About OMICS Group

OMICS Group is an amalgamation of Open Access Publications and worldwide international science conferences and events. Established in the year 2007 with the sole aim of making the information on Sciences and technology 'Open Access', OMICS Group publishes 500 online open access scholarly journals in all aspects of Science, Engineering, Management and Technology journals. OMICS Group has been instrumental in taking the knowledge on Science & technology to the doorsteps of ordinary men and women. Research Scholars, Students, Libraries, Educational Institutions, Research centers and the industry are main stakeholders that benefitted greatly from this knowledge dissemination. OMICS Group also organizes 500 International conferences annually across the globe, where knowledge transfer takes place through debates, round table discussions, poster presentations, workshops, symposia and exhibitions.

OMICS International Conferences

OMICS International is a pioneer and leading science event organizer, which publishes around 500 open access journals and conducts over 500 Medical, Clinical, Engineering, Life Sciences, Pharma scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

Constitutive Activity in Angiotensin Receptors

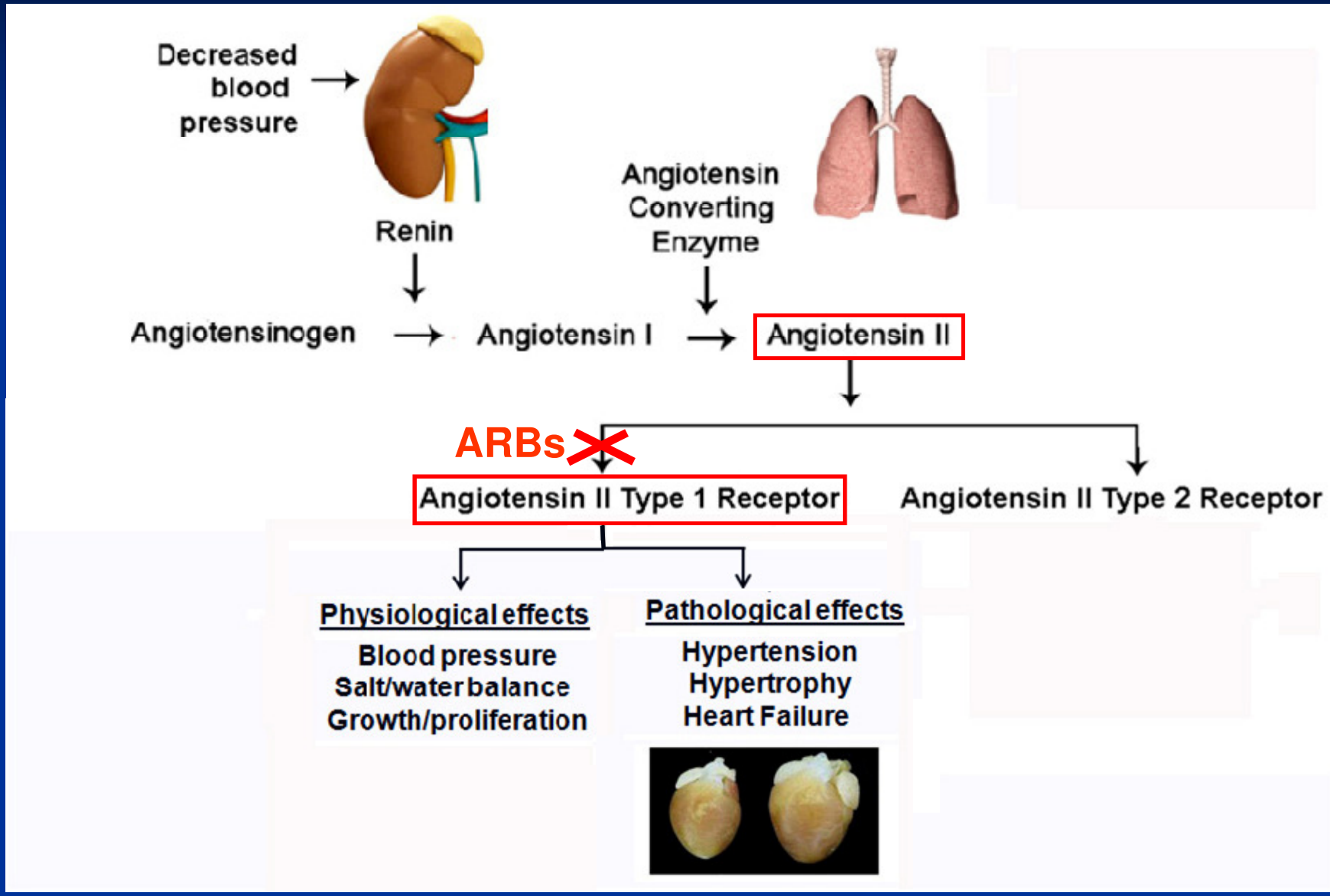
Discovery and Applications of CAM AT1R

Hamiyet Unal, Ph.D.

Cleveland Clinic, USA
Erciyes University, Turkey

Grant Support:
NRSA (HU) and NIH RO1 (SK) grants, Cleveland Clinic
TUBITAK Career Development Award to HU, Erciyes University

Renin Angiotensin System



Angiotensin Receptor Blockers (ARBs)

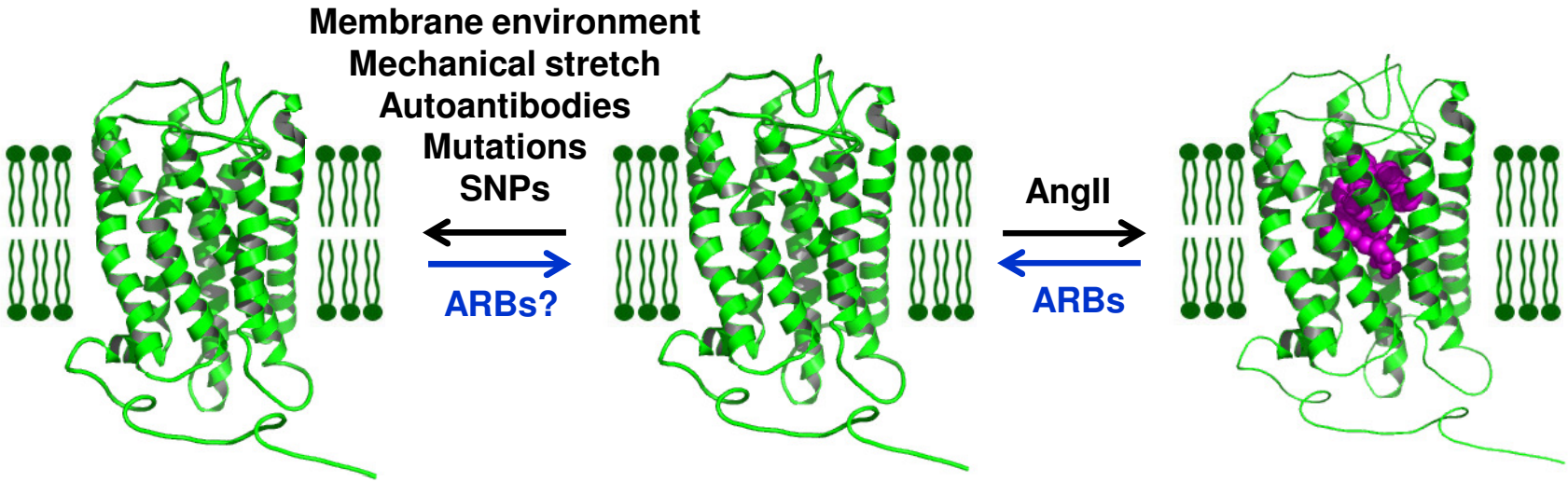
Losartan: $47.3 billion (2012)

Valsartan: $6.1 billion (2010)

Candesartan: $17.3 billion (2011)

Olmesartan: $11.2 billion (2012)

Ligand-induced conformational changes in AT1R



G-protein dependent (Gq/11)

G-protein independent (β-arrestin)

Physiological and pathological effects of AngII

Therapeutic?

G-protein dependent (Gq/11)

G-protein independent (β-arrestin)

Physiological and pathological effects of AngII

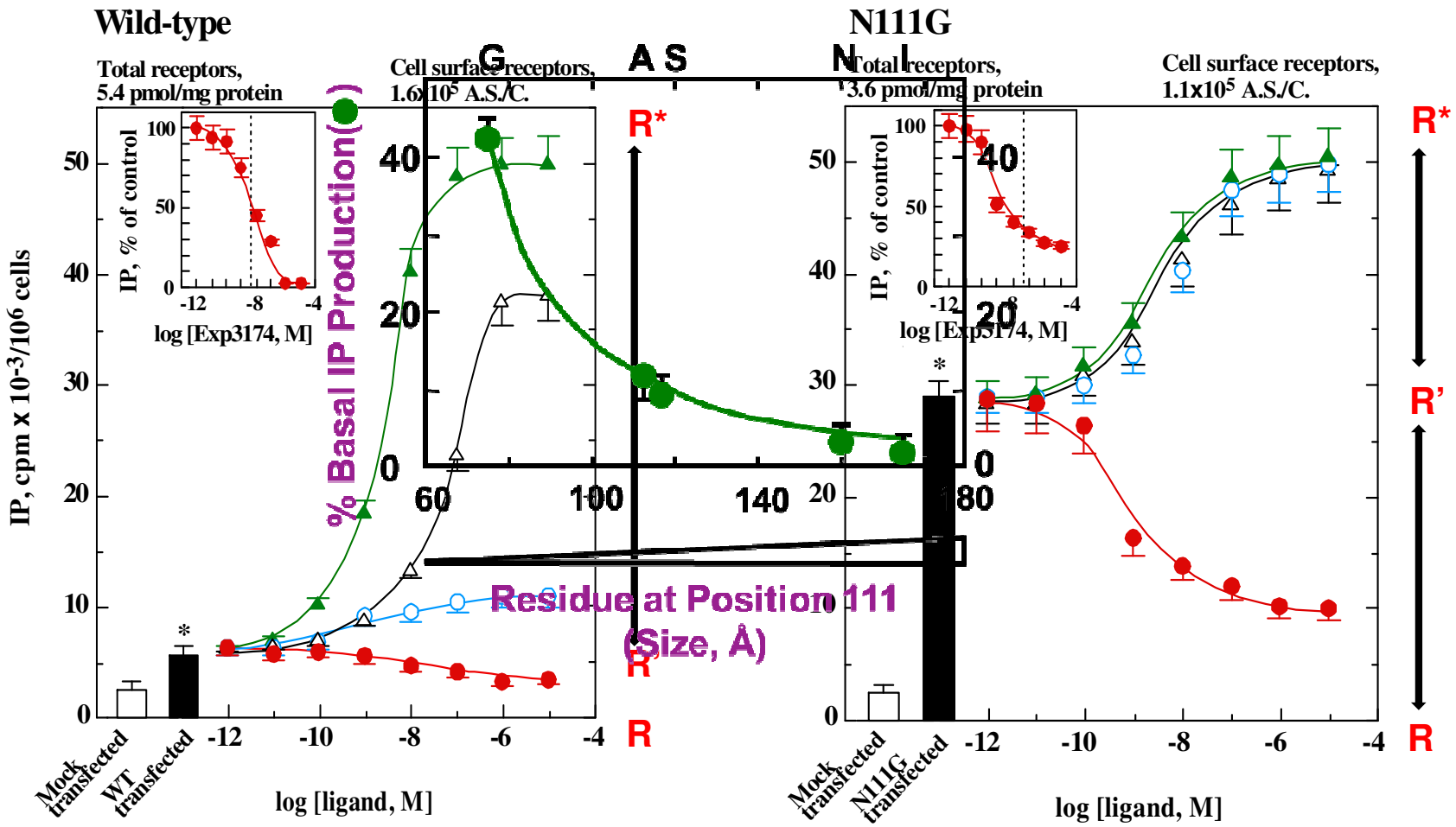
Therapeutic!

Definition of constitutive activity

- Constitutive activity is the ability of a receptor to spontaneously achieve a signaling conformation, without binding an agonist.
- It is also referred to as a "gain-of-function" phenotype.
- The constitutively active pool of AT1R is < 5% in a cell.

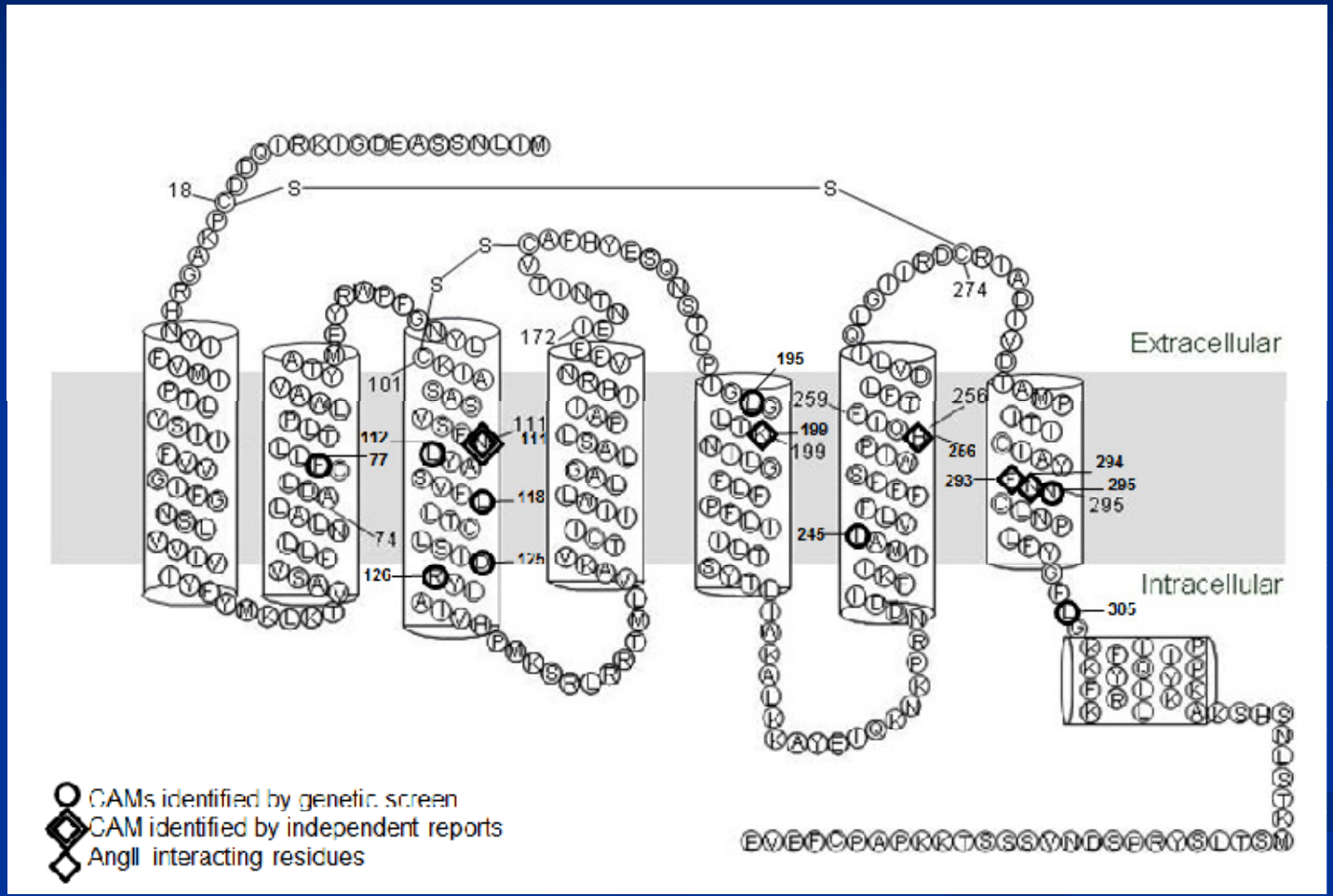
- Can constitutive activity of AT1R be increased?
- Do ARBs have the ability to inhibit constitutive activity?
- Can activated AT1R be used to better understand physiology?
- Is constitutive activity of AT1R important in vivo?

Smaller residues substituted for Asn^{111} in AT1R increases constitutive activity

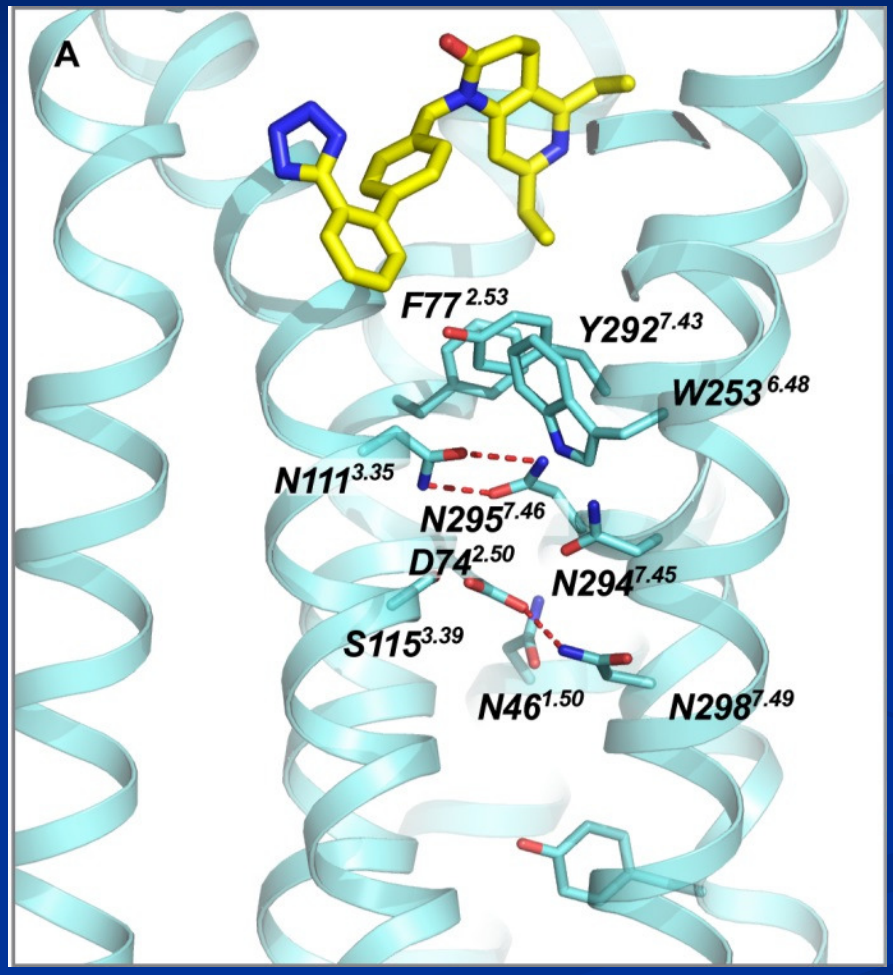


Other CAMs of AT1R

N111G/A/S
F77Y
L112H
L118H
L195P
I245T
N295A
L305Q

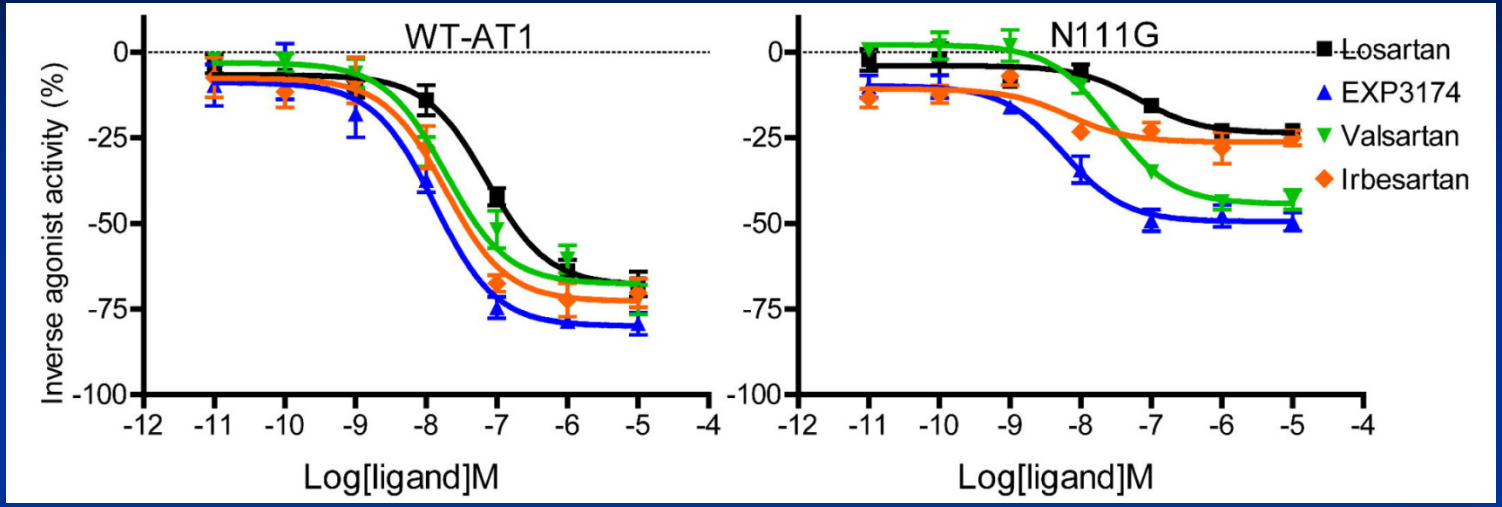


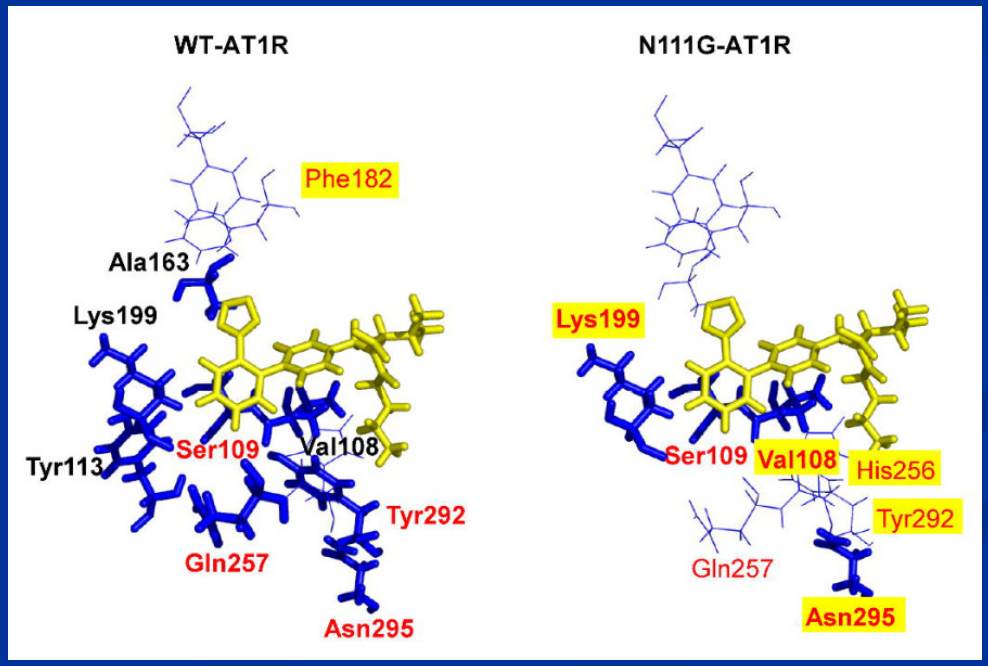
Mechanism of constitutive activation in AT1R



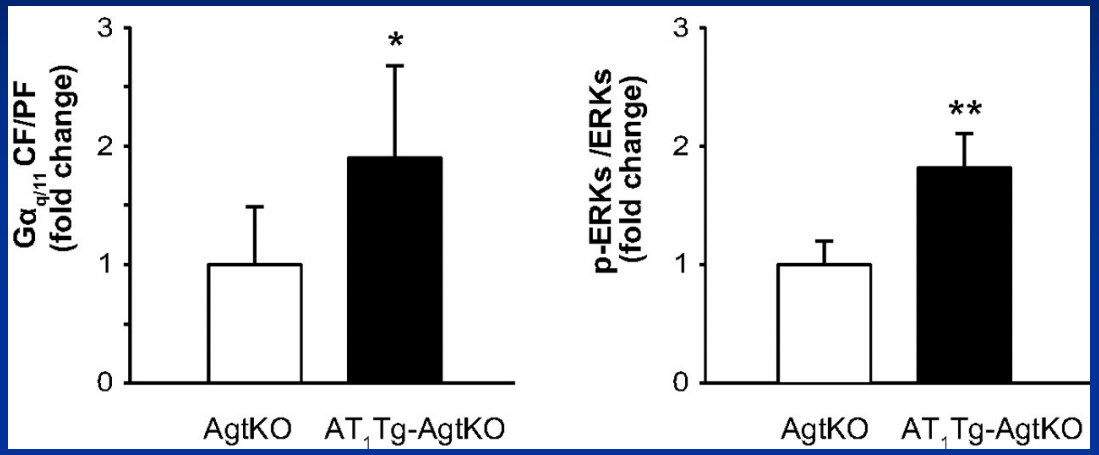
Zhang et al, 2015

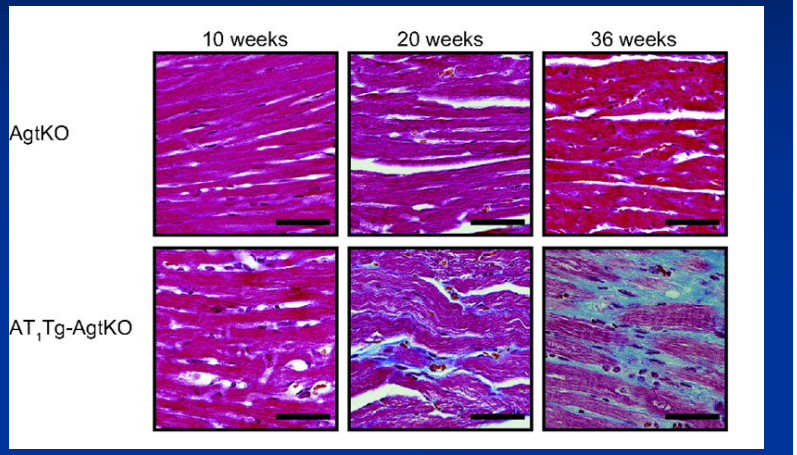
Inverse agonism of WT and N111G-AT1R

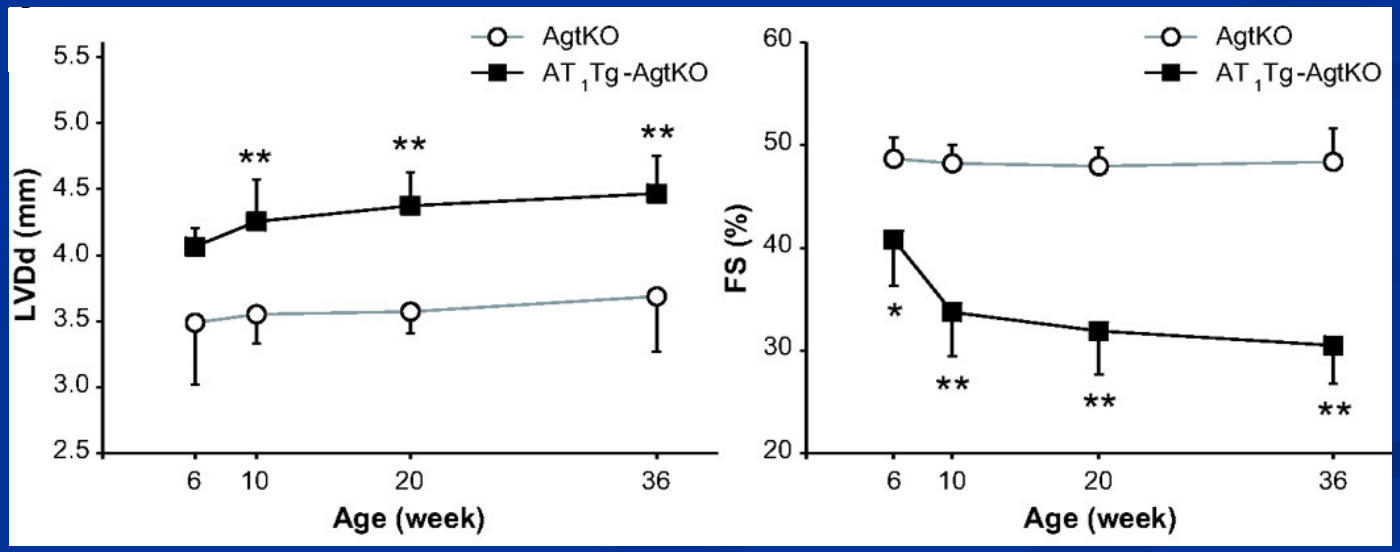




Constitutive activity of native AT1R in vivo

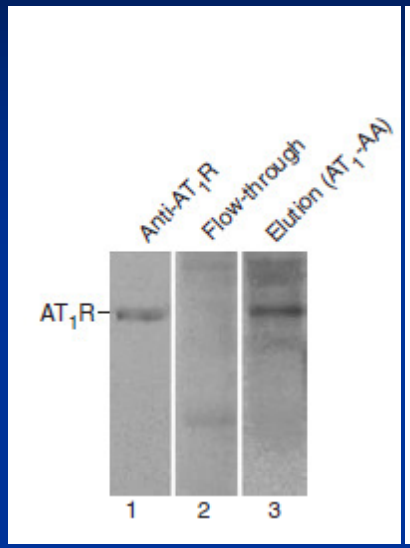


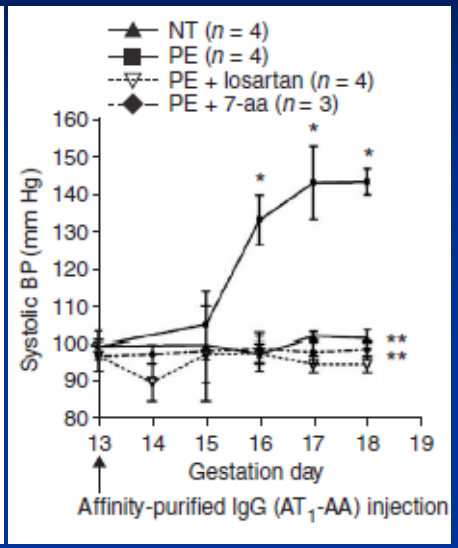




Yasuda et al, 2012

Pathophysiology of constitutive activity of native AT1R

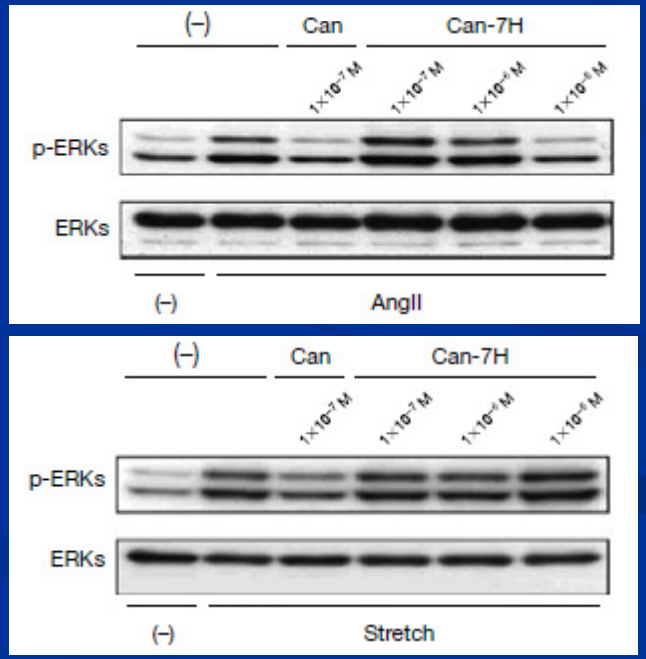




Zhou et al, 2008

Agonistic autoantibodies for the human AT1 receptor are shown to lead preeclampsia and vacular allograft rejection.

Mechanical stress is the primary stimulus for cardiac hypertrophy due to increased afterload in vivo

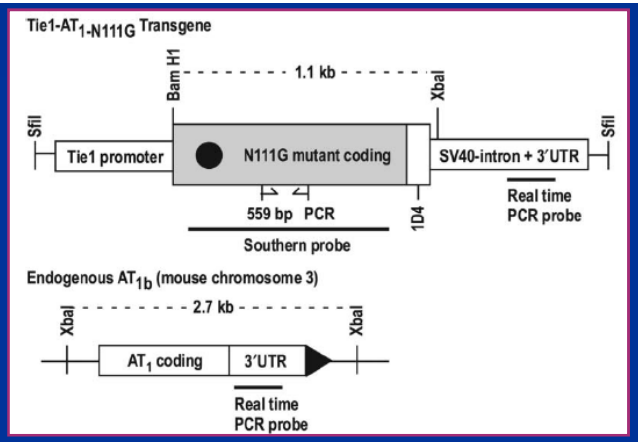


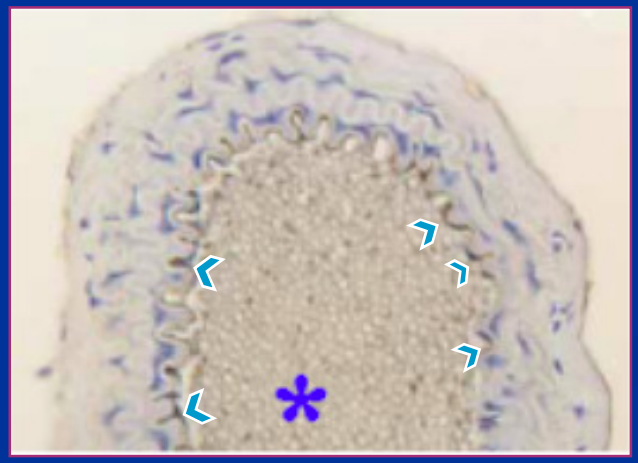
Yasuda et al, 2008

N111G-AT1R as a research tool for mimicking angiotensinergic stimulus

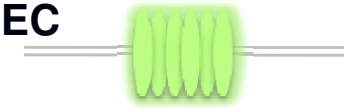
Angiotensinergic stimulation of vascular endothelium in mice causes hypotension, bradycardia, and attenuated angiotensin response

Ramaswamy Ramchandran*, Takanobu Takezako*, Yasser Saad*, Linda Stull†, Bruno Fink‡, Hirotsugu Yamada†, Sergey Dikalov‡, David G. Harrison‡, Christine Moravec†, and Sadashiva S. Karnik*§





N111G-AT1R in EC

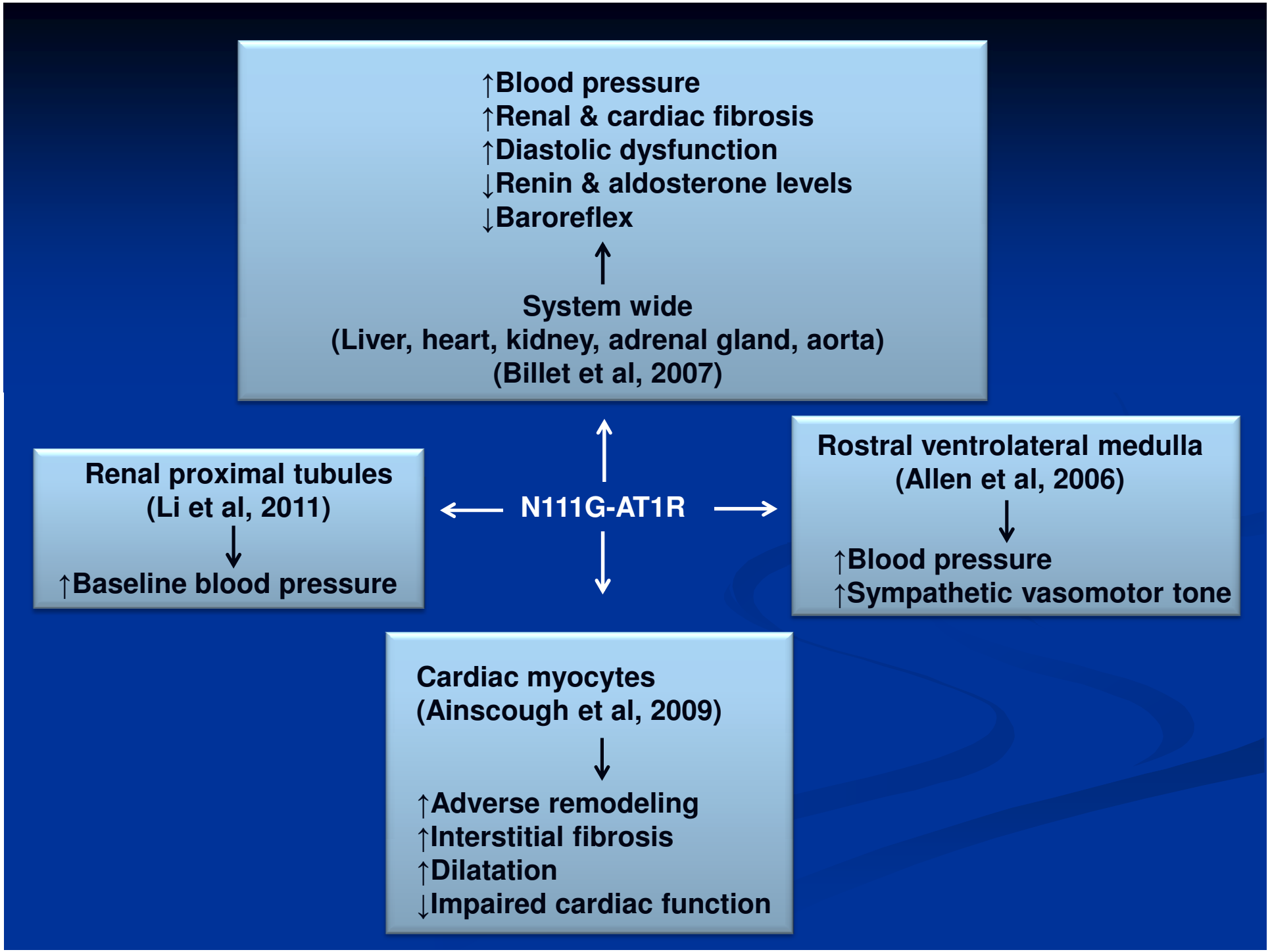


↓

1. ↑eNOS
2. ↑NO
3. ↑cGMP

↓

Reduced blood pressure


↑Blood pressure
↑Renal & cardiac fibrosis
↑Diastolic dysfunction
↓Renin & aldosterone levels
↓Baroreflex
System wide
(Liver, heart, kidney, adrenal gland, aorta)
(Billet et al, 2007)
Renal proximal tubules
(Li et al, 2011)
↑Baseline blood pressure
N111G-AT1R
Rostral ventrolateral medulla
(Allen et al, 2006)
↑Blood pressure
↑Sympathetic vasomotor tone
Cardiac myocytes
(Ainscough et al, 2009)
↑Adverse remodeling
↑Interstitial fibrosis
↑Dilatation
↓Impaired cardiac function

CONCLUSIONS

- CAM AT1 receptors have been extremely useful and powerful in establishing local RAS activity in different tissue pathogenesis.
- Upregulation of local AT1 receptor activity mimics various in vivo disease conditions.
- The inverse agonists are better therapeutics than neutral antagonists in treating diseases caused by constitutive activity of native GPCRs and constitutively activating mutations of GPCRs.

Acknowledgements

- Dr. Sadashiva S. Karnik

- Dr. Ram Ramchandran
- Dr. Takanobu Takezako
- Dr. Zaira P. Jara
- Dr. Keita Noda
- Dr. Ying-Hong Feng
- Dr. Shin-ichiro Miura

Let us meet again..

We welcome you all to our future conferences of OMICS International

3rd World Congress on Pharmacology

On

August 08-10, 2016 at **Birmingham, UK**

http://pharmacology.pharmaceuticalconferences.com/