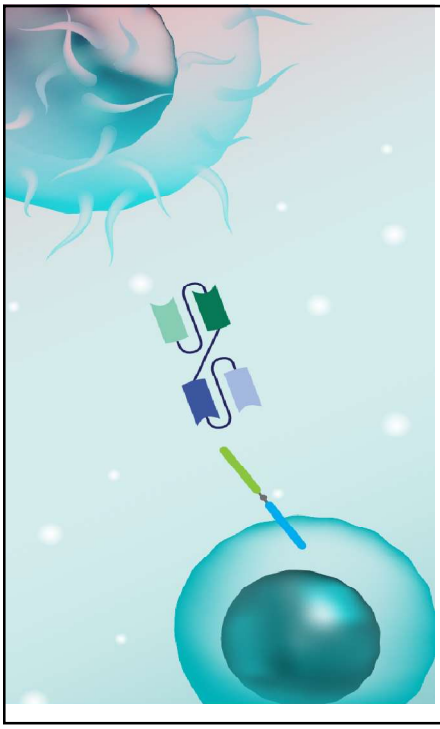

T-Cell Engaging Bispecific Antibody Therapy

AHCI Symposium

Sept 26, 2025

Fiona He, MD

Allina Health | ABBOTT NORTHWESTERN HOSPITAL

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Disclosures

- Dr. He served on advisory board for Astra Zeneca.

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Objectives

- Describe mechanism of action for T-cell engaging bispecific antibodies
- Describe pathophysiology and management of immune effector cell-associated neurotoxicity syndrome and cytokine release syndrome
- Recognize and treat common on-target, off tumor effects
- List indications for bispecifics in management of lymphoma, multiple myeloma, and small cell lung cancer

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Proc. Natl. Acad. Sci. USA
Vol. 92, pp. 7021–7025, July 1995
Immunology

Target = 17-1A (antigen expressed on EpCAM) - cell adhesion molecule that **may be upregulated in gastrointestinal tumors** (and others)

A small bispecific antibody construct expressed as a functional single-chain molecule with high tumor cell cytotoxicity

MATTHIAS MACK, GERT RIETHMÜLLER, AND PETER KUFER

Institut für Immunologie, Goethestrasse 31, D-80336 Munich, Germany

Communicated by Gunter Blobel, The Rockefeller University, New York, NY, April 14, 1995

ABSTRACT **Construction of a bispecific single-chain antibody derivative is described that consists of two different single-chain Fv fragments joined through a Gly-Ser linker. One specificity of the two Fv fragments is directed against the CD3 antigen of human T cells and the other is directed against the epithelial 17-1A antigen; the latter had been found in a clinical trial to be a suitable target for antibody therapy of minimal residual colorectal cancer. The construct could be expressed in CHO cells as a fully functional protein, while its periplasmic expression in *Escherichia coli* resulted in a non-functional protein only. The antigen-binding properties of the bispecific single-chain antibody are indistinguishable from those of the corresponding univalent single-chain Fv fragments. By redirecting human peripheral T lymphocytes against 17-1A-positive tumor cells, the bispecific antibody**

lems, we developed a procedure by which two single-chain Fv (sc-Fv) fragments (15, 16) directed at the 17-1A antigen and the CD3 antigen on T lymphocytes were linked by one or three Gly_4-Ser_1 units. The construct could be expressed in CHO cells as one functional single-chain molecule. An N-terminal Flag epitope was inserted for easy detection and a C-terminal histidine tail was attached for efficient purification from culture supernatants. The resulting recombinant protein proved to be highly cytotoxic for tumor cells at nanomolar concentrations. It thus appears as the ideal candidate for therapy of disseminated 17-1A-positive tumor cells during early phases of metastasis when these cells are lodging in interstitial tissue compartments easily accessible for macromolecules as well as for the required effector T cells.

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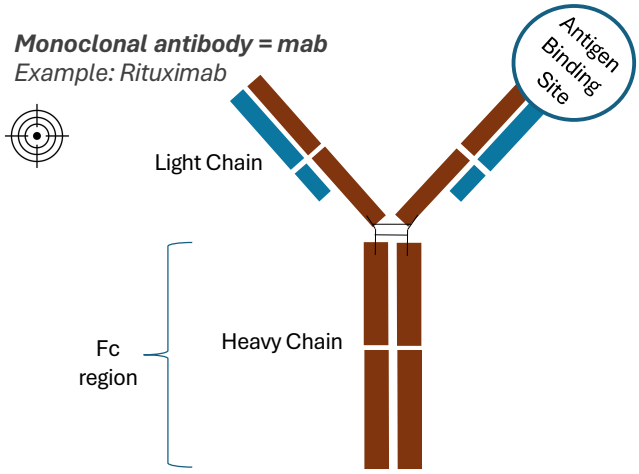
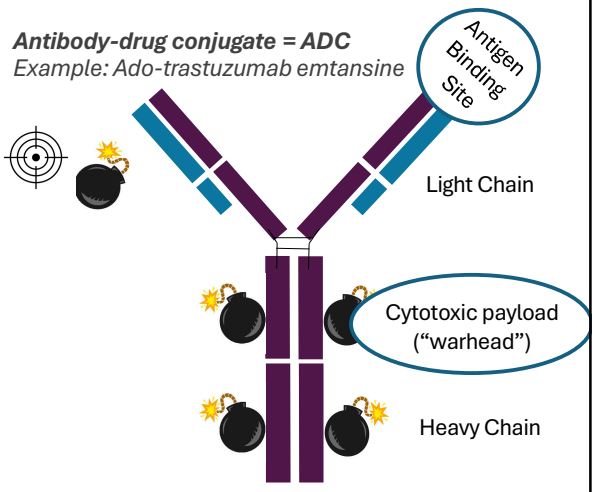
Using Immunoglobulins as Cancer Therapy

Monoclonal antibody = mab
Example: Rituximab



Antibody-drug conjugate = ADC
Example: Ado-trastuzumab emtansine



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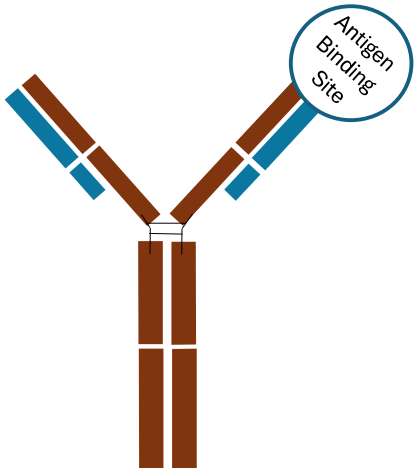
T-Cell Engaging Bispecific Antibodies



Antigen Binding Site on Tumor

Bispecific antibody =
BsAb ="Bispecific"
Example: Teclistamab

Antigen binding site on T-cell (CD3)

Not T-cell engaging antibodies: Emicizumab & Amivantamab

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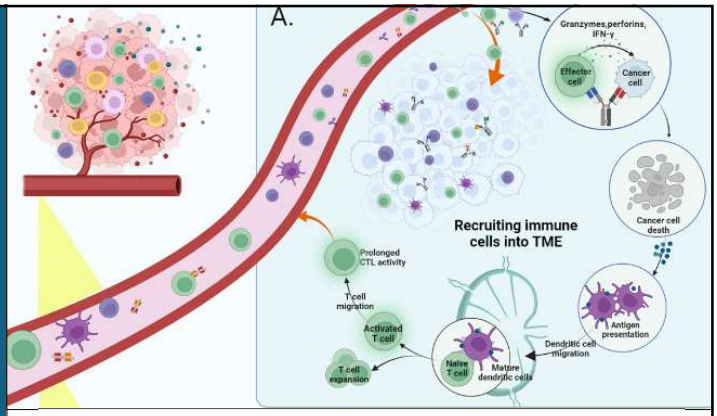
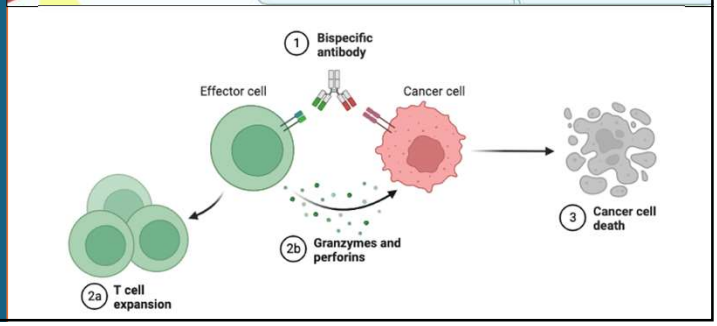
T-Cell Engaging Bispecific Antibodies

Mechanism of action: Bind to target antigen expressed on **tumor cells** and CD3 expressed on **T-cells**, bringing them in close proximity and mediating the cytotoxic activity of T-cells





Wei J, Yang Y, Wang G, Liu M. *Front Immunol.* 2022;13:1025276

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FDA Approved

Heme Malignancies

- **Acute lymphoblastic leukemia (ALL)**
  Target = CD19
- **Lymphoma**
  Target = CD20
- **Multiple myeloma**
  Targets = BCMA, GPRC5D

Solid Malignancies

- **Small cell lung cancer (SCLC)**
  Target = DLL3
- **Uveal melanoma**
  Target = GP100

FDA Approved TCE BsAbs

B-Acute Lymphoblastic Leukemia (ALL): Blinatumomab (Blincyto®)

Multiple Myeloma
- Teclistamab (Tecvayli®)
- Talquetamab (Talvey®)
- Elranatamab (Elrexfio®)

Diffuse Large B-Cell (DLBCL)
- Epcoritamab (Epikinly®)
- Glofitamab (Columvi®)

Follicular Lymphoma (FL):
- Mosunetuzumab (Lunsumio®)
- Epcoritamab (Epikinly®)

Uveal melanoma: Tebentafusp (Kimmtrak®)

Small Cell Lung Cancer (SCLC): Tarlatamab (Imdelltra®)

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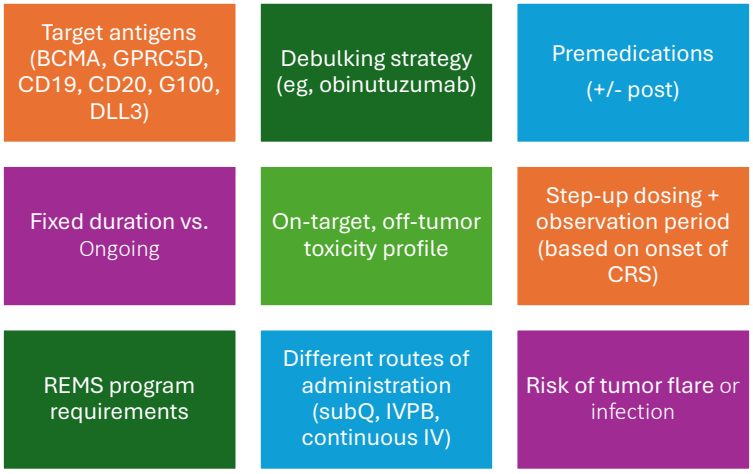
Comparison Between TCE BsAbs



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CAR-T

- **Advantages**:
- 1-time single infusion ("living drug")
- High response rates and high rate and long-lasting efficacy (functional cures in some diseases such as DLBCL)

Disadvantages:

- Requires time for manufacturing process (3-6 weeks from collection to infusion)
- Caregiver requirement at most facilities, driving restrictions generally 6 weeks
- Insurance may not approve ($$$)
- Higher risks of CRS/Neurotox Grade III/IV
- Requires lymphodepleting chemotherapy prior
- Access limited to certain tertiary care facilities, mostly academic

BISPECIFICS

- **Advantages**:
- "Off the shelf" therapy at REMS-trained facility, readily available for rapidly progressing disease
- Single agent activity with high response rates, high CR rates

- **Disadvantages**:
- Prolonged or continuous therapy
- Caregiver requirement at most facilities, generally 2 weeks
- May affect efficacy of future CAR-T therapy if given prior (especially with shared target antigens)
- Dependent on having enough functional T-cells
- No tails on PFS curves…yet
- Costs also high (but "pay as you go")

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Non T-cell Engaging Bispecific Antibodies

- Amivantamab (EGFR x MET) for non-small cell lung cancer
- Zanidatamab (HER2 x HER2) for biliary tract and gastric cancers
- Zenocutuzumab (HER2 x HRE3) for NRG1 fusion-positive tumors

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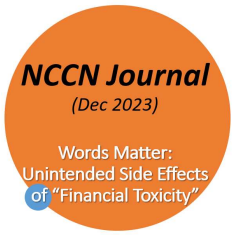
Toxicities of T-cell Engaging BSAs



- ***General Toxicity***
  - Infection/Pancytopenia
  - Target determines toxicity
  - Financial ~~Toxicity~~ Exploitation: $25-50k per month ($285-650k total)
    - "Toxicity" implies necessary risk of treatment — high costs are modifiable harms
  - CRS/ICANS (REMS)

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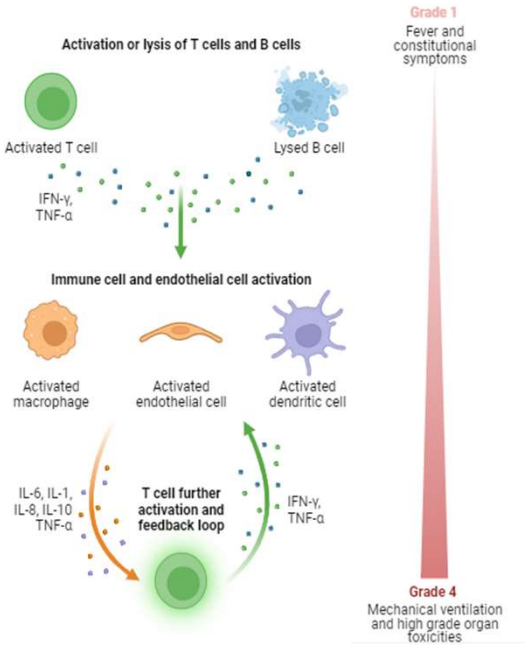
Cytokine Release Syndrome (CRS)

- **Symptoms:** **fever, hypotension, hypoxia, headache,** myalgia/arthralgia, headache, fatigue, hyperinflammatory syndromes, organ dysfunction
- **Risk factors**
  - Age & comorbidities
  - Dehydration
  - Aggressive disease biology
  - High tumor burden
  - Administration dose/schedule
  - Degree of T-cell activation and expansion
  - Generally confined to step-up doses or first full dose



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ASTCT Consensus Grading of CRS

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	≥ 38 ℃	≥ 38 ℃	**≥ 38 ℃**	**≥ 38 ℃**
***With* Hypotension**	None	No vasopressor	**Vasopressor +/- vasopressin**	**Multiple vasopressors (excluding vasopressin)**
***And/or* Hypoxia**	None	Low flow nasal cannula	**High-flow nasal cannula, facemask, non-rebreather, Venturi mask**	**Positive pressure (CPAP, bipap, mechanical ventilation)**

In patients who have CRS then receive antipyretic or anticytokine therapy, fever is no longer required to grade subsequent CRS severity (CRS grading then driven by hypotension and/or hypoxia)

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Managing CRS

General Principles

- Avoid growth factors during early period with higher CRS risk
- Consider early use of tocilizumab:
  - For patients at high risk of complications
  - For patients receiving scheduled steroids after BsAb dosing (eg, epcoritamab)
- For recurrent grade 3 or any grade 4 CRS, discontinue agent permanently

Does not include blinatumomab

CRS	Pharmacologic
Grade 1	• Administer APAP 1000mg PO up to 3 to 4 times daily as needed (may be able to manage with APAP alone in some cases) • Consider dexamethasone 10 mg (PO/IV) once if refractory or recurrent fever (within 6-8 hours); may schedule daily for persistent symptoms • Treat as grade 2 if persistent fever
Grade 2	Dexamethasone 10 mg PO/IV every 12 hours • If no improvement in 4 hours, consider tocilizumab 8 mg/kg IV (max 800 mg)
Grade 3 Medical Emergency	Dexamethasone 10-20 mg IV every 6 hours **PLUS** Tocilizumab 8 mg/kg IV (max 800 mg)
Grade 4 Life threatening	Dexamethasone 20 mg IV every 6 hours **PLUS** Tocilizumab 8 mg/kg IV (max 800 mg) (could consider increasing to methylprednisolone 1000 mg IV every 24 hours)

Consider anakinra for refractory CRS - if used, add levofloxacin and anti-mold coverage due to increased risk of infections
For tarlatamab & tebentafusp: May consider lower dexamethasone doses within the range provided

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3 Main Types of Neurotoxicity

1. **Immune effector-cell associated neurotoxicity syndrome (ICANS)**
   - Pathologic process involving CNS that results in activation of T-cells and/or other immune effector cells
   - Frequently overlaps with or follows CRS
   - Immune effector-cell encephalopathy (ICE) score utilized to grade ICANS
2. **Peripheral neuropathy**
   - Mostly sensory
   - Associated with a previous history of peripheral neuropathy
   - May require temporary interruption of BsAb therapy or short course of steroids
3. **Headache**
   - Non-specific (can also be associated with CRS)
   - Often responds to treatment with APAP or local measures (eg, cold)

Symptoms of Neurotoxicity & ICANS

ICANS

General slowing
Headache
Dizziness
Agitation or delirium
Cognitive skill impairment
Dysgraphia
Altered consciousness level
Encephalopathy
Seizures
Cerebral edema
Motor weakness

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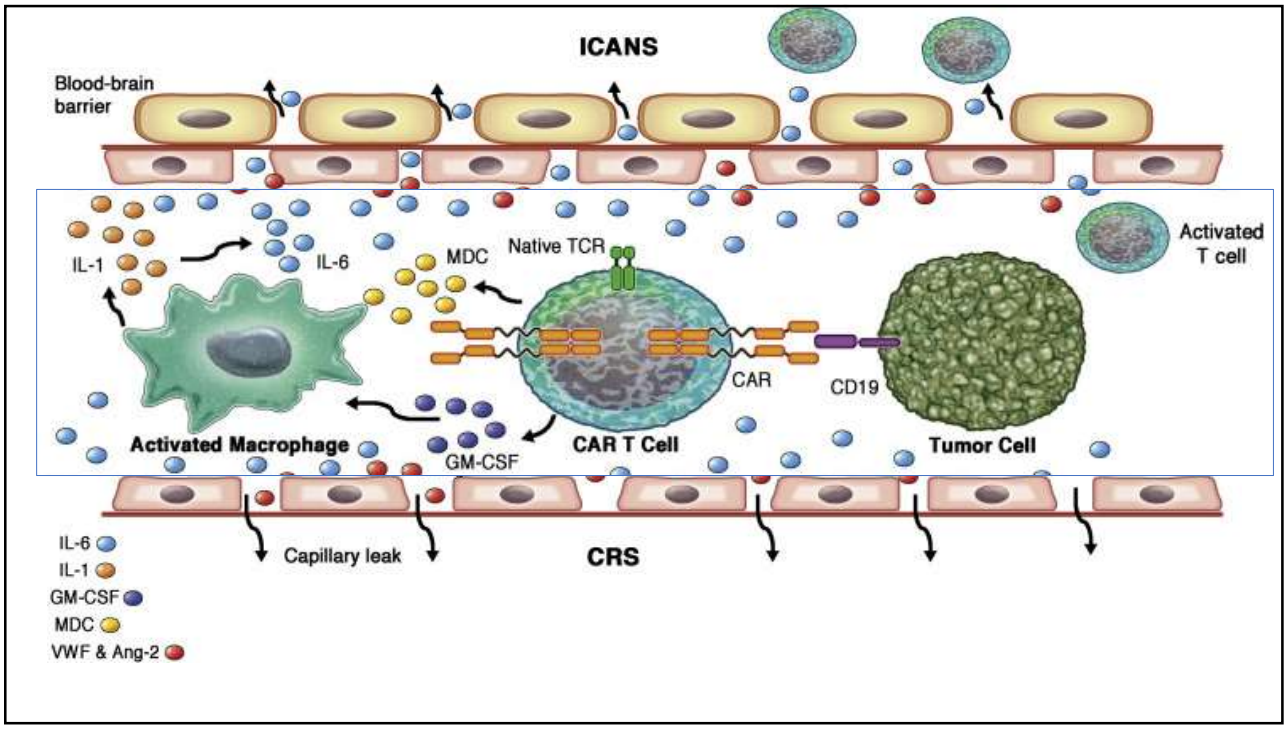

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ICE Score (points)	Parameter
4	Orientation: year, month, city, hospital (1 point for each)
3	Naming: ability to name 3 objects (eg, point to clock, pen, button" -1 point for each)
1	Following commands: ability to follow simple commands (eg, "show me 2 fingers" or "close your eyes and stick out your tongue")
1	Writing: ability to write the same simple sentence ("the quick brown fox jumps over the lazy dog")
1	Attention: ability to count backwards from 100 by 10

ASTCT Consensus ICANS Grading

Neurotoxicity	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score (10 – Grade 0)	7-9	3-6	**0-2**	**0**
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	**Awakens only to tactile stimulus**	**Stupor or coma**
Seizure	N/A	N/A	**Clinical seizure resolves rapidly**	**Prolonged seizure**
Motor Findings	N/A	N/A	**N/A**	**Deep focal motor weakness**
Elevated ICP	N/A	N/A	**Focal or local**	**Diffuse**

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