



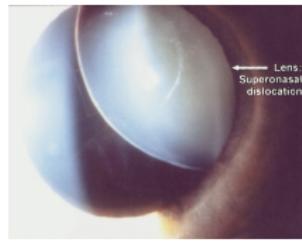
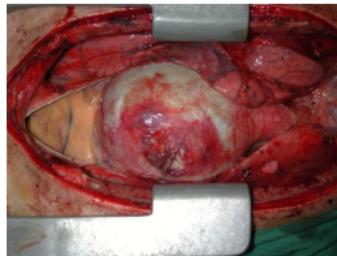
Antagnism of GxxPG fragments ameliorates manifestations of aortic disease in Marfan syndrome mice

3rd International Meeting on Aortic Diseases, Liège

Peter N. Robinson
Charité Universitätsmedizin Berlin

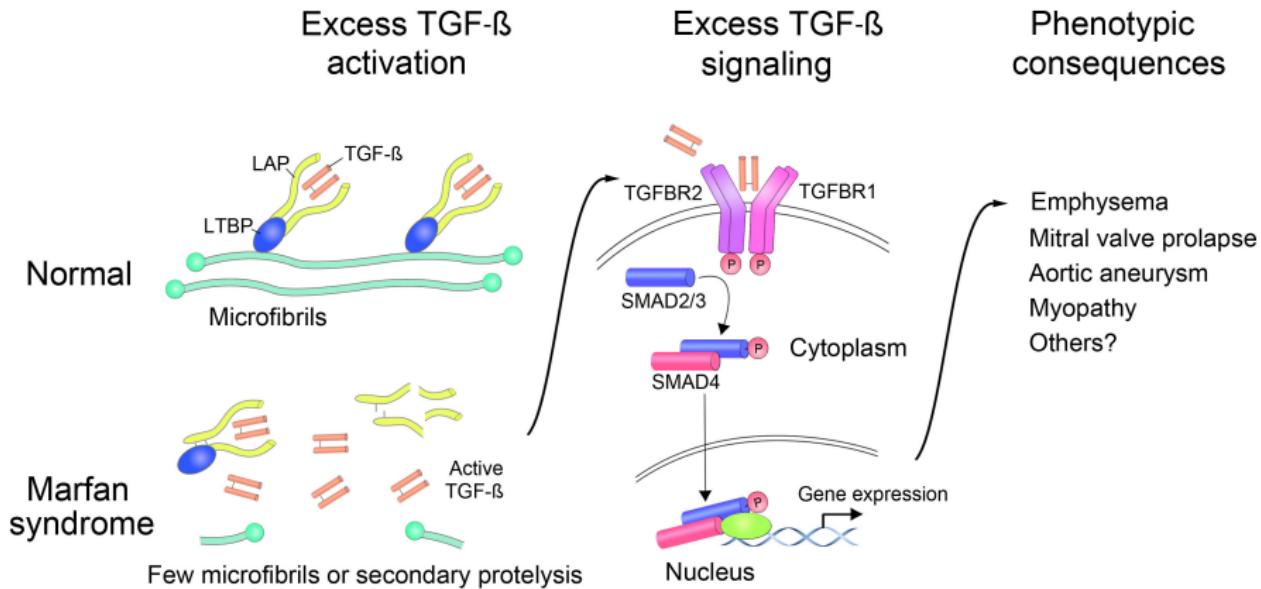
Marfan Syndrome

- ▶ Autosomal dominant
- ▶ Prevalence ca. 1:5,000–1:10,000
- ▶ Tall stature and various skeletal anomalies
- ▶ Ectopia lentis
- ▶ Progressive dilatation of aortic root and aortic dissection
- ▶ Mutations in gene for fibrillin-1 (*FBN1*)



Molecular etiology of MFS still not well understood

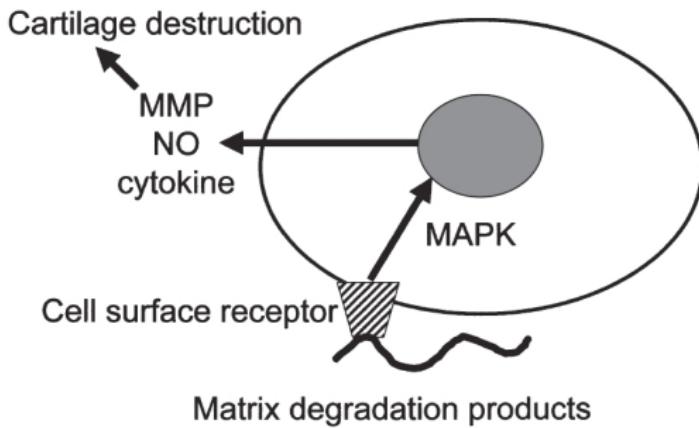
- ▶ Some of then ideas (chronological listing):
 - ▶ Dominant negativ pathogenesis
 - ▶ Reduced homeostasis
 - ▶ **Altered TGF β -Signaling**
 - ▶ Increased susceptibility of mutant fibrillin to proteolysis
 - ▶ Haploinsufficiency
 - ▶ Oxidative stress, impaired NO-mediated aortic relaxation
 - ▶ "Feedback" from Fibrillin/Elastin fragments: ↑ MMP aktivity
 - ▶ Chemotaxis/Inflammation Kiliç



- ▶ Fibrillin-1 controls TGF β bioavailability

Our Hypothesis: Matrikines

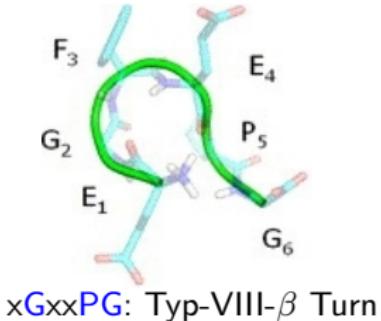
- ▶ It was known that Matrix degradation products (Fibronectin and Aggrecan fragments) themselves possess catalytic activity in osteoarthritis and rheumatoid arthritis



Yasuda T (2006) Cartilage destruction by matrix degradation products. *Mod Rheumatol*. 16:197-205.

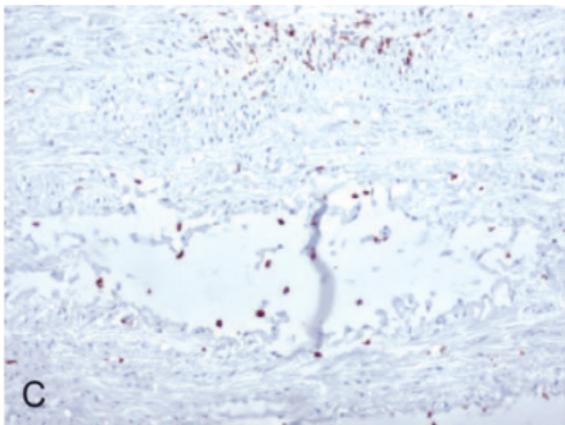
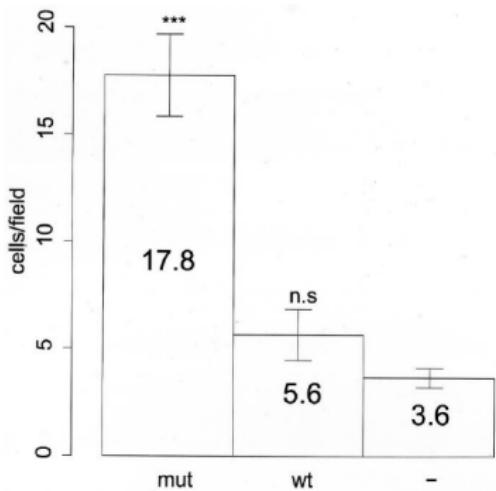
Matrikines in Marfan syndrome

- ▶ Mutant Fibrillin; susceptible to proteolysis. Booms et al. *Hum Genet* 2000
- ▶ RGD fragments of Fibrillin increase MMP production. Booms et al. *Hum Genet* 2005
- ▶ GxxPG fragments of Fibrillin increase MMP production. Booms et al *J Mol Cell Cardiol* 2006



- ▶ 27x in Elastin
- ▶ 3x in Fibrillin-1
- ▶ Statistically significant increase in occurrences of GxxPG in matrix proteins in general

mgR/mgR aortic extracts induce macrophage chemotaxis



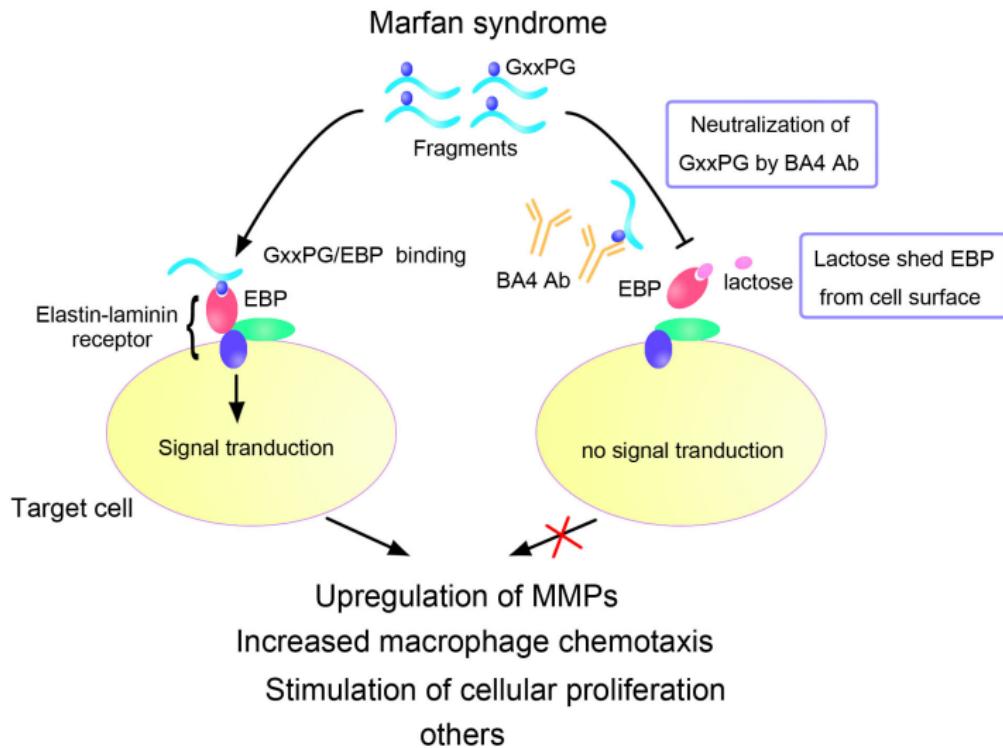
Chemotaxis induced by mgR/mgR aortic extracts

CD68 positive cells in area of cystic medial degeneration

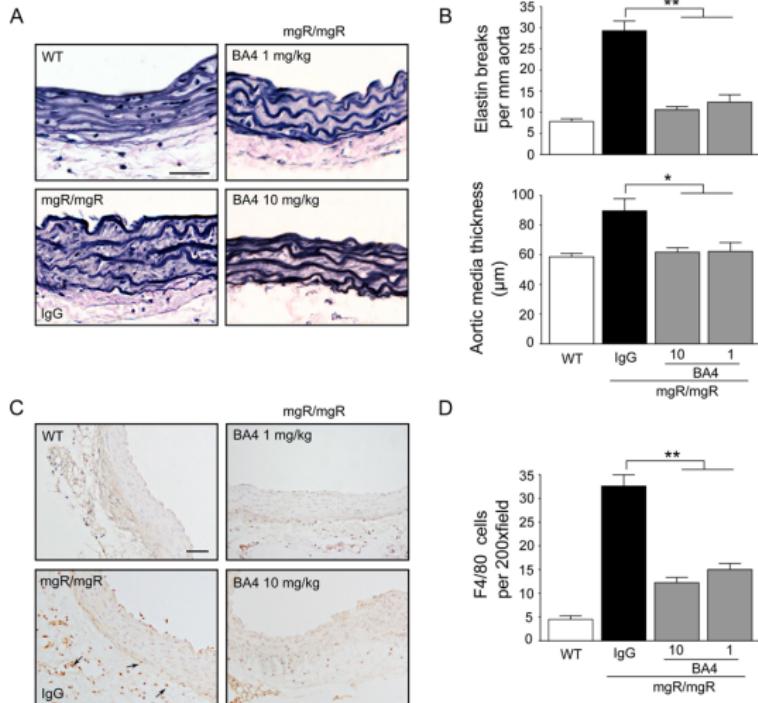
Guo G et al (2006) Induction of Macrophage Chemotaxis by Aortic Extracts of the mgR Marfan Mouse Model and a GxxPG-Containing Fibrillin-1

Similar results in **human Marfan syndrome**: Guo et al. (2011) Induction of Macrophage Chemotaxis by Aortic Extracts from Patients with Marfan Syndrome Is Related to Elastin Binding Protein. *PLoS ONE* 6: e20138.

Experimental strategy

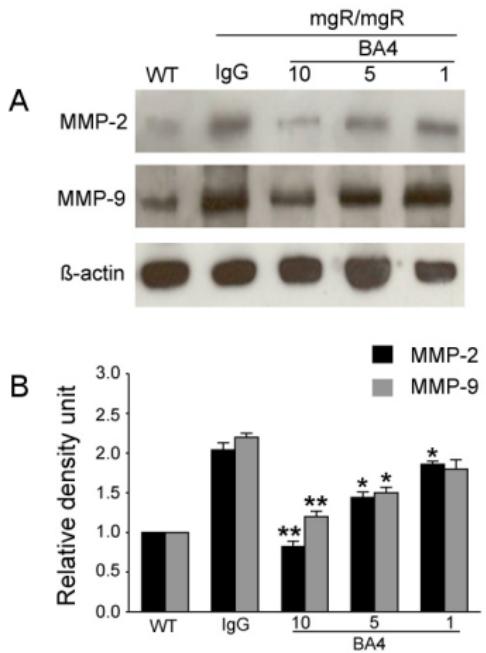


Treatment with BA4



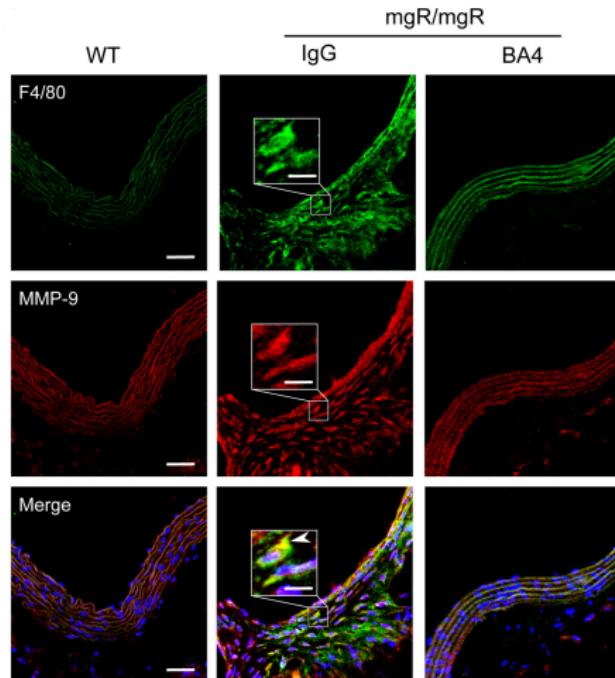
Treatment with BA4 reduces elastin fragmentation and prevents macrophage infiltration in the aorta of mgR/mgR Marfan mice

Treatment with BA4 (2)



Treatment with BA4 reduces upregulation of MMP expression in the aorta of mgR/mgR Marfan mice

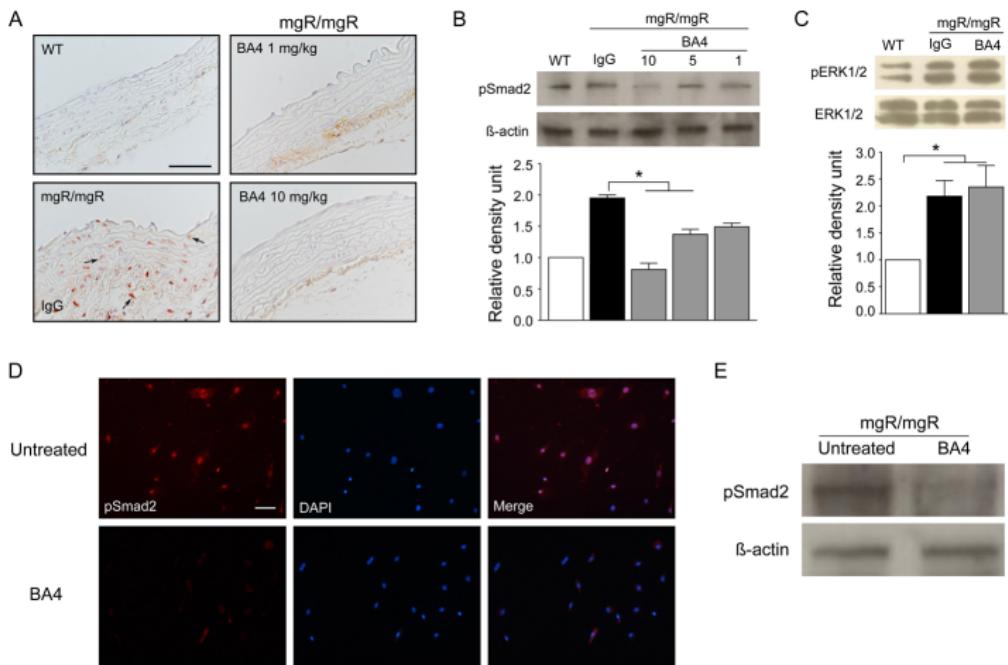
Treatment with BA4 (3)



Immunofluorescence: F4/80 (Makrophages) and MMP-9 expression

MMP-9 expression from macrophages is reduced by BA4

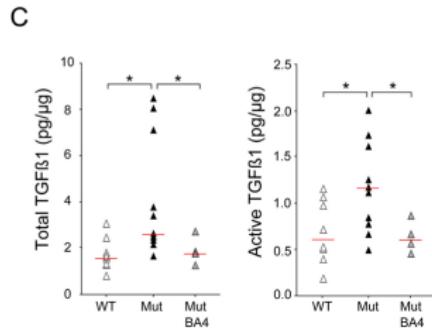
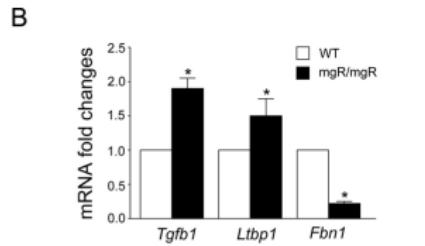
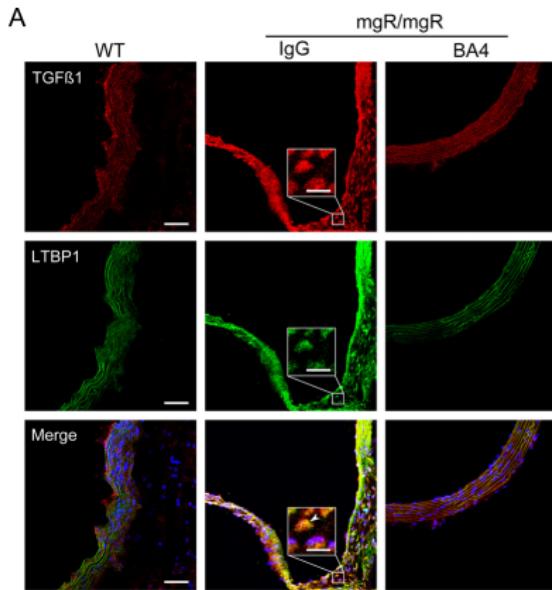
Treatment with BA4 (4)



Treatment with BA4 reduces upregulation of pSmad2 activity

⇒ In contrast to losartan, no effect on ppERK

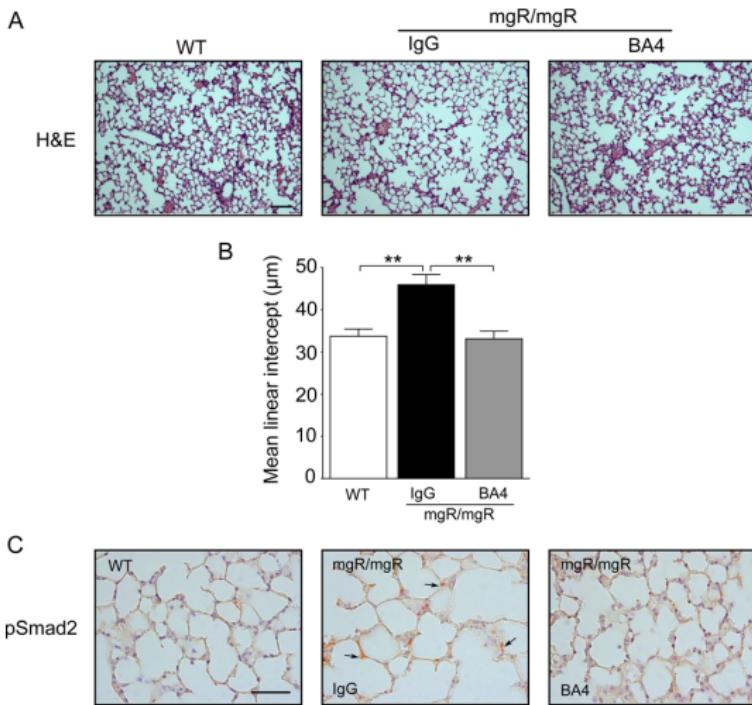
Treatment with BA4 (5)



TGF- β 1 and LTBP1-Expression in the Aorta

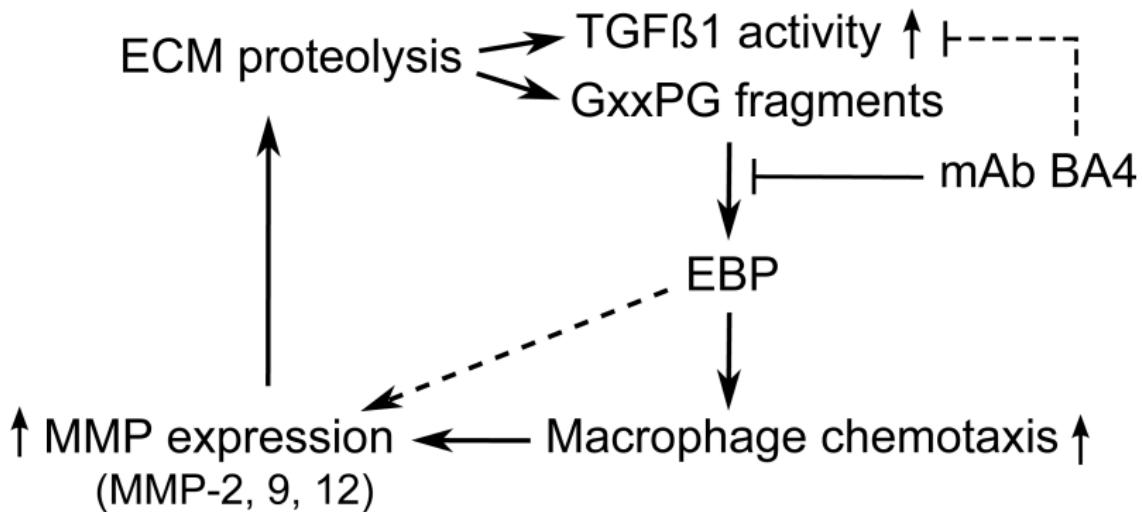
⇒ Health of matrix (fragmentation) and TGF- β metabolism are interconnected

Treatment with BA4 (6)



Treatment with BA4 reduces manifestations of pulmonary emphysema in mgR/mgR mice

Integrative model



Guo et al, under review.

Thank you for your attention



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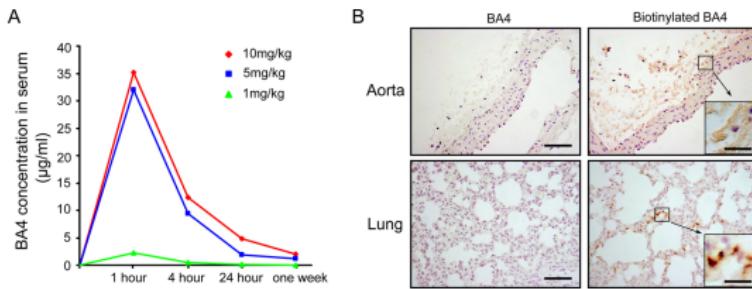
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Chris Mungall

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Additional slides

Treatment with BA4



BA4 reaches tissues at relevant concentrations