# *Discovery of Therapeutic & Functional GPCR mAbs GPCR by MoGRAA®*

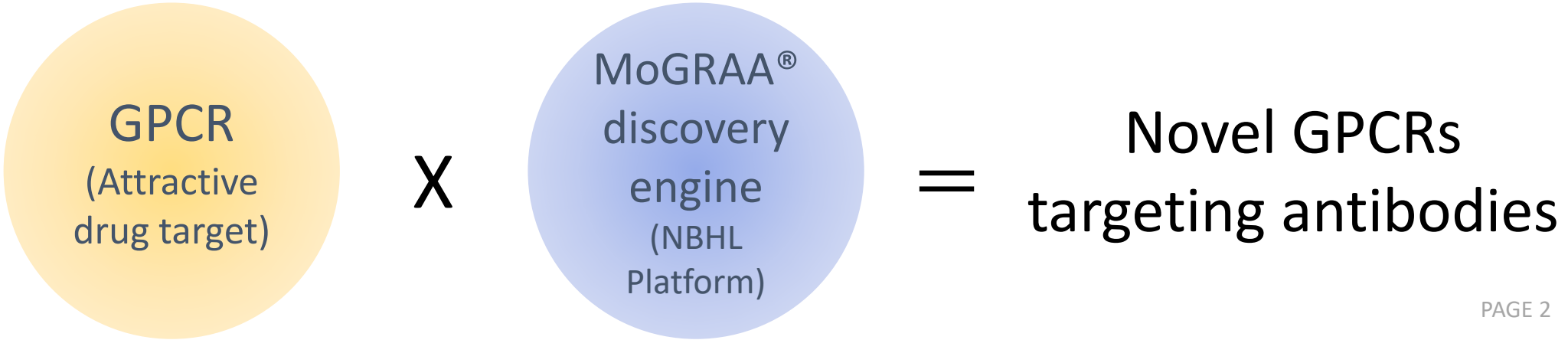
*NB Health Laboratory Co. Ltd.*

NB HEALTH LABORATORY

# Company Profile & Strategy

*We are an R&D-based global biotech focused on novel drug discovery*

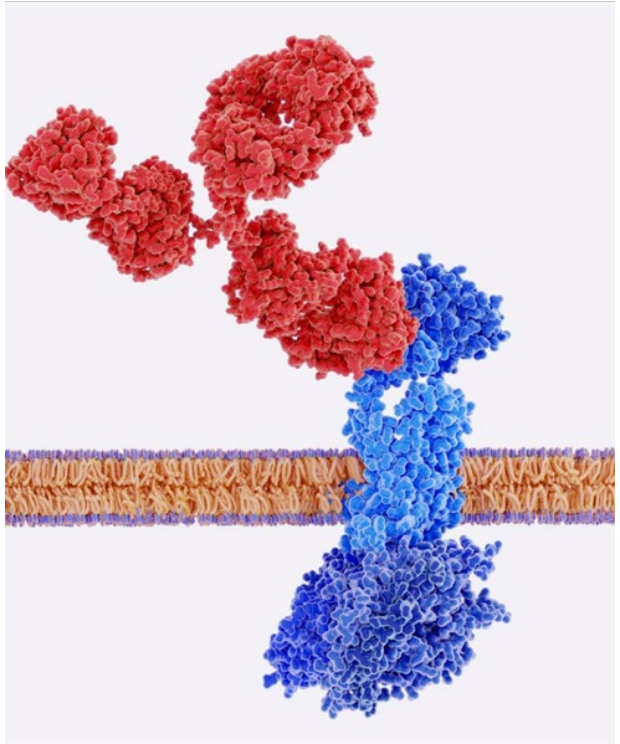
| | |
|---|---|
| Company name | NB Health Laboratory Co. Ltd. |
| Location | North 21, West 12-2, Kita-ku, Sapporo, Hokkaido, Japan |
| Founded | 2006 |
| Business | Research and development of novel biopharmaceuticals (antibodies) targeting GPCRs |



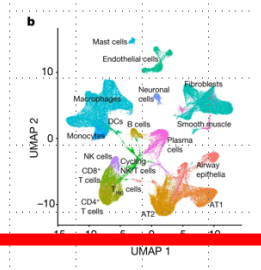
# Toolboxes of discovery of GPCR-targeting mAb in NBHL

NB HEALTH LABORATORY

## MoGRAA® mAb

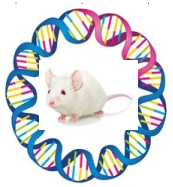


**Target Discovery**



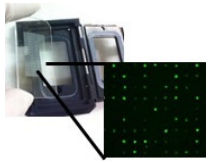

GPCRomics
RNAseq

**Antigen format immunization**



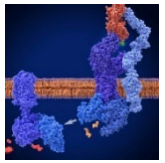
DNA immunization
WO2006041157

**Lead mAb screening**



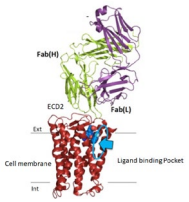
Single Cell Screening
WO2020171020, others

**Functional assay**



Shedding assay
WO2015128894

**humanization /optimization**




CDRx, RAMP methods

fusionantibodies

**In vivo study**

Comprehensive R&D strategy
( surrogate marker, diagnosis, PK/PD)

# Technology

## Landscape of GPCR-targeted antibody

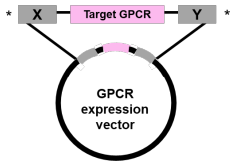
| Company | NB HEALTH LABORATORY | Nxera (ex Sosei Heptares) | DJS antibodies (acquired by AbbVie) | DOMAIN THERAPEUTICS | AbCellera |
|---|---|---|---|---|---|
| **Disease Area** | • Autoimmune<br>• Fibrosis | • Inflammation<br>• Immuno-oncology | • Chronic-inflammation | • Immuno-oncology | • Metabolic and endocrine |
| **Technology** | • DNA immunization<br>• Single cell screening<br>(GPCR antibodies generated within **18 months**) | • structure-based drug design (SBDD) | • Hybridoma screening<br>• In vitro maturation | • GPCR-mediated immuno-suppression<br>• target discovery concept | • Single cell screening<br>• AI |
| **Key future** | • Antibodies generated against difficult lipid ligand type GPCRs<br>• DNA immunization may cause quality and variability | • Quick antibody generation<br>• Recombinant proteins used; 3D structure not guaranteed in vivo | • Well-established traditional methods (Hybridoma) | • Excels in Profiling of GPCR antibody function | • Efficient antibody generation by AI |

NBHL has built a highly competitive portfolio of pipelines by MoGRAA® Discovery Engine.

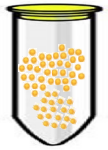
# NBHL's Platform
# MoGRAA® discovery engine for GPCR therapeutic antibody

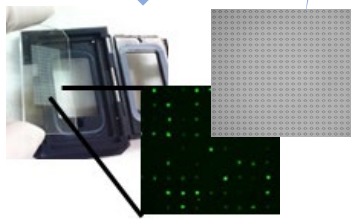
## MoGRAA® discovery engine is NBHL's platform unlocking creation of promising GPCR therapeutic antibody

**Antigen format**



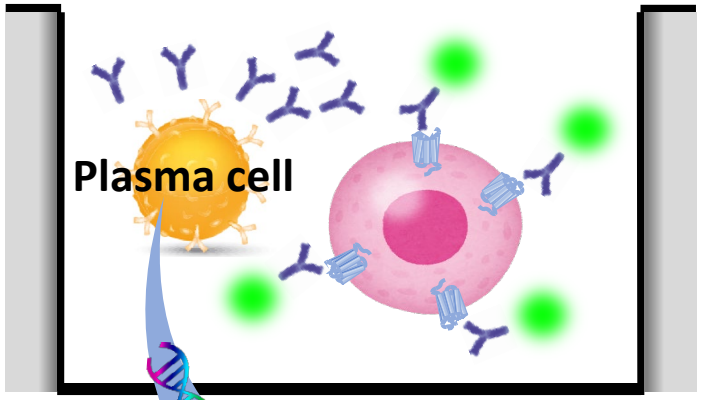

**Immunization**





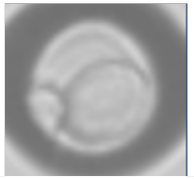
**Single cell Isolation chambers**

**NBHL's patented RiGRASS Technology**

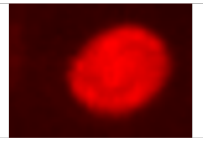



**Direct cloning**

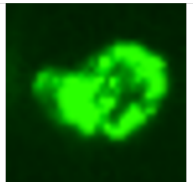

Plasma cell | GPCR expressing cell



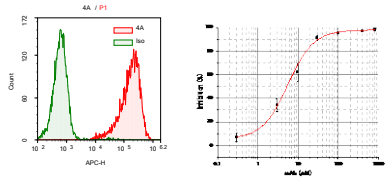
Staining signal of reporter cell



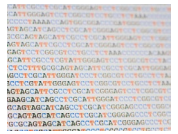
Fluorescence signal of mAb

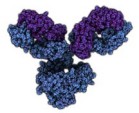


**Functional assay, PoC, Preclinical (*in vitro, in vivo*)**



**Sequence , humanization, optimization (*in silico*)**





# Development Summary

***MoGRAA® unlocks therapeutic GPCR-targeted antibody market to address unmet medical needs for respiratory diseases, inflammation, and severe virus infection***

## 2 preclinical

- Ankylosing spondylitis (AS)
- Blood cancer

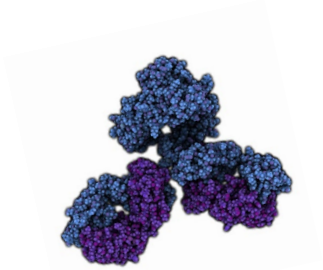
## 8 discovery

- Fibrosis
- Severe infection (COVID-19)
- Metabolic diseases
- Retinopathy
- Immuno-oncology
- Others

## 3 partnered

- Chronic inflammation
- Metabolic diseases
- Cancer

**mAb discovery**



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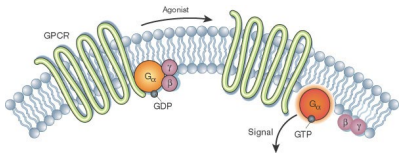
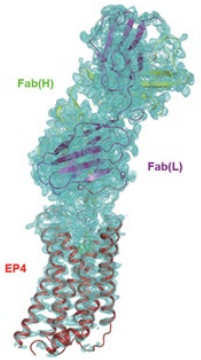
**GPCR drug discovery**




**MoGRAA® mAbs**



# NB Pipeline

| Project No | Target GPCR | Indications | Lead mAb discovery | Humanization Optimization | Preclinical study | Clinical study |
|---|---|---|---|---|---|---|
| NBA-1603 | EP4 | Ankylosing spondylitis | | | | |
| NBA-1901 | CCR7 | Autoimmune disease /Cancer | | | | |
| NBG025 | LPA1 | Fibrosis | | | | |
| NBG029 | CXCR3 | Autoimmune disease | | | | |
| NBG017 | Peptide | Hypoglycemia | | | | |
| NBG030 | FZD | Cancer/Fibrosis | | | | |
| NBG046 | Lipid | Metabolic diseases | | | | |
| NBG048 | Chemokine | Psoriasis | | | | |
| NBG051 | Chemical mediator | Fibrosis | | | | |
| NBG052 | Lipid | Pain/Itch | | | | |

# NB Projects List

1. Anti-LPA1 Antagonist Antibody
   - Indication:
     - ✓ Fibrosis(IPF, COPD, NASH, Systemic Sclerosis), Pain
   - R&D Status:
     - ✓ POC study (BLM mouse model)
   - Patent Status:
     - ✓ Filed on Oct 2022 (1st Patent)

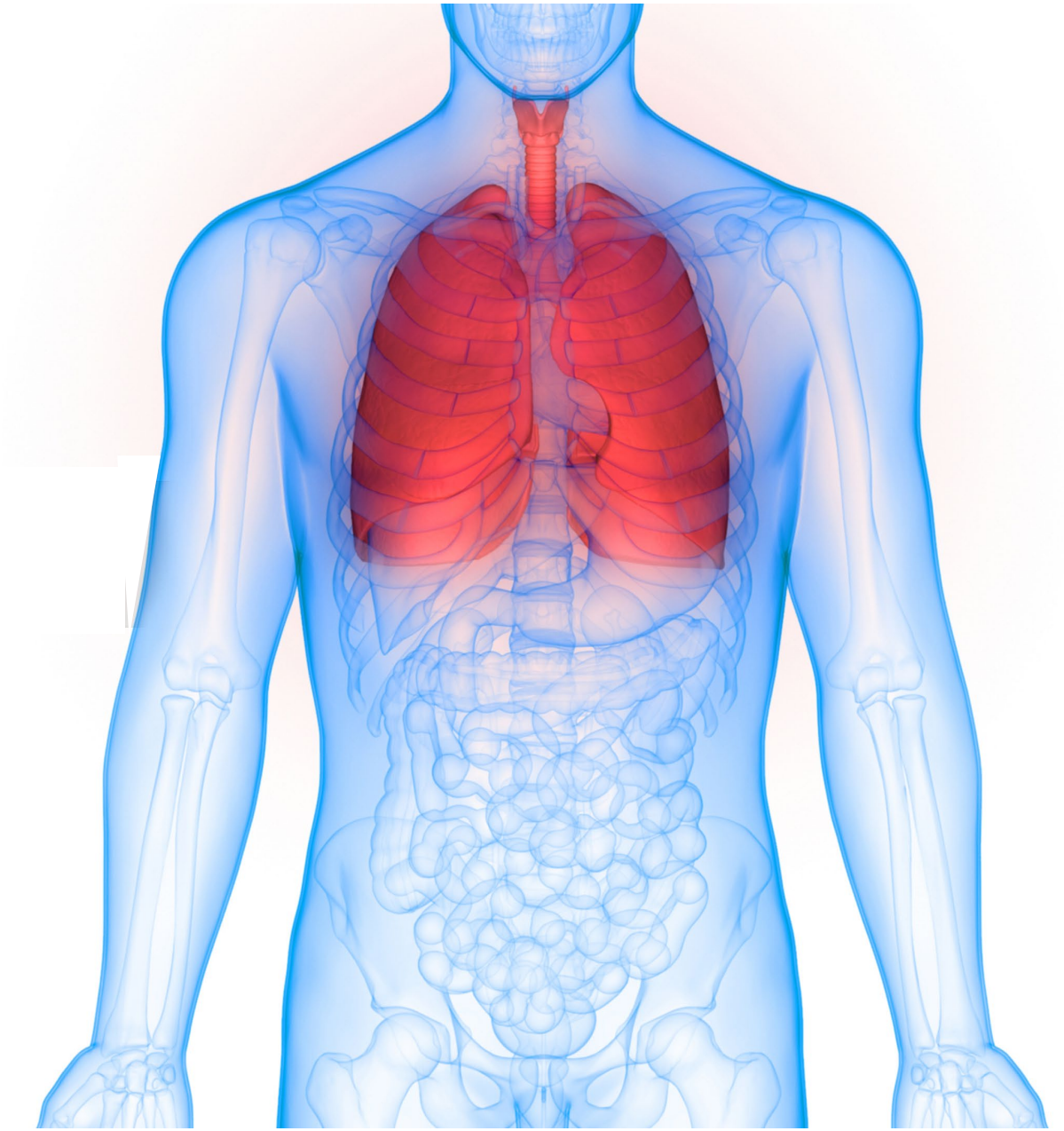
2. Anti-CXCR3 Antagonist Antibody
   - Indication:
     - ✓ Virus infection, acute and chronic inflammation, and autoimmune disease
   - R&D Status:
     - ✓ POC study
   - Patent Status:
     - ✓ Filed on Jan 2024

3. Anti CCR7 Antagonist Antibody
   - Indication:
     - ✓ Autoimmune disease & oncology
   - R&D Status:
     - ✓ Prior to CMC, Preclinical study
   - Patent Status:
     - ✓ Filed on March 2023 (3rd patent)

4. Anti EP4 Antagonist Antibody
   - Indication:
     - ✓ Ankylosing spondylitis [AS], Oncology
   - R&D Status:
     - ✓ Prior to CMC, Preclinical study
   - Patent Status:
     - ✓ Filed in 2023 (2nd patent)

# NBG025:

Anti **LPA1** antibody treatment can provide breakthrough therapy for **tissue fibrosis**



# Highlights: Why so many Mega-pharms are interested in LPA1 mAb

- A small molecule compound being developed by BMS has achieved human POC (currently in Phase 3).
  - ✓LPA1 is well validated drug target for fibrosis

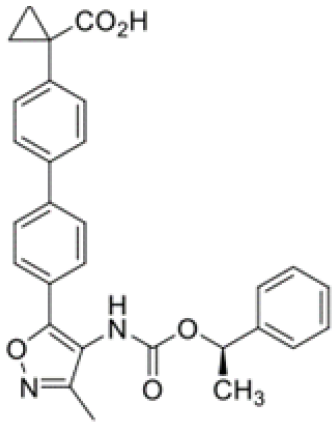
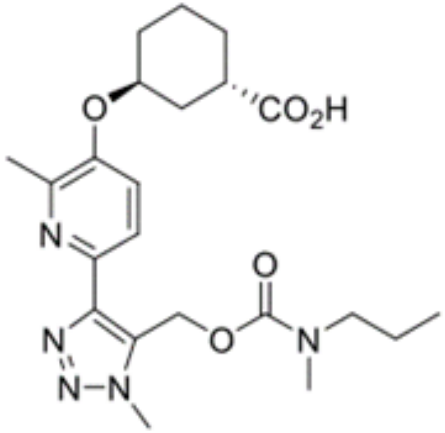
- Only two companies, NBHL and DJS, are developing LPA1 antibodies.
  - ✓DJS was acquired by AbbVie in 2022 (currently in preclinical)

- NBHL antibody showed good anti-fibrotic efficacy in mouse bleomycin IPF model.
  - ✓Greater efficacy than BMS small molecule compound

# NBG025
## Product Summary

| | |
|---|---|
| Target Molecule | LPA1 |
| | Ligands; lysophosphatidic acid |
| Target Product Profile | Long acting non-competitive inhibitor (First in class)<br>• Fibrosis; inhibition of migration, growth & cytokine production of fibroblast<br>• Pain; inhibition of demyelination & sprouting, microglia activation<br>• Cancer; inhibition of tumor cell growth & migration, tumor angiogenesis |
| Target disease | Fibrosis (IPF,NASH,CKD), Neuropathic Pain, Solid cancer |
| Property of Molecule | • Humanized monoclonal antibody selectively Inhibits both human and rodent LPA1<br>• Injectable via subcutaneous or IV |
| Patent Status | The 1st patent was filed on Oct 2022. |
| R&D Status | POC study |
| Competitor | • No mAbs in clinical test (no R&D tool)<br>• Small compound finished Phase III for lung fibrosis IPF (BMS) |

# Small compounds of LPA1 antagonist in Phase studies

| | BMS-986020 | BMS-986278 |
|---|---|---|
| Compounds |  |  |
| Antagonist activity | Strong | Moderate |
| Mode of antagonist | Non-competitive | Competitive |
| Selectivity | Low | High |
| Off-target | Hepatic transporter | No information |
| Clinical trial | Terminated due to adverse events | Ph3 |

# Potential benefit of MoGRAA antibody in drug discovery for lipid GPCR

| | MoGRAA® | Conventional GPCR Drug |
|---|---|---|
| Drug type | Monoclonal antibody | Small compound or peptide |
| Mode of action | Antagonist, Agonist, Modulator | Antagonist, Agonist, Modulator |
| Duration of action | Long | Short |
| Selectivity | High | Moderate |
| Off-target | Low frequency | High frequency |
| ADME profile | Relatively simple | Complicated and depend on chemical property |
| Biomarker survey | Good as diagnostic tool | New tools needed |
| Period of drug discovery | Short | Relatively long |

mAb is superior to small comp. in frequency AEs and PK profile

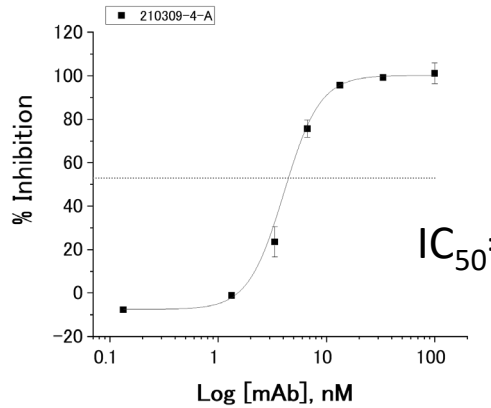
# Antagonist activity of anti LPA1 in cAMP assay

## Functional evaluation of cAMP assay

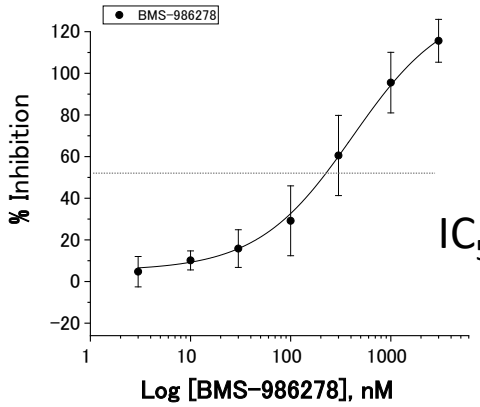
NBHL Antibody (210309-4-A)

Compound (BMS-986278)

### CHO/ humanLPA1

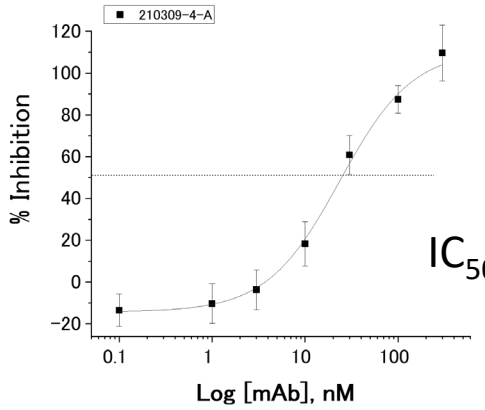



$IC_{50}$=4.8 nM

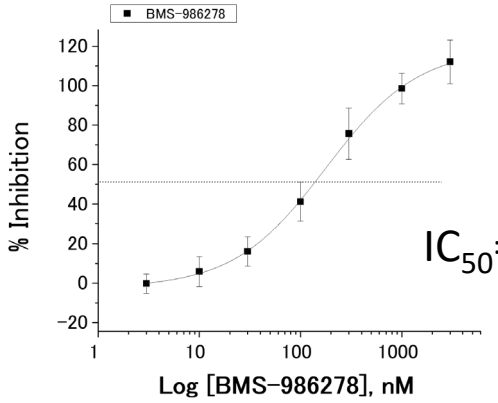



$IC_{50}$=220 nM

### CHO/ mosueLPA1




$IC_{50}$=24 nM



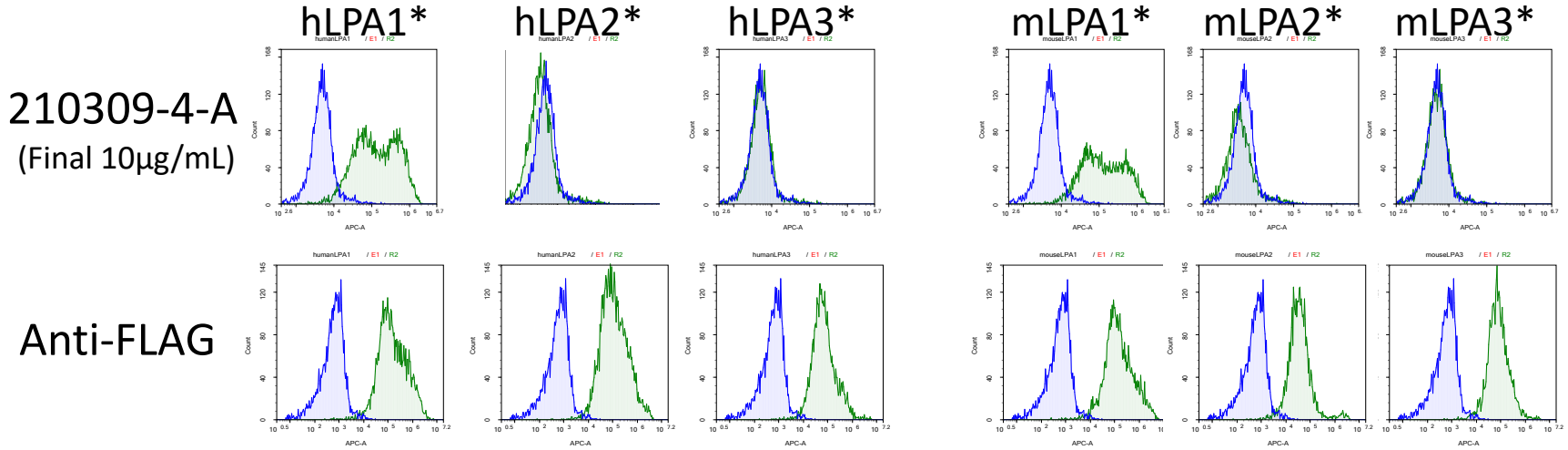

$IC_{50}$=131 nM

Kit: LANCE Ultra cAMP Kit (TRF0263)
Cell: CHO/hLPA1, CHO/mLPA1, 2500/well-96well Plate
Forskolin: Final 3µM (Sigma, F6886)
Ligand: Final 50nM LPA(Sigma, L7260)

NBHL antibody has more potent antagonist activity, comparing with the compound

# Binding selectivity of anti LPA1

## Highly selectivity for LPA1 in human and mouse




*FLAG-tagged

Non-transfected 293FT cells

Each subtype Expression transient cell

## Binding to endogenous human LPA1 in Lung Fibroblast

IMR-90
(Human fetal lung fibroblast cell line)

Human lung fibroblast, primary

210309-4-A
(Final 10μg/mL)

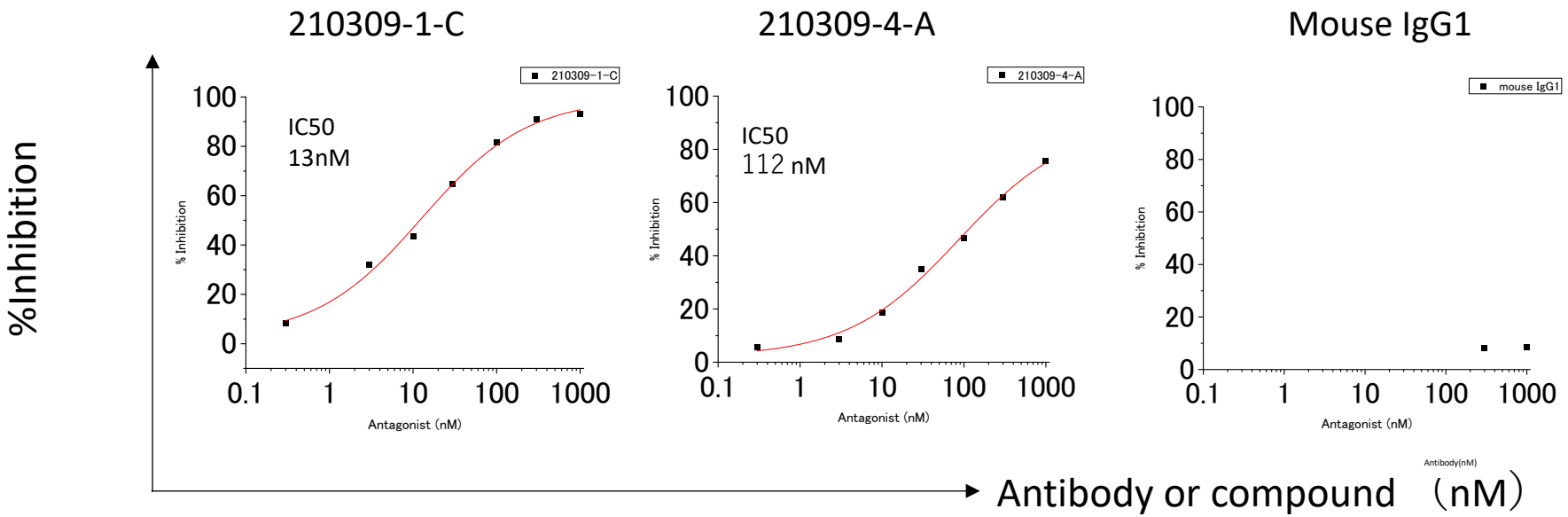

Mouse isotype

NBHL antibody

NBHL antibody has high selectivity and can bind endogenous human LPA1

# Intracellular signal inhibition in human fibroblast

## Inhibition of LPA-induced intracellular signaling $[Ca^{2+}]_i$ in Human Lung Fibroblast



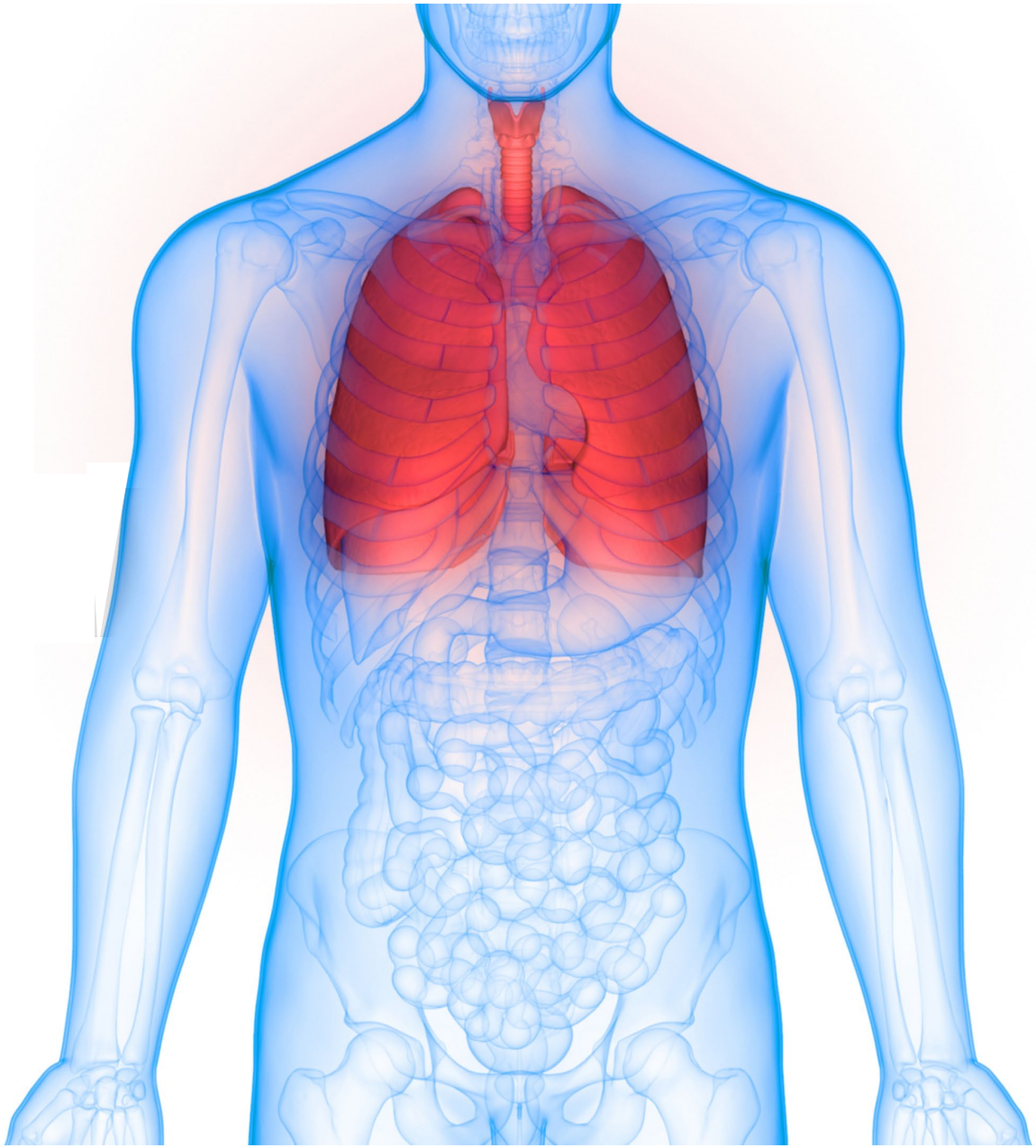

Cell: IMR-90
Ligand: 18:1-LPA 50nM

NBHL antibody inhibits LPA1 signaling in human lung fibroblast

# NBG025:

Anti **LPA1** antibody treatment can provide breakthrough therapy for **tissue fibrosis**

<u>Result of in vivo pharmacology in Bleomycin induced pulmonary fibrosis model (Mouse lead mAb)</u>



# Summary: in vivo pharmacology in Bleomycin induced pulmonary fibrosis model

## Background

Various studies implicated LPA1 as a key mediator in lung fibrosis. Clinical studies of LPA1 antagonists are in progress in idiopathic pulmonary fibrosis (IPF). We have developed a novel anti-LPA1 monoclonal antibody (NBHL anti-LPA1 lead mAb). This study's aim is to evaluate and compare the therapeutic efficacy of NBHL anti-LPA1 lead mAb, Nintedanib (a therapeutic approved drug for IPF) and BMS986278 (a LPA1 antagonist under clinical study in IPF therapy) in mouse model of bleomycin induced pulmonary fibrosis

## Methods

Pulmonary fibrosis was developed by single intranasal administration of bleomycin on Day 0.
Starting on Day7 and ending on Day 20, mice were treated with NBHL anti-LPA1 lead mAb, Nintedanib or BMS986278.
On Day21, pulmonary function were assessed. Inflammatory cell number in bronchoalveolar fluid were measured. Lung were collected and histopathological analysis (Ashcroft score and collagen immunohistochemistry) were performed to evaluate lung fibrosis progression.

## Summary: in vivo pharmacology in Bleomycin induced pulmonary fibrosis model

**Results**

- Single intranasal administration of bleomycin successfully induced lung fibrosis as increased Ashcroft score and percentage collagen content within lungs on Day21. Various lung function parameter and inflammatory cell infiltration in lung are also changed.
- Therapeutic treatment with NBHL anti-LPA1 lead mAb reduced bleomycin-induced lung fibrosis, characterized by collagen deposition. NBHL anti-LPA1 lead mAb treatment improved some lung function parameter worsened by bleomycin administration. NBHL anti-LPA1 lead mAb treatment also recovered body weight loss by bleomycin administration, demonstrating an enhanced overall state of health.
- Therapeutic treatment with Nintedanib reduced bleomycin-induced lung fibrosis, characterized by collagen deposition. Nintadenib treatment also improved many lung function parameter. However, body weight data showed the overall state of health was exacerbated.
- Therapeutic treatment with BMS986278 at low dose , but not at high dose, reduced bleomycin-induced lung fibrosis, despite that collagen deposition appeared to be unaffected. Although not significant, there is a trend of improvement of some lung functions.

**Conclusion**

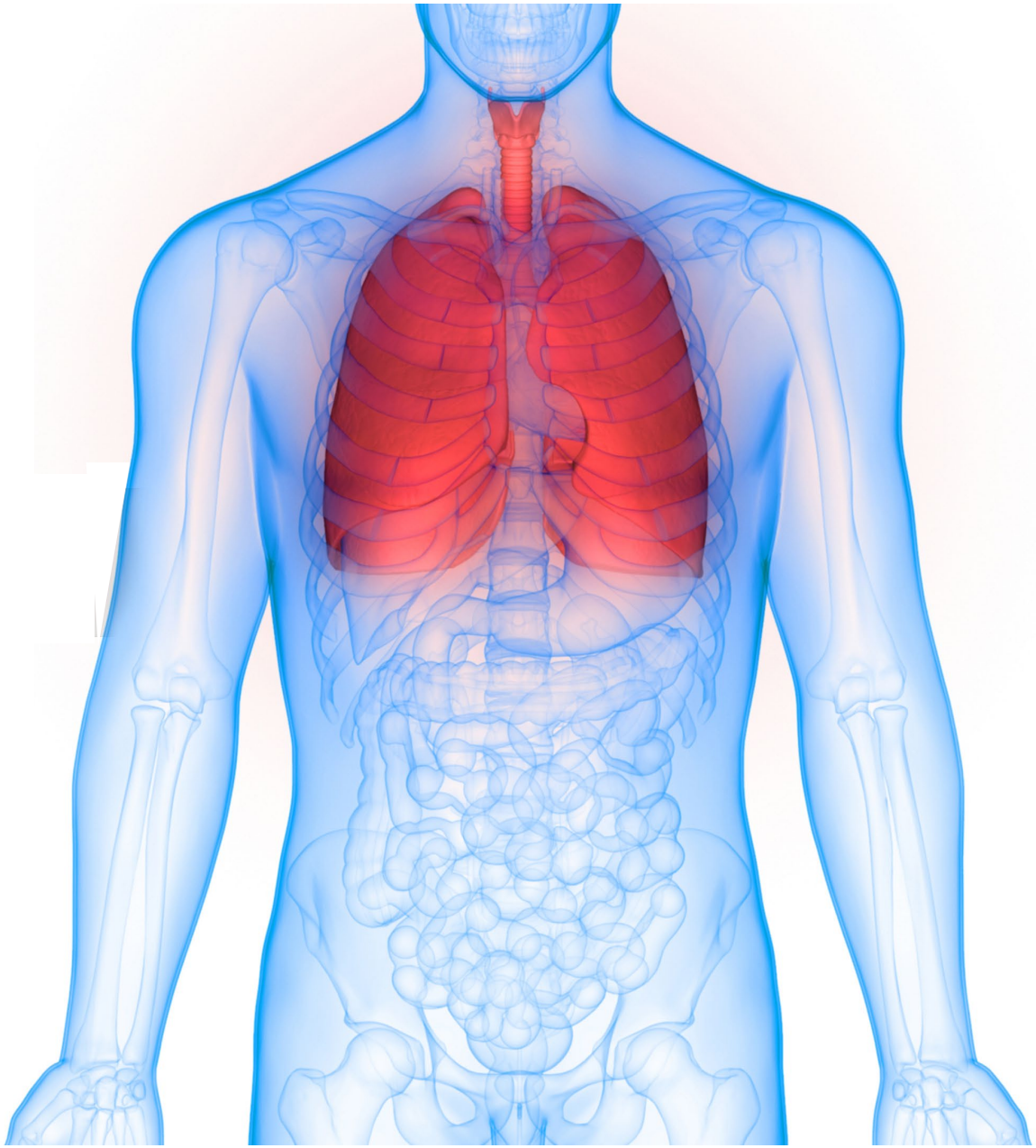
- NBHL anti-LPA1 lead mAb appeared to exhibit a similar anti-fibrotic efficacy but better overall state of health compared to Nintedanib, and to show greater efficacy than BMS986278.

Test reports will be disclosed after the CDA conclusion.

# NBG025:

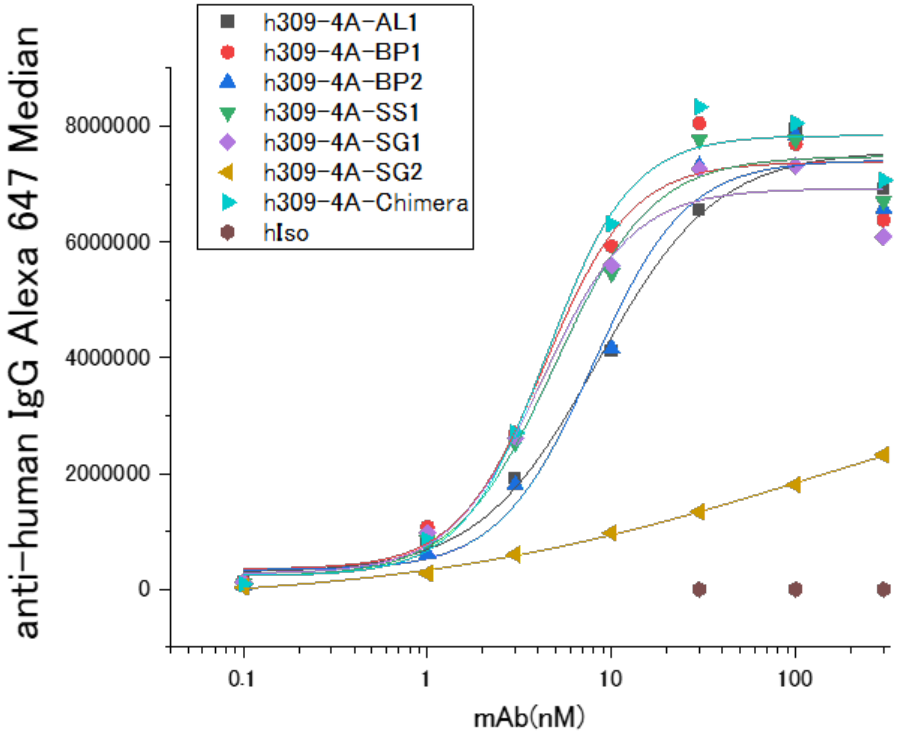
Anti **LPA1** antibody treatment can provide breakthrough therapy for **tissue fibrosis**

<u>Humanized antibodies</u>



# Humanization of Lead mAb for anti LPA1

## Binding titration assay with humanized mAbs

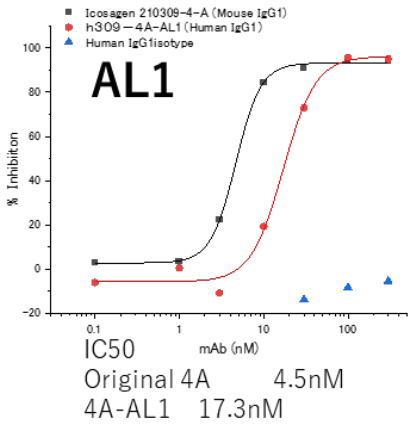


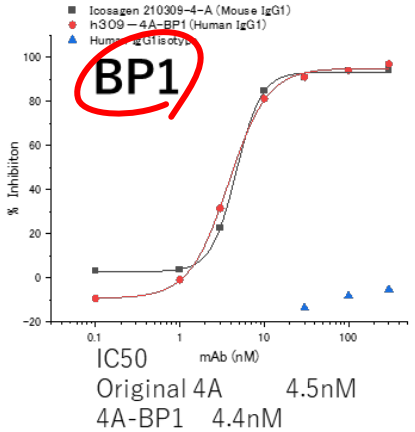

| mAb | EC50 | EC80 |
|---|---|---|
| h309-4A-AL1 | 8.4 | 23.6 |
| h309-4A-BP1 | 4.3 | 9.2 |
| h309-4A-BP2 | 7.9 | 17.7 |
| h309-4A-SS1 | 4.9 | 11.4 |
| h309-4A-SG1 | 4.2 | 9.2 |
| h309-4A-SG2 | 135.5 | 4865.1 |
| h309-4A-Chimera | 4.4 | 9.2 |

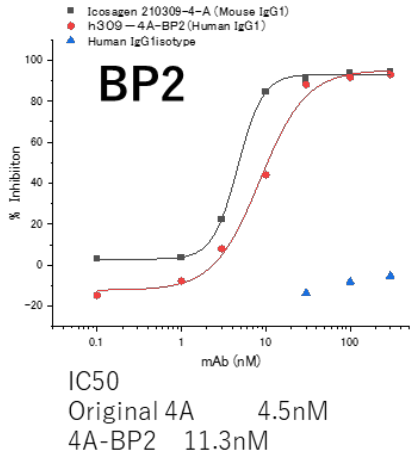
Five of six humanization designs clones keep binding activity to hLPA1

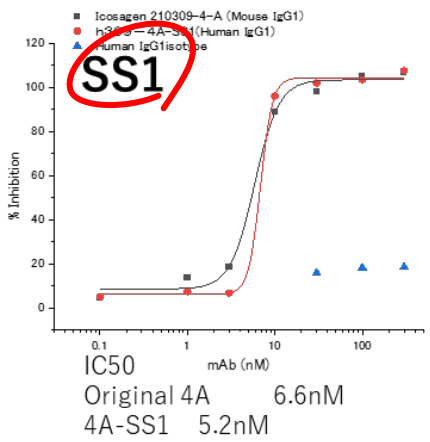
# Humanization of Lead mAb for anti LPA1

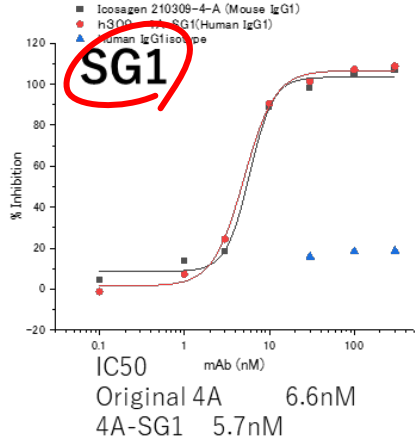
## Functional evaluation of cAMP assay



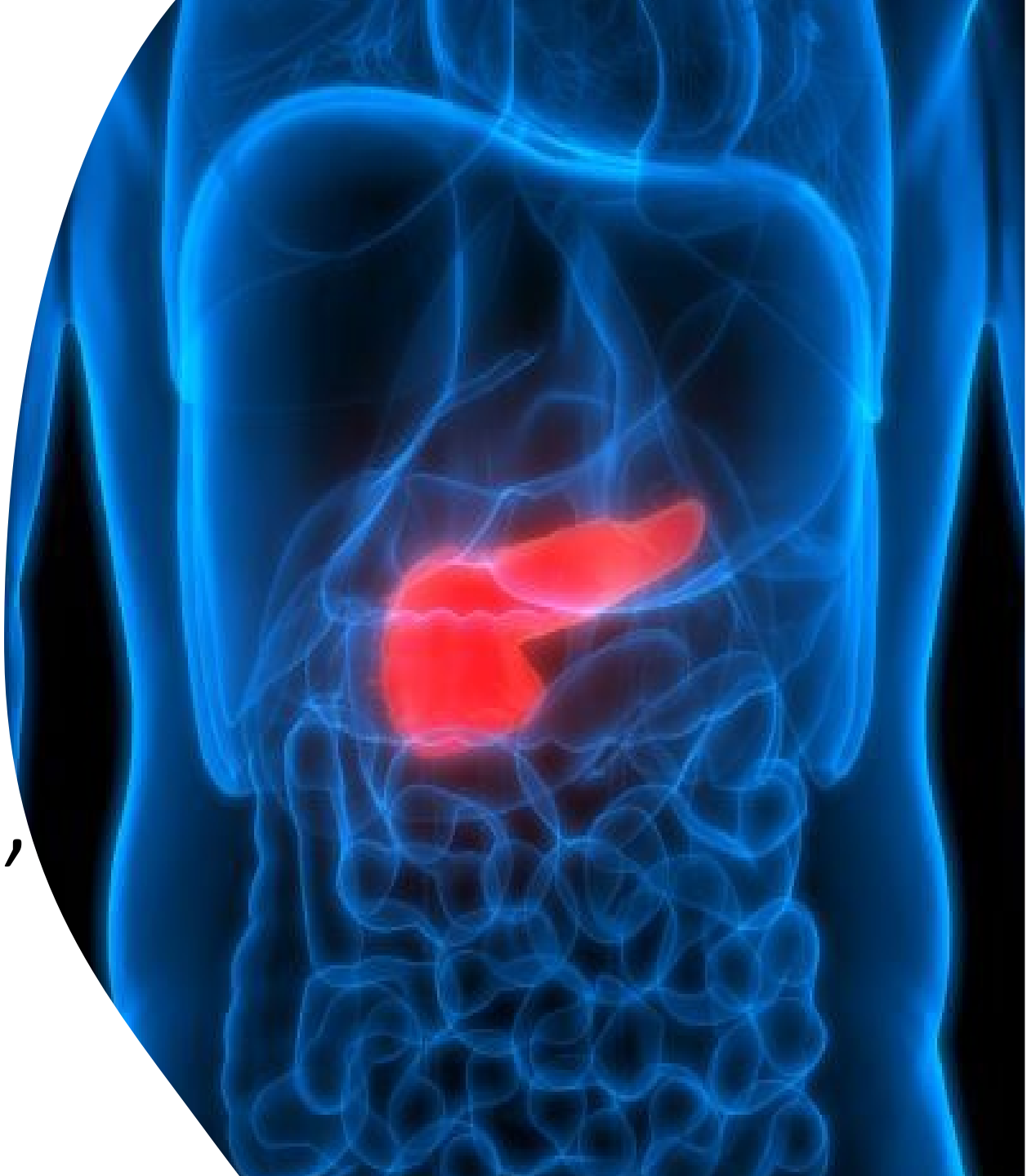

●Original mAb
●Humanized mAb

Kit: LANCE Ultra cAMP Kit (TRF0263)
Cell: CHO/hLPA1, CHO/mLPA1, 2500/well-96well Plate
Forskolin: Final 3μM (Sigma, F6886)
Ligand: Final 50nM LPA(Sigma, L7260)

BP1, SS1, SG1 keep the inhibitory potency and efficacy to hLPA1

# NBG029:

Anti **CXCR3** antibody for autoimmune disease, acute and chronic inflammation, and infection virus



## Highlights:

- A small molecule compound being developed by Idorsia Pharmaceutical Ltd has validated for  human PK, PD and safety in healthy adults.

- CXCR3 are attractive target for autoimmune diseases, acute and chronic inflammatory diseases, and infections.

- NBHL has developed potent humanized anti-human CXCR3 antibodies, and POC for autoimmune myositis using alternative antibodies is underway.

# NBG029
## Product Summary

| | |
|---|---|
| Target Molecule | CXCR3 |
| | Ligands; CXCL9, CXCL10 and CXCL11 |
| Target Product Profile | Long acting inhibitor (First in class)<br>• Autoimmune diseases<br>• Transplantation<br>• Infection<br>• Cancer |
| Target disease | Autoimmune diseases (Polymyositis and dermatomyositis ) |
| Property of Molecule | • Migration inhibition of activated human T cells<br>• Reduction of inflammation and mitigation chronic inflammatory diseases |
| Patent Status | Filed on Jan 2024 |
| R&D Status | POC study |
| Competitor | Small compound at Phase I for vitiligo (Idorsia Pharmaceuticals) |

# CXCR3 and its ligands are involved in various disease

**Table 2 CXCR3 and its ligands in human disease and murine disease models**

| *Disease/disease model* | *Receptor* | *Ligands* | | |
|---|---|---|---|---|
| | *CXCR3* | *CXCL9* | *CXCL10* | *CXCL11* |
| *Autoimmmune* | | | | |
| Psoriasis | | 91, 92 | 91, 93 | 91 |
| Sarcoid | 94, 95 | 95, 96 | 94, 95 | 95, 96 |
| Rheumatoid arthritis | 21, 97–100 | 98 | 99, 101 | |
| Asthma | 102, 103 | 102 | 102, 104–106 | 102 |
| Atherosclerosis | 107, 108 | 107 | 107, 109 | 107 |
| Multiple sclerosis | 110–116 | 111 | 110, 111, 117, 118 | |
| IBD | 119 | | 73 | |
| Idiopathic pulmonary fibrosis | 120, 121 | | 59, 60 | 122 |
| Type I diabetes mellitus | 70, 123 | | 69, 123, 124 | |
| SLE | 75, 125, 126 | 75 | 126, 127 | |
| Cigarette smoke injury/COPD | 128–131 | 131 | 128, 131 | 131 |
| Myocarditis | 132 | | 96, 133 | |
| *Transplantation* | | | | |
| Heart transplant | 86, 134–137 | 41, 138 | 41, 139 | |
| Lung transplant | 38, 140 | 38, 89 | 38, 89, 140 | 89 |
| GVH | 141, 142 | | 142 | |
| Small bowel | 72 | | 72 | |
| *Infections* | | | | |
| Leprosy | 143 | | | |
| Tuberculosis | | | 144, 145 | |
| Influenza | 146, 147 | | 146, 147 | |
| Toxoplasma gondii | | | 17, 148 | |
| Malaria | 42, 78 | 42, 78 | 42, 78, 79, 149 | |
| Dengue | 66 | | 66, 150 | |
| Hepatitis B and C | 151–153 | 151, 152 | 64, 151, 153, 154 | 151 |
| Herpes simplex | 22, 80 | 22, 80 | 22, 80, 155, 156 | |
| HIV-1 | 157 | 157 | 157–159 | 158 |
| Leishmania | 160 | 161 | 161, 162 | |
| Chlamydia trachomatis | 163, 164 | | 164 | |
| Lyme | 165 | 166, 167 | 166, 167 | |
| West nile virus | 67 | | 67 | |
| *Cancer* | | | | |
| Renal | 168 | 168 | 168 | 168 |
| Colon | | | 169, 170 | |
| Melanoma | 171 | 171 | 171 | |
| Lymphoma | 172–174 | | 175 | |
| Breast | 176 | | 176 | |

Abbreviations: COPD, chronic obstructive pulmonary disease; GVH, graft-versus-host; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; SLE, systemic lupus erythematosus.

Immunology and Cell Biology (2011) 89, 207–215

# Evidence in Autoimmune disease

## Polymyositis (idiopathic inflammatory myopathies)

- 【animal model】In CIM mice, anti-CXCL10 mab administrated group showed significant improvement of muscle inflammation (Arthritis Research & Therapy 2014, 16:R126)

## Type I diabetes

- 【animal model】Combination anti-CD3 with CXCR3 antagonist increased persistenbt remission in experimental models of type1 diabetes (Clinical and Experimental Immunology, 2023, 214, 131–143)

## IBD

- 【animal model】Anti-CXCL10 antibodies attenuated colitis and improved intestinal epithelial cell proliferation (Eur. J. Immunol. 2002. 32: 3197–3205, Inflamm Bowel Dis. Volume 11, Number 9, September 2005).
- 【clinical trial】 BMS-936557 showed efficacy in severely active UC patient in Phase 2 (Mayer L, et al. Gut 2014;63:442–450).

## MS

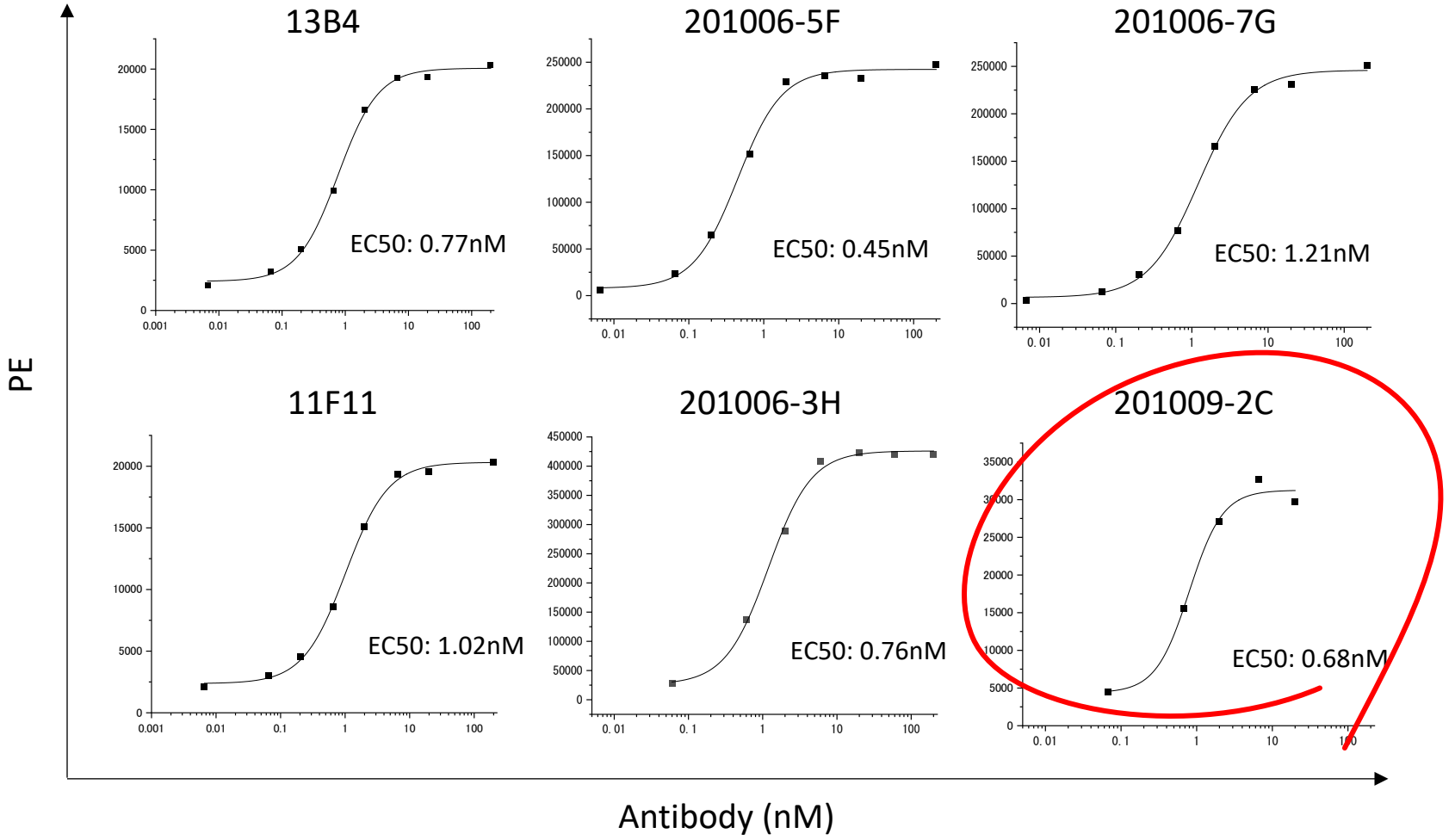
- 【animal model】Anti-CXCL10 mAb or small molecule CXCR3 antagonist significantly reduced disease severity in experimental autoimmune encephalomyelitis models (J Immunol. 2001. 166 (12): 7617–7624, Eur. J. Immunol. 2010. 40: 2751–2761, Jenh et al. BMC Immunology 2012, 13:2).

## RA

- 【animal model】CXCR3 antagonist attenuated disease progression in a murine collagen-induced arthritis model by inhibiting T cell migration (Cell Signal. 2019 Dec:64:109395, Immunol Lett. 2020 Sep:225:74-81.).

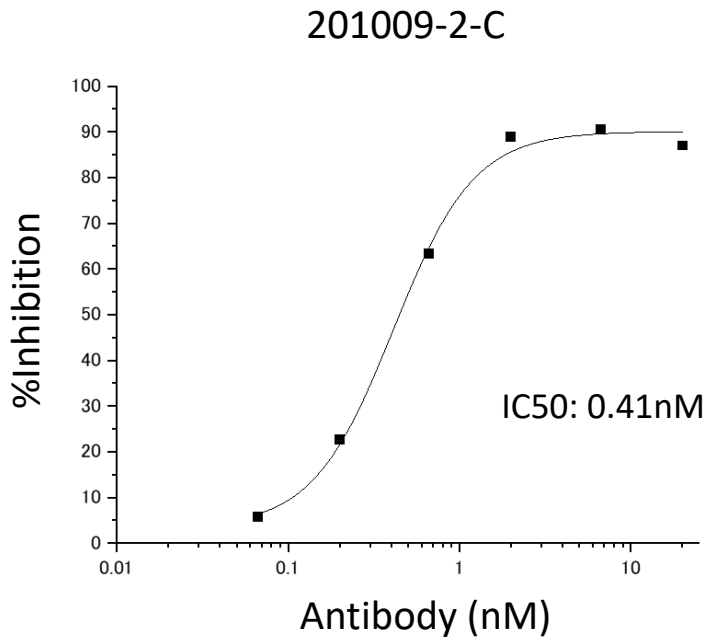
# In vitro profiling of CXCR3 Monoclonal Antibodies

## Binding titration assay with human T cell derived from PBMCs




NBHL mAbs can bind endogenous human CXCR3 with low concentration

## Chemotaxis assay with human T cell derived from PBMCs

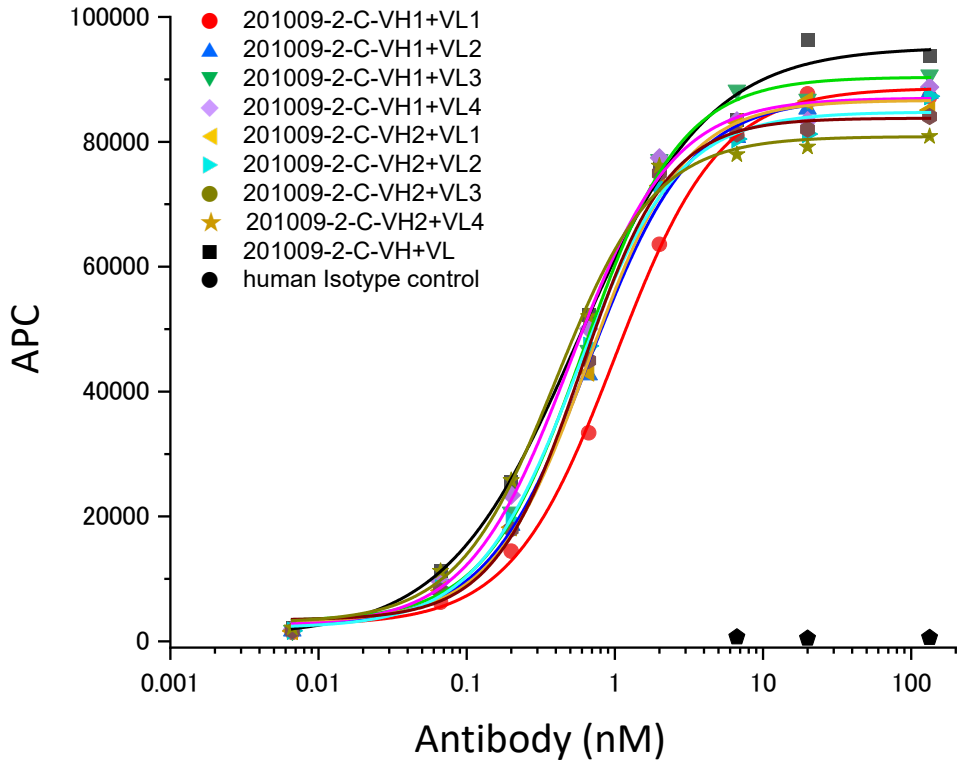



| Clone No. | host | % inhibition (2.4nM hCXCL-10) | | |
|---|---|---|---|---|
| | | 20nM | 6.6nM | 0.66nM |
| 13B4 | rat | 82 | 77 | 56 |
| 11F11 | rat | 84 | 78 | 50 |
| 201006-5-F | mouse | 90 | 66 | 34 |
| 201006-7-G | mouse | 68 | 56 | 21 |
| 201009-2-C | mouse | 87 | 78 | 43 |
| 201009-3-H | mouse | 65 | 56 | 21 |

Cell: Human T cell derived from PBMCs
Ligand: CXCL-10

NBHL mAbs inhibit CXCL-10-induced migration through endogenous human CXCR3

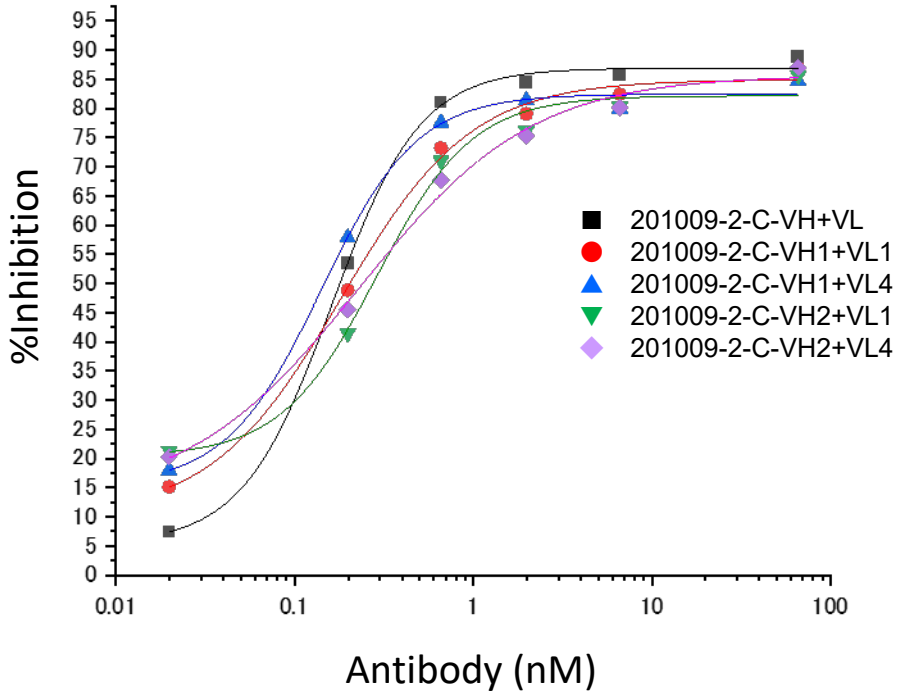
## Binding titration assay with human T cell derived from PBMCs




| Humanized mAbs | EC50 |
|---|---|
| 201009-2-C-VH1+VL1 | 1.01 |
| 201009-2-C-VH1+VL2 | 0.67 |
| 201009-2-C-VH1+VL3 | 0.62 |
| 201009-2-C-VH1+VL4 | 0.50 |
| 201009-2-C-VH2+VL1 | 0.66 |
| 201009-2-C-VH2+VL2 | 0.56 |
| 201009-2-C-VH2+VL3 | 0.59 |
| 201009-2-C-VH2+VL4 | 0.40 |
| 201009-2-C-VH+VL chimera | 0.56 |

All humanized antibodies keep binding activity to endogenous human CXCR3

# Chemotaxis assay with human T cell derived from PBMCs

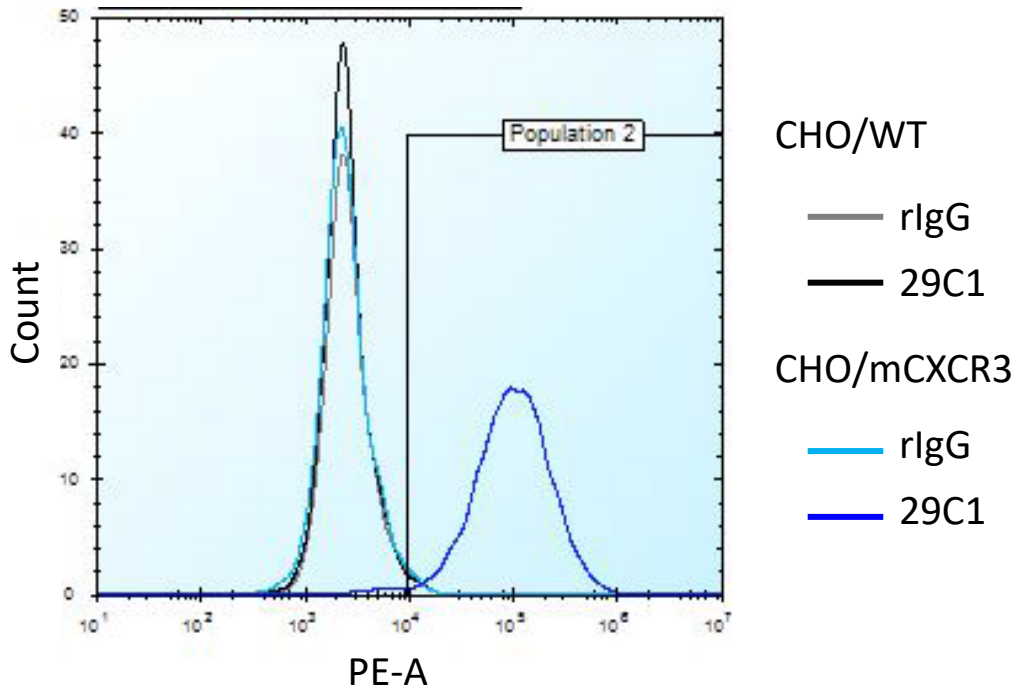



| Humanized mAbs | % inhibition (4.6 nM hCXCL-10) | | |
|---|---|---|---|
| | 66nM | 6.6nM | 0.66nM |
| 201009-2-C-VH1+VL1 | 83 | 78 | 65 |
| 201009-2-C-VH1+VL2 | 79 | 73 | 52 |
| 201009-2-C-VH1+VL3 | 76 | 83 | 58 |
| 201009-2-C-VH1+VL4 | 83 | 89 | 72 |
| 201009-2-C-VH2+VL1 | 92 | 81 | 71 |
| 201009-2-C-VH2+VL2 | 90 | 82 | 66 |
| 201009-2-C-VH2+VL3 | 90 | 89 | 60 |
| 201009-2-C-VH2+VL4 | 93 | 90 | 76 |
| 201009-2-C-VH+VL chimera | 92 | 91 | 83 |

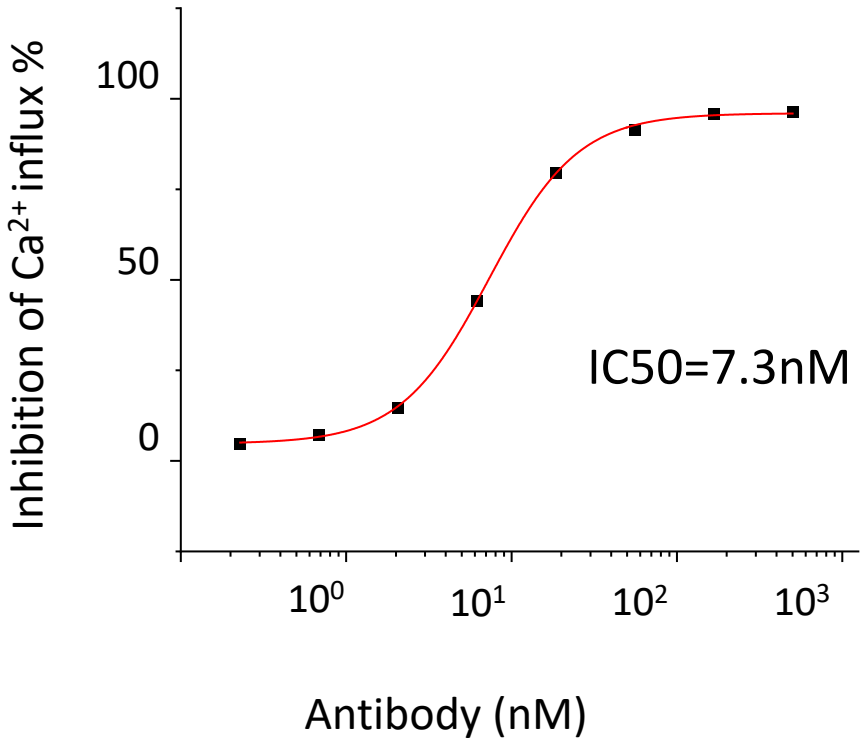
All humanized antibodies keep the activity in inhibiting CXCL-10-induced human T cell migration

# Surrogate antibody for Proof of Therapeutic Concept

- Clone 29C1 derived from rat specifically binds to CHO cells expressing mCXCR3.




- Clone 29C1 inhibits CXCL-10 induced Ca2+ influx in CHO cells expressing mCXCR3 with low concentration.




**NBHL surrogate antibody binds to mouse CXCR3 and inhibits CXCR3 signaling in CHO cell**

## Polymyositis (idiopathic inflammatory myopathies)

- 【animal model】In CIM mice, anti-CXCL10 mab administrated group showed significant improvement of muscle inflammation (Arthritis Research & Therapy 2014, 16:R126)

## Type I diabetes

- 【animal model】Cpmbination anti-CD3 with CXCR3 antagonist increased persistenbt remission in experimental models of type1 diabetes (Clinical and Experimental Immunology, 2023, 214, 131–143)

## IBD

- 【animal model】Anti-CXCL10 antibodies attenuated colitis and improved intestinal epithelial cell proliferation (Eur. J. Immunol. 2002. 32: 3197–3205, Inflamm Bowel Dis. Volume 11, Number 9, September 2005).
- 【clinical trial】 BMS-936557 showed efficacy in severely active UC patient in Phase 2 (Mayer L, et al. Gut 2014;63:442–450).

## MS

- 【animal model】Anti-CXCL10 mAb or small molecule CXCR3 antagonist significantly reduced disease severity in experimental autoimmune encephalomyelitis models (J Immunol. 2001. 166 (12): 7617–7624, Eur. J. Immunol. 2010. 40: 2751–2761, Jenh et al. BMC Immunology 2012, 13:2).

## RA

- 【animal model】CXCR3 antagonist attenuated disease progression in a murine collagen-induced arthritis model by inhibiting T cell migration (Cell Signal. 2019 Dec:64:109395, Immunol Lett. 2020 Sep:225:74-81.).

# Evidence in Polymyositis and dermatomyositis (NBHL main target disease)

## Polymyositis (idiopathic inflammatory myopathies)

- C protein-induced myositis model, which displays many of the histopathological and immunological characteristics of human idiopathic inflammatory myopathies (T cell-mediated inflammation).

- The CIM mice were treated with intraperitoneal injection of monoclonal anti-CXCL10 (200 µg/100 µL) or isotype control antibody (200 µg/100 µL) every other day from day 8 to day 20. Three weeks after induction, muscle inflammation was compared between treatment groups by the histologic score.

- The group treated with monoclonal anti-CXCL10 antibody showed significant improvement of muscle inflammation.

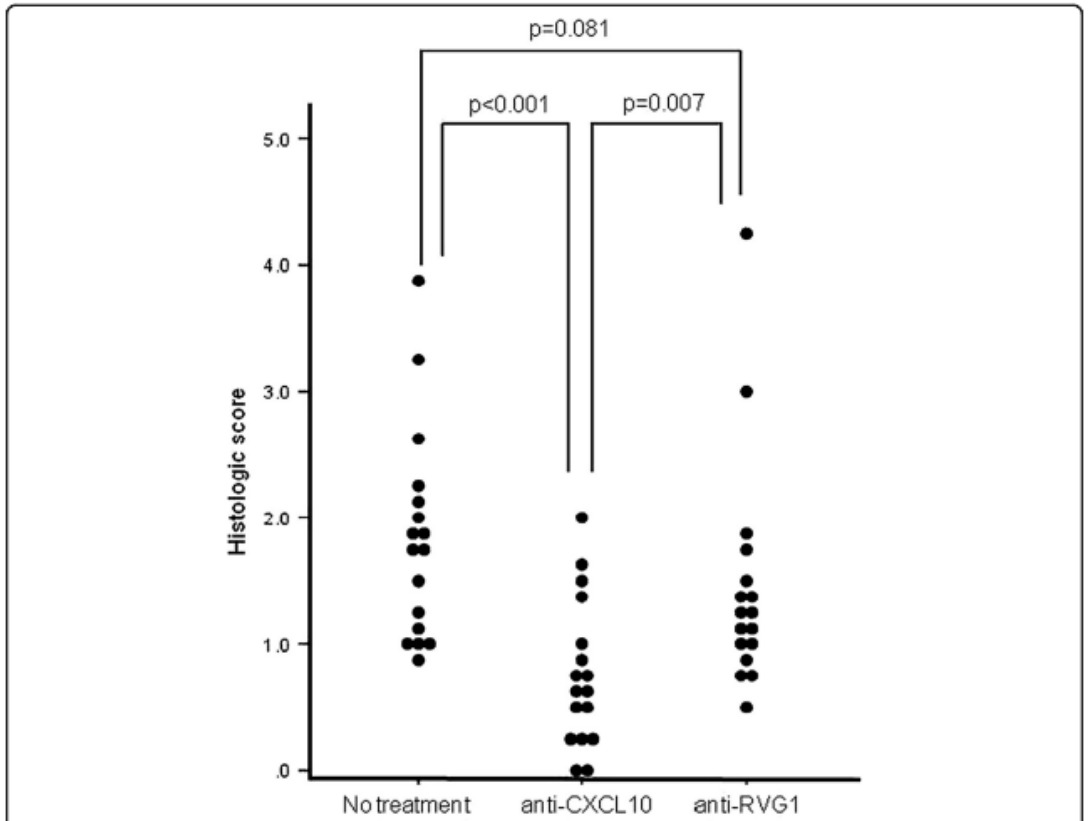
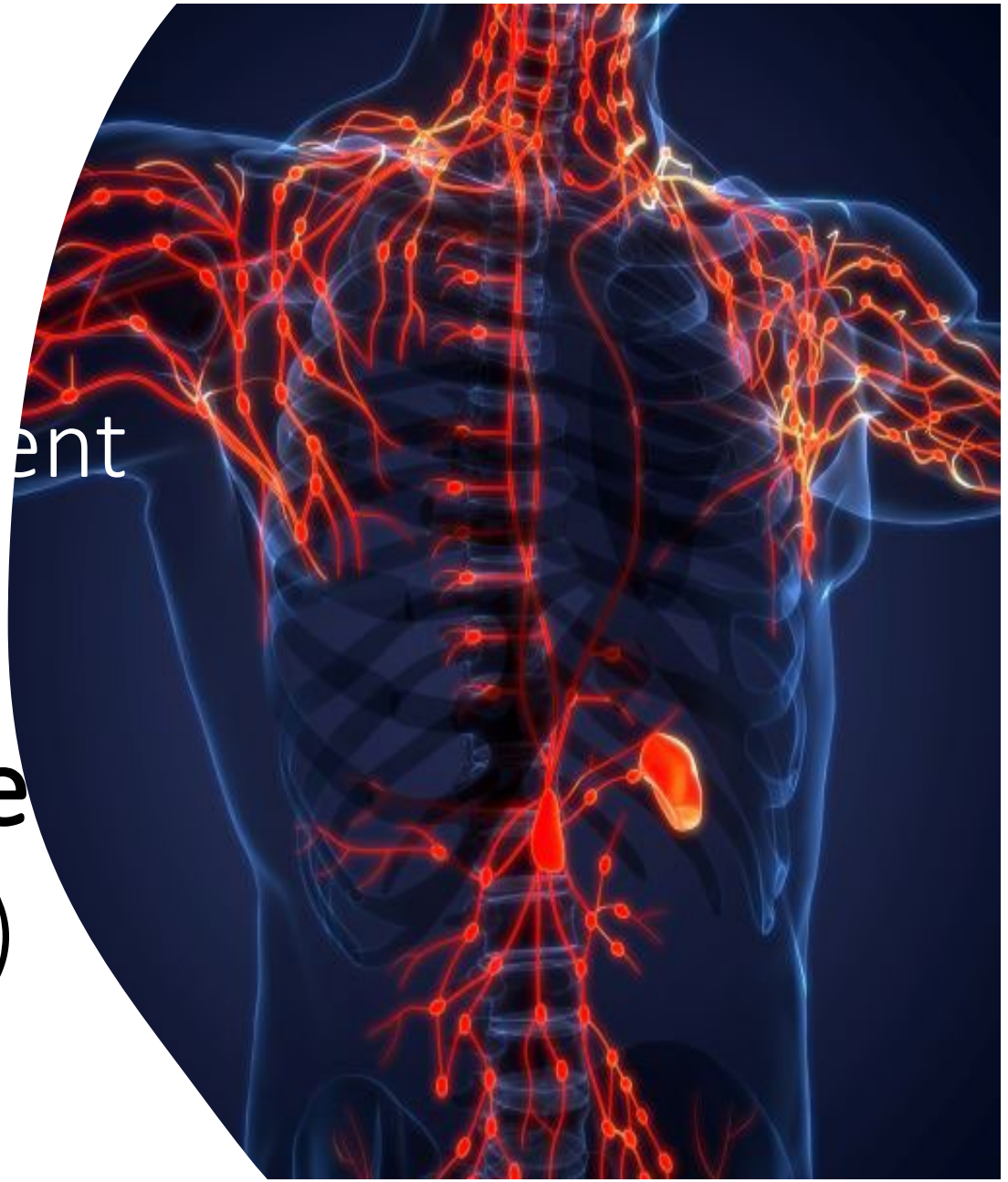



**Figure 4 Therapeutic effects of anti-CXCL10 or control antibody treatment in C-protein-induced myositis (CIM).** After inducing CIM, mice were treated with anti-CXCL10 antibody or control antibody (anti-RVG1) or were not treated (n = 17 per group). The group treated with anti-CXCL10 showed a lower inflammation score in muscles than those with anti-RVG1 or no treatment. No treatment: no treatment group, anti-CXCL10: anti-CXCL10 treatment group, anti-RVG1: anti-RVG1 treatment group. anti-RVG1, mouse anti-rotavirus IgG1.

Arthritis Research & Therapy 2014, 16:R126

# NBA-1901:

ADCC- enhanced anti **CCR7** antibody treatment can provide new therapeutic option for **Autoimmune disease** & Cancer (CLL & Solid)



*Other potential application: IPF*

# NBA-1901
## Product Summary

| | |
|---|---|
| Target Molecule | CCR7 |
| | Ligands; CCL19, CCL21 |
| Target Product Profile | Antagonist(ADCC ±), best in class<br>• Cancer; inhibition of LN invasion, metastasis, cell growth<br>• Fibrosis; inhibition of fibrocyte & inflammatory cell recruitment and activation |
| Target disease | • Autoimmune disease<br>• Cancer (CLL & Solid) |
| Property of Molecule | • ADCC enhanced humanized monoclonal antibody that selectively inhibits CCR7 signaling<br>• Injectable via subcutaneous |
| Patent Status | • The 1st patent was issued in Japan, USA, China, Australia, Europe and so on.<br>• The 2nd patent regarding new application for digestive system cancer was filed on April 2022.<br>• The 3rd patent for developing antibody was filed on March 2023. |
| R&D Status | Prior to CMC, Preclinical study |
| Competitor | CAP-100/Catapult Therapeutics in Ph1, JBH492 (ADC type mAb)/Novartis in Ph1 |

# CCR7 are highly expressed in aggressive B-cell lymphoma

*BBA - Reviews on Cancer 1875 (2021)*

**TABLE 1** | Summary of blood cancers with reported CCR7 expression studies (following 2016 WHO classification of blood neoplasms) (207).

| | | | | CCR7 | |
|---|---|---|---|---|---|
| | | | | GEP | Protein |
| **Lymphoid neoplasms** | **Precursor lymphoid neoplasms** | B-ALL and B-lymphoblastic lymphoma | | -/+ | -/+ |
| | | T-ALL and T-lymphoblastic lymphoma | | + | + |
| | **Mature B-cell neoplasms** | Chronic lymphocytic leukemia/small lymphocytic lymphoma | | + | + |
| | | Monoclonal B-cell lymphocytosis | | na | + |
| | | Splenic marginal zone lymphoma | | – | – |
| | | Hairy cell leukemia | | – | – |
| | | Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia | | na | -/+ |
| | | Monoclonal gammopathy of undetermined significance | | – | na |
| | | Plasma cell myeloma | | – | -/+ |
| | | Plasma cell myeloma variants | Smoldering myeloma | – | na |
| | | | Non-secretory myeloma | na | – |
| | | | Plasma cell leukemia | – | na |
| | | Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) | | -/+ | + |
| | | Nodal marginal zone lymphoma | | na | na |
| | | Follicular lymphoma | | -/+ | -/+ |
| | | Primary cutaneous follicle center lymphoma | | -/+ | na |
| | | Mantle cell lymphoma | | + | + |
| | | Diffuse large B-cell lymphoma | GCB type | -/+ | -/+ |
| | | | ABC type | + | + |
| | | T-cell/histiocyte-rich large B-cell lymphoma | | -/+ | na |
| | | Primary diffuse large B-cell lymphoma of the central nervous system | | na | + |
| | | EBV-positive diffuse large B-cell lymphoma | | -/+ | na |
| | | Primary effusion lymphoma | | + | na |
| | | Burkitt lymphoma | | -/+ | + |

CCR7 are highly expressed in aggressive B-cell lymphoma

# NBA-1901

## CCR7 are highly expressed in not only lymphoma but solid tumors

Expression of CCR7 in various cancers.

| Cancer type | Metastatic site | Methods | Expression |
|---|---|---|---|
| Nonsmall cell lung cancers (nsclc) | Lymph Node Metastasis (n = 71) | qRT-PCR/IHC | 63.3% |
| Gastric carcinoma | Lymph Node Metastasis (n = 64) | IHC | 66 % |
| Breast cancer | Skin Metastasis & Lymph Node Metastases (n = 142) | IHC | 67% |
| Cervical cancer | Lymph Node Metastasis & Vaginal Invasion (n = 174) | IHC | 59 % |
| Oral squamous cell carcinoma | Lymphoid Tissue Metastasis (n = 85) | qRT-PCR/ WB/ IHC | 65.9% |
| Esophageal squamous cell carcinoma | Lymph Node Metastasis (n =96) | IHC | 93.8% |
| Pancreatic cancer | Lymph Node Metastasis (n= 89) | IHC 3 | 2.6% |
| Hepatocellular cancer | Intrahepatic & Lymphatic Metastasis (n = 39) | IHC/WB | 100% |
| Oral & oropharyngeal squamous cell carcinomas | Lymph Node Metastasis (n=54) | IHC | 60% |
| Colorectal carcinoma | Lymphoid Tissue Metastasis (n = 99) | IHC | 72% |
| Papillary thyroid carcinomas | Lymphoid Tissue Metastasis (n = 65) | IHC/ qRT-PCR | High-intensity staining |
| Uveal melanoma | Liver Metastasis (n = 19) | IHC/ SNP | 76% |
| B-cell chronic lymphocytic leukemia | Lymph Nodes (n = 45) | FCM | High |
| Lung adenocarcinoma | Lymph Node Metastasis | FCM | 65% |
| Urinary bladder cancer | Lymph Node Metastasis (n = 62) | IHC | Significantly high |
| Urothelial carcinomas | Lymph Node Metastasis (n = 57) | IHC | 82.5% |

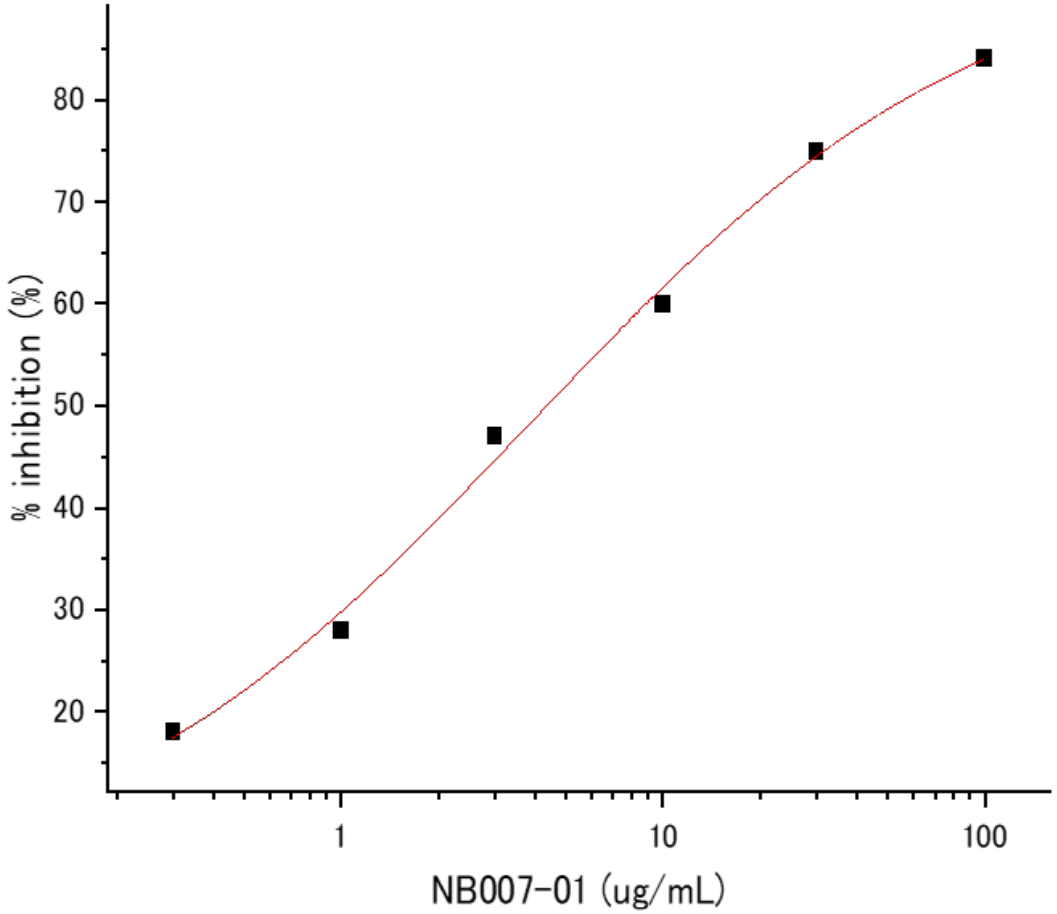
FCM = flow cytometry, qRT-PCR = quantitative real-time reverse transcriptase-polymerase chain reaction, IHC = immunohistochemistry, WB = western blot, (n) = Patients number, SNP = Single nucleotide polymorphism, PBMC = peripheral blood mononuclear cell.

*BBA - Reviews on Cancer 1875 (2021)*

High expression of CCR7 has been shown to correlate with LN metastasis in breast, endometrial, and cervical, esophageal, thyroid, pancreatic, lung, tonsillar, and many other cancers.

# In vitro profiling of Humanized CCR7 Monoclonal Antibodies - function -

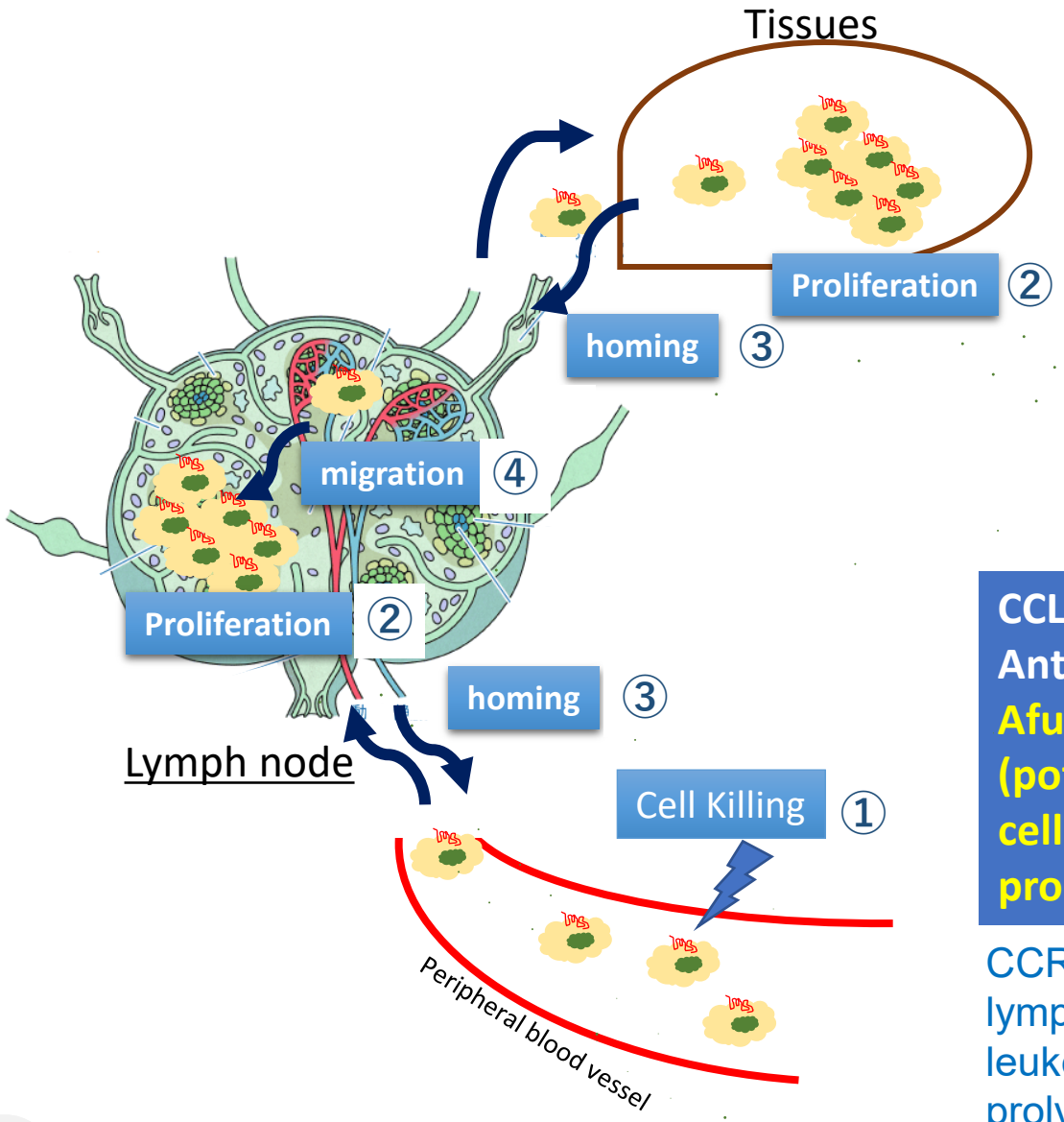
## Chemotaxis Assay




Cell: Granta-519 (human B cell lymphoma)
Ligand: CCL19
Ligand conc. : 50ng/mL

**NBHL mAb inhibited CCL19-induced migration through endogenous human CCR7**

# Positioning in Chronic Lymphocytic leukemia treatment




**1st line**

- Fludarabine + Cyclophosphamide (FC)→①
- FC + Rituximab→①

**↓relapse, refractory**

**2nd line**

- anti-CD20 ; Ofatumumab→①
- Anti-CD52; Alemtuzumab→①
- BTK inhibitor; iburitinib*→②

**Current problem: patients that discontinue ibrutinib and/or progress to ibrutinib relapsed/refractory CLL is increasing*

- Under development; BTK. PI3K, SYK, BCL2・・→①②

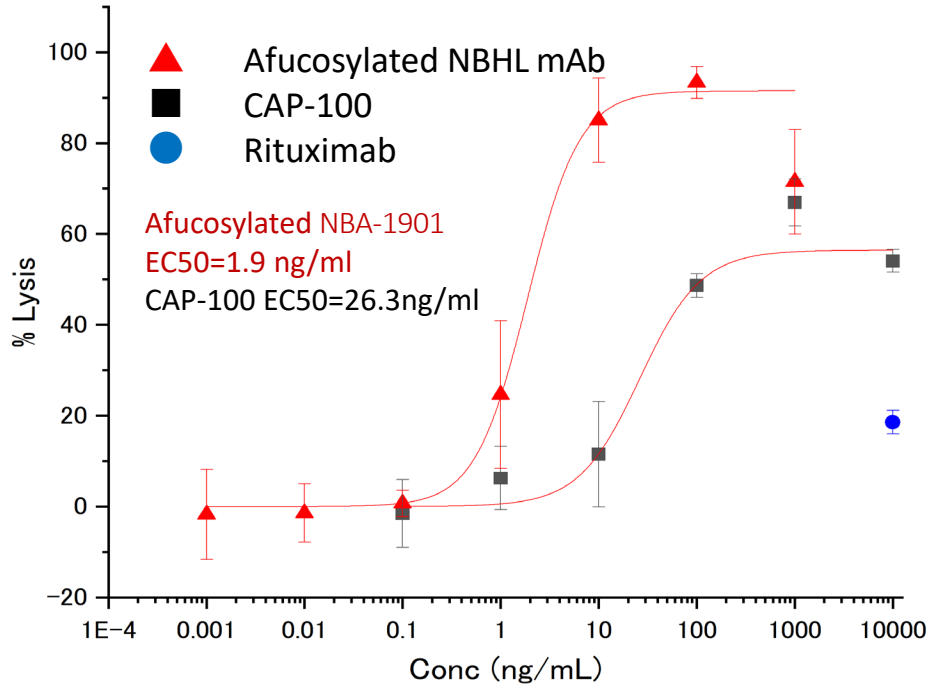
**CCL-CCR7 axis inhibit →②③④**
**Anti-CCR7 Fc effector function→①**
**Afucosylated anti-CCR7 antagonist provides novel 2nd line (potentially 1st line) therapeutic option with affecting both direct cell killing and prevention to homing CLL cells to niches of proliferative microenvironment**

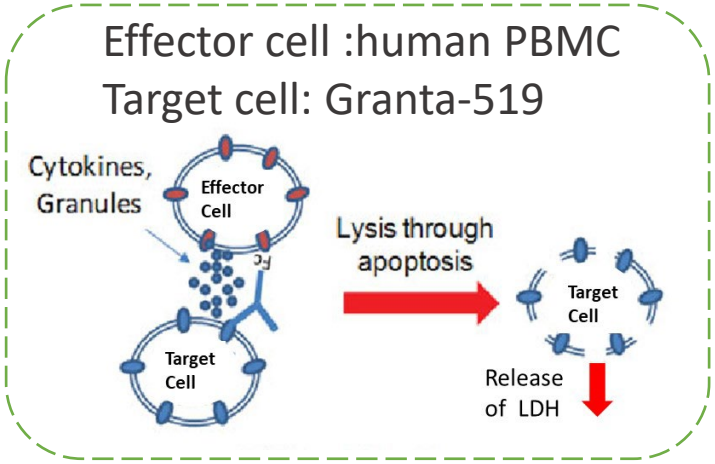
CCR7 high expression in other **B cell leukemia**: MCL (mantle cell lymphoma); FL (follicular lymphoma); B-ALL (acute lymphoblastic leukemia); MM (multiple myeloma), and **T cell leukemia**: T-PLL (T-cell prolymphocytic leukemia); SS (Sézary syndrome); T-ALL (acute lymphoblastic leukemia);

# NBA-1901

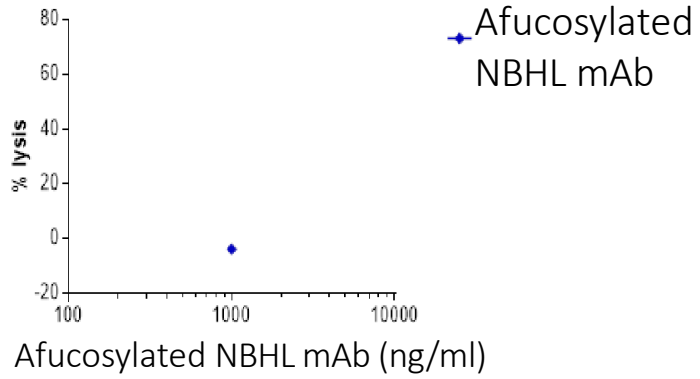
## In vitro profiling of Humanized CCR7 Monoclonal Antibodies - ADCC activity -

ADCC activity to B-cell lymphoma(Granta-519 Cell) with human PBMC (Donor ID;Z0093) E:T ratio = 50:1




In the case of E:T ratio = 1:0

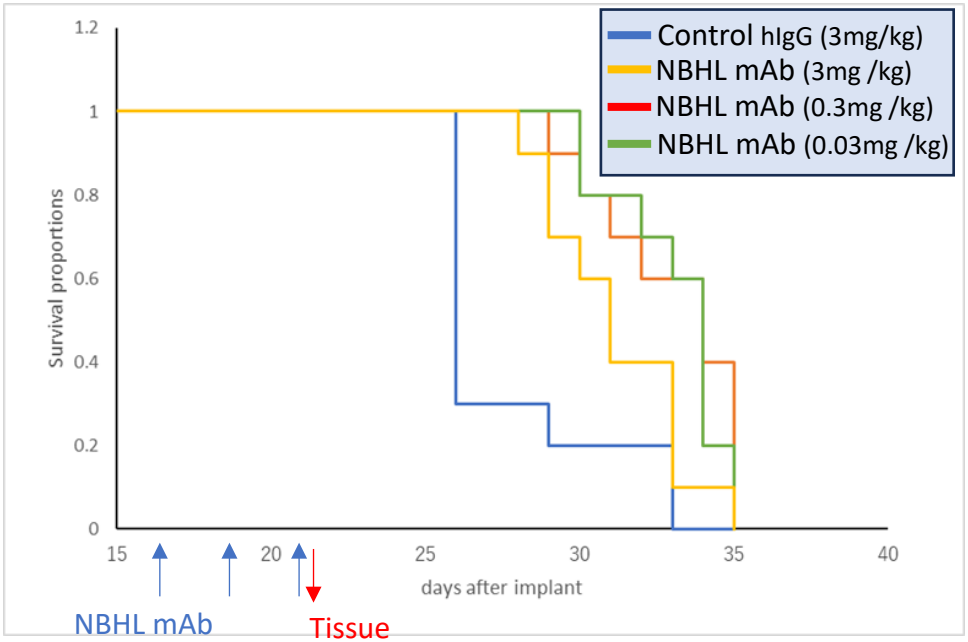



- Afucosylated NBHL mAb was stronger ADCC efficacy than naked type and stronger potency than Rituximab in all donors.
- Afucosylared NBHL mAb did not have cytotoxicity to non-tumor cells (incubate of PBMC+ NBA-1901; E:T=1:0 case).

# *In vivo* systemic xenograft study by using B Lymphoma cell line Granta-519

- ✓ *Sever CLL model in which cancer homing into lymph node is major feature.*
- ✓ *CCR7 is considered to contribute to the cancer homing into lymph node.*

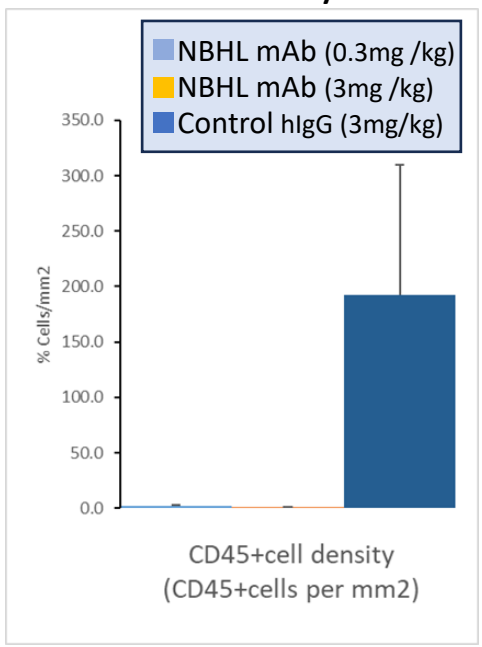
## Survival rate



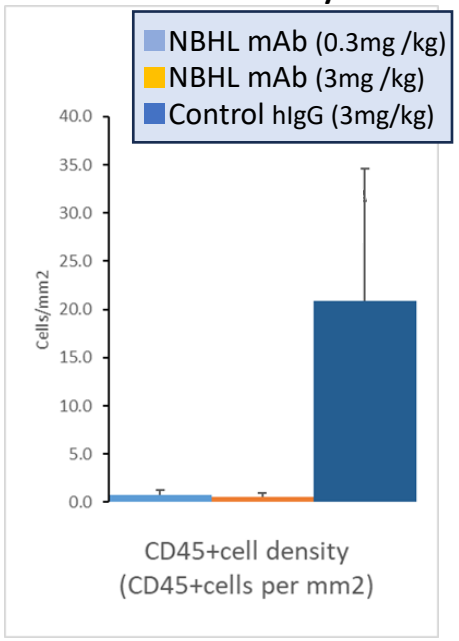

NBHL mAb iv, every 3 day (D1-D21)

Tissue collection on D21

## Infiltration in Liver on Day 21



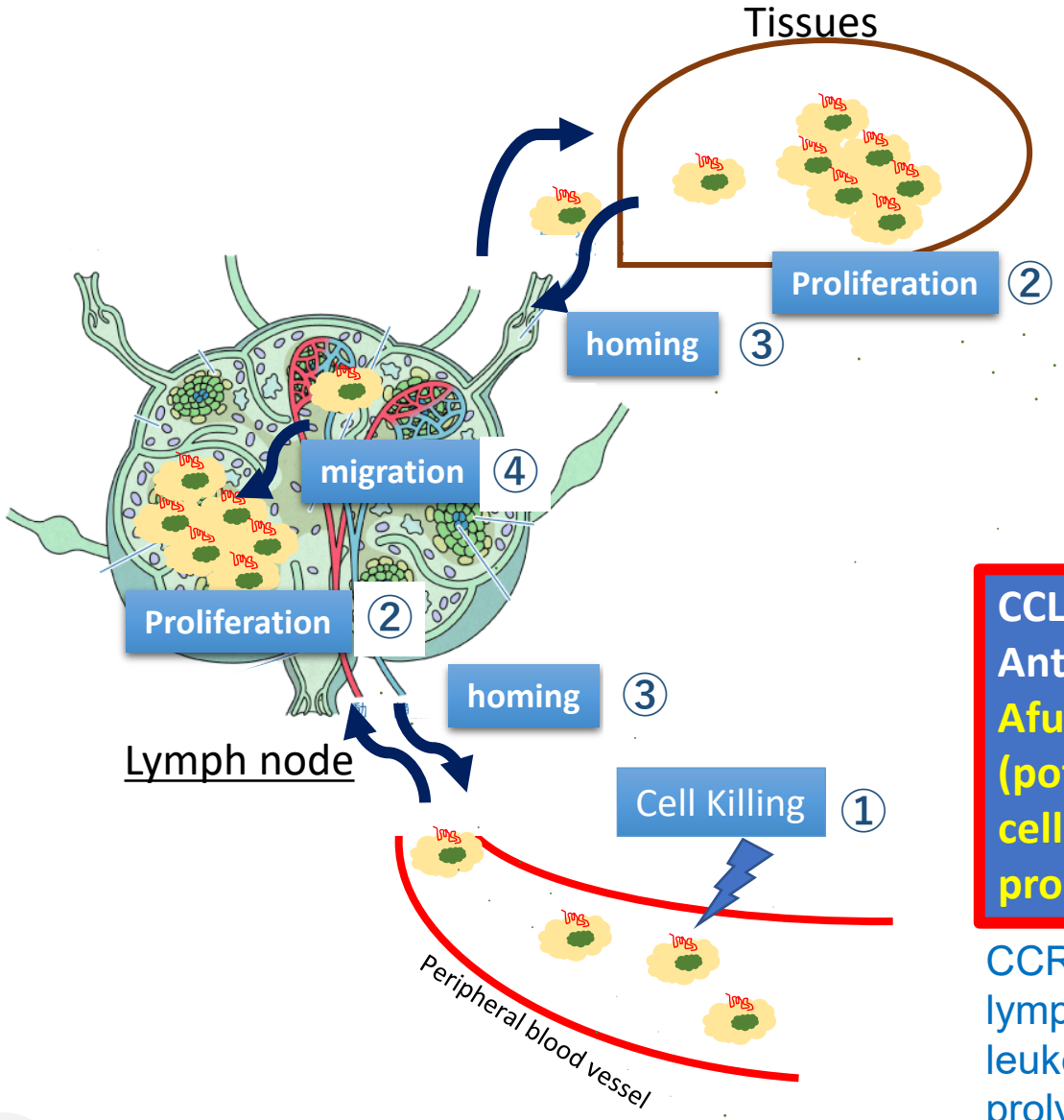

## Infiltration in LN on Day 21




- ✓Strain; CB17/SCID mice
- ✓ Tumor cell were inoculated intravenously
- ✓Drugs are administered iv twice a week (n=10, each drug group)
- ✓Survival rate are monitored until 35 days after tumor implant
- ✓Tissue infiltration of Granta519 are monitored.

**NBHL mAb prolonged the survival rate in B cell lymphoma Systemic Xenograft model**

# Positioning in Chronic Lymphocytic leukemia treatment




**1st line**

- Fludarabine + Cyclophosphamide (FC)→①
- FC + Rituximab→①

**↓relapse, refractory**

**2nd line**

- anti-CD20 ; Ofatumumab→①
- Anti-CD52; Alemtuzumab→①
- BTK inhibitor; iburitinib*→②

**Current problem: patients that discontinue ibrutinib and/or progress to ibrutinib relapsed/refractory CLL is increasing*

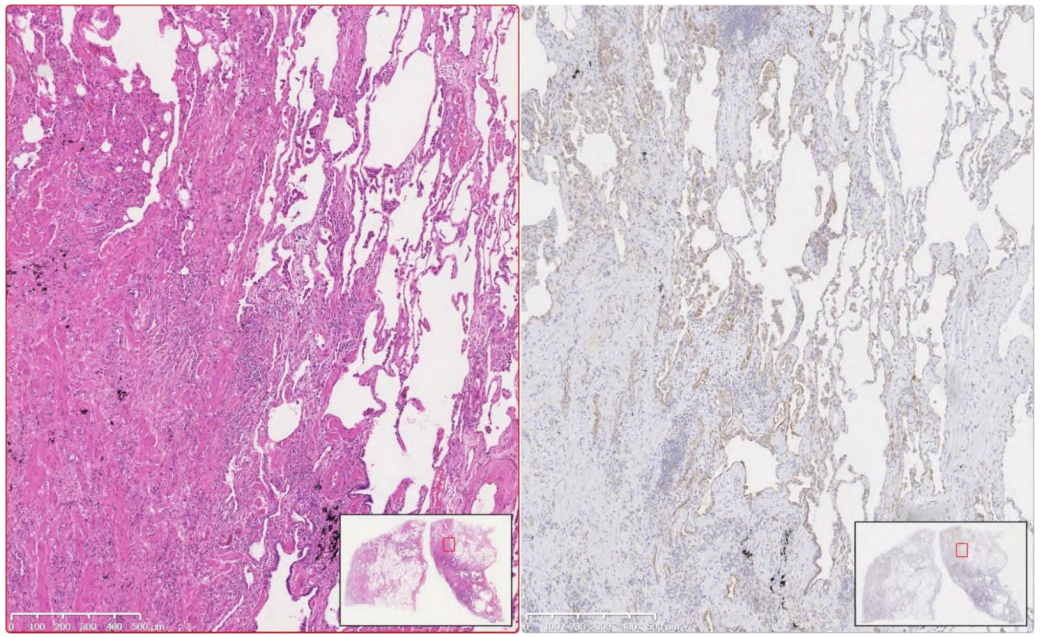
- Under development; BTK. PI3K, SYK, BCL2・・→①②

**CCL-CCR7 axis inhibit →②③④**
**Anti-CCR7 Fc effector function→①**
**Afucosylated anti-CCR7 antagonist provides novel 2nd line (potentially 1st line) therapeutic option with affecting both direct cell killing and prevention to homing CLL cells to niches of proliferative microenvironment**

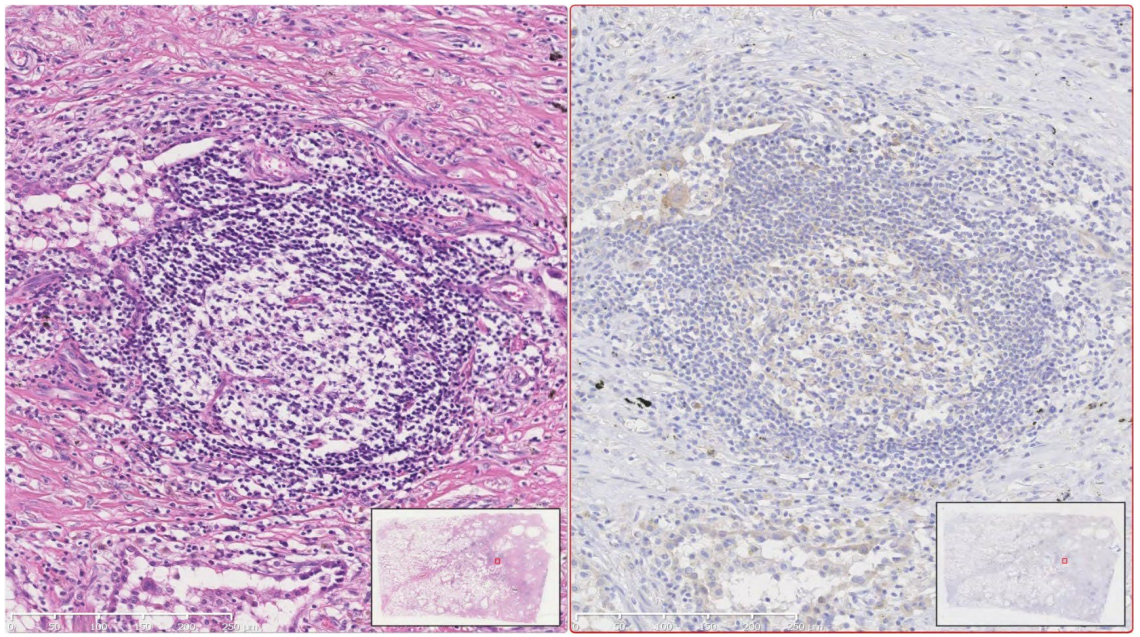
CCR7 high expression in other **B cell leukemia**: MCL (mantle cell lymphoma); FL (follicular lymphoma); B-ALL (acute lymphoblastic leukemia); MM (multiple myeloma), and **T cell leukemia**: T-PLL (T-cell prolymphocytic leukemia); SS (Sézary syndrome); T-ALL (acute lymphoblastic leukemia);

# Fibrosis is the target of NBHL anti CCR7 mAbs

## IHC of CCR7 with NBHL mAb in Human pulmonary fibrosis tissues*



The expression of CCR7 was observed in epithelium cell



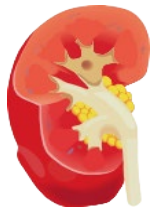
The expression of CCR7 was observed in B cells of lymphoid follicle

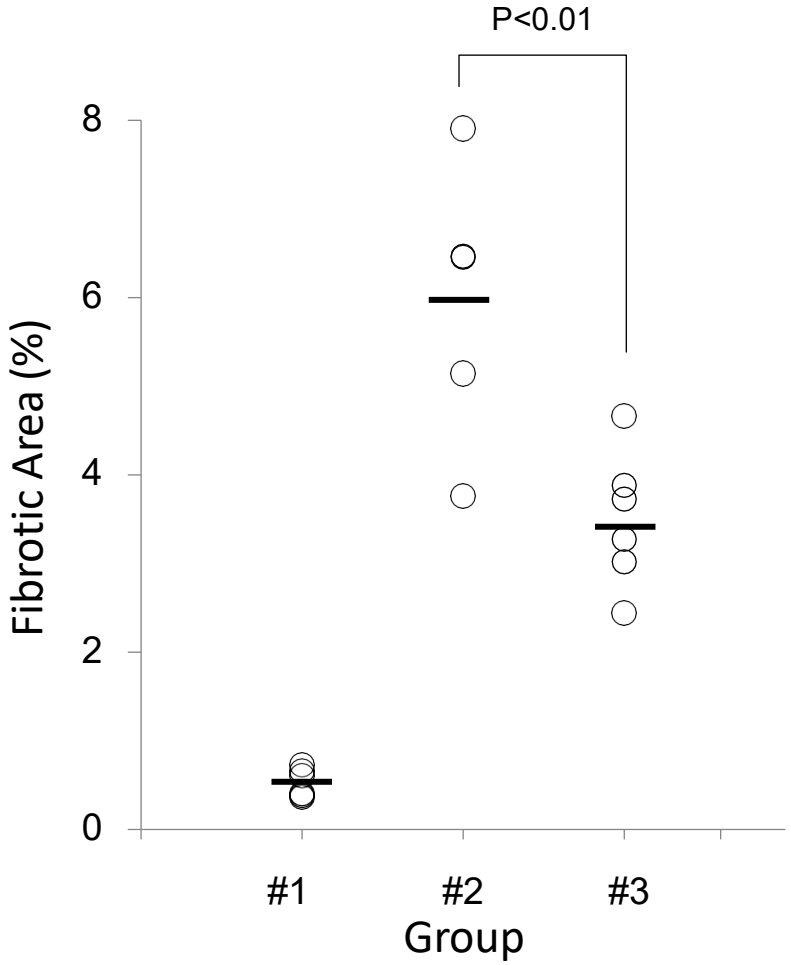
**Collaboration Research with Hokkaido Univ. (2018.12~2019.03) Lung fibrosis 23 samples*

**Anti-CCR7 has potential benefit for Fibrosis**

# Proof of Therapeutic Concept with Anti-Rat CCR7 mAb (Surrogate mAb)

## Unilateral Ureteral Obstruction Model (UUO)






**Model**

Unilateral Ureteral Obstruction Model (UUO)

**Surrogate mAb**

Anti-Rat CCR7 Antibody #74

**Group**

#1 Saline

#2 UUO + Isotype IgG

#3 UUO + CCR7 Antibody

**Dosing of Antibody**

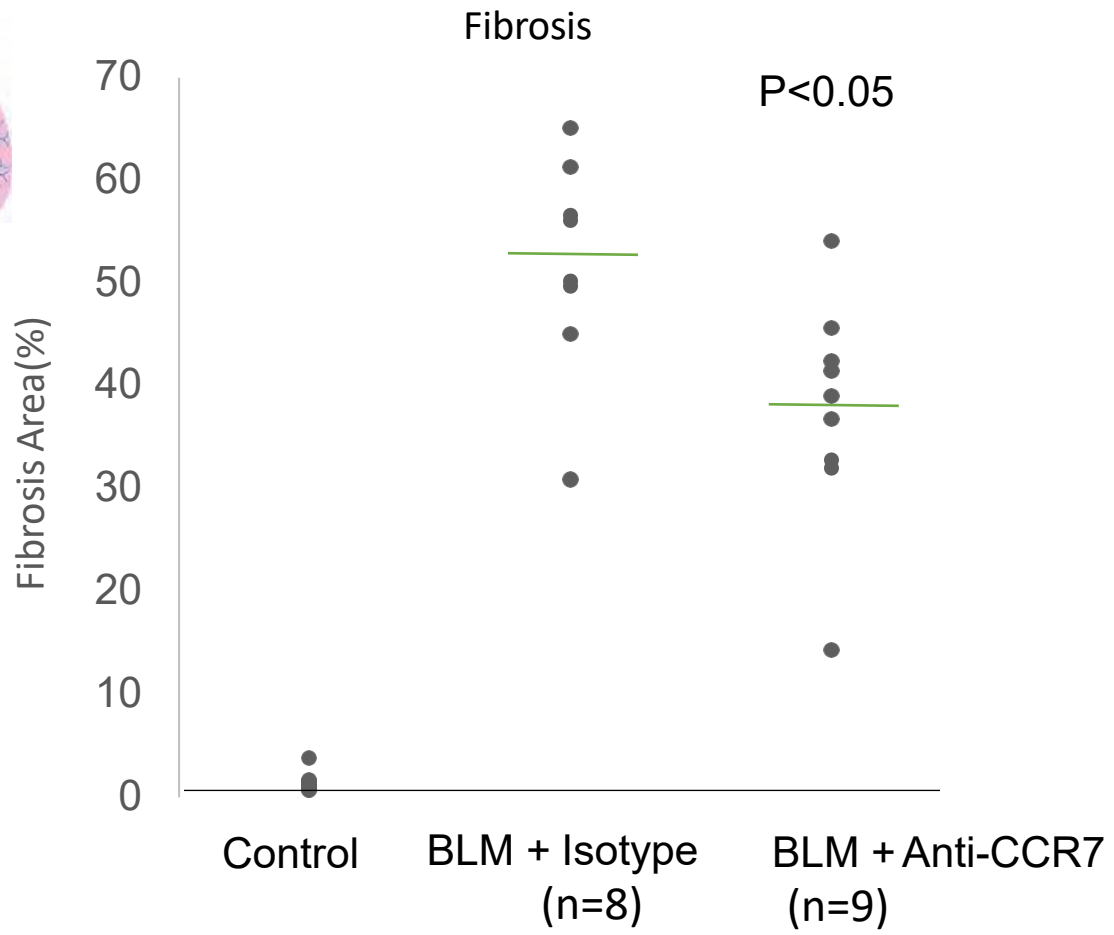
3mg/kg iv  Day 0

Scoring of Fibrosis in Day 10

Anti-CCR7 treatment has potential benefit for kidney fibrosis

# Proof of Therapeutic Concept with Anti-Rat CCR7 mAb (Surrogate mAb)

## Lung Fibrosis Induced with Bleomycin




**Model**

Lung Fibrosis Induced with Bleomycin

**Surrogate mAb**

Anti-Rat CCR7 Antibody #27

**Dosing of Antibody**

2mg/kg sc

Day 3, 7 and 11

**Criteria of the Onset of Disease**

SP-D >500 ng/ml in Day 5

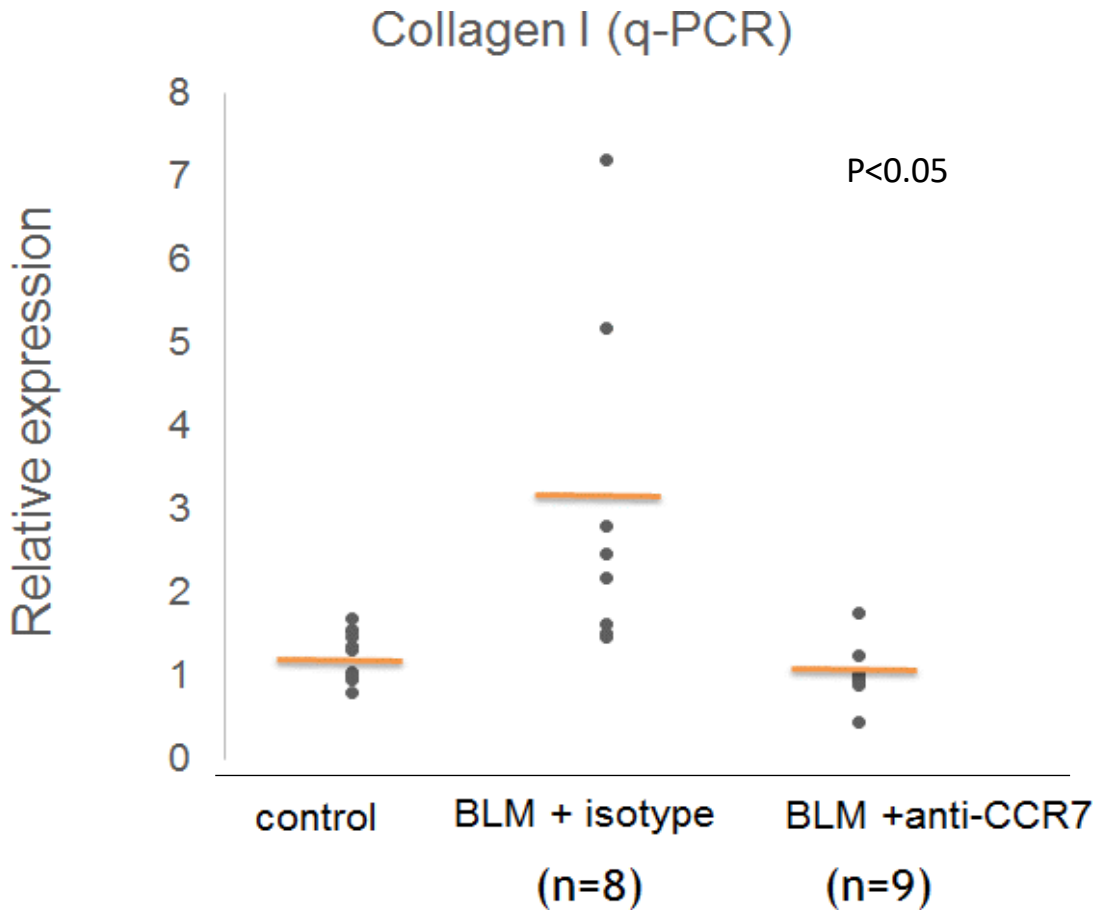
**Sampling**

Day 17

Anti-CCR7 treatment after the onset of the disease has potential benefit for lung fibrosis

# Proof of Therapeutic Concept with Anti-Rat CCR7 mAb (Surrogate mAb)

## Lung Fibrosis Induced with Bleomycin (Collagen I data)




Anti-CCR7 treatment after the onset of the disease has potential benefit for lung fibrosis

# Business model: R&D status of Anti-CCR7 Antagonist in NBHL by MoGRAA discovery engine

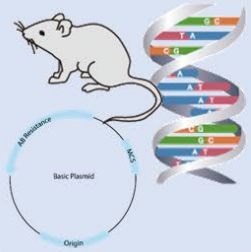
Input Concept

MoGRAA discovery engine

Patents

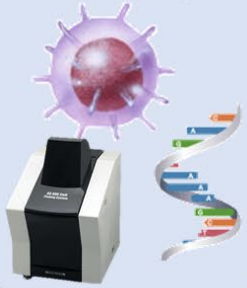
Target validation


Immunization

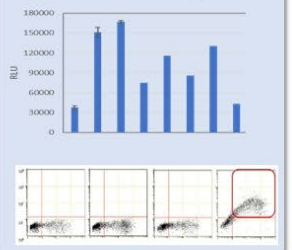


Genes

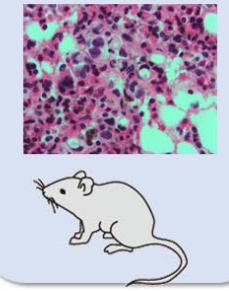
Screening



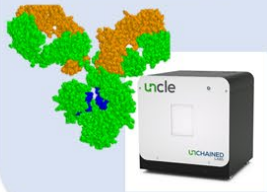
Profiling



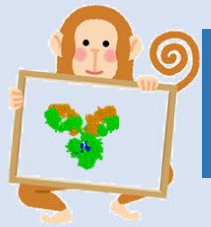
PoC



Humanized Developability assessment



Early preclinical



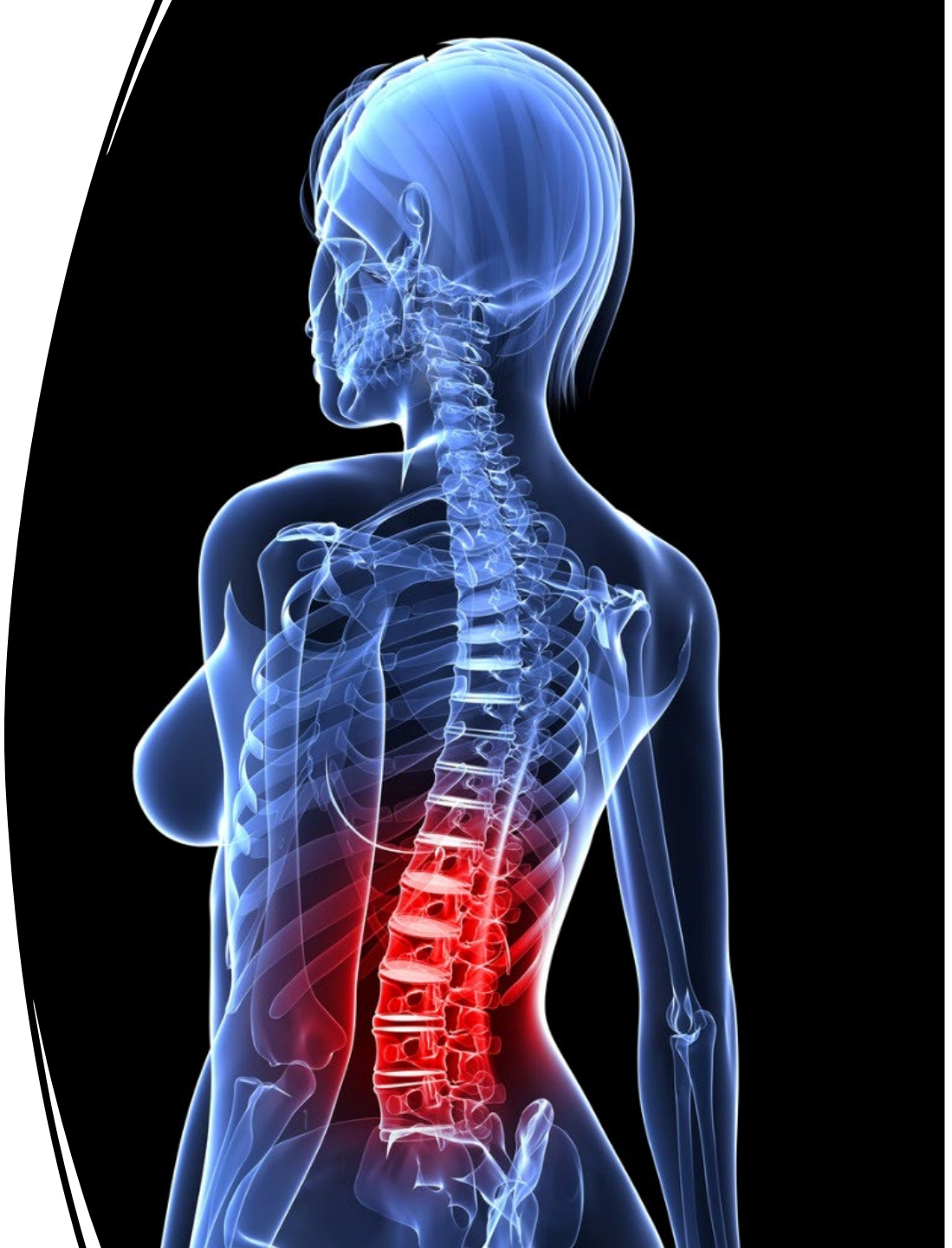
Early out-license To Pharmaceuticals

**We are here .**

- Start of Ph1 : After raising funds
- The 3rd patent for developing antibody was filed on March 2023 and expired in 2043.
- We are seeking for pharmaceutical partner for development and commercialization.

# NBA1603

Anti **EP4** antibody treatment can provide new therapeutic option for **Ankylosing spondylitis**



# NBA1603
## Product Summary

| | |
|---|---|
| Target Molecule | EP4 |
| | Ligands; PGE2 |
| Target Product Profile | Long acting EP4 antagonist (First in Class)<br>• Inflammation; Inhibition of Th17 & DC activation<br>• Pain; inhibition of sensory neuron activation<br>• Immuno-oncology; inhibition of Treg & MDSC activation, recover from NK-DC crosstalk suppression |
| Target disease | • Autoimmune disease (Ankylosing spondylitis )<br>• Immuno-oncology<br>• Psoriasis, IBD, RA |
| Property of Molecule | • A humanized mAb that selectively inhibits EP4 signaling<br>• Injectable via subcutaneous |
| Patent Status | • The 1st patent was issued in Japan (April 2013), Europe (2014), USA , China (2015) and other major countries.<br>• The patent issued in Europe covers any “antagotistic mAb for EP4”<br>• The 2nd patent has been filed in 2021. |
| R&D Status | Prior to CMC (The cell line development can start immediately), Preclinical study |
| Competitor | LMW EP4 antagonists for immuno-oncology |

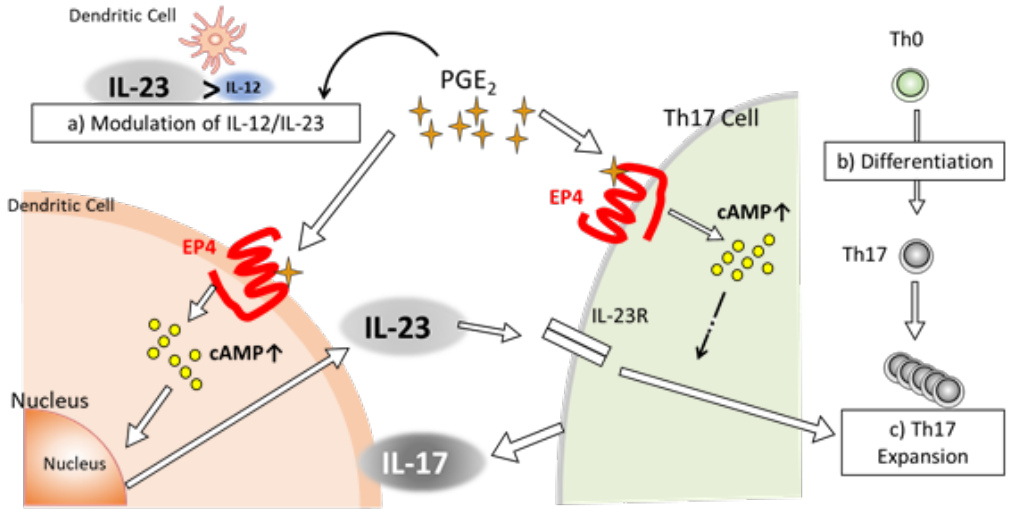
# Feature of anti EP4

**The Role of EP4 in Chronic Inflammation**

- Function : IL-23R upregulate in Th17, Th17 expansion
- Ligand : PGE2
- Target Cell : Th17, DC

**The expected effect of EP4 Antagonist**

- Inhibition of the IL-23R upregulation
- Inhibition of Th17 expansion and inflammation
- Relief of Pain caused by inflammation




<Inflammation>

- EP4 involvement in the generation of pathogenic Th17 cells in AS.
- PGE2 binds to the EP4 receptor and inhibits FoxO1 expression in Th17 cells.
- IL-23 receptor (IL-23R) is upregulated.
- Activation of IL-23 receptor leads to Th17 cell accumulation and to an upregulation of EP4 in a positive feedback loop. (Arthritis Research & Therapy volume 21, Article number: 159 (2019) )
- IL-23 inhibition is ineffective to AS (Drug Delivery System 35-5, 2020)

<Pain>

- PGE2 has a great impact on pain signals, and pharmacological intervention in upstream and downstream signals of PGE2 may serve as novel therapeutic strategies for the treatment of intractable pain (Biol Pharm Bull. 2011;34(8):1170-3)
- EP4 is a potential target for the treatment of inflammatory pain (J Pharmacol Exp Ther December 2006, 319 (3) 1096-1103)
- PGE2 have an active role in the induction of pain (Biomedicines. 2021 Jan; 9(1): 54.)

**Anti EP4 antibody suppress cytokine production and inflammatory pain**

## The Role of EP4 in Chronic Inflammation

- Function : IL-23R upregulate in Th17, Th17 expansion
- Ligand : PGE2
- Target Cell : Th17, DC

## The expected effect of EP4 Antagonist

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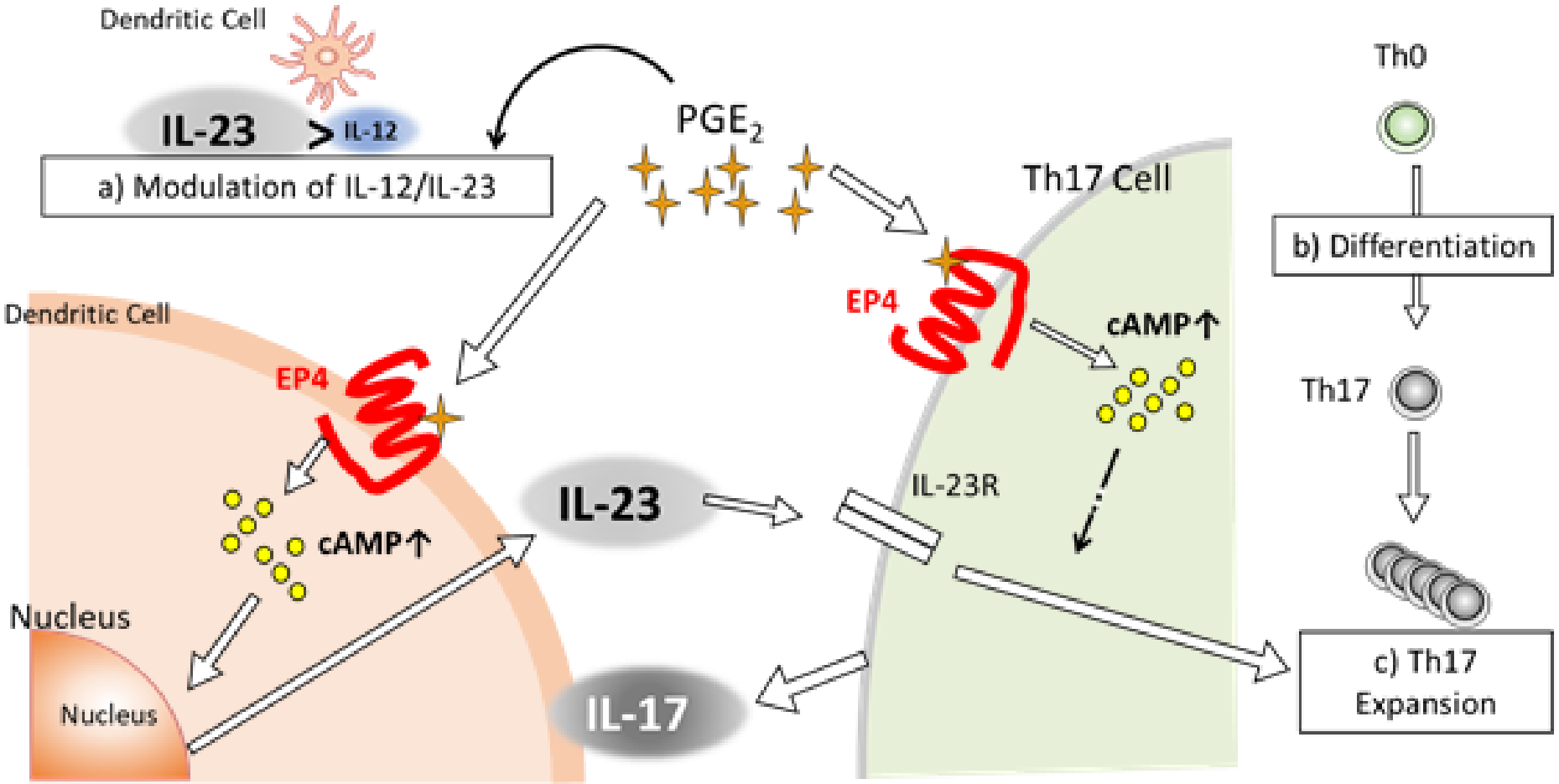
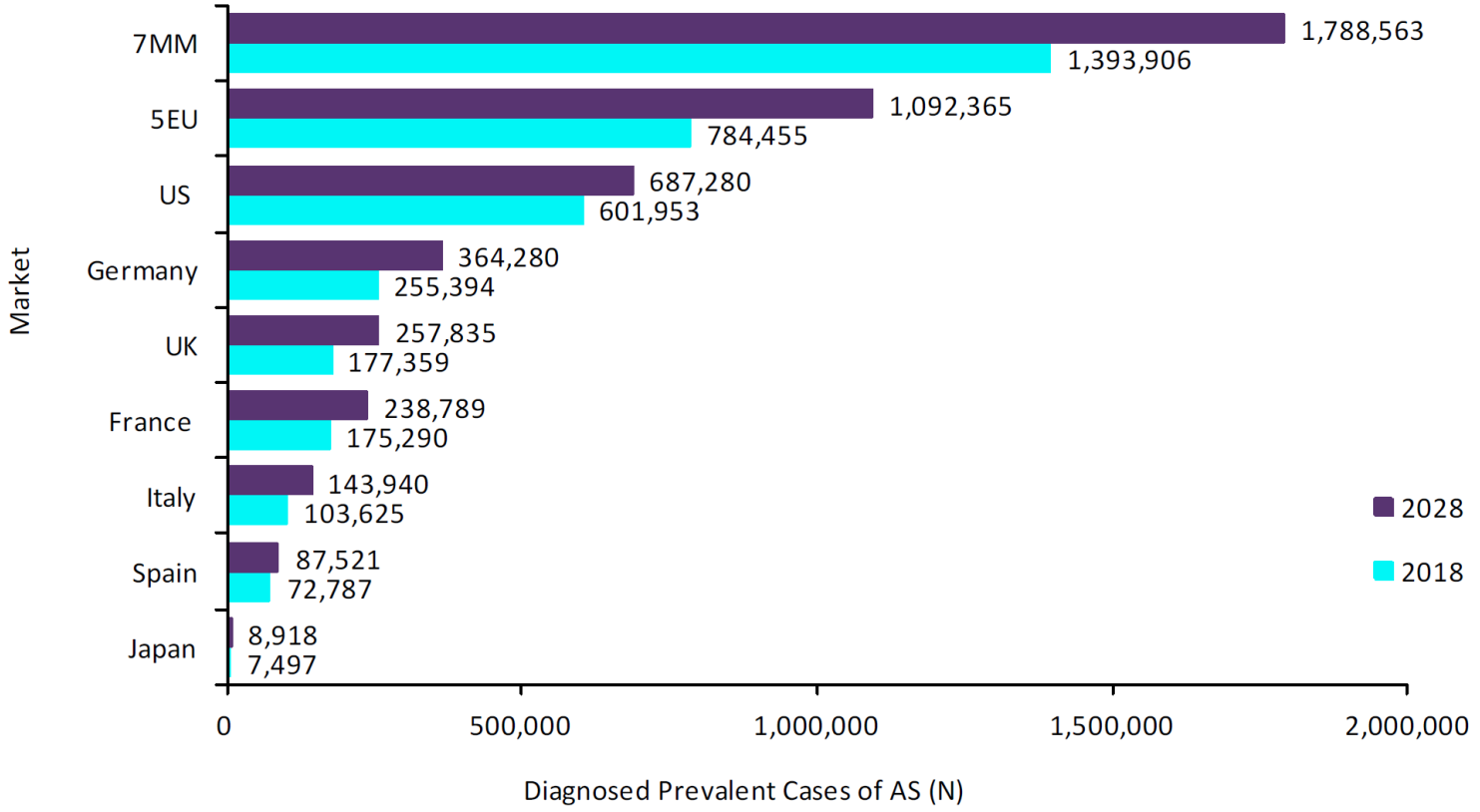


# Diagnosed Prevalent Cases of ankylosing spondylitis (AS) , All Ages, Both Sexes, N, 2018 and 2028




Source: GlobalData; Carter *et al.*, 1979; Hukuda *et al.*, 2001; Collantes *et al.*, 2007; Costantino *et al.*, 2015; Primary Market Research

5EU = France, Germany, Italy, Spain, and UK; 7MM = US, 5EU, and Japan

© GlobalData

Diagnosed Prevalence (%) of AS ： EU (0.3%) and US( 0.1%)

The association of *HLA-B*27* with AS is amongst the strongest of any known association of a common variant with any human disease.

# Competitor landscape in AS

| Drug Name | Brand Name | Company Name | Stage | Target | Molecule Type |
|---|---|---|---|---|---|
| brodalumab | Lumicef | Kyowa Kirin Co Ltd | Marketed | Interleukin 17 Receptor (IL17R) | Monoclonal Antibody |
| secukinumab | Cosentyx | Novartis | Marketed | Interleukin 17A | Monoclonal Antibody |
| ixekizumab | Taltz | Eli Lilly | Marketed | Interleukin 17A | Monoclonal Antibody |
| bimekizumab | | UCB SA | Phase III | Interleukin 17A | Monoclonal Antibody |
| adalimumab | Humira | AbbVie | Marketed | TNF | Monoclonal Antibody |
| upadacitinib ER | Rinvoq | AbbVie | Marketed | Tyrosine Protein Kinase JAK1 | Small Molecule |
| tofacitinib citrate | Xeljanz | Pfizer Ltd | Marketed | Tyrosine Protein Kinase JAK3 | Small Molecule |

*Seven anti IL-17A antibody pipelines are on-going Phase I~III.*

## *Other treatment*

*NSAID (COX-I/II inhibitor) for pain,  PDEIV inhibitor*

Current therapeutic options for AS is so limited.

# The existing therapies still have room for improvement in efficacy in AS

Effective

remarkable effective

**Table 1.** Characteristics of individual studies included in the network meta-analysis

| Study | Drugs | *N* | Drugs | Patients, *n* | ASAS20 | ASAS40 |
|---|---|---|---|---|---|---|
| Van der Heijde et al. [15] | JAK inhibitor | 187 | Upadacitinib 15 mg | 93 | [illegible] | 48 |
| | | | Placebo | 94 | 38 | 24 |
| Van der Heijde et al. [14] | JAK inhibitor | 116 | Filgotinib 200 mg | 58 | [illegible] | 22 |
| | | | Placebo | 58 | 23 | 11 |
| Van der Heijde et al. [12] | JAK inhibitor | 103 | Tofacitinib 5 mg | 52 | [illegible] | 24 |
| | | | Placebo | 51 | 21 | 10 |
| Kivitz et al. [13] | Anti-IL-17A | 168 | Secukinumab 150 mg | 85 | [illegible] | 34 |
| | | | Placebo | 83 | 41 | 25 |
| Pavelka et al. [11] | Anti-IL-17A | 116 | Secukinumab 150 mg | 57 | [illegible] | 25 |
| | | | Placebo | 59 | 23 | 14 |
| Baeten et al. [10] | Anti-IL-17A | 247 | Secukinumab 150 mg | 125 | [illegible] | 52 |
| | | | Placebo | 122 | 35 | 16 |

| Comparison | Study number | Patients, *n* |
|---|---|---|
| Placebo | 6 | 467 |
| Secukinumab 150 mg | 3 | 267 |
| Upadacitinib 15 mg | 1 | 93 |
| Filgotinib 200 mg | 1 | 58 |
| Tofacitinib 5 mg | 1 | 52 |

ASAS20 or 40, Assessment of SpondyloArthritis International Society 20 or 40 response criteria (improvement of ≥20% and absolute improvement of ≥1 unit [on a 10-unit scale] in at least three of the four main ASAS domains, with no worsening by ≥20% in the remaining domain) [19]; anti-IL-17A, anti-interleukin-17A monoclonal antibody.

**New Mode of action added to the current therapy are needed !**

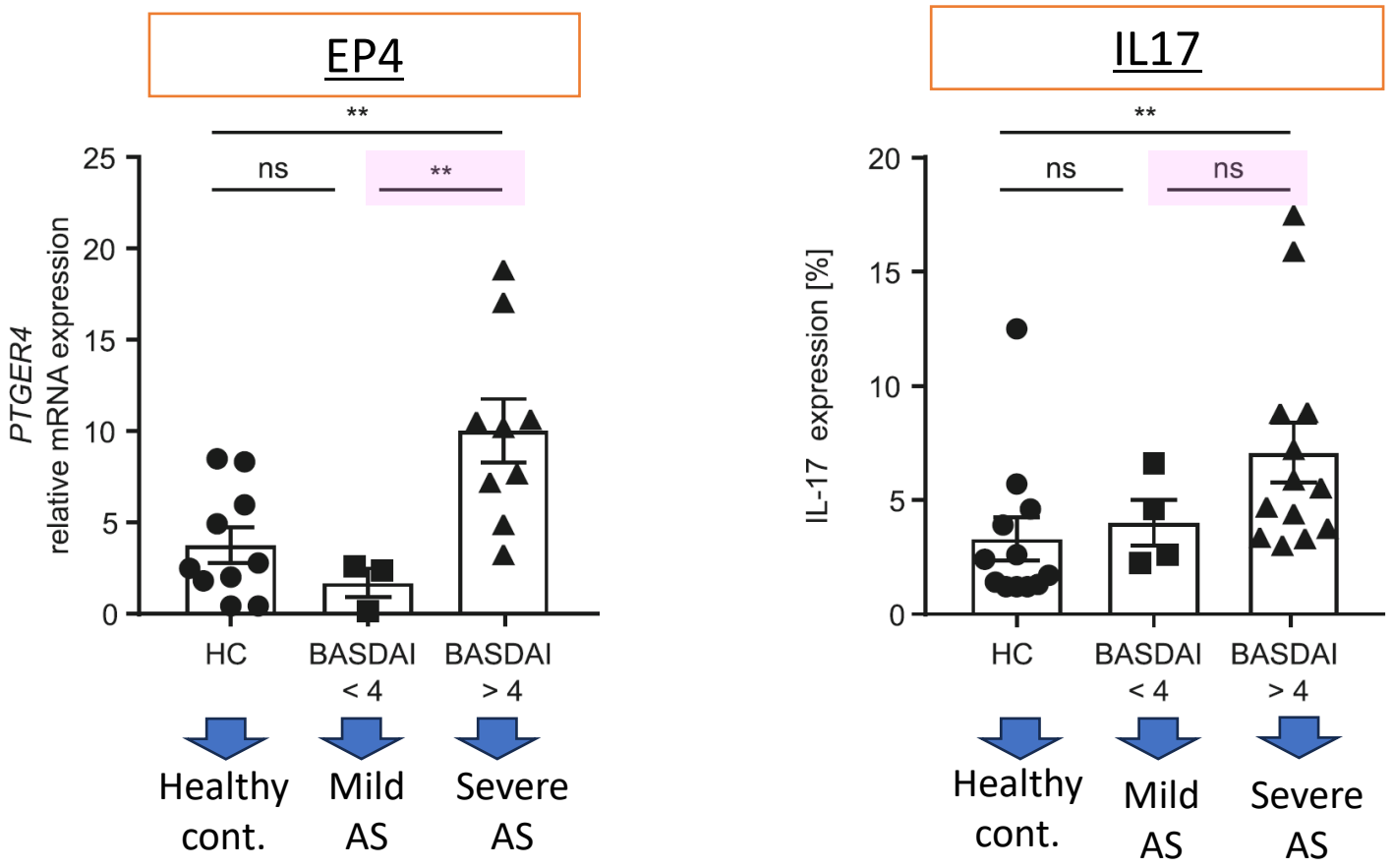
# NBA1603
## Competitors and differentiation

| Product | NBA1603 | CR-6086 | Grapiprant | ONO-4578 | E-7046 |
|---|---|---|---|---|---|
| Developer | **NB Health Laboratory** | Rottapharm Biotech. | AskAt, RaQualia Pharma | Ono, BMS | Eisai, Adlai Nortye Bio. |
| Modality | **Monoclonal Antibody** | Small Molecule | | | |
| Function | **Antagonist** | Antagonist | Antagonist | Antagonist | Antagonist |
| Stage | **Pre-clinical** | Phase 2 | Phase 2 | Phase 2 | Phase 2 |
| Indication | **Autoimmune Chronic inflammatory** | Cancer (incl. Solid tumor) RA | Solid tumor Pain | Solid Tumor | Solid tumor |
| Clinical results | - | Phase2 on going | Insufficient in Tumor Well Control in Pain | >50% of the IO-treated subjects achieved tumor shrinkage. | Not Disclosed |

NBA1603 is the only therapeutic antibody for EP4 and expected to have high selectivity

# EP4 expression by Th17 cells is associated with high disease activity in ankylosing spondylitis

## mRNA expression in AS



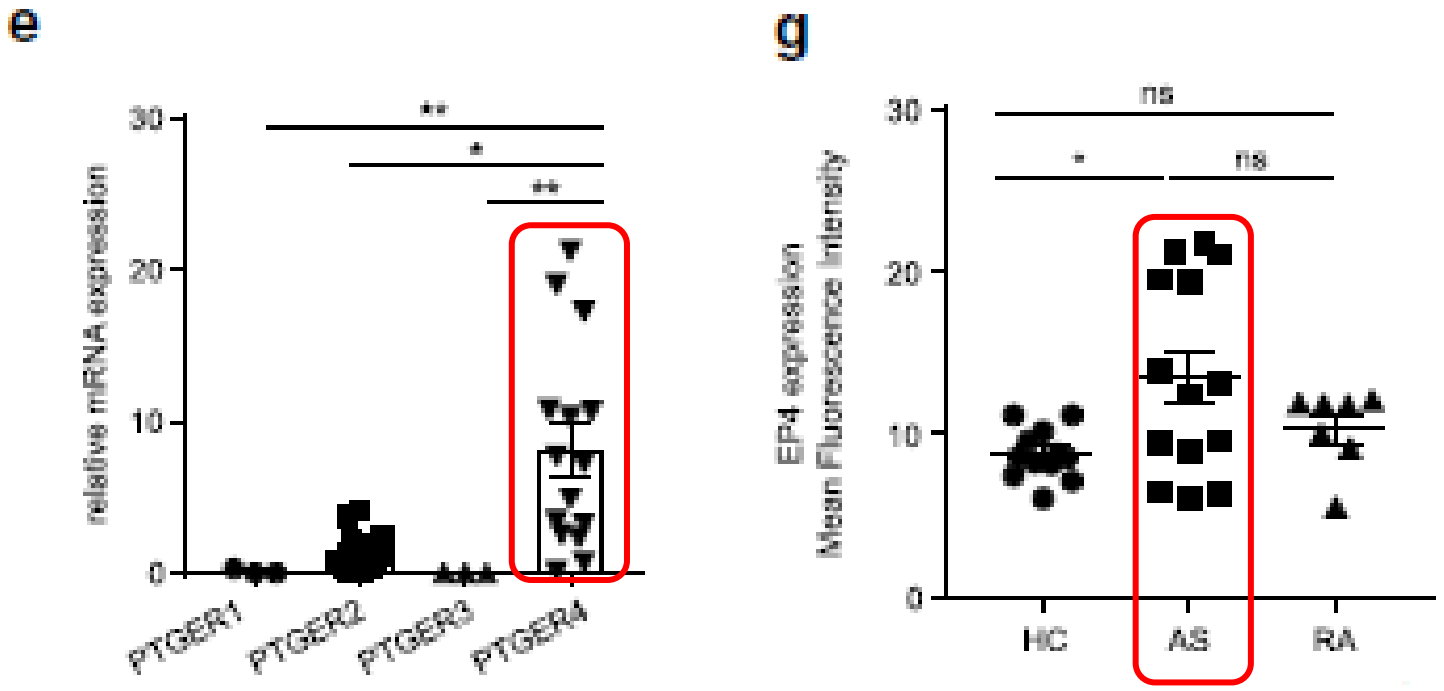

EP4 expression in Th17 cells is associated with high disease activity in AS.
(left) PTGER4 expression in patients with low or high BASDAI values. PTGER4 expression was assessed by RT-PCR. Th17 cells were induced in vitro for 4 days from naïve $CD4^+CD45RA^+$ T cells under Th17-skewing conditions.
(Right) IL-17 expression in AS patients with low or high BASDAI values. Cells were analyzed by flow cytometry. The percentage of positive cells is shown.

*Arthritis Res Ther. 2019; 21: 159.*

**Compare to IL-17, EP4 expression by Th17 cells is well associated with AS severity**

# EP4 expression by Th17 cells is associated with high disease activity in ankylosing spondylitis

## EP4 mRNA expression




EP4 is overexpressed in Th17 cells from patients with ankylosing spondylitis.
(left) RT-PCR analysis of $PGE_2$ receptor genes in Th17 cells from patients with AS. Th17 cells were generated from naïve $CD4^+CD45RA^+$ T cells under Th17 skewing conditions ($n = 15$; $^{**}p < 0.01$; $p$ value calculated using Kruskal-Wallis test). The values are represented as the difference in $C_t$ values normalized to β2-microglobulin for each sample using the following formula: relative RNA expression = $(2^{-dCt}) \times 10^3$.
(right) EP4 expression in Th17 cells (HC $n = 12$, AS $n = 14$, RA $n = 7$; $^*p < 0.05$; $p$ value calculated using Mann-Whitney test)

*Arthritis Res Ther. 2019; 21: 159.*

EP4 is specifically expressed in patients with AS.
-> EP4 mAb has potential benefit for Ankylosing spondylitis.

# NBA1603

## SNPs of EP4 vs Autoimmune diseases （beyond Ankylosing spondylitis )

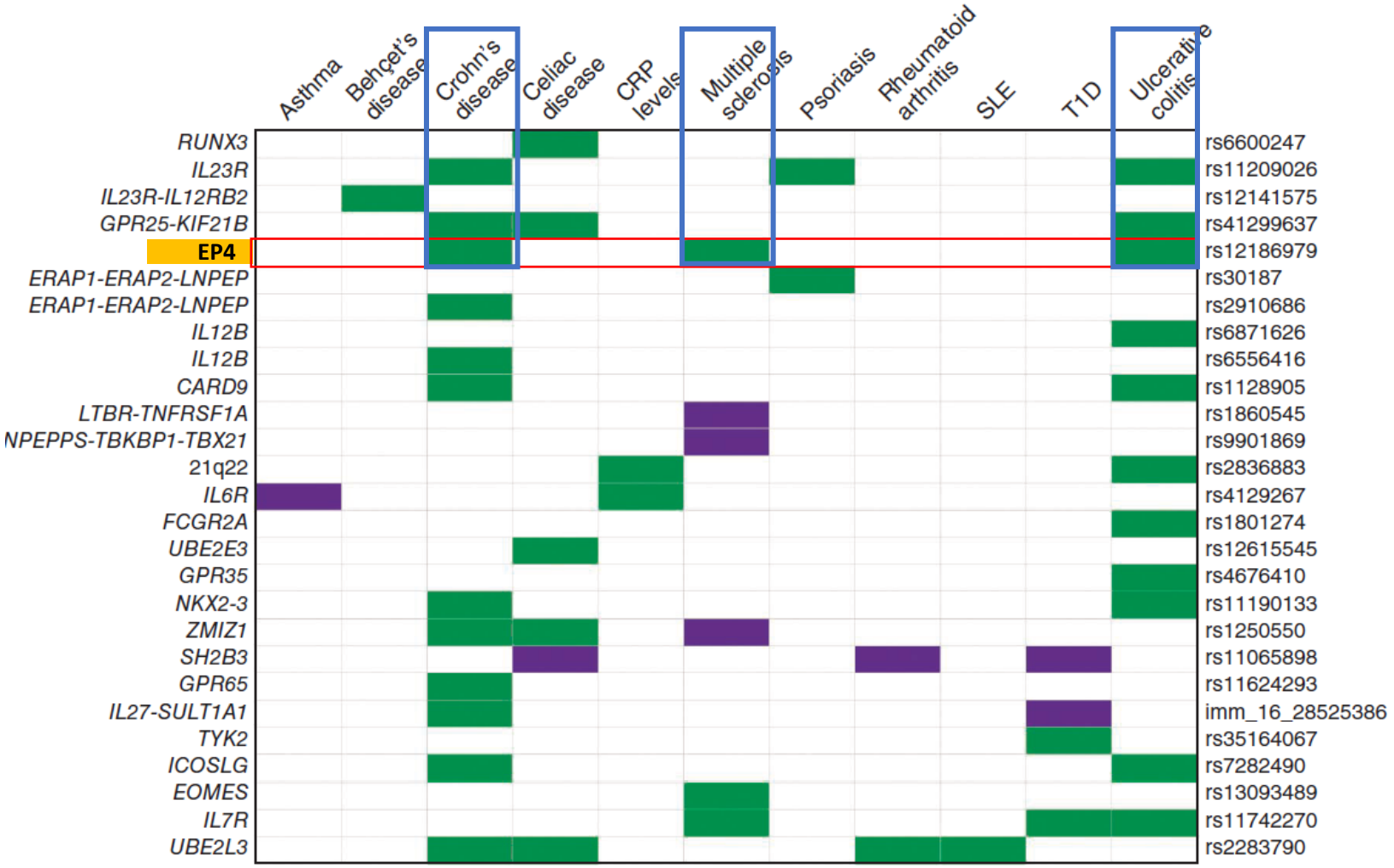


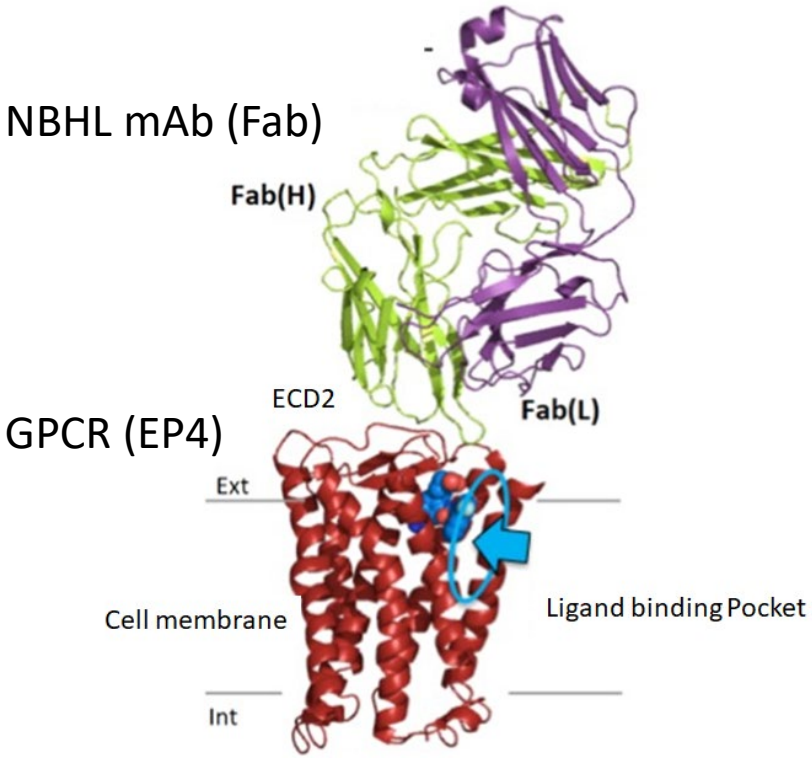

**Figure 3** Ankylosing spondylitis genetic susceptibility loci overlap with those of other autoimmune diseases. Diseases are represented in columns, and ankylosing spondylitis susceptibility loci are represented in rows. Shared susceptibility loci are colored green if effect size is concordant and purple if effect size is discordant. Data are shown in **Supplementary Table 8**. SLE, systemic lupus erythematosus; T1D, type 1 diabetes.

*Identification of multiple risk variants for ankylosing spondylitis through high-density genotyping of immune-related loci*

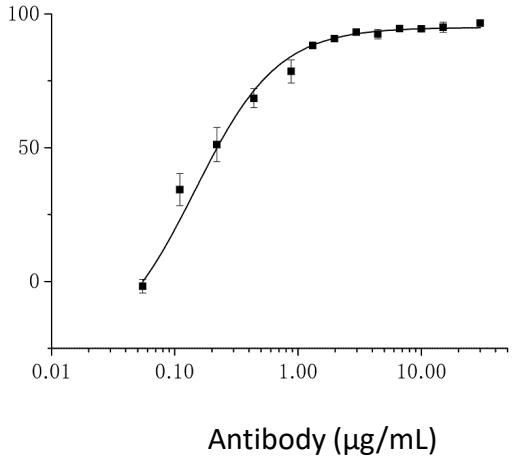
VOLUME 45 | NUMBER 7 | JULY 2013 **Nature Genetics**

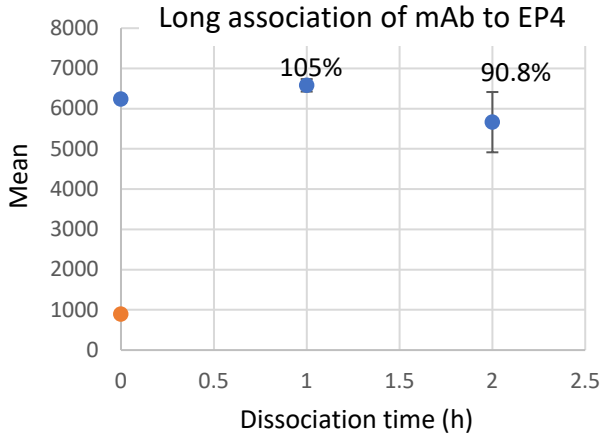
EP4 is the potential target for Th17 cell- associated inflammatory diseases such as Ankylosing spondylitis, Ulcerative Colitis and Multiple sclerosis

# Difference of NBHL mAb from Small Compounds



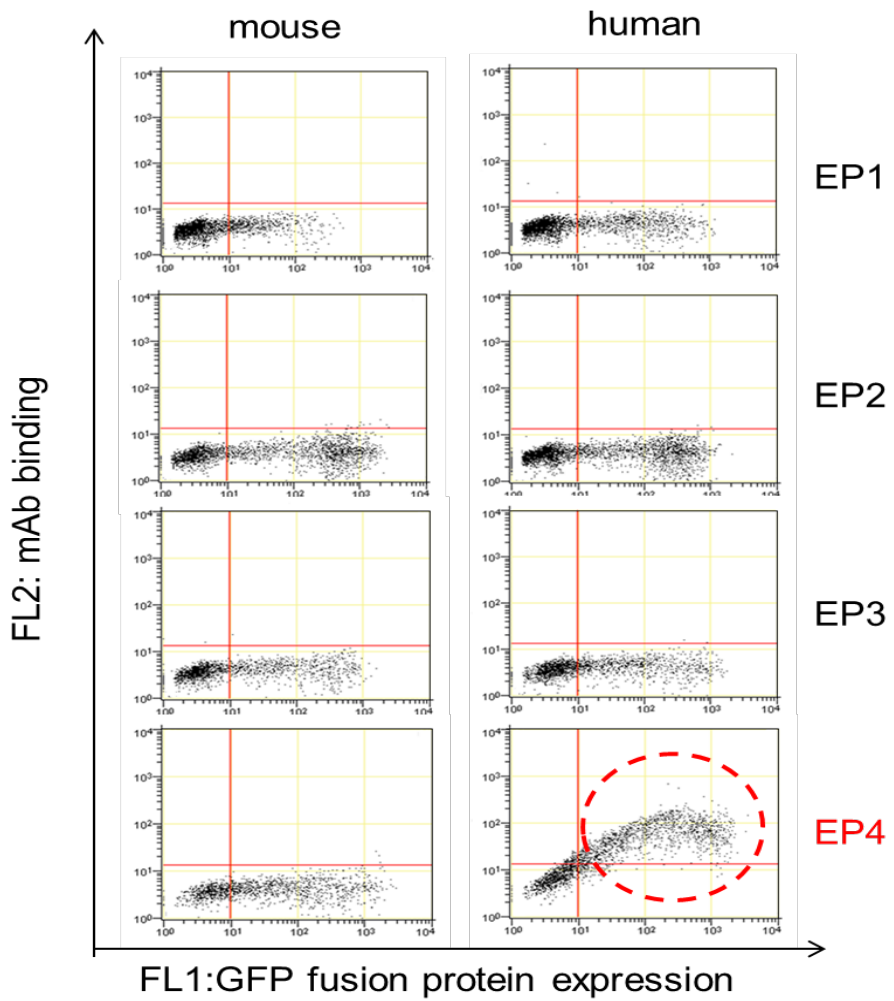

*(Nat Chem Biol 15: 18, 2019)*




## NBHL antibody inhibits EP4 signaling in human

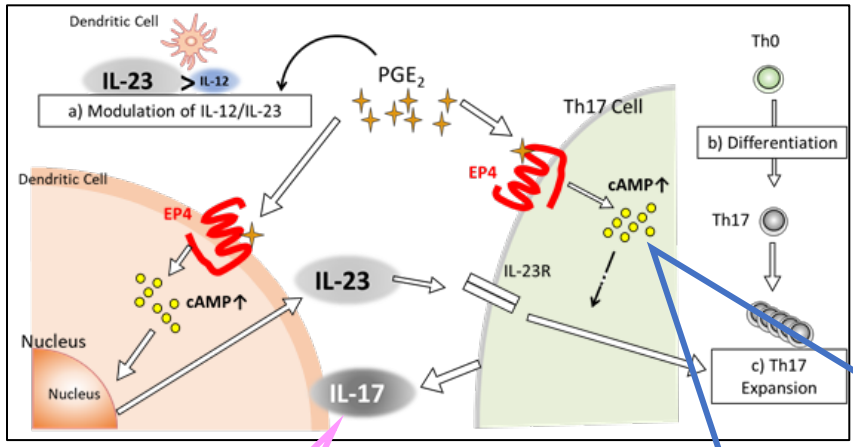
## FACS analysis of NBHL mAb binding to human EP4



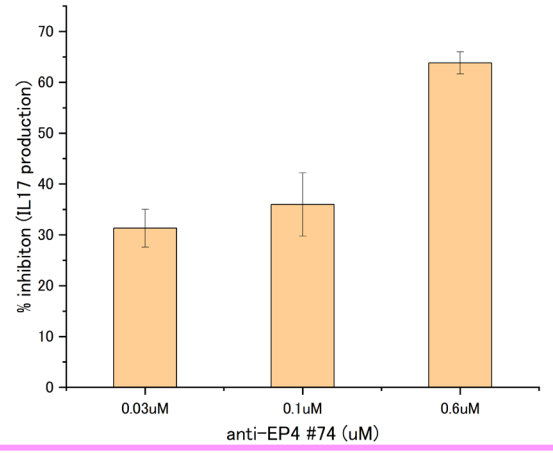

NBHL mAb has good selectivity for EP4 in human

# NBA1603

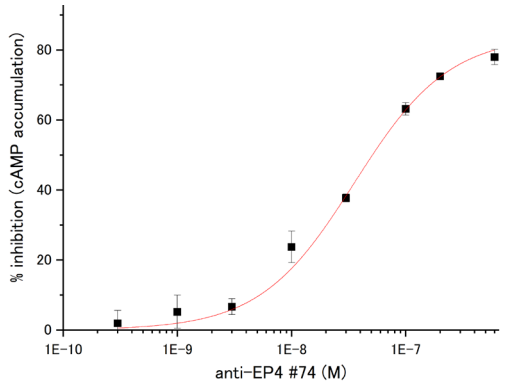
## Effect of Humanized Anti-EP4 mAb to biological activity of healthy human Th17 cells




Inhibition of PGE2-induced IL17 production in human Primary Th17




Inhibition of PGE2-induced intracellular cAMP accumulation in human Primary Th17



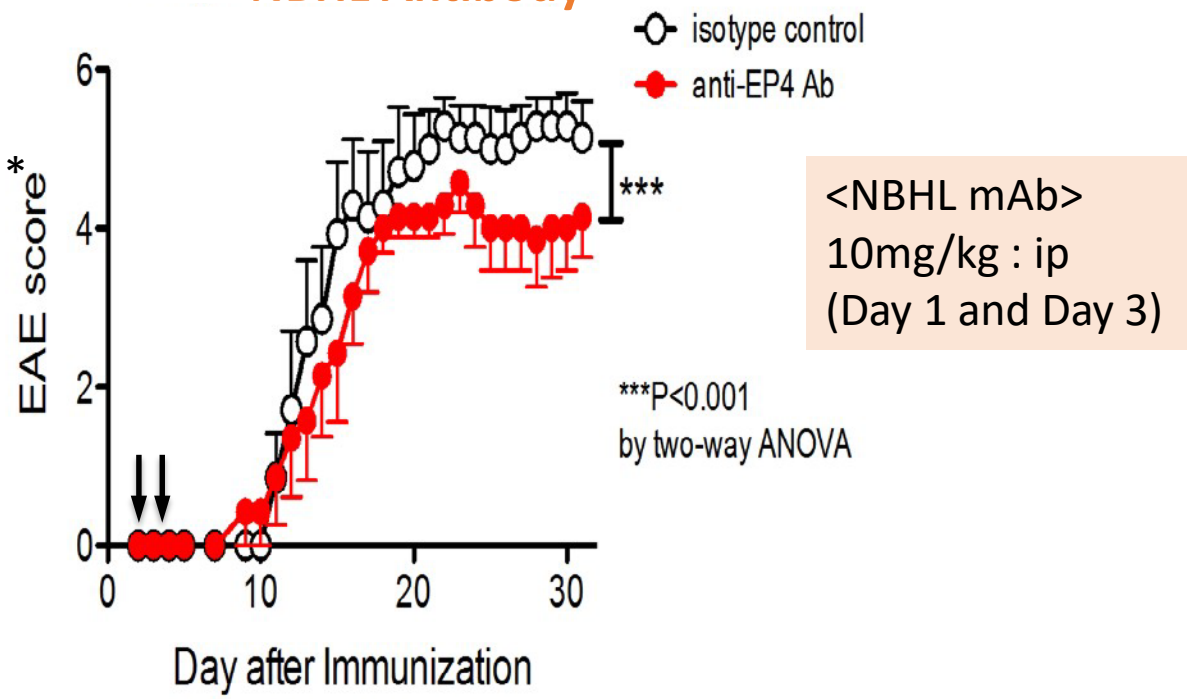

NBHL mAb inhibited IL17 production in human primary Th17 (left fig) and 70-80% of PGE2-induced intracellular cAMP accumulation (right fig).

# Potential Benefit of Anti-EP4 Treatment for AID

(EAE Animal Mode with Surrogate mAb)

## EAE model

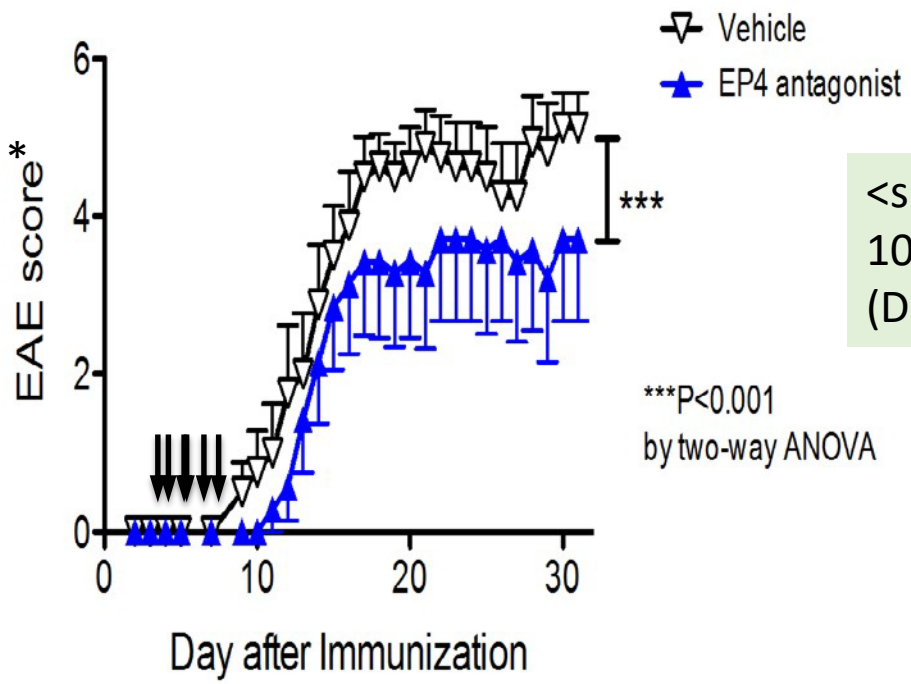
### NBHL Antibody




<NBHL mAb>
10mg/kg : ip
(Day 1 and Day 3)

***P<0.001
by two-way ANOVA

### EP4 antagonist (small comp.)




<small comp.>
100mg/kg : po
(Day 3 ~ Day 7)

***P<0.001
by two-way ANOVA

*EAE score: Experimental autoimmune encephalomyelitis score

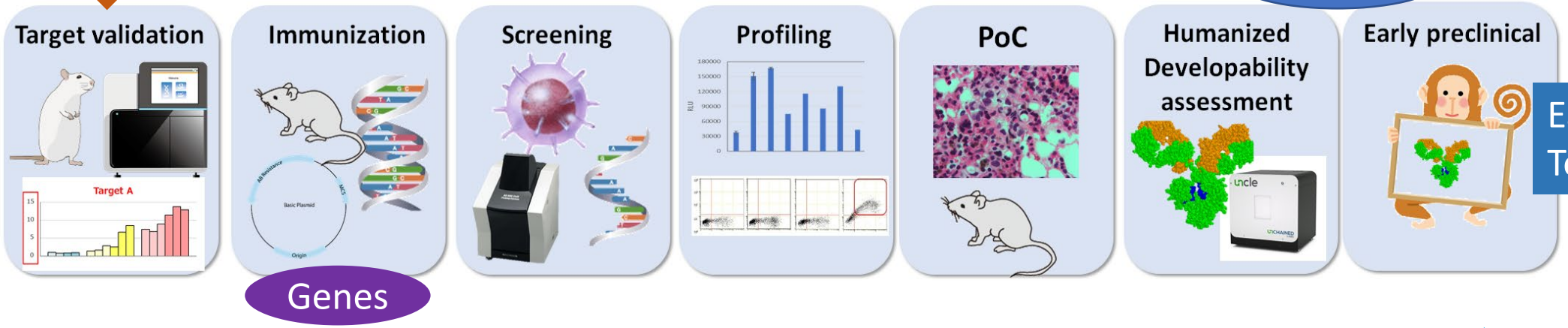
Pharmacological inhibition of EP4 with NBHL mAb may have benefit for persistent chronic inflammation

# Business model: R&D status of Anti-EP4 Antagonist in NBHL by MoGRAA discovery engine

Input Concept

MoGRAA discovery engine

Patents




Early out-license To Pharmaceuticals

**We are here .**

- The result of knock-in mouse will be obtained 2025/Q3.
- Anti EP4 is expected breakthrough therapy designation for the treatment of Ankylosing spondylitis as an “orphan diseases” in Japan .
- We are seeking for pharmaceutical partner for development and commercialization.