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

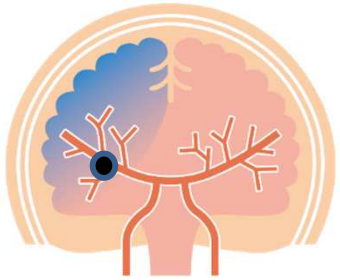
◆ Developing **first-in-class biologics** which target **immunoreceptors** and their **ligands** discovered by Professor Akira Shibuya, University of Tsukuba

Pipeline

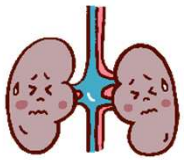
		Target ID/Validation & Lead Generation	Optimization	Preclinical	IND	First-In-Human
TNAX101A/ IMB1001	DNAM-1 /CD226	CD, UD, SLE	→	→	→	Partnered with IMIDomics
TNAX103	CD300A	AIS, AKI, SCI, AMI	→	→	→	Unpartnered
Undisclosed	Undisclosed	Undisclosed	→			

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

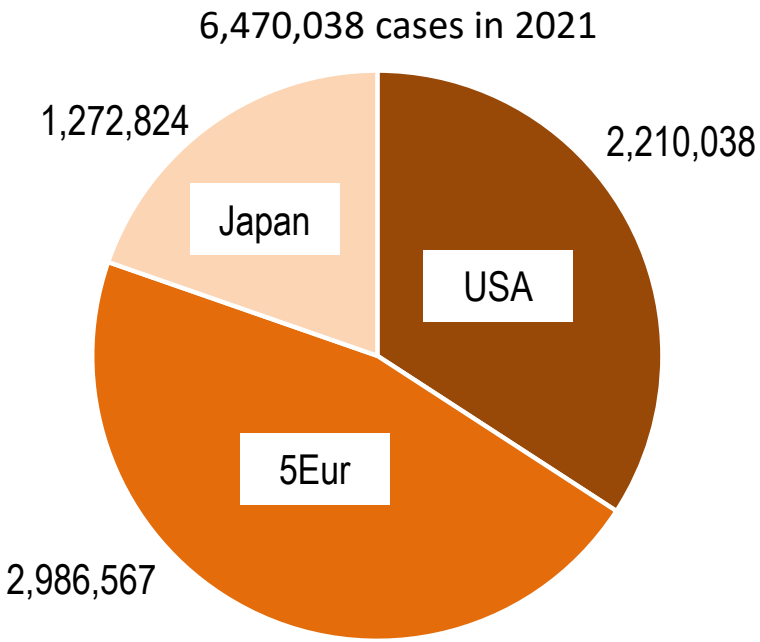


Acute Kidney Injury

◆ Robust IP exclusively licensed from University of Tsukuba

Exclusive license agreement with sublicensing rights

Acute kidney injury (AKI)



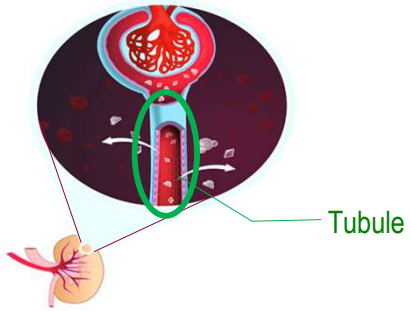
Huge market!

Total market
$5,208M

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

Source DelveInsight Business Research (September 2022)

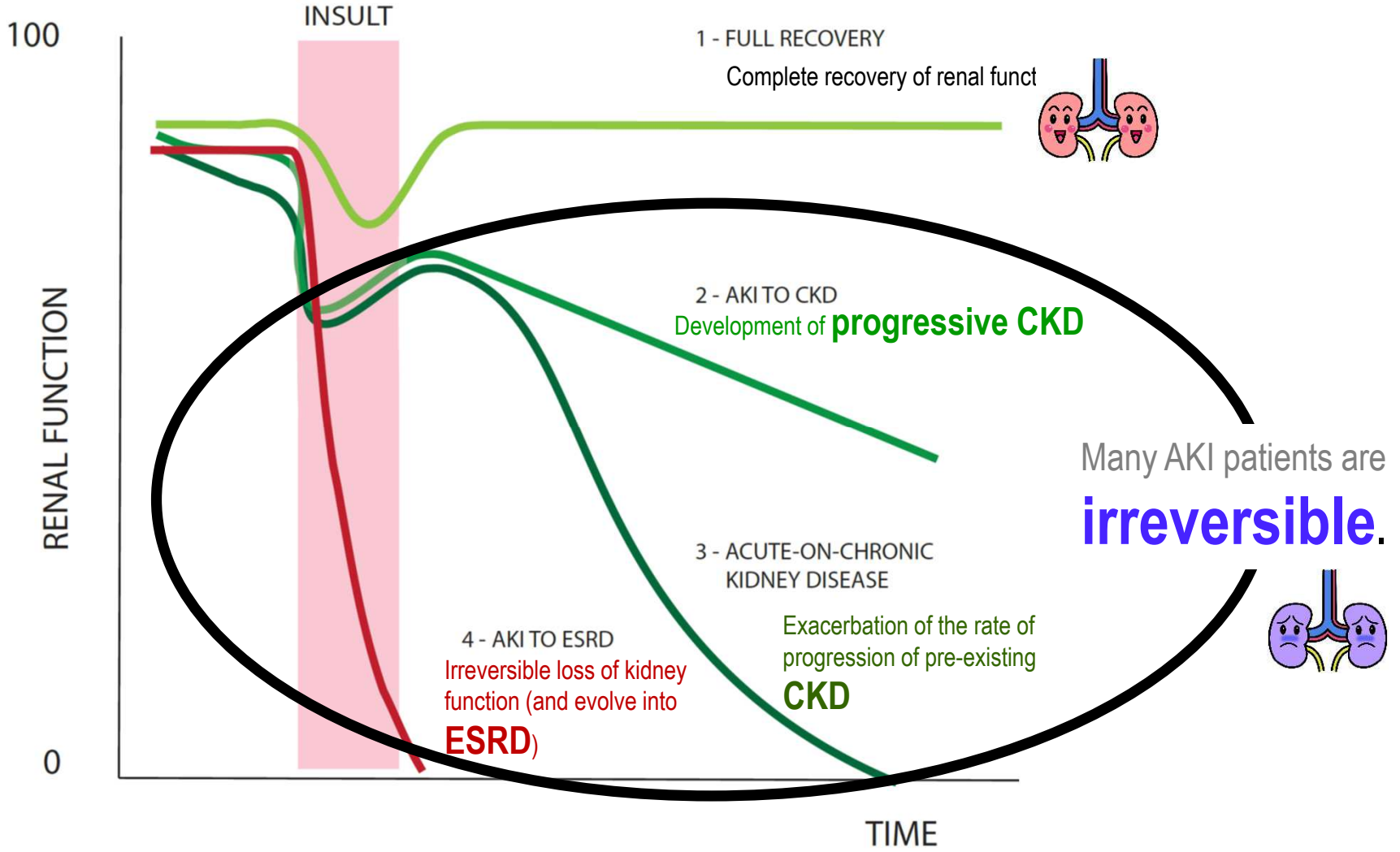
- Can be seen in up to **7% of hospital admissions** and **30% of ICU admissions**.
- **Mortality** rate for hospitalized patients: **40 – 50%**
- **Mortality** rate for ICU patients: **>50%**
- The most common (45%) cause of AKI in hospitalized patients: **ATN**
- Injury to the renal **proximal tubular 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*

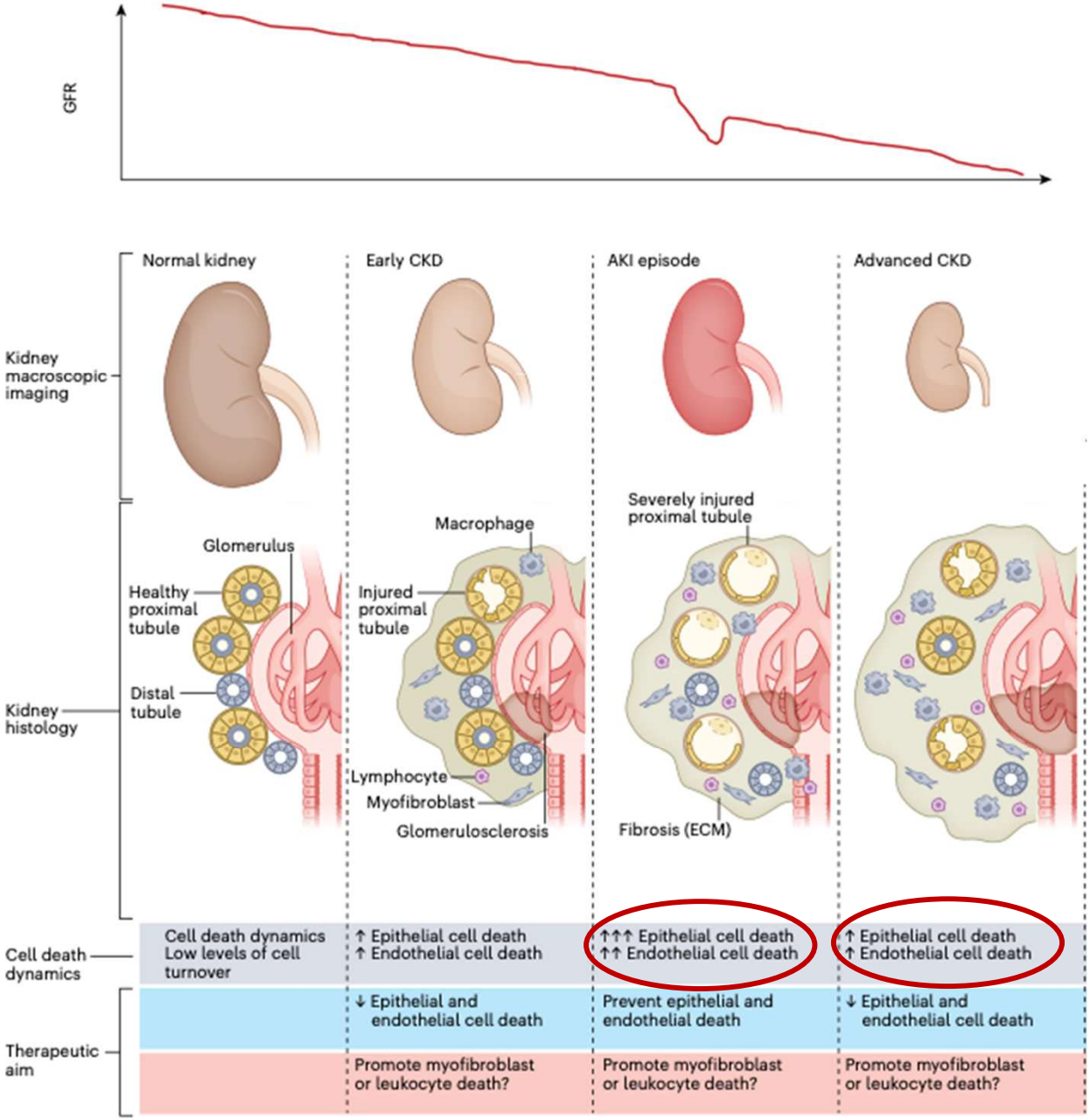
Natural history of AKI

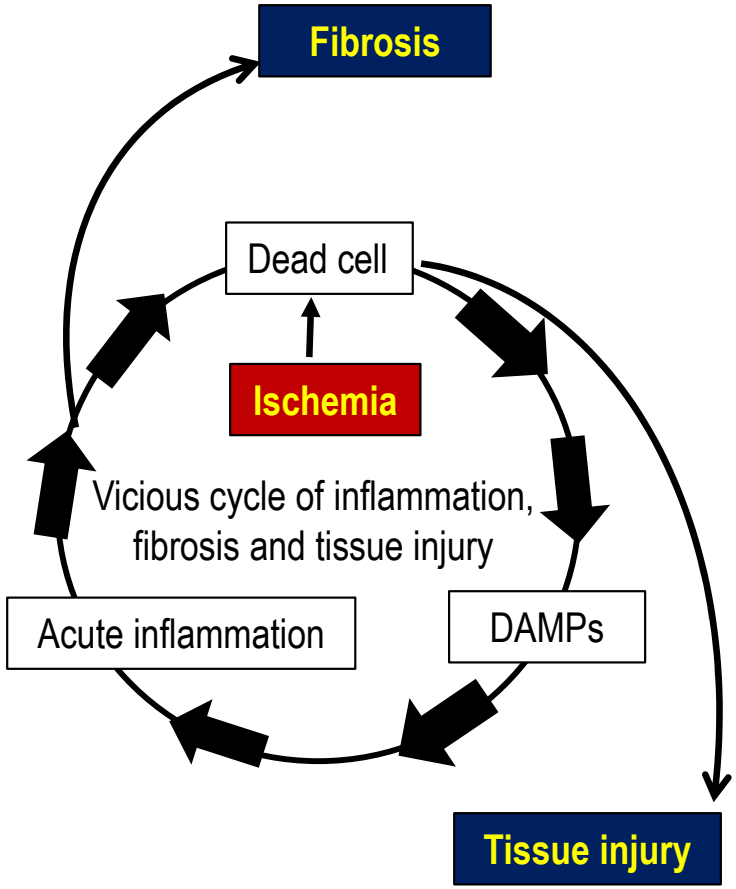
Renal function is expected to be **completely recovered by TNAX103.**



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

Cell death of vascular endothelium and renal tubular epithelium plays an important role in the pathological progression from AKI to AKD to CKD.



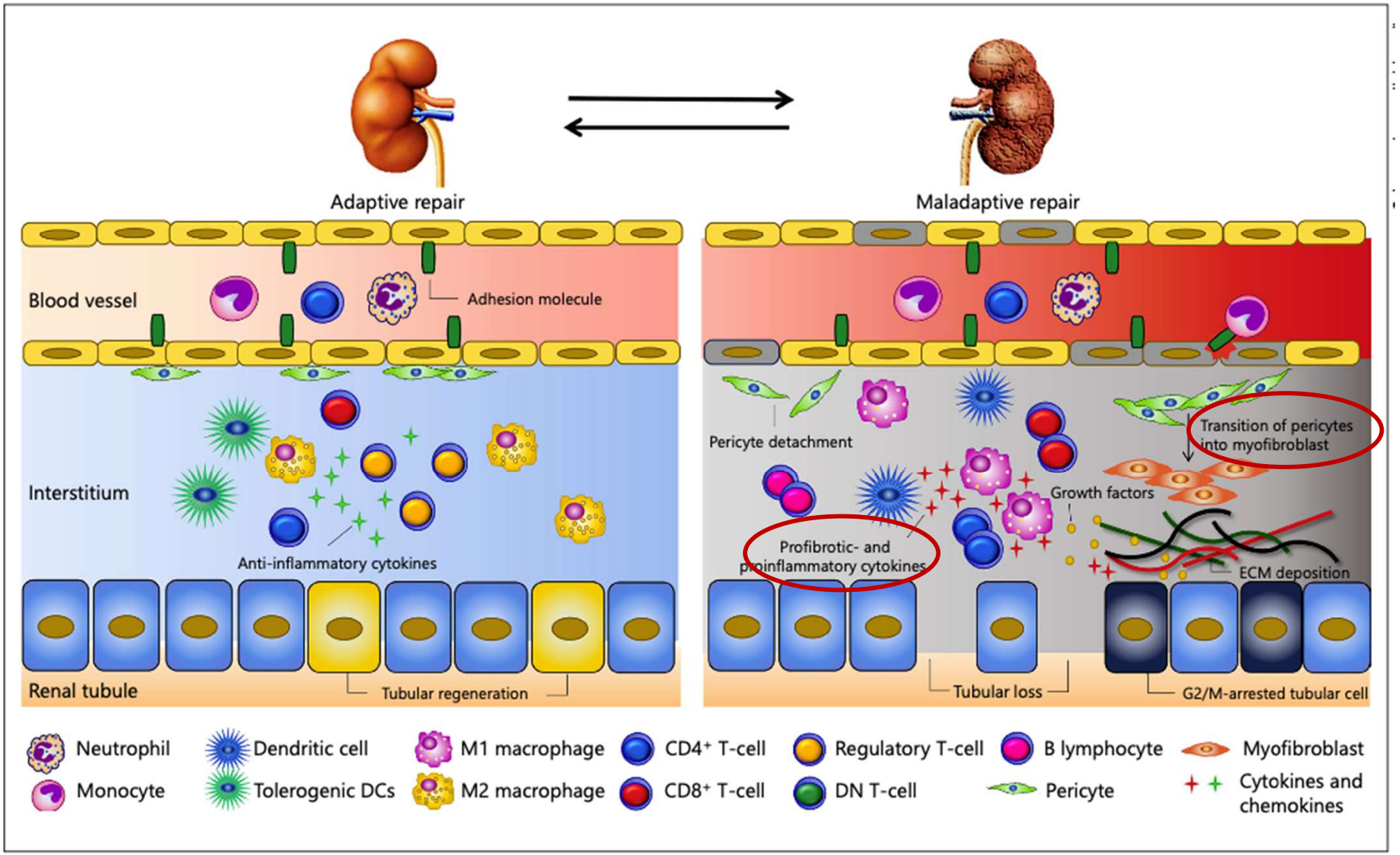


Nature Reviews Nephrology | Volume 19 | May 2023 | 281–299

TNAX Biopharma

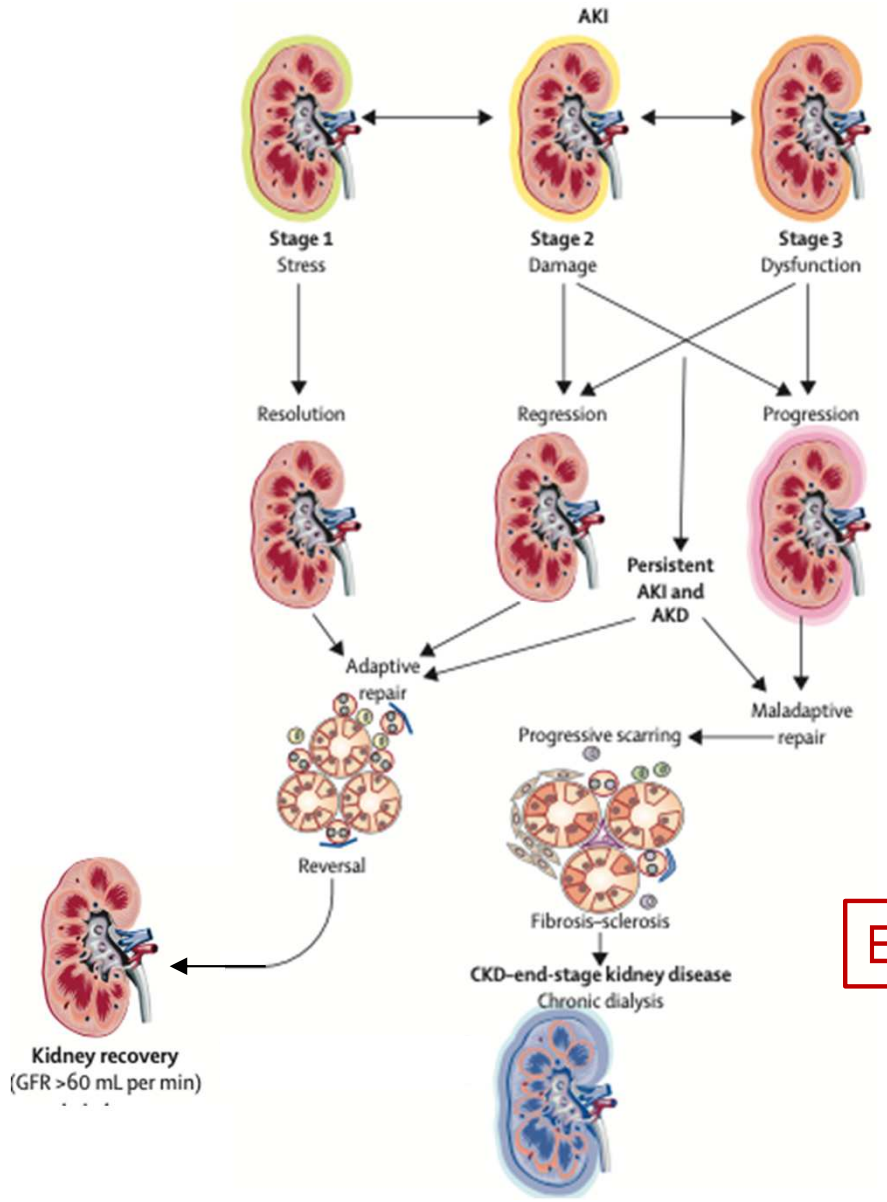
Inflammation after AKI causes renal dysfunction and fibrosis.

筑波大学
University of Tsukuba

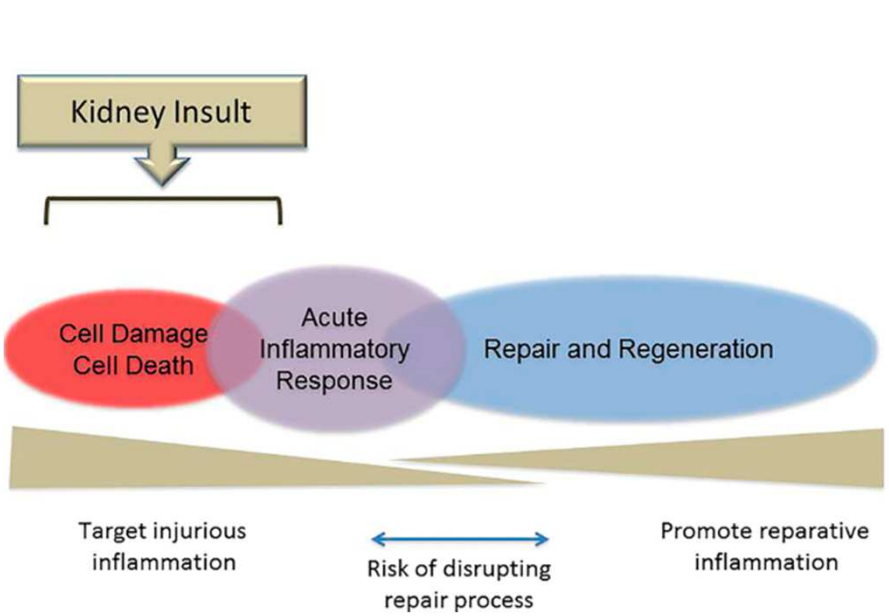


Nephron 2017;137:282–286
DOI: 10.1159/000477181

Efferocytosis promotor is indicated to restore normal kidneys from AKI and AKD and prevent progression to CKD.



www.thelancet.com Vol 394 November 23, 2019

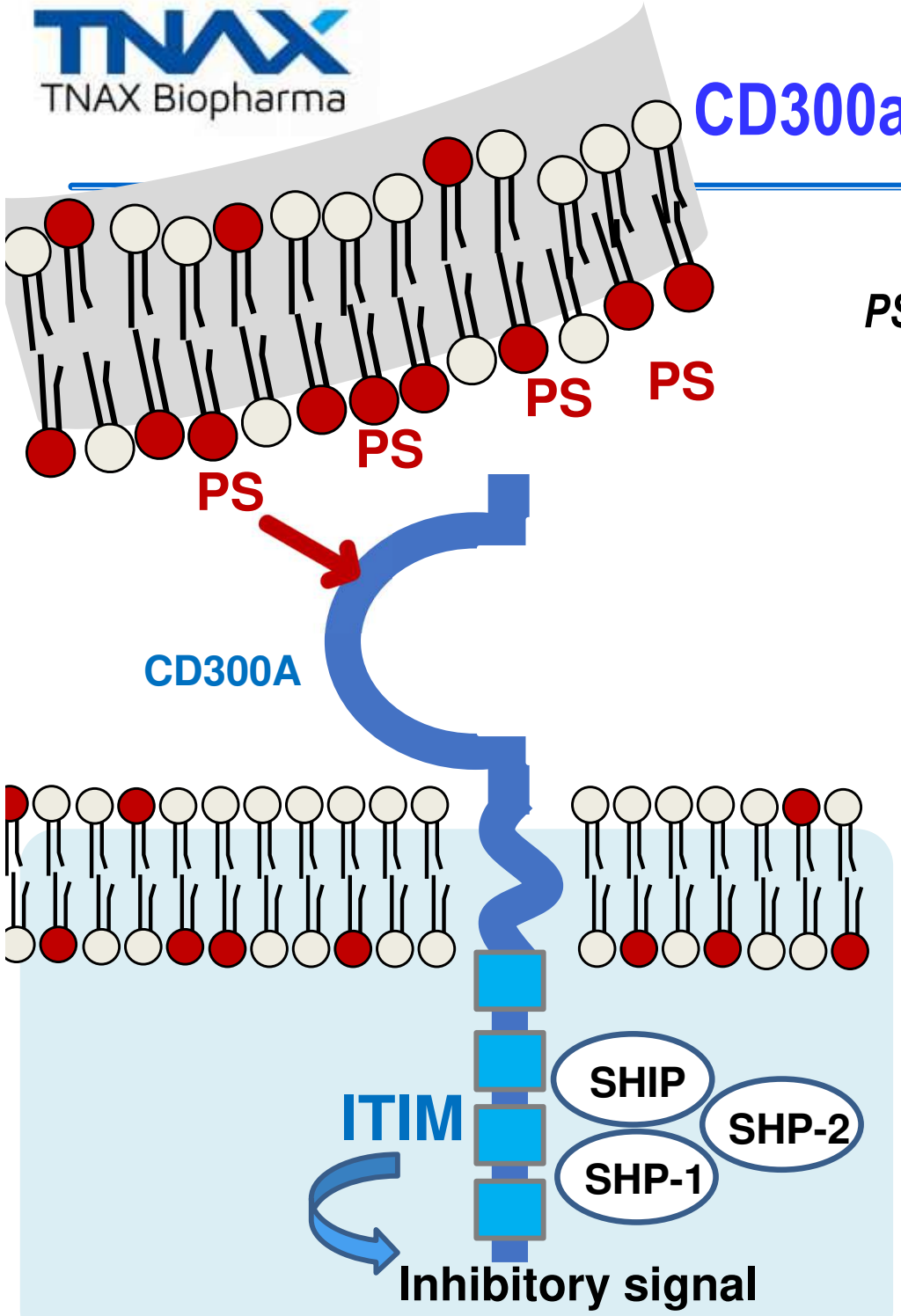


J Am Soc Nephrol 27: 371–379, 2016

Efferocytosis promotor

Increased phagocytosis of dead cells by macrophages reduces DAMPs release, suppresses acute inflammation and prevents the vicious cycle of induction of further dead cells and tissue injury.

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.)

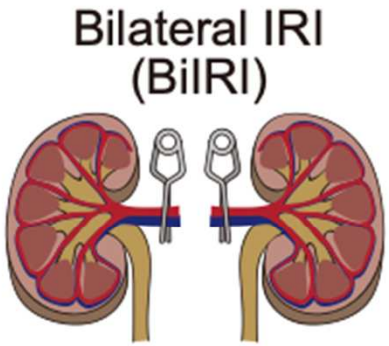
CD300a

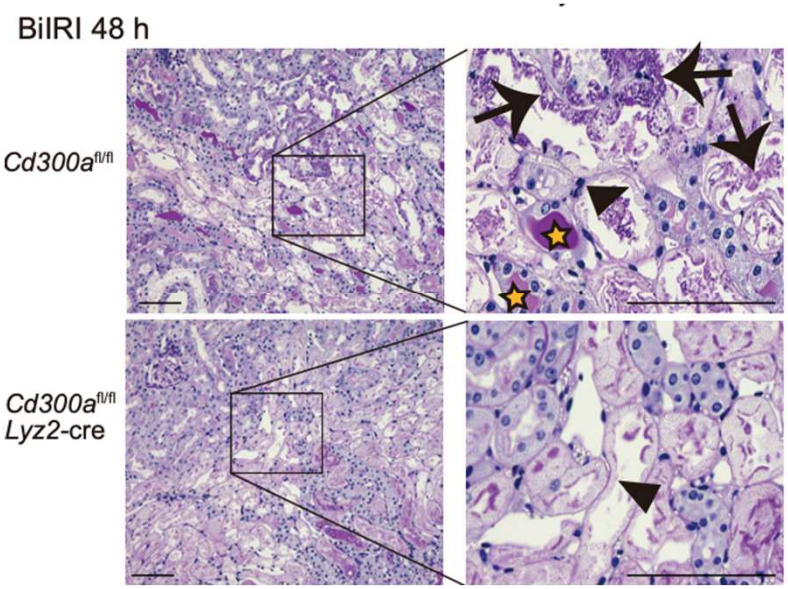
Expressed on macrophages, DCs, neutrophils and mast cells.

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

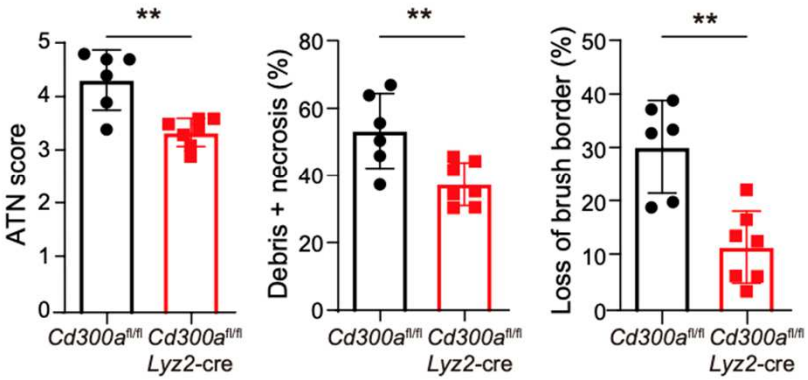
CD300a expressed on macrophages is a key anti-efferocytic molecule.

Macrophage-specific CD300a KO mice attenuate AKI induced by bilateral IRI.

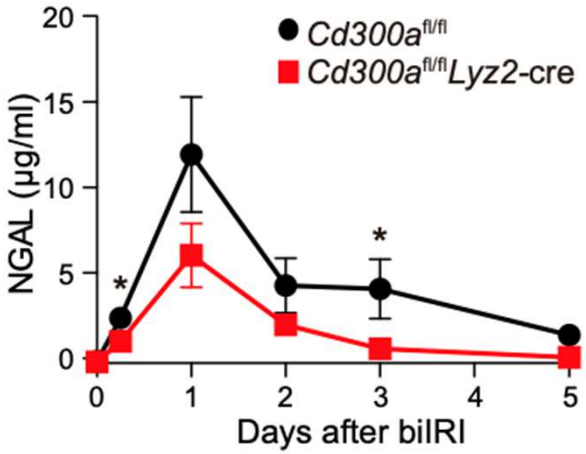




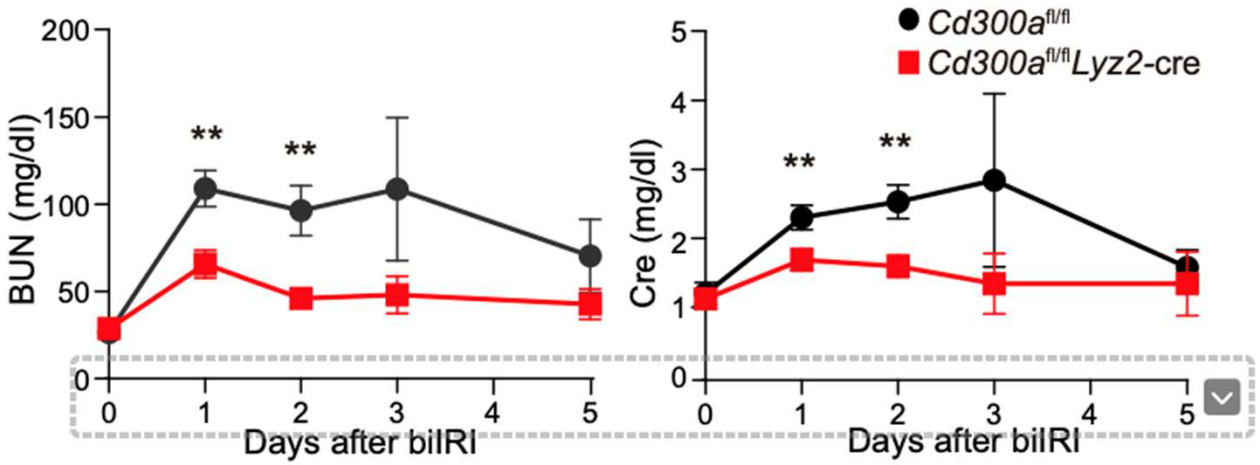
Suppression of renal tissue injury



Suppression of tubular damage

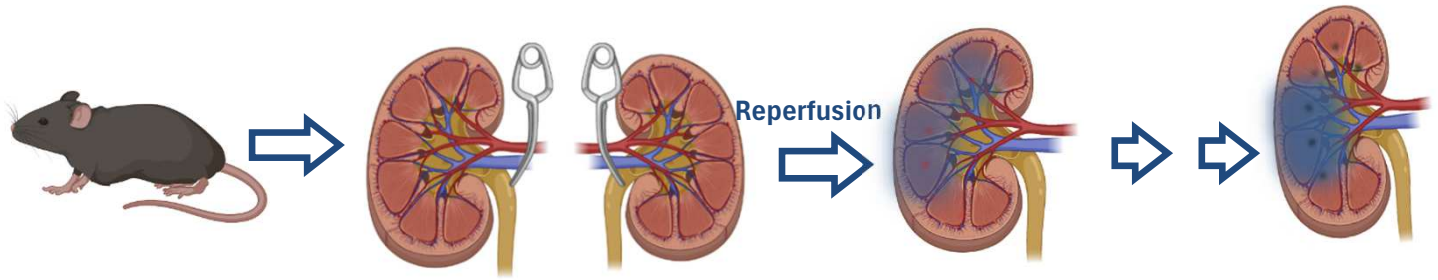


Suppression of renal dysfunction



Macrophage-specific CD300a KO mice attenuate progression from AKI to CKD (kidney fibrosis).

Ischemia-reperfusion injury (IRI) model in mice

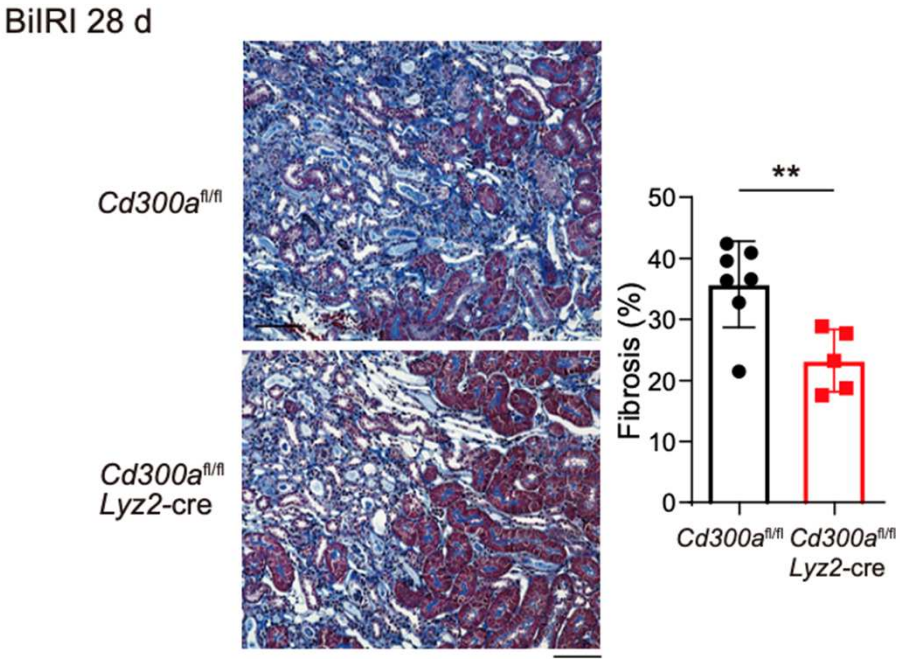


Bilateral kidney ischemia
for around 15 min

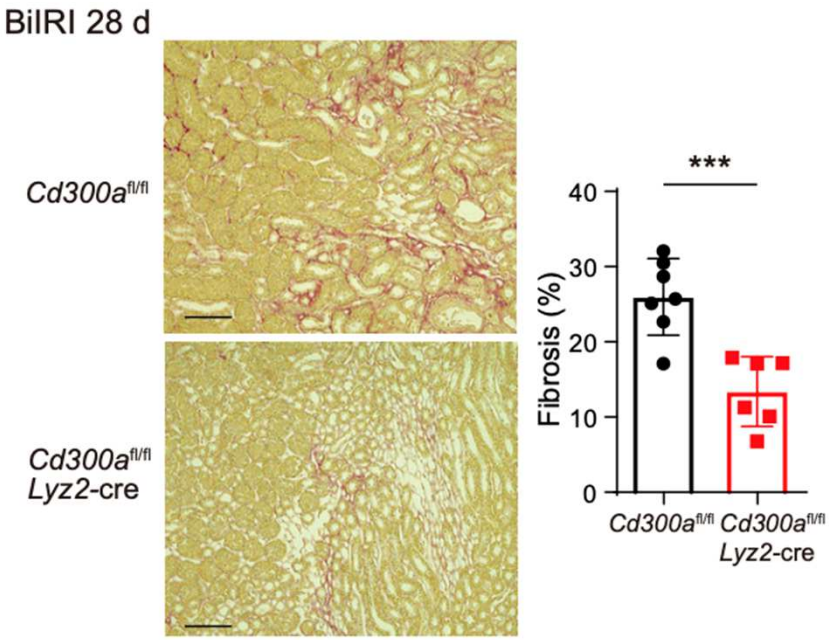
Acute kidney injury
1~2 days after IRI

Chronic kidney injury
with fibrosis
28 days after IRI

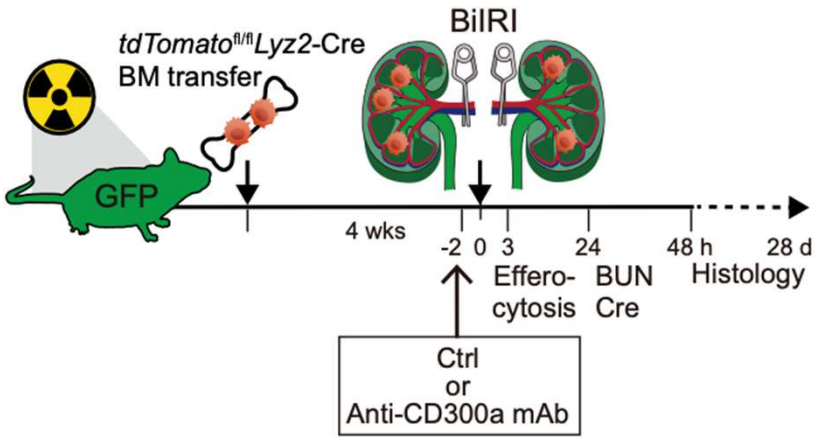
Suppression of kidney fibrosis (Masson Trichrome)



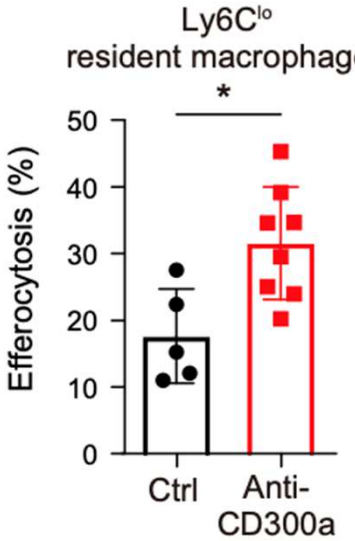
Suppression of kidney fibrosis (Sirius Red)



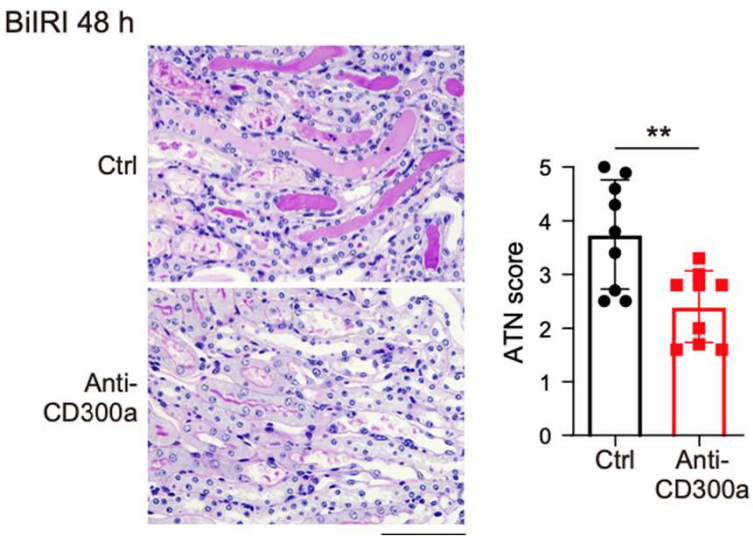
Anti-CD300a mAb promotes efferocytosis and attenuates AKI and kidney fibrosis.



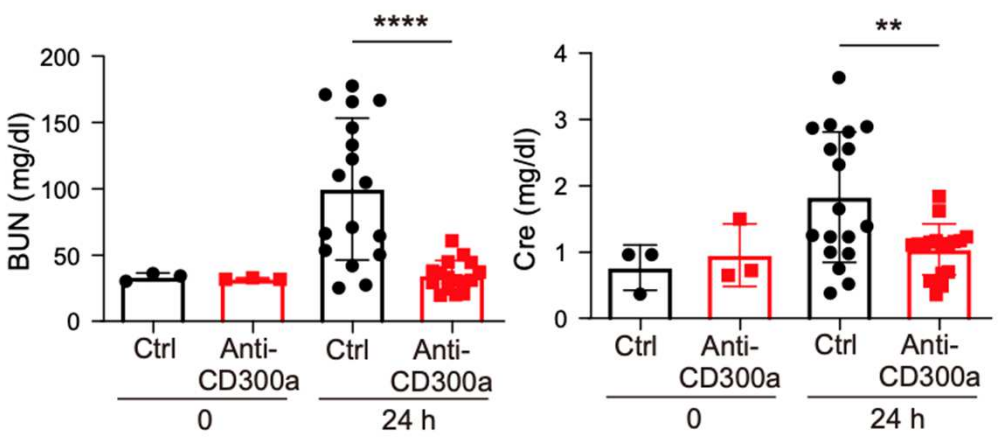
Enhancement of efferocytosis



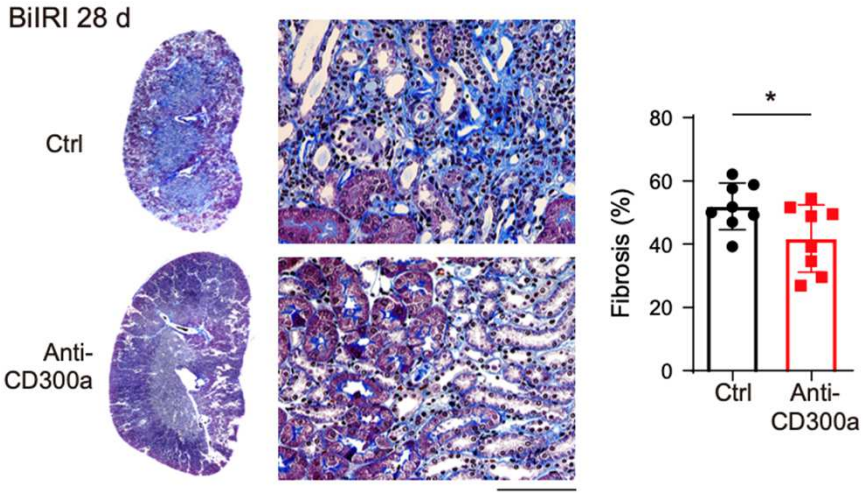
Suppression of renal tissue injury



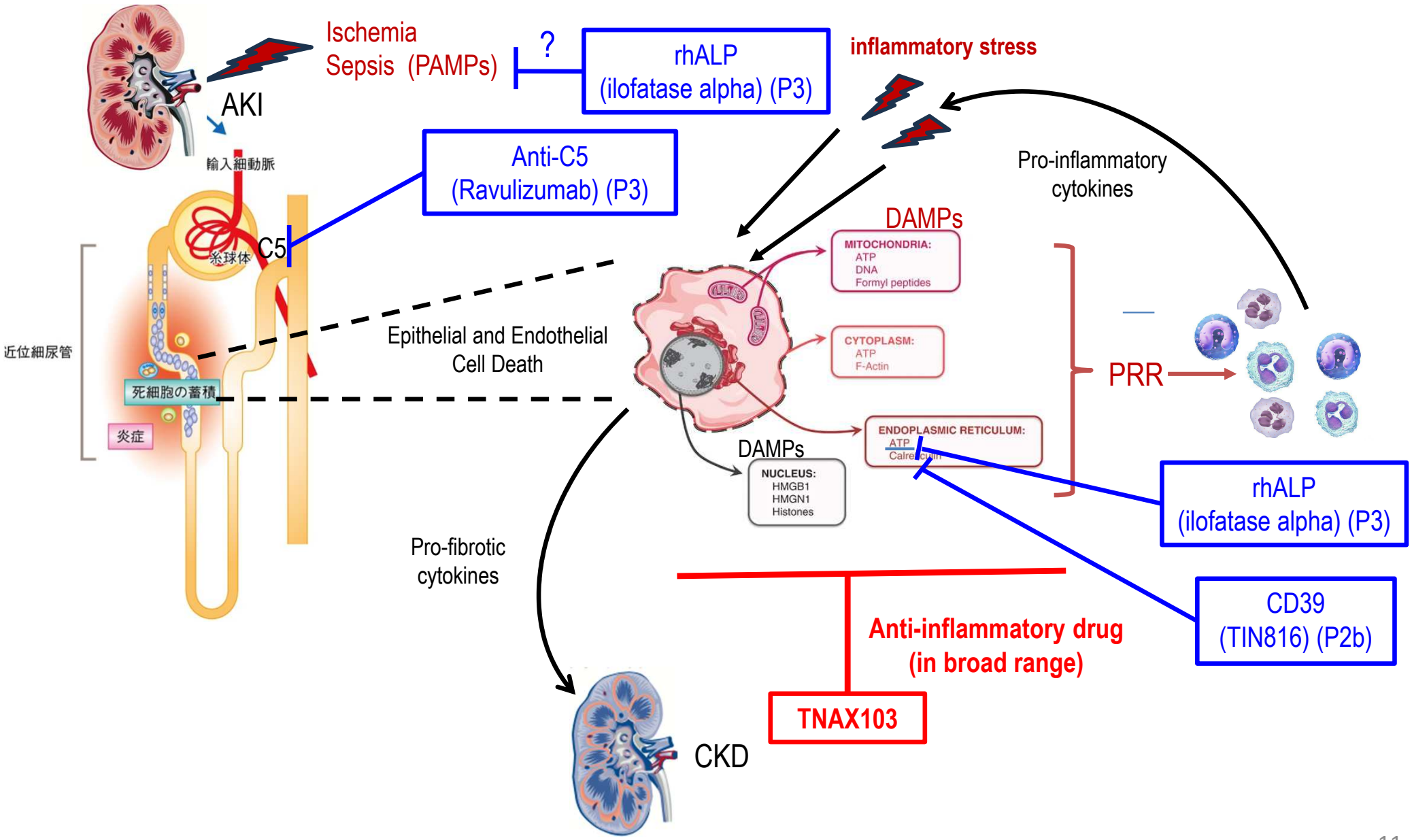
Suppression of renal dysfunction



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.)

Other data available (disclosable under CDA)

1. Other AKI & CKD models (2-step unilateral IRI & UUO)

2. Mechanism of action of anti-CD300a mAb in AKI and CKD

3. Generation of humanized anti-CD300A mAb

4. Effects of humanized anti-CD300A mAb in humanized mouse AKI model

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*

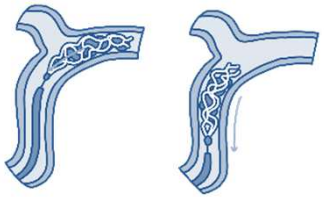
*2: including the costs of health care services, stroke medications and days away from work

Recanalization therapies

Thrombolytic therapy

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

Endovascular thrombectomy

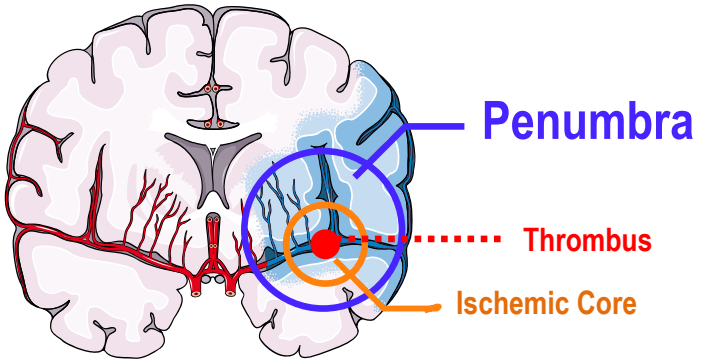


Stent Retriever and/or Aspiration

- **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.

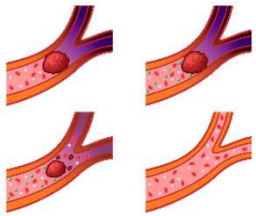
Over 50% of patients cannot attain good outcomes despite timely and complete recanalization.

Sudden restoration of blood flow may bring further damage.

Solutions

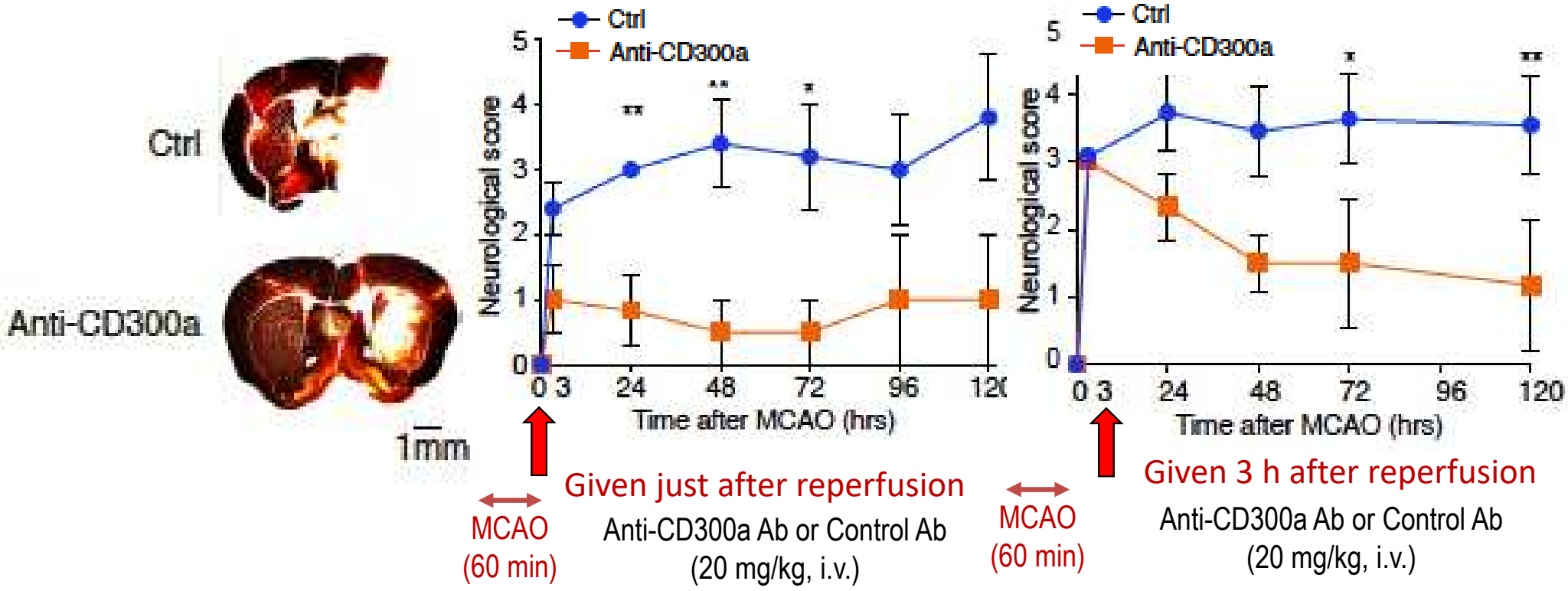
Efferocytosis promotors

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



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

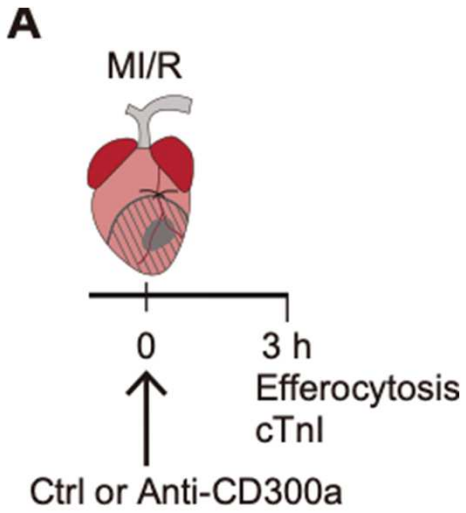
Anti-CD300a mAb decreased neuronal damage and ameliorates neurological scores after MCAO and reperfusion.



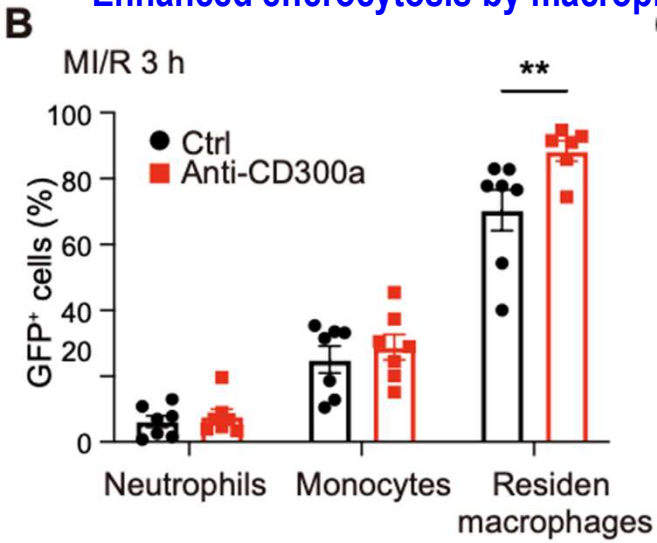
MCAO: Middle Cerebral Artery Occlusion

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

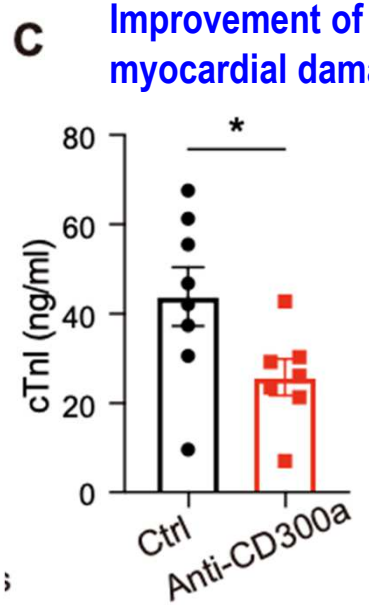
Possibility of expanding indication into AMI



Enhanced efferocytosis by macrophages

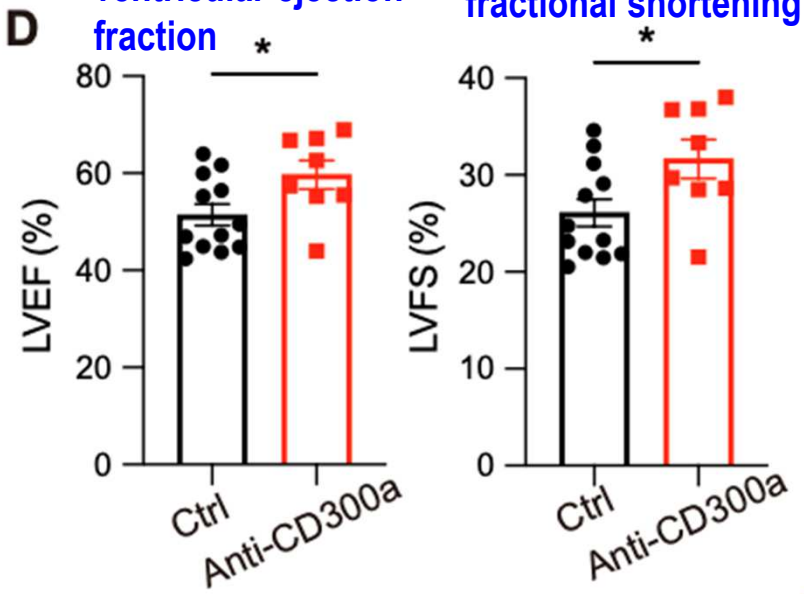


Improvement of myocardial damage



Increase in left ventricular ejection fraction

Increase in left ventricular fractional shortening



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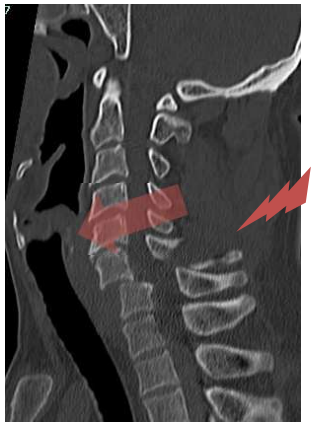
Spinal cord injury (SCI)

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

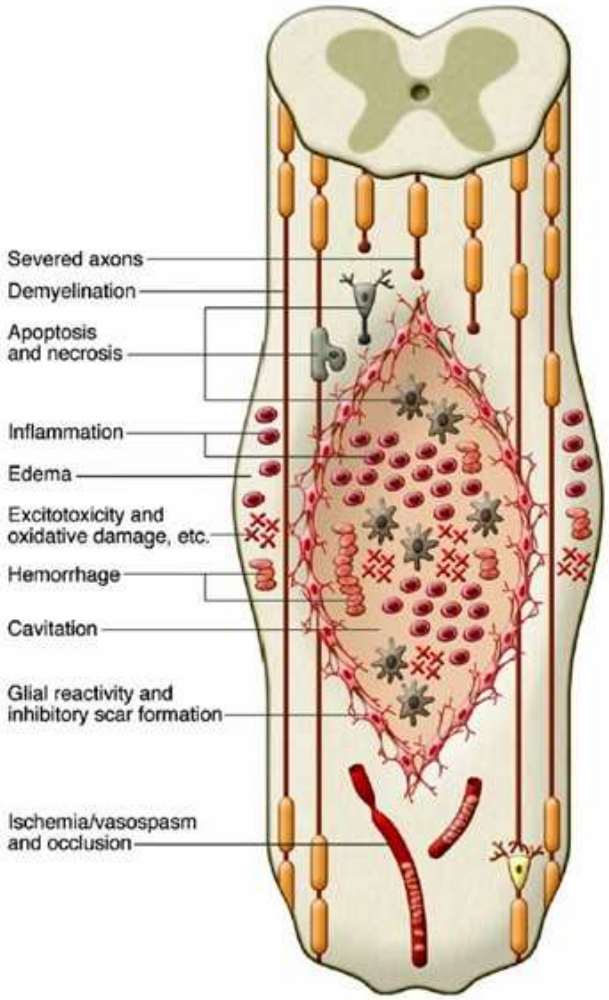
- Demyelination (oligodendrocyte death)

- 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

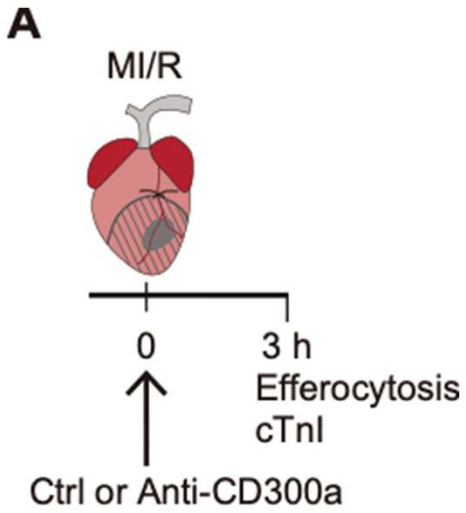


(Mothe, J Clin Invest, 2012)

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



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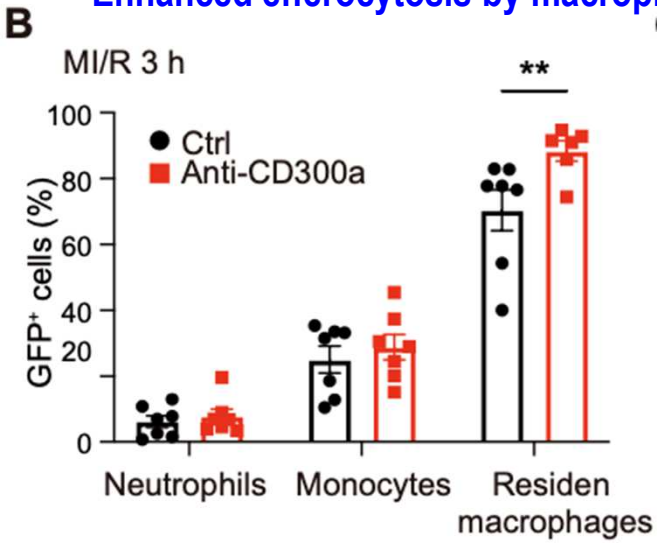
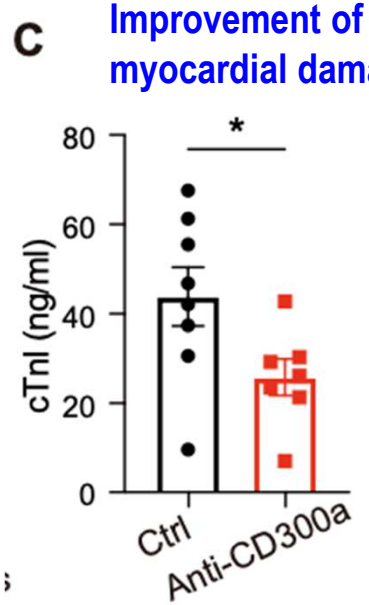


Improvement of myocardial damage



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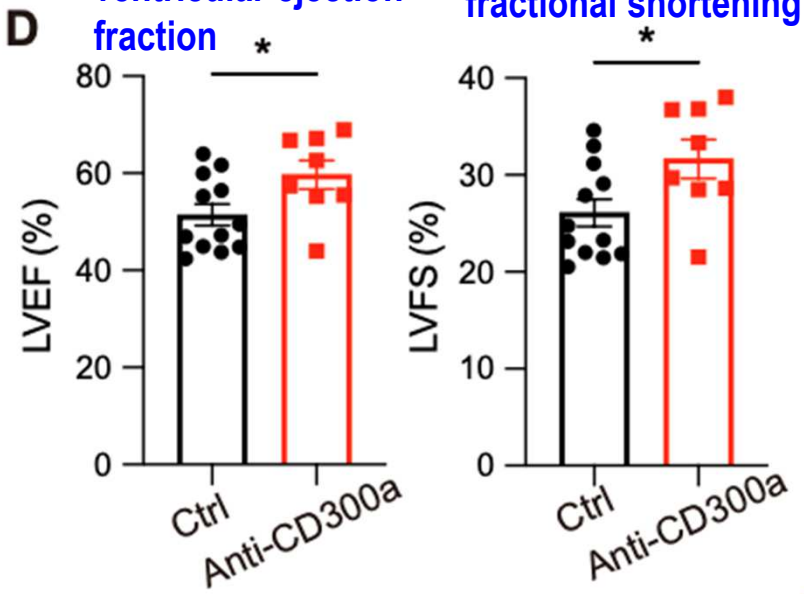


CD300A IP

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

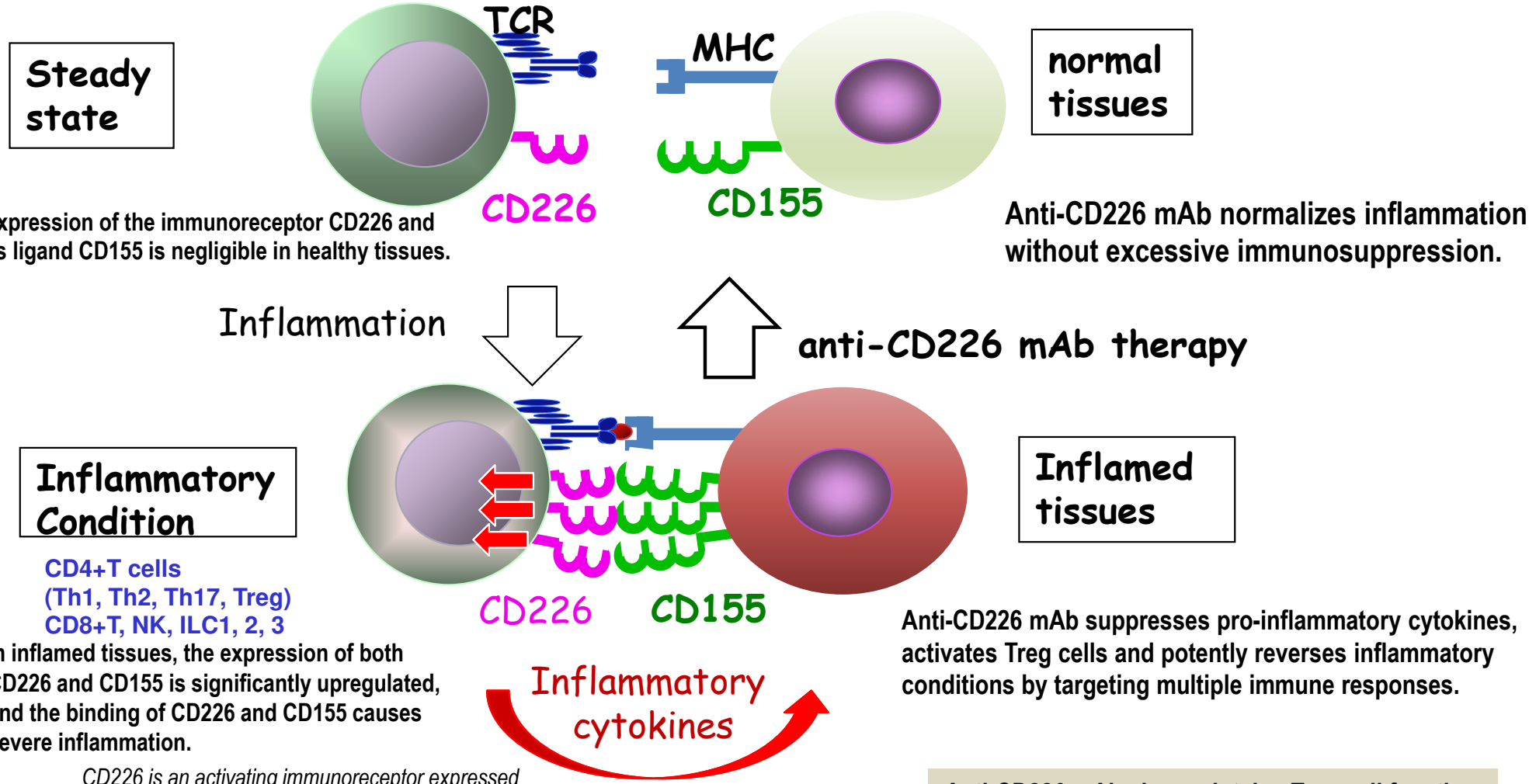
Major publications on CD300a

筑波大学 University of Tsukuba

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.