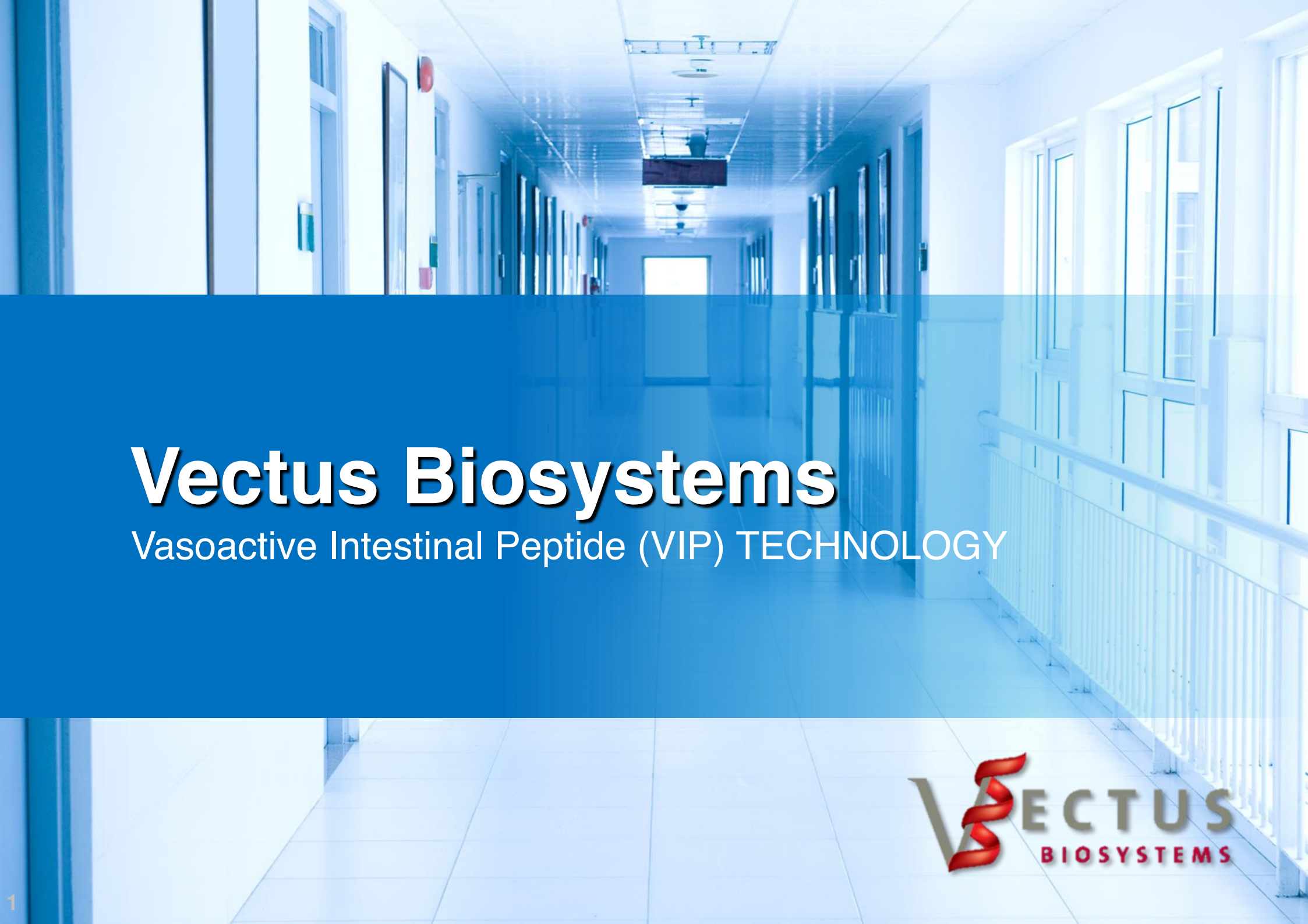

Vectus Biosystems

Vasoactive Intestinal Peptide (VIP) TECHNOLOGY

Oral VIP Agonists

A Platform Technology for the Management of Fibrotic Diseases

VECTUS BIOSYSTEMS

VIP AGONISTS FOR THE MANAGEMENT OF HYPERTENSION, CARDIOVASCULAR AND RENAL DISEASE

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Background

21st Century Health Challenges

- **Hypertension affects 40% of the adult population worldwide, less than 25% of patients achieve target blood pressure, it is a major risk factor for**
  - heart failure
  - kidney failure
  - stroke
  - dementia

- **Heart failure**
  - affects 5% of those >50 yrs
  - averaged annual mortality 30%
  - largest single item on US health care budget ($US32b in 2013)

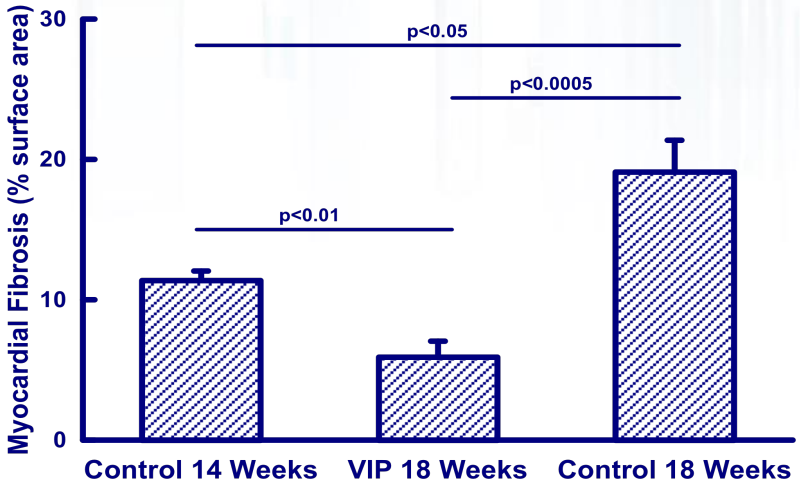
- **Kidney failure**
  - increasing - patient numbers on dialysis have trebled in last 2 decades
  - Dialysis and renal transplant costs in the US reached $49.2b in 2011

Vasoactive Intestinal Peptide (VIP)

- First isolated by Said and Mutt in 1970
- 28 amino acid peptide
- Amino acid sequence identical across all mammalian species except the guinea pig
- Described as "*the most potent vasodilator known*"
- Participates in sodium homeostasis as a humoral mediator of gastric sodium monitor where it
  - increases renal sodium excretion
  - down regulates Ang II (the main vasoconstrictor) via down regulation of Angiotensinogen synthesis
  - vasodilator
- In the heart VIP
  - is a positive inotrope increasing the force of contraction
  - myocardial VIP concentration is inversely proportional to the degree of myocardial fibrosis
  - is virtually absent in end stage cardiomyopathy in humans and experimental animals
  - is not taken up from the circulation by the normal heart

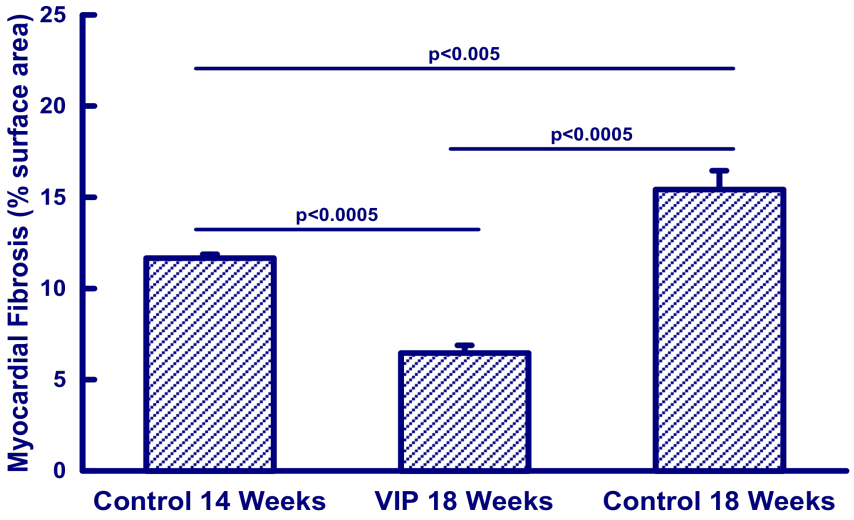
VIP Reverses Fibrosis – 3 Models

a

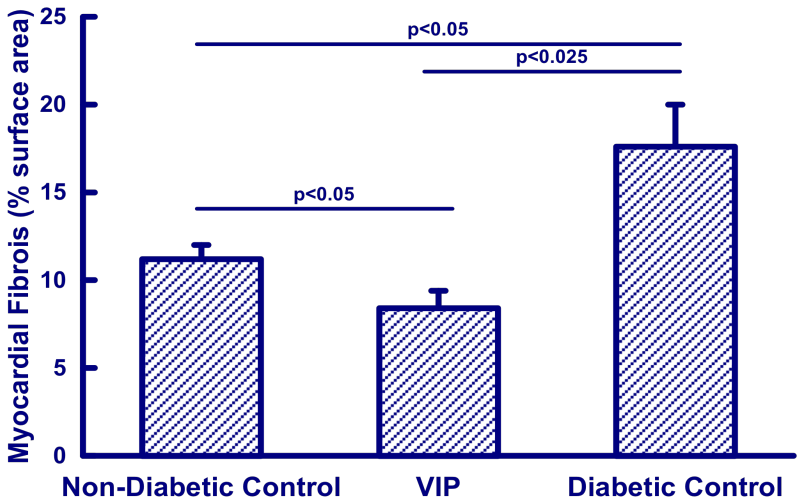


a normotensive rats on 4.4% salt diet treated with VIP (5pmol/kg/min) or control vehicle infusion for 4 weeks
b rats on 4.4% salt diet plus L-NAME (10mg/kg/day) treated with VIP (5 pmol/kg/min) or vehicle control infusion for 4 weeks
c fibrosis in rats streptozotocin (60mg/kg) induced diabetes at 14 weeks. After 8 weeks diabetes (i.e. 22 weeks of age) VIP (5 pmol/kg/min) or vehicle commenced and continued for 4 weeks

b

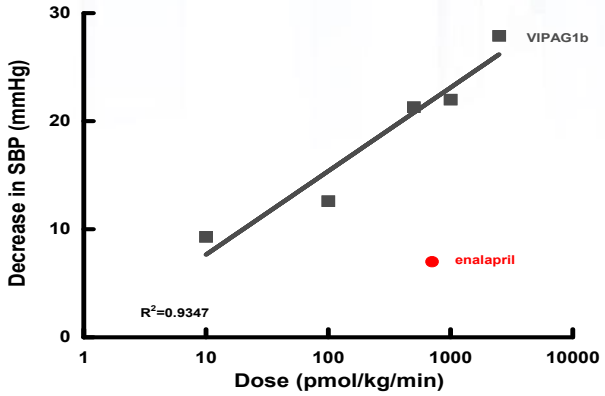


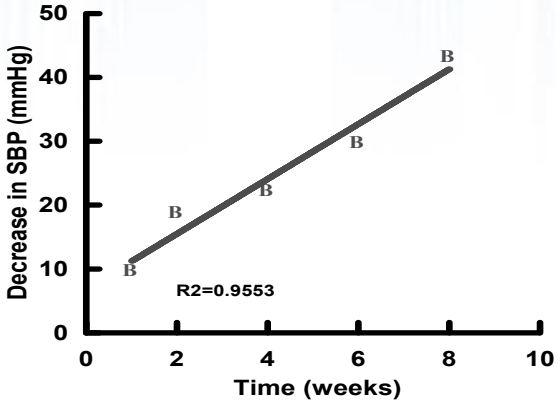
c

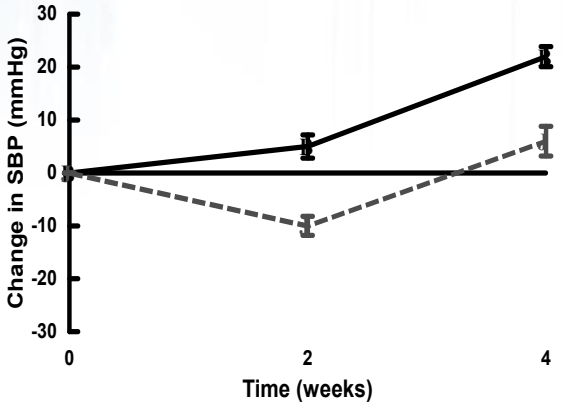


Systolic Blood Pressure Effects

Systolic Blood Pressure







- Left: Decrease in SBP from controls in 18 week old SHR treated with VB0004 at 10, 100, 500, 1,000 and 2,500 pmol/kg/min for 4 weeks. Enalapril dose to achieve 7mmHg was 705 pmol/kg/min. SBP continued to decrease with increasing dose to 2,500 pmol/kg/min
- Middle: Difference in SBP from control for SHR treated with VB0004 at 2,500 pmol/kg/min at 1, 2, 4, 6 and 8 weeks. The maximal effect of VB0004 in lowering SBP was not reached after 8 weeks treatment
- Right: Change in SBP from levels at the commencement of the experiment in Vehicle control for 4 weeks (solid line) SHR treated with VB0004 2,500pmol/kg/min for 2 weeks then vehicle for 2 weeks (dotted line) SBP in increased in parallel with vehicle control after cessation of VB0004

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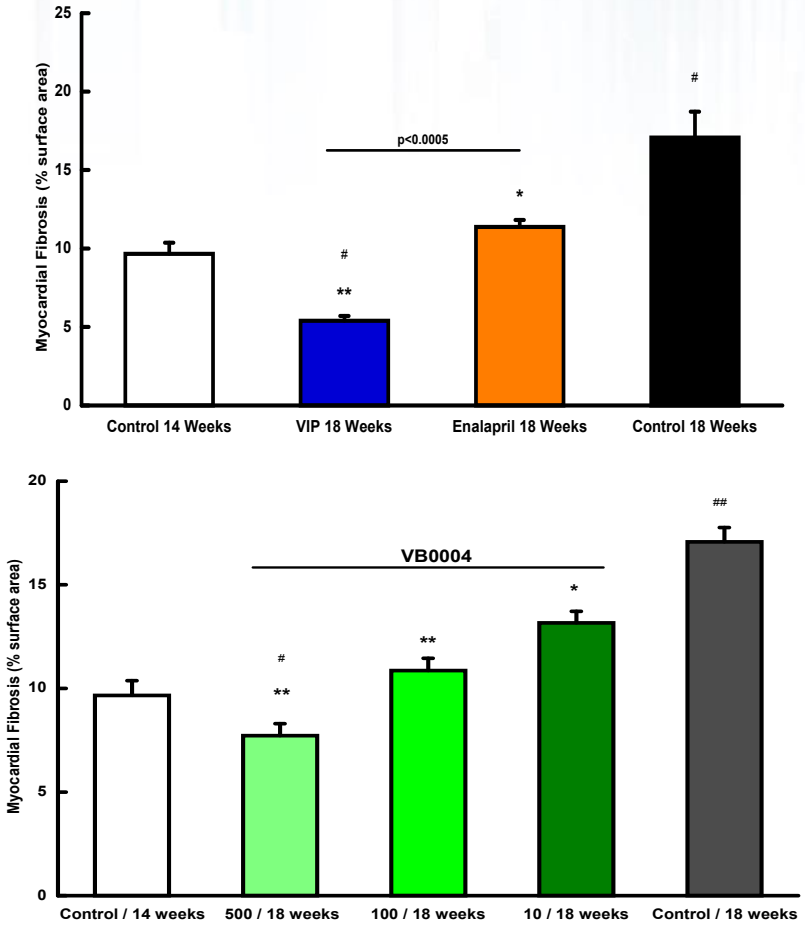
Anti-Fibrotic Actions

Myocardial Fibrosis

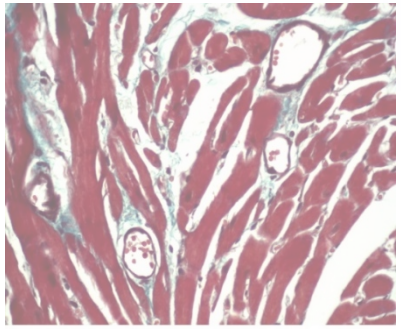


* p<0.005, **p<0.0005 vs 18 week control ; # p<0.05 vs 14 week control

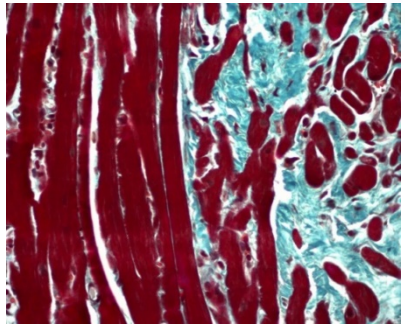
- Upper Panel: Myocardial fibrosis after 4 weeks treatment with VIP (5pmol/kg/min) or enalapril (dose adjusted to maintain the same BP reduction as VIP average dose 705 pmol/kg/min). * p<0.005, ** p<0.001, *** p<0.0005 vs 18 week control and ## p<0.0005 vs 14 week control
- VIP (5pmol/kg/min) reversed fibrosis present at commencement of infusion while enalapril (705pmol/kg/min) could only attenuate the amount of progression over the 4 weeks
- Lower panel: fibrosis in the heart in from left :
  - 14 week old controls,
  - 18 week old SHR treated with:
    - VB0004 500 pmol/kg/min for 4 weeks,
    - VB0004 100 pmol/kg/min for 4 weeks
    - VB0004 at 10 pmol/kg/min 4 weeks
  - 18 week old vehicle controls
- The amount of fibrosis present decreased with increasing dose of VB0004
- At the highest dose, fibrosis was significantly less than in rats studied at the beginning of the infusions at 14 weeks i.e. existing fibrosis was reversed

Cardiac Histology

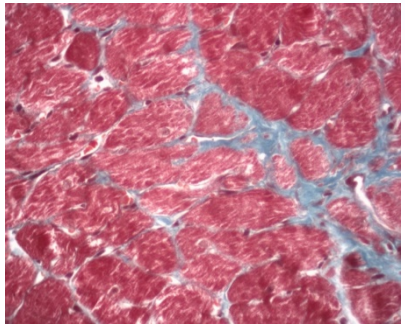
Control 14 weeks

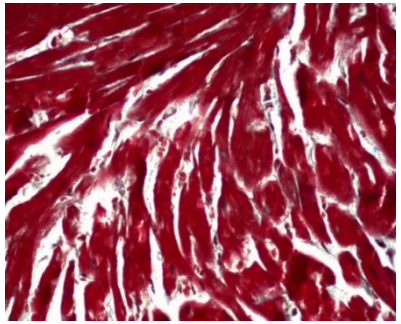


Control 18 Weeks

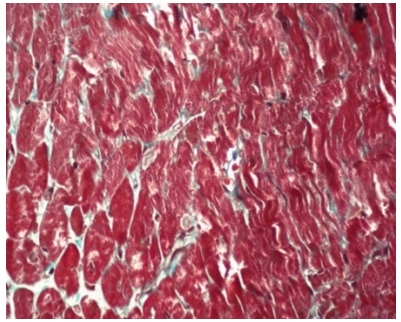


18 Weeks 5% EtOH

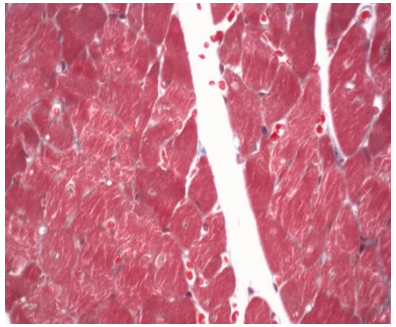




VIP 18 Weeks



Enalapril 18 Weeks



VB0004 18 Weeks

Heart sections stained with Masson trichrome, fibrous tissue appears blue-cyano in colour.

Upper Panels: 14 week control fibrosis is predominantly around blood vessels with some interstitial extension 18 week vehicle control marked increase in interstitial fibrosis surrounding muscle fibres and loss of muscle fibres 18 week 5% ethanol drinking solution. Fibrosis is visible as blue stained tissue and is present throughout the section.

Lower Panels: VIP infusion show restoration of normal tissue architecture after 4 weeks treatment. Enalapril treated - fibrosis is visible between most muscle fibres. 18 week old SHR after 4 weeks treatment with VB0004 delivered in the drinking solution (5% ethanol) for 4 weeks at a dose of 500pmol/kg/min. As with VIP treatment normal tissue architecture is restored by treatment.

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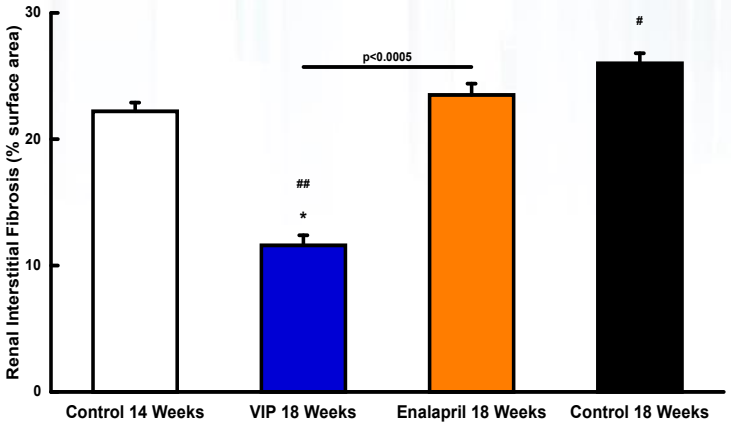
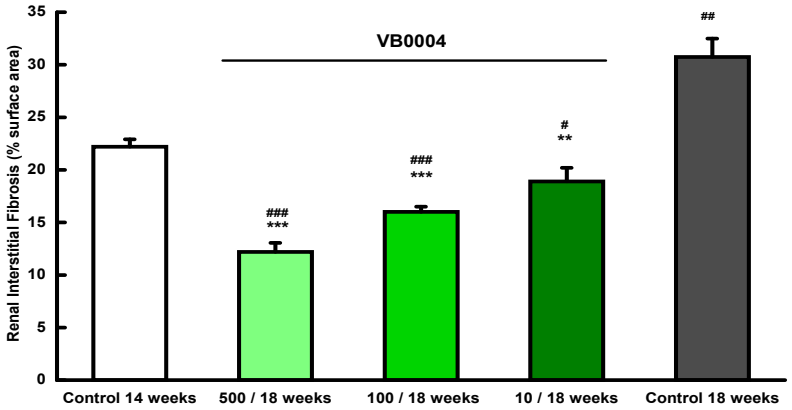
Effects on Kidney Fibrosis





- In humans increasing interstitial fibrosis in the kidney parallels the decline in renal function leading to dialysis
- Upper panel shows results from 14 week old SHR on 2.2% salt diet which were randomised to
  - 14 week control (open bar)VIP (5pmol/kg/min) infusion for 4 weeks (solid blue bar)
  - enalapril dose adjusted to match BP reduction of VIP for 4 weeks (cross hatched bar)
  - 18 week control vehicle (Hartman's Solution) infusion for 4 weeks (hatched bar)
- Lower panel fibrosis in the kidney in from left
  - 14 week old controls (open bar)
- 18 week old SHR treated with
  - VB0004 10 pmol/kg/min for 4 weeks
  - VB0004 100 pmol/kg/min for 4 weeks
  - VB0004 500 pmol/kg/min 4 weeks (hatched bars)
  - 18 weeks old vehicle controls (cross hatched bars)
- There is progression of fibrosis from 14 to 18 weeks
- VIP and VB0004 reversed the fibrosis which was present at commencement of the infusion

•# p<0.05, ##p<0.005 and ###p<0.0005 vs 14 week control; * p<0.005, ** p<0.0005 vs 18 week control

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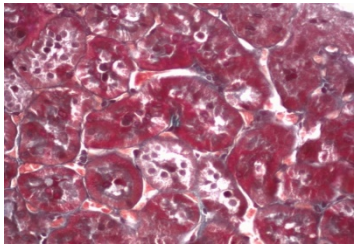
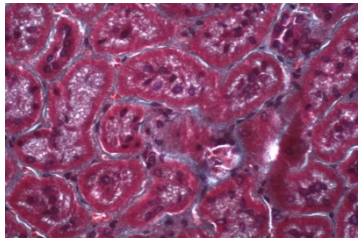
Renal Histology

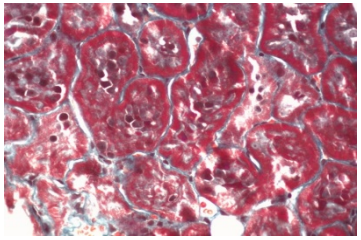
Control 14 weeks

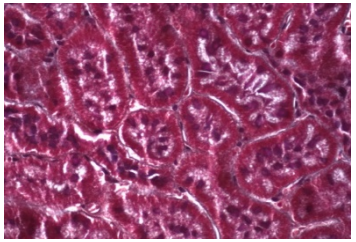


Control 18 Weeks

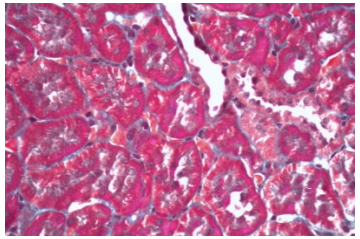


18 Weeks 5% EtOH

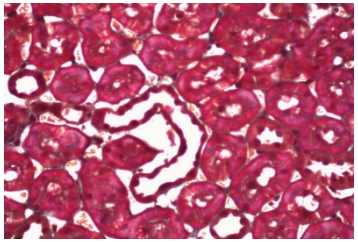




VIP 18 Weeks



Enalapril 18 Weeks



VB0004 18 Weeks

Kidney sections stained with Masson trichrome, fibrous tissue appears blue in colour
Upper Panels: 14 week control: fibrosis surrounds some but not all tubules 18 week vehicle control: marked increase in interstitial fibrosis surrounding all renal tubules 18 week 5% ethanol drinking solution. Fibrosis is present surrounding tubules throughout the section

Lower Panels: VIP: restoration of normal tissue architecture – tubules are "back to back". Enalapril: fibrosis is visible around virtually all renal tubules
18 week old SHR after 4 weeks treatment with VB0004 delivered in the drinking solution (5% ethanol) at a dose of 500pmol/kg/min. As with VIP treatment normal tissue architecture is restored by treatment with tubules showing no surrounding fibrosis

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VB0004 Data Summary

VB0004 in SHR animal term:

- decreased BP in a dose dependent manner in the SHR animal model
- BP reduction via both direct and endothelium dependent mechanisms
- more effective than enalapril on SBP treatment (greater reduction at lower dose)
- reversed fibrosis in the heart
- reversed renal fibrosis
- parallelled VIP effects on fibrotic mediators
- in the doses studied (up to 2500 pmol/kg/min) VB0004 did not show adverse effects in SHRs

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VB0004 ADME and Toxicology

ADME Toxicology - Summary

- No behavioural evidence of toxic effects in rats
- No effect on cardiac rate or evidence of cardiac arrhythmias
- No residual effects after cessation
- No significant inhibition of Cytochrome P450's in therapeutic range
- No mutagenic effect i.e. negative Ames test
- No cytotoxicity at concentrations up to 0.5mM
- No histological evidence of toxic changes in tissues from rats after 8 weeks treatment at the highest dose
- Human and rat hepatic microsome studies showed same metabolite profile

Current Status

- GMP synthesis almost complete
- Animal toxicology and pharmacokinetic studies commenced
- Tendering process for Phase1 underway

VIP AGONISTS FOR THE MANAGEMENT OF FIBROTIC DISEASE IN THE LIVER

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Hepatic Cirrhosis (Liver Fibrosis)

- Causes
  - genetic
  - infectious (Hep A, B, C)
  - alcohol related
  - diabetic
  - due to obesity
  - cryptogenic (no discernible cause)
- Prevalence
  - varies to >40% of the population in countries such as India, Cambodia, Vietnam and China due to endemic Hep B & C.

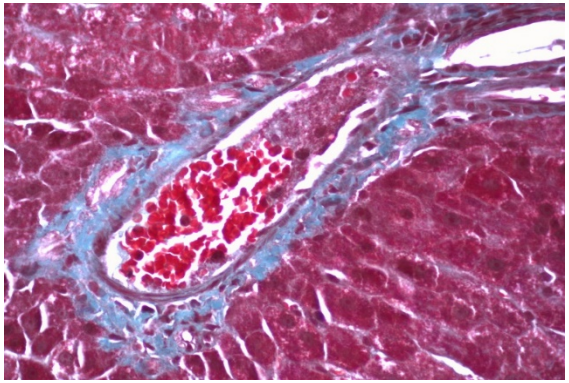
Current Therapies

- vaccination Hep A, Hep B for preventionn
- abstinence to prevent further damage
- weight loss
- diabetes management
- symptom relief (albumin infusion, ascites removal)
- Sofosbuvir and related agents for Hepatitis C

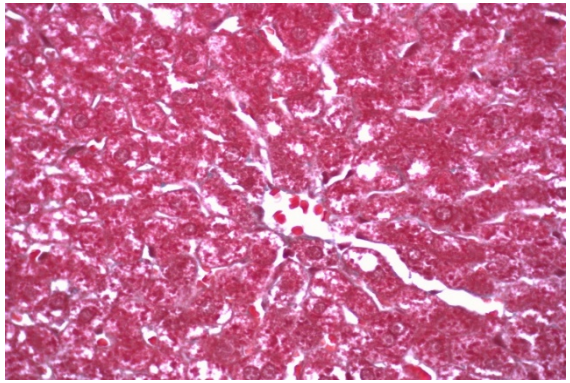
  (note this treats the infection but does not prevent progression of the established fibrosis for which lifetime monitoring is required)
- transplantation

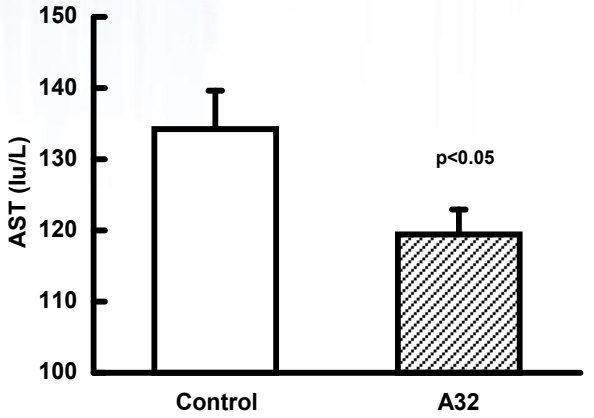
A32 – Liver

20 Week Control

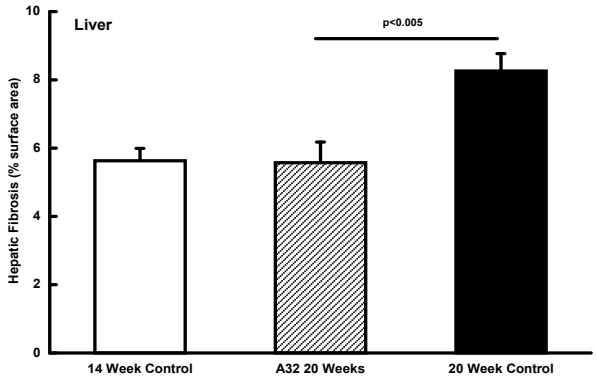


A32 20 Weeks

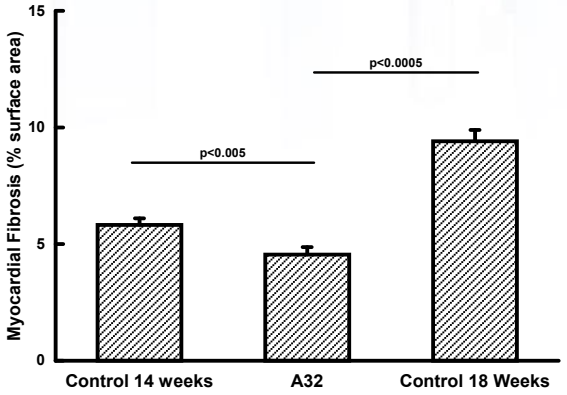


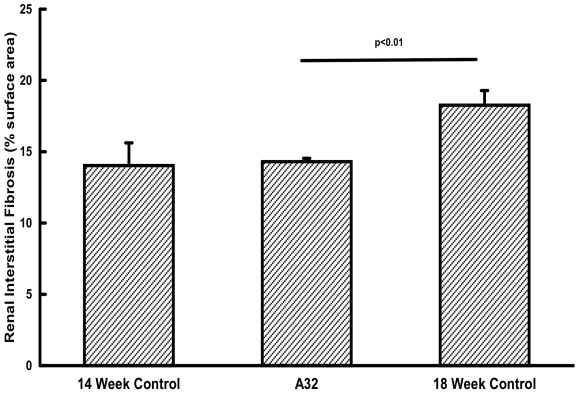


Treatment with A32 for 6 weeks in a rat model of liver cirrhosis resulted in significant improvement in liver function (above right) and decreased fibrosis (above and lower right).



A32 – Other Organs





Cardiac (upper panel) and renal (lower panel) fibrosis in SHR on a 2.2% salt diet after 4 weeks treatment with A32 at 500pmol/kg/min. In the heart A32 reversed pre-exisitng fibrosis as compared with the 14 week controls, while in the kidney progression of fibrosis was halted at this dose.
A32 had no effect on blood pressure.

Intellectual Property

IP Position

- **VIP patents for heart, kidney and aortic fibrosis -** *granted most jurisdictions*
- **VIP fragment patents compositions and methods of use for hypertension, cardiac, renal and aortic fibrosis –** *granted most jurisdictions*
- **VB0004 compositions and methods of use for hypertension, cardiac and renal fibrosis -** *granted US patent*
- **VB0004 library of approx 70 related compounds compositions and methods of use for treatment of hypertension, cardiac and renal fibrosis -** *entering national phase*
- **A32 and library of related compounds compositions and methods of use for treatment of hepatic, cardiac and renal fibrosis -** *PCT application*

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IP Position (cont)

- **P5 and library of related compounds compositions and methods of use for treatment of renal cell death, renal fibrosis and hepatic fibrosis -** *PCT application*
- **GMP method of synthesis VB0004 -** *PCT application*
- **A79 and related compounds compositions and use for treatment of pulmonary fibrosis -** *Provisional application*
- **VB0001 and related compounds compositions and use for management of hypertension and fibrotic disease -** *Provisional application*
- **VB0002, VB0003 and VB0005 and related compounds compositions and use for management of hypertension and fibrotic disease -** *Provisional application*
- **<u>Since IPO, patent library has been extended from 70 to over 1000 compounds.</u>**

VECTUS BIOSYSTEMS

VIP Agonists:

the benchmark in anti-fibrotics

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