Antibody Drug Conjugates: Biology and Opportunities for Gynecologic Cancers

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VERBAL DISCLOSURE

• I serve on advisory boards for Astra Zeneca, Abbvie, Aravive, Blueprint pharmaceuticals, Eisai/Serono, Elevar, Genentech/Roche, Hengrui, Immunogen, INXmed, Imab, Lilly, VBL Therapeutics, Mersana, Myriad, Mereo, Merck, Novartis, Vavotar, Tarveda, GSK/Tesaro

• I serve on steering committees for Genentech/Roche, Immunogen, and VBL Therapeutics

• I receive research funding from PTC Therapeutics, Lilly, GSK/Tesaro, Merck

• I serve as Associate Director for GOG Partners and am on the GOG Foundation BOD
Antibody Drug Conjugates: Continuing the Paradigm Shift Towards Individualized Therapy

Treatment for Gynecologic Malignancies is becoming more individualized
  - PARP inhibition for BRCA and HRD
  - Immune checkpoint inhibition for MSI-Hi/MMRd

Antibody Drug Conjugates are the next frontier in personalized therapy, allowing us to
  - target specific tumor associated antigens
  - deliver highly potent chemotherapy directly to the tumor
  - offer patients a differentiated safety profile
  - offer combination therapies in the near future which may replace standard, systemic chemotherapy

Antibody Drug Conjugates: A Paradigm Shift

Highly selective monoclonal antibodies (mAb) for a tumor associated antigen that has limited to no exposure on normal cells

A potent cytotoxic

A linker that is stable in circulation but releases the cytotoxic in the target cell

https://www.adcreview.com/the-review/antibody-drug-conjugate-development/
Targets

Antibody targets should have high expression levels on tumor and not on normal tissue.

Antibody targets should be present on the cell surface so the ADC can find them.

Antibody targets should be internalizing so that the ADC is transported into the cell, like a Trojan Horse.
ADCs are already changing the landscape in oncology

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Generic Name</th>
<th>Conjugate</th>
<th>Indication</th>
<th>Target</th>
<th>Year approved</th>
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<tbody>
<tr>
<td>Mylotarg</td>
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<td>Tisotumab vedotin</td>
<td>MMAE</td>
<td>Solid tumor (cervix)</td>
<td>Tissue Factor</td>
<td>2021</td>
</tr>
</tbody>
</table>

ADC Components

1. **Antibody**: A highly selective monoclonal antibody for a tumor-associated antigen that has restricted expression on normal cells.

2. **Linker**: A potent cytotoxic agent designed to induce target cell death when internalized in the cell and released.

3. **Drug**: A linker that is stable in circulation, but releases the cytotoxic agent in target cells (controlled by altering stability and degree of hindrance around disulfide bond).
Monoclonal Antibody

Antibody producing cells were immortalized by fusing them with myeloma cell line → production of mAbs with predefined specificity

Allowed for large volume production

Unconjugated mAbs depend on host immune effector mechanisms such as ADCC and CDC

Resistance is a problem

Target Antigen

**Target Antigen Selection is a key requirement for ADCs**

1. The target antigen must have high expression in the tumor and no or low expression in healthy cells. (ie: HER2 is expressed 100x more in tumor vs normal cells)

2. The target antigen must be expressed on the surface of the tumor cell to be expressed to circulation and the circulating monoclonal antibody

3. The target antigen has to possess internalization properties to transport the ADC into the cell

Targeting Folate Receptor Alpha (FRα) – an ideal target for ovarian cancer

• FRα is a cell surface folate receptor which mediates folate transport into epithelial cells
• FRα expression is limited on normal cells, but is upregulated on cancers, primarily ovarian, but also endometrial, and triple negative breast
• It is most highly expressed on the surface of serous epithelial ovarian cancers (EOC) – As assessed by immunohistochemistry (IHC)
NaPi2b is an Ideal Antibody-Drug Conjugate (ADC) Target Assay Developed to Measure Antigen Expression

- ADC internalizing sodium phosphate transporter; not an oncogene
- Broadly expressed in ovarian cancer and NSCLC adenocarcinoma
- Limited expression in normal tissues
- IHC assay calibrated to distinguish wide range of expression

Epithelial ovarian cancer

H score = 293

Lung adenocarcinoma

H score = 265

**Ovarian Cancer Patient-Derived Xenograft Models**

Response correlated with NaPi2b Expression

H-score measures the percentage of cells staining multiplied by their intensity (0, 1+, 2+, 3+) for a range of 0 - 300
Mechanism of Action:

The ADC localizes to tumor and binds to target antigen

The ADC is internalized

The internalized vesicles fuse with other vesicles and enter the endosome-lysosome pathway

Proteases digest the antibody to release the toxins which → apoptosis

https://www.adcreview.com/the-review/antibody-drug-conjugate-development/
Internalization is Antigen Dependent

Hammood et al. Pharmaceuticals 2021, 14, 674
Internalization is Antigen Dependent- and can be a source of resistance

Hammood et al. Pharmaceuticals 2021, 14, 674
## Cytotoxic Warheads

<table>
<thead>
<tr>
<th>Cytotoxic Drug (warhead)</th>
<th>Mechanism of Action</th>
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<tbody>
<tr>
<td>Auristatins</td>
<td>Tubulin polymerase inhibitor</td>
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<tr>
<td>Maytansines</td>
<td>Tubulin depolymerisation</td>
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<tr>
<td>Calicheamicins</td>
<td>DNA cleavage</td>
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<tr>
<td>Duocarymycins</td>
<td>DNA minor groove alkylating agent</td>
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<td>PBD dimers</td>
<td>DNA minor groove cross-linker</td>
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<tr>
<td>α-Amanitin</td>
<td>RNA polymerase II inhibitor</td>
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Microtubule Disrupting Agents

Monomethyl Auristatin E (MMAE)

- Family of auristatins
- Blocks polymerization
- 100-1000x more potent than doxorubicin

Maytansine (s)

- Derived from Ethiopian Shrub Maytenus serrata
- Inhibits microtubule assembly, induces disassembly and disrupts mitosis
DNA Modifying Agents

Duocarmycin Analogues

- DNA minor groove binding, alkylating agents

Calicheamicin

- Cleaves DNA
- 4000x more potent than doxorubicin
Linkers are Key

- High drug linker stability in circulation

- Cleavable

- Non-Cleavable

- Control of DAR

- PEG Linkers
  - Hydrophilic poly(ethylene glycol) linkers
  - Allow higher DAR
    - (can be multi-arm and/or escort hydrophobic toxins into cell)
That’s Simple – But What Could Go Wrong?

• Efficacy
  – Inadequate binding to the target cell
  – Inadequate internalization
  – Inadequate drug concentrations released into the target cell
  – Target cell not sensitive to drug

• Toxicity
  – Suboptimal monoclonal antibody specificity
  – Drug is toxic even when linked to antibody
  – Drug releases in circulation
  – Drug leaches out of target cell

G Wiener, ASCO 2013
<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Conjugate</th>
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Conclusions

• The approval of antibody drug conjugates for the treatment of Her2+ breast cancer and Hodgkins lymphoma has created great enthusiasm for the technology as a proven paradigm.

• Antibody drug conjugates against novel targets are in development for a large number of solid tumors and blood cancers.

• The possibilities for developing and utilizing these agents are limited only by the discovery of suitable targets, both highly expressed on and relatively specific to cancer cells.

• ADCs allow more precise delivery of chemotherapy to cancer cells, which should improve effectiveness relative to toxicity.