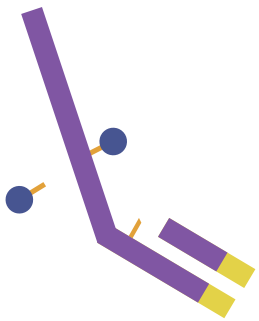
Medicilon ADC R&D Service Platform

In developing the ADC preclinical integrated research services, Medicilon engages in thorough communication with our clients. Drawing upon years of practical experience and technical expertise, our scientific research team meticulously integrates the unique characteristics of each case to craft high-quality experiments and deliver exceptional results to our clients.



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To date, Medicilon has spearheaded over 100 significant IND application biopharmaceutical projects, encompassing monoclonal antibodies, bispecific antibodies, polyclonal antibodies, ADCs, viral vaccines, and fusion proteins. As of April 2024, Medicilon has successfully assisted clients on the IND approval of **24** ADC drugs and has multiple ADC projects on going.

Synthesis of ADC Payloads

Medicilon's compound library boasts a diverse array of chemical ADC payloads, each with unique mechanisms of action, providing customers with a wide selection to choose from. Additionally, we offer the flexibility for ADCs to be tailored and synthesized according to the specific requirements of our clients, ensuring their needs are met with precision and efficiency.

- Tubulin inhibitors
- DNA damaging agents
- Immunomodulators

Provides 6 payloads of all marketed ADCs
Provides 20+ payload derivatives of marketed ADCs
Provides independent R&D payloads

Medicilon High Potency Laboratory

The three main components of ADCs are the antibody, the linker, and the payload

Medicilon Case:

ADC crosslinking strategy based on cysteine

ADC Binding Assay

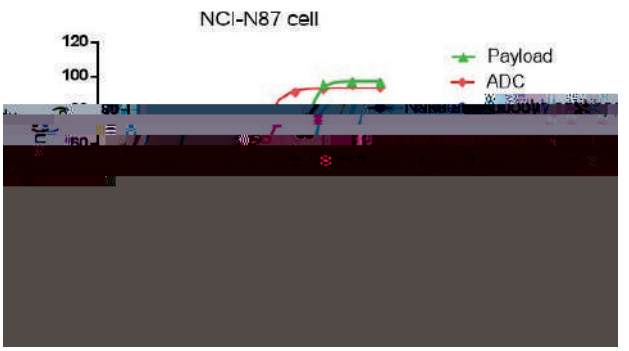
ADC Internalization: Confocal Imaging

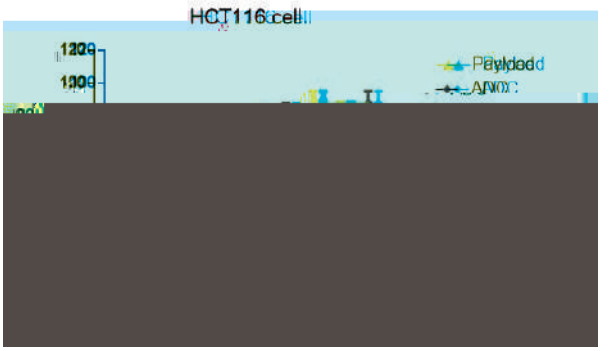
ADC were labeled with fluorophore（e.g. ADC-FITC, ADC-Cy5).

Internalization of ADC-FITC was analyzed through con-focal (co-localization of lyso-tracker with ADC-FITC indicating internalization of ADC).

Internalization could also be analyzed through LICOR (In cell Western) and FACS.

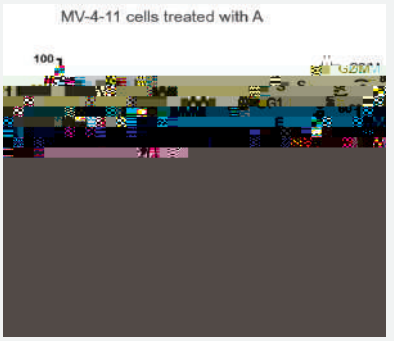
Medicilon Case:

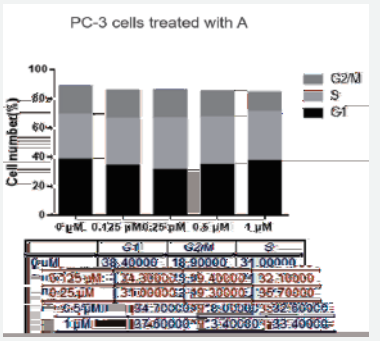




Cytotoxicity of Payloads or ADC

Medicilon Case:





Cell Cycle Analysis

MV-4-11 cells and PC-3 cells were treated with compound A and stained with PI for FACS-based cell cycle analysis. The data shown that compound A dramatically block the cell cycle of

MV-4-11 cells were treated with Compound A and stained with PI/Annexin V for FACS-analysis. The data shown that Compound A promotes the apoptosis of MV-4-11 cells.

Apoptosis Analysis

Pharmacology Research of ADC

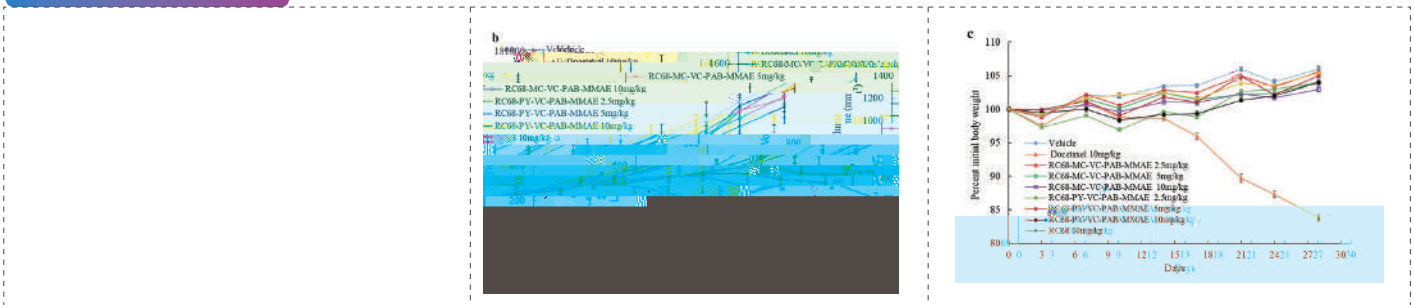
- Target antigen binding activity
- Related pharmacology of target antigen (e.g.: ADCC CDC)
- Mechanism of payloads and metabolites (focus on the difference in pharmacology mechanism ADCs, naked antibodies, payload and metabolites).

Pharmacology Evaluation of ADC

An essential pharmacological parameter for assessing an ADC is its *in vivo* efficacy, which directly correlates with its potency and significantly informs clinical trial designs. Our animal models adhere strictly to AAALAC regulations, ensuring ethical standards and rigor in research practices. Currently, Medicilon has established **400+** tumor evaluation models across six categories, providing a comprehensive platform for evaluating the efficacy of ADCs and other therapeutic agents.

- Tumor models for multiple tumor diseases
- Diverse selections of model types
  - CDX models
  - PDX models
  - Syngeneic models
  - Humanized models
  - Orthotopic models
- Various laboratory animal
  - Rodents: Mouse/Rat, Rabbit
  - Non-Rodents: Beagle Dog, Mini Pig, Non-human Primate

Medicilon Case:



The grown tumors | The dynamic growth of tumors | The body weights of mice

In vivo antitumor activity of RC68-based ADCs.

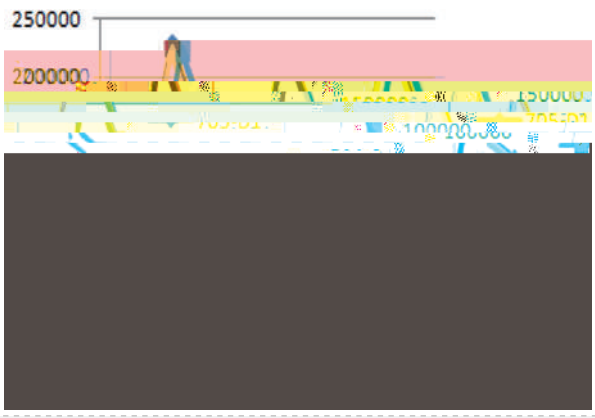
A humanized anti-EGFR monoclonal antibody (named RC68) was purifed and conjugated with MMAE using a MC-VC-PAB or PY-VC-PAB linker. The *in vivo* antitumor activity of RC68-MC-VC-PAB-MMAE and RC68-PY-VC-PAB-MMAE were performed by **Medicilon**.

BALB/c nude mice were implanted subcutaneously with H125 cells and when the solid tumor reached 100-300 mm^3, the mice were randomized and treated intravenously with indicated drug weekly. The effect of each treatment on the growth of tumors was measured by monitoring tumor volumes and their body weights were measured twice per week. At the end of the experiment, the tumors were dissected and photoimaged.

ADC Pharmacokinetics Study

ADC raises difficulties in PK study as each component ADC molecules has unique PK characteristics. Combining our antibody department and pharmacology department expertise, Medicilon provides high quality quantification assays for each key parameter in ADC PK study, presenting accurate results.

Description		
Conjugated Anitbody	Antibody with minimum of DAR ≥ 1	LBA
Total Antibody	Conjugated, partially unconjugated and fully unconjugated (DAR >= 0)	LBA
Small Molecules	Released/free samll molecule and its metabolities	LC-MS/MS
ADA	Antibodies against antibody of ADC, linker or drug	LBA



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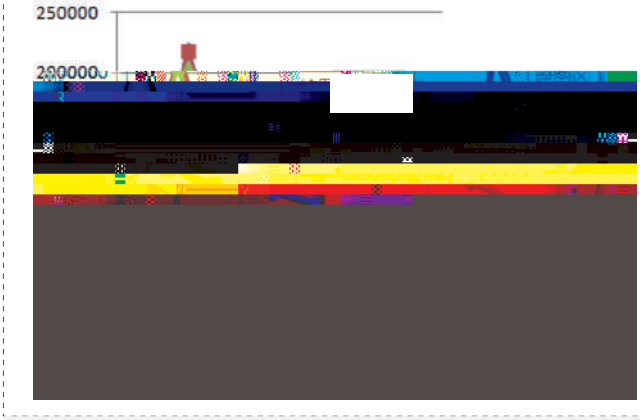

ADC

Benchmarking with global lab standard for results with high consistency. Developing stable and reliable methods for results with high correlation.

ADC Immunogenicity

Immunogenicity is a key parameter when evaluating biologic therapeutics. It could increase the potential risk of adverse effects and reduced ADC efficacy. Medicilon fully understands the complexity of ADA evaluation and offers our clients with comprehensive immunogenicity assays.

ADC Safety Assessment

Medicilon offers rigorous and specific safety assessment services strictly following S6 & S9 Regulation of ICH and in compliance with the requirement of NMPA, FDA, OECD and TGA.

- Single dose/Repeat dose toxicity (With TK)
- Tissue cross-reactivity
- ADA test

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