

タンパク質工学の未来と創造性

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<https://ishiharalab.net/>

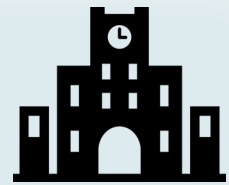
IMPERIAL



国立研究開発法人
国立がん研究センター
National Cancer Center Japan

新薬の開発とは？

多くのシーズはアカデミアでのサイエンスの進歩から始まる



大きなギャップ



**日本の科学
技術は優れ
ているが、事
業に繋げると
ころに問題を
抱えている**



製薬会社



バイオベンチャー

#社会にいいこと #医療・福祉 #起業・スタートアップ #がん #研究

創薬をもっと日本から | 国内研究者が持つ薬のタネが花開く場所を東京に



Flox Bio



支援総額

1,305,000円

目標金額 5,000,000円

26%

支援者 残り

68人 46日

⊕ フォローする

応援コメント



角南 有紀

10時間前

四谷に住んでいるので、Incubatorの前をよく通ります。お店の方がこんな素敵な取り組みをされていると知って驚きました...

プロジェクトの支援にすすむ

<https://readyfor.jp/projects/floxbio>

Science Bar in Tokyo

INCUBATOR

The Place People Talk over Drinks with Scientists



Experimental
Food and drinks

Ratings and reviews

5.0  69 reviews

#1 of 340 Bar in Shinjuku

#23 of 5,185 Restaurants in Shinjuku

 Certificate of Excellence 2018 Winner

Drug delivery system for cancer, inflammatory diseases and wounds

2014 PhD Univ. Tokyo: Hematopoietic stem cell biology

2014-2016 EPFL, Switzerland

2016-2020 Univ. Chicago

2020- Imperial College London Bioengineering

2024- National cancer center, Japan

Other diseases: IBD, asthma

Nature Biomed Eng 2020^b

Multiple sclerosis

Science Adv, 2019^c

Fibrosis

Cancer

Science Adv, 2019^c
Arthritis Res Ther, 2019
Rheumatol res 2020

Arthritis

Wounds

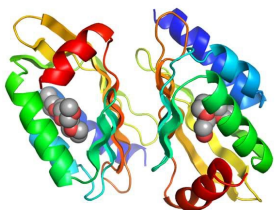
Science Transl Med, 2017
Mol Cancer Ther, 2018
Science Transl Med, 2019
Science Adv, 2023, 2019^a 2019^b
Nature Comm 2023 2023
Cell rep med 2023
Nature Biomed Eng, 2022, 2020^a 2025 2025

Nature Commun 2018
Blood (plenary paper) 2019
Npj Regenerative med 2023

2020年7月より自分の研究室を持つことができました。癌免疫療法、自己免疫疾患の薬、ワクチンの開発

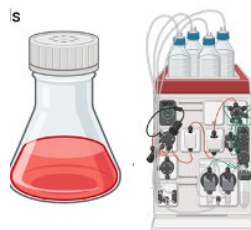
Drug discovery lab capability

(AI-based) protein design

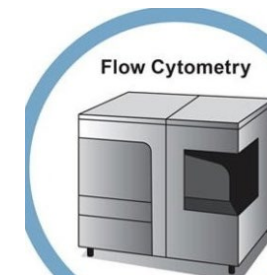


Cytokines

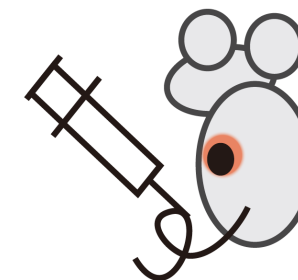
Production



In vitro cell culture

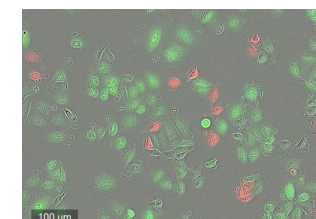


Mouse experiments

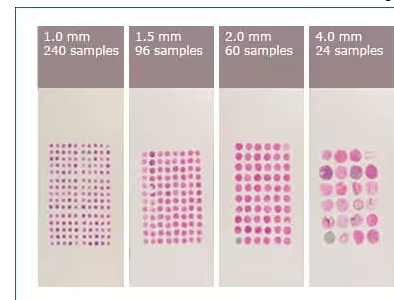


Mono- Bi- tri-specific
Antibodies

Stability and
yield optimisation



Human tissue array



Efficacy

MoA

Side effects

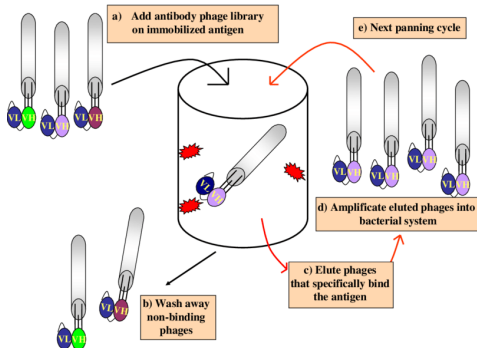
(Biochem, haematology)

PK/PD

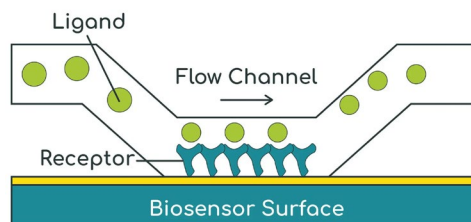
Biomarker discovery

Human cancer (PDX, humanised)

(AI-based)
Antibody discovery display



Affinity
Characterisation



My capability

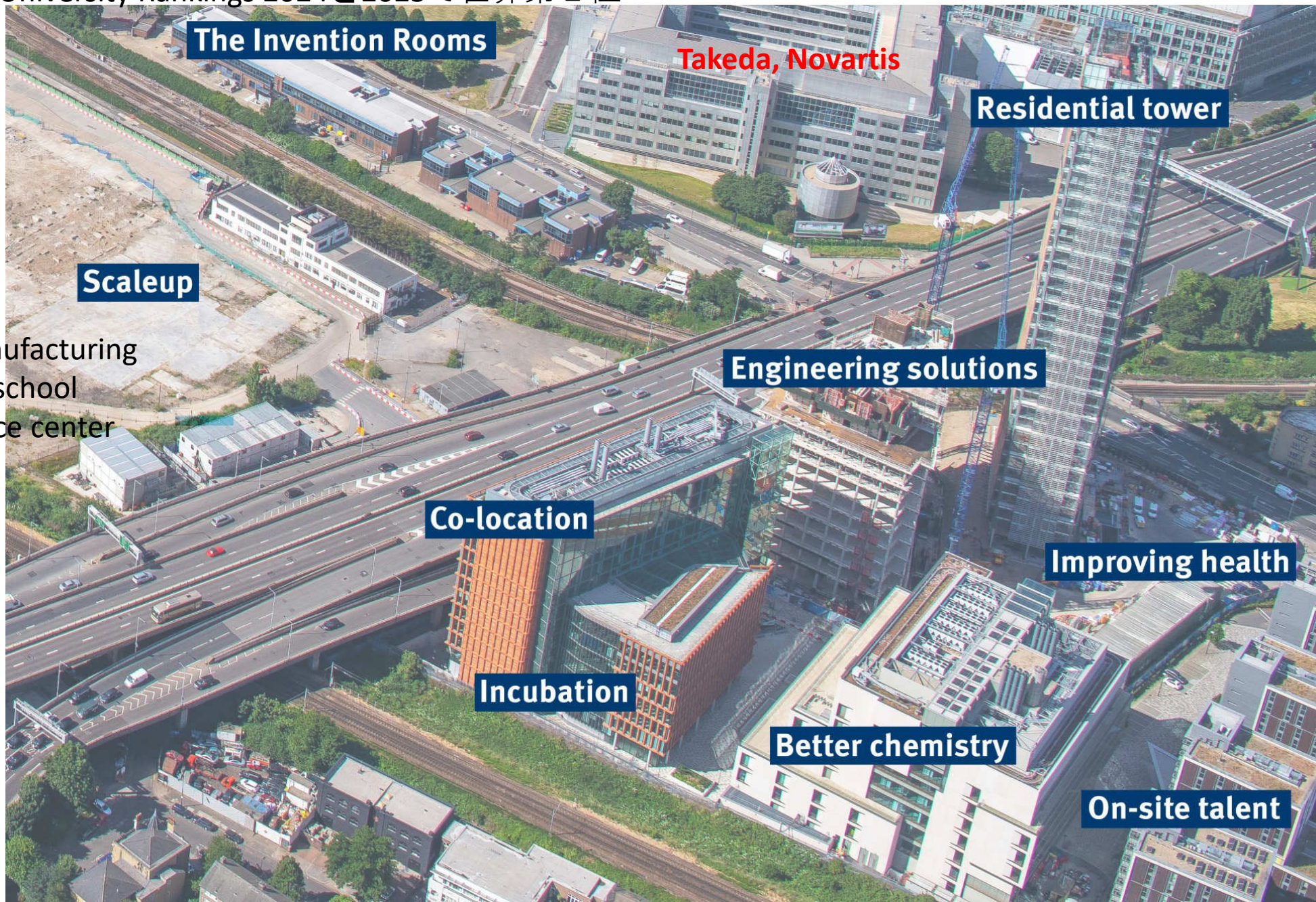
- Made >20 different cytokines (IL-1b...IL-38, TNF, IFN)
 - Made >30 types of antibodies (anti-PD-1 etc)
 - Functional peptide discovery
 - and then engineer: bi-specific antibody, ADC, antibody-cytokine fusion, CAR-T cells
-
- Immunology
 - Drug delivery
 - Pharmacology
 - Toxicology

インペリアル・カレッジ・ロンドン の第2キャンパス：医工連携、産学連携キャンパスWhite City

QS World University Rankings 2024と2025で世界第2位

GMP manufacturing
Business school
Conference center

AI center



10 min walk:
Hospital

90mポンド Series A をインペリアルカレッジのADC start upが獲得

Imperial and Crick cancer drug spinout raises £90m to begin clinical development

by [Ian Mundell](#)

08 July 2024



Myricx founders (l-r) Dr Andrew Bell, Dr Roberto Solari and Professor Ed Tate, with CEO Dr Robin Carr

Myricx Bio is bringing new therapeutic possibilities to the highly promising area of antibody-drug conjugates for treating cancer.



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RELATED STORIES



英国：産業革命を起こした国としてAIにも積極的に参戦



£100 billion (1 8 兆円)
investment from UK government

Charlotte Deane
Frank von Delft
David Baker

Imperial College will be the HUB

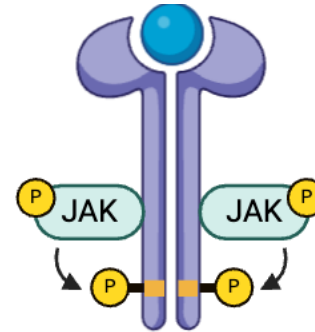
Imperial College London to partner with World Economic Forum to deliver new AI-Driven Innovation Centre
- boosting AI adoption and innovation to grow the economy

多様化する免疫療法のモダリティ

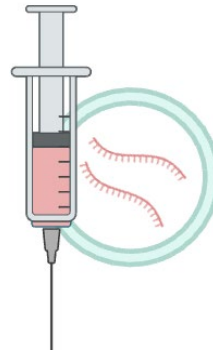
抗体



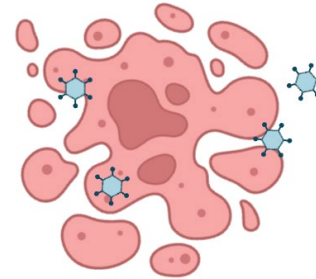
サイトカイン



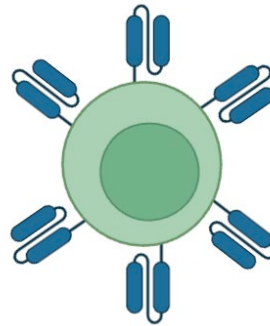
mRNA



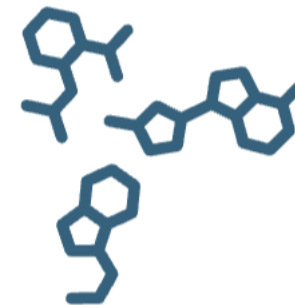
Oncolytic Virus



CAR-T細胞

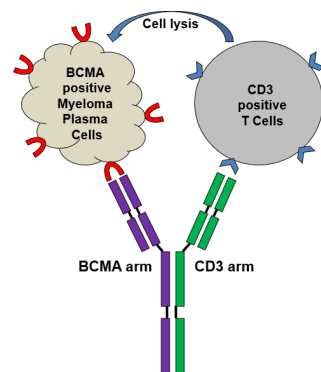


小分子 (STING やIDO)



エンジニアリングで多様化する抗体の形

Bi-specific 抗体



CD3—癌抗原
T細胞を癌細胞とくっつける

エプコリタマブ

Figure 1. Teclistamab
Tecvayli

MEDI5752
PD-1
xCTLA4



PD-1+ X
PD1抗体の効果増強を狙う

米国FDAは、2024年に50の新薬と18のバイオシミラーを承認

バイオリジクス

tislelizumab-jsgr: Tevimbra, enzyme for subcutaneous injection of PI

- nogapendekin alfa inbakicept-pmln : Anktiva, IL-15 for bladder ca
- tarlatamab-dlle: Imdelltra, bispecific ab for lung cancer
- Zanidatamab: modified HER2 for biliary tract cancer
- zenocutuzumab-zbco: Her2 and HER3 bi-specific
- Cosibelimab-ipdl: modified anti-PD-L1 for cScc

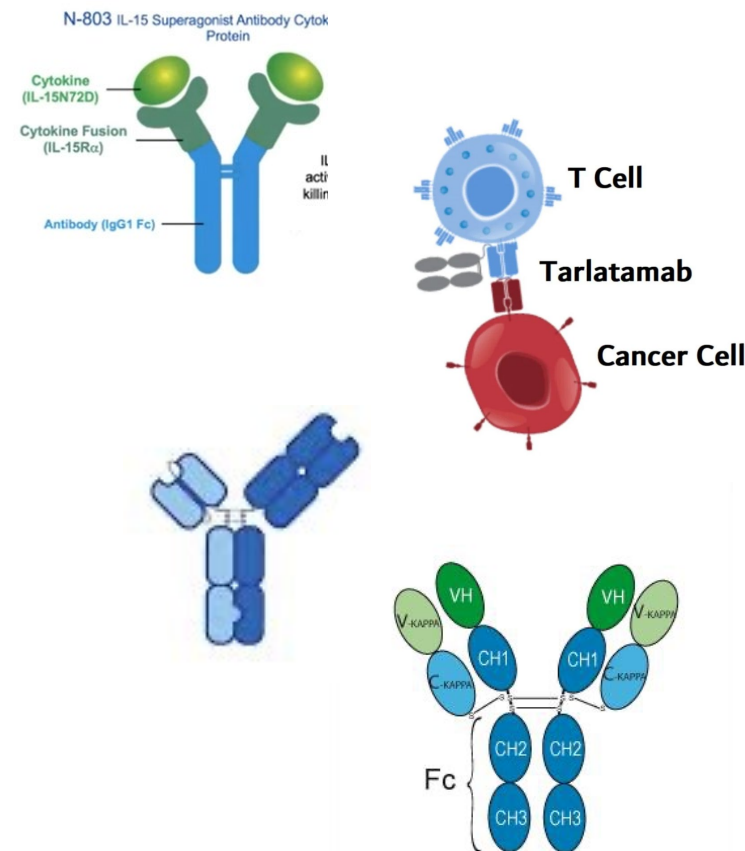
ADC

- zolbetuximab-clzb: Vyloy: anti-CLDN18.2 for GI cancer

化学

Tovorafenib: Ojemda for pediatric low grade glioma

- Vorasidenib: Voranigo for astrocytoma/oligodendroglioma
- Lazertinib: Lazcluze for lung cancer
- Inavolisib: breast cancer
- Ensartinib: lung cancer



米国FDAは、2024年に7個はエンジニアタンパクを承認

- tislelizumab-jsgr: Tevimbra, **enzyme** for subcutaneous injection of PD-L1
- nogapendekin alfa inbakicept-pmln : Anktiva, **cytokine IL-15** for bladder cancer
- tarlatamab-dlle: Imdeltra, **bispecific** ab for lung cancer
- Zanidatamab: **modified HER2** for biliary tract cancer
- zenocutuzumab-zbco: Her2 and HER3 **bi-specific**
- Cosibelimab-ipdl: **modified anti-PD-L1** for cScc

ADC

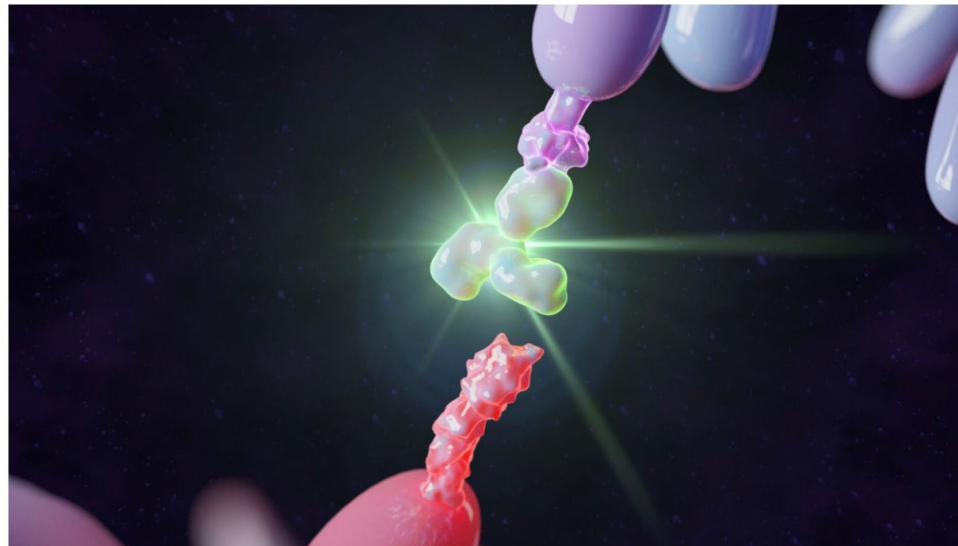
- zolbetuximab-clzb: Vyloy: anti-CLDN18.2 for GI cancer

去年、Bispecific抗体がゴールドラッシュに

STAT+ | BIOTECH

Cancer therapy's new 'gold rush': bispecific antibodies that hit key combination of targets

Summit and BioNTech results raise hope of new 'broad, pan-tumor platform' like Keytruda



Bispecific antibodies that bind to a PD-1 molecule as well as a VEGF protein have shown promise against cancers. Adobe

CANCER
BRIEFING

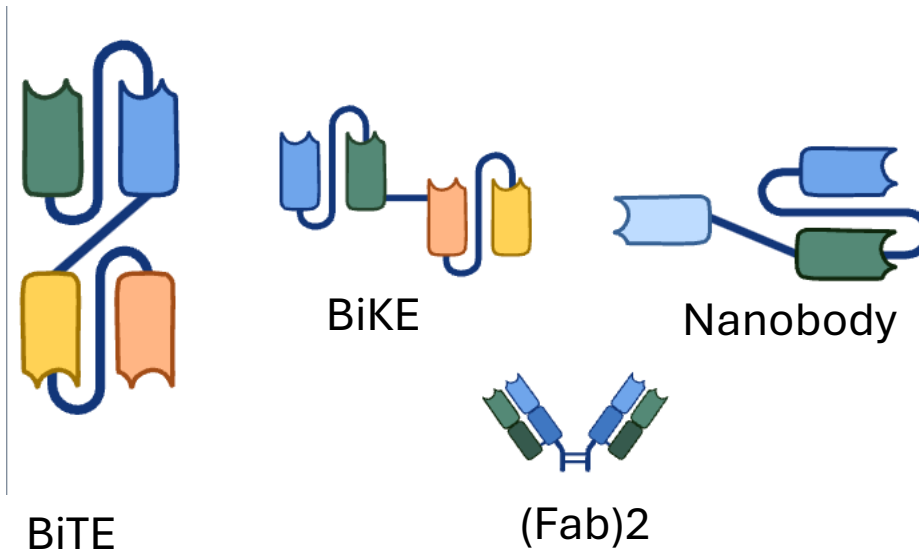
NEWSLETTER

Critical updates on the
world of cancer re
treatment, and pati

SIGN UP

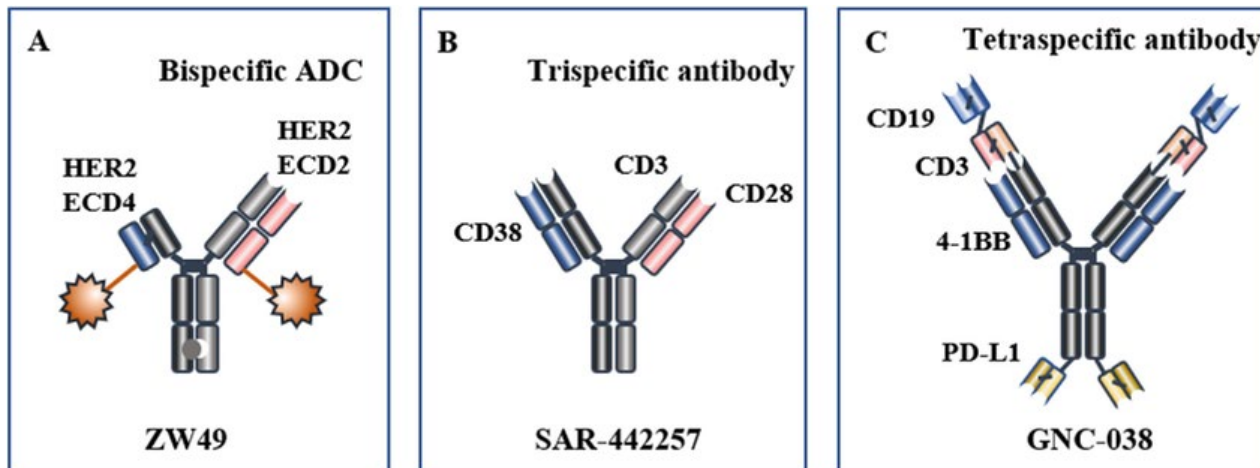
MOST POPULAR

エンジニアリングで多様化する抗体の形

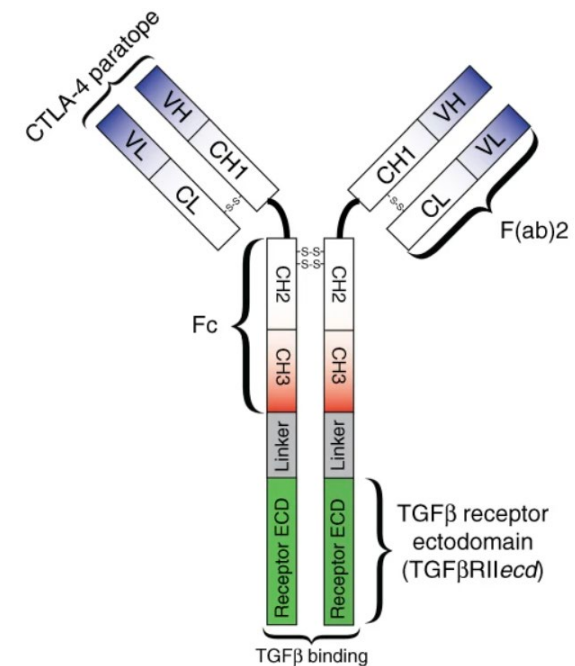


Full bispecific antibody

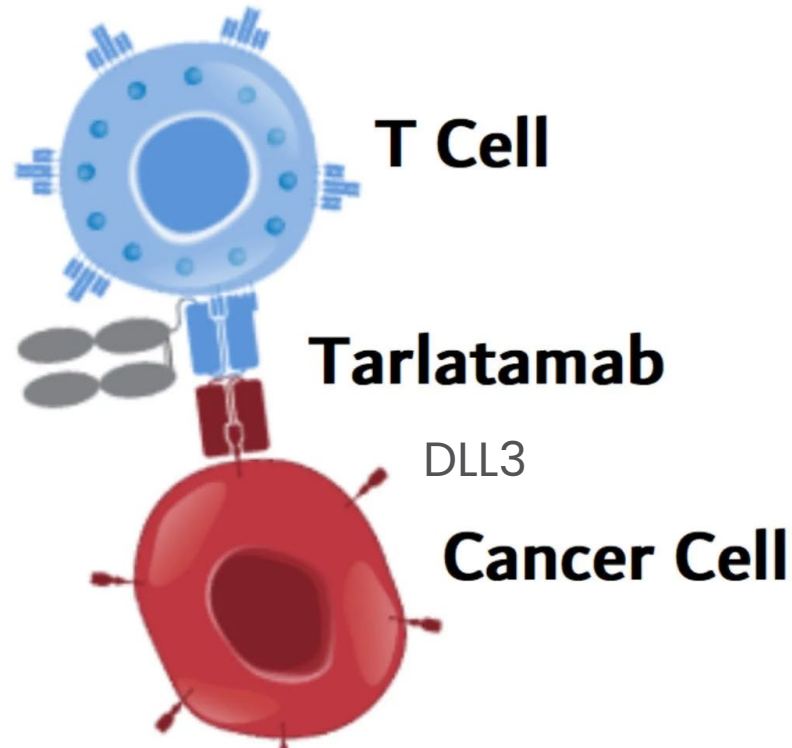
Blinatumomab: CD19xCD3



a α -CTLA4-TGF β R11ecd 抗体—受容体結合型



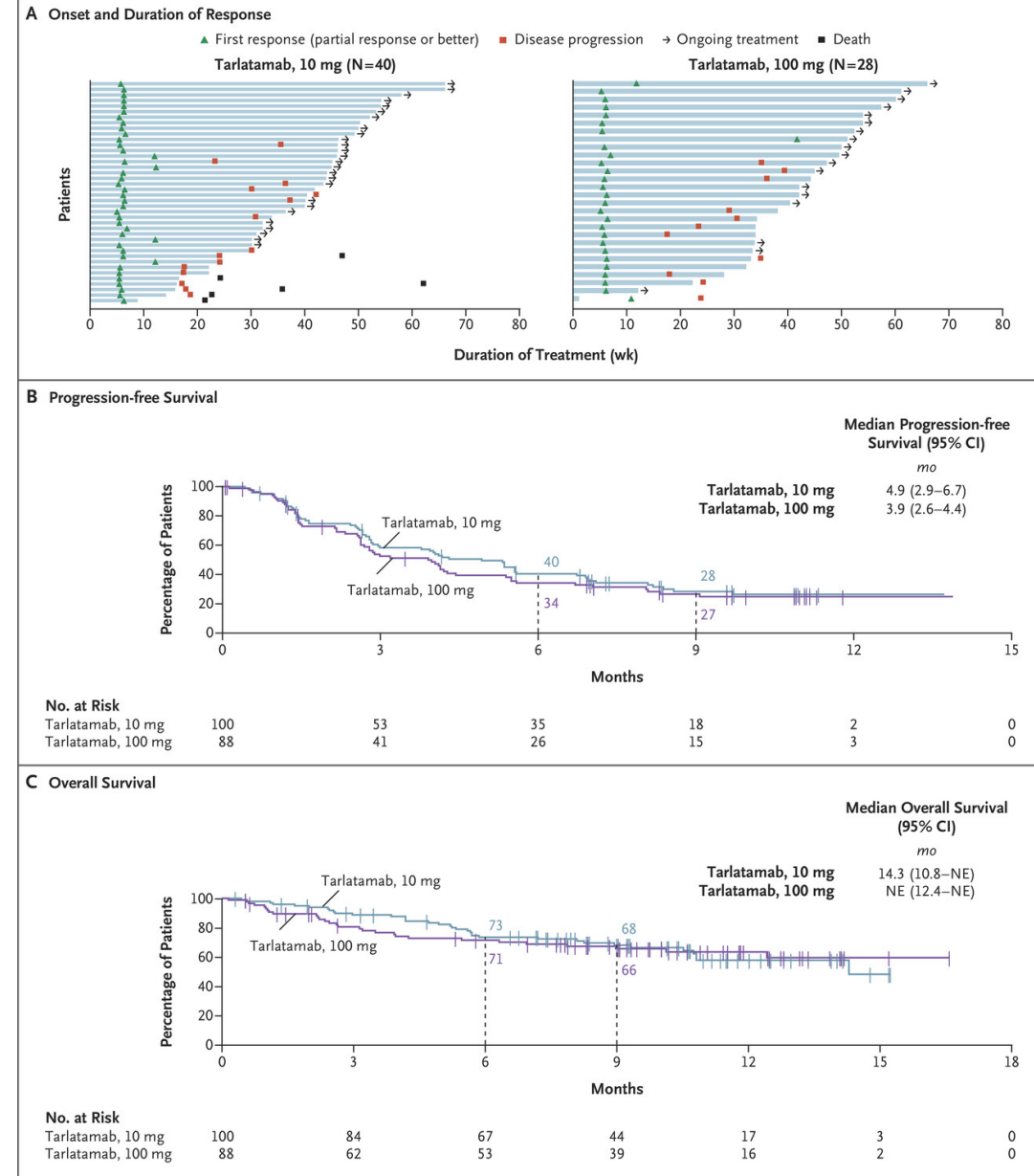
肺がんに対するTarlatamab (BiTE) のFDA承認



extensive-stage small cell lung cancer (ES-SCLC)

Tarlatamab is a bispecific T-cell engager (BiTE), a two-armed drug that simultaneously latches onto tumor cells and T cells, bringing them close together and helping the T cells recognize and destroy cancer cells.

Credit: Adapted and used with permission from Amgen



Non-Muscle Invasive Bladder Cancer に対するANKTIVA（IL-15改変サイトカイン）のFDA承認

Efficacy Profile

Complete Response^{1,2}

62%

N=77¹

(FDA Efficacy Population)

71%

N=82²

(NEJM Evidence)

Cystectomy Free at 24 Months²

84%

Overall Survival at 24 Months²

94%

Prolonged Duration of Response

Range of DoR¹

47+ Month & Ongoing

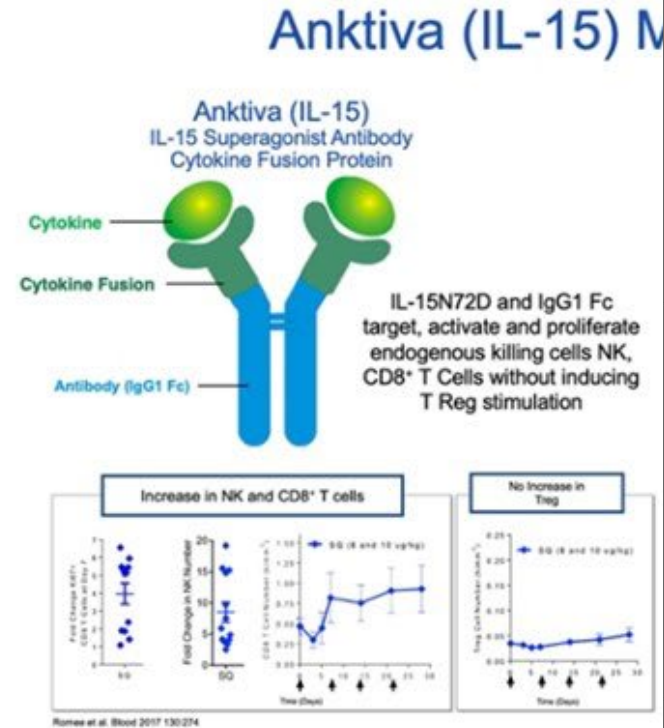
% with duration ≥12 months¹

58%

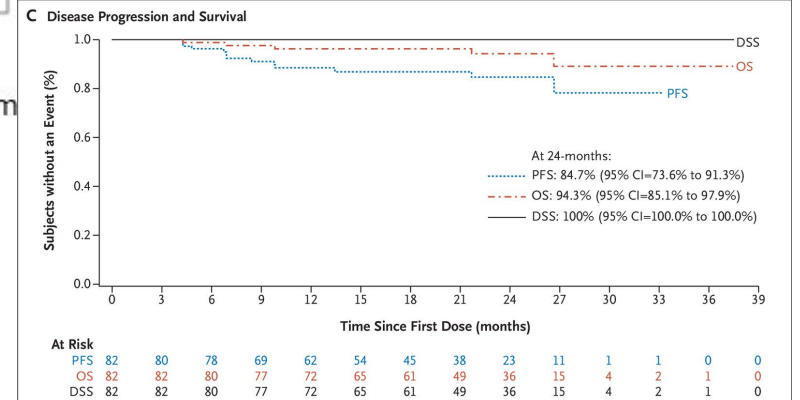
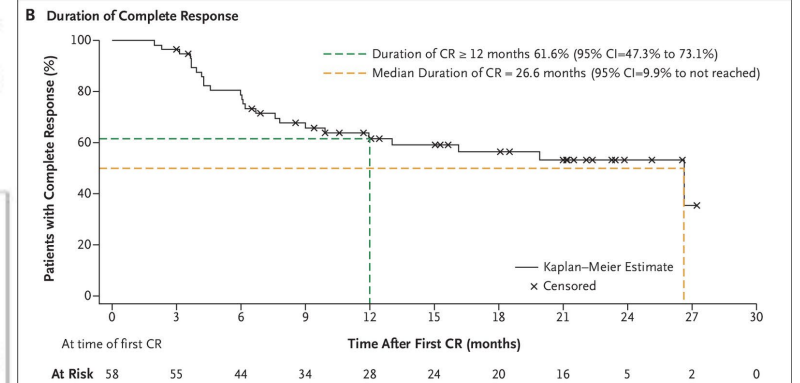
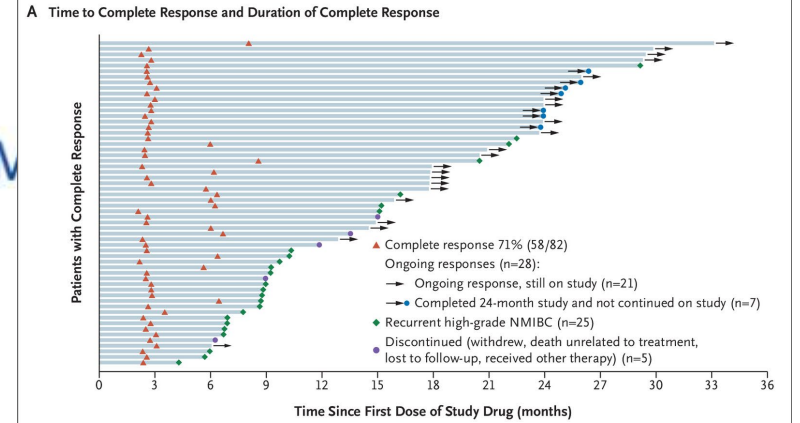
(Exceeds IBCG Recommendations³)

% with duration ≥24 months¹

40%



ANKTIVA (N803) comprises mutated (N72D) hum



膀胱への局所注射で

改変抗体、改変サイトカインが創薬の主流に

今までの創薬

癌で発現が高い → 抗体を作ろう
新しい分子見つけた → 治験で試そう

これからの創薬

抗体Aの改善点 → 改変抗体Aを作ろう

想像力、創造力、勇気、資金、実験、多角的視点、異分野のエキスパートが必要

ADC, Bi-specific antibody and IL-15 became very hot

Passive targeting

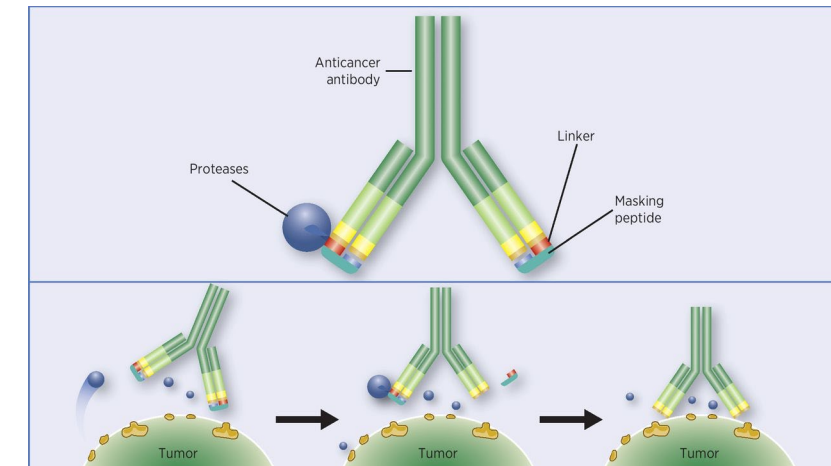
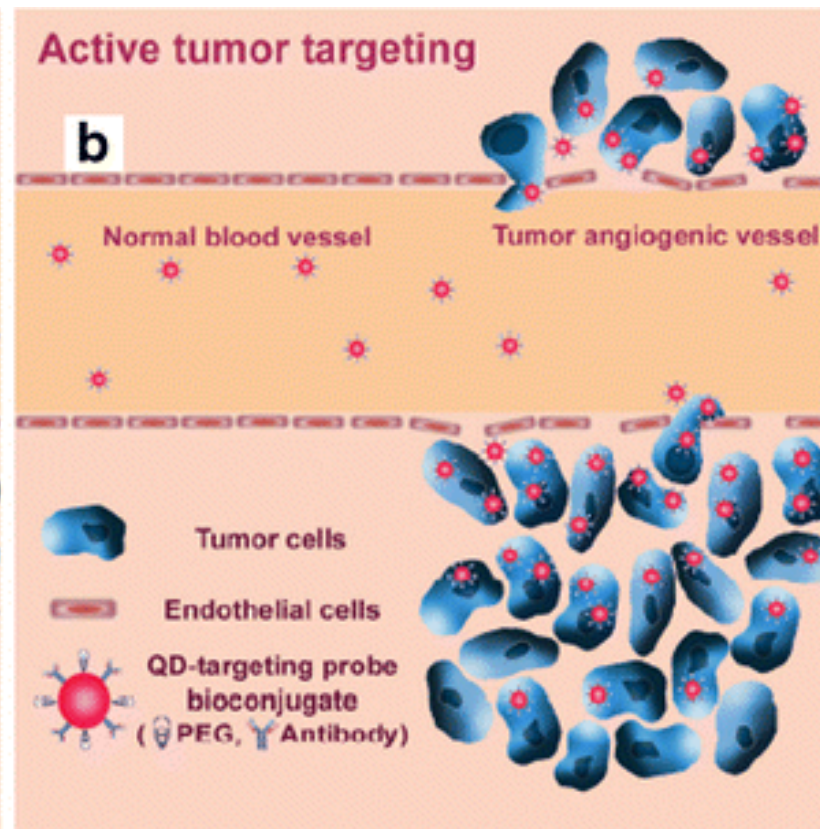
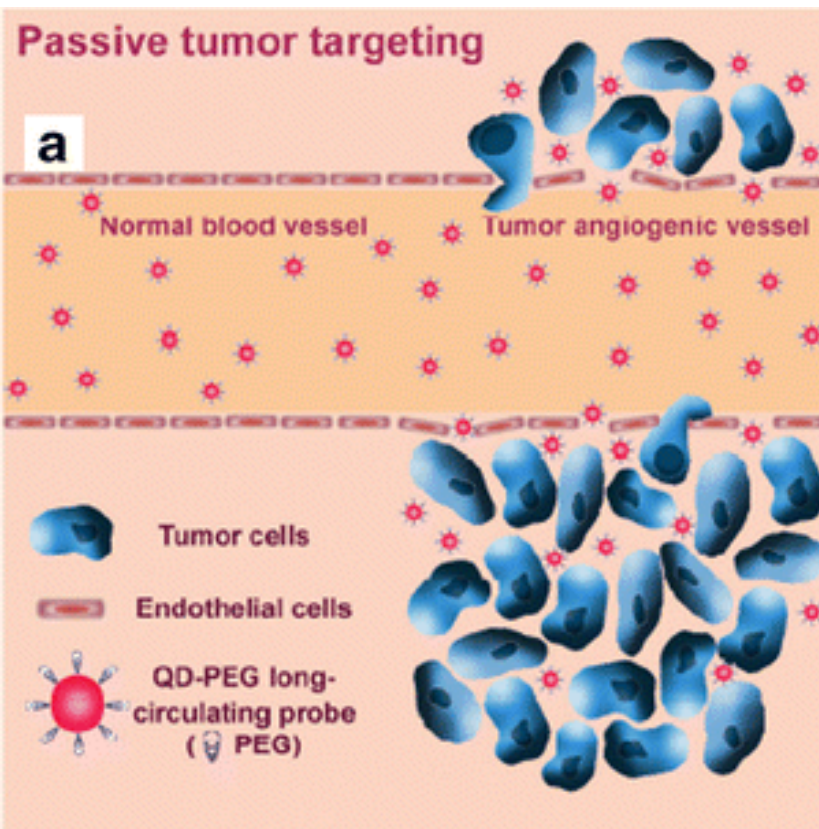
Increasing blood concentration of drugs

Active targeting

Binds to cancer specific molecules

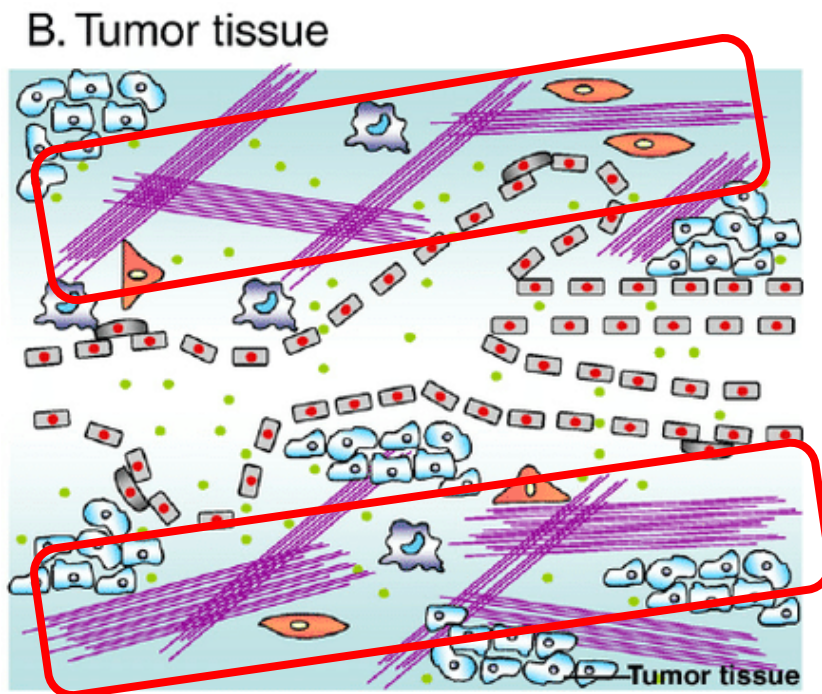
Pro-drugs

Binding site is masked and exposed by cancer enzyme



Idea: 癌の細胞外マトリクスを薬の貯蔵庫にする

どんな癌でも固形癌であれば必ずECMは存在



Extracellular matrix proteins

Danhier et al., J Control. Release 2010

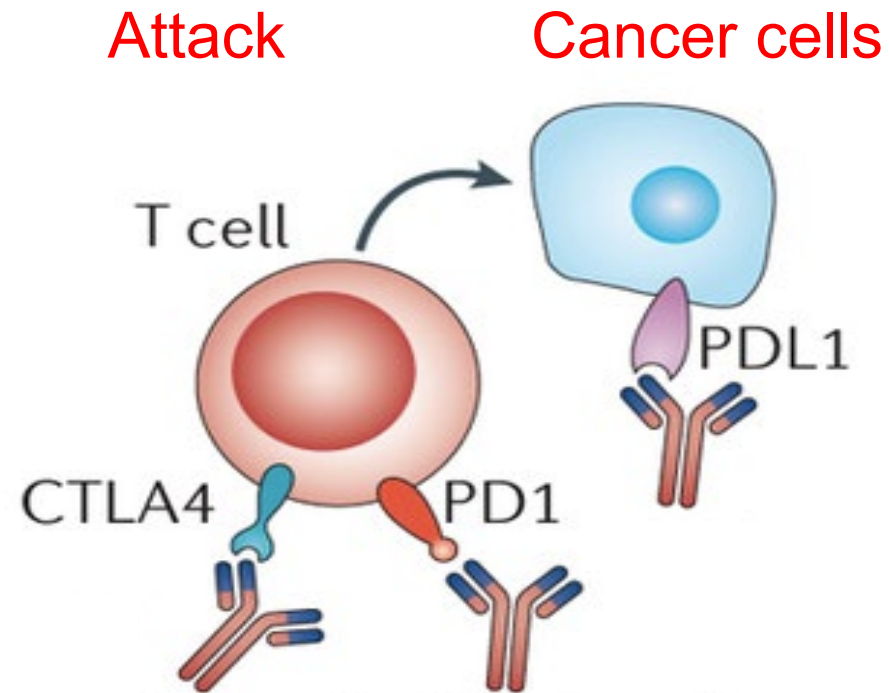
がん免疫療法：デザインに改善の余地あり

薬効
副作用
コスト
滞留性
投与ルート

Bioengineering to solve problems!!

Immune checkpoint inhibitor (CPI) for cancer therapy – breakthrough

Activates anti-tumor immunity
FDA approved in multiple cancer types



Immune checkpoint inhibitor (CPI) against melanoma in the clinic

Therapeutic efficacy (PD-1+CTLA4 combo)

Objective response rate: **58%**

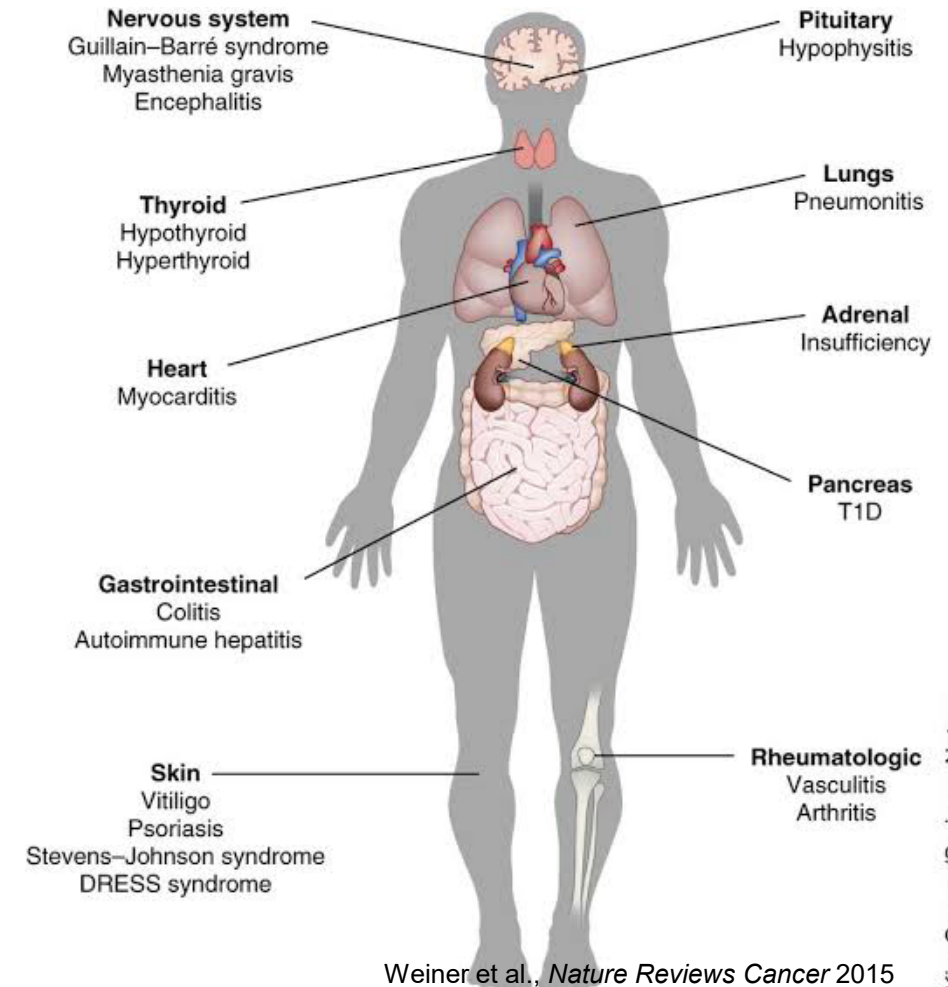
Complete response rate: **11%**

Adverse events

Any adverse events: **99%**

Patients discontinued the therapy: **36%**

Larkin et al., NEJM 2015



Need: Decrease side-effects and increase efficacy

Immune checkpoint inhibitor (CPI) against melanoma in the clinic

Therapeutic efficacy (PD-1+CTLA4 combo)

Objective response rate: 58%

Complete response rate: 11%

Adverse events

Any adverse events: 99%

Patients discontinued the therapy: 36%



Systemic immune activation occurs, but not necessarily in a therapeutic manner

Larkin et al., NEJM 2015

Minimal research focusing on solving CPI **toxicity** (Nat Med 2017)

Cause: systemic distribution of CPI.

→ **There is a need to target the tumor.**

Passive targeting

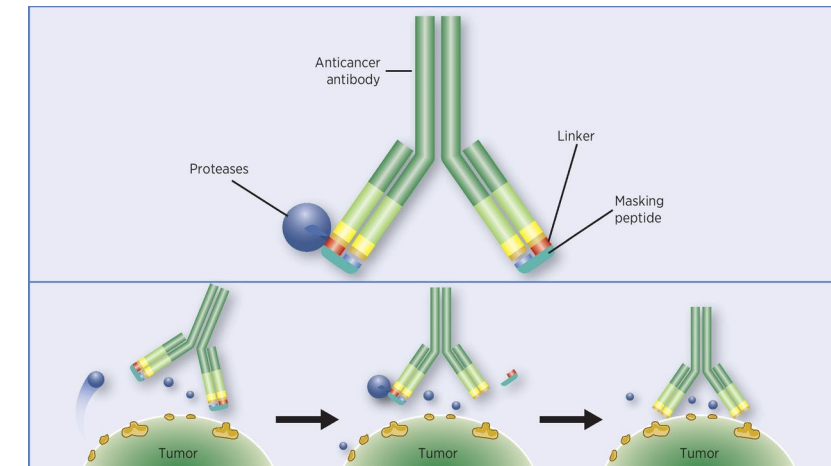
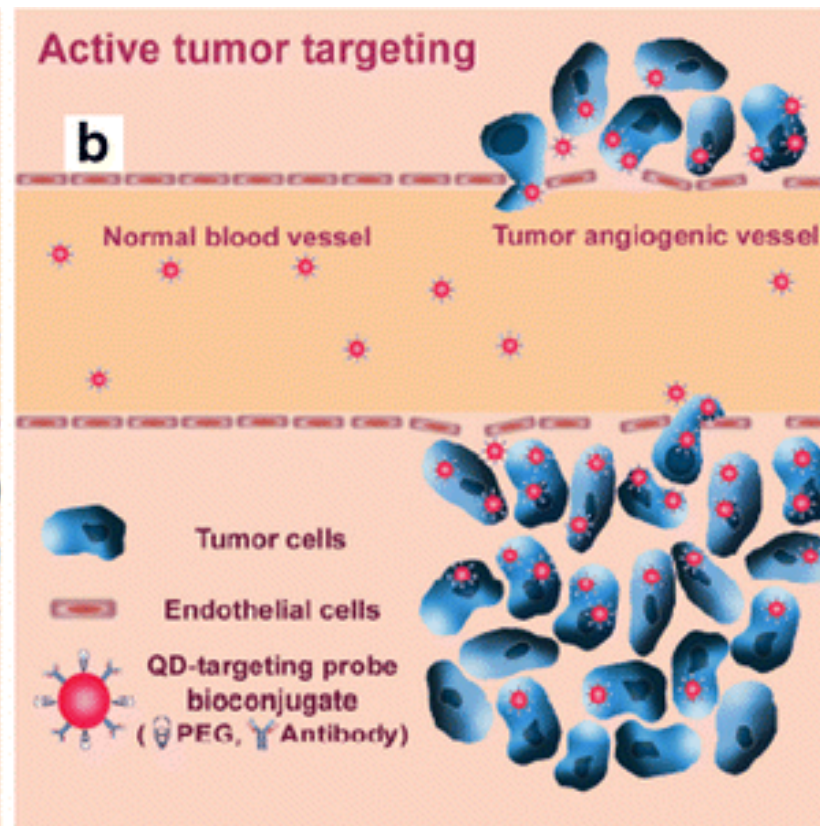
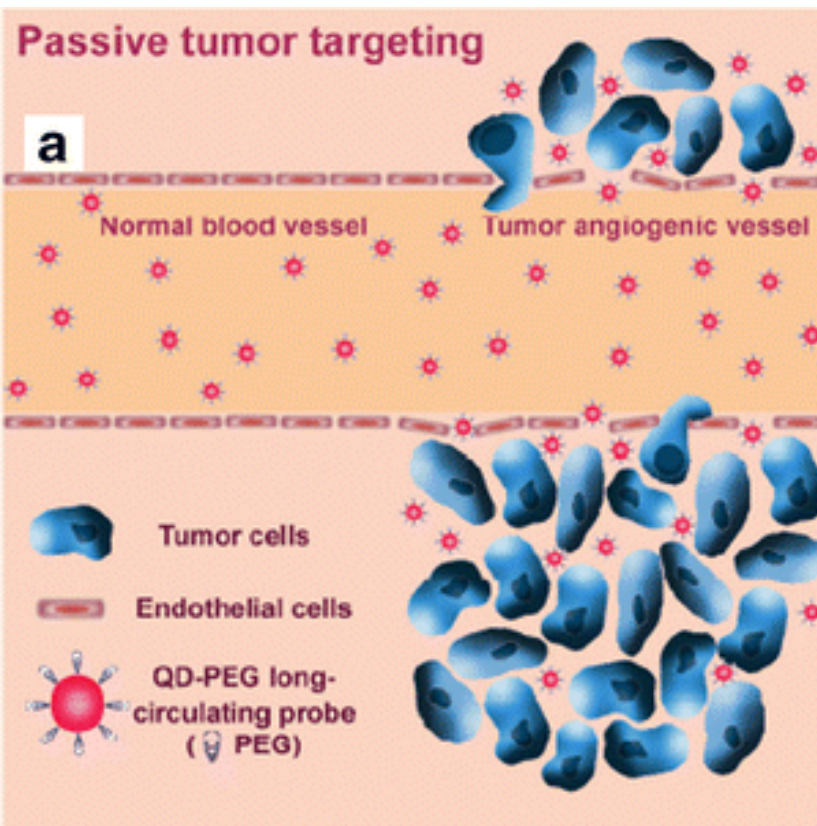
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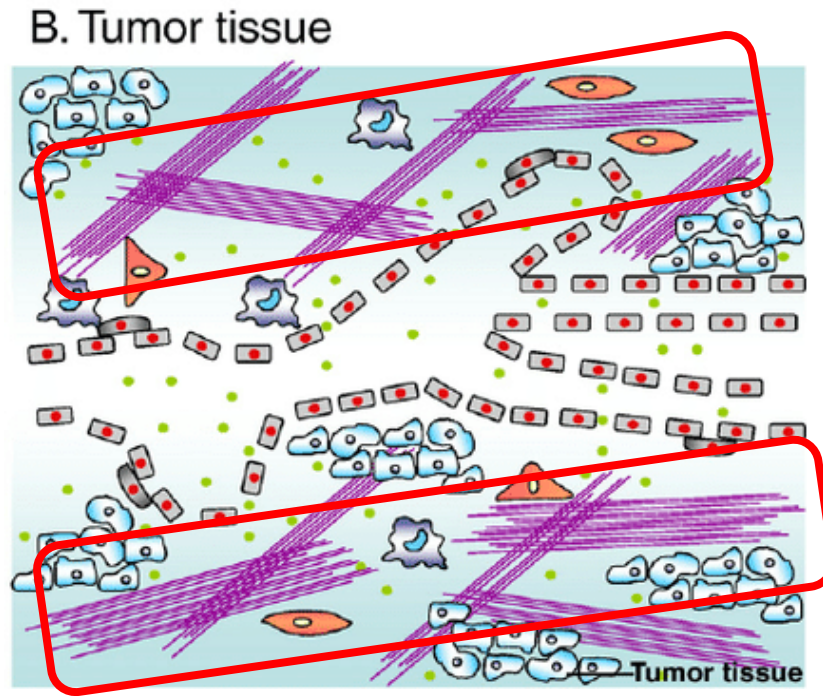
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Idea: 癌の細胞外マトリクスを薬の貯蔵庫にする

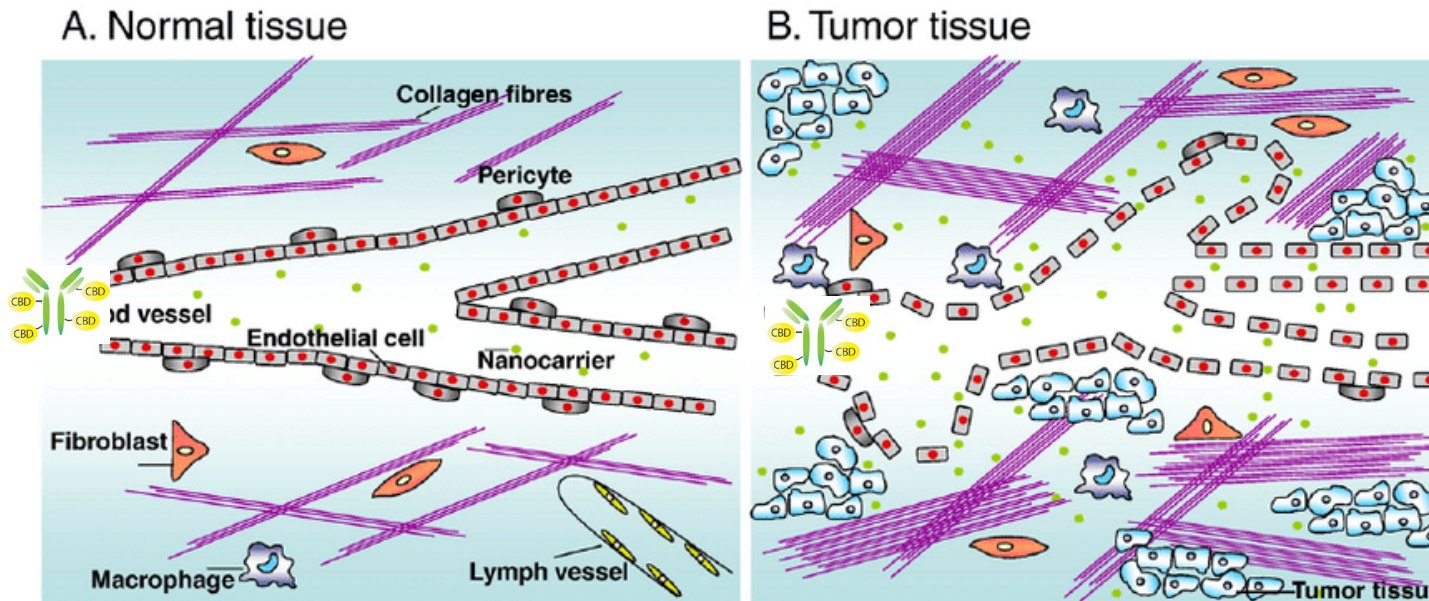
どんな癌でも固形癌であれば必ずECMは存在



Extracellular matrix proteins

Danhier et al., J Control. Release 2010

コラーゲンは癌の中でのみ、血中に露出されている

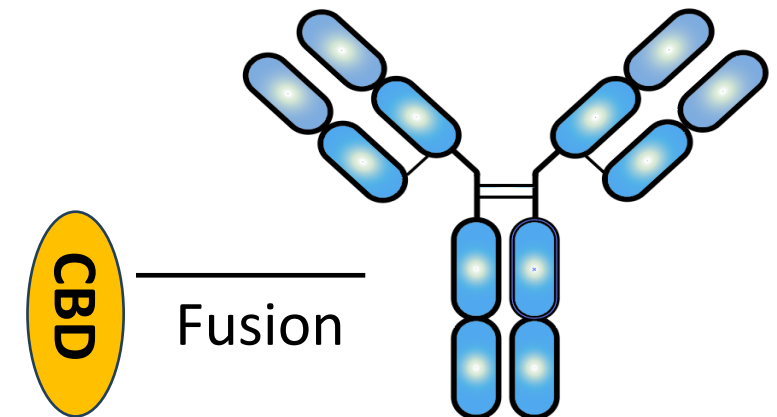


Danhier et al., J Control. Release 2010

Tumor:
Vasculature leakiness ↑

Collagen expression ↑

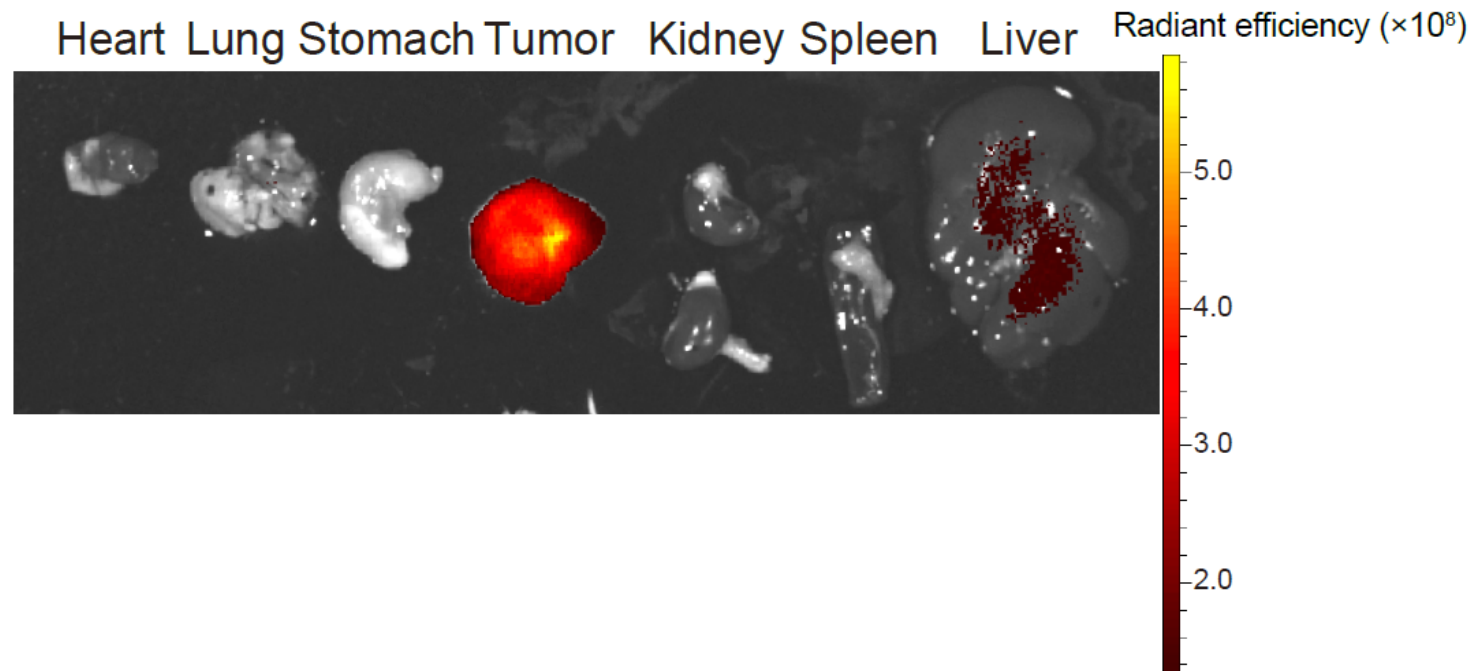
Von Willebrand Factor A3 domain由来
Collagen binding domain (CBD)
を免疫チェックポイント阻害剤に融
合させれば静脈注射で癌に集積？



CBD: the von Willebrand Factor A3 domain.

静脈注射したコラーゲン結合ドメイン（CBD）は癌に集積

MMTV-PyMT tumor	Dylight800 CBD	Euthanize Imaging
	0	48 hr

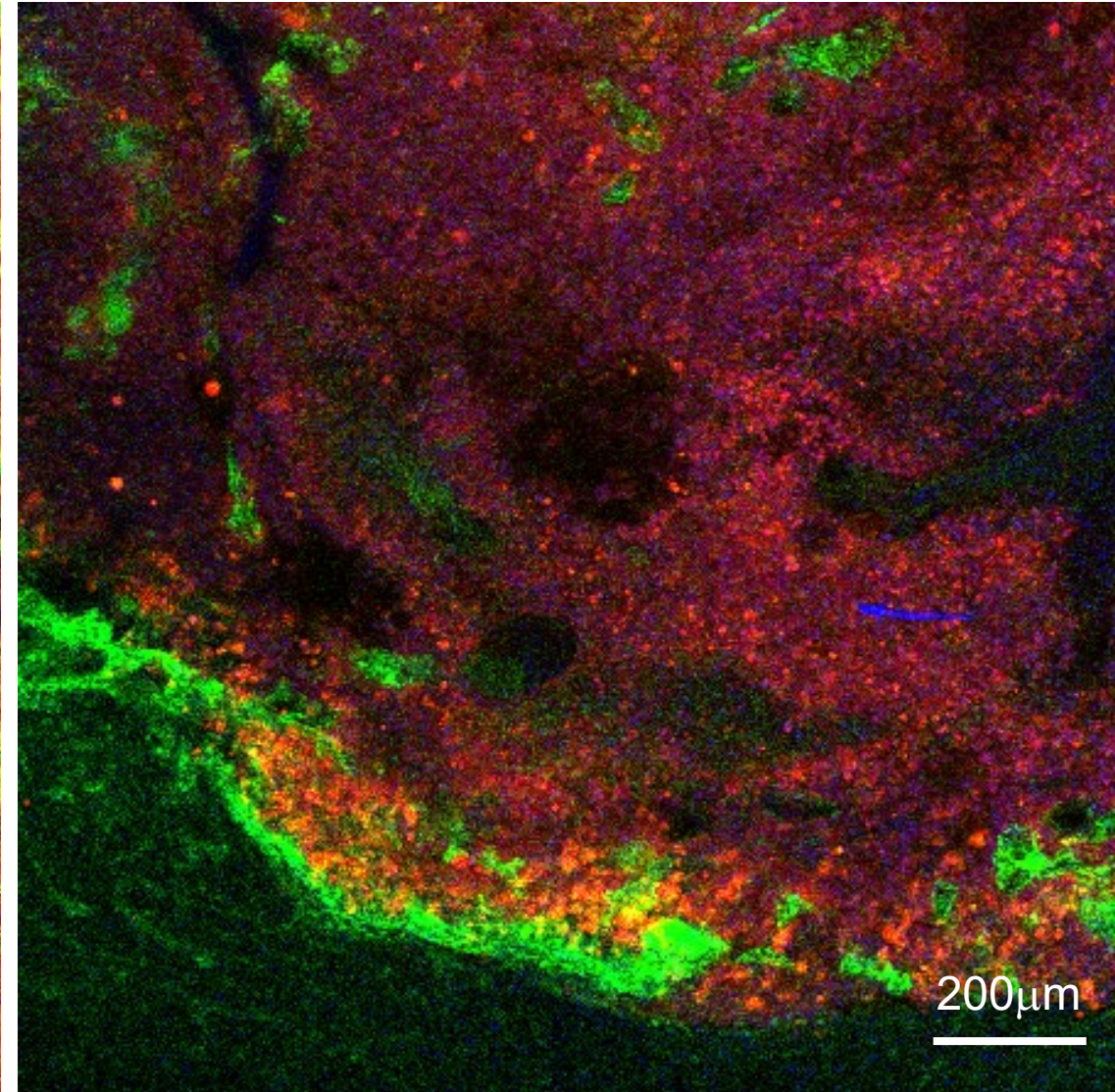
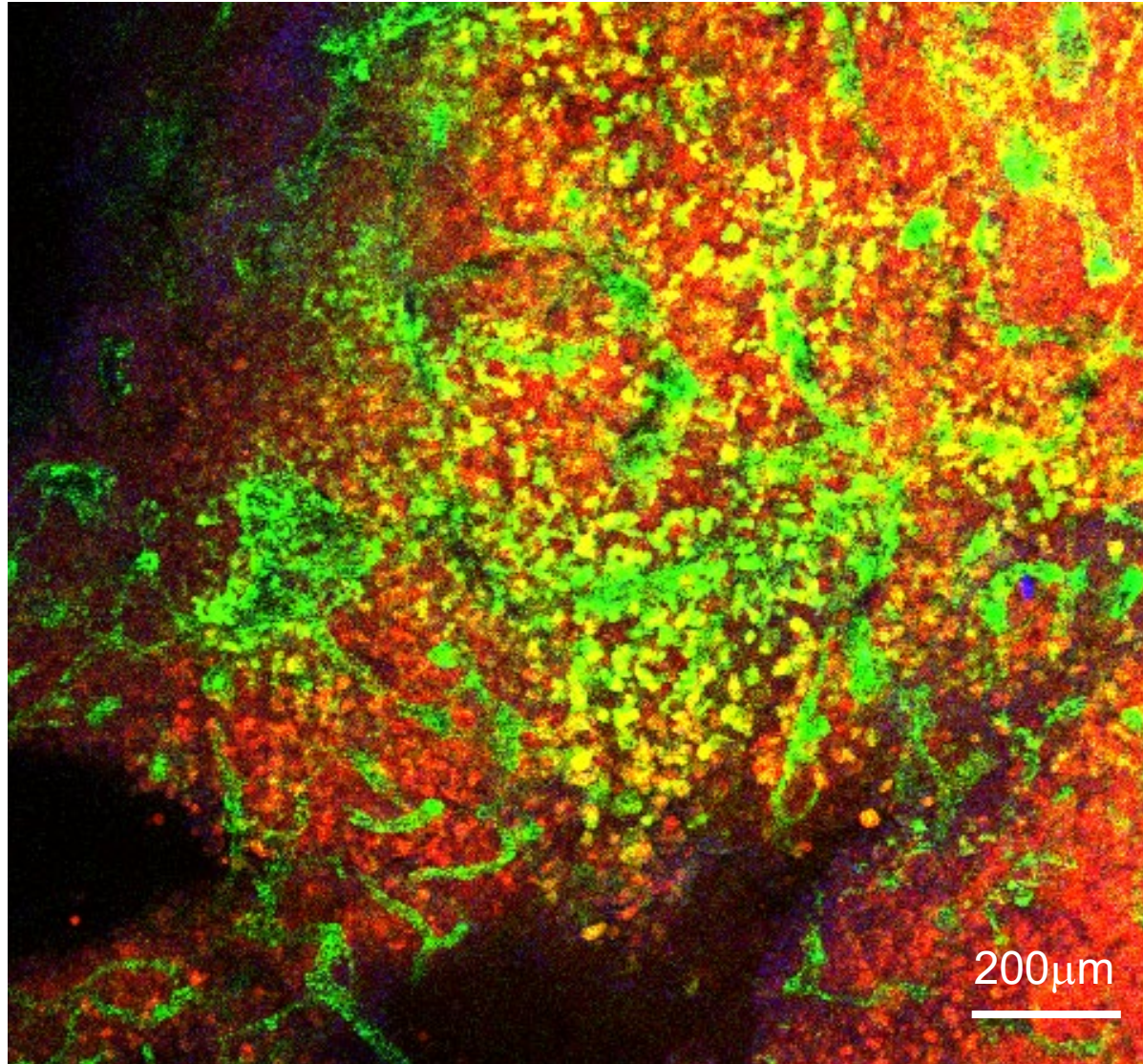


CBD-antibody は腫瘍内に集積

CBD-antibody treatment

antibody treatment

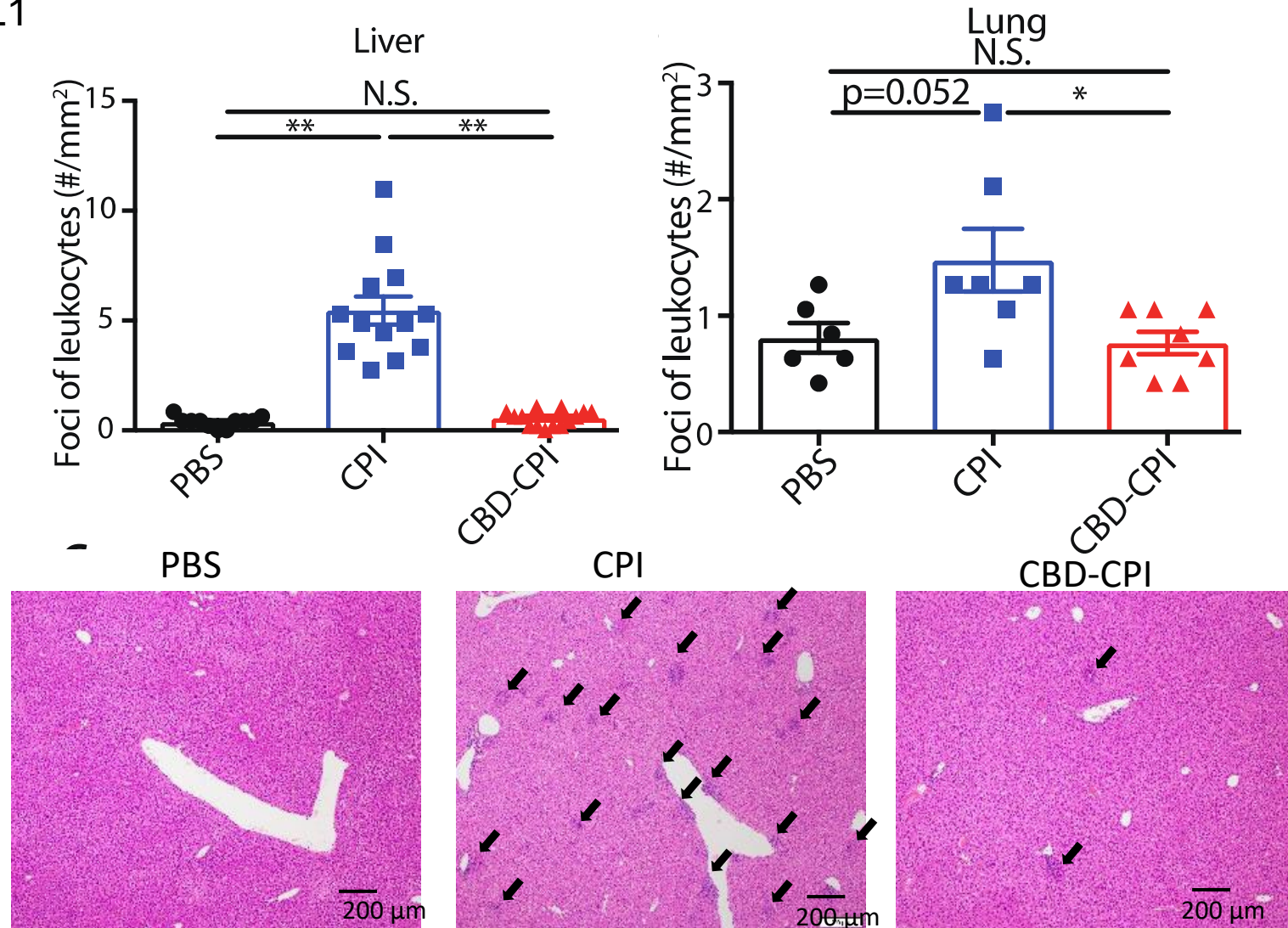
Nuclei / mCherry (tumor) / Alexa 647 (α GITR)



CBD融合させると、免疫チェックポイント抗体は副作用を低減

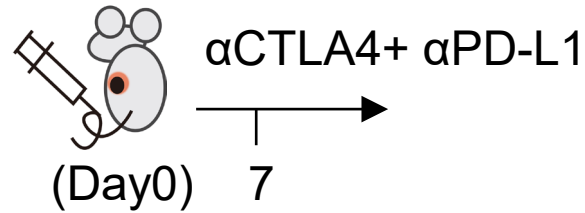
副作用：肝臓と肺へのリンパ球浸潤

CPI: α CTLA4 + α PD-L1

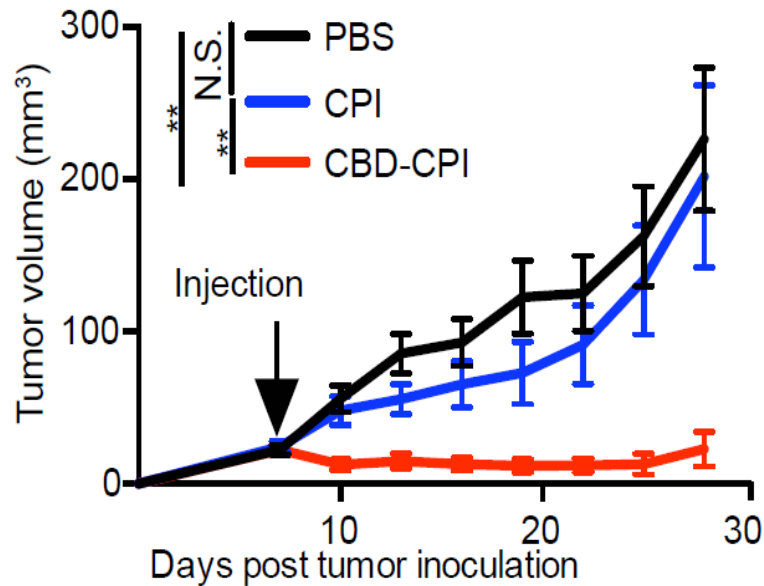


CBD融合させると、免疫チェックポイント抗体は薬効を上昇

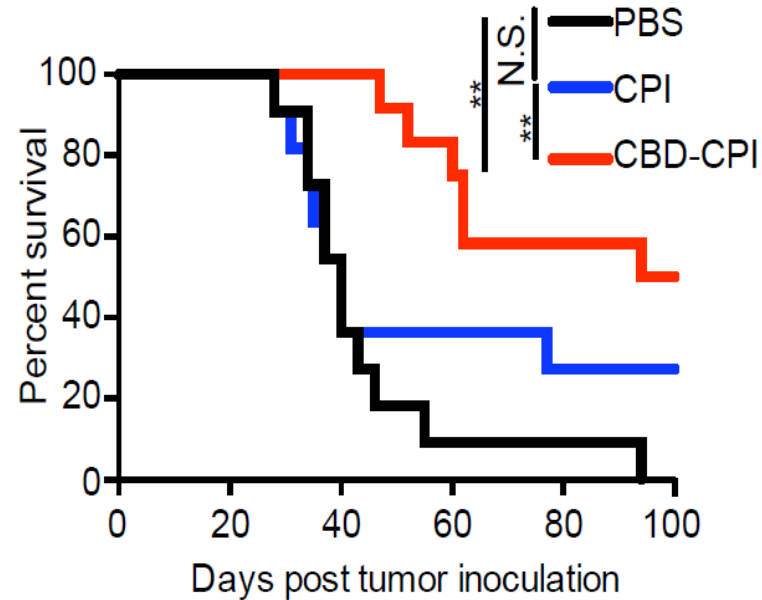
MMTV-PyMT: breast cancer



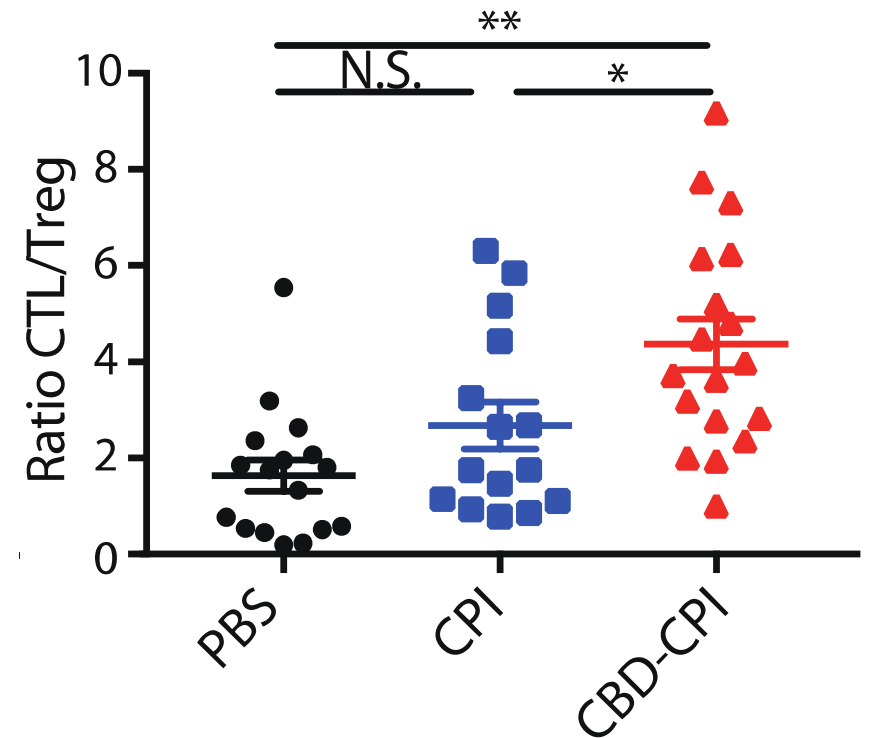
MMTV-PyMT breast cancer



MMTV-PyMT breast cancer



癌の中で免疫の活性化
Effector memory CD8^+ /Treg

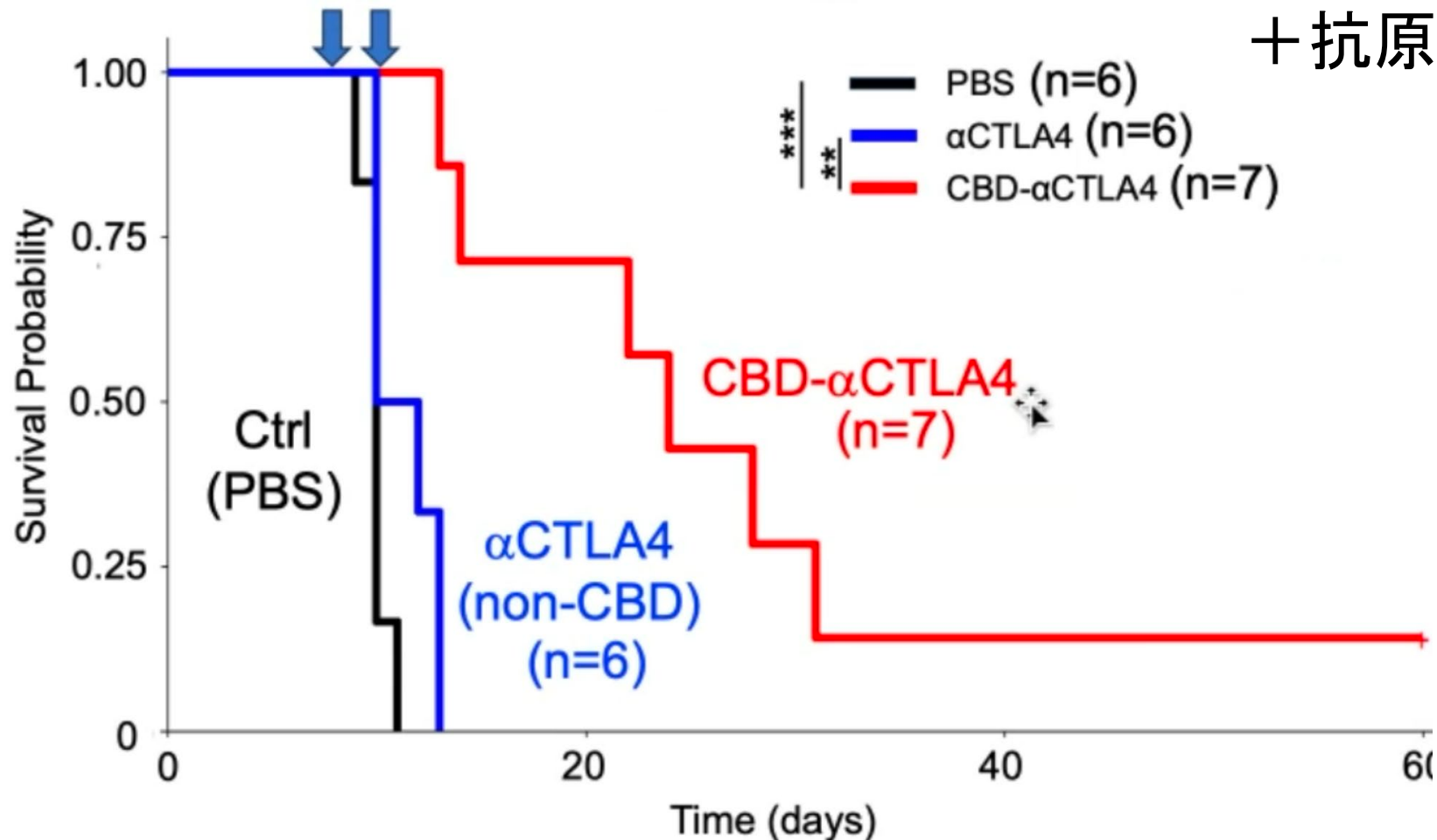


CBD融合は薬効も副作用も改善させる

CBD融合させると、脳腫瘍でもCTLA4抗体は薬効を上昇

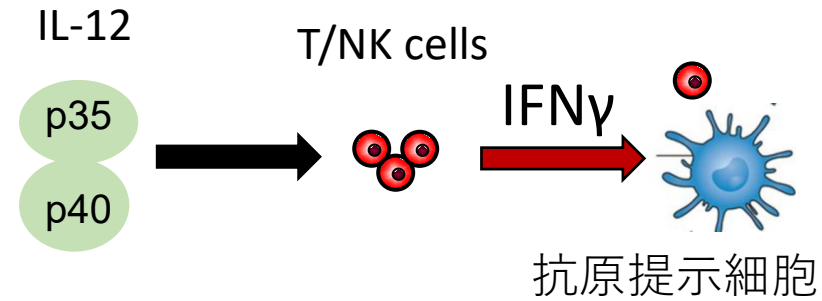
脳腫瘍 GBMモデル

CBD New : 腫瘍内のTregを除去
+ 抗原提示細胞の活性化



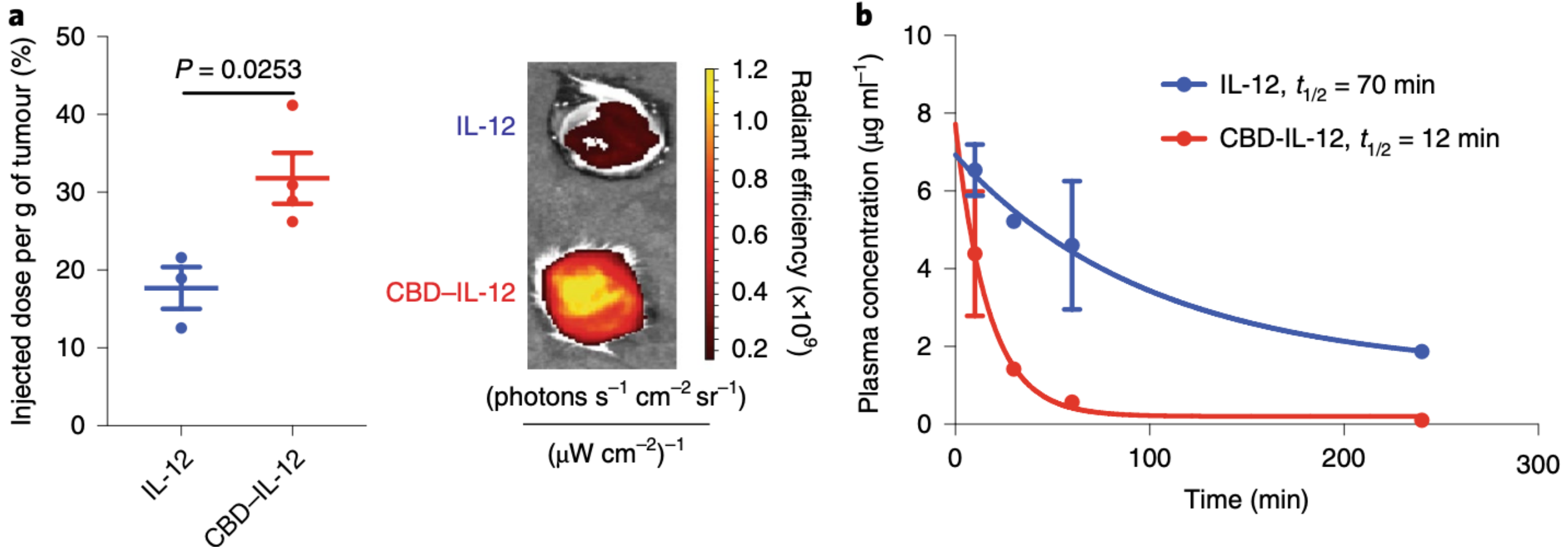
サイトカインIL-12の腫瘍ターゲット

IL-12 – 強力な抗癌サイトカイン



- T/NK 細胞に働いてIFN γ を産生させる
- 抗がん活性が高い
- 毒性が高い

CBD-IL-12 quickly accumulates to the tumor with shorter blood half-life

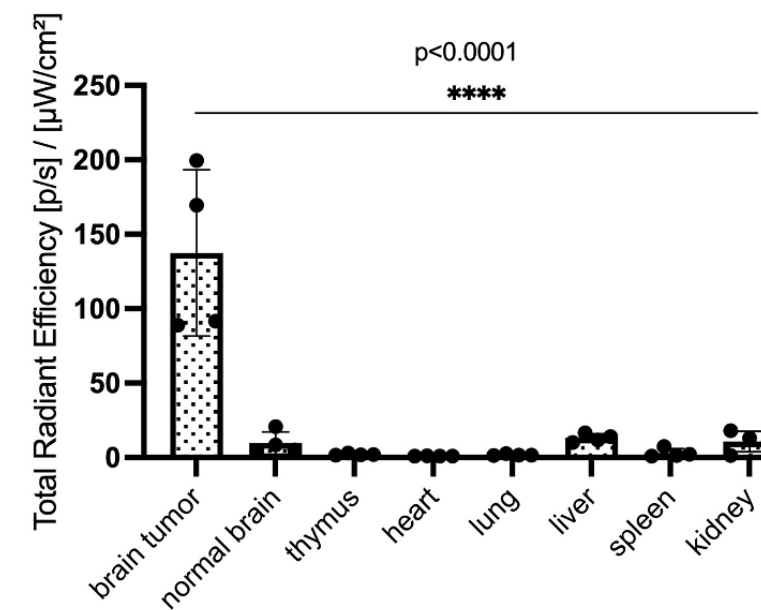
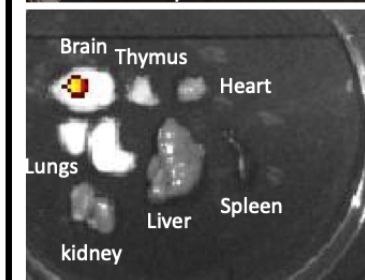


CBD-IL-12 はコラーゲンIII依存的に 癌に局在。脳GBMモデル

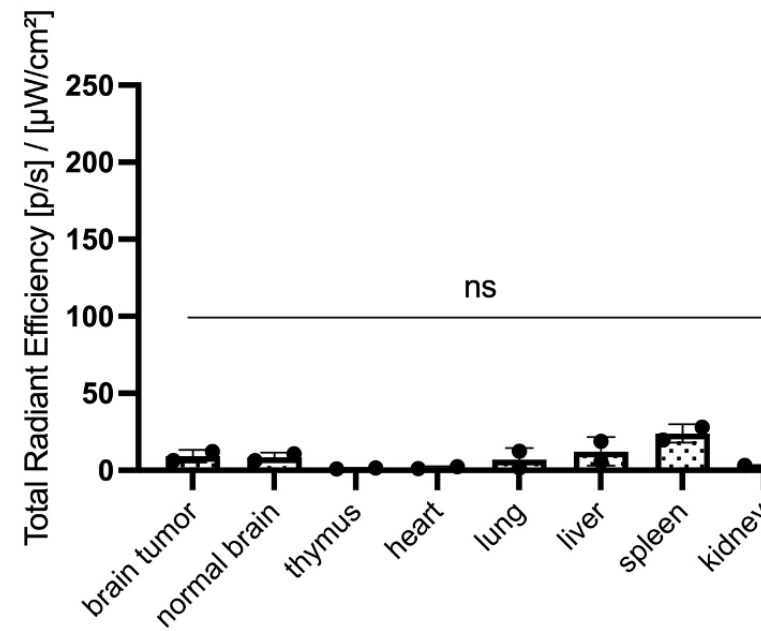
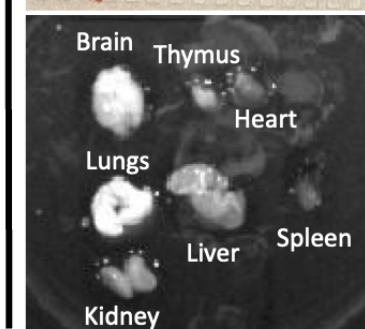
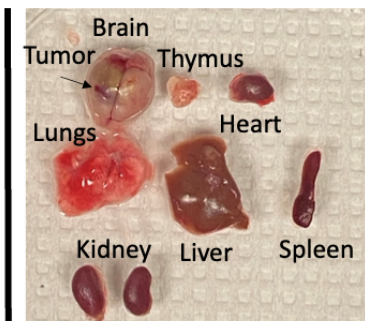
Orthotopic model of GBM

- Alexa647-tagged CBD-IL-12
- imaging at 1 hr post-tail vein injection

GBM



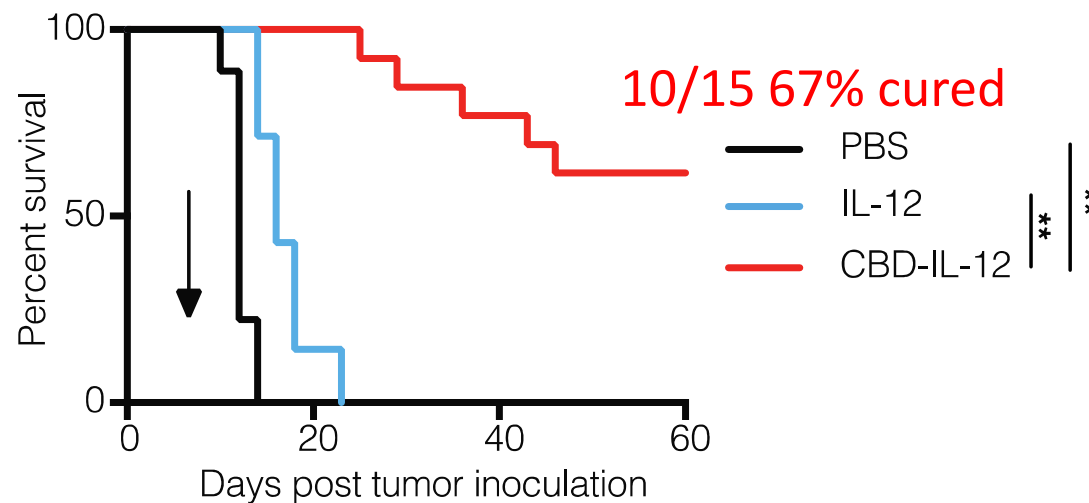
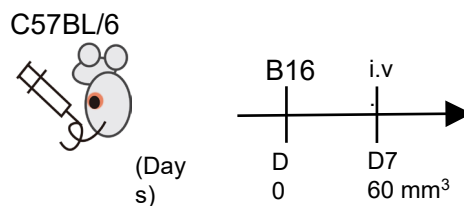
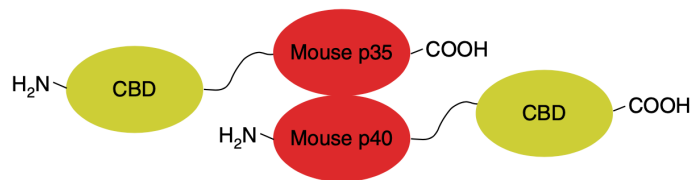
GBM
COLIII
KO



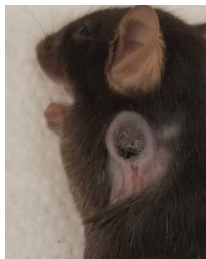
0 Fluor 5 x 10⁹

CBD-IL-12は一回の静脈注射でB16皮膚癌を治すことができた

Day7 B16F10: antigen non-specific approach to cure



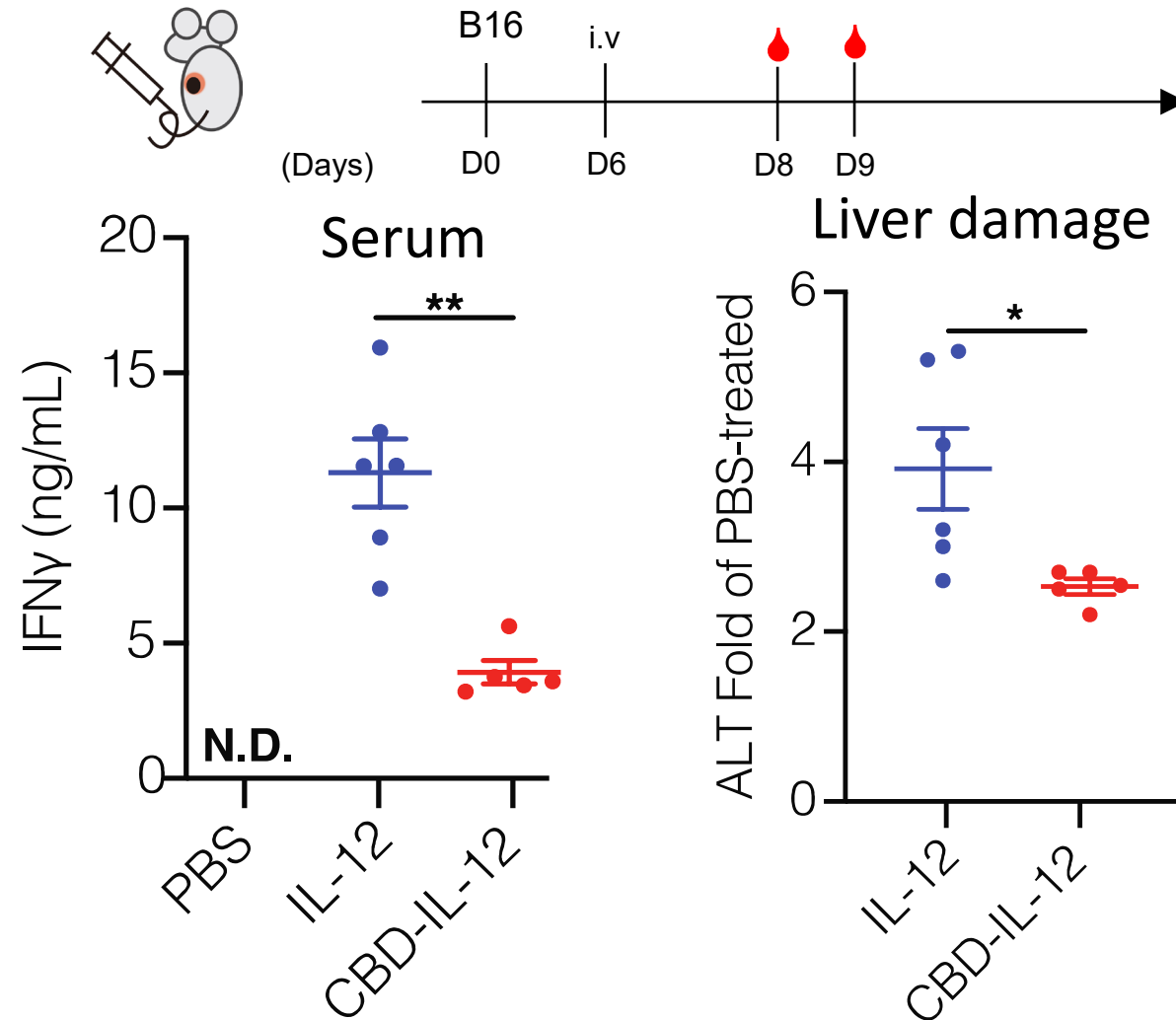
Day 9 B16F10 After CBD-IL-12



脳腫瘍
頭頸部癌
肺がん
乳がん
肝臓癌
膵臓癌
大腸癌
サルコーマ
前立腺癌
卵巣がん
皮膚癌
転移腫瘍
再発腫瘍

Mansurov* and J. Ishihara*# et al, Nature Biomedical Engineering, accepted

CBD-fusion decreases systemic toxicity of IL-12



Human CBD-IL-12 demonstrates target engagement and is safe at 15 $\mu\text{g}/\text{kg}$ healthy beagles



- 1 $\mu\text{g}/\text{kg}$ human CBD-IL-12 (n = 2 male beagles), completed
 - 5 $\mu\text{g}/\text{kg}$ human CBD-IL-12 (n = 2 male beagles), ongoing
 - 15 $\mu\text{g}/\text{kg}$ human CBD-IL-12 (n = 2 male beagles), ongoing
- Intravenous treatment on days 0 and 14.

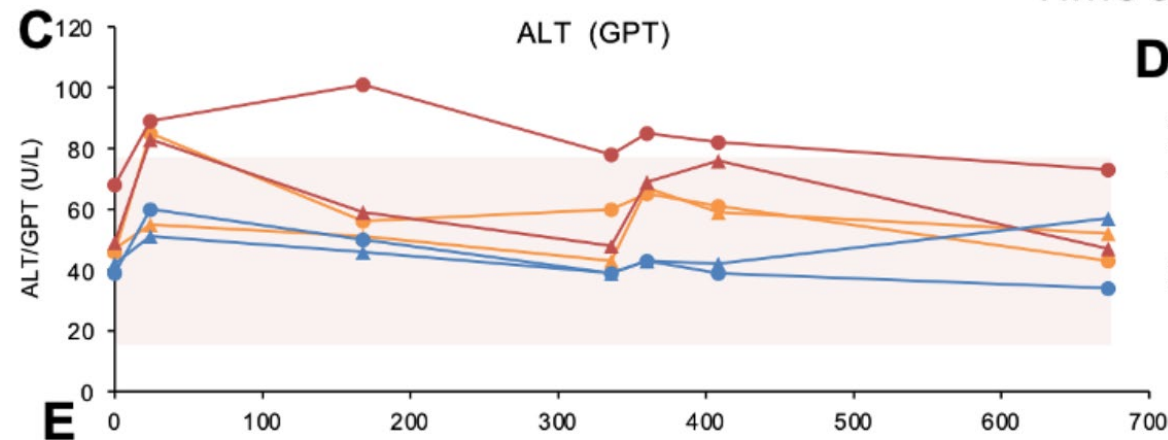
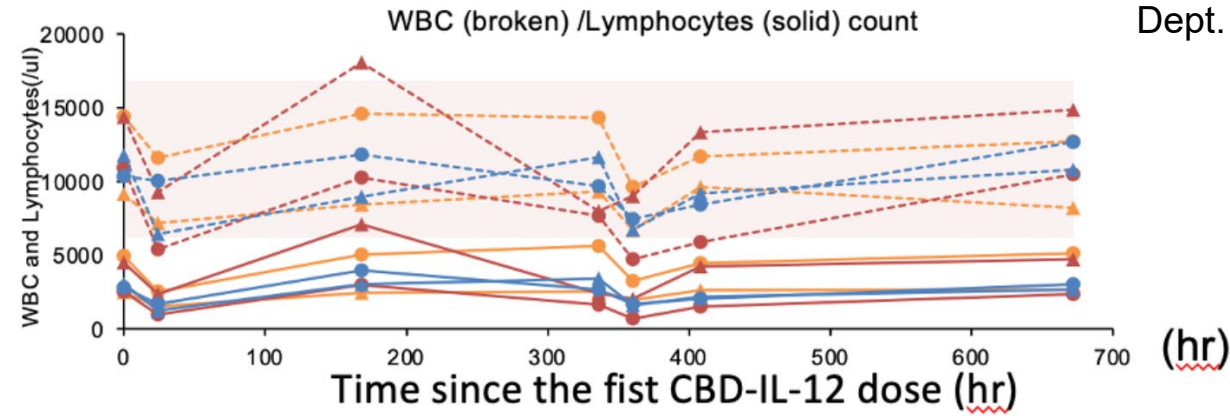


YAMAGUCHI
UNIVERSITY



Collaboration with Prof. Mizuno
Dept. Chair of Veterinary Medicine

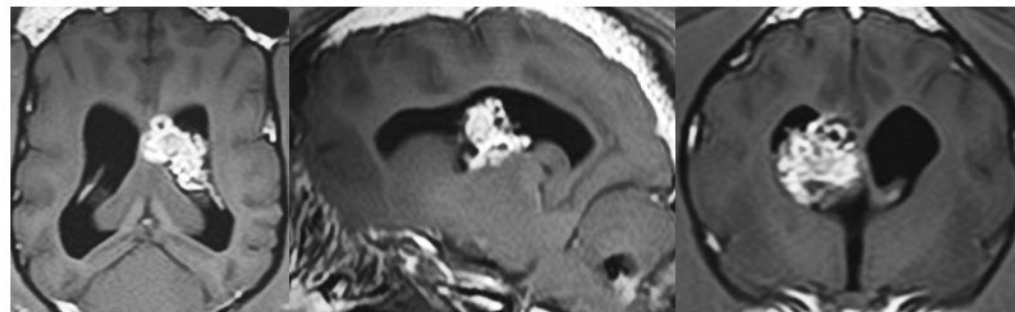
—●— No.3_1 $\mu\text{g}/\text{kg}$
—▲— No.4_1 $\mu\text{g}/\text{kg}$
—▲— No.1_5 $\mu\text{g}/\text{kg}$
—●— No.6_5 $\mu\text{g}/\text{kg}$
—▲— No.2_15 $\mu\text{g}/\text{kg}$
—●— No.5_15 $\mu\text{g}/\text{kg}$



Five melanoma bearing dogs were treated

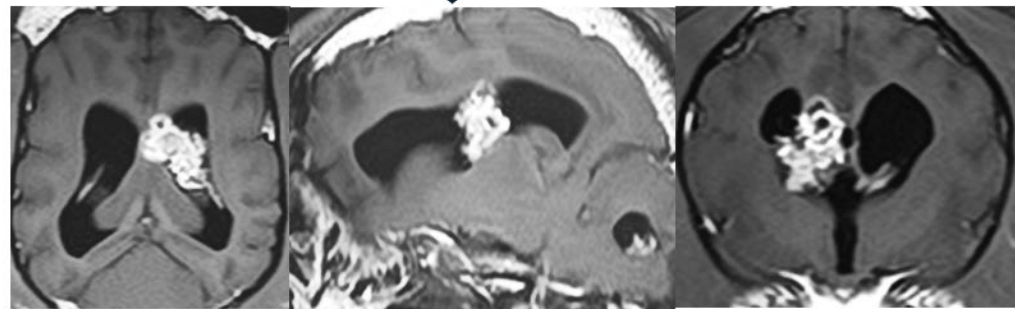
CBD-IL-12 : 犬の脳腫瘍での 薬効の確認

Primary
tumor



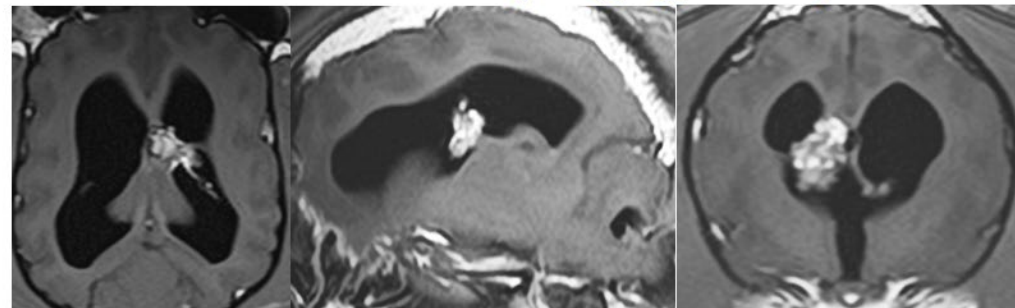
↓ IR (5.5Gy x 6; total 33Gy, Day 36-71)

Post-
irradiation
(Day189)



↓ CBD-IL-12
(15ug/kg, i.v. day 213 and 227)

Post-
CBD-IL-12
(Day 371)



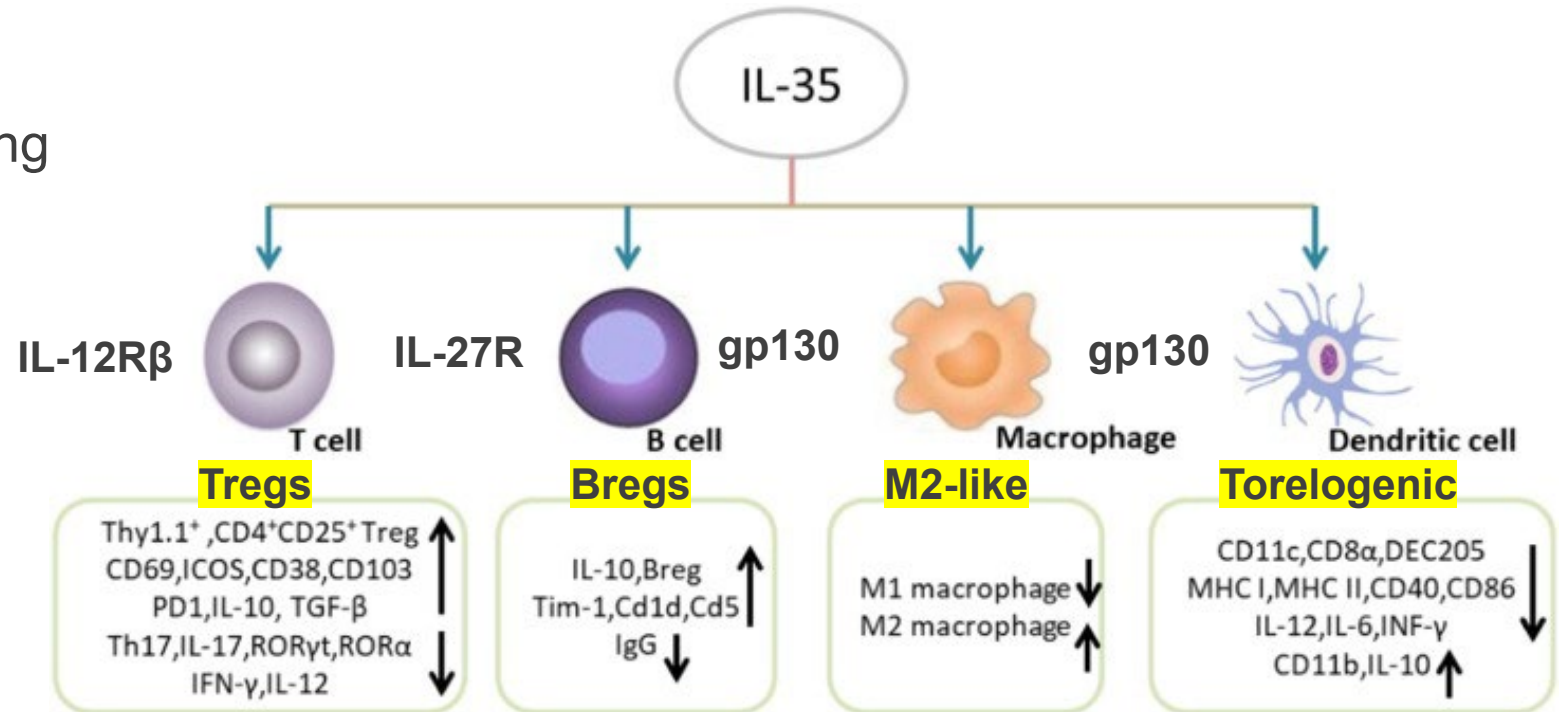
57% reduction

免疫を抑える

IL-35: a robust immunosuppressive cytokine

- Expressed by Tregs, Bregs and Tolerogenic dendritic cells
- Antagonizes IL-12 and IL-6 signaling

Induces every immunosuppressive pathway!



Therapeutic effects on:

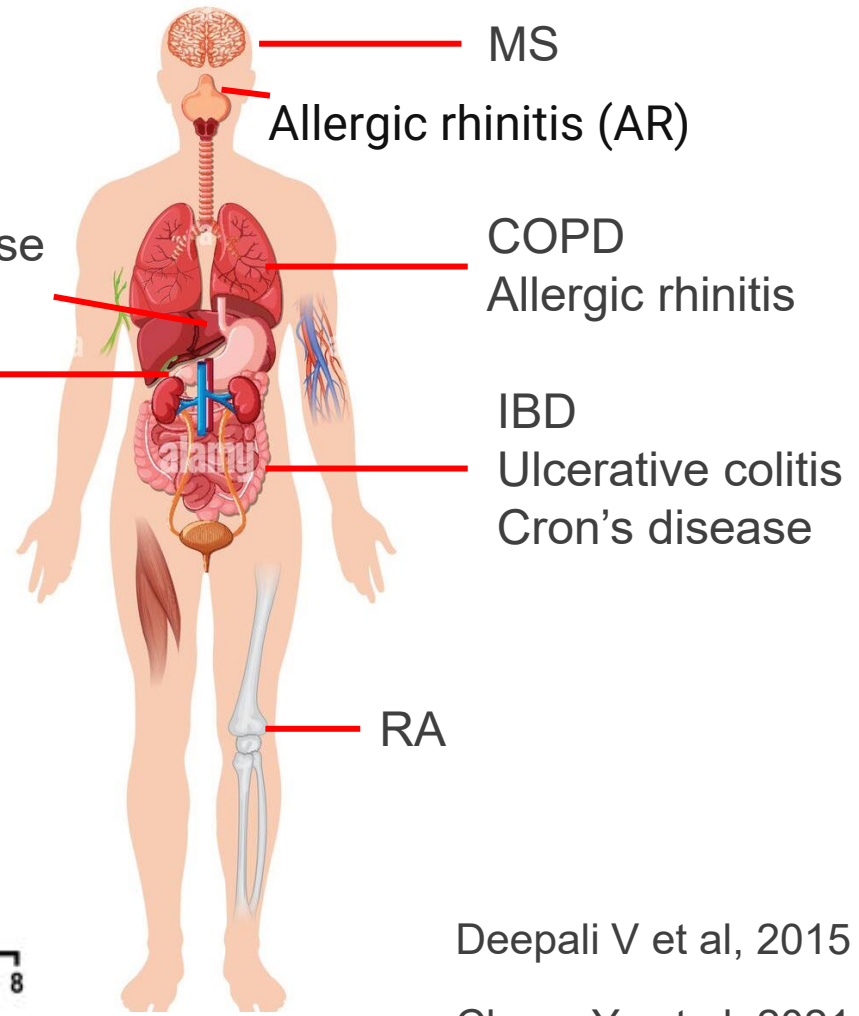
IBD (*Nat Immunol* 2010, *Gastroenterology* 2011), **RA** (*Eur J Immunol.* 2007), **T1D** (*Diabetes* 2012),
Atopic dermatitis (*An Bras Dermatol* 2016), **MS** (*J. Neuro sci* 2019), **Allergic ARDS** (*J Immunol* 2011),
Brain stroke (*Ann Transl Med* 2022), **Atherosclerosis** (*Exp Ther Med* 2016), **ILD** (*Immunology* 2023),
GVHD (*Leukemia* 2015, *Transplantation* 2024), **Psoriasis** (*J Immunol* 2016), **ITP (2024)**, **Kawasaki disease (2020)**

IL-35: Implications in disease

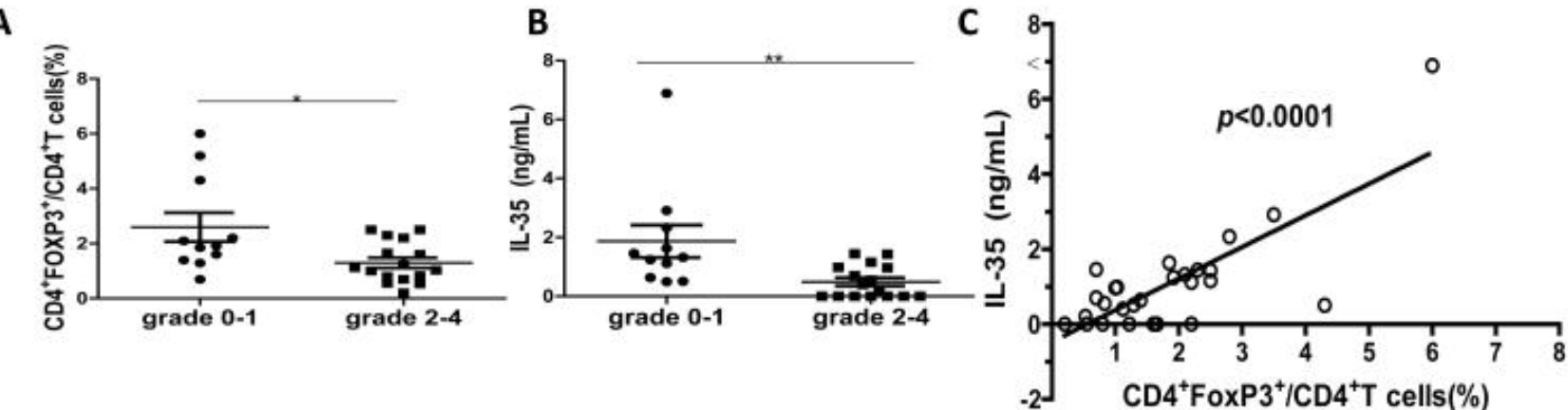
Reduced expression in the serum/disease site of autoimmune and inflammatory disease patients

- Guillain-Barré Syndrome (2015)
- Immune Thrombocytopenic Purpura (2020, 2024)
- SLE
- Systemic sclerosis
- Immune thrombocytopenia
- Recurrent pregnancy loss (RPL) and PE

Atherosclerosis
Coronary artery disease



GVHD specific:



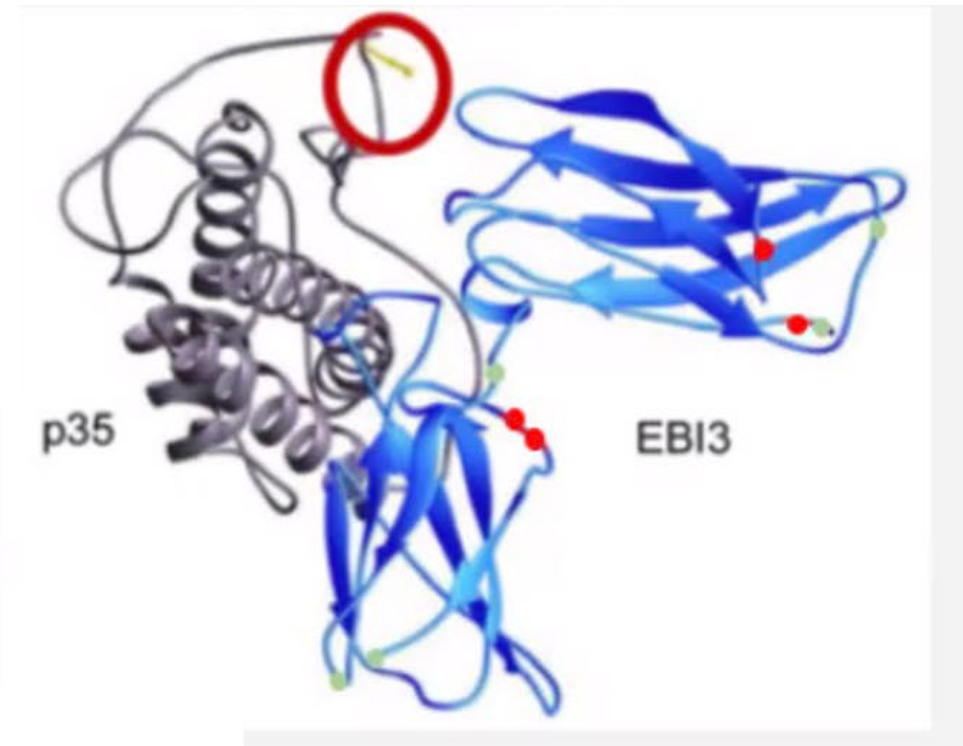
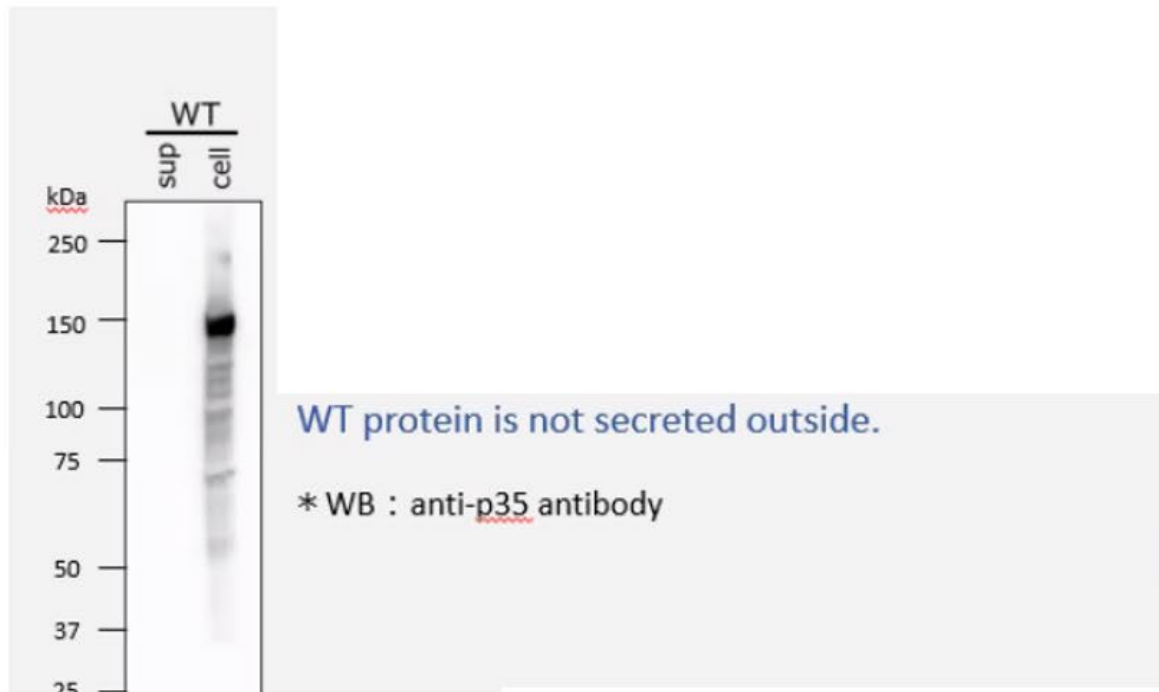
Deepali V et al, 2015
Cheng Ye et al, 2021

IL-35: a **difficult-to-produce** protein

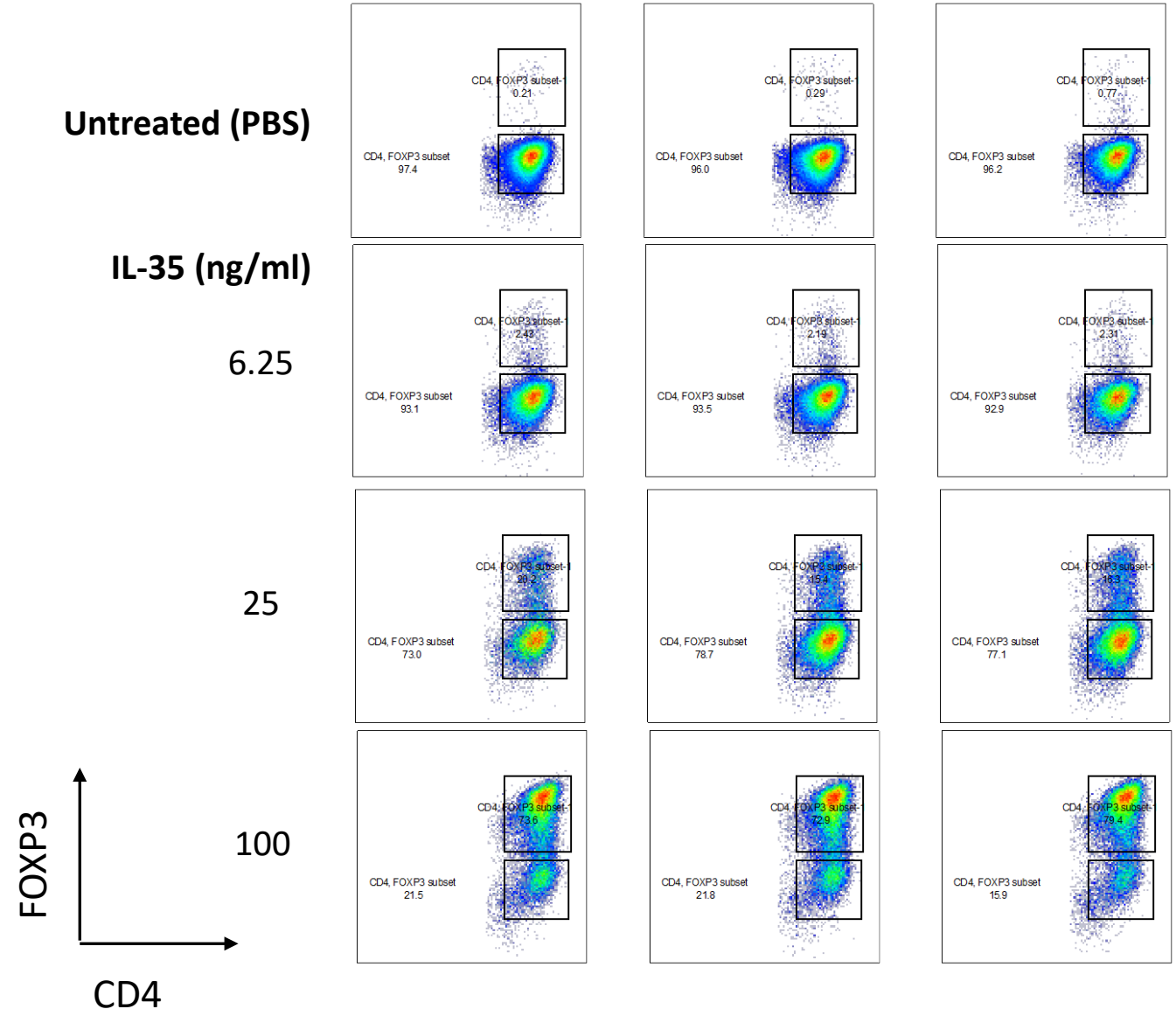
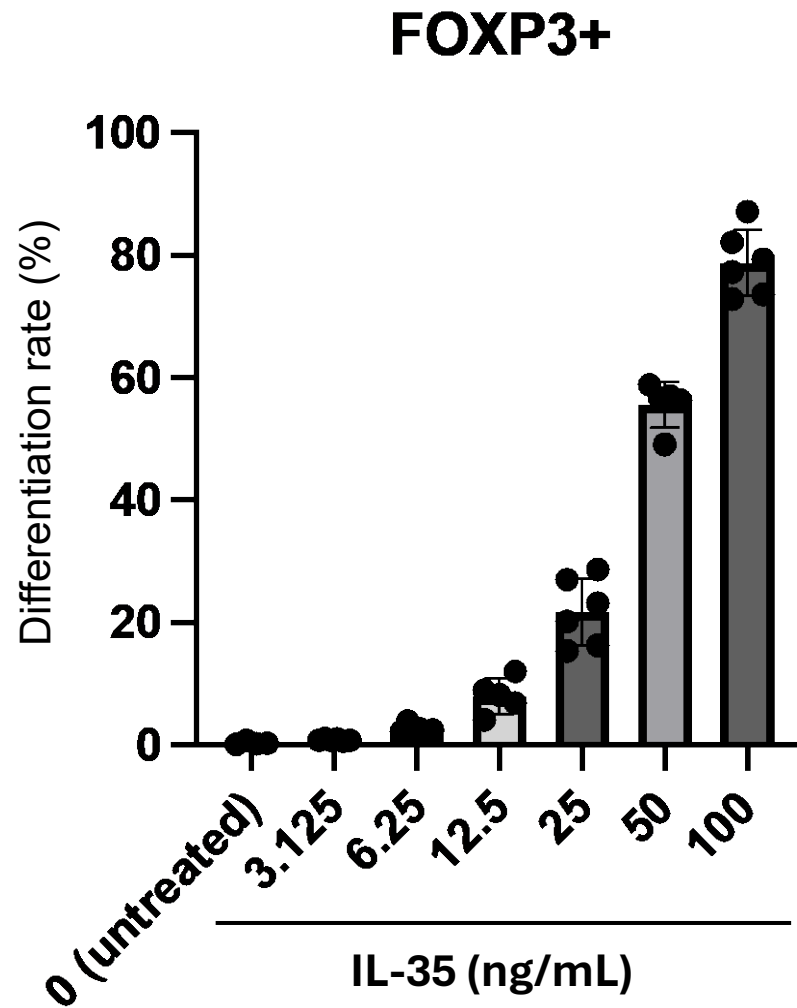
✓ Developed methodology to produce IL-35

Unmodified IL-35: mostly sticking to an intracellular protein

AlphaFold 2 protein structure prediction



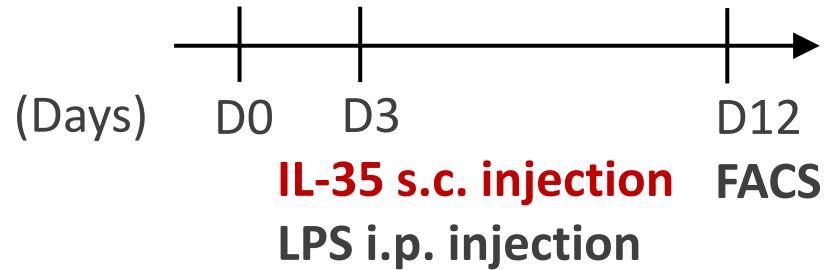
IL-35 induces a profound **Treg** phenotype in naïve CD4⁺ T cells cultured in Th1-skewing media



IL-35 decreases CAIA disease score in **rheumatoid arthritis** model

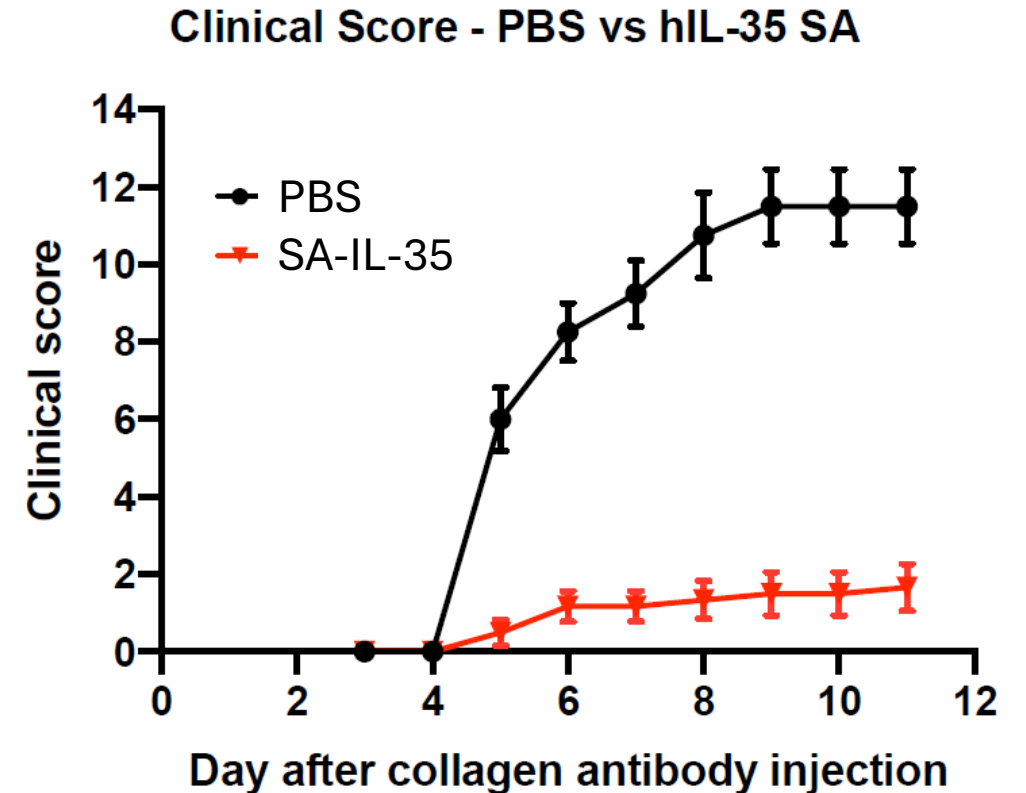
1. Experimental outline

Collagen antibody, i.p.



- Female mice, Jax, 8 wk old
- n = 7 mice/group

2. Clinical Score



My lab is supported by the following funders



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