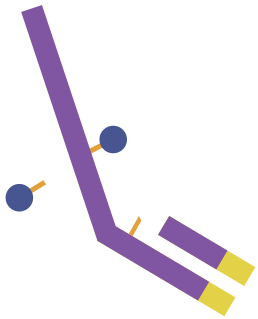
Medicilon ADC R&D Service Platform

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.



Solutions

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

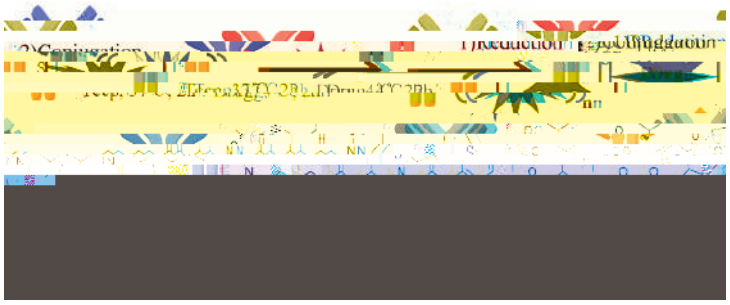
Provides 6 payloads of all marketed ADCs
Provides 20+ payload derivatives of marketed ADCs
Provides independent R&D payloads

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

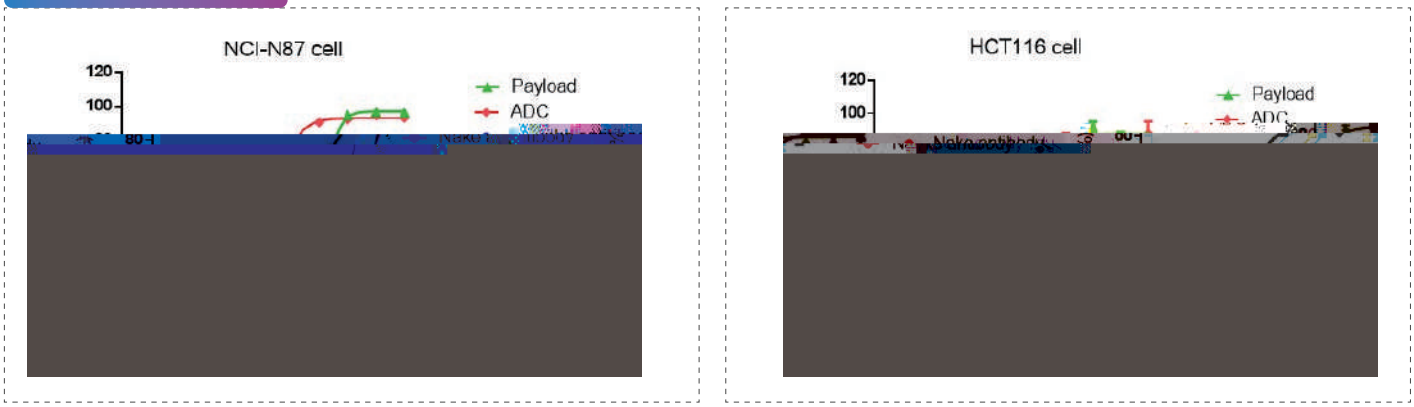
ADC Internalization: Confocal Imaging

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.

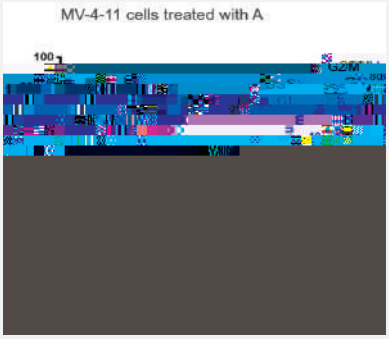
Medicilon Case:

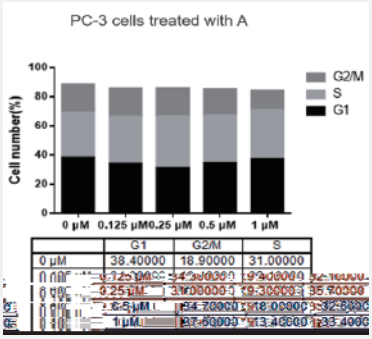


Cytotoxicity of Payloads or ADC

Payload, nake antibody and ADC were incubated with target cells, cell viability were analyzed through CCK-8, CTG and MTT.

Medicilon Case:

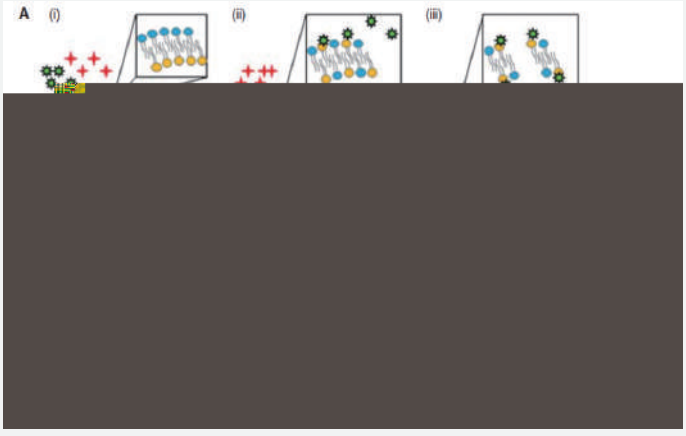


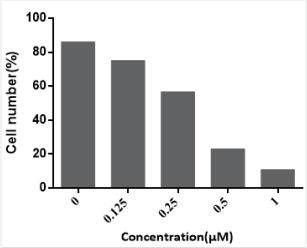


Cell Cycle Analysis

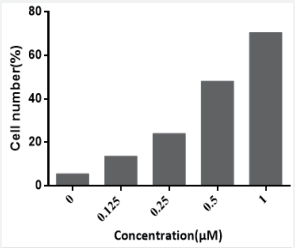
MV-4-11 cells and PC-3 cells were treated with compound A and stained with PI for FACS-based cell cycle analysis. The data shown that compound A dramatically block the cell cycle of MV-4-11 cells and did not affect PC-3 cells too much.

Medicilon Case:





MV-4-11 treated with A-live



MV-4-11 treated with A-Apoptotic

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

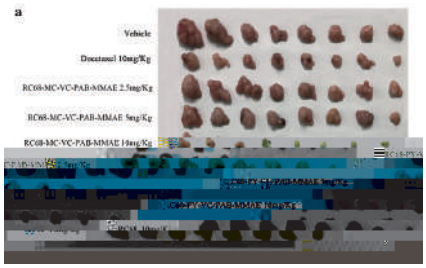
- Target antigen binding activity
- Related pharmacology of target antigen (e.g.: ADCC，CDC)
- Mechanism of payloads and metabolites (focus on the difference in pharmacology mechanism ADCs, naked antibodies, payload and metabolites).

Pharmacology Evaluation of ADC

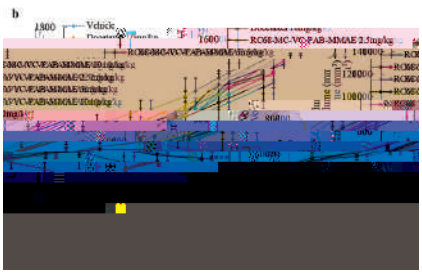
An essential pharmacological parameter for assessing an ADC is its *in vivo* efficacy, which directly correlates with its potency and significantly informs clinical trial designs. Our animal models adhere strictly to AAALAC regulations, ensuring ethical standards and rigor in research practices. Currently, 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

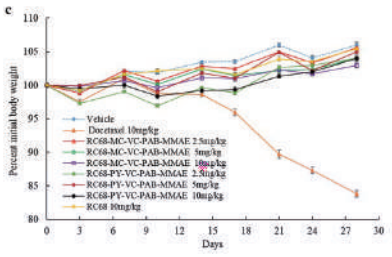
Medicilon Case:



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**.

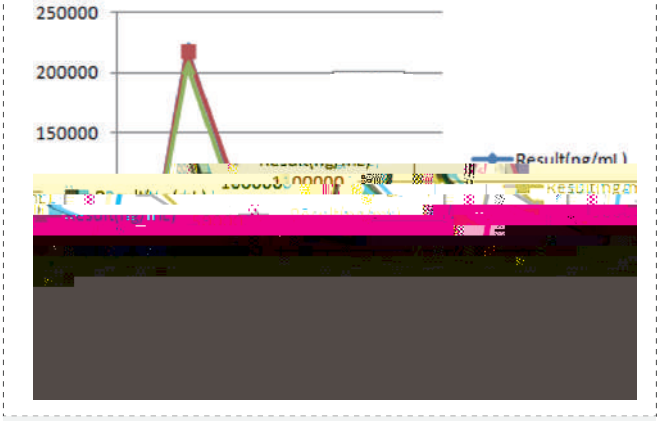
BALB/c nude mice were implanted subcutaneously with H125 cells and when the solid tumor reached 100-300 mm^3, the mice were randomized and treated intravenously with indicated drug weekly. The effect of each treatment on the growth of tumors was measured by monitoring tumor volumes and their body weights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

Total Ab



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

Medicilon Assisted Projects

DAC-002

In July 2020, DAC Biotech's new ADC drug development, TROP2-ADC—DAC-002 was approved of clinical study by NMPA for the indication of solid malignant tumor. DAC-002 is an ADC anti-Trop2 monoclonal antibody conjugated by an intelligent ligand against Tubulysin B analogue. It is used to treat Trop2 triple negative breast cancer, small cell lung cancer, non-small cell lung cancer and pancreatic cancer.

Medicilon completed preclinical pharmacokinetic and toxicological studies in this project, accelerating the development process.

Muc1-ADC

In July 2021, a recombinant humanized anti-MUC1 monoclonal antibody-Tub201 coupling agent (hereinafter referred to as "Muc1") for the treatment of advanced solid tumor class 1 ADC drug injection from Dac Biotechnology was approved for clinical use. This is the first clinically approved Muc1-ADC drug in China.

Medicilon has provided a full set of preclinical research services including pharmacology, pharmacokinetics and safety evaluation in the research and development of new Muc1 drugs, helping the project to be successfully approved for clinical trials.

BAT8006

In May 2022, Bio-Thera Solutions, Ltd. (Bio-Thera) has been approved for clinical application of BAT8006 for injection, a product under development for the treatment of advanced solid tumors. BAT8006 is composed of a recombinant humanized anti-FRα antibody and a toxic small molecule topoisomerase I inhibitor connected by a self-developed cleavable linker. BAT8006 has efficient anti-tumor activity, and the toxin small molecule has strong cell membrane penetration ability.

During the R&D of BAT8006, Medicilon's ADC preclinical research and development service platform has extensive practical technology and experience in the field of ADC drug preclinical R&D, followed the ICH guidelines S6 and S9 and combined with the specific situation of the BAT8006 project, to customize a personalized safety evaluation plan and overcome the complexity and diversity of drug-to-antibody ratio (DAR), stability, for BAT8006.

KM501

In March 2023, Xuanzhu Biopharmaceutical (Xuanzhu) and its wholly-owned subsidiary Beijing Xuanzhu Bio, obtained clinical trial approval for the double-antibody ADC drug KM501. This product is suitable for the treatment of advanced/metastatic solid tumors with positive/expression, amplification or mutation of HER2, including related advanced tumors with low expression of HER2. The drug is the world's first double-antibody ADC drug that completely knocks out fucose, and is expected to become the "Best in Class" drug.

Medicilon, as a partner of Xuanzhu, provided KM501 with GLP-compliant preclinical research services based on the Medicilon Antibody Development Service Platform, including pharmacokinetic studies and safety evaluation.

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