

# MINC: A Platform to Enhance CNS Drug Delivery and Safety for an Effective Treatment

## An example of STM-003 for treating AD

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Wednesday-0009

### Background

MINC features are: (1) deliver drugs to the brain, (2) reduce drug toxicity, (3) Protect neural cells from oxidative stress and inflammation and promote neural cell regeneration. MINC technology does not change drug structure and develops multi-functional drugs to treat Alzheimer's disease (AD), Parkinson's disease (PD) and other neurodegenerative diseases (NDD).

### MINC Technology Principle

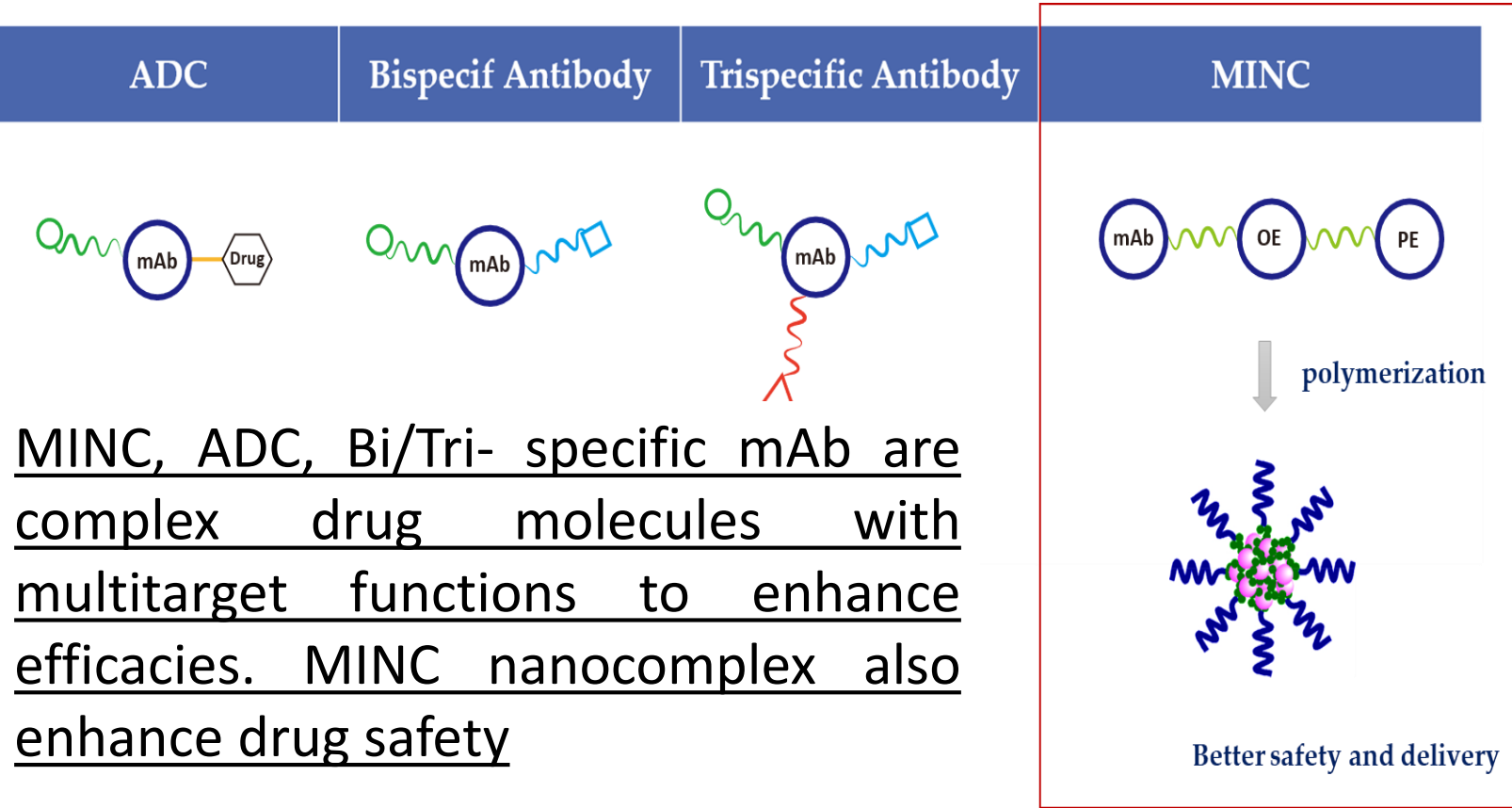


**Fig. 1. MINC develops complex molecules, similar to ADC, Bi/Tri specific mAb, with multi-targeting to enhance efficacies, slow-release mechanism to reduce drug toxicity.** OE/PE penetrates BBB to carry drugs to the brain.

### Methods

- Brain delivery: BBB penetration efficacy was studied using a small compound (doxorubicin) in zebrafish and endothelial cells. A fluorophore-labeled antibody (trastuzumab) was tested in a mouse model.
- Enhance drug safety: Safety of MINC-doxorubicin and MINC-anti-CD3 were compared with the naked drug by body weight reduction and survival.
- Efficacy in AD: Cognition behavior was examined by water maze analysis. Neuronal activity was tested by FDG-PET.

### Retain Drug Integrity

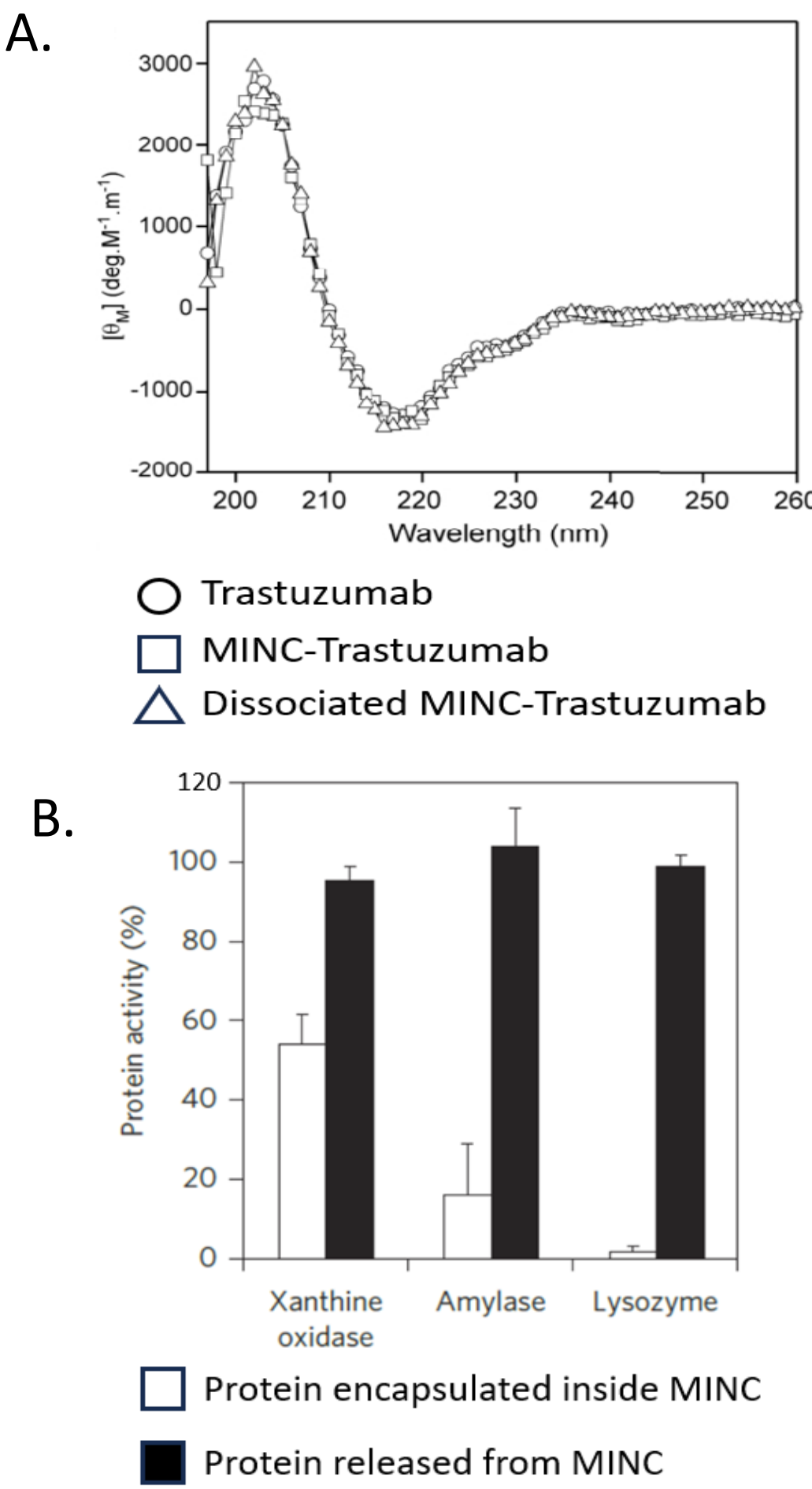


**Fig. 2. MINC retains the structural and functional integrity of the payload (antibody and proteins were used as example)**

(A) Circular dichroism (CD) analysis confirmed that the structure of the protein remained unchanged.

(B) Proteins regained full activity after released from MINC. Three example proteins (ranged from 14-290 kDa) regain their activity (filled bar) after released from MINC

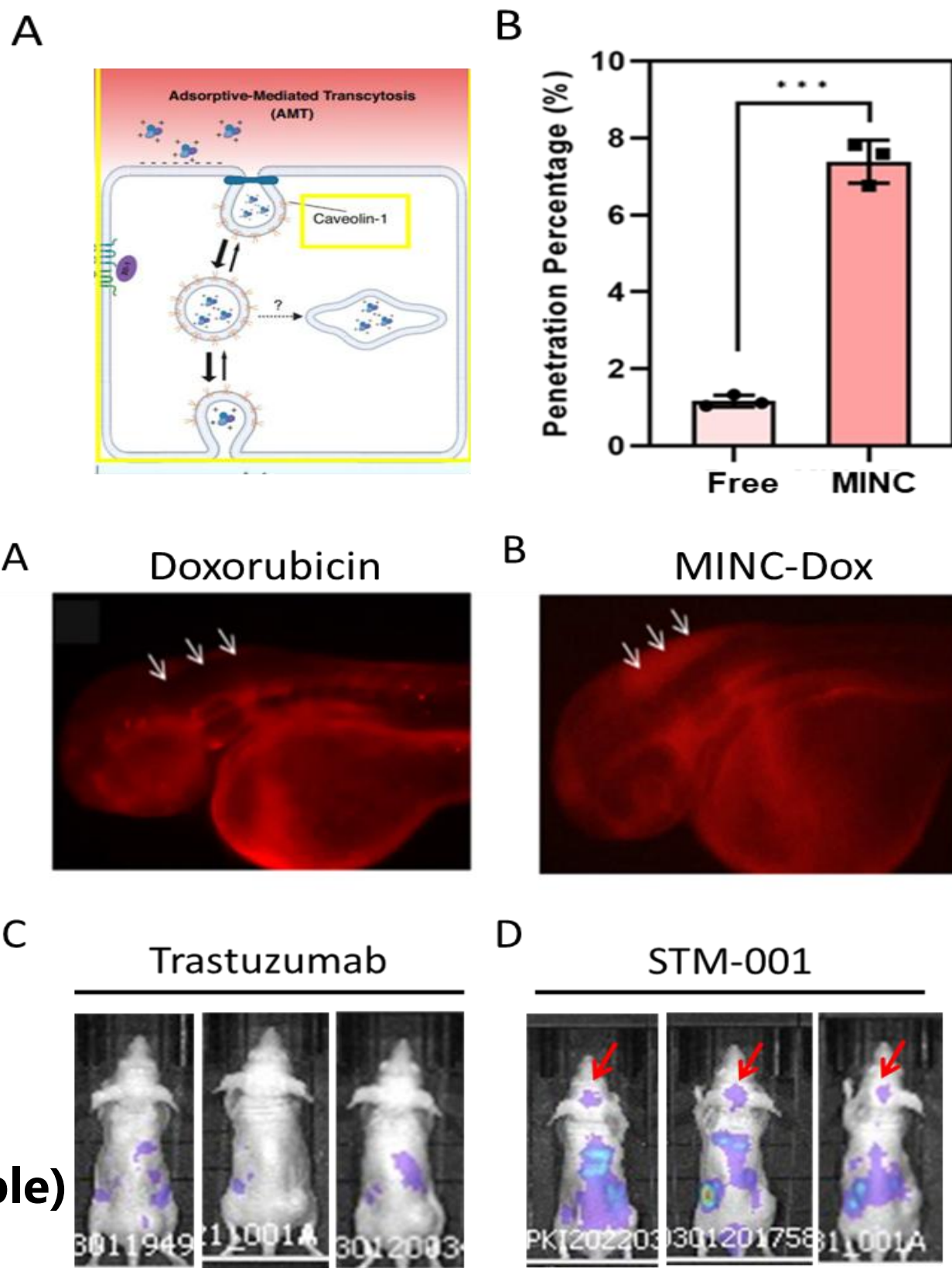
### Carry Drugs to the Brain

**Mechanism:** MINC platform delivers drugs into the brain via caveolin-dependent adsorptive mediated transcytosis (Fig 3A, 3B).

**Application:** MINC can carry small chemical, protein drugs, gene therapy and vaccine without changing drug structure and original activities.

**Example (brain delivery):**

- Doxorubicin was used as a small molecule example (Fig. 4A, 4B).
- Trastuzumab was used as a large protein example (Fig. 4C, 4D).



Doxorubicin (A) or MINC-doxorubicin (B) was intravenously injected into zebrafish via sinus venosus. MINC-Dox enters the brain of zebrafish (white arrow) while Dox does not.

Trastuzumab (C) or STM-001 (MINC-trastuzumab) (D) was intravenously injected into nude mice via tail vein. STM-001 enters the brain while Trastuzumab does not.

### Results

### Enhance Drug Safety

**Mechanism:** MINC platform has a slow-release mechanism to extend tissue elimination rate (T1/2) to 29x more than the unencapsulated drugs (Fig. 5A). Therefore, the toxicity of unencapsulated drugs is significantly reduced.

**Application:** small chemical, protein drugs, gene therapy and vaccine.

**Examples (enhanced safety):**

- Doxorubicin was used as a small molecule example. (Fig 5B, 5C).
- Anti-CD3 was used as a large protein example (Fig. 5D, 5E).

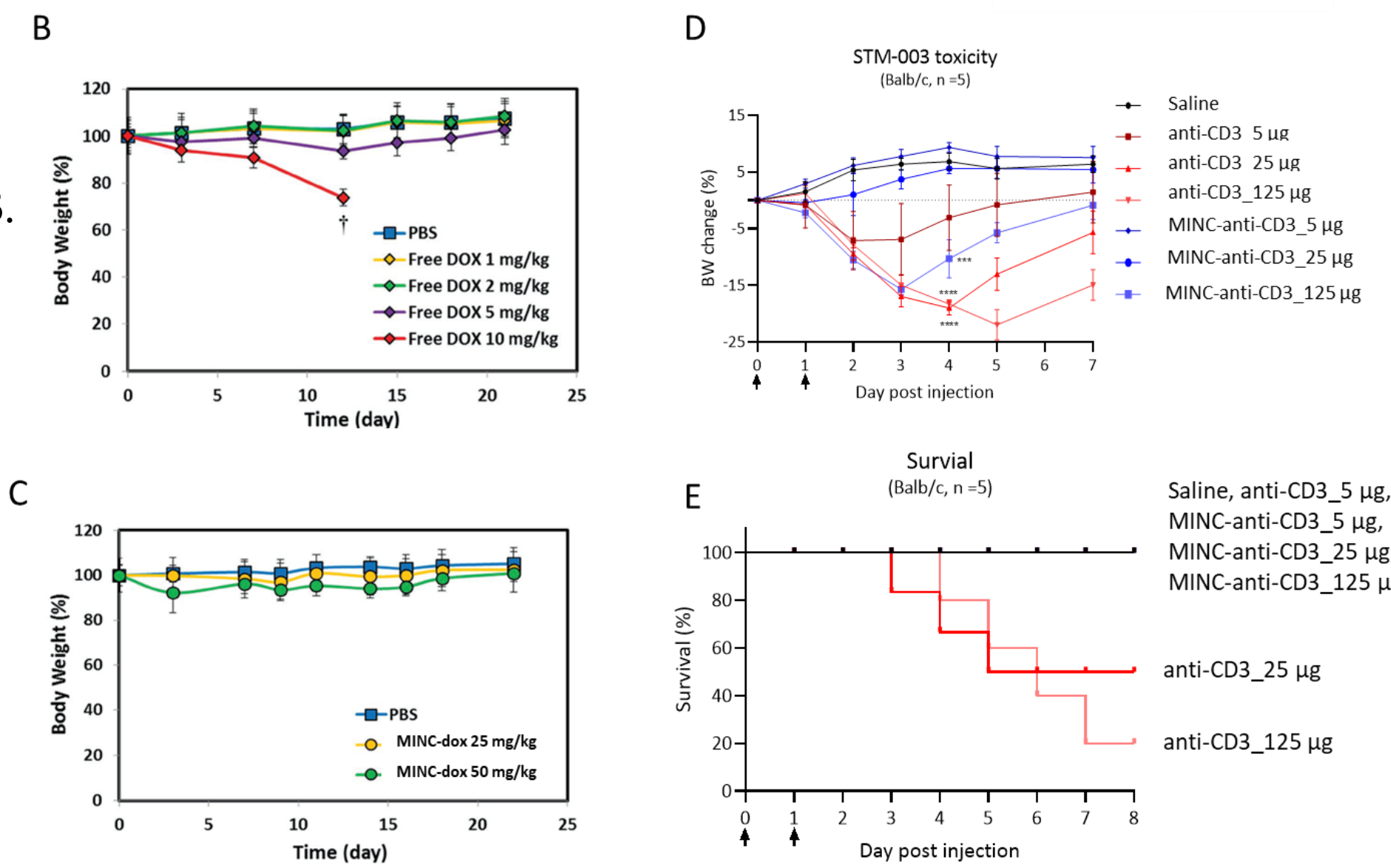


**Fig. 5. MINC improves safety of small compound and large protein.**

(A) STM-001 has 29x increased tissue elimination rate (T1/2) compared to trastuzumab. (B, C) MINC-doxorubicin (C) has a 5x improved safety compared with free doxorubicin (B) in mice. (D, E) MINC-anti-CD3 (D) has also 5x improved safety compared with free Dox anti-CD3 (E) in mice.

### Enhanced Efficacy for AD

STM-003, developed by MINC technology, is effective in restoring brain activities (Fig. 6A) and cognitive behavior of 12-18 month aged 3xTg AD mice (Fig. 6B).

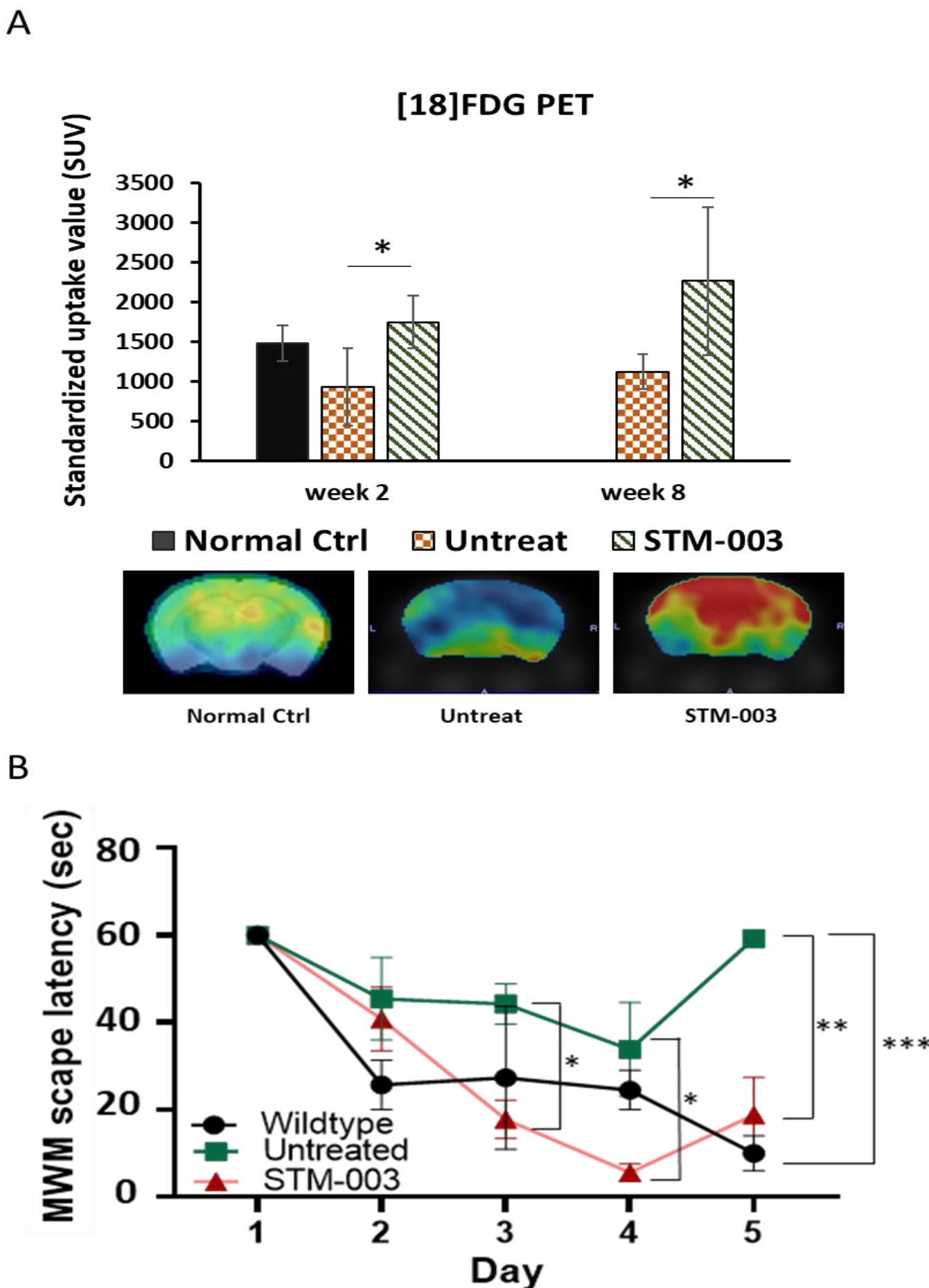


**Figure 6. STM-003 improves brain activities (A) and cognitive behaviors (B) in AD mice.** (A) [18F]-FDG PET was used to assess the brain activity. \*p < 0.05. (B) The Morris Water Maze escape latency was used to assess the cognitive behavior in the STM-003 treated group. \*p < 0.05. \*\*p < 0.01, \*\*\*p < 0.001.

### Conclusions

For small molecules, large biologics, and gene-based therapeutics, the MINC can lower drug toxicity even at concentrations up to 25-fold above the therapeutic level, reducing both CNS and systemic adverse effects.

**STM-003 is effective in halting AD progression in late-stage AD.** It is a highly promising candidate for treating both early- and late-stage AD/PD.