Getagozumab: A Therapeutic Monoclonal Antibody Targeting Endothelin Receptor A for Pulmonary Arterial Hypertension

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ABSTRACT

Background: Endothelin receptor A (ETa) is a G protein-coupled receptor and a major therapeutic target for pulmonary arterial hypertension (PAH). Approved small molecule endothelin receptor antagonists (ERAs) have been beneficial to PAH patients (1-4); however, low target specificity and chemical structure-based liver toxicity of the ERAs limited their ability to further improve patient's quality of life and extend their survival (5, 6).

Methods: To overcome the shortcomings of the existing drugs, we developed an antagonistic monoclonal antibody (Getagozumab) against ETa. Cell-based binding and calcium influx assays were set up for *in vitro* studies of Getagozumab. Both acute hypoxia-induced and MCT-induced PAH monkey models were also established to assess the pharmacodynamic and pharmacokinetic characteristics of Getagozumab.

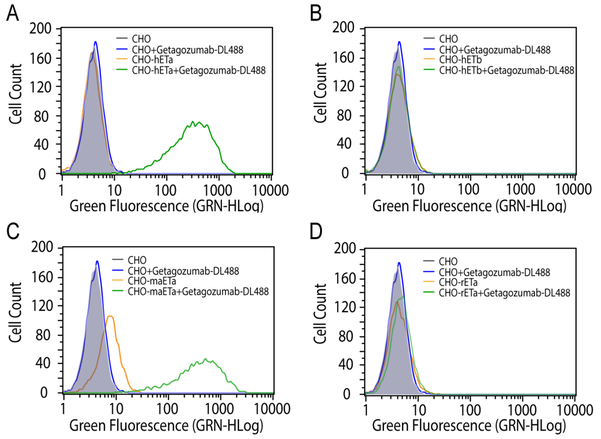
Results: Getagozumab displayed a Kd of 8.7 nM *in vitro* and an IC50 of 37.9 nM in the cell-based functional assay. Getagozumab could significantly lower pulmonary artery pressure in both hypoxia-induced and MCT-induced monkey models and further attenuate the pulmonary arterial wall thickness and right ventricular hypertrophy in MCT-induced PAH monkeys. The preclinical studies demonstrated that Getagozumab is safe, long-lasting and significantly more efficacious than Ambrisentan. A phase I clinical trial of Getagozumab to study safety and PK in healthy volunteers is just finished in Australia.

Conclusions: Getagozumab could serve as a novel and best-in-class treatment option for PAH and may be able to further improve patient's quality of life and extend their survival.

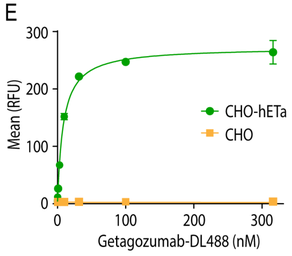
IN VITRO ACTIVITY

Getagozumab binding to human ETa specifically

Getagozumab binds to hETa specifically and only cross-reacts with maETa, but not hETb and rETa



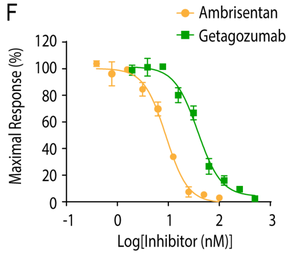
Saturation Binding



Kd = 8.7 nM

In Vitro Functional Activity

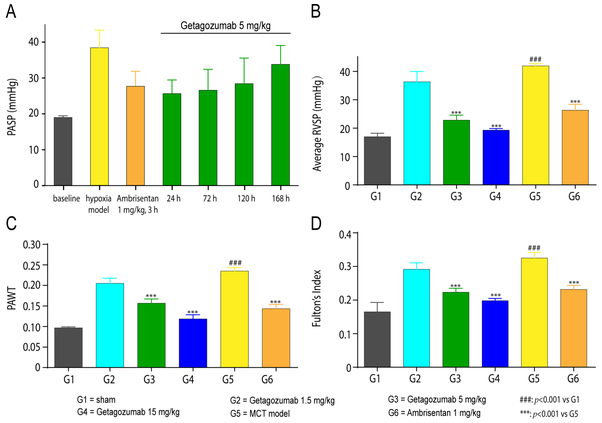
Cell-based calcium influx assay



IC_{50} = 37.9 nM

EFFICACY IN CYNOMOLGUS

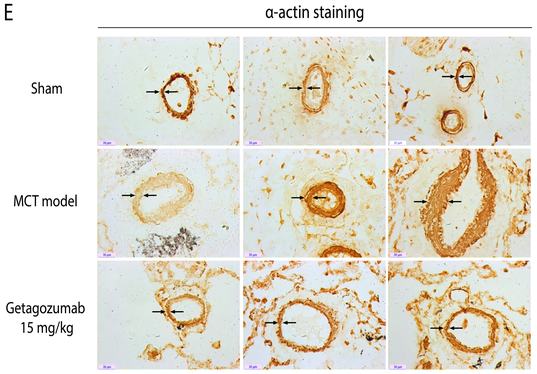
Efficacy of Getagozumab in Hypoxia-induced (A) and MCT-induced (B-E) Cynomolgus



A. Attenuation of right ventricular systolic pressure (RVSP) after a single administration of Getagozumab at 5 mg/kg *iv* dose in acute hypoxia-induced PAH cynomolgus.

B-D. Attenuation of RVSP, pulmonary arterial wall thickness and right ventricular hypertrophy after *iv* injection of Getagozumab at 1.5, 5 and 15 mg/kg, twice a week for six-week in MCT-induced PAH cynomolgus.

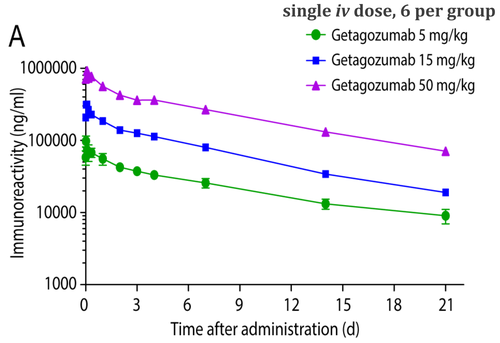
E. Reduced pulmonary arterial hypertrophy in MCT-induced PAH cynomolgus.



Getagozumab significantly reduced pulmonary arterial hypertrophy (as indicated by arrows)

PK AND SAFETY IN CYNOMOLGUS

PK of Getagozumab in Cynomolgus



Summary of PK parameters

Dose (mg/kg)	T1/2 (d)	Cmax (μg/mL)	AUCinf (h·mg/mL)
5	9.90±1.33	98.22±16.81	18.23±3.12
15	7.21±2.63	317.57±38.19	40.26±15.21
50	7.23±1.03	1014.96±73.63	137.50±23.34

Toxicology of Getagozumab in Cynomolgus

Study	Route of Admin.	Dose (mg/kg)	Dosing Frequency	Major Observations
Single dose toxicity	*iv*	75 250 750	Single dose observation for 2 weeks	No obvious toxicity on blood pressure, heart rate, ECG and body temperature; no peripheral edema, neither in dosing groups nor in controls; NOAEL is 750 mg/kg.
Repeated dose toxicity	*iv*	25 75 250	Twice per week for 4 weeks, observation for 6 weeks	A clean safety profile with no abnormalities in body weight, food consumption, ECG and clinical pathology tests; NOAEL is 250 mg/kg.

FIRST-IN-HUMAN

A Randomized, Placebo-controlled, Double-blind, Semi-sequential Dose Escalation Study to Evaluate Safety and Pharmacokinetics of Single Dose of Getagozumab in Healthy Volunteers

Study Subjects and Treatment

Healthy volunteers (n=32, 4 cohorts) in Australia;
A single *iv* dose of Getagozumab (75, 200, 500 and 1000 mg)

Clinical Outcome

A good safety profile: After giving drugs that are much higher than the future clinically proposed doses, not only there were no severe adverse events, but also no significant TEAE being observed in every dosing group. 75mg of Getagozumab single iv administration shows the half-life can reach 500 hours.

CONCLUSION

- Getagozumab is a novel antagonistic monoclonal antibody targeting human ETa
- Getagozumab was significantly more efficacious than Ambrisentan, a small molecule ERA
- In first-in-human trial, T1/2 of Getagozumab is 500 hours in human at dose of 75 mg, and there is no significant TEAEs have been observed in every dosing group from 75mg to 1000mg
- Getagozumab is going to be studied further in multi-national clinical trials, including USA, Europe, Australia and China

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