TRPC3／6を標的とした革新的肺高血圧治療薬L862の開発

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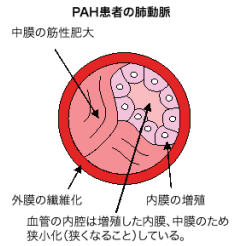
プロジェクト概要

肺動脈性肺高血圧症（PAH、指定難病）

- 肺動脈が異常に狭くなり、また硬くなることで肺動脈圧が上昇する病態をいう。軽い動作で息切れや呼吸困難といった症状が現れる。
- 患者数は日本では約4,200人(R02年度)で年々増加し、世界市場の規模は2034年には93.4億米ドルと予測されている(Research and Markets.)。
- 特に強皮症に伴う肺高血圧症では予後は極めて不良であり、依然、unmet medical needsが高い。
- 肺高血圧の成因として肺動脈リモデリング（内膜の増殖、中膜の筋性肥大、外膜の線維化）があり、血管拡張薬である既存経口薬では進行した病変や静脈病変、強皮症等の膠原病合併肺高血圧への効果は得にくい。

→直接リモデリングに介入できる経口剤が必要

肺動脈リモデリング



（東京大学循環器内科HPより）

TRP（Transient Receptor Potential）C3/6について

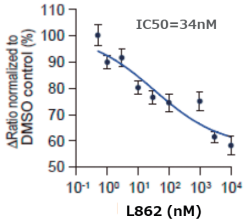
- TRPチャネルは、脂質膜上に存在する膜タンパク質で、28種類のスーパーファミリーを形成。
- 4量体を形成しNaやCaイオンを透過させ非選択的なカチオンチャネルとして機能。
- 細胞外の種々のシグナルを検出するセンサーとして作用。
- TRPC3/6がPAHとリモデリングに関与する様々なエビデンス（Kuwahara et.al. JCI 2006; 116: 3114）など。

→TRPC3/6阻害剤がPAHのリモデリングに直接関与する治療薬となる可能性

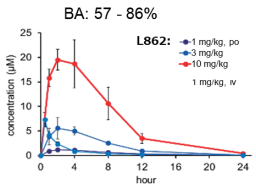
新規TRPC3/6阻害薬L862

- 新規TRPC3/C6、デュアルのチャネル阻害剤：L862 の創製に成功。
- L862はTRPC3/C6チャネルを低濃度で阻害し、他TRP family、各種受容体、チャネル、酵素等に対し高い選択性を示す。
- 物理化学的特性、薬物動態特性、安全性にすぐれ、製造に問題が無い。
- 物質特許出願（WO2019208812）は日本、米国、欧州、中国で特許査定を受ける。
- L862を含む心不全および急性腎症関連用途特許は日、米、欧、中国に、蛋白尿関連用途特許は日、米、欧に移行済み。
- PMDA対面助言において、医師主導P1臨床試験のための非臨床試験の充足性、提示したP1臨床試験プロトコル案は受け入れ可能との回答をいただく。

Inhibition of TRPC6

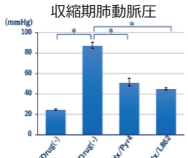


PK Profiles in Rats

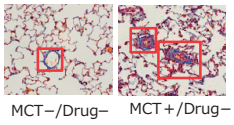


肺高血圧モデルラット、及び肺高血圧患者由来肺動脈平滑筋細胞(PASMC)におけるL862の効果

モノクロタリン誘発性肺高血圧モデル
収縮期肺動脈圧

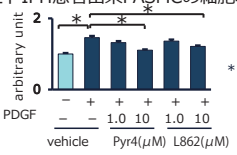


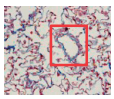
モノクロタリン誘発肺高血圧モデルの肺組織像
(Masson-Trichrome染色)



L862(5mg/kg/day)

ヒトIPH患者由来PASMCの細胞増殖能





L862の投与により肺高血圧モデルの肺組織における血管周囲線維化が抑制された

Moriuchi, Kuwahara et al. in preparation 2021

L862は確立した複数の肺動脈性肺高血圧症モデル動物において肺高血圧を改善した

対 象 疾 患：肺動脈性肺高血圧症
現在の状況：GLP非臨床試験を完了し、医師主導P1臨床試験の準備中
技術の特徴：新規作用メカニズムに基づく経口低分子肺高血圧症治療薬
共同研究・ライセンスに関するお問い合わせ窓口：

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Development of L862, an Innovative Pulmonary Hypertension Treatment Targeting TRPC3/6

Principal Investigator

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2. Shinshu University School of Medicine

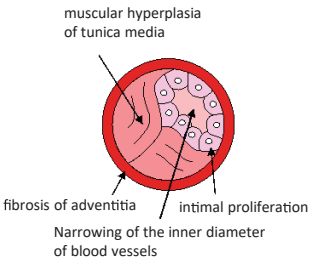
Associate Professor Ryu NAGATA[1]　Professor Koichiro KUWAHARA[2]

Project Outline

Pulmonary arterial hypertension (PAH, designated as an intractable disease)

• It is a condition in which the pulmonary arteries become abnormally narrowed and stiffened, resulting in increased pulmonary artery pressure. Symptoms such as shortness of breath and dyspnea appear with light movements.
• The number of patients in Japan is approximately 4,200 (FY 2020) and increasing every year. The global market size is projected to be USD 9.34 billion by 2034 (Research and Markets).
• The prognosis of PAH associated with systemic sclerosis is particularly poor, and unmet medical needs are still high.
• PAH is caused by pulmonary artery remodeling (intimal proliferation, muscular hyperplasia of tunica media, and fibrosis of adventitia), and existing oral vasodilator drugs are not effective in treating PAH associated with advanced lesions, venous disease, and collagen diseases such as systemic sclerosis.
→ Oral drugs that can directly intervene in remodeling are needed.

Vascular remodeling In PAH patients



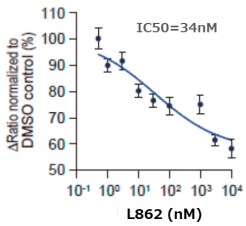
About TRP (Transient Arterial Potential) C3/6

• TRP channels are membrane proteins that exist on lipid membranes and form a superfamily of 28 types.
• They form tetramers and function as non-selective cation channels by permeating Na and Ca ions.
• It acts as a sensor to detect various extracellular signals.
• Various evidences that TRPC3/6 is involved in PAH and remodeling (Kuwahara et.al. JCI 2006; 116: 3114, etc.).
→ TRPC3/6 inhibitors may be therapeutic agents directly involved in PAH remodeling.

L862, Novel TRPC3/6 inhibitor

- L862 inhibits TRPC3/C6 channels at low concentrations and exhibits high selectivity for other proteins.
- L862 shows excellent physicochemical properties, and PK/safety profiles, with no manufacturing concerns.
- The substance patent application (WO2019208812) has been granted in JP, US, EP, and CN.
- Use Patent applications for heart failure, acute kidney injury, and so on containing L862 were filed.
- At a PMDA face-to-face consultation, we received confirmation that the nonclinical studies submitted for the physician-initiated Phase 1 clinical trial were adequate and that the proposed Phase 1 clinical trial protocol was acceptable.

Inhibition of TRPC6



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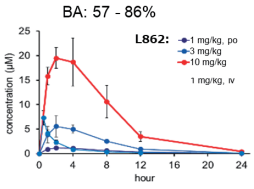
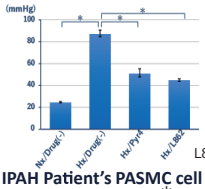
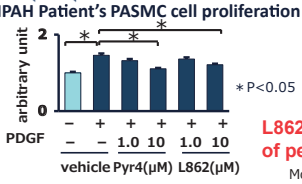


Effects of L862 on PAH model rats and patient-derived pulmonary arterial smooth muscle cells

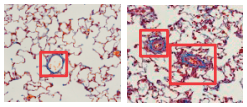
Monocrotaline induced PAH model Rats
systolic pulmonary arterial pressure

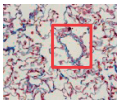


IPAH Patient's PASMC cell proliferation



Monocrotaline-induced PH rats (Masson-Trichrome Staining)





L862 administration suppressed fibrosis of perivascular tissues in the PH model.
Moriuchi, Kuwahara et al. in preparation 2021

L862 improves pulmonary hypertension in various established animal models of PAH.

Target disease: Pulmonary arterial hypertension
Current status: GLP-preclinical studies have been completed and Execution of a P1 clinical trial is under preparation.
Description of technology: Oral small molecule therapeutic agent for PAH based on a novel mechanism of action
Contact for inquiries regarding joint research and licensing: Department of Medical Innovation, The University of Osaka Hospital, Ms. Sasajima, Email: michiyo.sasajima@dmi.med.osaka-u.ac.jp