CellMosaic, INC
10A Roessler Road
Woburn, MA 01808
USA

Phone: 781-463-0002
Fax: 781-998-4694
Email: info@cellmosaic.com
Website: www.cellmosaic.com

ANTIBODY-DRUG CONJUGATE (ADC) SOLUTIONS

ADC Preparation Kits, Tailored Services, and In-Process Assay Kits

Since 2017, CellMosaic® is providing PerKits™ to help our customer quickly evaluate if their antibody is a candidate for an effective ADC. Kits are available in many configurations with a variety of conjugation strategies. Kits are complete with all reagents and procedures for attaching the selected payload directly to customer's antibody and purifying the final ADC. A typical ADC kit starts with 1-3 mg of antibody and results in an ADC with 40-60% recovery in buffer and an average drug-to-antibody ratio (DAR) of 2-4. Purities are typically >90% for the conjugates free of or with less than 5% of unreacted payload. Kit instructions are complete, easy to follow, and can typically be carried out within 6 hours (with less than 1-hour hands-on time).

Tailored Services: Customer can choose to send their samples to CellMosaic® for HPLC and MS analysis (setup fee waived), determination of DAR, and further purification for single DAR compound.

Tailored In-Process Assay Kits: CellMosaic® provides in-process assay kits for our advanced customer to optimize the loading.

Selected Citations using CellMosaic Kits:

1. Lofgren K.A. *et. al. Antibody Therapeutics* **2021**, *4* (4), 252-261.
2. Neetha P. *et. al. Leukemia* **2023,** *37*, 2050-2057.
3. Micalizzzi D. S. *et. al. PNAS* **2022**, *43* (119), e2209563119.

Name	Product No.
Antibody **Doxorubicin** Conjugation Kit	CM11406 (x1, x3)
Antibody **Methotrexate** Conjugation Kit	CM11407 (x1, x3)
Antibody **SN38** Conjugation Kit	CM11408 (x1, x3)
Antibody **MMAE** Conjugation Kit (with VC-PAB Linkage)	CM11409 (x1, X3)
Antibody Mertansine (**DM1**) Conjugation Kit	CM11410 (x1, X3)
F(ab')2 **MMAE** Conjugation Kit (with VC-PAB Linkage)	CM11416 (x1, x3)
F(ab')2 **DM1** Conjugation Kit	CM11419 (x1, x3)
Antibody Mc-**MMAF** Conjugation Kit	CM11422 (x1, x3)
Antibody **MMAF** Conjugation Kit (with VC-PAB Linkage)	CM11425 (x1, x3)
Antibody **Deruxtecan** Conjugation Kit	CM11431 (x1, x3)
Antibody Small Molecule Acid Conjugation Kit	CM51403
ADC Control Kit with VC-PAB Linker	CM11429

Currently: 7 Drugs with cleavable or non-cleavable linkers

Tailored services and assay kits for ADC kits

Name	Product No.
Thiol Assay Kit with Purification	CM90005
Maleimide Assay Kit	CM90002
SEC HPLC Analysis	AS0023
HIC HPLC Analysis	AS0025
MALDI-TOF MS	MS0015

Stabilizing Buffers, HPLC Standards and Buffers for ADC

Proprietary ADC Stabilizing Buffer: These proprietary buffers keep the ADCs in solution when stored below freezing. Stabilizers also help preserve the structure of the ADCs during lyophilization. Stabilizing buffers are biocompatible and will not interfere with any *in vitro* or *in vivo* studies. The buffer does not contain preservatives, protease inhibitors, reducing agents, metal chelators such as EDTA, or other carrier proteins. If needed, all buffer components can be removed by dialysis or desalting before use in downstream assays.

HPLC Standards and Buffers: Size exclusion chromatography (SEC) HPLC standards and hydrophobic interaction chromatography (HIC) buffer set for customer's convenient analysis of ADCs in house.

Name	Product No.
ADC Stabilizing PBS Buffer (5x)	CM02022
ADC Stabilizing Citrate Buffer (5x)	CM02023
ADC Stabilizing General Buffer (5x)	CM02024
SEC (Gel filtration) HPLC Protein Standard (7 components, lyophilized)	CM92004
SEC (Gel filtration) HPLC Low Molecule Weight (LMW) Protein Standard	CM92005
HIC Buffer Set (for HPLC analysis)	CM02025

ADC Standards and Controls

CellMosaic® commercializes various drug standards, control ADC kit, and pre-made ADC controls (positive, negative, or non-binding) for customer to use in parallel for *in vitro* and *in vivo* ADC studies. **hIgG non-binding controls**: Low endotoxin level and fully characterized (UV, HPLC, and MS). Prepared with the same linking chemistry matching our corresponding ADC kits with the same drug. **Drug Standards:** High purity and stable counterparts of the drug used for ADC synthesis.

Name	Product No.
ADC Control hIgG1-**MMAE**	CM51100
ADC Control hIgG1-**SN38**	CM51102
S-Methyl **DM1** Standard	CM11016
S-Methyl **DM4** Standard	CM11015

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ADC Assay Reagents

To facilitate our customers' ADC research, CellMosaic® commercializes a variety of pre-made drug conjugates for ADC *in vitro* and *in vivo* bioassay. Most of these drug conjugates are designed with the same or similar linker and conjugation strategies matching our ADC kits.

BSA Conjugates	Product No.	HRP Conjugates	Product No.
BSA-Deruxtecan	CM52140	HRP-Deruxtecan (Dxd) (1:1)	CM53215
BSA-DM1	CM52110	HRP-MMAE (1:1)	CM53209
BSA-DM4	CM52112	HRP-MMAE (1:2)	CM53210
BSA-MMAE	CM52113	HRP-MMAF (1:1)	CM53216
		HRP-VC-PAB-MMAF (1:1)	CM53217

ADC Ruotine Synthesis with set price

CellMosaic® created standardized and routine bioconjugation services for a variety of ADCs. Customers can place the order online with their choice of linkers, scale of the reaction, purification and characterization, and formulation methods. The service can usually be completed within 2-4 weeks.

Name	Service Code
Routine Small-Scale ADC Synthesis (3, 5, and 10 mg)	RS0001
Routine **Medium and Large-Scale** ADC Synthesis (**30, 100, and 200 mg**)	RS0002

ADC Discovery, ADC Development and Manufacturing at CellMosaic

CellMosaic offers complete ADC discovery, development, and manufacturing services for our customer.

Each antibody is unique, as the particular drug, linker, and chemistry that works for one ADC may not apply to others. CellMosaic has the in-house capability and expertise to devise and execute appropriate linker and conjugation strategies to fit customer's ADC development plan. Specifically, CellMosaic will provide **custom design and development of linker and conjugation strategies** to fit customer's needs. CellMosaic has various in-house ADC processes to quickly synthesize ADCs for initial proof-of-concept studies with minimum development efforts/time.

CellMosaic advances its customer's ADC projects under the following three incremental stages.

✓ ADC Discovery (Stage I)

- Screening various small drug molecules to optimize ADC performance.
  - PerKit™ ADC: MMAE, Deruxtecan, MMAF with or without VC-PAB, DM1, SN38, Doxorubicin, Methotrexate
  - Customer specific toxins or drugs can be added depending on the properties of the drugs
- Evaluation of the deciding on the antibody labeling sites.
  - PerKit™ ADC: surface amines and reduced thiols
  - Other supported: single Cys mutated antibody, glycolysation sites, N-terminal amino site, enzymatic labeling sites
- Optimize the linkage chemistry.
  - PerKit™ ADC with different chemistries
    - Stable bond via maleimide thiol coupling or amide
    - Releasable linkage via Val-C-PAB or ester bond
  - Other supported chemistries
    - Releasable oxime, hydrazone bond, pyrophosphate
    - Stable bond via DBCO-azide click chemistry, amide direct linkage, thiol ether
    - Other selections developed at CellMosaic or customer recommended
- Evaluation linker type & length
  - PerKit™ ADC: ethylene, PEG, peptide
  - Other selections of conventional linker developed at CellMosaic
  - In the event an ADC cannot be made using classical linkers or the effectiveness of the ADCs are compromised by the number of toxins loaded onto the antibody, Customer has the option to try super-hydrophilic and water soluble proprietary AqT™ Linkers under licensing/collaboration

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✓ ADC Development (Stage II):

- Stability and formulation studies
  - Stability study design & protocol
  - PerKit™ ADC: ethylene, PEG, peptide
  - Other selections of conventional linker developed at CellMosaic
- Purity profile establishment and characterization
  - Established bio-analytical methods for ADC at CellMosaic
  - HPLC: reversed-phase, HIC, SEC, cation or anion exchange
  - Mass Spectrometric: MALDI-TOF MS, LC/MS Profiling
  - DAR determination by UV/Vis, HPLC, and MS
  - Gel
- Purification optimization
  - Established purification methods for ADCs that can be extrapolated to customer ADCs
  - Capacity to purify ADC in large scale using various media.
- Pharmacokinetic and pharmacodynamic studies
  - pK studies of ADCs in blood and tissue extracts
  - As benchmark, pK studies of ADCs with many of CellMosaic selected linkages/linkers have been established in preclinical or clinical studies

✓ Process Development, Scale Up & Manufacturing (Stage III)

- Supply chain and manufacturing strategy.
  - Material sourcing from qualified CellMosaic's vendors
  - Identify site of manufacturing based on GMP/non-GMP requirement (CellMosaic or Partner)
  - Forecast production scale using info from Stage II
  - Define process development and manufacturing pathway
- Safety, quality, and compliance.
  - Safety assessment and documentations: establishment of hazard categorization and control system, SDS
  - Risk Assessments
  - Technical and process auditing
  - Pre-approval inspection preparation and remediation
  - Cleaning and sterility validation
  - Quality management system development
- Process development and optimization.
  - Incoming raw materials QC: Antibody, Drug, Linker (or Linker-Drug), Crosslinkers (using QC methods from Stage II)
  - Process development from mg to gram scale (info from Stage II)
  - Process optimization and validation at the desired scale
  - Formulation, stability, analytical testing, product specifications
  - SOP documentation
  - Prototype lot manufacturing
- Non-GMP/GMP manufacturing and technology/process transfer.
  - Non-GMP manufacturing
  - GMP SOP documentation and approval
  - Technology/process transfer if necessary
  - GMP manufacturing
    - Setting up the QC instrumentation and process
    - Manufacturing and purification instrumentation
    - Planning and oversight of manufacturing
    - Packaging and labeling
    - Inventory and distribution

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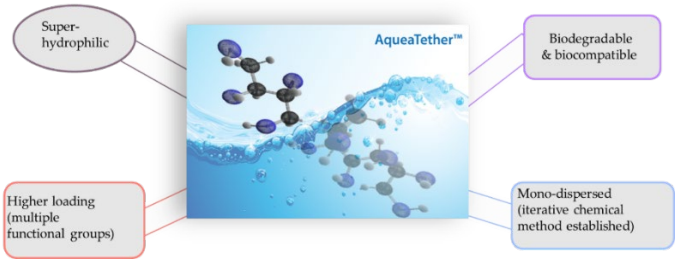
Proprietary Water Soluble AqT™ Linkers for Novel ADC Development

In the event an ADC cannot be made using classical linkers or the ADC effectiveness is compromised by the number of toxins loaded onto the antibody, CellMosaic has developed novel super-hydrophilic and high-loading AqT™ linkers specifically to solve these problems.

Benefit of AqT® ADC

- Decreased toxicity
  - Less aggregated with no or limited precipitation
  - More biocompatible
- Increased efficacy
  - Increase antibody stability (prevent enzymatic degradation of the antibody during circulation)
  - Less heterogeneous (increased label efficiency)
  - Retention of binding activities
  - Higher loading if necessary
- Strong Intellectual Property (IP) position
  - The first company in the sugar alcohol IP space. Freedom of operation.
  - Patent protection for broad composition matters of AqT® molecules and their conjugates.
  - Worldwide issued patents.



Example Preparation of AqT™-ADC-MMAE with VC-PAB

	AqT™-ADC-MMAE with VC-PAB	MMAE ADC with VC-PAB
DAR	5.2 by HIC, 4.6 by UV ratio (SEC HPLC)	4.7 by HIC, 4.4 by UV ratio (SEC HPLC)
Aggregation by SEC	<10%	34%
Unreacted Antibody	0.9%	2.5%
Heterogenicity by HIC	Mainly DAR 5 and 6 conjugates	spread evenly between DAR 1 to 7 conjugates

AqT® ADC Development Path

Early-stage evaluation of AqT® technologies
To facilitate the Customer's evaluation of CellMosaic's AqT®-drug for Customer's internal development and drug screening with short timeline and low cost, CellMosaic provides easy access to AqT® technologies without any license fee under CellMosaic's standard material transfer agreement (MTA).

- **No accessing or license Fee for evaluation**
  - Preparing AqT® ADC at CellMosaic with standard custom bioconjugation cost rate.
  - AqT® ADC are transferred under MTA.
  - Scale of the production: 1-3 mg (up to total 30 mg AqT®-ADC per drug) of Ab.
- Selected AqT®-Drugs: **AqT®-SN38**, **AqT®-VC-PAB-MMAE**, **AqT®-VC-PAB-Deruxtecan**
- Selected AqT® Linker and Linkage Chemistry: T4 linker for surface NH2 and reduced thiol labeling

Full AqT® ADC development plan
For Customers who wish to work from the beginning using AqT® technologies or after the completion of the early-stage evaluation, CellMosaic offers a flexible ways/term to work with for a full AqT® ADC development plan.

- Development partnership
- Option to license
- Joint-venture or equity partnership
- Grant mechanism

Full AqT® ADC Discovery, Development & Manufacturing (Process similar to standard ADC development & manufacturing)

- No limitation of AqT® drugs.*
- No limitation of AqT® linker and linkage chemistry.*
- No limitation of the reaction scale or production scale
- License terms and technology transfer to be negotiated

*: with compatible chemistry

Example Preparation of AqT™-SN38 for Cell Toxicity Assay (A great toxicity increase was obtained for AqT™-SN38-ADC.)

Cell lines	IC50 (pM)			Increased toxicity (AqT™ vs classical linker)
	SN38-ADC	AqT™-SN38-ADC	MMAE-ADC	
NCI-H1975	19529	8373	102.5	2.3
NCI-H226	8302	1142	N/A	7.5
A549	53594	788	N/A	68.0
PC9	35874	2584	205.4	7.0
	18183	788	N/A	3.6

Ref: IC50 for T-DM1 in BT-474 cell line: 2710 pM (Cancer research 2008, 68, 9280-9290)