## Supramolecular Drug Project

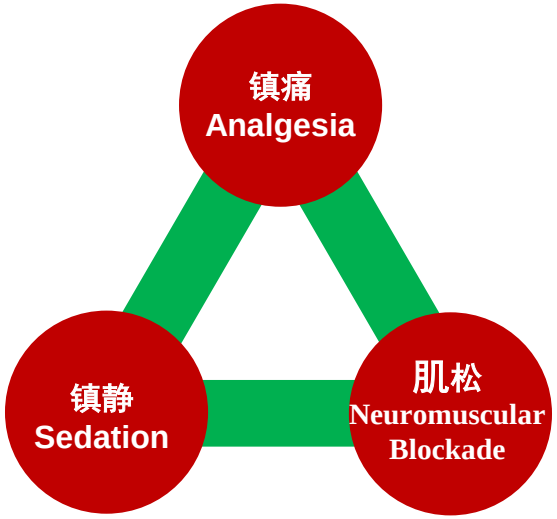
# Universal Antagonist That Rapidly Reverses Clinically Used Neuromuscular Blockers

**Gang Zhao**

# Content

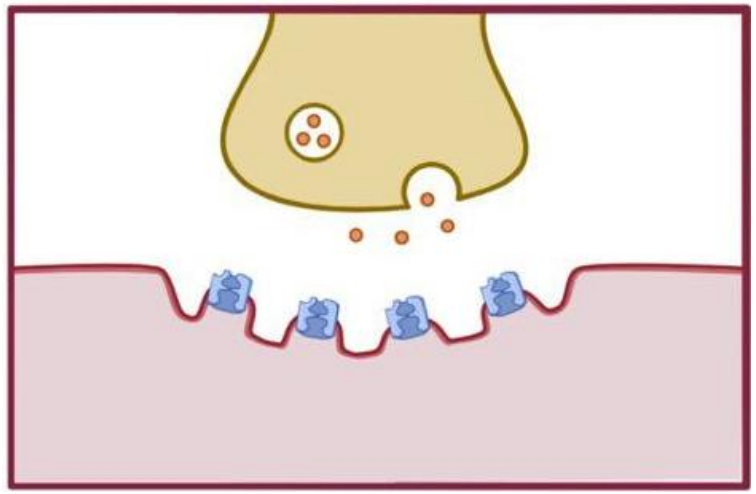
# 1. Supramolecular drug design: the status quo

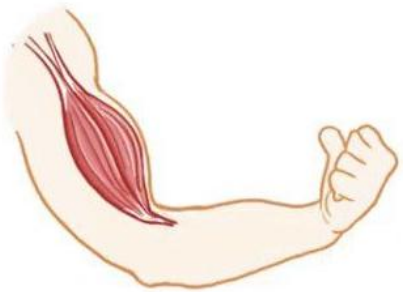
## Neuromuscular Blocking Agents (NMBAs): One of Triad for General Anesthesia




临床全麻三要素

Triad for general anesthesia





神经肌肉阻滞剂阻断乙酰胆碱与运动神经终端乙酰胆碱受体接触：

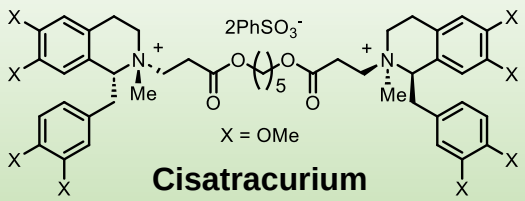
- 为气管插管提供条件
- 满足手术中的肌松要求
- 消除自主呼吸和机械通气的对抗
- 减弱或终止痉挛性疾病引起的肌肉僵直

**NMBAs: block the contact of acetylcholine with the motor nerve terminal acetylcholine receptors:**

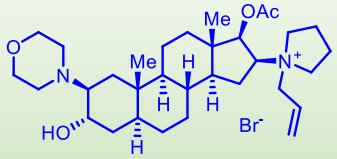
- **Provide conditions for endotracheal intubation.**
- **Meet the requirements of muscle relaxation during surgery.**
- **Eliminate the opposition to spontaneous breathing and mechanical ventilation.**
- **Reduces or terminates muscle rigidity caused by spasmodic diseases.**

# NMBAs in general anesthesia for surgeries: huge case number and high residual ratio

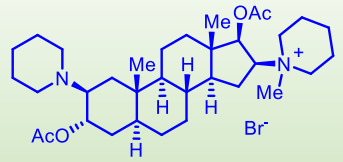
**Currently, clinically used NMBAs include:**




**Cisatracurium**
**顺阿曲库铵**



**Rocuronium**
**罗库溴铵**



**Vecuronium**
**维库溴铵**

- **In China, annual total selling amount: 60-70 million injections.**
- **Cisatracurium and rocuronium account for 85-90% market.**
- **In China, cisatracurium accounts for 50-60% market.**

**The number of annual surgery procedures:**

- ✓ **globally (2021): ~350 million**
- ✓ **in China (2022): ~82.7 million**
- ✓ **in the USA (2023): ~26.2 million**

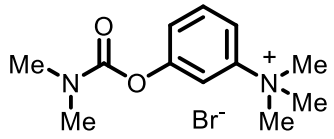
**All NMBAs have high residual ratio (30-60%):**

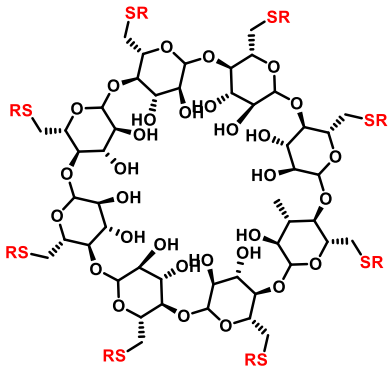
**Residual causes many side effects or even lethality: Impairring regulation of ventilation during hypoxia, pharyngeal function and airway protection; patient distress, postoperative respiratory complications and mortality; increase of the clinical burden to patients, healthcare facilities, and healthcare resource use.**

**肌松残留导致多种呼吸并发症，致死率占麻醉致死病例的25%，监护时间延长，手术资源利用率降低，治疗成本增加。**

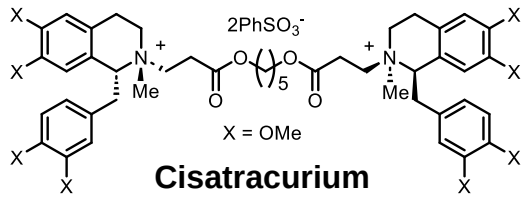
# Existing antagonists: neostigmine and sugammedex

**Neostigmine**
**(1933)**
**(新斯的明)**

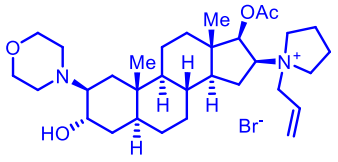




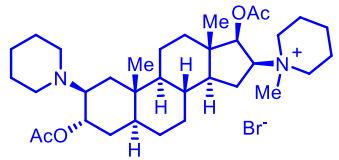
**Sugammadex**
**(EU: 2008)**
**(USA: 2015, China: 2017)**
**(舒更葡糖钠)**



**Cisatracurium**
**顺阿曲库铵**



**Rocuronium**
**罗库溴铵**



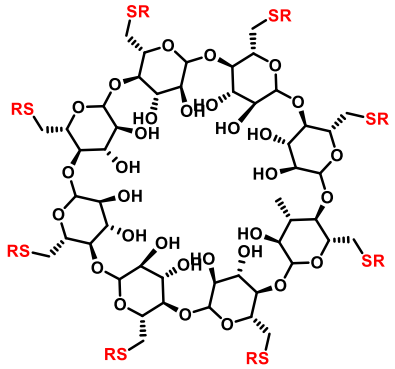
**Vecuronium**
**维库溴铵**

**General reversal agent (通用), cannot realize rapid reversal (不能快速逆转), does not work for deep blockade (不能用于深度肌松), has ceiling effect (封顶效应), adverse effects (副作用多), contraindications (禁忌症多).**

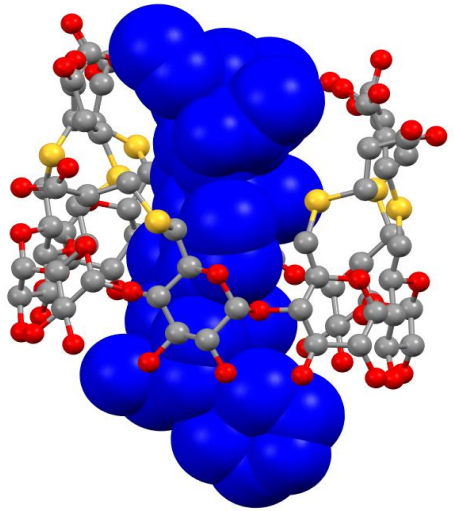
**For rocuronium and vecuronium, but not for cisatracurium (非通用), an rapid reversal (能快速逆转), work for deep blockade (能用于深度肌松)**

- **In China, annual total selling amount: 60-70 million.**
- **Cisatracurium and rocuronium account for 85-90% market.**
- **In China, cisatracurium accounts for 50-60% market.**

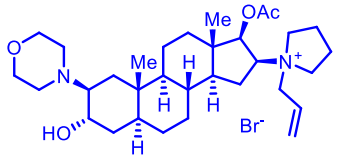
# Sugammadex is the 1st and only drug developed using supramolecular mechanism




**Sugammadex**
**舒更葡糖钠**
**Developed by Organon**



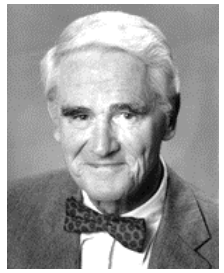
**Supramolecular host-guest binding**
**(Crystal structure)**



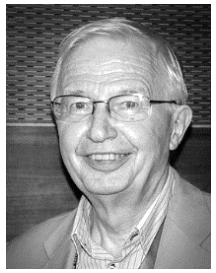

**Rocuronium**
**罗库溴铵**

# Two times for supramolecular chemists to win Nobel prize

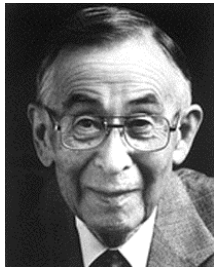
**In 1987, for selective binding:**



**D. J. Cram**
**(UCLA, USA)**



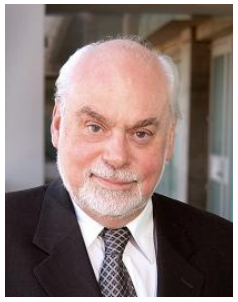
**J.-m. Lehn**
**(Strasbourg, France)**



**C. J. Pedersen**
**(DuPont, USA)**

**In 2016,for the design and synthesis of molecular machines:**

**J.-P. Sauvage**
**(Strasbourg, France)**



**J. F. Stoddart**
**(Northwestern, USA)**

**B. L. Feringa**
**(Groningen, Netherlands)**

**Since the establishment of supramolecular chemistry in 1967, fundamental research in the research field has not brought out important application in drug design.**

# 2. Project goal

- **Develop the 1st universal supramolecular antagonist that rapidly reverses all the three clinically used NMBAs.**
- **Expected to be the 1st supramolecular drug originally developed by an academic institution.**
- **Expected to set a new paradigm in China for industry-research organization combination.**

# 3. Supramolecular R&D team for this project

**Harbin Institute of Technology, Shenzhen**

**Prof. Jiaheng Zhang**

**Prof. Gang Zhao**

**Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences**

**Prof. Zhanting Li**

**Assoc. Prof. Shangbo Yu**

**Fudan University, Shanghai**

**Prof. Da Ma**

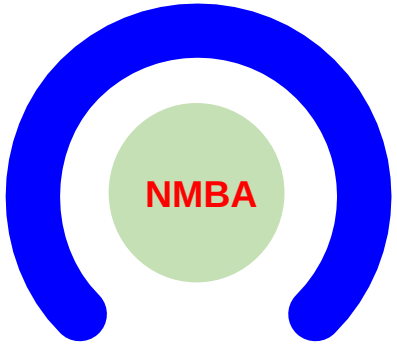
**Prof. Danwei Zhang**

**Assoc. Prof. Wei Zhou**

# Solid research foundation for the project


1. Liu, H.-K.; Lin, F.; Yu, S.-B.; Wu, Y.; Lu, S.; Liu, Y.-Y.; Qi, Q.-Y.; Cao, J.; Zhou, W.; Li, X.; Wang, H.; Zhang, D.-W.; Li, Z.-T. Ma, D. Highly Water-Soluble Cucurbit[8]uril Derivative as a Broad-Spectrum Neuromuscular Block Reversal Agent. *J. Med. Chem.* **2022**, *65*, 16893-16901.
2. Wu, Y.; Liu, Y.-Y.; Liu, H.-K.; Yu, S.-B.; Lin, F.; Zhou, W.; Wang, H.; Zhang, D.-W.; Li, Z.-T.; Ma, D. Flexible organic frameworks sequester neuromuscular blocking agents in vitro and reverse neuromuscular block in vivo. *Chem. Sci.* **2022**, *13*, 9243-9248
3. Wu, Y.; Yang, J.; Zhuang, S.-Y.; Yu, S.-B.; Zong, Y.; Liu, Y.-Y.; Wu, G.; Qi, Q.-Y.; Wang, H.; Tian, J.; Zhou, W.; Ma, D.; Zhang, D.-W.; Li, Z.-T. Macrocycles and Acyclic Cucurbit[n]urils as Pseudo[2]catenane Partners for Long-Acting Neuromuscular Blocks and Rapid Reversal In Vivo. *J. Med. Chem.* **2024**, *67*, 2176-2187.
4. Feng, K.; Liu, Y.-Y.; Zong, Y.; Lei, Z.; Wu, Y.; Yang, J.; Lin, F.; Qi, Q.-Y.; Li, Q.; Zhuang, S.-Y.; Zhang, J.; Tian, J.; Zhou, W.; Ma, D.; Zhang, D.-W.; Li, Z.-T.; Yu, S.-B. Discovery of Highly Water-Soluble and Biocompatible Acyclic Cucurbit[n]uril FY-3451 as a Universal Antagonist That Rapidly Reverses Neuromuscular Blocking Agents in Vivo. *J. Med. Chem.* **2024**, accepted.

# 4. Unique and innovative supramolecular mechanism




**ACD-4**

- **Develop a folded molecular entity to achieve high binding affinity.**
- **Utilizing conformational adaptability to achieve universal for all NMBAs.**
- **The design well reflects the supramolecular host-guest binding mechanism.**

# ACD-4 meets key properties of an ideal antagonist

## Ideal properties of an antagonist for NMBAs:

- **Ideal properties of a reversal agent:** Certain characteristics are prerequisites to developing a new reversal agent for antagonising neuromuscular block in the 21st century. These are listed in Box 1.
- **To date, no reversal agent fulfils all these characteristics** and hence the search continues

J. M. Hunter
University of Liverpool, UK
*BJA Education* 2020, *20*, 259-265

**Box 1. Ideal characteristics of a reversal agent to antagonize neuromuscular block:**

- Can be used to reverse any neuromuscular blocking drug /通用
- Can be used to reverse any depth of neuromuscular block /拮抗深度肌松
- A rapid onset of maximal effect (within a few minutes) /快速拮抗
- No adverse cardiovascular effects/无心血管毒性
- No adverse muscarinic effects (e.g. bradycardia, bronchospasm, abdominal pain, nausea and vomiting)/无毒蕈碱副作用
- No histamine release or risk of anaphylaxis/无组胺释放或过敏风险
- Not dependent on organ elimination/不依赖于器官消除
- No ceiling effect/无顶量效应
- Does not produce depolarising block if given in excess/过量不产生去极化肌松
- Low cost/低价格
- Available as a solution/可配成溶液

# 5. Antagonization activity assessment

## Antagonization activity for profound block of cisatracurium

### Head-to-head comparative study with neostigmine (rat model)

| Antagonists | Dose (mg/kg) | Male/female | Recovery time (s) (TOF → 0.9) |
|---|---|---|---|
| Neostigmine | 0.24 | 3 M | 463 |
| | | 3 F | |
| ACD-4 | 75 | 6 M | 33 |
| | | 6 F | |

- Neostigmine dose: transformed from top dose for adults
- Cisatracurium dose: transformed from 2 × ED95 dose for adults.

# Antagonization activity for moderate block of cisatracurium

## Head-to-head comparative study with neostigmine (rat model)

| Antagonists | Dose (mg/kg) | Male/female | Recovery time (s) (TOF → 0.9) |
|---|---|---|---|
| Neostigmine | 0.24 | 6 M | 188 |
| | | 6 F | |
| ACD-4 | 25 | 6 M | 30 |
| | | 6 F | |

- Neostigmine dose: transformed from top dose for adults.
- Cisatracurium dose: transformed from 2 × ED95 dose for adults.

# Antagonization activity for profound block of rocuronium

## Head-to-head comparative study with sugammadex (rat model)

| Antagonists | Dose (mg/kg) | Male/female | Recovery time (s) (TOF → 0.9) |
|---|---|---|---|
| Sugammadex | 25 | 6 M | 30 |
| | | 6 F | |
| ACD-4 | 25 | 6 M | 18 |
| | | 6 F | |

**Rocuronium dose (3.6 mg/kg): transformed from 2 × ED95 dose for adults.**

# Antagonization activity for moderate block of rocuronium

## Head-to-head comparative study with sugammadex (rat model)

| Antagonists | Dose (mg/kg) | Male/female | Recovery time (s) (TOF → 0.9) |
|---|---|---|---|
| Sugammadex | 12.5 | 6 M | 17 |
| | | 6 F | |
| ACD-4 | 12.5 | 6 M | 15 |
| | | 6 F | |

**Rocuronium dose (3.6 mg/kg): transformed from 2 × ED95 dose for adults.**

# Antagonization activity for profound block of vecuronium

## Head-to-head comparative study with sugammadex (rat model)

| Antagonists | Dose (mg/kg) | Male/female | Recovery time (s) (TOF → 0.9) |
|---|---|---|---|
| Sugammadex | 25 | 6 M | 18 |
| | | 6 F | |
| ACD-4 | 25 | 6 M | 9 |
| | | 6 F | |

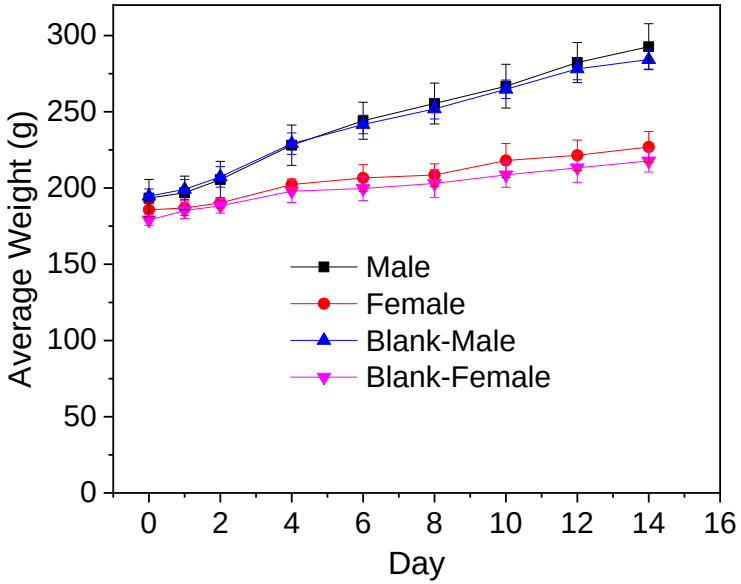
Vecuronium dose (0.7 mg/kg): transformed from 2 × ED95 dose for adults.

# 6. Biosafety assessment

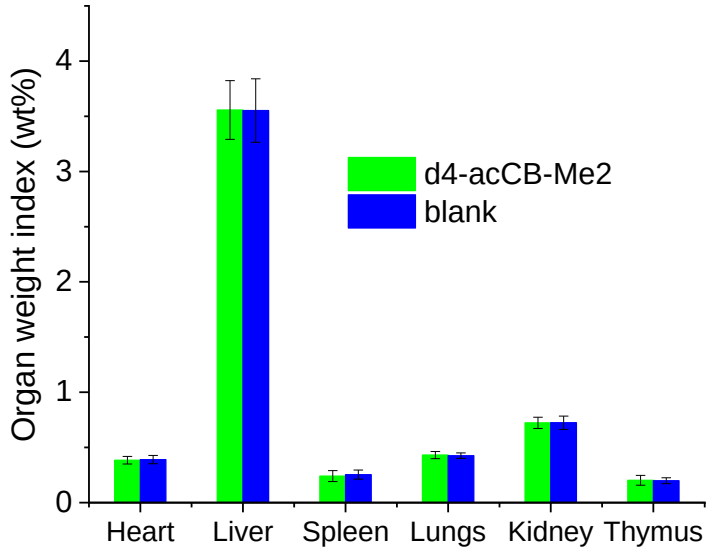
| | Result |
|---|---|
| 1. hERG test | Negative |
| 2. Ames test | Negative |
| 3. Hemolytic | Negative |
| 4. Cause coagulation | Negative |
| 5. Allergic reaction | Negative |
| 6. Skin irritation | Negative |
| 7. Drug interaction | Negative with 18 related drugs |

# Acute toxicity assessment: maximum tolerated dose (MTD)

- **With rat model**
- **1440 mg/kg (4M + 4F) (最大试验剂量)**
- **Control: saline (4M + 4F)**



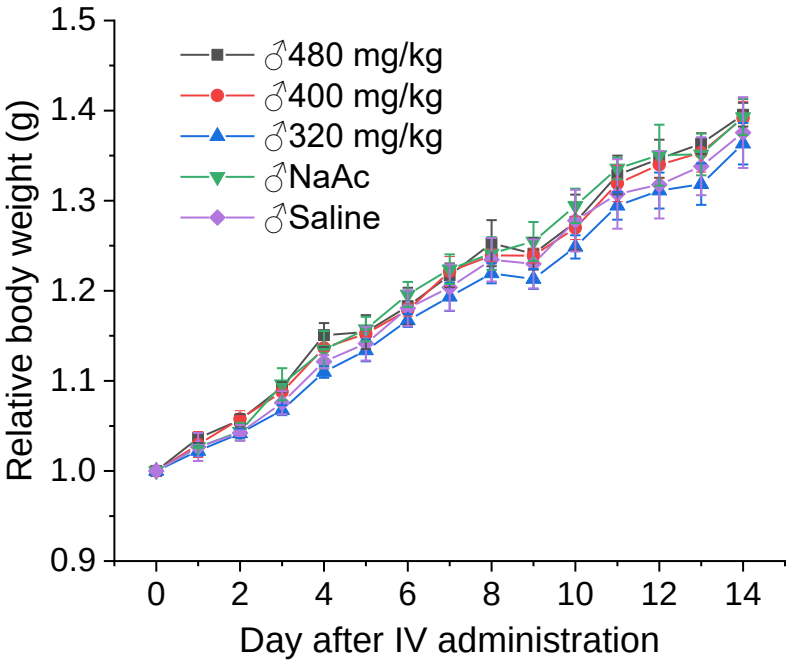

**Body weight changes in 14 days**



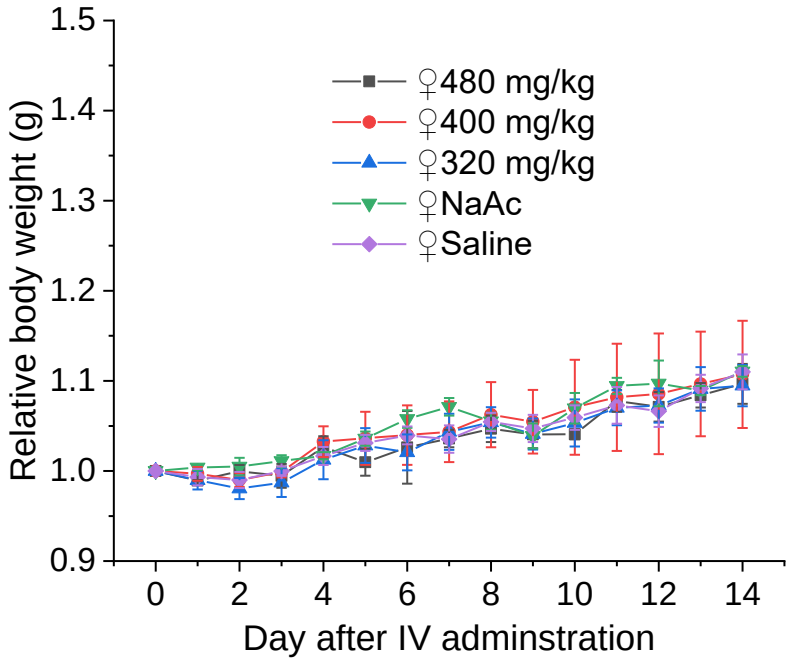

**Organ weight index on day 15**

**No observable damage for main organs.**

# Long-term toxicity assessment with rat model




**Male**




**Female**

- **With every day administration of six times the maximum efficient dose for 14 days, all the rats exhibited good toleration.**
- **Histopathological imaging showed no severe organ damage.**
- **Head-to-head tests showed that the nephrotoxicity is at least not high as that of sugammadex.**
- **Bone accumulation was not observed, which exists for sugammadex.**

# 7. ADME study

- **Method for plasma protein binding has been established and the binding study has been conducted.**
- **Method for distribution in blood has been established, which revealed short half-life in blood.**
- **Method for renal excretion analysis has been established, which revealed main excretion mechanism of API.**
- **Method for organ distribution analysis has been established, which revealed no long-term accumulation in organs.**
- **Drug interactions have been conducted, which revealed low possibility of such interactions.**

# 8. Preparation and Cost Assessment

- **Estimation of reagent and solvent cost: ￥~28/g**
- **Purchase prices on lab reagent scales (≤1 kg).**
- **No solvent recycling was considered.**
- **Totally 9 steps (6+2+1).**
- **Total 6-step synthesis yield: 9.9%**
- **API and all intermediates are purified by distillation and recrystillization.**
- **No column purification is involved.**
- **No transition metal catalysis is involved.**

**说明：**

1. **价格为试剂价格。**
2. **未考虑溶剂回用。**
3. **未考虑其它生产成本。**
4. **全部蒸馏和重结晶纯化。**

# 9. Analysis of market potential in China

- **Sugammadex enters health insurance in China: 1) rapid market expanding, 2) raise the market of rapid antagonism, 3) raise market percentage of rocuronium, 4) enhance the demand for rapid antagonist for cisatracurium.**
- **Surgery case number in China: >80 million**
- **NMBA residual ratio: ~55%**
- **Potential need for rapid antagonists: ~44 million**
- **Sugammadex price: ￥136 per injection**
- **Market potentials of rapid antagonists in China: totally ￥5-6 billion**

**Global sales of sugammadex in 2023:**

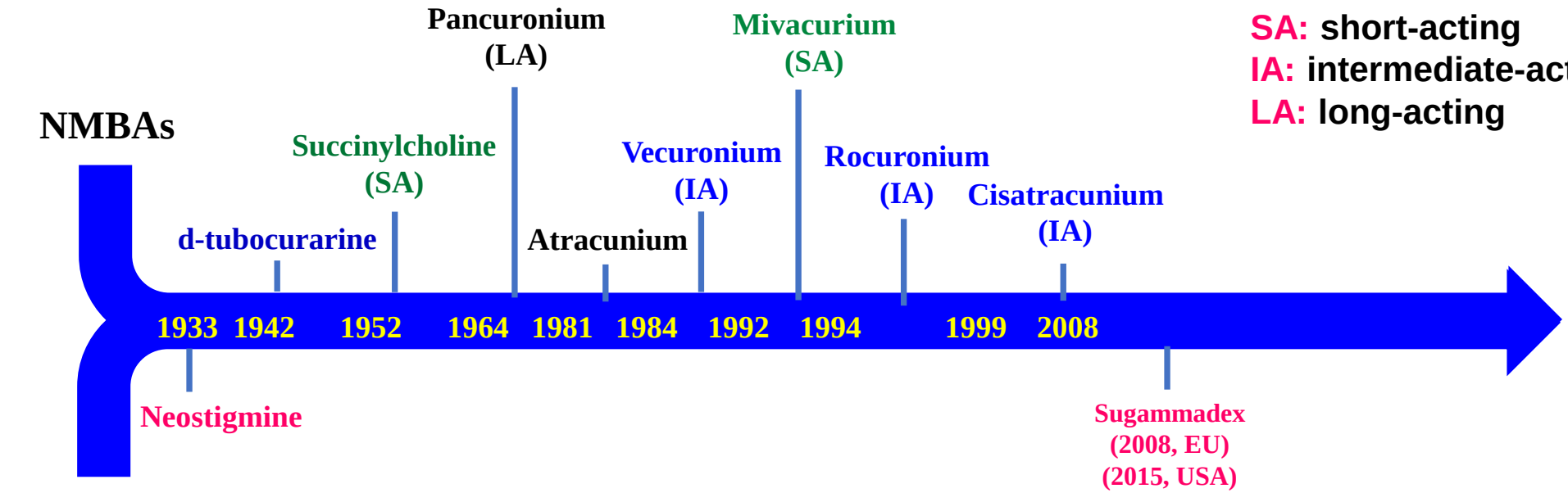
**$1.84 billion**

# Summary of activity, biosafety, ADME and preparation

**ACD-4 as the 1st universal antagonist for NMBAs:**

- **Can rapidly reverse profound block of cisatracurium (neostigmine cannot).**
- **Can rapidly reverse moderate block of cisatracurium, much shorter than that by neostigmine.**
- **1st antagonist for rapid reversal of cisatracurium.**
- **More efficient than sugammadex in reversing the profound block of rocuronium and vecuronium.**
- **Has excellent biosafety.**
- **Mainly through renal excretion and no body accumulation.**
- **Preparation cost is competitive.**

# History of NMBAs and antagonists for general anesthesia




## Antagonists

- Since 2008, no new NMBAs or antagonists have been approved for clinical use.
- Renewal of both NMBAs and antagonists is very slow.
- A new successful drug is expected to be used clinically for many years.

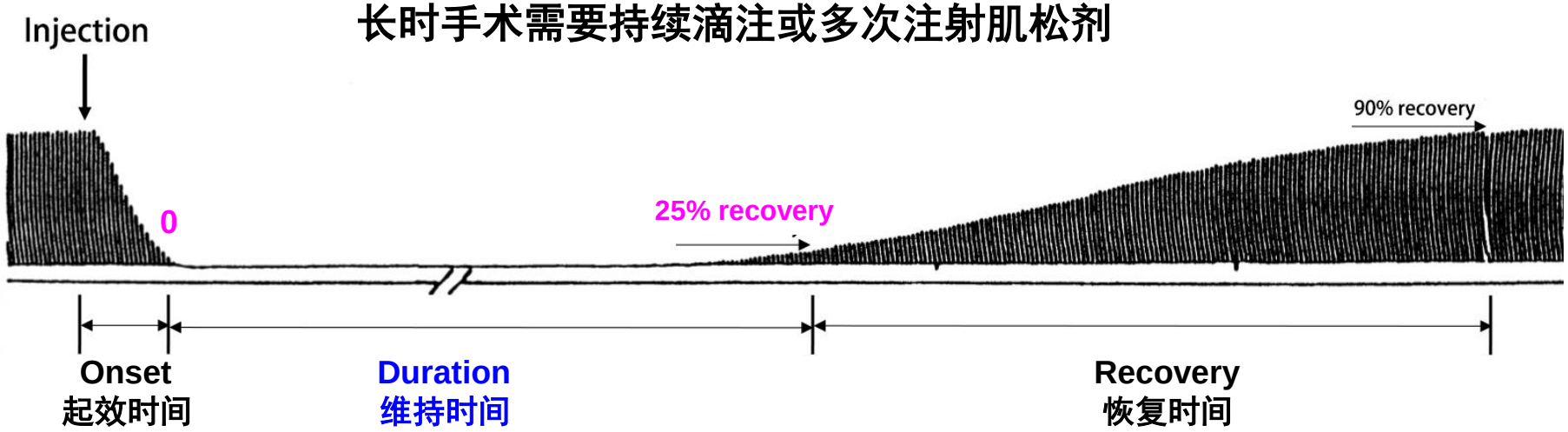
# Impact of ACD-4

- **Have huge economic benefit.**
- **The 1st antagonist to rapidly reverse cisatracurium, representing the realization of a large unmet clinical need.**
- **The 1st supramolecular drug coming from the academic institution.**
- **Represent a milestone in drug design via supramolecular principle.**

# 10. Subsequent project: NMBA and antagonist partner development

## Prolonged surgeries require continuous injection or multiple injection of NMBAs

## 长时手术需要持续滴注或多次注射肌松剂




**Prolonged surgeries (45 min ~ ≥10 h):**

- **Account for -80% of general anesthesia operations.**
- **Cannot be covered by one injection of NMBAs.**
- **Need repetitive or continuous injection:**
- **Lead to:**
  - ✓ **Fluctuation of vital signs (生命体征波动).**
  - ✓ **Enhanced human resource (anesthetist and nurse).**
  - ✓ **Intensive monitoring.**
  - ✓ **Increased economic cost.**

| | Onset time (min) | Duration time (mine) |
|---|---|---|
| Cisatracurium | 2.7 | 45 |
| Rocuronium | 1.5 | 36 |
| Vecuronium | 2.4 | 44 |

# Project goal: block and antagonism partner

**Develop a new ultralong-acting NMBA that can cover >90% of prolonged surgeries by one injection:**

- **Duration time: up to 10 h for adults.**
- **With onset time comparable to existing NMBAs.**
- **With high therapeutic index.**
- **With high biosafety.**
- **With competitive price.**
- **Can be rapidly antagonized at any stage by ACD-4.**

**Clinical application goal:**

**One time injection of the NMBA + one time post-operation antagonism**

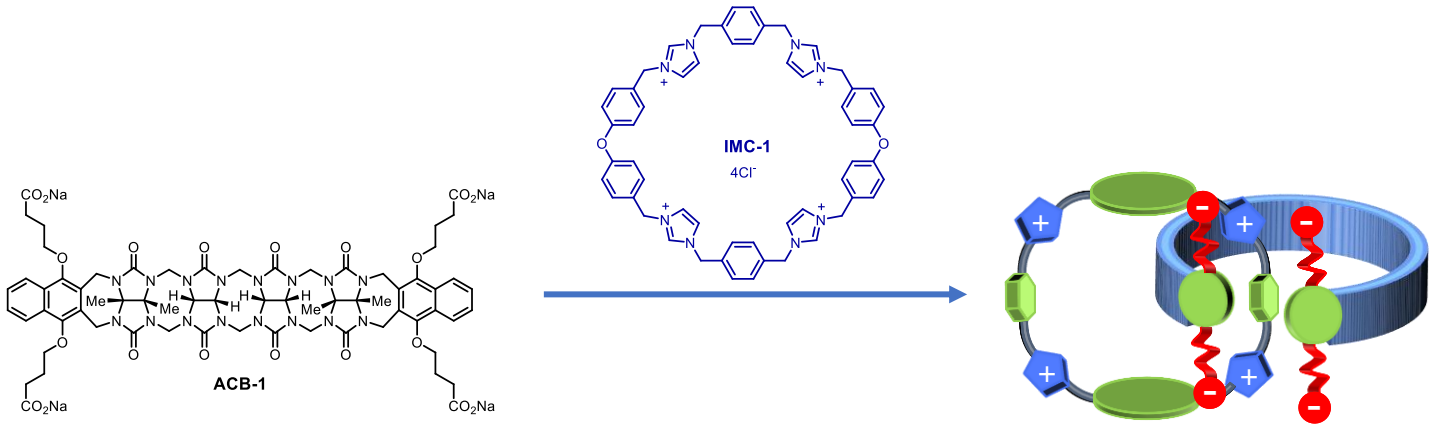
**主客体搭档：**

**客体长效肌松 + 主体快速拮抗**

**术前一次注射 术后一次注射**

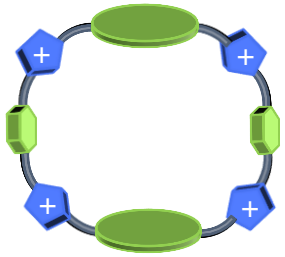
# Proof of concept: new application of supramolecular chemistry

**Host-guest partner approach works for achieving both long-acting blockade and rapid reversal:**




**Y. Wu, J. Yang, S.-Y. Zhuang, S.-B. Yu, Y. Zong, Y.-Y. Liu, G. Wu, Q.-Y. Qi, H. Wang, J. Tian, W. Zhou, D. Ma, D.-W. Zhang, Z.-T. Li, *J. Med. Chem.* 2024, 67, 2176−2187.**

# Key results for the new ultralong-acting NMBA (IMC-9)



IMC-9

## In vivo (rat model) results:

- Has >10 h of blocking time related to adults.
- With onset time comparable with that of cisatracurium.
- Has high biosafety: ≥20 therapeutic index.
- Can be rapidly antagonized by ACD-4 at any stage.
- Very low cost of preparation.

- **Total market potential for the partner drugs in China: ￥14 billion.**
- **The two projects will promote each other.**
- **A new concept for drug design.**
- **Excellent exhibition of supramolecular chemistry for drug design.**

# Thanks