

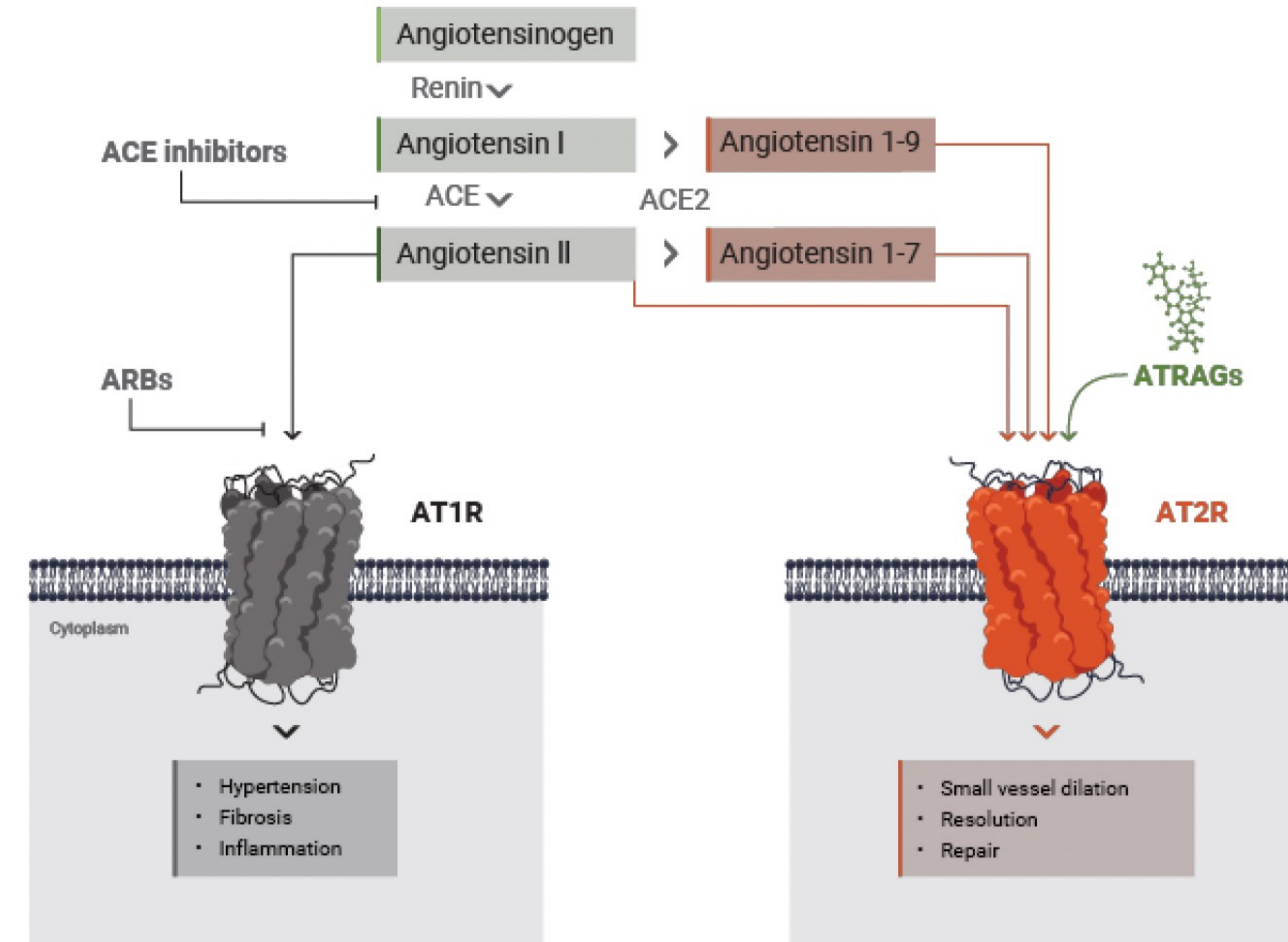
Development of angiotensin II type 2 receptor agonists (ATRAGs) for treatment of pulmonary fibrosis and pulmonary hypertension

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Introduction

The renin-angiotensin system (RAS) is an important physiological regulator of blood pressure and fluid homeostasis. Angiotensin II (Ang II), the major effector peptide of the RAS, acts via two specific receptors, the angiotensin II type 1 receptor (AT1R) and angiotensin II type 2 receptor (AT2R). The AT1R is mainly involved in blood pressure regulation through several different mechanisms related to vasoconstriction and fluid retention, while the AT2R mediates resolution and repair after tissue injury through anti-inflammatory, anti-fibrotic and vasodilatory effects.



The AT1R is ubiquitously expressed, while the expression of the AT2R is generally low in most adult tissues but can be up-regulated in disease states. In the healthy lung, however, the AT2R is highly expressed on alveolar epithelial cells type 2 (AEC2), probably because of continuous micro-injury due to inhalation of different environmental factors/particles. Senescent or dysfunctional AEC2 results in a failed healing process triggering fibrosis formation and decreased lung function in IPF.

Background and objectives

Compound 21 (C21) is the first-in-class low molecular weight, orally available, selective, high affinity AT2R agonist (ATRAG). Industry group report that only 10 % of drug development projects make it all the way from phase 1 to approval (Mullard et al. 2016). Vicore are seeking new ways to improve the probability of success. The objective was to characterize the pre-clinical pharmacodynamic profile of C21, and to create and evaluate models for screening and identifying promising ATRAGs for diseases such as pulmonary fibrosis and pulmonary hypertension, where the AT2 receptor plays a significant role in disease pathology.

Results

Figure 1. Receptor autoradiography shows that C21 specifically binds to the AT2R and potently and dose-dependently displaces Ang II binding in human lung tissue.

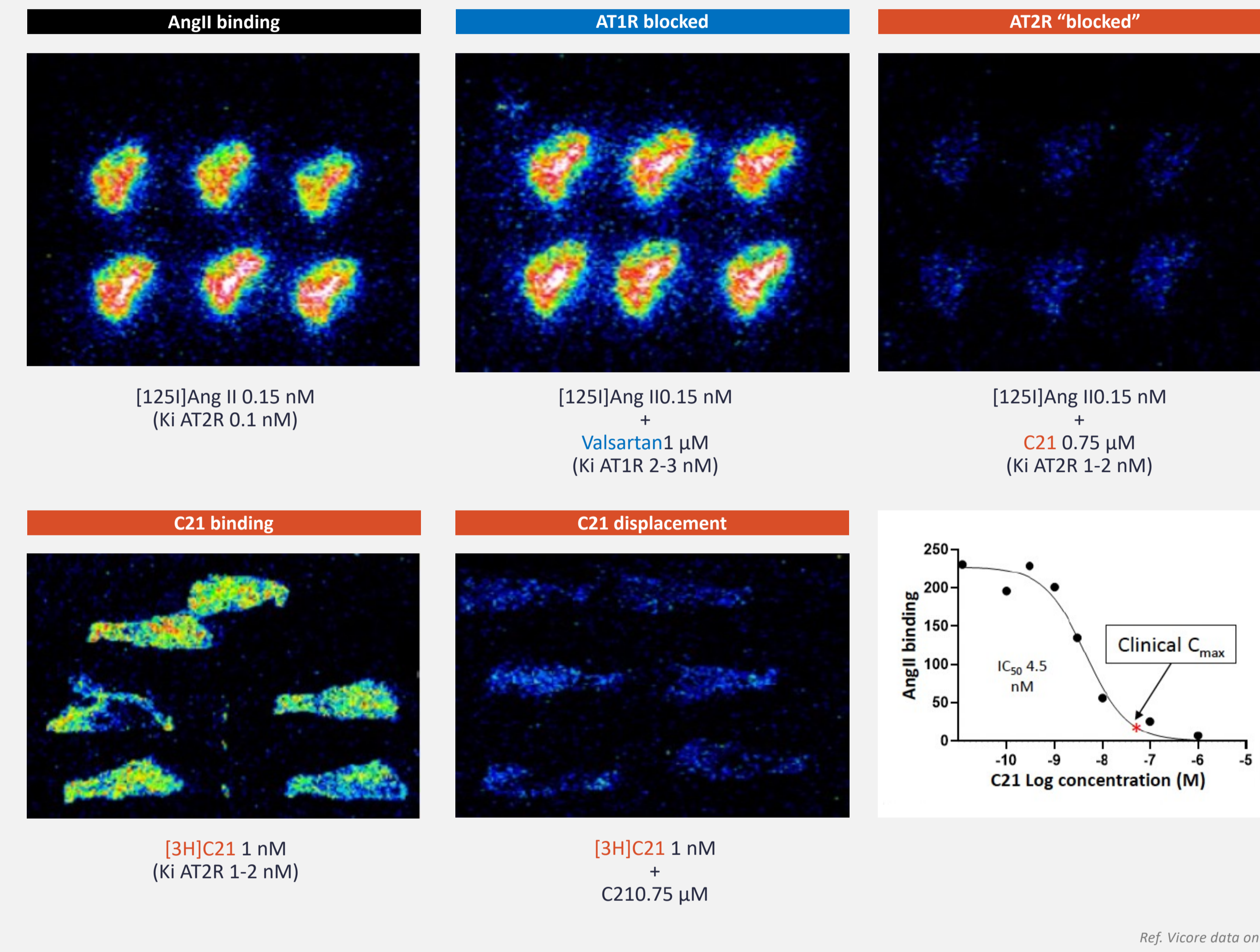
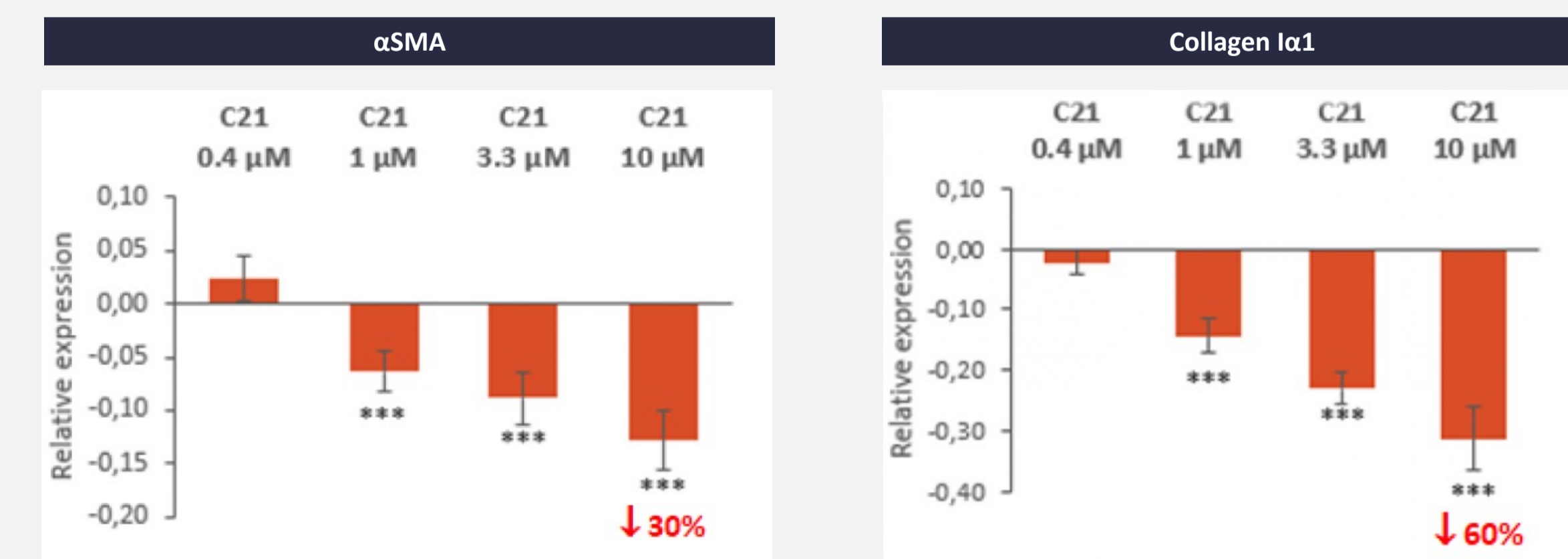
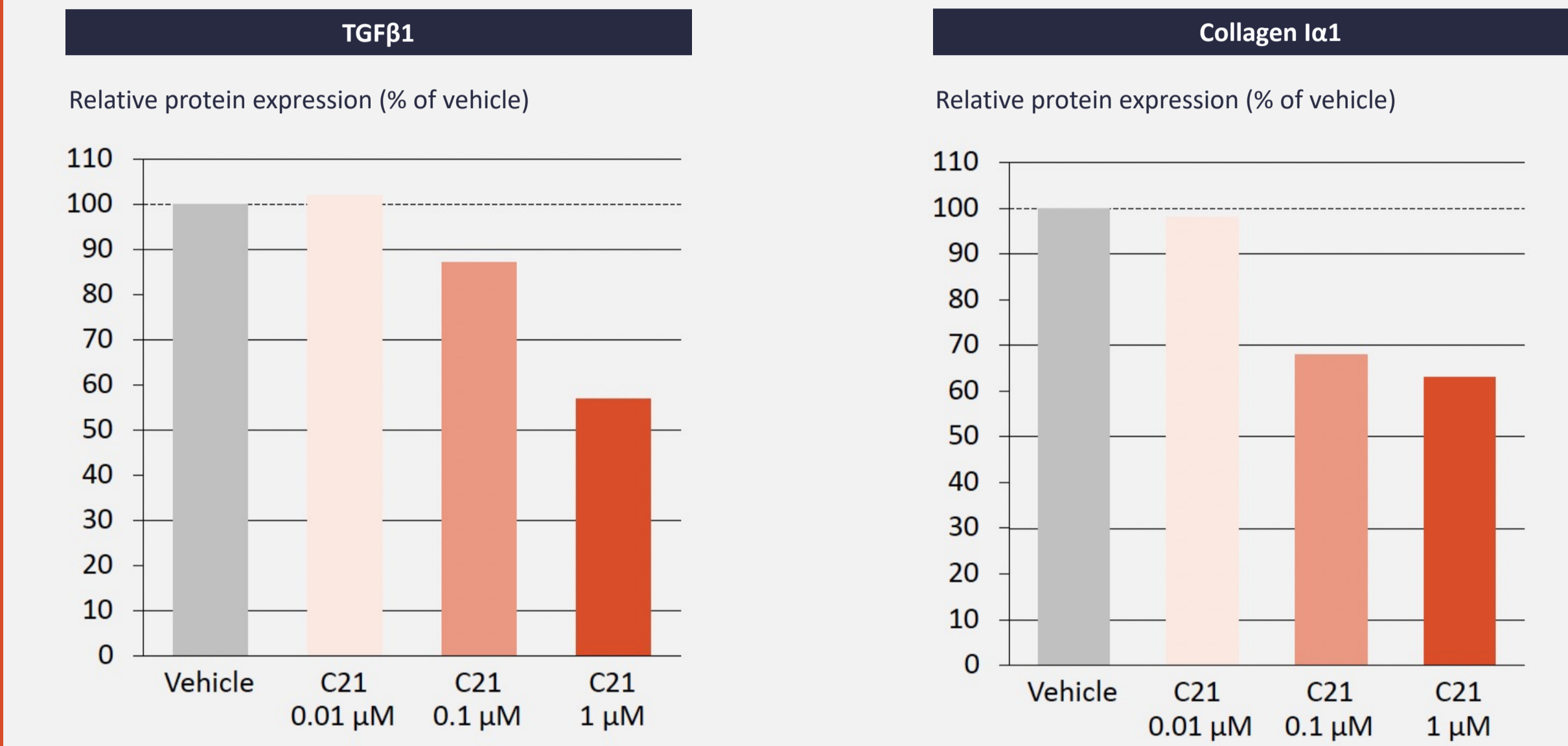


Figure 2: In co-cultures of human primary airways epithelial cells + lung fibroblasts stimulated with TGFβ1 and TNF, C21 dose-dependently decreases myofibroblast activation marker α-Smooth Muscle Actin and fibrosis marker Collagen 1α1.



- C21 decreased myofibroblast activation marker α -smooth muscle actin (α SMA)
- C21 decreased fibrosis marker Collagen 1 α 1
- Reference substances (nintedanib and pirfenidone) did not significantly reduce α SMA or Collagen 1 α 1

Figure 3. In precision cut human IPF lung slices, C21 dose-dependently reduces spontaneous release of TGFβ1 and Collagen 1α1.



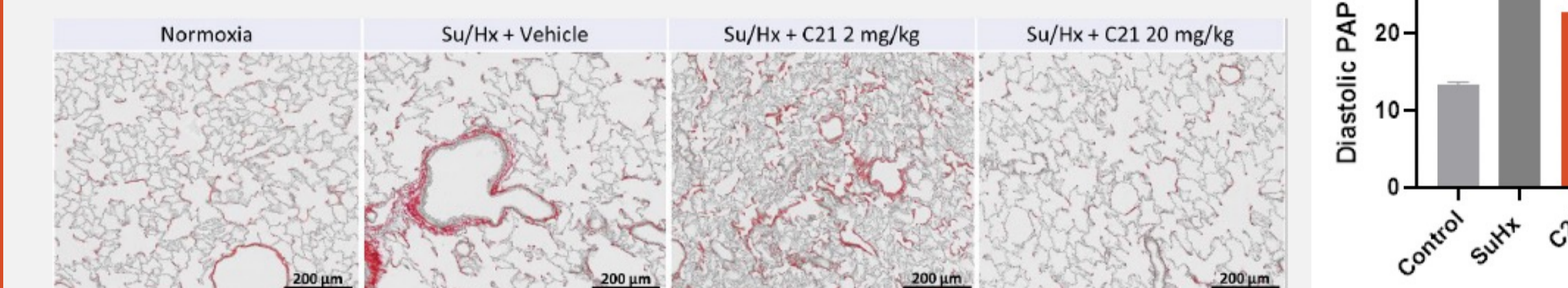
Ref. Vicore data on file

Figure 4: In Sugen-Hypoxia (SuHx), Bleomycin, and Monocrotaline models of pulmonary fibrosis and vasculopathy C21 is seen to be effective in reducing fibrosis, collagen content and reversing vascular remodeling.

C21 treatment highly effective, consistent results across models:

Parameter	Sugen-Hypoxia	Bleomycine	Monocrotaline
Lung fibrosis	↓	↓	↓
Muscularisation of pulmonary vessels	↓	↓	↓
Vascular and cardiac remodeling	↓	↓	↓
Pulmonary hypertension	↓	↓	↓
Cardiac function	↑	↑	↑

C21 normalizes collagen content and reduces diastolic PAP in the SuHx-model:



The rodent Sugen 5416 and hypoxia model resembles human Group 3 PH with vasculopathy. Control: Normoxia 56 days (N=5). Vehicle: SuHx followed by DMSO twice daily Day 22-55 (N=11). C21 groups: SuHx followed by C21 2 mg/kg (N=10) or 20 mg/kg in DMSO twice daily Day 22-55 (N=11). Animals sacrificed on Day 56. Note right hand graph: Mean \pm SEM. C21 dose groups pooled in post-hoc analysis.

Ref. Bruce et al. 2015, Rathinasabapathy et al. 2018, Tornling et al. 2023

Conclusions:

- Targeting the AT2 receptor with ATRAGs is a novel therapeutic approach in pulmonary fibrosis and pulmonary hypertension
- A battery of preclinical studies have demonstrated that the first-in-class ATRAG, C21, reduces pulmonary fibrosis and pulmonary hypertension
- C21 is currently in clinical development for idiopathic pulmonary fibrosis (IPF)
- New ATRAGs for different indications are currently in development (C106 in phase 1, C103 and C112 in preclinical development)