PAB-MMAE} \]

Second Generation Antibody-Drug Conjugates

Auristatin Antibody-Drug Conjugates

Improved mechanism of selective drug release

- Valine-citrulline dipeptide moiety is known to be selectively cleaved by the protease cathepsin B
- $p$-aminobenzyl group is self immolating - fragments to release the MMAE drug without any residual groups

Second Generation Antibody-Drug Conjugates

Auristatin Antibody-Drug Conjugates

Mechanism of cellular processing of mal-caproyl-val-cit-MMAE conjugate

Mal-caproyl-val-cit-PAB-MMAE

cathepsin B mediated peptide cleavage

free MMAE
good bystander killing

Second Generation Antibody-Drug Conjugates

Auristatin Antibody-Drug Conjugates

chimeric cAC10 mAB

mal-caproyl (non-cleavable) linker

monomethyl auristatin

\[ \text{Mal-caproyl-MMAF} \]

**Second Generation Antibody-Drug Conjugates**

*Auristatin Antibody-Drug Conjugates*

**Cellular Processing of Non-Cleavable Mal-caproyl-MMAF Conjugates**

*lysosomal processing*

*poor bystander killing*

charged nature prevents diffusion into neighboring cells

Second Generation Antibody-Drug Conjugates

Calicheamicin Antibody-Drug Conjugates

- calicheamicin $\beta_1^{Br} - X = Br, R = iPr$
- calicheamicin $\gamma_1^{Br} - X = Br, R = Et$
- calicheamicin $\gamma_1^{I} - X = I, R = Et$

$N$-acetyl calicheamicin $\gamma_1^{I} - X = I$

- calicheamicins
  - DNA damaging agent

- insanely cytotoxic class of anti-tumor antibiotics (0.15µg/kg dose)
- aryl tetrasaccharide moiety binds in minor groove of DNA, placing enediyne warhead within double helix
- too toxic for use as drug warhead - 20 fold less potent $N$-acetyl analogue developed for applications to ADCs
- trisulfide converted to disulfide - provides a handle for conjugation

Second Generation Antibody-Drug Conjugates

Calicheamicin Antibody-Drug Conjugates

Mechanism of Action of the Calicheamicins

Second Generation Antibody-Drug Conjugates

Calicheamicin Antibody-Drug Conjugates

hP67.6 humanized mAB

AcBut linker
(4-(4'acetylphenyl)butanoic acid)

N-acetyl calicheamicin

hP67.6 N-Ac-γ-calicheamicin DMH AcBut

Second Generation Antibody-Drug Conjugates

Calicheamicin Antibody-Drug Conjugates

hP67.6 N-Ac-γ-calicheamicin DMH AcBut

Improved mechanism of selective drug release

- Linker specifically designed to provide high stability prior to internalization into tumor cells, but is readily cleaved once inside the lysosome - hydrazone formed from ketone rather than aldehyde
  - only 6% hydrolysis observed at pH = 7.4
  - 97% hydrolysis observed at pH = 4.5 at 37°C over 24 hrs

- Inclusion of a hindered disulfide moiety in the linker provides a second handle for selective drug cleavage via glutathione reduction upon internalization inside cell

Antibody-Drug Conjugates
A Brief Introduction and History

Current Trends in Research in Antibody-Drug Conjugates
Controlling the Drug to Antibody Ratio (DAR) and Achieving Site-Specific Conjugation

Though the underlying protein scaffold is constant in a heterogeneous population of antibody-drug conjugates, each conjugate has its own set of pharmacokinetic, toxicity, aggregation, antigen affinity, and drug release properties.

Forefront of research in this field currently lies in achieving:

1. Populations of antibody-drug conjugates with a homogenous DAR
2. Site-specific conjugation of drugs on a given antibody

Current Trends in Research in Antibody-Drug Conjugates

Methods of Homogeneous Conjugation Using Natural Antibodies

- N-terminal conjugation leveraging differences in pK\(_a\) between terminal and internal amino acids

![Chemical structure]

- Though conjugation via this method is in the antigen binding domain, drug conjugation here does not seem to impact antigen recognition and binding

- Resulting ketone product can be easily further functionalized through reaction with oximes bearing a linker or drug

- Limitation: Reaction sensitive to nature of terminal amino acid - works best for alanine, glycine, aspartate glutamate, and asparagine

- Limitation: Some antibodies may not be able to tolerate elevated temperatures required for transamination

Site-specific functionalization of glutamines through enzymatic conjugation

Selectively functionalizes only Q295 residue (flanked by a consensus recognition sequence for a bacterial transaminase)

Q295 residue is distant from antigen binding domain

Limitation: Requires deglycosylation in the CH₂ domain prior to functionalization, which may impact function and properties of the antibody-drug conjugate

Current Trends in Research in Antibody-Drug Conjugates

Methods of Homogeneous Conjugation Using Engineered Antibodies

THIOMABs
- engineered Cys at positions
- with minimal interference to antibody function

C-terminal selenocysteine
- engineered selenocysteines
- (more nucleophilic)
- selectively at C-terminus

aldehyde tagging
- engineered recognition sequence for formylglycine
- generating enzyme (FGE)

Clinically Successful Antibody-Drug Conjugates

FDA Approved Antibody-Drug Conjugates

**brentuximab vedotin (Adcetris)**
Seattle Genetics
FDA approved in 2011 for Hodgkin lymphoma and anaplastic large cell lymphoma (ALCL)

**ado-trastuzumab emtansine (Kadycla)**
Roche/Genentech/ImmunoGen
FDA approved in 2013 for metastatic breast cancer

Clinically Successful Antibody-Drug Conjugates

*FDA Approved Antibody-Drug Conjugates*

**Gemtuzumab ozogamicin (Mylotarg)**

Wyeth/Pfizer

FDA approved in 2000 for acute lymphoblastic leukemia

Withdrawn in 2010 due to toxicity concerns and lack of improvement in patient survival time

Clinically Successful Antibody-Drug Conjugates

Antibody-Drug Conjugates Currently in Clinical Evaluations

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<th>Antigen</th>
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