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.

July 17, 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	UC, CD, SLE				Partnered with IMIDomics
TNAX103	CD300A	AKI, AIS, SCI, AMI				Unpartnered
Undisclosed	Undisclosed	Undisclosed				

Exclusively licensed out to IMIDomics for worldwide territory

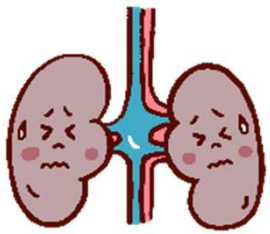
➢ **TNAX101A** = Humanized **anti-DNAM-1 (CD226) mAb**

✓ **Anti-inflammatory/fibrotic** drug for **immune-mediated inflammatory diseases**

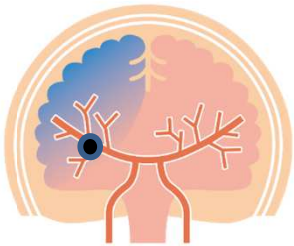
Inflammatory Bowel Diseases

➢ **TNAX103** = Humanized **anti-CD300A mAb**

✓ **Efferocytosis** promotor for **acute ischemic diseases**



Acute Kidney Injury



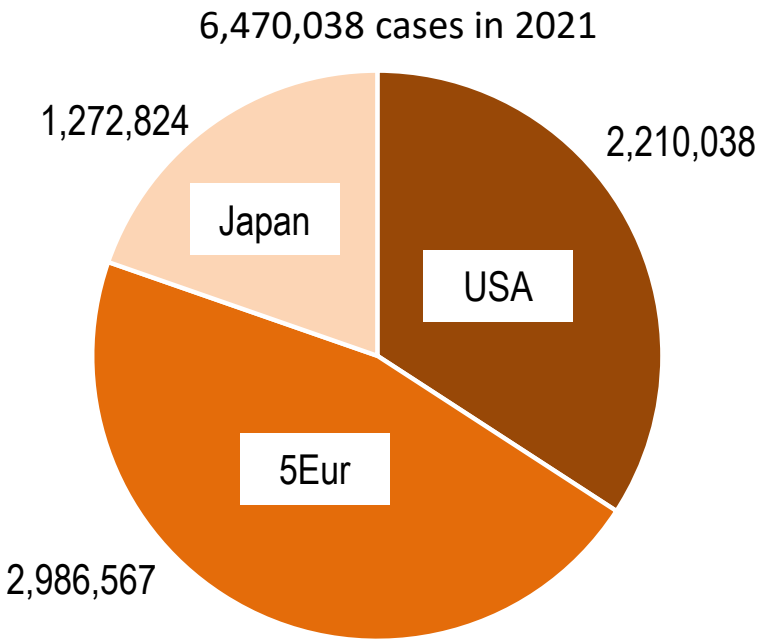
Acute Ischemic Stroke

➢ An undisclosed early stage research program is underway.

◆ Robust IP exclusively licensed from University of Tsukuba

Exclusive license agreement with sublicensing rights

Acute kidney injury (AKI)



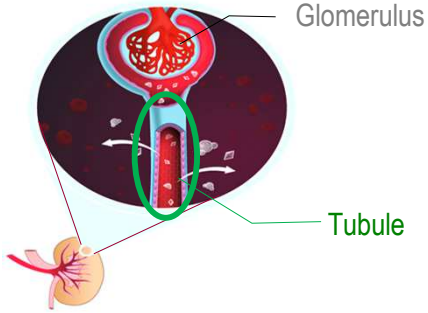
Huge market!

Total market
$5,208M

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

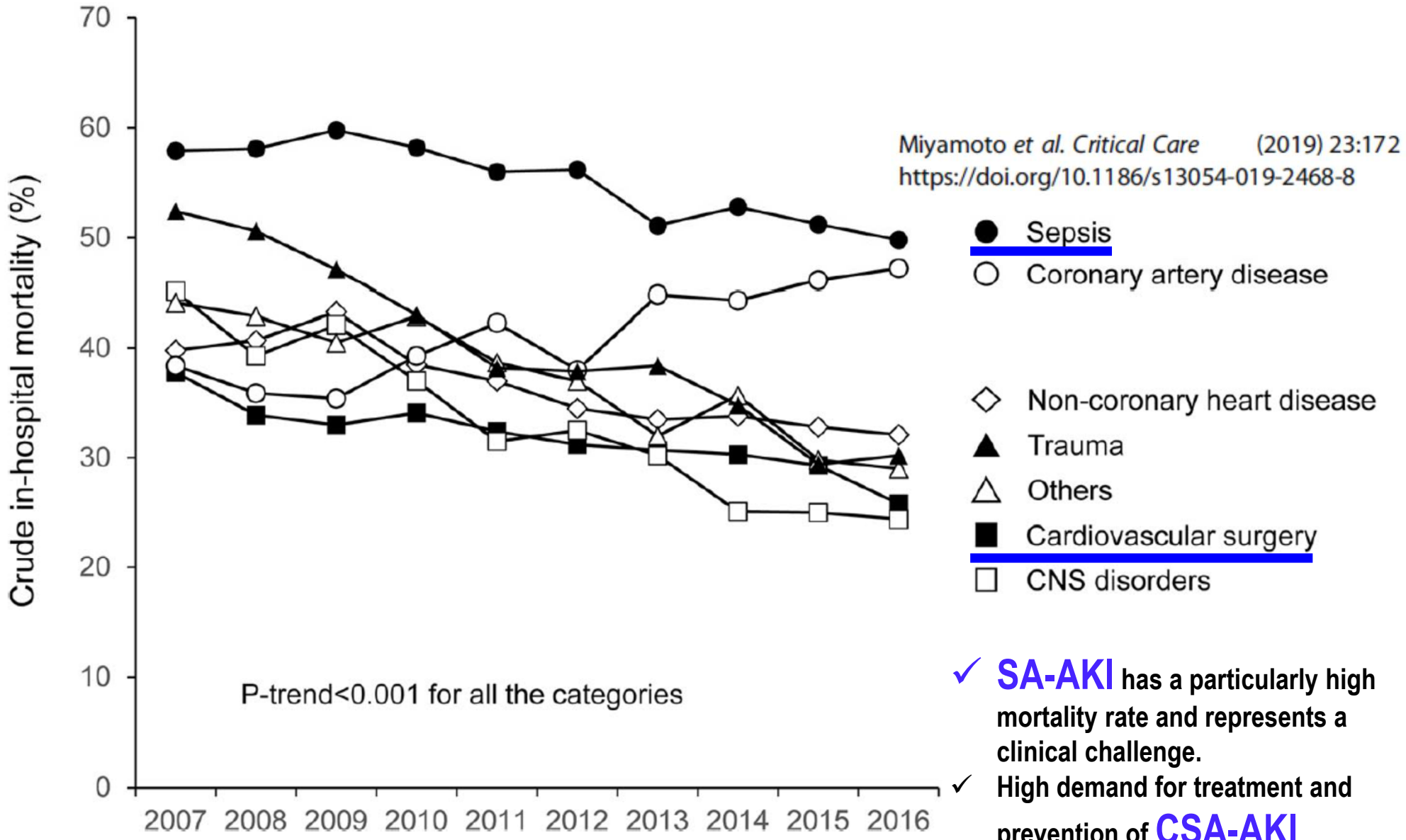
Source DelveInsight Business Research (September 2022)

- 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 (renal proximal tubular epithelium injury)**
- **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*

The mortality rate of AKI is very high.



Mortality in AKI patients receiving RRT in ICU: Nationwide database in Japan

- ✓ **SA-AKI** has a particularly high mortality rate and represents a clinical challenge.
- ✓ High demand for treatment and prevention of **CSA-AKI**

Pathogenesis of AKI and solution

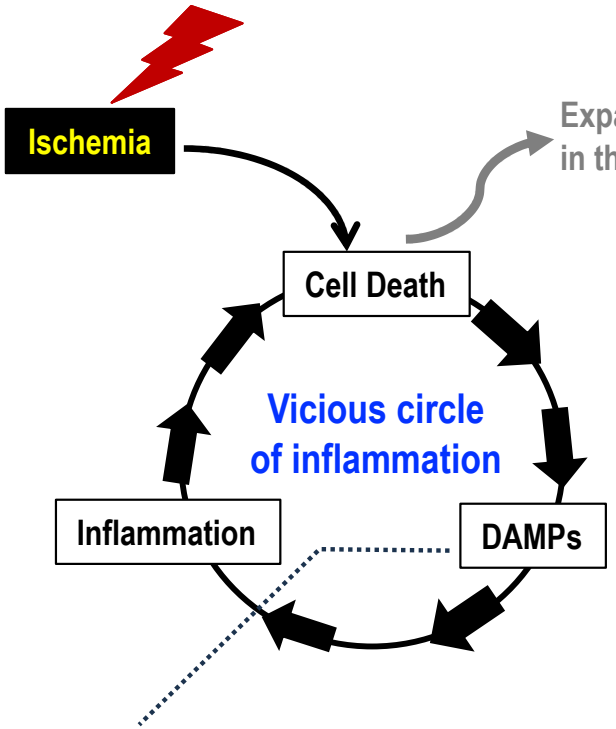
Injury and **necrosis** of **tubular epithelium** and
(**vicious cycle** of) **Inflammation**

Solution

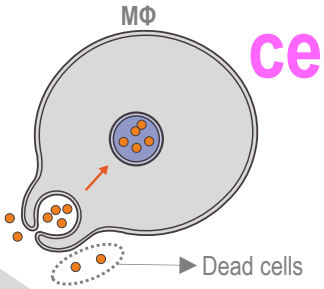
Promotion of **Efferocytosis** (phagocytosis and clearance of dead cells)

- ✓ Suppression of **vicious cycle of Inflammation**
- ✓ Suppression of **ischemia-reperfusion injury**
- ✓ Recovery from **kidney fibrosis**

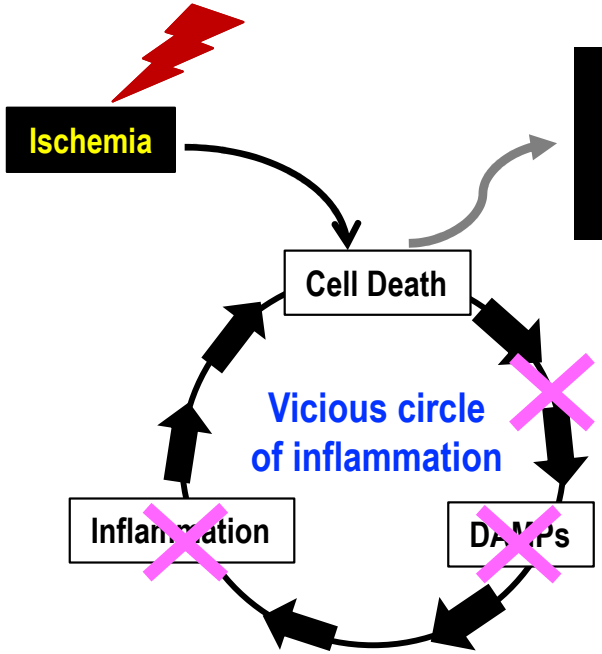
Efferocytosis promotors block vicious circle of inflammation induced by organ ischemia.



Macrophages remove dead cells by efferocytosis.



Solutions

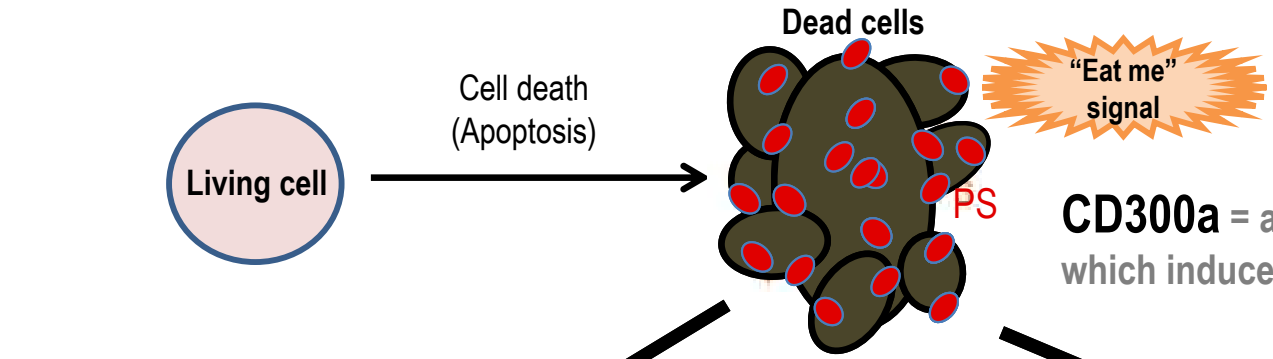


Preventing the tissue damage from spreading

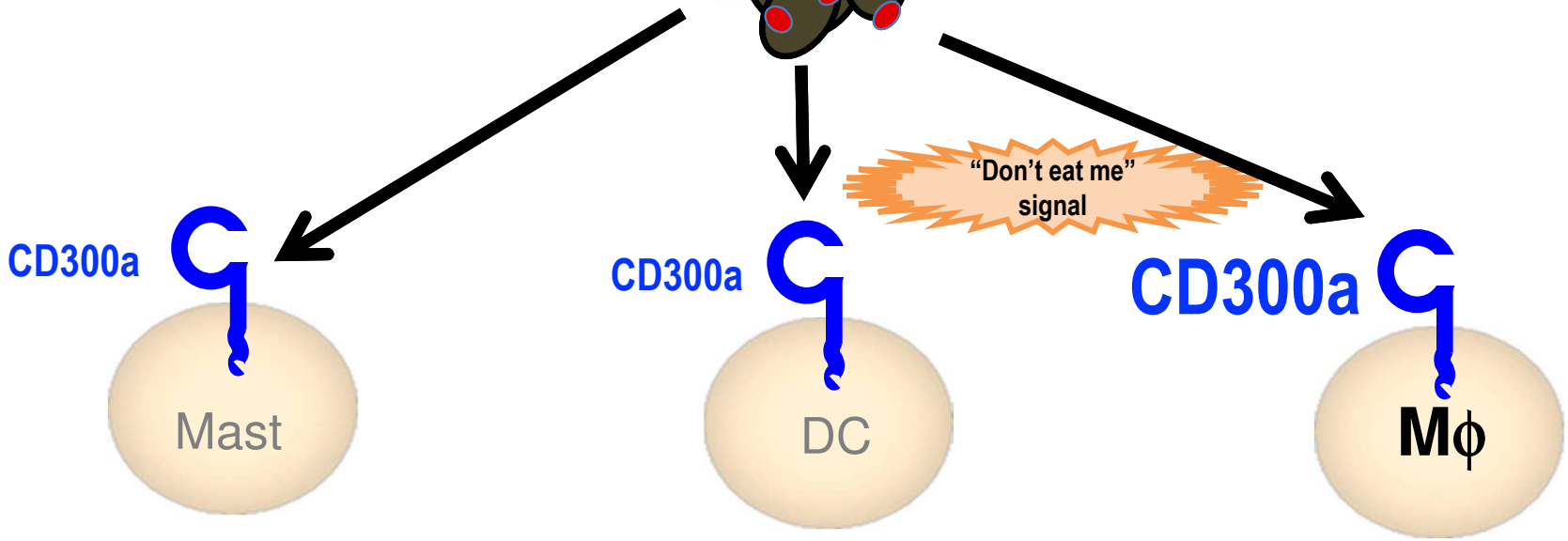
Efferocytosis promotor

DAMPs: damage-associated molecular patterns

CD300a inhibits myeloid cell activation via interaction with phosphatidylserine (PS) on dead cells.



CD300a = a key **anti-efferocytic molecule**, which induces resistance to dead cell removal



CD300a blockade enhances neutrophil-chemoattractants such as CXCL-1 and ameliorates the pathology of cecal ligation and puncture-induced sepsis

CD300a blockade enhances Treg cell expansion via augmenting IFN-b production and ameliorates the pathology of barrier surface inflammation such as DSS-induced colitis, atopic dermatitis, and allergic airway inflammation

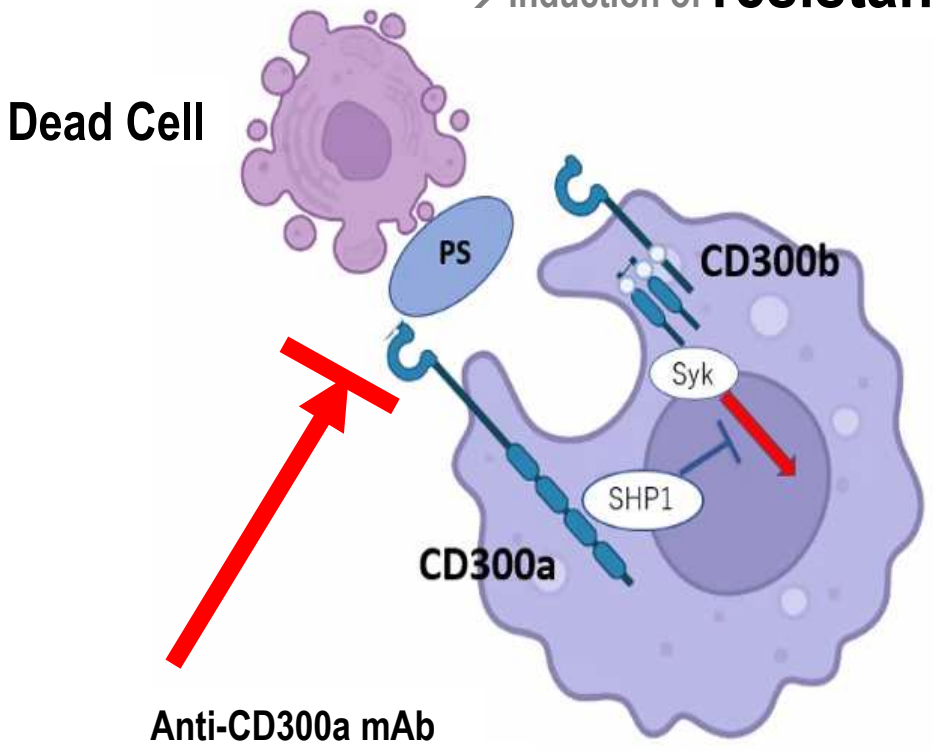
CD300a blockade enhances efferocytosis and ameliorates the pathology of **ischemia** and **reperfusion injury** in the **brain**, **heart** and **kidney**.

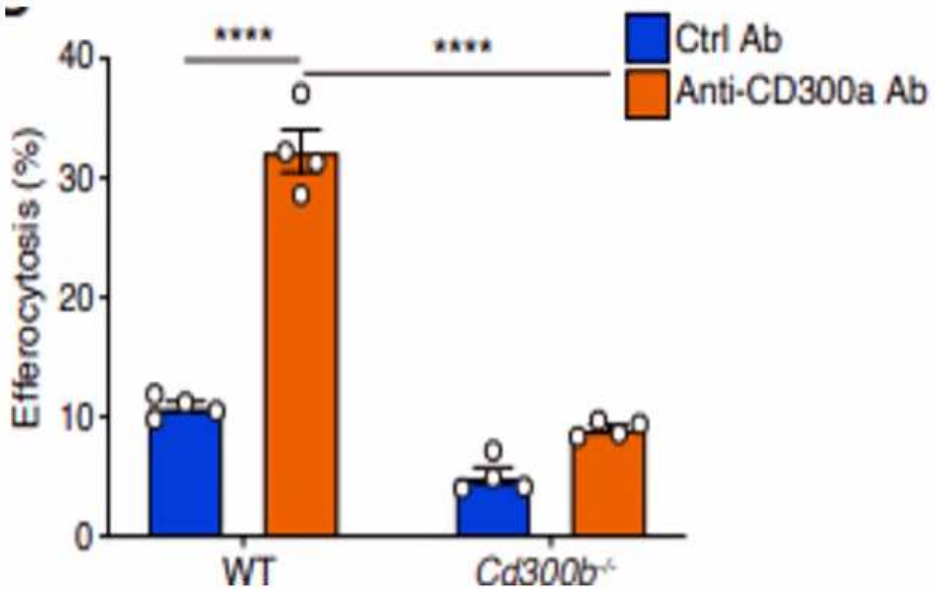
1) **Dead cells expose PS**, which displays "Eat Me" signals, and **macrophages induce efferocytosis to clear dead cells.**
2) **However, PS bound to CD300a expressed on macrophages**, which displays "Don't Eat Me" signals, **induces resistance to efferocytosis.**

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

Binding of **CD300a** expressed on **macrophages** to **PS** exposed on the surface of **dead cells**

→ Induction of **resistance** to **efferocytosis** (dead cell removal)

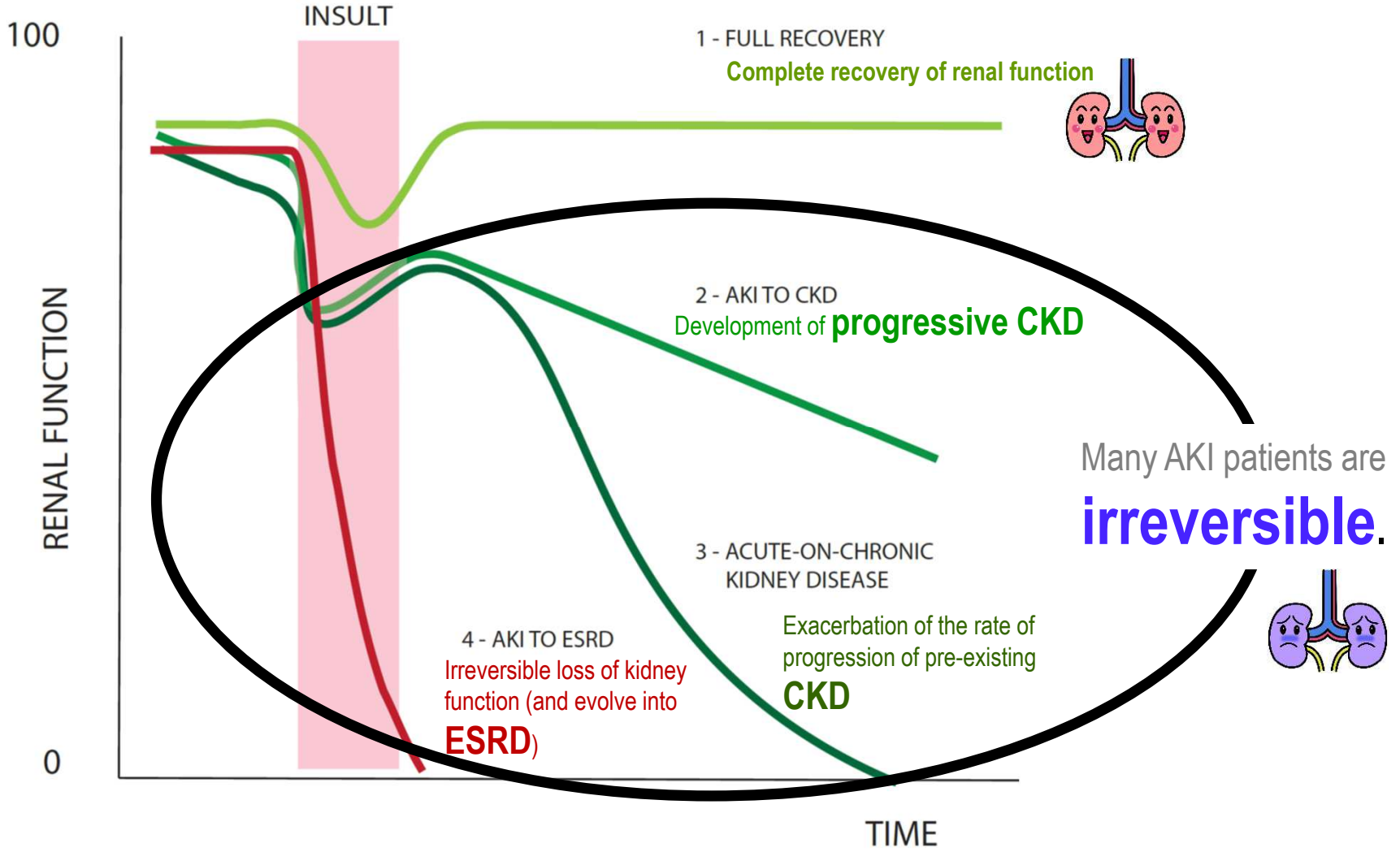




Anti-CD300a mAb → **Recovery** of defects in **efferocytosis** → **Normalization** of diseased tissue **clearance**

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

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

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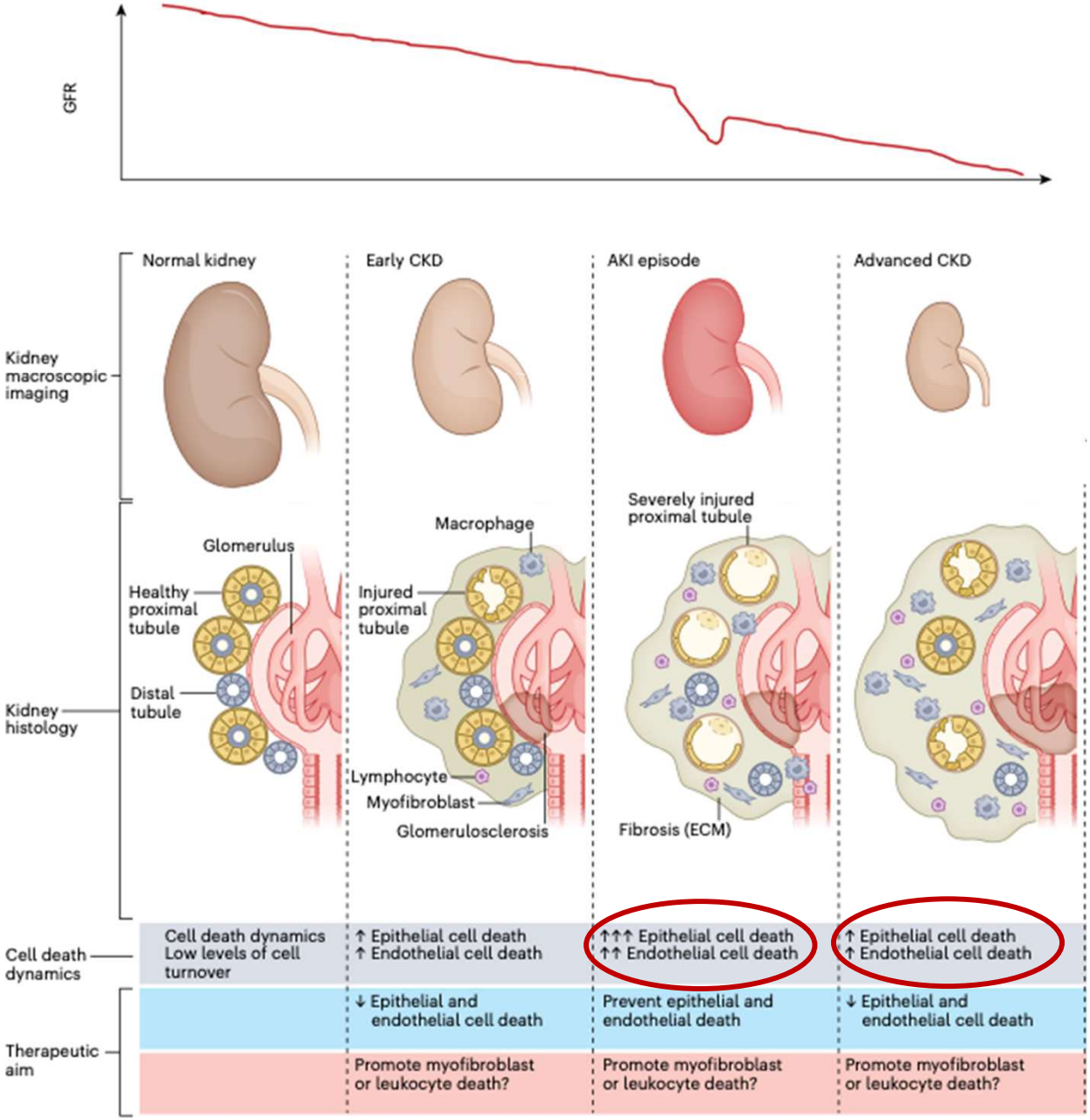

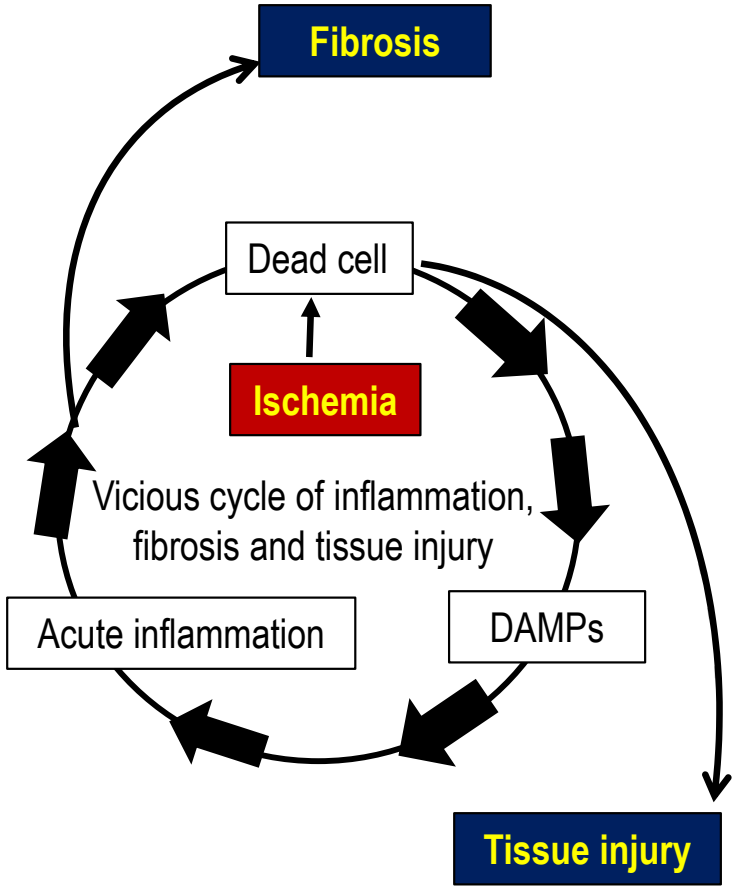

Nature Reviews Nephrology | Volume 19 | May 2023 | 281–299

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Inflammation after AKI causes renal dysfunction and fibrosis.

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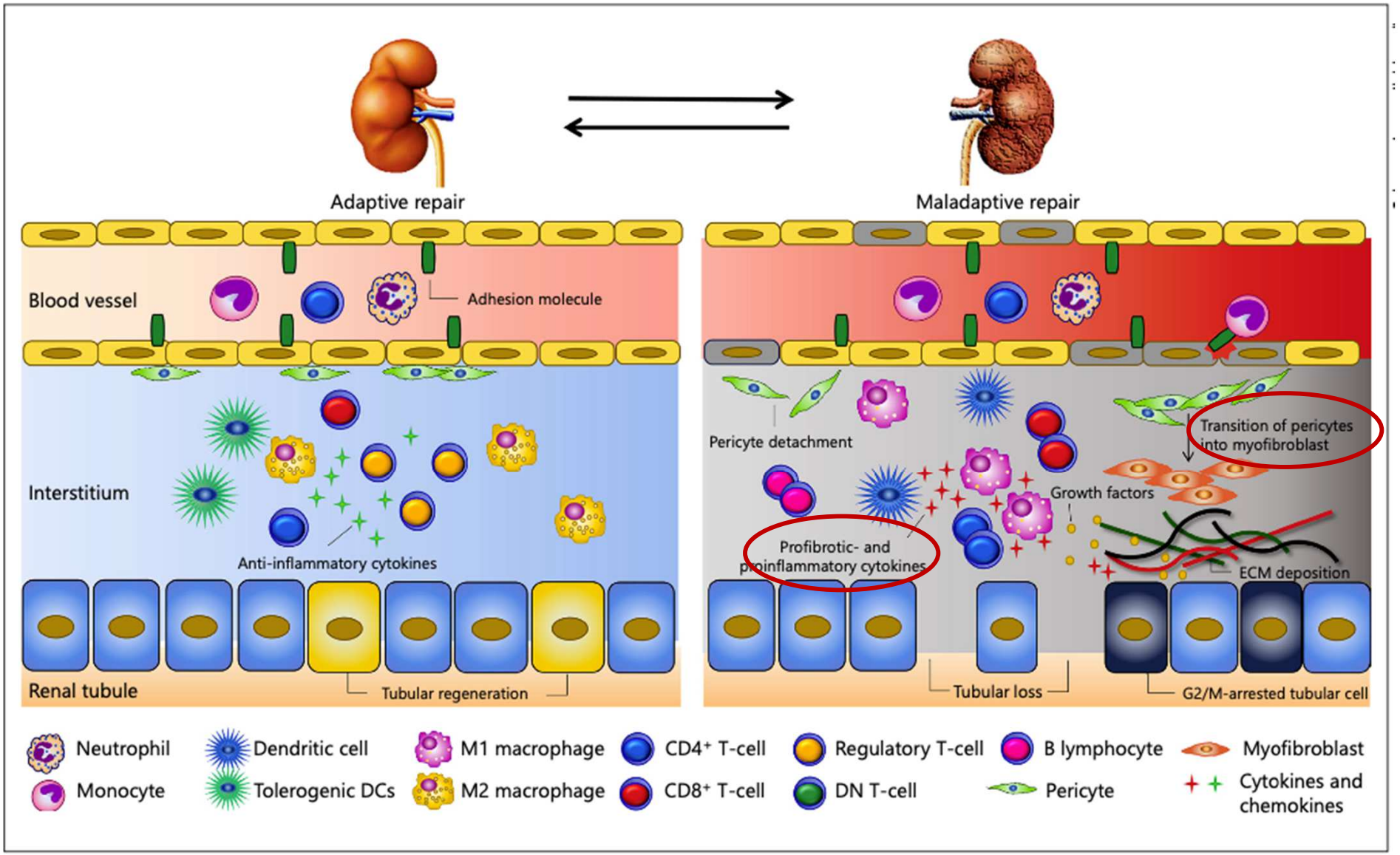
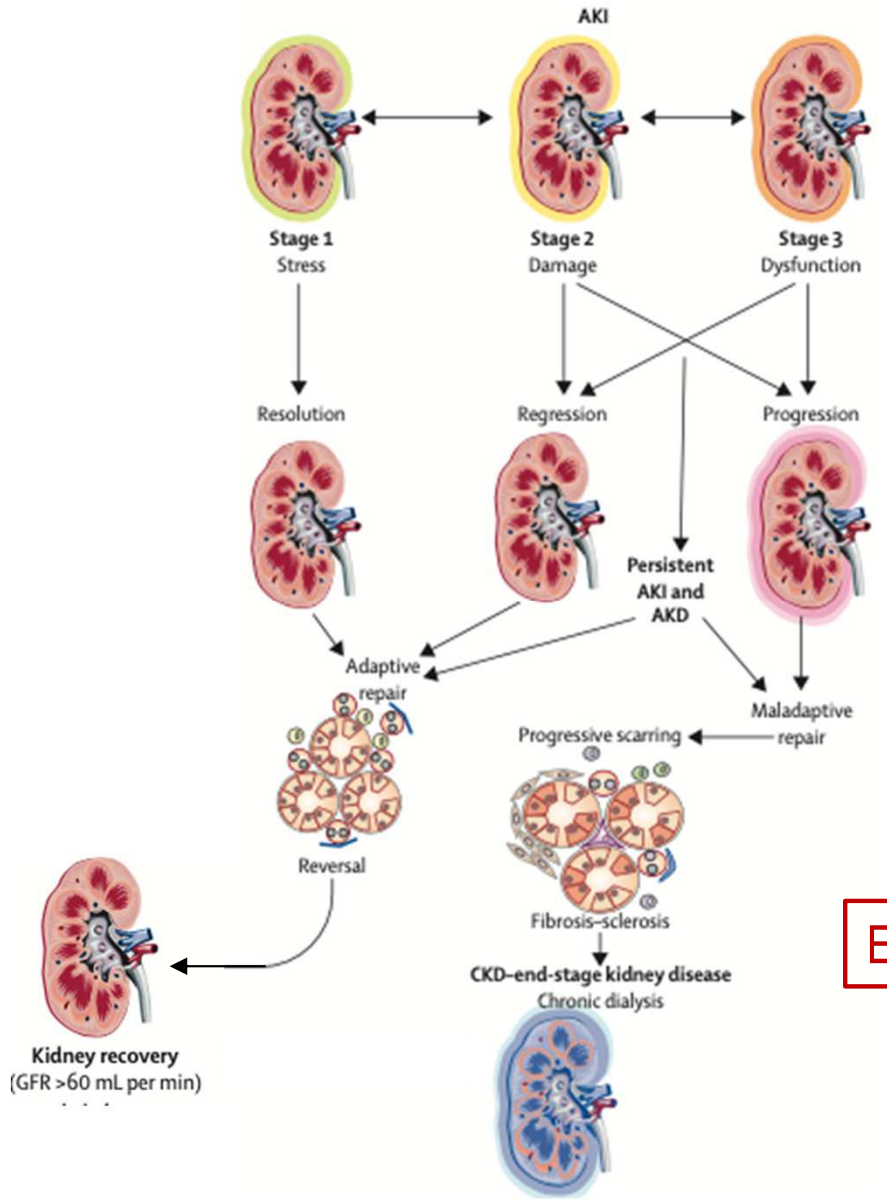
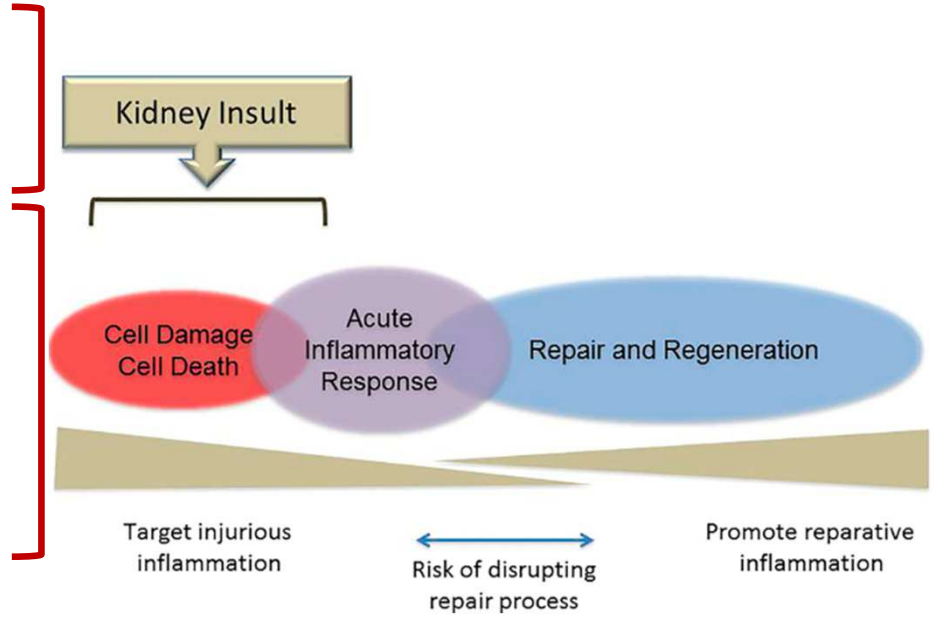


Nephron 2017;137:282–286
DOI: 10.1159/000477181

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





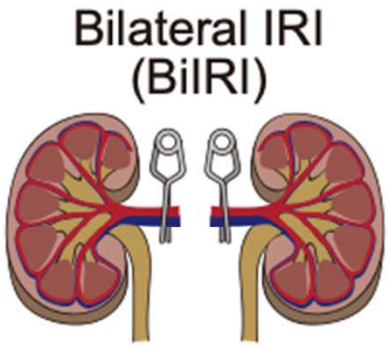
J Am Soc Nephrol **27:** 371–379, 2016

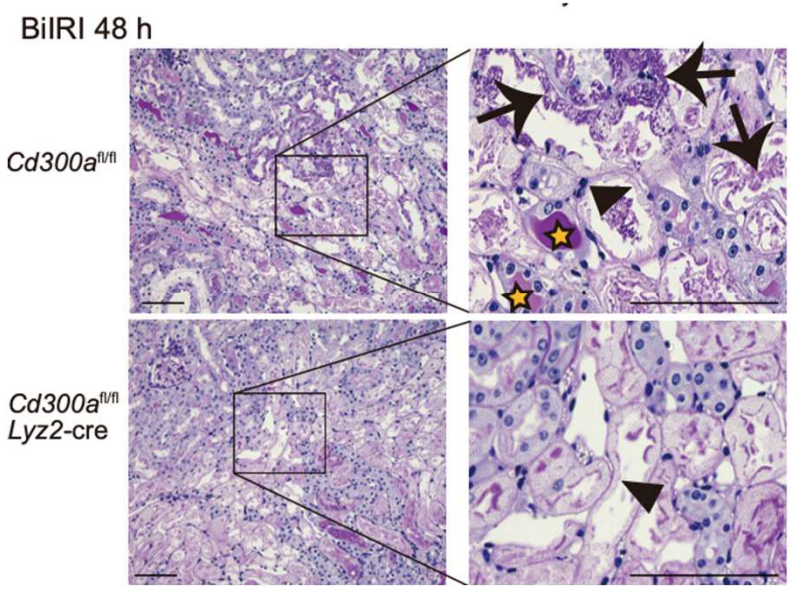
www.thelancet.com **Vol 394 November 23, 2019**

Efferocytosis promotor

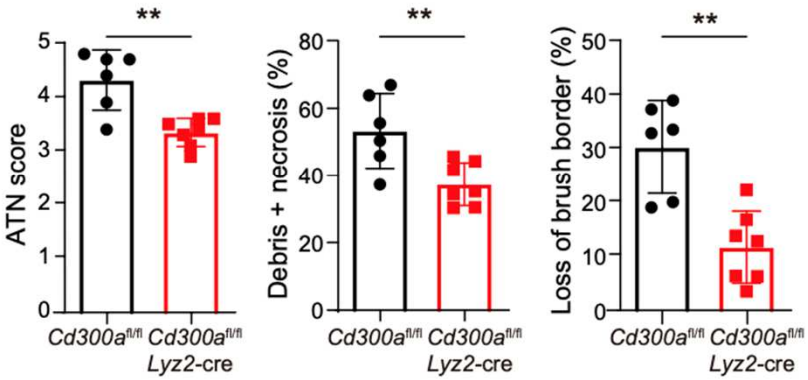
Increased phagocytosis of dead cells by macrophages reduces DAMPs release, suppresses acute inflammation and prevents the vicious cycle of induction of further dead cells and tissue injury.

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

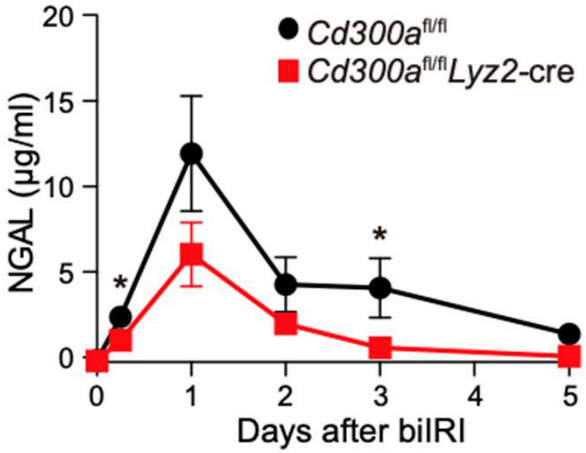




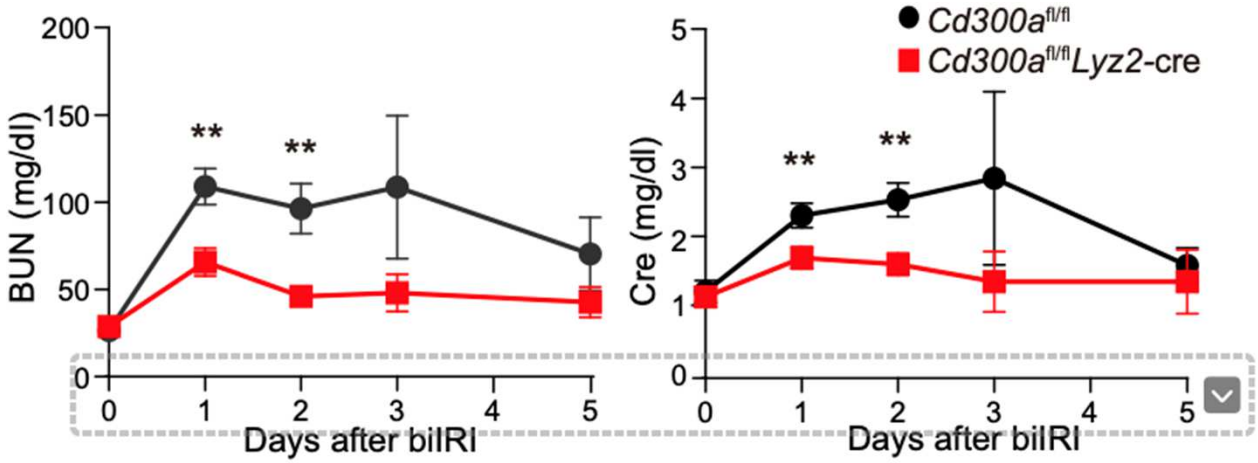
Suppression of renal tissue injury



Suppression of tubular damage

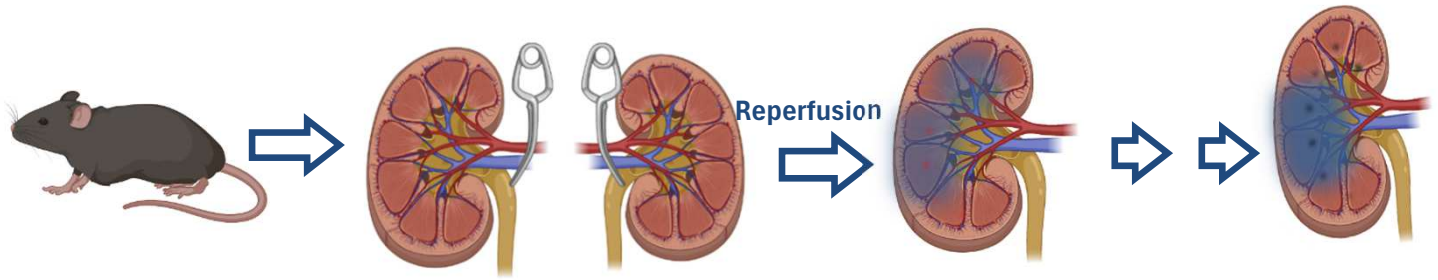


Suppression of renal dysfunction



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

Ischemia-reperfusion injury (IRI) model in mice

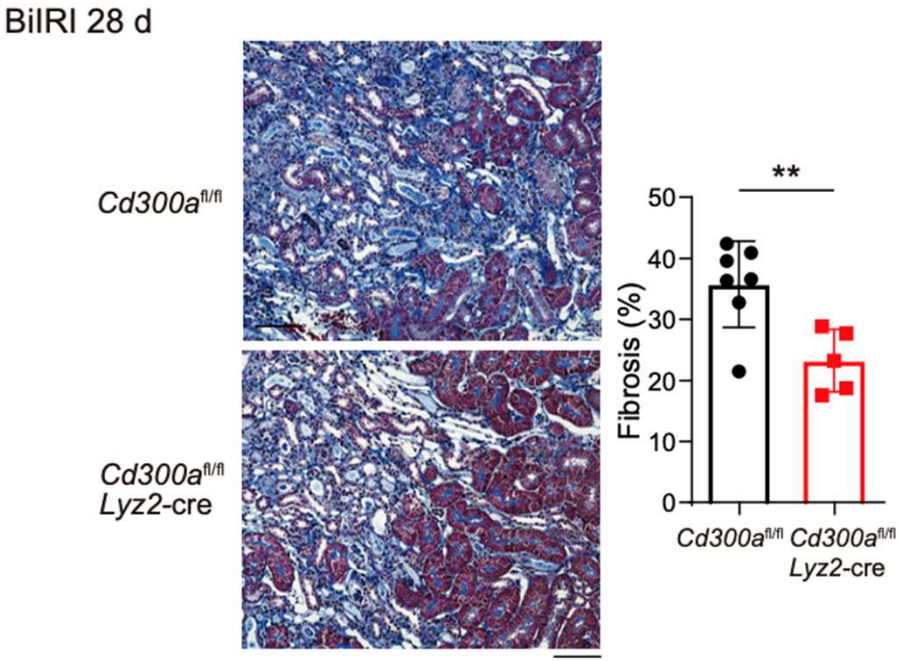


Bilateral kidney ischemia
for around 15 min

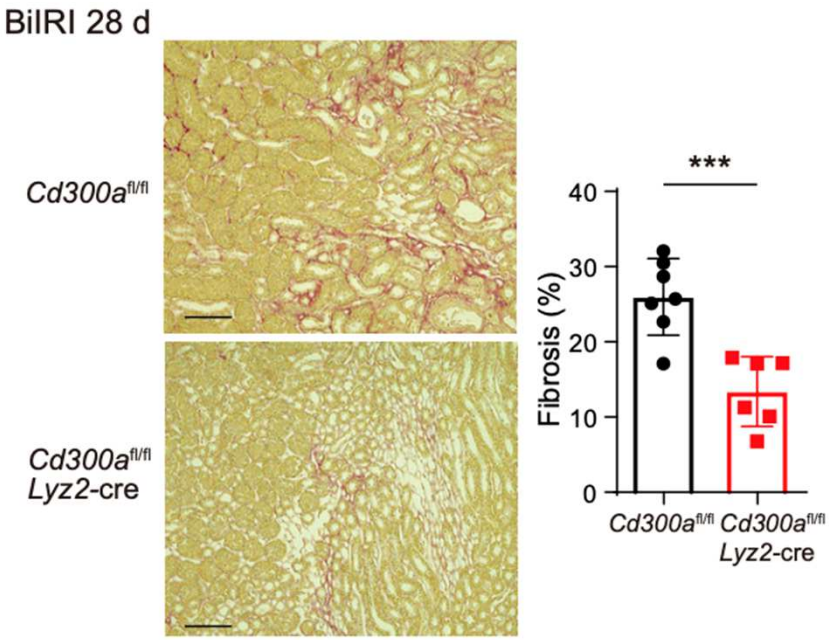
Acute kidney injury
1~2 days after IRI

Chronic kidney injury
with fibrosis
28 days after IRI

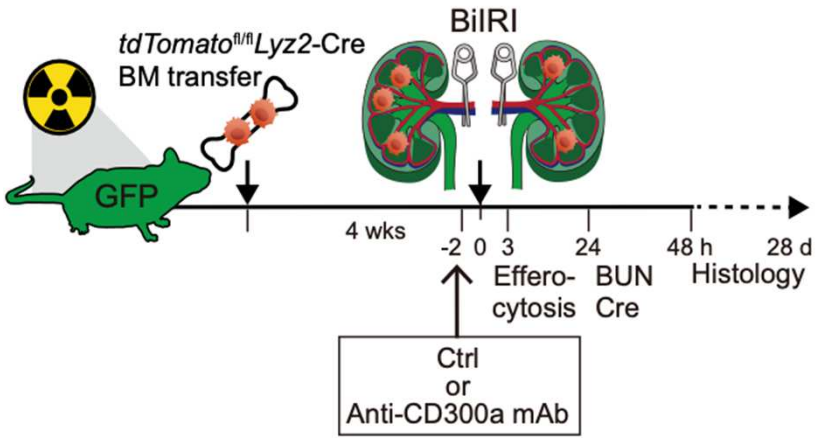
Suppression of kidney fibrosis (Masson Trichrome)



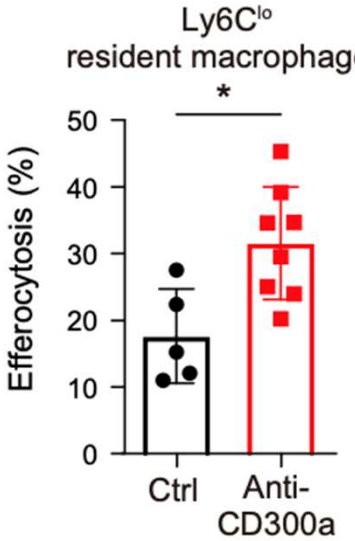
Suppression of kidney fibrosis (Sirius Red)



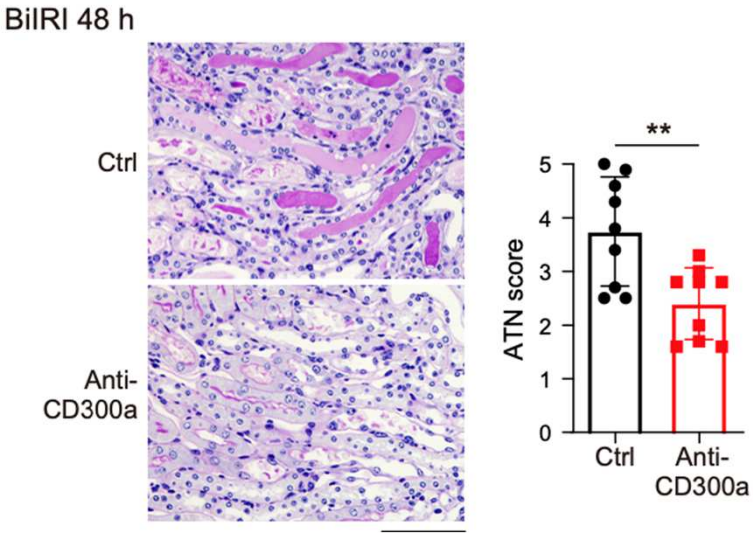
Anti-CD300a mAb promotes efferocytosis and attenuates AKI and kidney fibrosis.



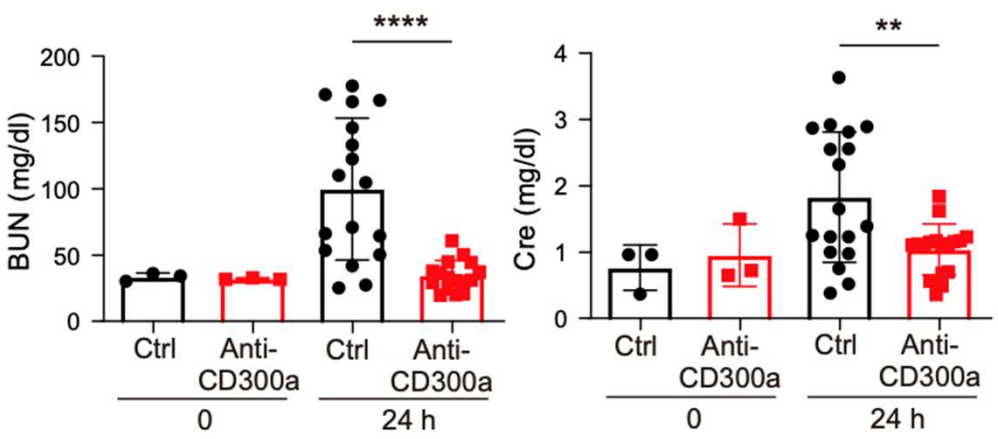
Enhancement of efferocytosis



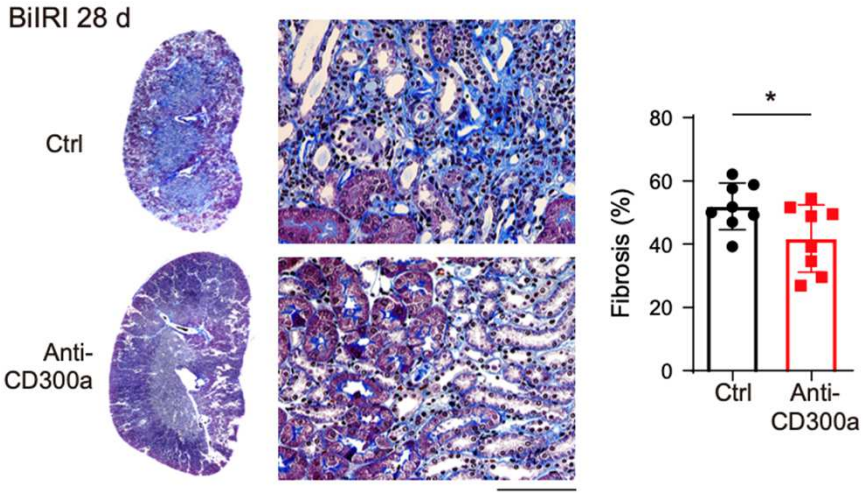
Suppression of renal tissue injury



Suppression of renal dysfunction

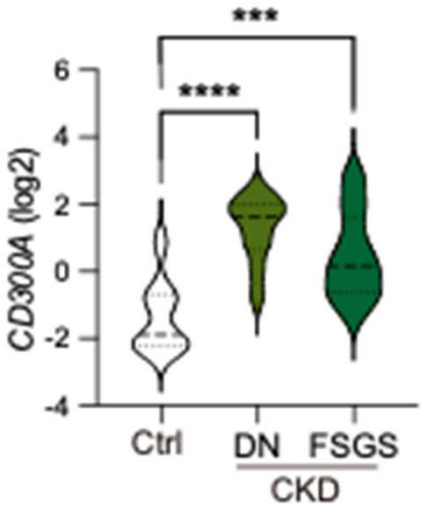


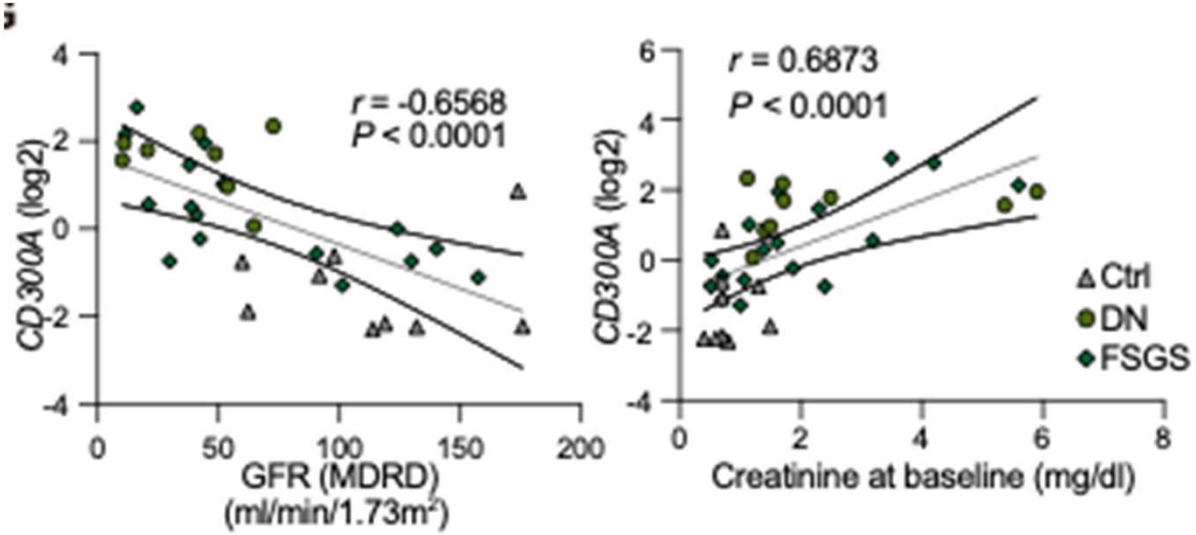
Suppression of kidney fibrosis (Masson Trichrome)



Patients with CDK express higher levels of CD300A than healthy controls, and CD300A expression is positively correlated with impaired renal function.

CD300A expression may be a good marker for patient selection.





Nephroseq v5 online database
（http://v5.nephroseq.org）

DN: diabetic nephrosis
FSGS: focal segmental glomerulosclerosis

Target Product Labels of TNAX103 in AKI

✓**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.)*

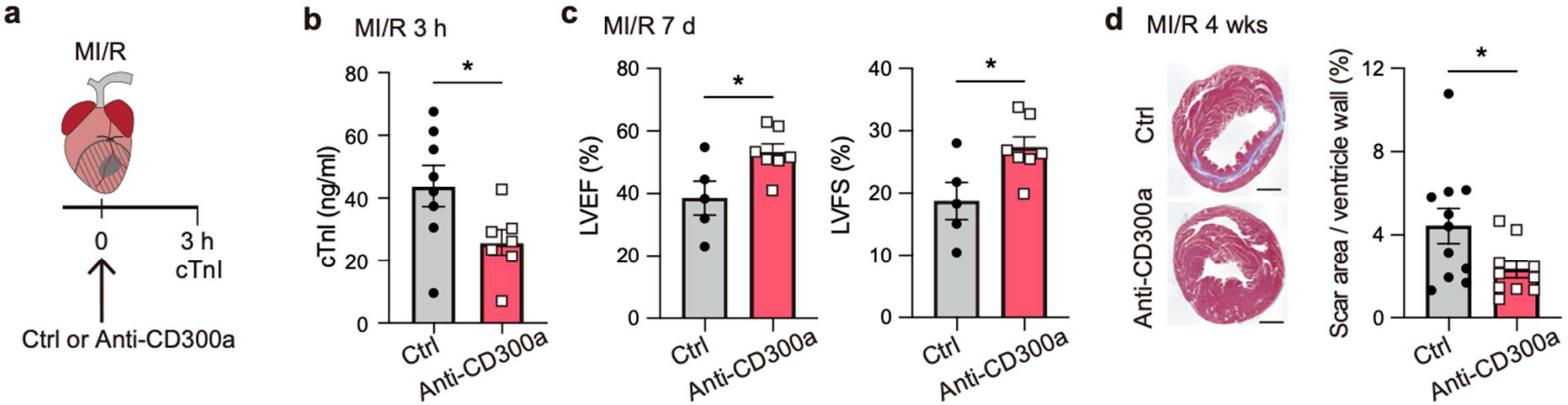
✓**Treatment** of **diagnosed ischemic-AKI** in patients **following cardiac surgery**

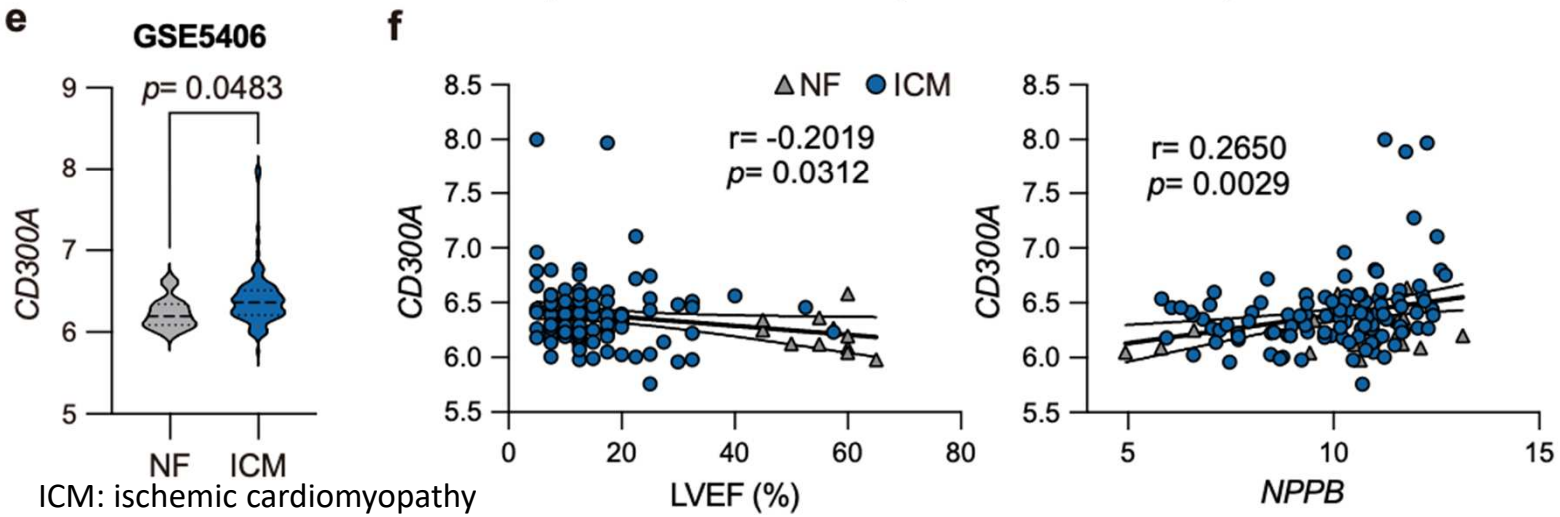
Anti-CD300a mAb is expected to improve the prognosis of AKI associated with ischemic heart disease.

Improvement of myocardial damage

Increase in cardiac function

Improvement of fibrosis





ICM: ischemic cardiomyopathy

Over-expression of CD00A in ICM patients

CD300A expression is negatively correlated with cardiac function in patients with ICM.

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Anti-CD300a mAb is expected to improve the prognosis of AKI associated with sepsis.

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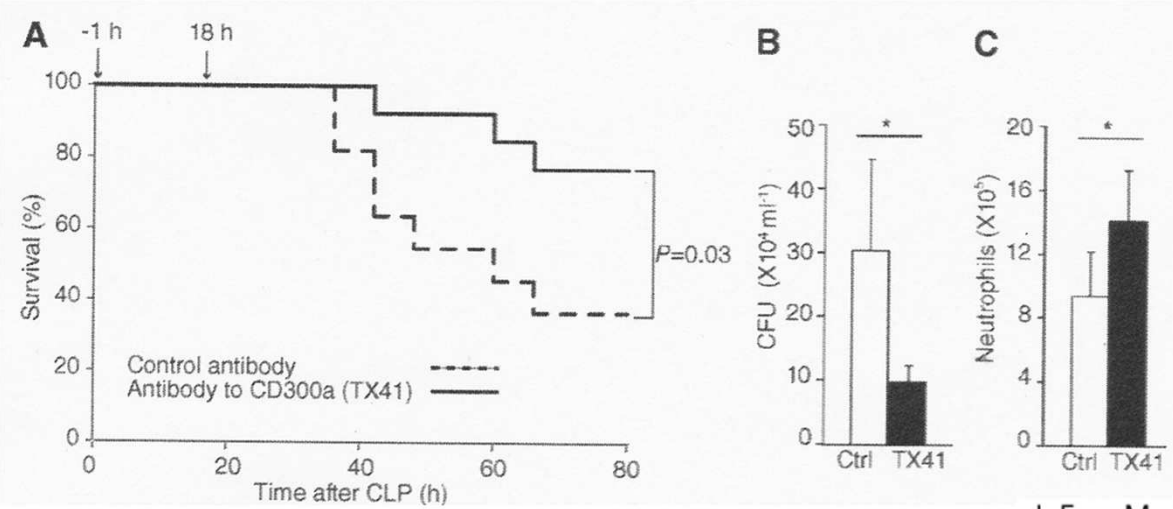


J. Exp. Med. 2012 Vol. 209 No. 8 1493-1503
www.jem.org/cgi/doi/10.1084/jem.20120096

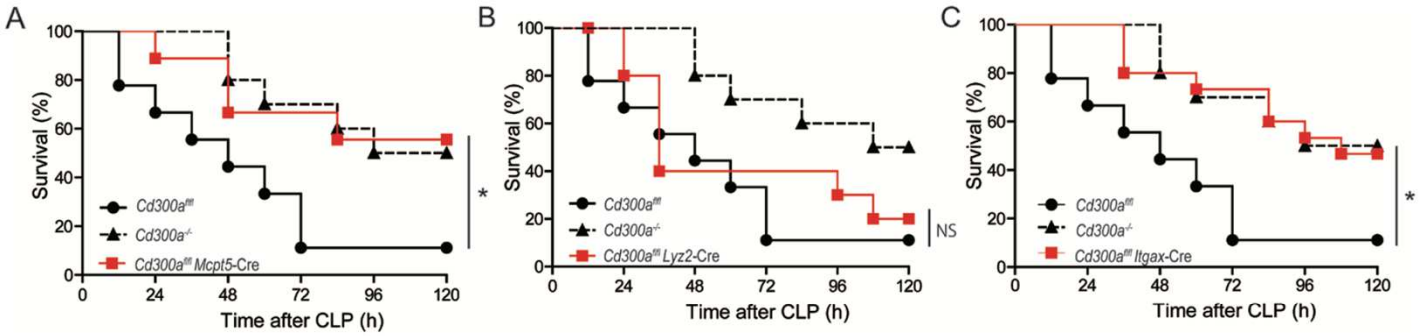


Fig. 2. CD300a on MCs and DCs influences survival after CLP. (A–C) Mice of the indicated lines underwent CLP, after which their survival was observed. In all experiments, *Cd300a*$^{-/-}$ mice served as the positive control group (n = 10 in each group). Survival rate was compared between (A) *Cd300a*$^{fl/fl}$ and *Cd300a*$^{fl/fl}$*Mcpt5*-Cre mice (n = 10 in each group), (B) *Cd300a*$^{fl/fl}$ and *Cd300a*$^{fl/fl}$*Lyz2*-Cre mice (n = 10 in each group) and (C) *Cd300a*$^{fl/fl}$ and *Cd300a*$^{fl/fl}$*Itgax*-Cre mice (n = 10 in each group). All the data were pooled from two independent experiments. *P < 0.05 (Kaplan–Meier log-rank test).

International Immunology, Vol. 28, No. 12, pp. 611–615
doi:10.1093/intimm/dxw047

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*

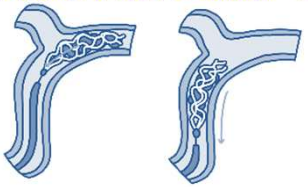
*2: including the costs of health care services, stroke medications and days away from work

Recanalization therapies

Thrombolytic therapy

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

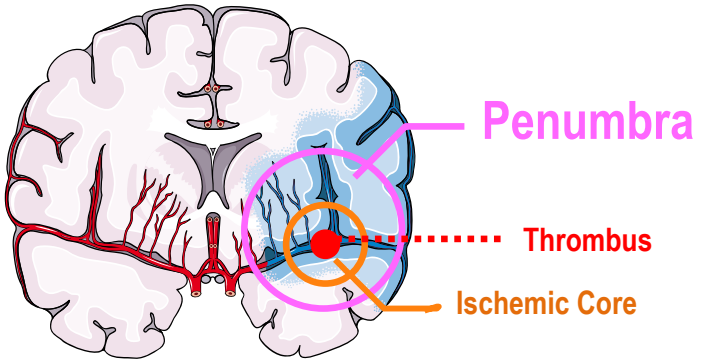
Endovascular thrombectomy



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.

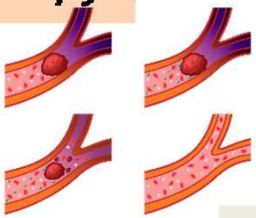


Penumbra = ***Tissue at-risk of cell death around the ischemic core***

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-reperfusion injury** (IRI)

Sudden restoration of blood flow may bring further damage.

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

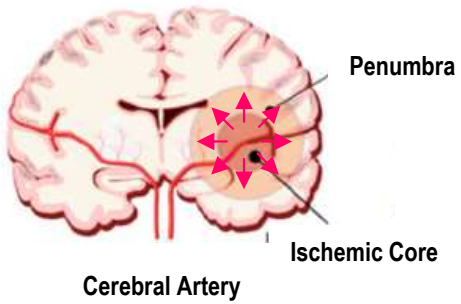
With recent advancement in recanalization therapy, IRI has become an increasingly critical challenge in stroke treatment.

Solutions

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

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

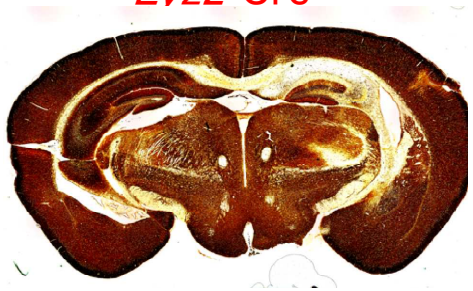


CD300a KO mice improved neuronal damage and neurological scores in acute ischemic stroke model.

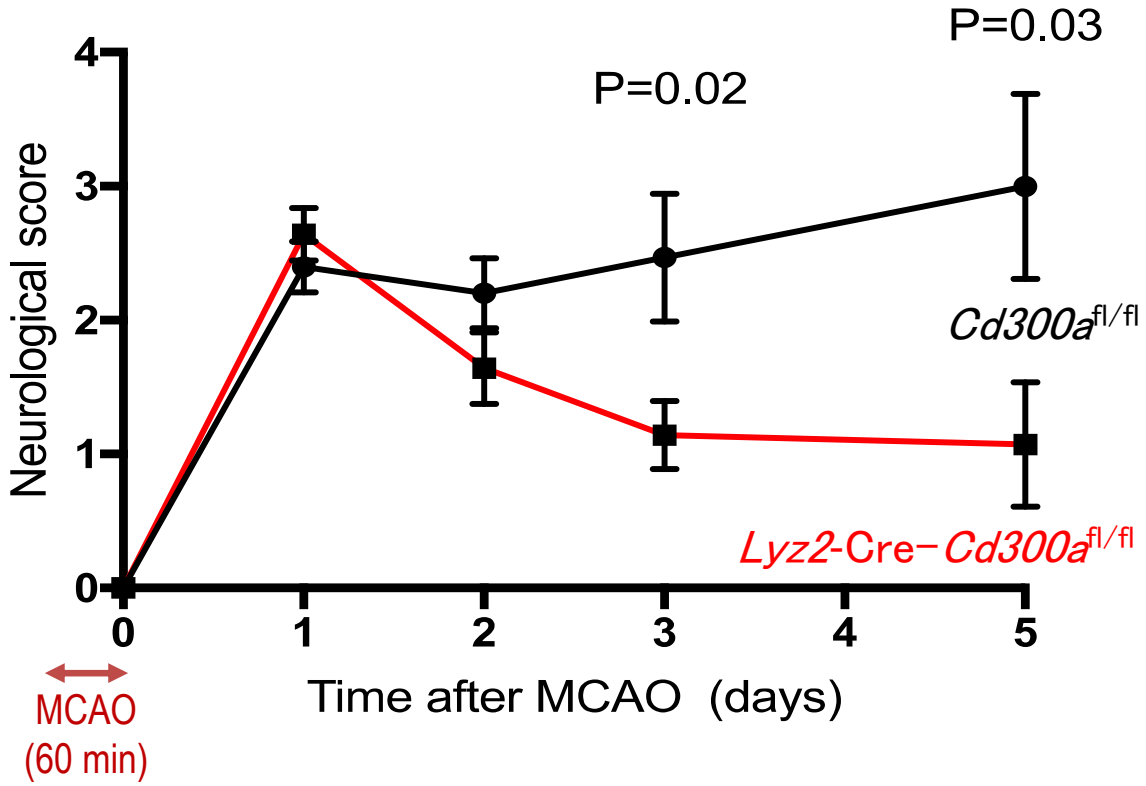
Mice deficient in CD300a on macrophages decreased neuronal damage and ameliorated neurological scores after MCAO and reperfusion.

Cd300a$^{fl/fl}$

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



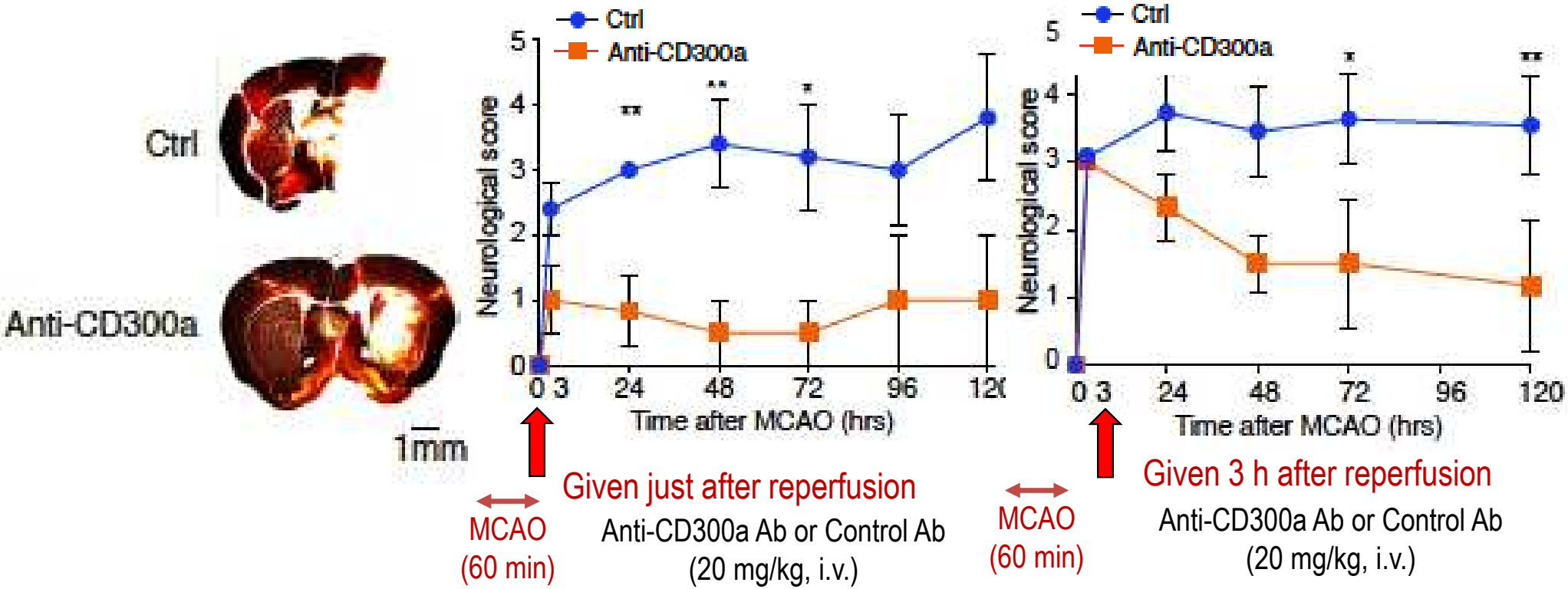
Anti-MAP2 Ab



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

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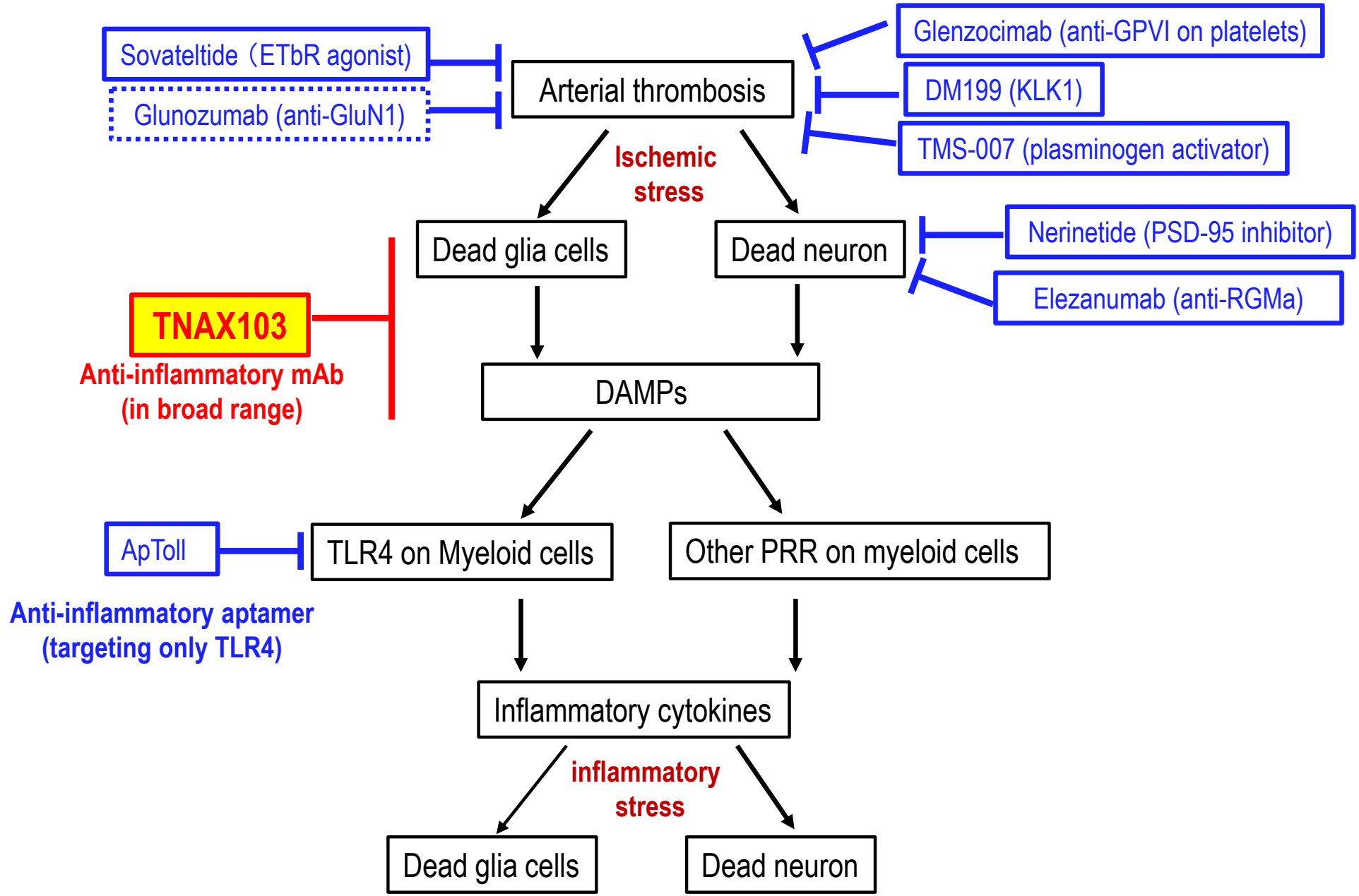

Clinical Positioning of TNAX103 in AIS Management

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?

→ Yes → **Alteplase**

→ No → Is Patient Suitable for Endovascular Thrombectomy?

- Yes → **Endovascular Thrombectomy** (If thrombolysis fails, **Alteplase**) → ≦24 hours from KLN
- No → **Non-invasive Therapy**
  - ・Anti-cerebral edema: Glycerol
  - ・Anti-thrombin: Argatroban
  - ・Anti-platelet: Aspirin
  - ・Anti-coagulant: LMWHz

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

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Spinal cord injury (SCI)

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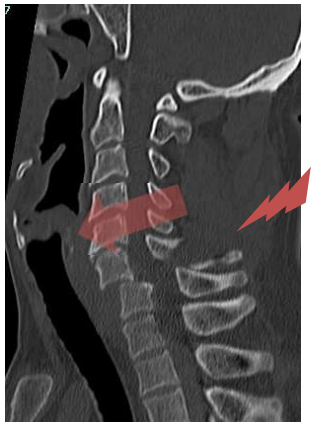
- Incidence: Approx. 17,730 new cases (US) and approx. 5,000 new cases (Jpn) each year
- Prevalence: Approx. 291K cases (US) and approx.100K cases (Jpn)
- Resulting from motor vehicle collisions, fall from height, etc.
- **No effective treatment**
- SCI total market = $6,784 million in 2021 **Huge market!**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

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

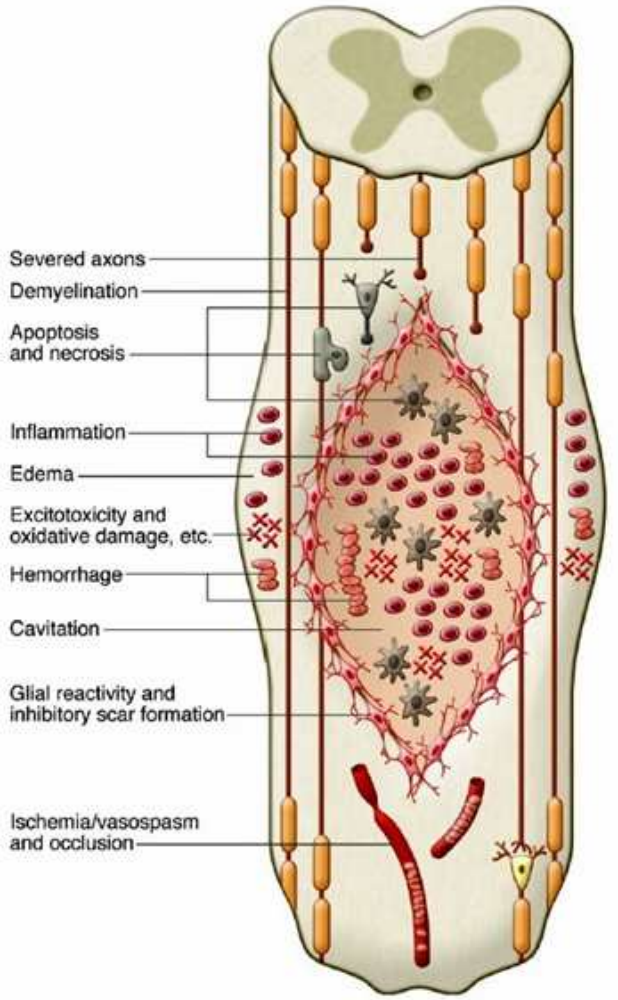
- Demyelination (oligodendrocyte death)

- 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



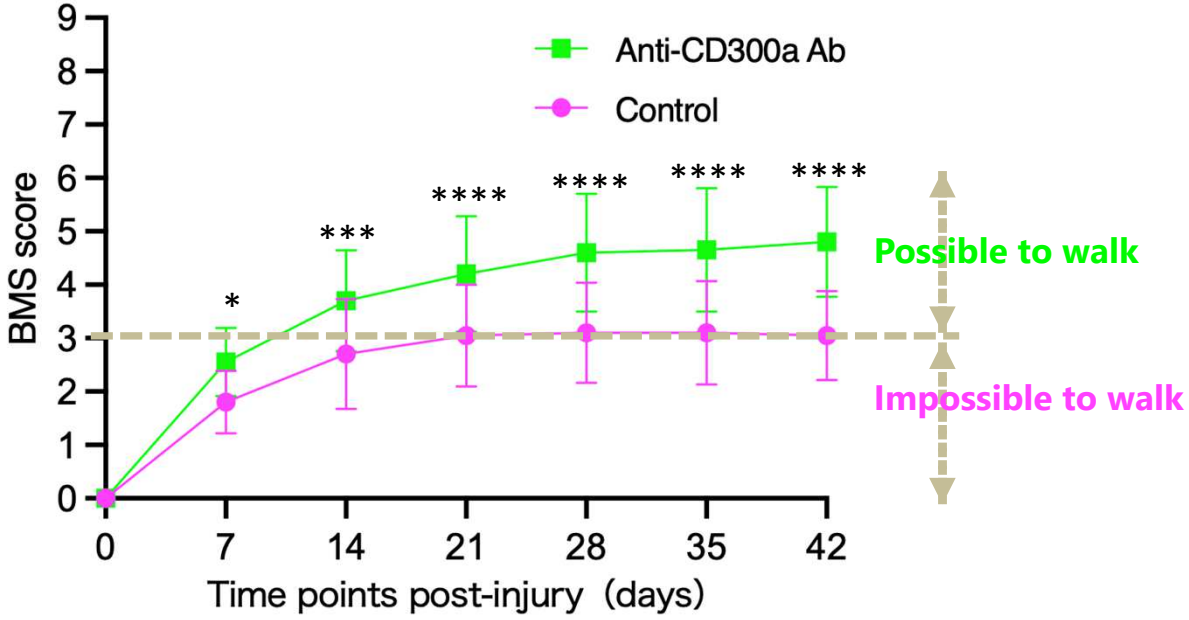
(Mothe, J Clin Invest, 2012)

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

Possibility of expanding indication into SCI

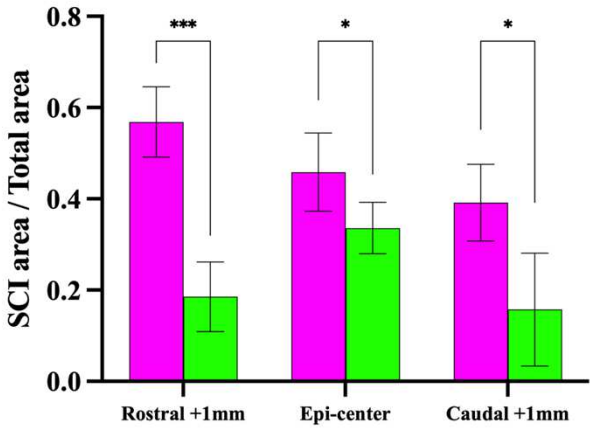
In a mouse SCI model, anti-CD300a mAb ameliorated locomotor ability and decreased areas of SCI (H&E staining) and demyelination (LFB staining).

Waling performance (BMS score)



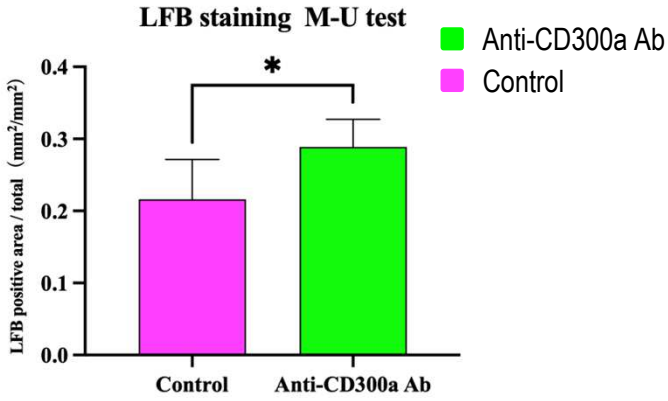
3 Points: Borderline between “walkable” and “unwalkable”.

HE staining in axial



*p<0.05, ***p<0.001

LFB staining M-U test



Anti-CD300a mAb facilitates locomotion in SCI model mice.

CD300A IP

As of May 27, 2024

- **PCT/JP2018/043862**
  - Japan, Canada, China, Hong Kong, South Korea, Taiwa, New Zealand, Russia → Granted
  - US, EP → Pending

Activity modulator (Anti-CD300a antibody for treating ischemic diseases)

- **New patent application filed in April 2023**

Humanized anti-CD300A monoclonal antibody, and its antigen-binding fragments

- JP6124261/US10519233/EP2808028 → Granted
- JP6226333/US9850309 → Granted

Activity modulator, medicinal agent comprising same, use of CD300A gene-deficient mouse, and anti-CD300A antibody

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

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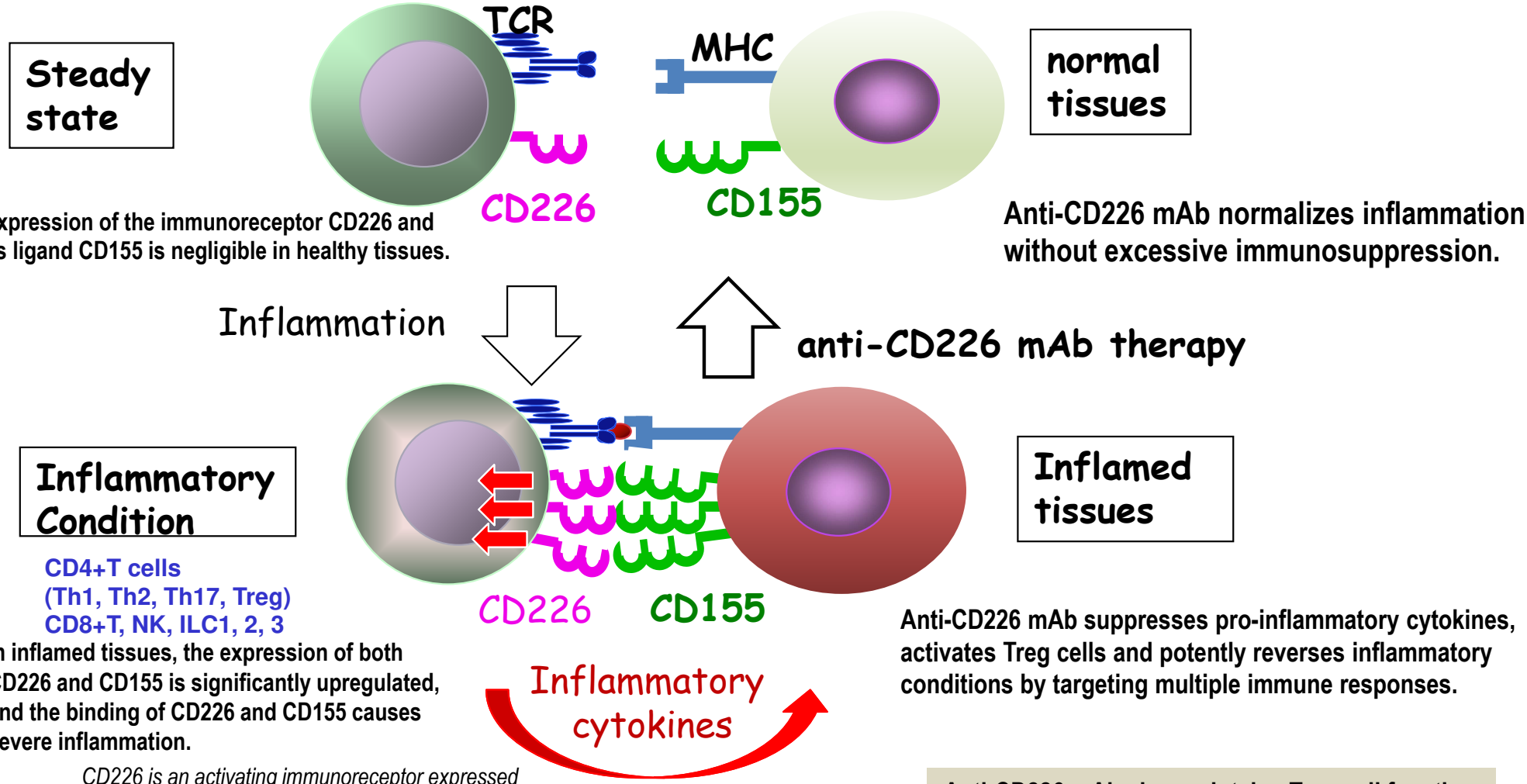
1. Koizumi H, Nakahashi-Oda C, Fujiyama S, Li J, Lee H, Lyu W, Bao TTW, Abe F, Tabuchi K Kazuko Shibuya S, Shibuya A. Enhanced efferocytosis by CD300a blockade ameliorates acute kidney injury and subsequent fibrosis. Submitted under review.
2. Nakazawa Y, Nishiyama N, Koizumi H, Kanemaru K, Nakahashi-Oda 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.