First-in-Class Antibody–Drug Conjugates Targeting Tumor-Specific Tn-Glycoforms of MUC1 and MUC4: Preclinical Efficacy and Translational Potential of GO-M100B and GO-M400

#6923

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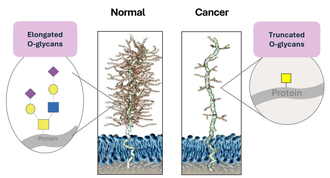
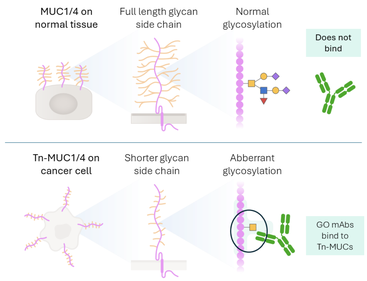
Platform overview



The truncated O-glycan Tn is cancer specific

- Broad expression in epithelial-derived tumors
- No expression in normal tissue
- Stable expression across all cancer stages
- Increased expression in metastases
- Stable expression after chemo treatment
- Drive tumor formation and immune tolerance
- Overlap (>50%) with PDL1



mAb M100B targeting Tn-MUC1

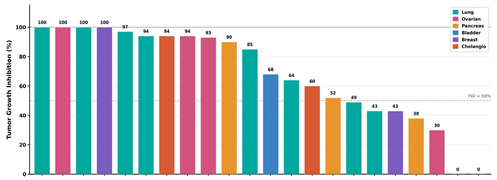
- Humanized mAb targeting a Tn-peptide specific epitope in MUC1 expressed in multiple solid tumors
- Low nM affinity and improved target profile vs existing MUC1 mAbs such as Daiichi's DS-3939 or mAbs targeting C-MUC1

mAb M400 targeting Tn-MUC4

- Humanized mAb targeting a a Tn-peptide specific epitope in MUC4 with low nM affinity. Tn-MUC4 is expressed in multiple solid tumors.

Potent efficacy in multiple PDX/CDX models over large range of expression

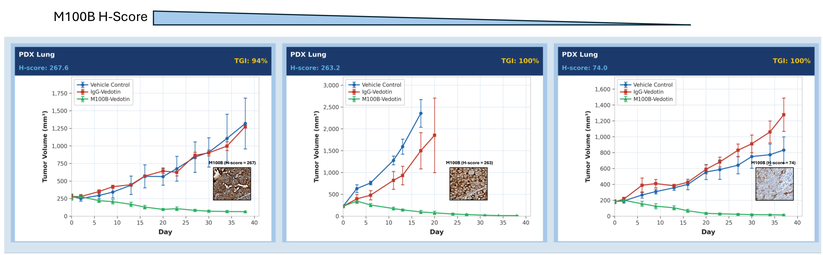
M100B-Vedotin: Tumor Growth Inhibition across PDX/CDX models



- Potent, broad antitumor activity was observed across 22 PDX/CDX models representing six indications.
- GO-M100B-vedotin (6 mg/kg, IV) achieved TGI ≥90% in 11 of 22 models, including 3 complete regressions.
- Tumor types included lung, ovarian, pancreatic, bladder, breast, and cholangiocarcinoma.

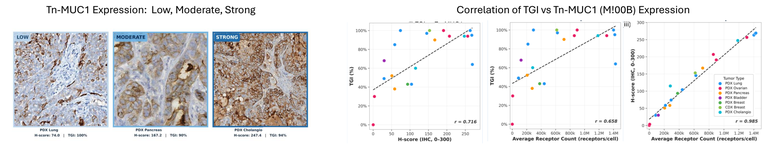
Models are ranked from highest to lowest TGI. Dashed line marks the TGI = 50% threshold. Values above each bar show percent TGI relative to IgG-vedotin; 100% corresponds to a complete response. Bar colors indicate tumor type, as defined in the legend. Values shown below each model indicate H-score.

M100B-Vedotin: PDX efficacy in low target expression models



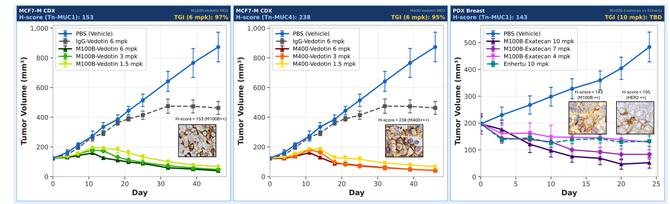
Representative tumor growth curves for three PDX models (ordered left-to-right by decreasing M100B IHC H-score). Mice with established subcutaneous tumors were treated IV (6 mg/kg) with GO-M100B-vedotin (green), IgG-vedotin control (red), or vehicle (blue). Data shown as mean ± SEM (n=3). Adjacent IHC images show M100B staining in each model. TGI calculated vs. IgG control at the final time point.

Efficacy of M100B-Vedotin correlates with Tn-MUC1 Expression



Correlation of M100B-vedotin efficacy with Tn-MUC1 expression. *(i)* TGI versus M100B IHC H-score (Spearman ρ = 0.716, p < 0.001). *(ii)* TGI versus average Tn-MUC1 receptor count per cell (Spearman ρ = 0.658). *(iii)* H-score versus average receptor count per cell (Spearman ρ = 0.985), confirming that IHC H-score is a reliable surrogate for antigen density. Representative IHC images illustrate low (PDX Lung, CTG-0158; H-score: 74), moderate (PDX Pancreas, CTG-1122; H-score: 167), and strong (PDX Cholangio, CTG-0941; H-score: 247) Tn-MUC1 expression.

MED: M100B-Vedotin, M100B-Exatecan & M400-Vedotin

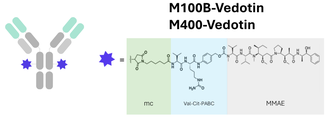


ADC	Model	TGI (6 mpk)	H-Score	MED	Notes
GO-M100B-Vedotin	MCF7-M CDX	97%	153	1.5 mg/kg	Dose-dependent; H-score 153
GO-M400-Vedotin	MCF7-M CDX	95%	238	1.5 mg/kg	Dose-dependent; H-score 238
GO-M100B-Exatecan	PDX Breast	TBD	143	<4 mg/kg	Superior to Enhertu at equivalent dosing

- Dose-dependent TGI in the MCF7m CDX s
- MED was 1.5 mg/kg in MCF7 CDx for GO-M100B and M400-vedotin ; n=5.
- GO-M100B-Exatecan (DAR8) induced TGI across 4-10 mg/kg in Breast PDX
- GO-M100B-exatecan outperformed Enhertu at matched doses
- MED in breast PDXs < 4 mg/kg; n=5.
- IHC confirmed target expression

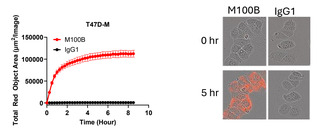
In Vitro activity

ADC Platform



- Site-specific, DAR2 ADC (mc-vc-PAB-MMAE)
- Potent killing across multiple in-vivo models

Internalization



Cell binding

Cell Line	Tn Status	M100B EC50 (µg/mL)	M400 EC50 (µg/mL)	Result
MCF7-M	Tn+ MUC1+/MUC4+	0.32	0.39	✓ Binds
T47D-M	Tn+ MUC1+MUC4+	1.53	0.84	✓ Binds
HaCaT	Tn - MUC1+/MUC4+	N/D	N/D	✗ No binding
T47D-M MUC1 KO	Tn+ MUC1−	N/D	Not Meas. ured	✗ No binding

In vitro cytotoxicity

Cell Line	IC_{50} (M100B -vedotin)	IC_{50} (M400-vedotin)	Notes
T47D-M (Tn+/MUC1+)	0.56 nM	1.79 nM	Tn+ tumor cell line
MCF7-M (Tn+/MUC1+)	1.83 nM	2.32 nM	Tn+tumor cell line
T47D-M MUC1 KO	No cytotox	Not Measured	Tn+ MUC1- tumor cell line
Normal primary cells: *AC16 cardiomyocytes, keratinocytes, SAECs*	No cytotox	No cytotox	*No off-target toxicity in normal cells*

In vitro plasma stability

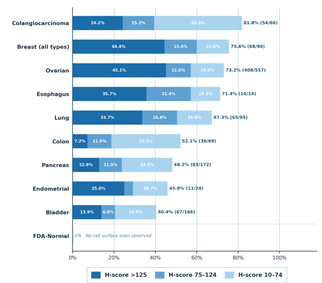
Day	M100B-Vedotin: DAR (% of starting material)		
	Cyno	Hu	Mu
0	100	100	100
1	91.89	97.84	92.20
3	90.47	92.25	94.50
7	84.67	88.81	93.44
14	81.90	87.23	88.71

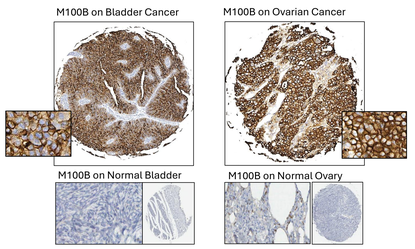
Day	M400-Vedotin DAR (% of starting material)		
	Cyno	Hu	Mu
0	100	100	100
1	96.94	95.13	98.42
3	97.08	95.33	96.56
7	91.09	94.16	94.00
14	93.82	93.65	90.78

In vitro characterization of GO-M100B and GO-M400 ADCs Site-specific DAR2 ADCs targeting Tn-MUC1 (M100B) and Tn-MUC4 (M400) with MMAE payload. Selective binding to Tn+/MUC1+/MUC4+ tumor cells; no binding to antigen-negative controls. Rapid receptor-mediated internalization to endolysosomal compartments.Potent, antigen-dependent cytotoxicity in Tn+ cells (low nM IC_{50}s) with no activity in MUC1 KO or normal cells.(E) Stable DAR across species in plasma for M100B-vedotin. And M400-vedotin.

Expression Prevalence of Tn-MUC1 and Tn-MUC4

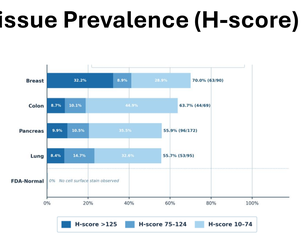
M100B Tissue Prevalence (H-score)

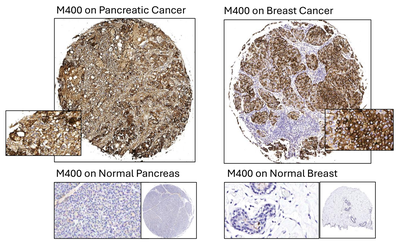




GO-M100B (Tn-MUC1) Tumor Selectivity. IHC prevalence across tumor indications compared to normal tissue. Immunohistochemical staining was performed on commercially sourced tissue microarrays. Bars represent the proportion of tumor cores scoring H-score ≥10, stratified by H-score intensity: >125 (dark blue), 75–124 (medium blue), and 10–74 (light blue). Total percent positive and sample fraction (n/N) are indicated at the end of each bar. Indications are ordered by descending total prevalence. FDA-approved normal tissue panels showed no cell surface staining.

M400 Tissue Prevalence (H-score)





GO-M400 (Tn-MUC4) Tumor Selectivity. IHC prevalence across tumor indications compared to normal tissue. Immunohistochemical staining was performed on commercially sourced tissue microarrays. Bars represent the proportion of tumor cores scoring H-score ≥10, stratified by H-score intensity: >125 (dark blue), 75–124 (medium blue), and 10–74 (light blue). Total percent positive and sample fraction (n/N) are indicated at the end of each bar. Indications are ordered by descending total prevalence. FDA-approved normal tissue panels showed no cell surface staining.

GO-M100B-Vedotin shows a clean safety profile

GO-M100B-vcMMAE — Mean TK Parameters: Intact ADC, Total Antibody & Free MMAE Payload

Female Cynomolgus Monkey - n=2/group IV infusion Q3W × 2 doses (Days 1 & 22) 5, 10, 18 mg/kg

Analyte	Dose (mg/kg)	Cmax Dose 1 (µg/mL)	Cmax Dose 2 (µg/mL)	AUClast Dose 1 (h·µg/mL)	AUClast Dose 2 (h·µg/mL)	T½ Dose 1 (h)	T½ Dose 2 (h)	Tmax Dose 1 (h)	Notes
Intact ADC	5	140	188	19000	26000	224	265.8	0.54	Cmax and AUC proportional to dose; no accumulation
	10	254	339	36200	53000	264.8	286.8	0.08	Dose-proportional exposure (Ratio D1: 1.0×→1.8×→3.6×)
	18	509	509	67700	65200	211.1	184.3	0.08	STD_{10} dose; all findings non-adverse
	5	162	184	22200	27400	248.3	265.6	0.08	Similar kinetics to intact ADC; no accumulation
Total Antibody (TAb)	10	286	355	43800	60900	329	320.2	0.08	Dose-proportional exposure
	18	529	604	78100	85800	271	190.1	0.08	Slightly higher Cmax than ADC (deconjugated antibody)
Free MMAE Payload	5	BQL	BQL	BQL	BQL	—	—	—	Below quantification limit at all timepoints
	10	0.061 ng/mL	0.098 ng/mL	2.94 h·ng/mL	12.0 h·ng/mL	NC	NC	36	Very low exposure; Tmax 24–36 h post-dose
	18	0.142 ng/mL	0.186 ng/mL	25.7 h·ng/mL	60.1 h·ng/mL	NC	NC	36.5	Cmax <0.2 ng/mL; ~3–4 orders of magnitude below ADC

Units: ADC and TAb Cmax in µg/mL; AUClast in h·µg/mL; T½ in hours. Free MMAE Cmax in ng/mL; AUClast in h·ng/mL (~3–4 orders of magnitude lower than ADC/TAb). BQL = below quantification limit (5 ng/kg). NC = not calculable (slow-release kinetics; empirical T½ estimates unreliable). Tmax of 0.08 h = 5 min post end-of-infusion, n=2/group.

- Dose-proportional PK (Cmax, AUClast) with long half-life (184–329 h); minimal free MMAE exposure
- Well tolerated: no mortality or clinical signs; only transient, non-adverse hematologic and liver enzyme changes
- STD_{10} = 18 mg/kg (Q3W ×2)

Safety Findings Summary

GO-M100B (M100B-vcMMAE) | NHP Safety Study | Female cynomolgus monkeys | Q3W × 2 doses

Endpoint	5 mg/kg	10 mg/kg	18 mg/kg	Timepoint / Note
Mortality	✓ None	✓ None	✓ None	All survived to Day 43
Clinical Signs	✓ None	✓ None	✓ None	No test-article-related signs
Body Weight	✓ Stable	✓ Stable	✓ Stable	Within normal variation
WBC	✓ Normal	✓ Normal	⚠ ↓ ~57%	Day 15 (transient, 1 animal)
Neutrophils	✓ Normal	✓ Normal	⚠ ↓ ~84%	Day 15 (transient, 1 animal)
Lymphocytes	✓ Normal	✓ Normal	⚠ ↓ ~52%	Day 29 (transient, both animals)
ALT	✓ Normal	⚠ ↑ +229%	⚠ ↑ +262%	Day 4 only; resolved Day 8
AST	✓ Normal	⚠ ↑ +160%	⚠ ↑ +525%	Day 4 only; resolved Day 8
CK	✓ Normal	⚠ ↑ +365%	⚠ ↑ +1239%	Day 4 only; resolved Day 8

PK Highlights

GO-M100B (M100B-vcMMAE) | NHP Safety Study | Female cynomolgus monkeys | Q3W × 2 doses

Highlight	Detail
Dose-proportional Cmax & AUC	ADC & TAb exposure increases linearly across 5–18 mg/kg; supports predictable dose escalation.
Long half-life ~184–329 h	Intact ADC T½ 184–329 h across all dose groups and both cycles; consistent with Q3W dosing interval.
Free MMAE BQL at 5 mg/kg	Free MMAE payload below LLOQ at 5 mg/kg on both Day 1 and Day 22; low systemic payload exposure at therapeutic-range doses.
Transient heme & liver changes	WBC/neutrophil/lymphocyte decreases and ALT/AST/CK elevations confined to 18 mg/kg (and partly 10 mg/kg); all fully resolved by Day 8–36.
No ADA impact observed	Stable ADC and TAb exposure across Cycle 1 (Day 1) and Cycle 2 (Day 22); no evidence of immunogenicity-driven clearance.

GO-M100B-vedotin demonstrates a favorable safety and tolerability profile in non-human primates. Female cynomolgus monkeys (n=2/group) received 5, 10, or 18 mg/kg IV Q3W ×2 (Days 1, 22). Intact ADC and total antibody showed dose-proportional Cmax and AUClast on Days 1 and 22, with terminal half-lives of 184–329 h. Free MMAE was below quantification at 5 mg/kg and remained at sub-nanomolar levels at higher doses. No mortality or test article–related clinical signs were observed; body weight and food consumption were stable. Transient, non-adverse decreases in WBCs, neutrophils, and lymphocytes occurred at 18 mg/kg. ALT, AST, and CK elevations (single animals, 10 and 18 mg/kg) were observed on Day 4, resolved by Day 8, and did not recur after Dose 2. Overall, the profile shows dose-proportional exposure, long half-life, minimal systemic payload exposure, and no evidence of immunogenicity-driven clearance. STD_{10} was 18 mg/kg. Note M400-vedotin showed a similar safety profile (data not shown).

Summary

- GO-M100B (Tn-MUC1) & GO-M400 (Tn-MUC4) targets aberrant O-glycosylation on mucins selectively expressed in cancer
- Lead ADCs GO-M100B & GO-M400: Site-specific DAR2 mc-vc-PAB–MMAE conjugates; exatecan (β-Glu, DAR8) payloads in development
- Broad expression across epithelial cancers (CRC, PDAC, lung, breast, ovarian, esophageal, bladder)
- Designed for strong tumor penetration and efficient internalization
- Potent activity across multiple PDX models and target expression levels (MED ~1 mg/kg)
- Favorable tolerability: well tolerated in pilot NHP studies up to 18 mg/kg (M100B-vedotin) and 10 mg/kg (M400-vedotin)