Patent grant for anti-RAMP2 antibodies

January 10, 2023

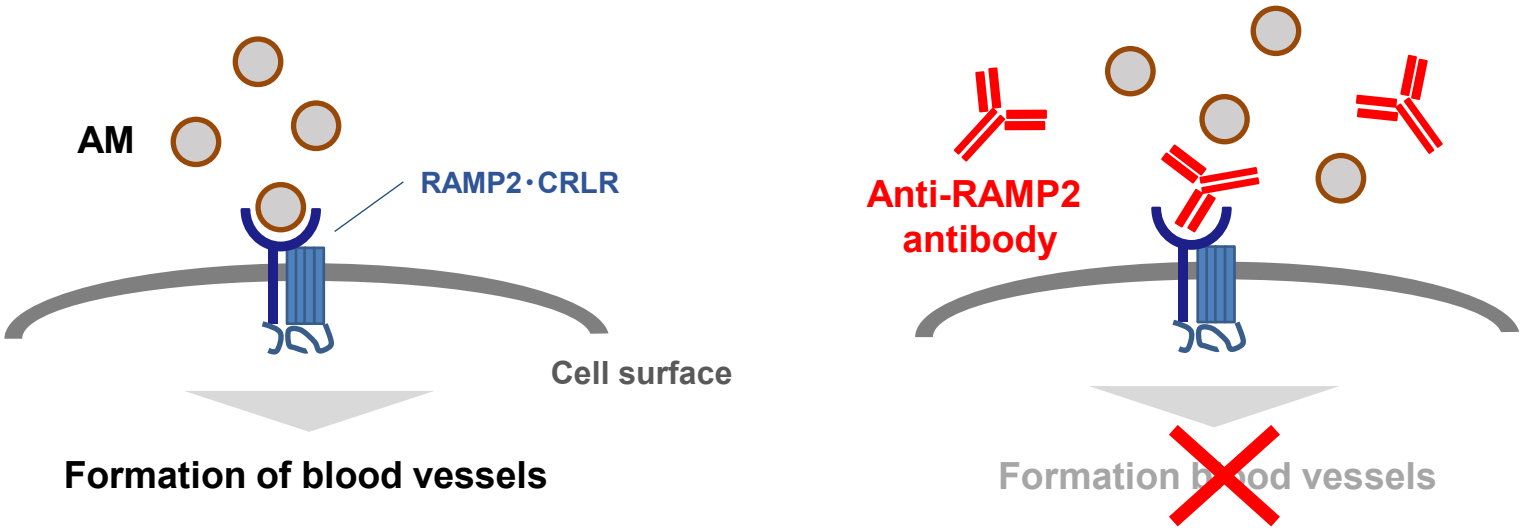
Kidswell Bio Corporation

Outline

Application No./ Filing date	Name of invention	Patent No.	Patentee
2022-136364 (2022-8-29)	**Anti-RAMP2 antibodies**	7202011	**Kidswell Bio Corporation**

- RAMP2 (Receptor Activity-Modifying Protein 2):
  Form RAMP2/CRLR with Calcitonin Receptor-Like Receptor (CRLR) in a cell surface and combine with Adrenomedullin (AM) and have variety of bioactivities such as formation of new blood vessels and vascular protection by transmitting angiogenesis signals into cells.
  (e.g., growth of tumor by activating formation of new blood vessels, etc.)

- **Anti-RAMP2 antibodies:**
  Combine with RAMP2・CRLR and inhibit the formation of new blood vessels
  ⇒ Expect a high possibility of inhibition of abnormal angiogenesis.



Application possibility for retinopathy of prematurity (1)

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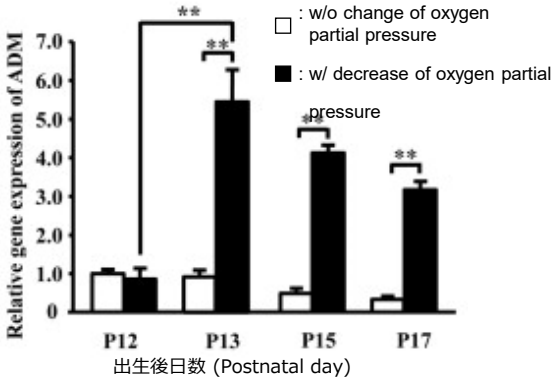
- **Adrenomedullin (AM), which selectively binds to RAMP2, is known to stimulate formation of blood vessels in ischemic diseases.**
- **⇒ Expect an inhibitory effect for the formation of blood vessels in ischemic diseases.**

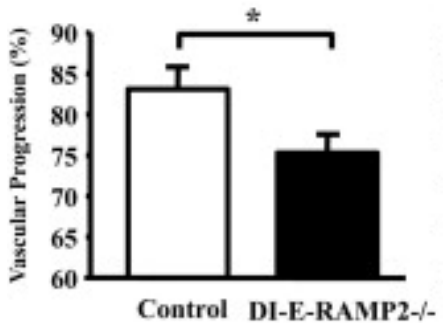
Diseases caused by the formation of blood vessels by ischemia

⇒ Application possibility for retinopathy of prematurity

Inhibition effect in a prematurity retinopathy model mouse model※



Increased AM expression was observed due to decrease of oxygen partial pressure (ischemic state).
（＝stimulate the formation of blood vessels）



Inhibition of the formation of blood vessels was observed with blocking the binding of RAMP 2 and AM.

Confirmed inhibition of the formation of blood vessels in retinopathy of prematurity mouse model by blocking RAMP2 effect

⇒ Expected for clinical application for retinopathy of prematurity.

※*Shindo et al.Am J Pathol.2013 Jun;182(6):2380-90*

Application possibility for retinopathy of prematurity (2)

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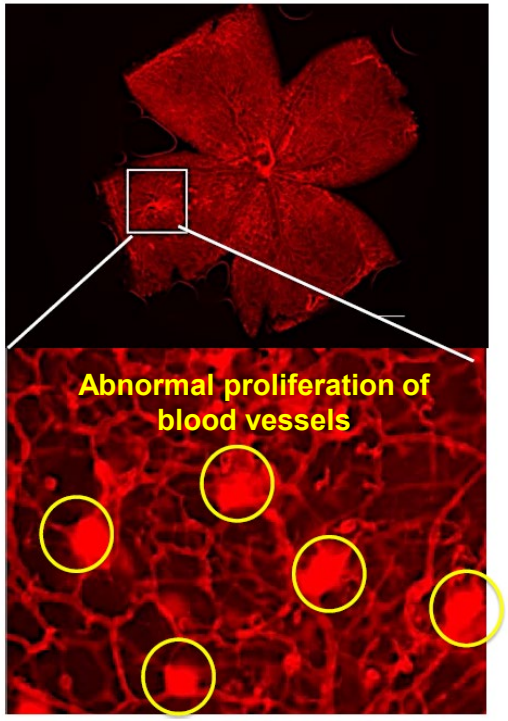
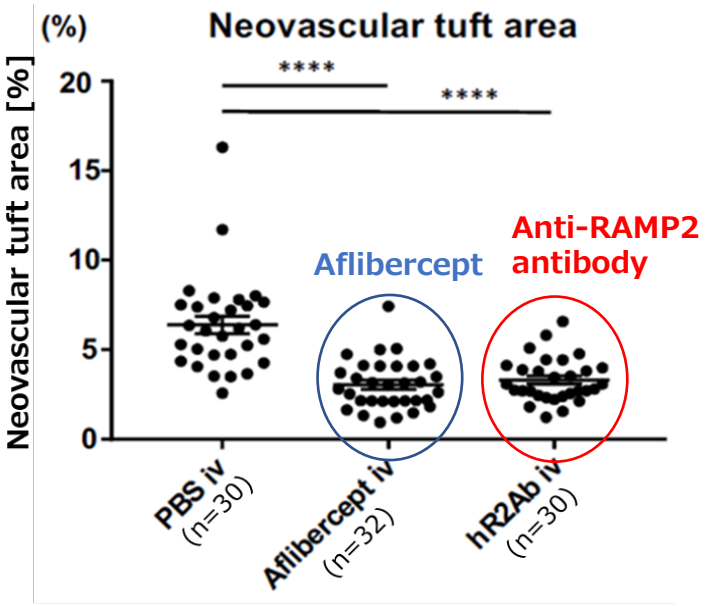
- **Comparative investigation of drug effect between anti-VEGF drugs (angiogenesis inhibitors) and anti-RAMP2 antibodies in the abnormal formation of blood vessels**
  ⇒ Confirmed equivalent inhibition effect.

Enlarged view of neovascular tuft (NVT)



Fluorescent staining image of retinal vessel



Comparison of areas (%) where abnormal proliferation of blood vessels (Neovascular tuft) was observed

Unmet Medical needs for retinopathy of prematurity

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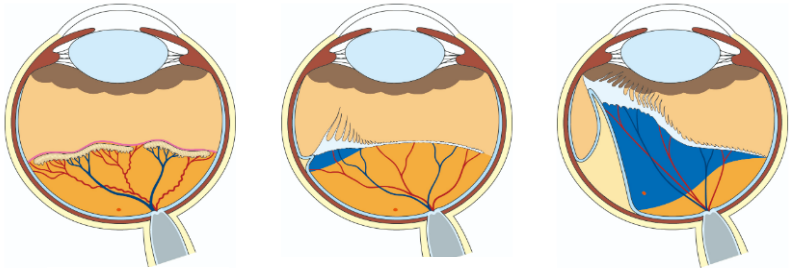
Retinopathy of prematurity (ROP):

- Disease in premature infants that makes retinal blood vessels abnormally proliferated when the sudden environment changes from a stable mother's body.
- As a baby is born with immature retinal blood vessels, retina ischemia is developed, and abnormal formation of blood vessels is stimulated.
- While ROP progresses, potential for retinal detachment becomes higher and some eyes with ROP progress to severe visual disorder and permanent vision loss.

  (The top cause of childhood blindness, about 40% of all)



Progression of retinopathy of prematurity

(*Source : National Center for Child Health and Development HP*)

Current treatments have a high probability of relapse, and no effective treatment has been established yet.

Treatment method	Treatment results
Photocoa-gulation	• First option of standard therapy • Photocoagulate avascular areas where blood vessels have not yet grown and inhibit the release of angiogenesis factors. • Many disease complications such as severe cicatrization and narrowing of visual field
Anti-VEGF Drug	• Bevacizumab, ranibizumab and aflibercept are current medicines. • It is said that 20.8 to 83.0% of patients administrated ranibizumab have relapse of retinopathy.

Source : Nippon Ganka Gakkai Zasshi 2020 issued by Japanese Ophthalmological Society 124(12) 1013-1019

VI Observation method

On the first day, third to fourth day after injection, adverse events such as endophthalmitis were checked to see if the activity of retinopathy is reduced. Since relapse occurs at a high rate after intravitreal injection of ranibizumab, regular fundus examination is required even when retinopathy is relieved.

For AP-ROP*, anti-VEGF therapy alone is difficult to treat and requires additional treatment in 75.0 to 87.5% of cases. There are cases of early recurrence within 1 to 3 weeks after administration, and frequent fundus examination is required.

(**AP-ROP: Aggressive Posterior Retinopathy of Prematurity "Fulminant ROP"*)

Source: Excerpt from the guidance of anti-VEGF treatment for retinopathy of prematurity (Ganka Gakkai Zasshi 124 (12))

Novel mechanism different from anti-VEGF drug

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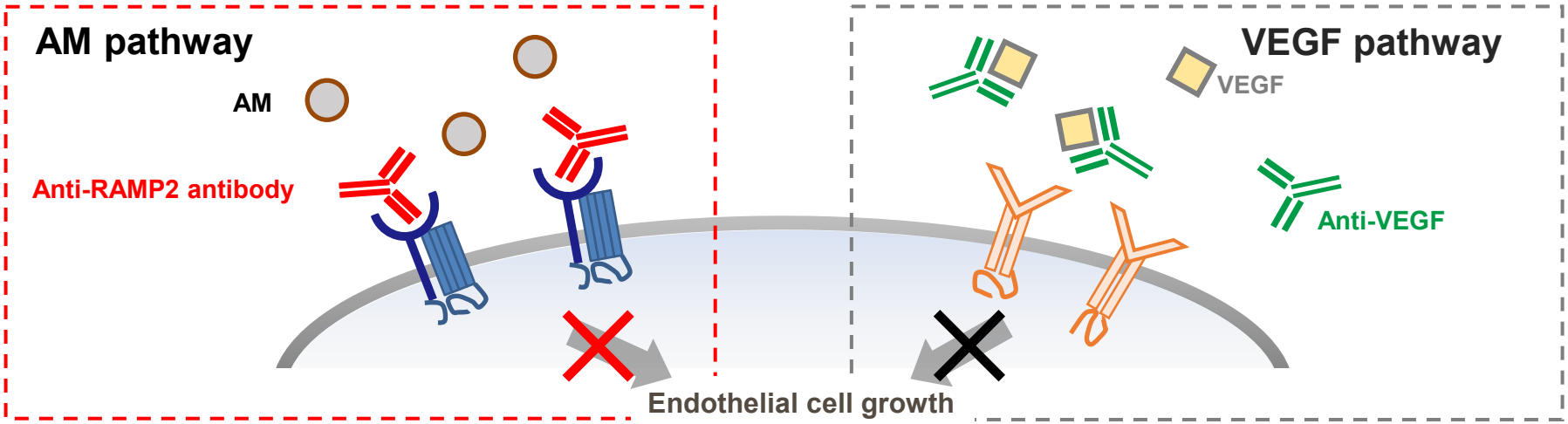
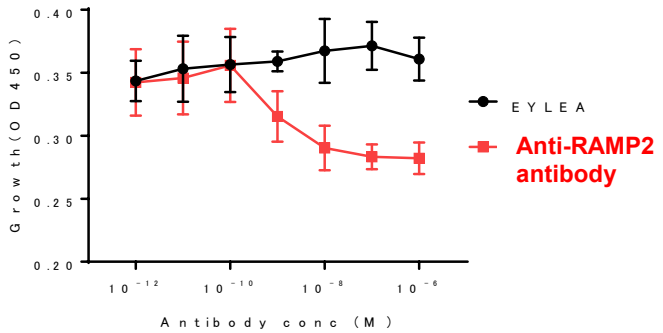
Different pathways of the formation of blood vessels（AM and VEGF pathway）

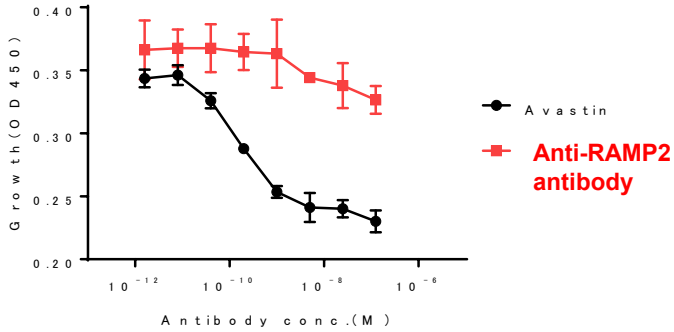


Inhibition effect of HUVEC proliferation in AM pathway



Anti-RAMP2 antibodies inhibit vascular endothelial cell growth
(Anti-VEGF drug has less inhibition effect of cell growth)

Inhibition effect of HUVEC proliferation in VEGF pathway



Anti-VEFG drug inhibits vascular endothelial cell growth
（Anti-RAMP2 antibodies have less inhibition effect of cell growth）

Anti-RAMP2 antibodies inhibit HUVEC proliferation in AM pathway.
（Anti-VEGF drugs can't inhibit it.）

※HUVEC: ヒト臍帯静脈内皮細胞

Licensing activities

- **Confirmed equivalent inhibition effect between anti-RAMP2 antibodies and anti-VEGF drug (aflibercept).**
- **Anti-RAMP2 antibodies inhibit the formation of blood vessels in different pathway from anti-VEGF drug.**
- **In combination with anti-VEGF drug, expect better treatment effect and inhibition of relapse.**

⇒ Expect positive therapeutic effects for both patients who have not been treated well with currently available anti-VEGF drugs and have relapsed after using anti-VEGF drugs.

KWB accelerates licensing activities for anti-RAMP2 antibodies while differentiating current medical treatments.

Market potential of retinopathy of prematurity

	Japan	Global
Number of patients	**5,000 patients/ year** (2009) ※1	**23,800～45,600人／年** (2010) ※2
Estimate in FY 2021 (drug price standard) Ranibizumab	**7 00 million yen**	**4 to 7.5 billion yen** ※3

Source ※1: Japan Intractable Diseases Information Center_ retinopathy of prematurity, ※2: Pediatr Res. 74 Suppl 1:35-49. 2013., ※3: 1USD=JPY135

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KIDS WELL, ALL WELL

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