TNAX Biopharma Corporation

We improve the quality of life of patients with intractable diseases by discovery of truly valuable pharmaceuticals through innovative research on immunoreceptors.

March 25, 2024

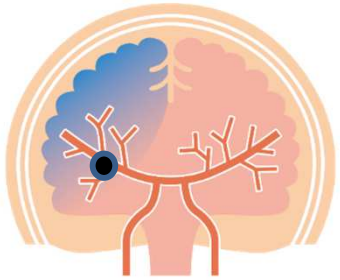
◆ Developing **first-in-class biologics** which target **immunoreceptors** and their **ligands** discovered by Professor Akira Shibuya, University of Tsukuba

Pipeline

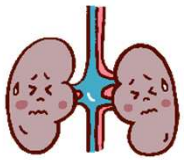
		Target ID/Validation & Lead Generation	Optimization	Preclinical	IND	First-In-Human
TNAX101A/ IMB1001	DNAM-1 /CD226	CD, UD, SLE	→	→	→	Partnered with IMIDomics
TNAX103	CD300A	AIS, AKI, SCI, AMI	→	→	→	Unpartnered
Undisclosed	Undisclosed	Undisclosed	→			

Exclusively licensed out to IMIDomics for worldwide territory

- **TNAX101A** = Humanized **anti-DNAM-1 (CD226) mAb**
  - ✓ **Anti-inflammatory/fibrotic** drug for **immune-mediated inflammatory diseases**
- **TNAX103** = Humanized **anti-CD300A mAb**
  - ✓ **Efferocytosis** promotor for **acute ischemic diseases**
- An undisclosed early stage research program is underway.



Acute Ischemic Stroke



Acute Kidney Injury

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Acute Ischemic Stroke (AIS)

- >795K Americans have strokes (610K new cases each year)*1.
- ～142K deaths a year in the US in 2019: 5th leading cause of mortality
- 40% of bedridden patients and 30% of dementia are caused by AIS.
- Total annual stroke-related costs in the US*2 = $56.6B
- 325K ischemic strokes are caused by large vessel occlusion annually in the US.
- Only 20% are treated with recanalization therapy

*1: The CDC statistics published in April 2022

- *880K AIS cases in Europe*
- *3.3M deaths from ischemic stroke WW*

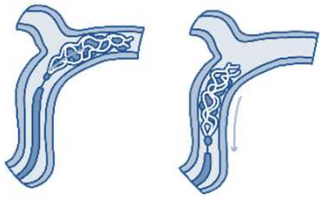
*2: including the costs of health care services, stroke medications and days away from work

Recanalization therapies

Thrombolytic therapy

rtPA/Alteplase: The only thrombolytic medication approved by the US FDA

Endovascular thrombectomy

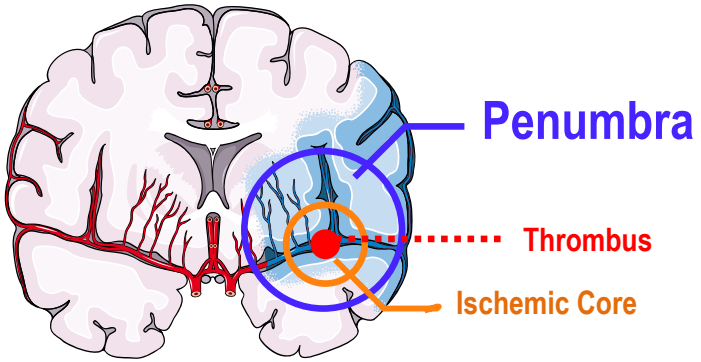


Stent Retriever and/or Aspiration

- **Apoptotic** and **inflammatory** pathways begin beyond several hours to days, and **the penumbra zone survives** for hours to days.

→ Leading to **neuronal cell death**

The penumbra zone may be salvaged with proper reperfusion and drug treatment.



***Penumbra* = Tissue at-risk of cell death around the ischemic core**

Rescue of penumbra by efferocytosis promotor

Efferocytosis promotors are believed to be safe and effective **neuroprotectants**.

Problems of Recanalization Therapy

rtPA

- Short therapeutic window (≦4.5 h)
- Impossible to treat large clots
- Increase in risk of hemorrhagic transformation
- Induction of **ischemia-reperfusion injury** (IRI)

Endovascular thrombectomy (EVT)

- Few medical facilities can perform EVT.
- Induction of **ischemia-perfusion injury** (IRI)

IRI = Tissue injury with inflammatory responses (cerebral edema, hemorrhage, neuronal death, etc.)

With recent advancement in recanalization therapy, IRI has become an increasingly critical challenge in stroke treatment.

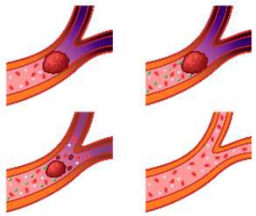
Over 50% of patients cannot attain good outcomes despite timely and complete recanalization.

Sudden restoration of blood flow may bring further damage.

Solutions

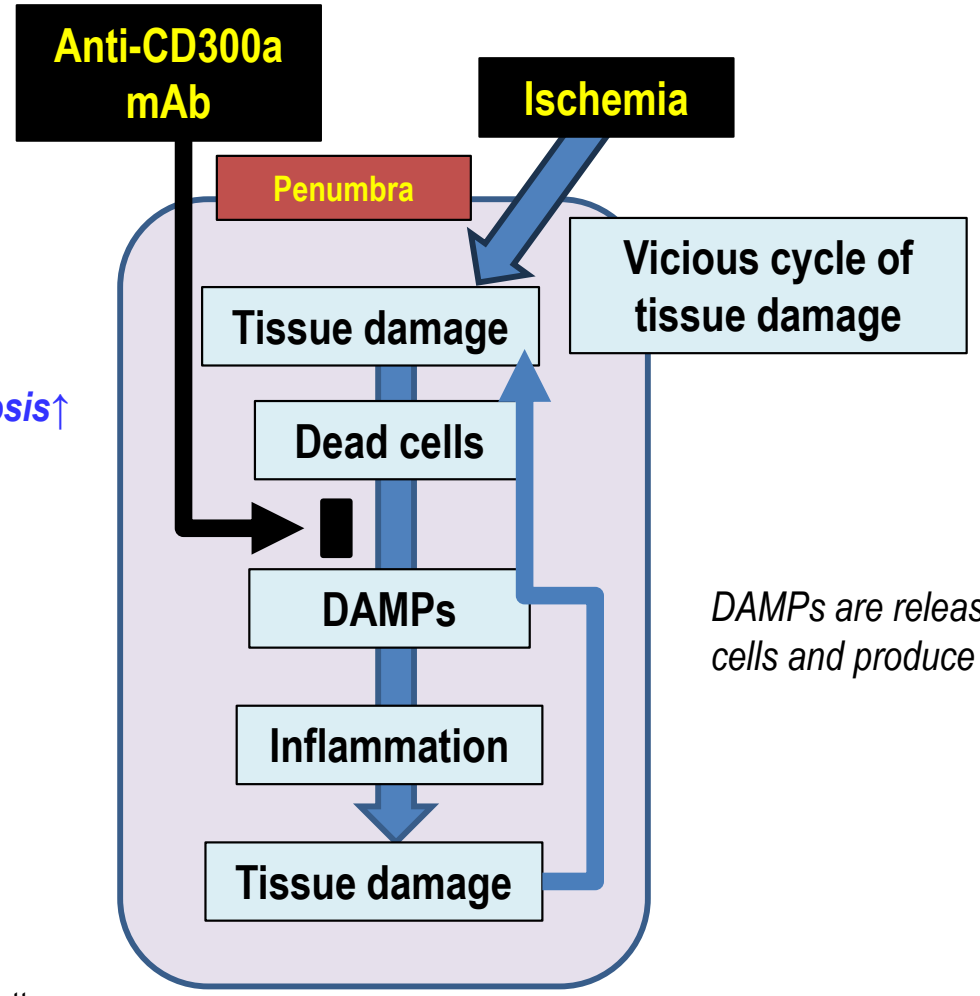
Efferocytosis promotors

- **Attenuate IRI after recanalization**
- **Rescue penumbra tissue**
  - **Have no effect on hemorrhagic transformation**
  - May be added on to recanalization therapy
  - May be used alone



Rescue of penumbra by controlling inflammation induced by cell death

Ischemic cell death induces inflammation, resulting in further cell death and tissue damage in the penumbra (i.e., a vicious cycle of tissue damage). The penumbra region can be rescued by controlling cell death-induced inflammation.



Anti-CD300a mAb

1) Early-stage dead cell efferocytosis↑

2) DAMPs release↓

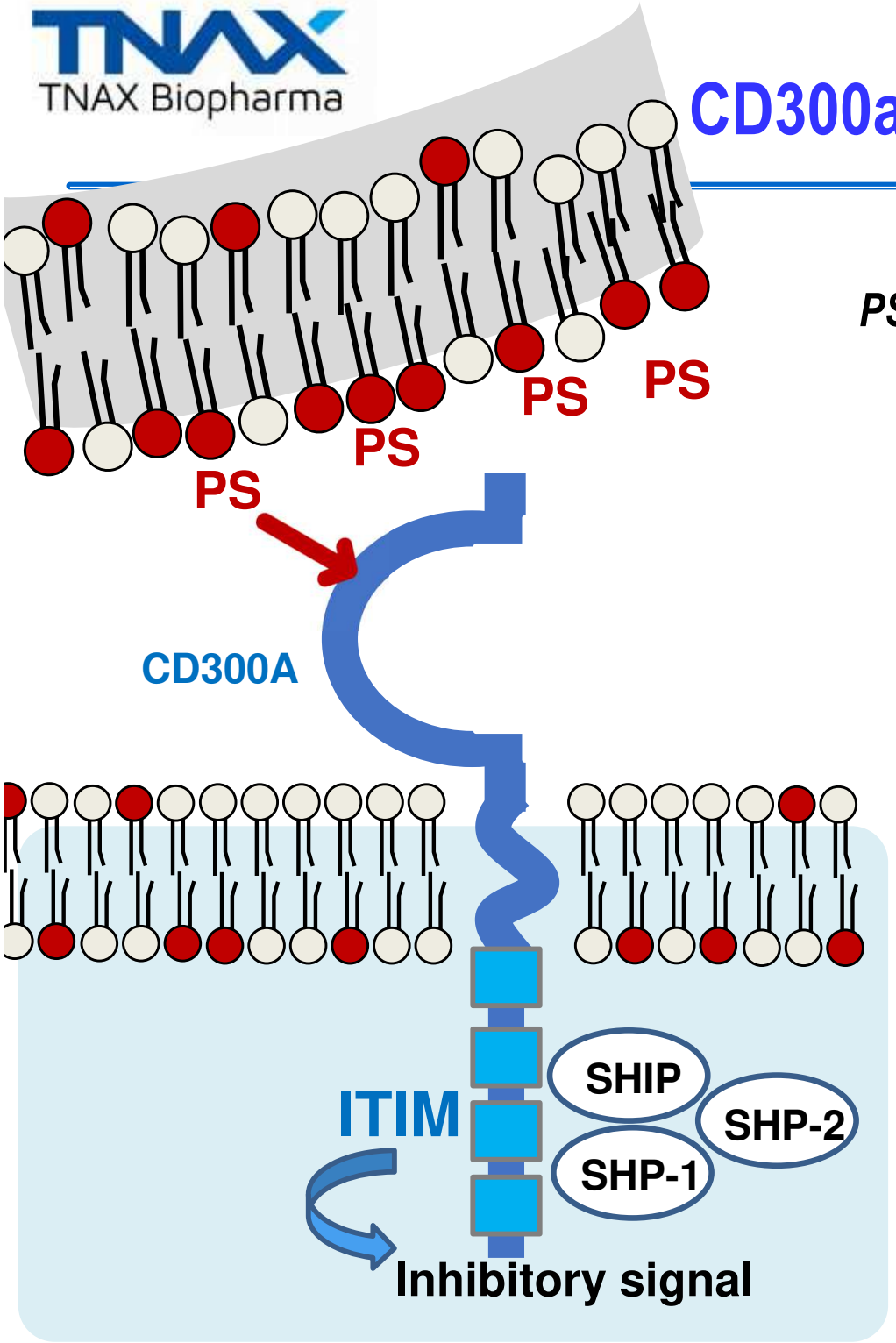
3) Inflammation↓

4) Tissue damage↓

DAMPs are released from ischemia-induced dead cells and produce proinflammatory cytokines.

DAMPs: damage-associated molecular patterns

CD300a & phosphatidylserine (PS)



PS is a key ligand of CD300A.

PS

Exposed on the outer membrane of dead cells

(Normally PS is confined in the inner membrane leaflet of viable cells.)

CD300a

Expressed on macrophages, DCs, neutrophils and mast cells.

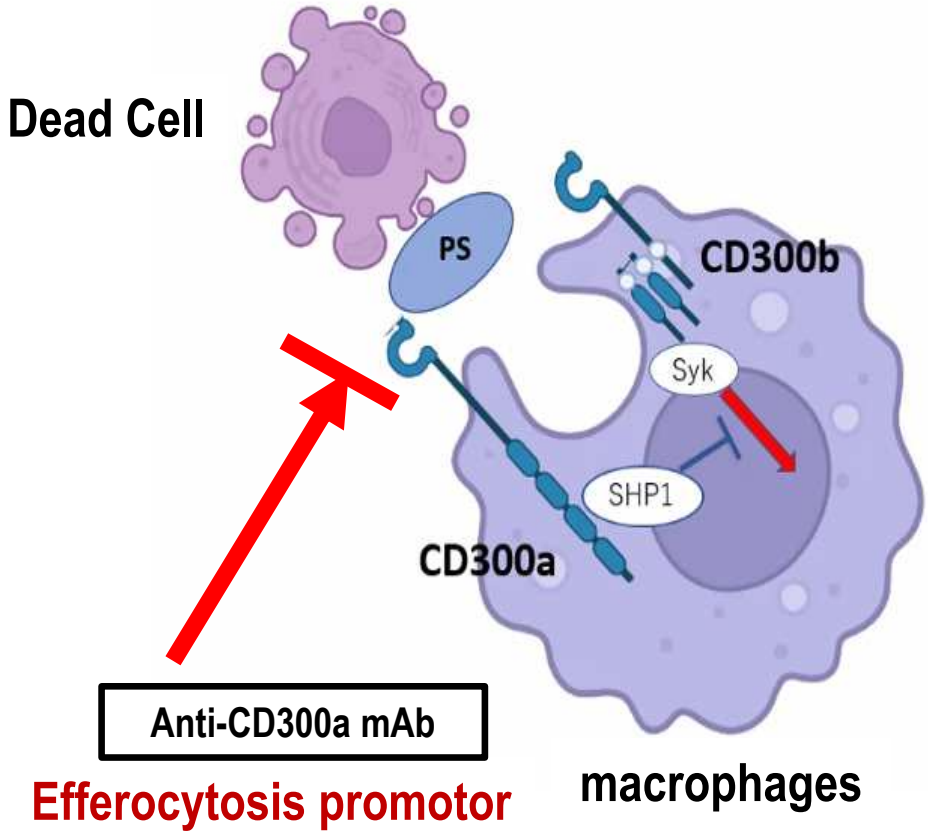
- **Macrophages: Efferocytosis ↓ (in cerebral infarction model)**
- **DCs: IFNβ production ↓**
- **Mast cells: Degranulation ↓**

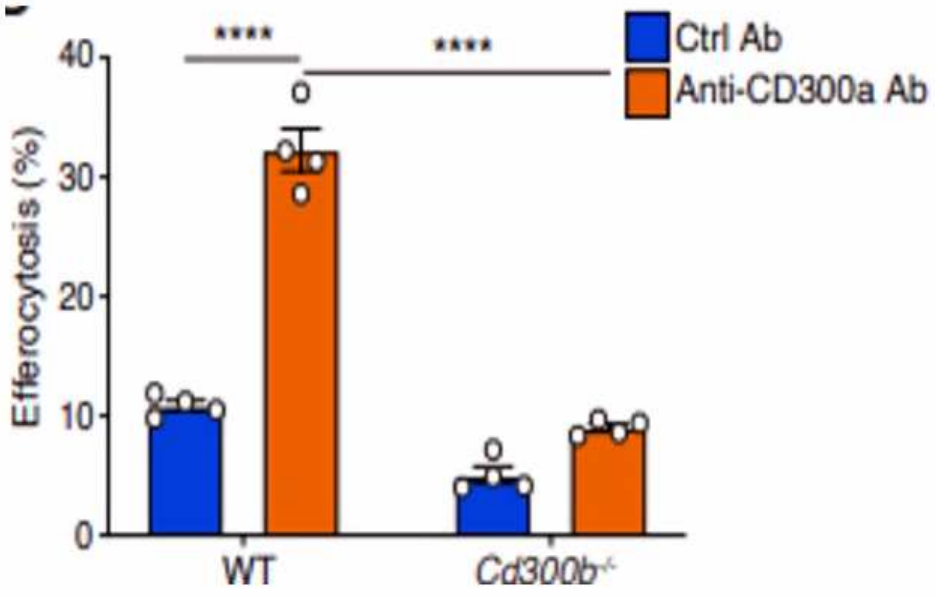
CD300a expressed on macrophages is a key anti-efferocytic molecule.

Anti-CD300a mAb promotes CD300b-mediated efferocytosis by macrophages and enhances dead cell removal.

CD300a inhibits efferocytosis on macrophages

Efferocytosis is a special form of phagocytosis in which macrophages engulf dead cells.





CD300a expressed on macrophages binds to PS exposed on the surface of dead cells and induces resistance to dead cell removal.

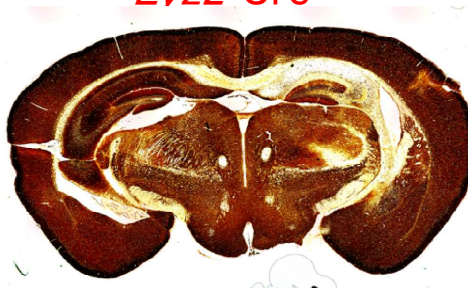
1) Dead cells expose PS, which displays “Eat Me” signals, and macrophages induce efferocytosis to clear dead cells.
2) PS bound to CD300a expressed on macrophages induces resistance to efferocytosis.
3) Anti-CD300a mAb normalizes clearance of diseased tissue.

CD300a KO mice improved neuronal damage and neurological scores in acute ischemic stroke model.

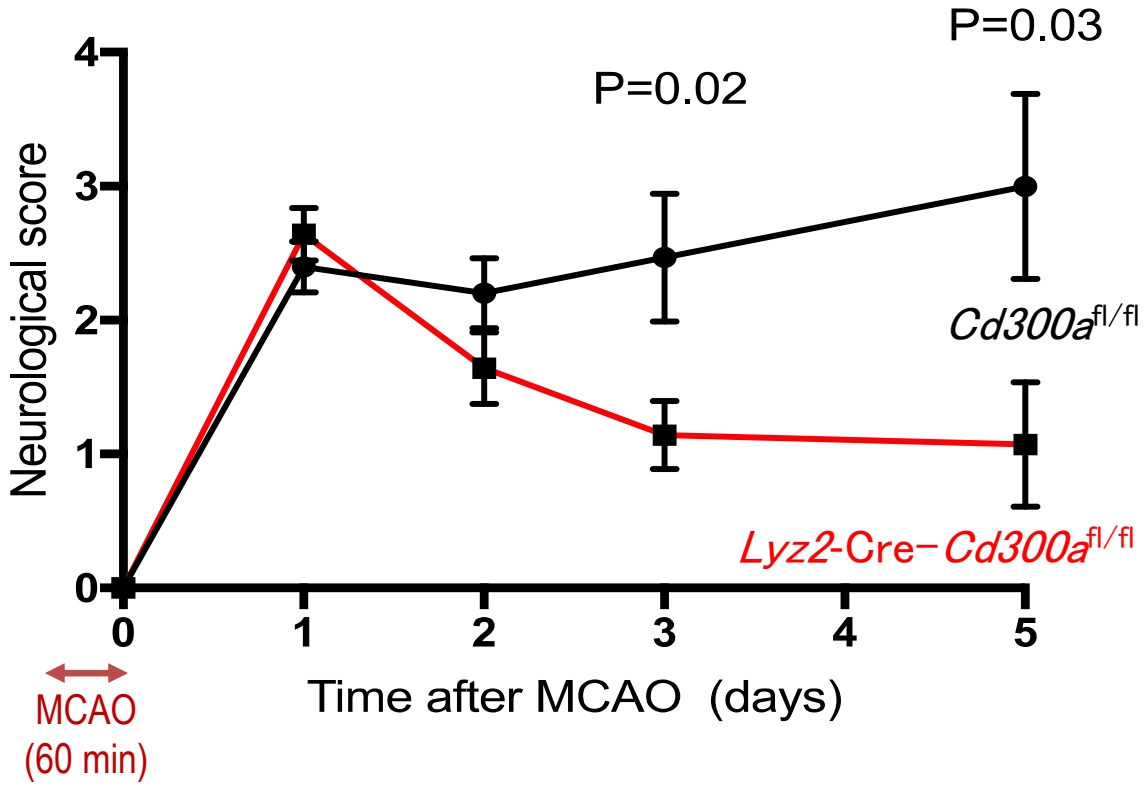
Mice deficient in CD300a on macrophages decreased neuronal damage and ameliorated neurological scores after MCAO and reperfusion.

Cd300a$^{fl/fl}$

Cd300a$^{fl/fl}$
Lyz2-Cre



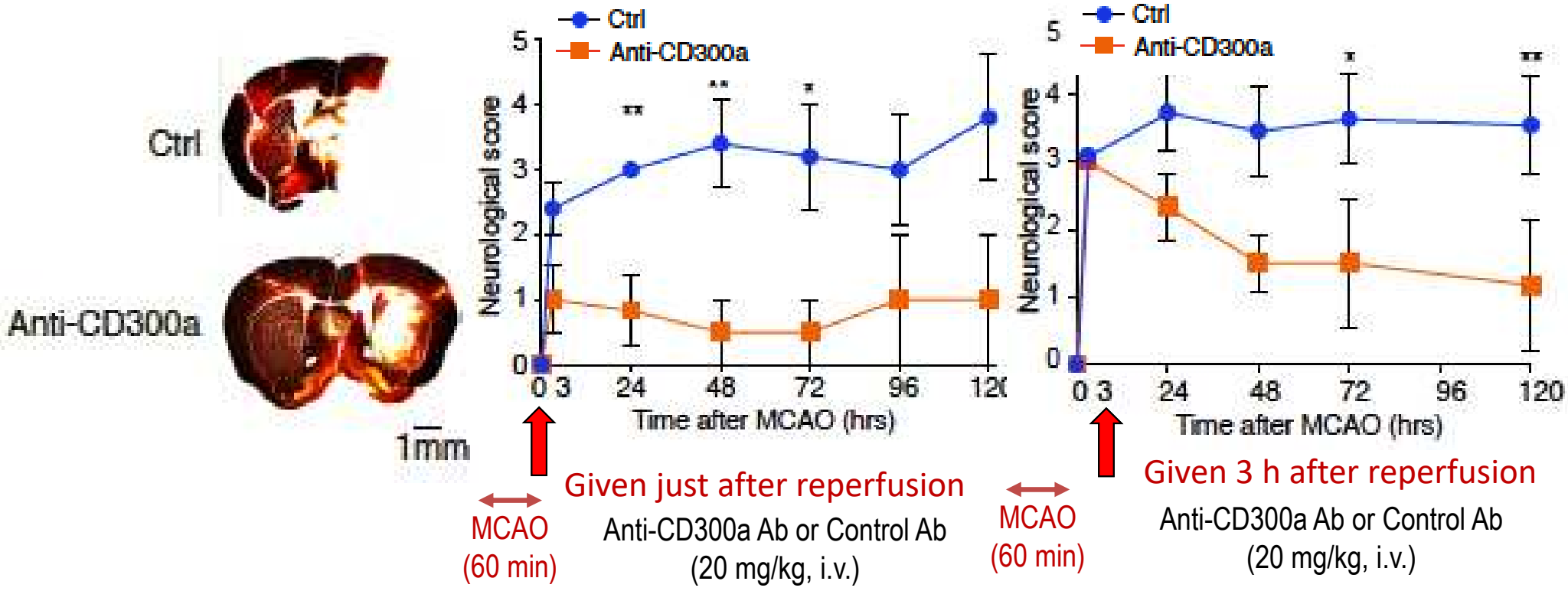
Anti-MAP2 Ab



MCAO: Middle Cerebral Artery Occlusion

Anti-CD300a mAb improved neuronal damage and neurological scores in acute ischemic stroke model.

Anti-CD300a mAb decreased neuronal damage and ameliorates neurological scores after MCAO and reperfusion.



MCAO: Middle Cerebral Artery Occlusion

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Anti-CD300a mAb ameliorated behavior in mouse MACO model. (video)

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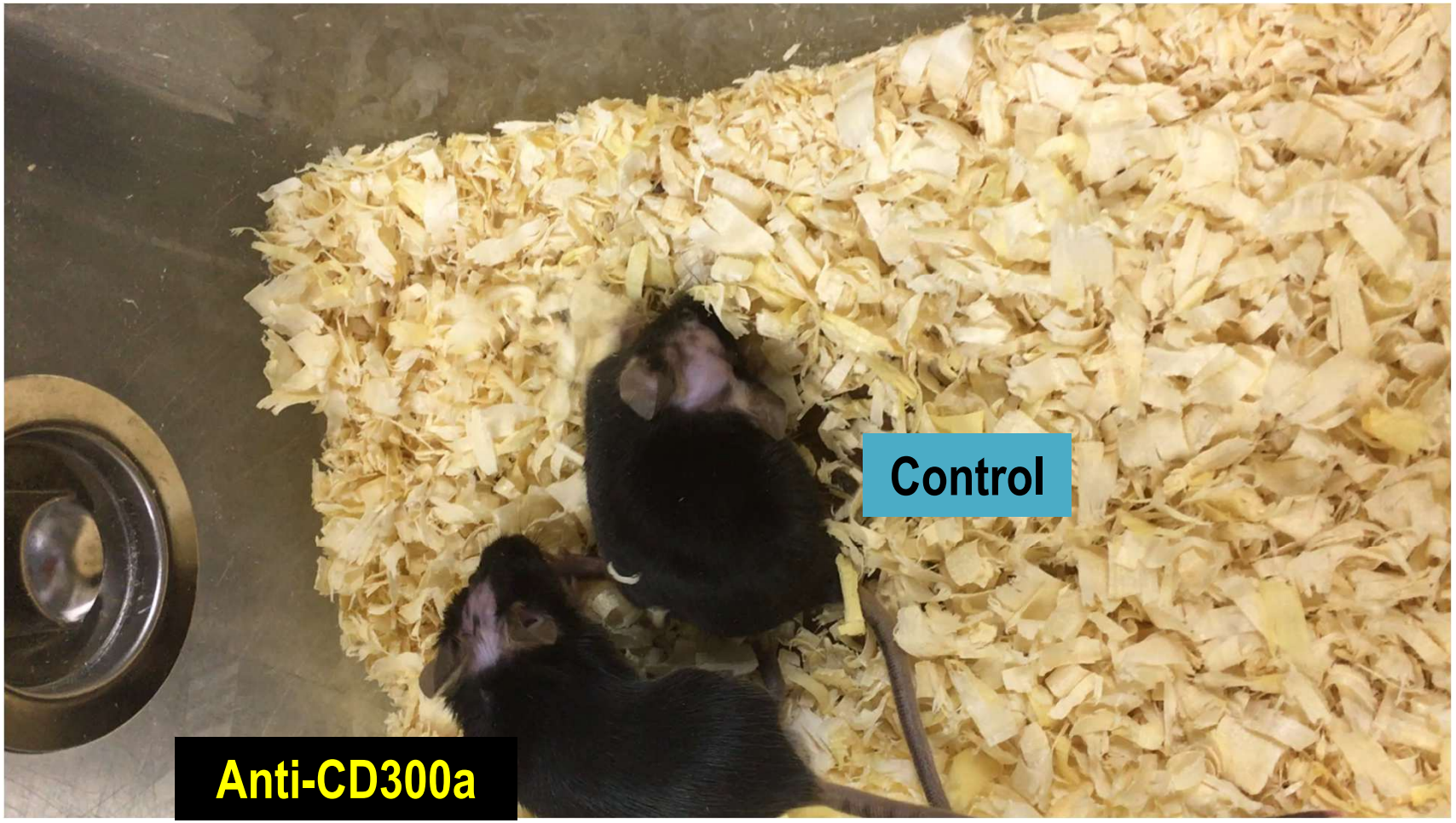

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Comparison with drugs in clinical trials
--- TNAX103 is the only anti-inflammatory neuroprotectant that fundamentally inhibits ischemia-reperfusion injury. ---

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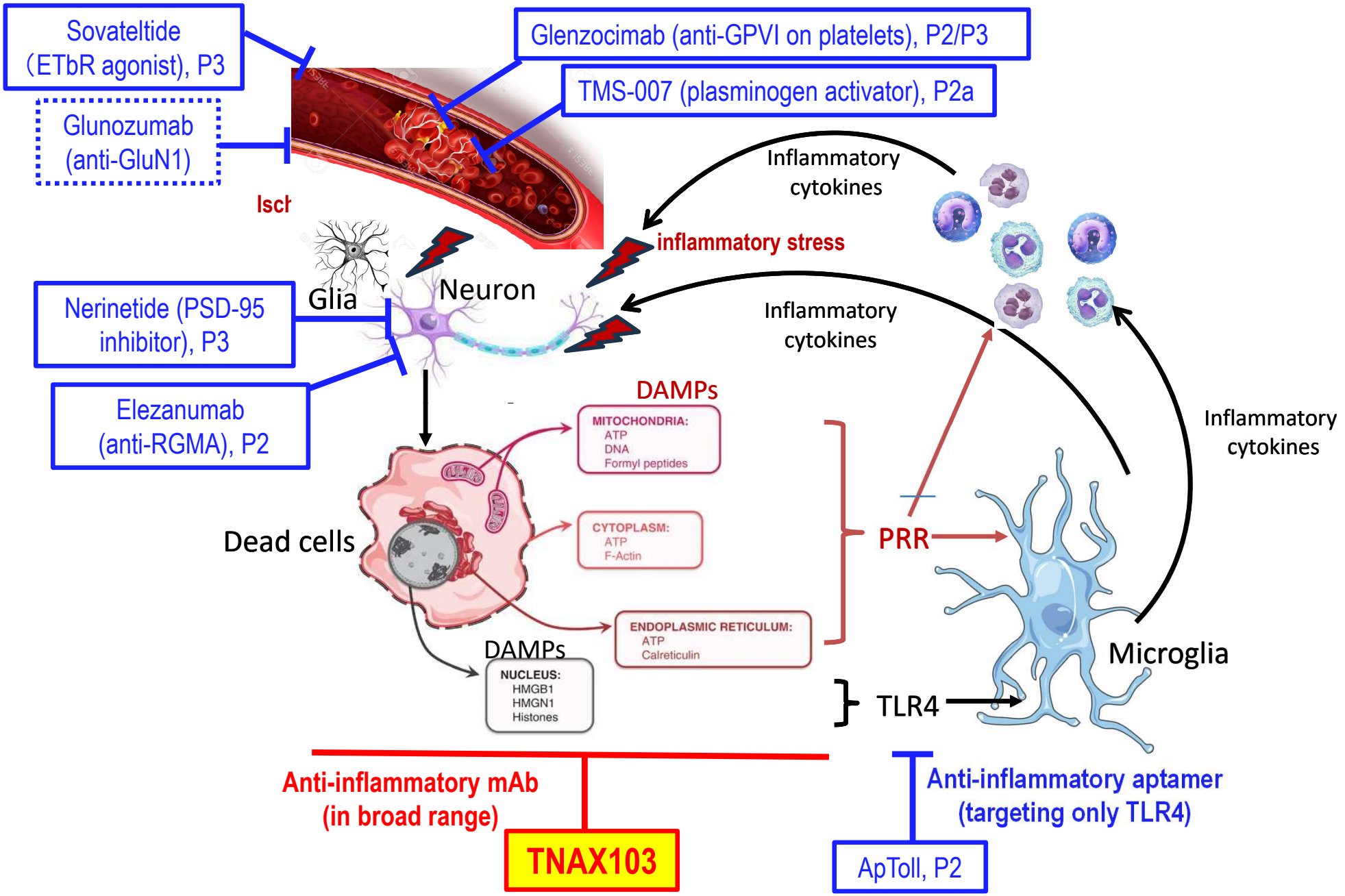

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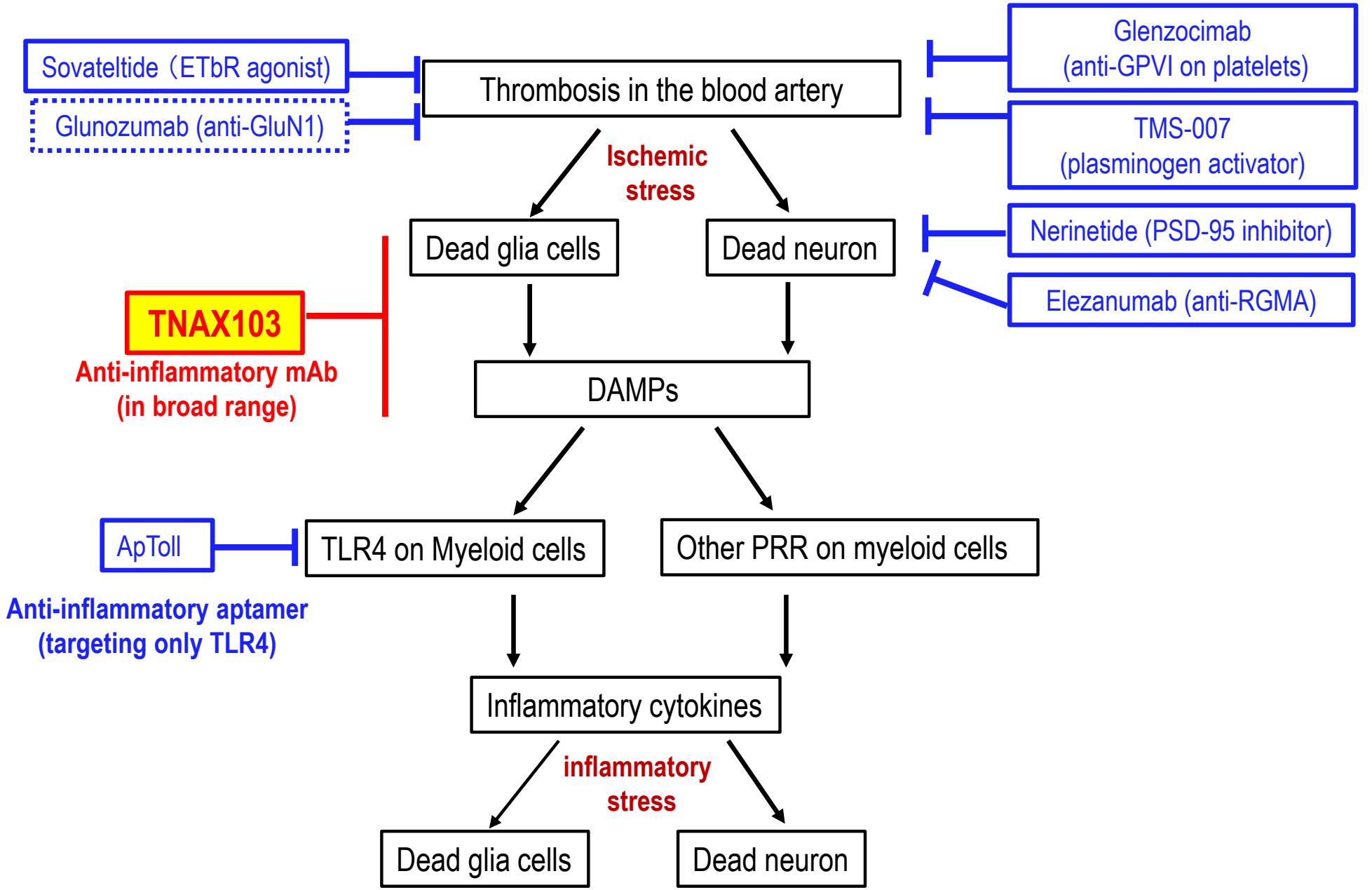


Clinical Positioning of TNAX103 in AIS Management

Post-launch product image

Pre-Hospital Recognition (**FAST**)

- ✓ **F**ace dropping
- ✓ **A**rm weakness
- ✓ **S**peech difficulty
- ✓ **T**ime to get help

Emergency Department → Immediate Diagnosis (MRI, CT, NIHSS) → **TNAX103** (**Bolus Injection**)

Evaluation for Alteplase

- ✓ ≦4.5 hours from symptoms onset?
- ✓ Indicated for alteplase?

No → Is Patient Suitable for Endovascular Thrombectomy?

Yes → **Alteplase**

If thrombolysis fails, → **Endovascular Thrombectomy**

Is Patient Suitable for Endovascular Thrombectomy?

- Yes → **Endovascular Thrombectomy**
- No → **Non-invasive Therapy**

Endovascular Thrombectomy: ≦24 hours from KLN

Non-invasive Therapy

- ・Anti-cerebral edema: Glycerol
- ・Anti-thrombin: Argatroban
- ・Anti-platelet: Aspirin
- ・Anti-coagulant: LMWHz

Alteplase / **Endovascular Thrombectomy** / **Non-invasive Therapy** → Stroke Sequalae↓, QOL↑ (Prevent Complications and Recurrence)

The clinical POC study will examine the safety and efficacy of TNAX103 in AIS in combination of endovascular thrombectomy. (Draft)

Pre-Hospital Recognition (**FAST**)

- ✓ **F**ace dropping
- ✓ **A**rm weakness
- ✓ **S**peech difficulty
- ✓ **T**ime to get help

Add-on to EVT only (excluding subjects treated with tPA)

Emergency Department → Immediate Diagnosis (MRI, CT, NIHSS) → Evaluation for Alteplase

- ✓ ≦4.5 hours from symptoms onset?
- ✓ Indicated for alteplase?

→ Yes → Alteplase → If thrombolysis fails, → Endovascular Thrombectomy (EVT)

No → Is Patient Suitable for EVT?

- Yes → **TNAX103 or Placebo** Bolus Injection → Endovascular Thrombectomy (EVT)
- No → Non-invasive Therapy

Endovascular Thrombectomy (EVT) → ≦24 hours from LKN

Non-invasive Therapy:
- Anti-cerebral edema: Glycerol
- Anti-thrombin: Argatroban
- Anti-platelet: Aspirin
- Anti-coagulant: LMWHz

Stroke Sequalae↓, QOL↑ (Prevent Complications and Recurrence)

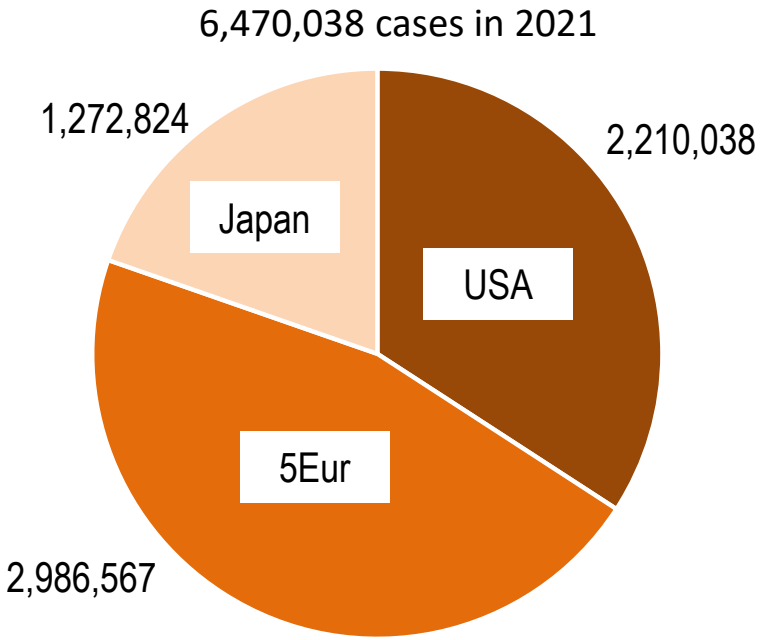
Administered "**before**" recanalization

Target subjects: Patients with ICA or M1 area occlusion who undergo EVT within 24 hours after LKN

TPP of TNAX103 (in AIS)

Modality and Target Molecule	Humanized anti-CD300A mAb
Characteristic Profile	TNAX103 suppresses dead cell-induced inflammation by promoting the removal of dead cells that occur after the onset of acute ischemic stroke. TNAX103 suppresses ischemia-reperfusion injury, which is a problem with recanalization therapy (thrombolysis and endovascular thrombectomy). TNAX103 reduces mortality and ameliorates patient prognosis.
Advantages over Competitors	The only product currently on the market is a thrombolytic drug (tPA/Alteplase), and many competing products in development also claim thrombolytic effects. Unlike TNAX103, they cannot suppress ischemia-reperfusion injury, which is a problem. TNAX103, which extensively inhibits the release of DAMPs upstream of the inflammatory cascade, will show higher efficacy than other anti-inflammatory compounds in development..
Target Disease (Typical Disease)	Acute Ischemic Stroke (AIS)
Target Patient Population (Post-Launch Image)	Patients who undergo thrombolysis and/or endovascular thrombectomy
Early Clinical Trial (Human POC Study) Design	As endovascular thrombectomy (EVT) is becoming the first-line treatment for AIS, we will select patients with internal carotid artery occlusion or acute occlusion of M1 area to undergo EVT within 24 hours of the last known normal. TNAX103 or placebo (saline) will be administered intravenously (single dose) to the subjects in combination with EVT. The primary endpoint will be mRS score (3 – 6) at day 90. The safety will be evaluated with a focus on the incidence of hemorrhage.
Route of Administration	i.v. (bolus)
Safety/Toxicity	TNAX103 does not potentiate the hemorrhagic transformation induced by tPA and exhibits a high safety profile.

Acute kidney injury (AKI)



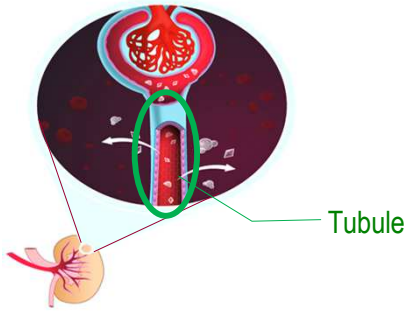
Huge market!

Total market
$5,208M

Renal replacement therapy & Off-label drugs (including ACEIs, ARBs, Diuretics and NSAIDs)

Source DelveInsight Business Research (September 2022)

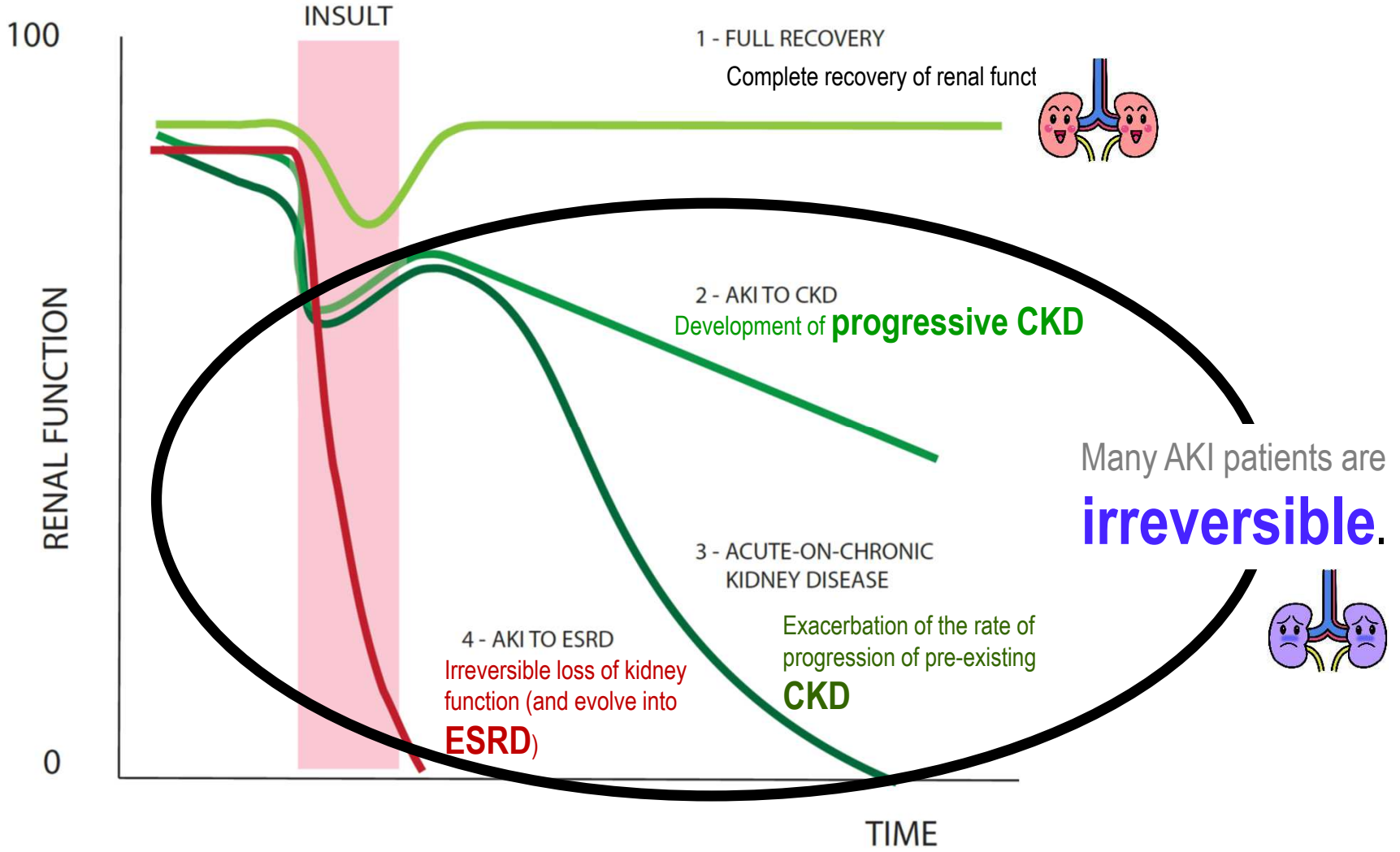
- Can be seen in up to **7% of hospital admissions** and **30% of ICU admissions**.
- **Mortality** rate for hospitalized patients: **40 – 50%**
- **Mortality** rate for ICU patients: **>50%**
- The most common (45%) cause of AKI in hospitalized patients: **ATN**
- Injury to the renal **proximal tubular epithelium**
- **High risk of developing progressive CKD and ESRD over time**
- **No effective means for preventing or treating AKI**



ATN: Acute tubular necrosis *CKD: Chronic Kidney Disease* *ESRD: Endo-Stage Renal Disease*

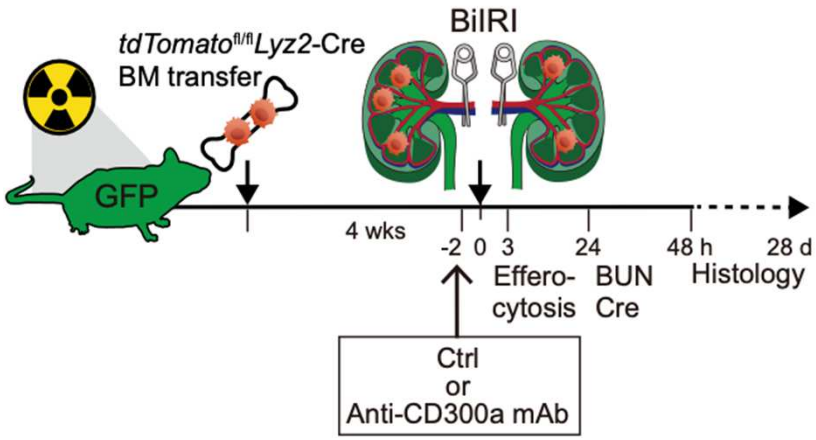
Natural history of AKI

Renal function is expected to be **completely recovered by TNAX103.**

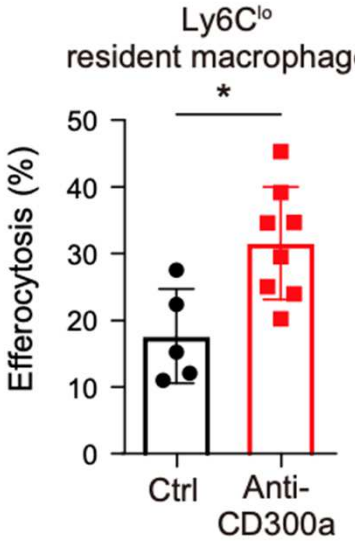


Clin J Am Soc Nephrol. 2008 May;3(3):881-6

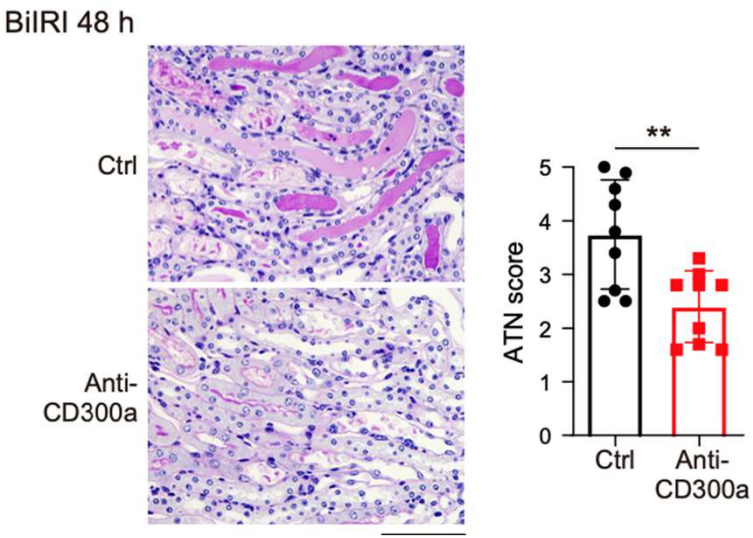
Anti-CD300a mAb promotes efferocytosis and attenuates AKI and kidney fibrosis.



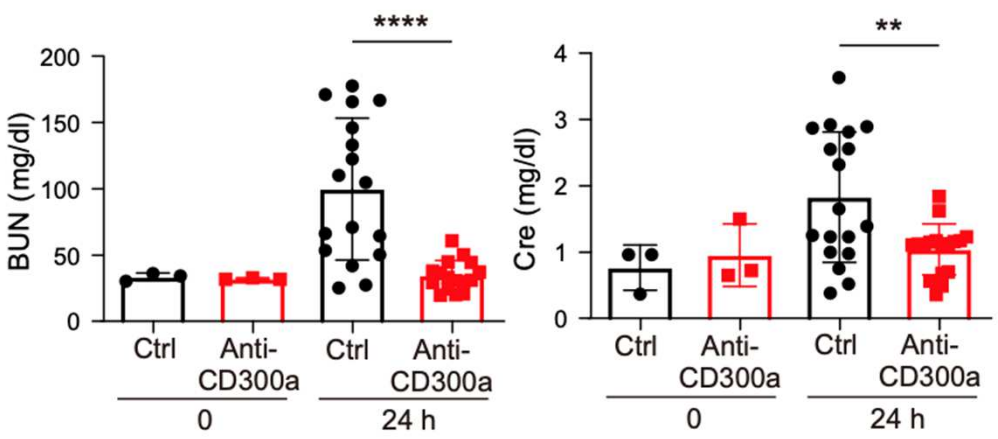
Enhancement of efferocytosis



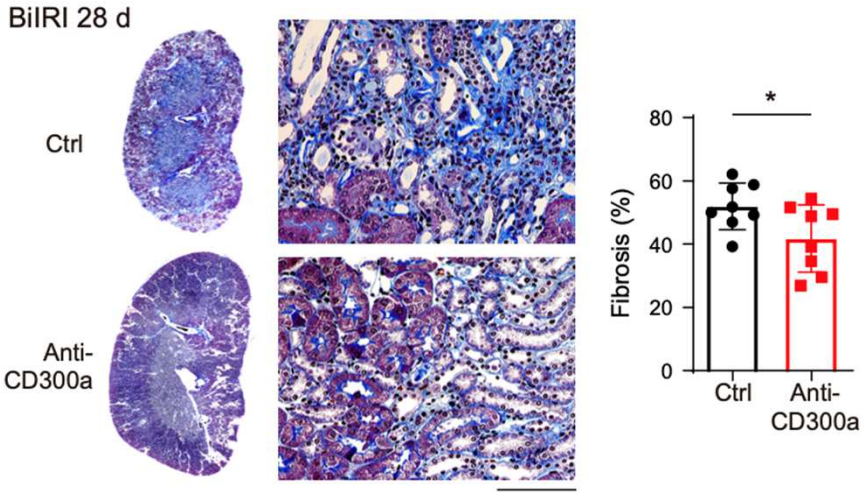
Suppression of renal tissue injury



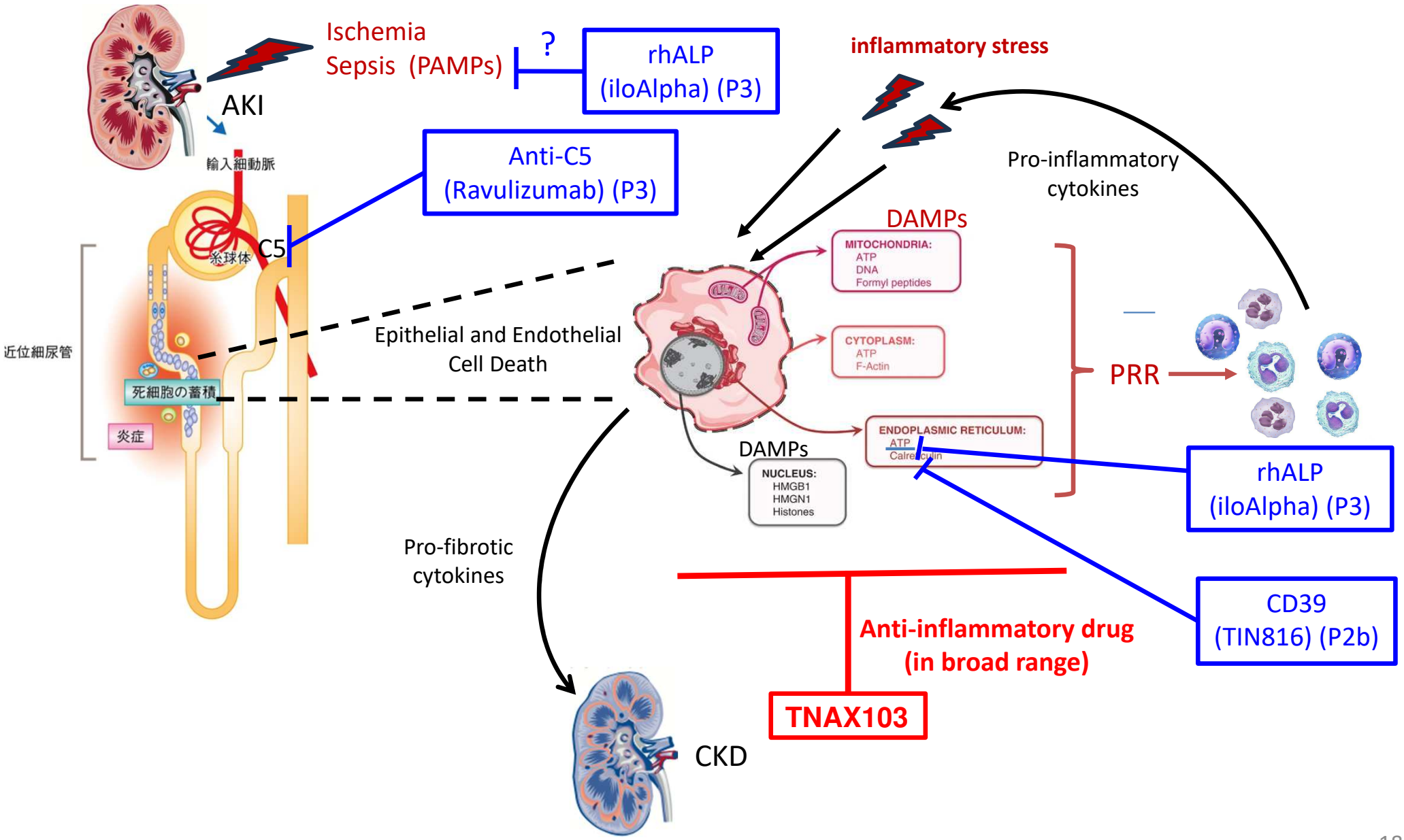
Suppression of renal dysfunction



Suppression of kidney fibrosis (Masson Trichrome)



TNAX103 is different from other drugs in clinical study.



Target Product Labels of TNAX103 in AKI

- ✓ **Treatment** of **diagnosed ischemic-AKI** in patients **following cardiac surgery**
- ✓ **Prevention** of **ischemic-AKI** (due to **cardiac surgery**) in an "**at risk**" **population**

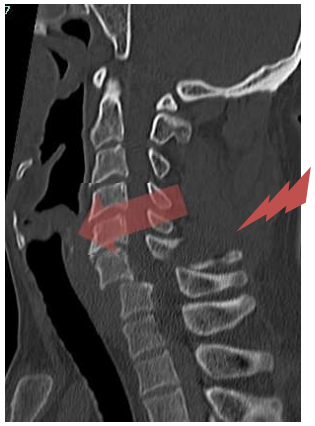
✓ ≧65 years of age
✓ Suffering from a kidney problem (such as CKD)
✓ Suffering from a chronic disease (such as heart failure, liver disease, diabetes, etc.)
✓ Dehydrated or unable to maintain fluid intake independently
✓ Having a blockage in urinary tract or being at risk of this
✓ Having a severe infection or sepsis
✓ Taking nephrotoxic medicines (NSAIDs, ACEIs, ARBs, diuretics, aminoglycosides, contrast media, etc.)

TNAX Biopharma

Spinal cord injury (SCI)

筑波大学 University of Tsukuba

- Incidence: Approx. 17,730 new cases (US) and approx. 5,000 new cases (Jpn) each year
- Prevalence: Approx. 291K cases (US) and approx.100K cases (Jpn)
- Resulting from motor vehicle collisions, fall from height, etc.
- **No effective treatment**
- SCI total market = $6,784 million in 2021 **Huge market!**
  - Corticosteroids (epidural injections), NSAIDs, Anti-depressants, Anti-convulsants, etc.



Severity of Injury	Average Yearly Expenses (in 2018 dollars)		Estimated Lifetime Costs by Age at Injury (discounted at 2%)	
	First Year	Each Subsequent Year	25 years old	50 years old
High Tetraplegia (C1–C4) AIS ABC	$1,129,302	$196,107	$5,010,748	$2,753,822
Low Tetraplegia (C5–C8) AIS ABC	$816,019	$120,303	$3,661,165	$2,251,944
Paraplegia AIS ABC	$550,381	$72,909	$2,450,234	$1,608,015
Motor Functional at Any Level AIS D	$368,562	$44,766	$1,674,012	$1,181,564

- Data source: Economic Impact of SCI published in the journal Topics in Spinal Cord Injury Rehabilitation, Vol. 16, No. 4 in 2011
- ASIA Impairment Scale (AIS) is used to grade the severity of a person's neurological impairment following SCI.
- These estimates do not include any indirect costs (losses in wages, fringe benefits or productivity).

Anti-CD300a mAb ameliorated locomotor performance and histological findings in a mouse SCI model.

Pathology of SCI

Primary injury

Axonal rupture and contusion due to direct external force

Secondary injury

Surrounding cells undergo apoptosis or necrosis, causing further damage. *Beatie M, J Neurotrauma, 2000*
Popovich PG, J Neuropathol Exp Neurol ,2002

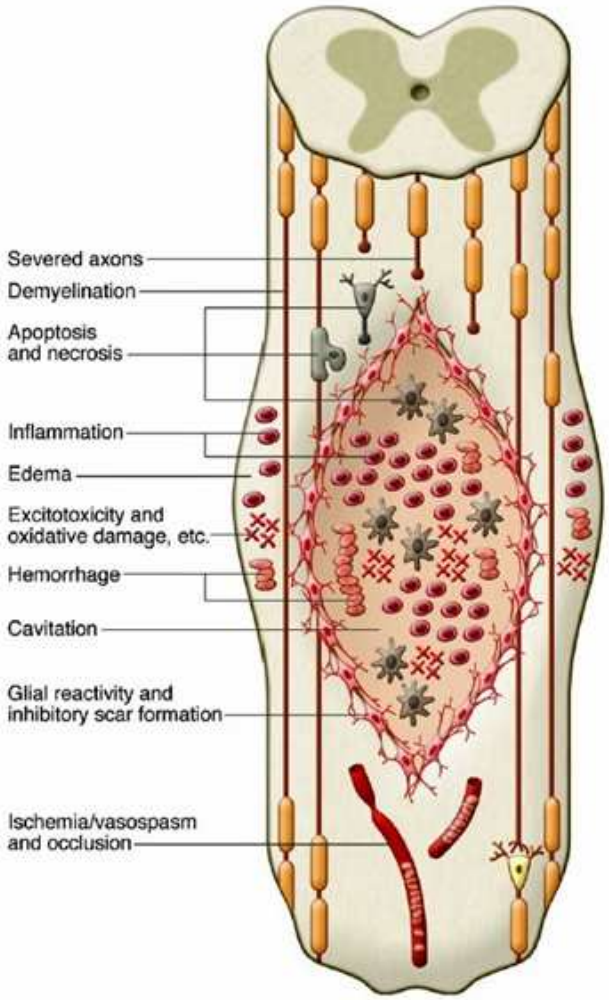
- Demyelination (oligodendrocyte death)

- Apoptosis and necrosis (Breakdown in BCSFB)

→ Migration of myelocytes including neutrophils and macrophages

- Interaction of reactive astrocytes with type 1 collagen

→ Scarring astrocyte formation, glial scar and cavity formation

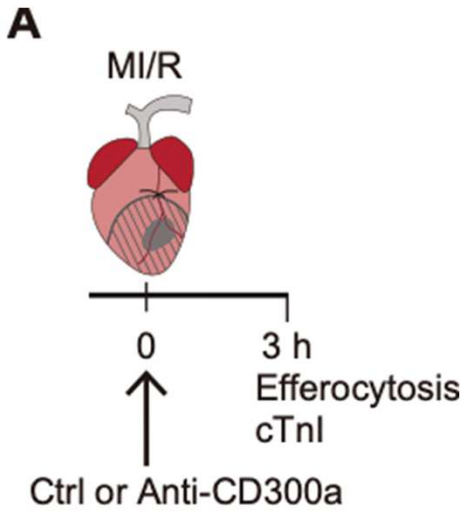


(Mothe, J Clin Invest, 2012)

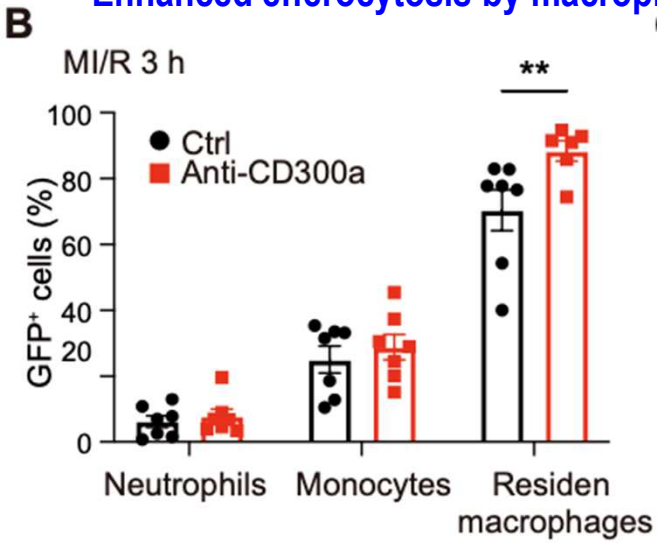
In a mouse SCI model, anti-CD300a mAb ameliorated locomotor ability and decreased areas of SCI (H&E staining) and demyelination (LFB staining). [Data coming soon]

Anti-CD300a mAb ameliorates myocardial infarction induced by ischemia-reperfusion.

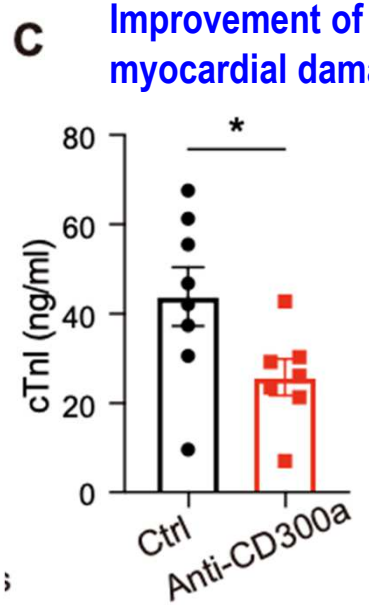
Possibility of expanding indication into AMI



Enhanced efferocytosis by macrophages

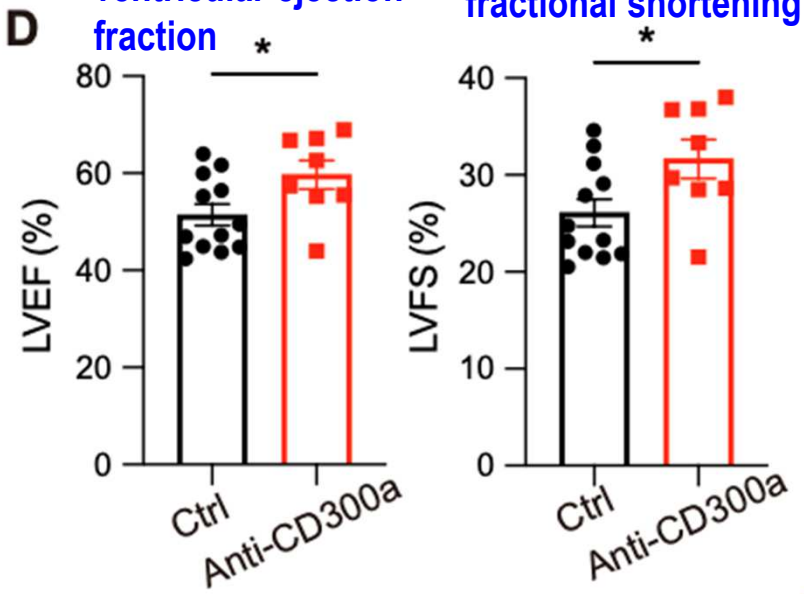


Improvement of myocardial damage



Increase in left ventricular ejection fraction

Increase in left ventricular fractional shortening



CD300A IP

As of February 29, 2024

- **PCT/JP2018/043862** — Activity modulator (Anti-CD300a antibody for treating ischemic diseases)
  - Japan, Canada, China, Hong Kong, South Korea, New Zealand, Russia → Granted
  - US, EP, Taiwan → Pending
- **New patent application filed in April 2023** — Humanized anti-CD300A monoclonal antibody, and its antigen-binding fragments

- JP6124261/US10519233/EP2808028 → Granted — Activity modulator, medicinal agent comprising same, use of CD300A gene-deficient mouse, and anti-CD300A antibody
- JP6226333/US9850309 → Granted — Medicament comprising activity modulator for CD300a-expressing cell associated with allergic disease, CD300a gene-deficient mouse, and use of activity modulator for CD300a-expressing cell

TNAX Biopharma

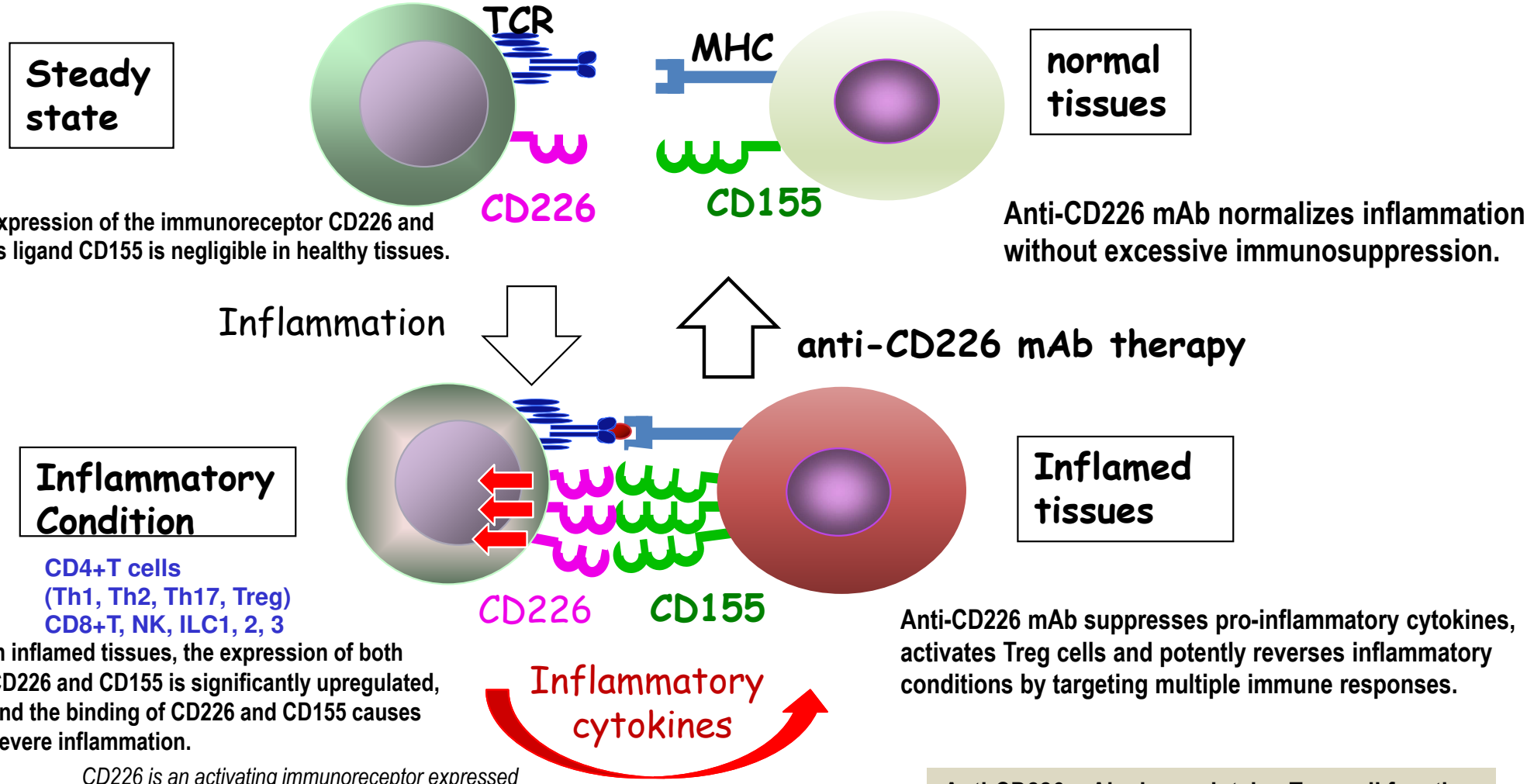
筑波大学
University of Tsukuba

Major publications on CD300a

1. Koizumi H, Nakahashi-Oda C, Fujiyama S, Li J, Lee H, Lyu W, Bao TTW, Abe F, Tabuchi K Kazuko Shibuya S, Shibuya A. Enhanced efferocytosis by CD300a blockade ameliorates acute kidney injury and subsequent fibrosis. Submitted under review.
2. Nakazawa Y, Nishiyama N, Koizumi H, Kanemaru K, Nakahashi-Oda C, Shibuya A. Tumor-derived extracellular vesicles regulate tumor-infiltrating regulatory T cells via the inhibitory immunoreceptor CD300a. ***Elife.*** 10:e61999, 2021
3. *Nakahashi-Oda C, Fujiyama S, Nakazawa Y, Kanemaru K, Wang Y, Lyu W, Shichita T, Kitaura J, Abe F, Shibuya A. CD300a blockade enhances efferocytosis by infiltrating myeloid cells and ameliorates neuronal deficit after ischemic stroke. ***Science Immunol,*** 6(64):eabe7915, 2021 **DOI**: **10.1126/sciimmunol.abe7915**
4. Wang Y, Nakahashi-Oda C, Okayama Y, Shibuya A. Autonomous regulation of immunoglobulin E-mediated mast cell degranulation and immediate hypersensitivity reaction by an inhibitory receptor CD300a. ***J. Allergy Clin. Immun***, 144(1):323-327, 2019
5. Nakahashi-Oda C, Udayanga KGS, Nakamura Y, Nakazawa Y, Miki H, Iino S, Tahara-Hanaoka S, Shibuya K, Shibuya A. Apoptotic epithelial cells control the abundance of Treg cells at barrier surfaces. ***Nature Immunol***, 17(4):441-450, 2016
6. Nakahashi-Oda C, Tahara-Hanaoka S, Shoji M, Okoshi Y, Nakano-Yokomizo T, Ohkohchi N, Yasui T, Kikutani H, Honda S, Shibuya K, Nagata S, Shibuya A. Apoptotic cells suppress mast cell inflammatory responses via the CD300a immunoreceptor. ***J Exp Med***, 209(8):1493-1503, 2012
7. Nakahashi-Oda C, Tahara-Hanaoka S, Honda S, Shibuya K, Shibuya A. Identification of phosphatidylserine as a ligand for the CD300a immunoreceptor. ***Biochem Biophys Res Commun***, 417:646-650, 2012
8. Yotsumoto K, Okoshi Y, Shibuya K, Yamazaki S, Tahara-Hanaoka S, Honda S, Osawa M, Kuroiwa A., Matsuda Y, Tennen D. G, Iwama A, Nakauchi H, Shibuya A. Paired activating and inhibitory immunoglobulin-like receptors, MAIR-I and MAIR-II, regulate mast cell and macrophage activation. ***J. Exp. Med.*** 198:223-233, 2003

CD226 (DNAM-1) is a promotor of immune responses and produces inflammatory cytokines from immune cells including effector T cells.

Anti-CD226 mAb, which has a low risk of serious infections, is expected to be used in patients who do not respond to or cannot tolerate the SoC.



CD226 is an activating immunoreceptor expressed on both adaptive and innate immunocytes.

Upon binding to CD155, CD226 mediates an activating signal for cytokine production and/or cytotoxic activity in effector lymphocytes (T cells, NK cells, etc.)

Anti-CD226 mAb also maintains Treg cell function.

CD226 is also expressed on the surface of Treg cells and attenuates effector T cell function.

Senior Management (CxO)

- **Takahiro (Tak) Mukohira**: Co-founder, CEO & Representative Director
  - Business development, corporate planning, international business, etc. in the pharma/healthcare industry
    - Mitsubishi Tanabe Pharma, Life Science Institute, APIC, MHCS
      - Licensing fingolimod, joint research labs with Scottish universities, M&A, Regenerative medicine, Digital health, etc.
  - Boston-based CVC
    - MP Healthcare Venture Management, Inc.
  - MIT Sloan School of Management, SM in MOT
  - Kyoto University, Pharmaceutical Sciences, R.Ph.

- **Akira Shibuya,** M.D. Ph.D.: Co-founder, CSO & Board Director
  - Director, R&D Center for Innovative Drug Discovery
  - Professor, Immunology, University of Tsukuba
  - Academic staff/researcher in Riken, Okayama University & DNAX
  - Physician (hematologist) at University of Tsukuba, Tokyo Metropolitan Bokutoh Hospital and Mitsui Memorial Hospital
  - University of Tsukuba, Ph.D.
  - Hokkaido University, M.D.
  - Awards 1996 Hajime Memorial Award (Nobel Prize Laureate Arthur Kornberg & Paul Berg)
    2005 Japan Medical Association Research Encouragement Award
    2009 Princess Takamatsu Cancer Research Fund Encouragement Award
    2015 Tsukuba Award (Nobel Prize Laureate Leo Esaki)
    2020 Education, Culture, Sports, Science & Technology Minister Science & Technology Award etc.