Acute Intravenous Infusion of Human Stresscopin (JNJ-39588146) Improves Left Ventricular Systolic Function Without Increasing Myocardial Oxygen Consumption in Dogs with Advanced Heart Failure

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## Corticotropin Releasing Factor Family Members

<table>
<thead>
<tr>
<th>Year</th>
<th>Peptide</th>
<th>Institute</th>
</tr>
</thead>
<tbody>
<tr>
<td>1981</td>
<td>Corticotropin Releasing Factor (CRF) – Ovine</td>
<td>Wylie Vale Clayton Institute</td>
</tr>
<tr>
<td>1996</td>
<td>Urocortin (UCN) Human</td>
<td>-</td>
</tr>
<tr>
<td>2001</td>
<td>Urocortin II &amp; III (UCN II &amp; UCN III) – Human</td>
<td>Wylie Vale Clayton Institute</td>
</tr>
<tr>
<td>2001</td>
<td>Stresscopin &amp; SRP Human</td>
<td>Aaron Hsueh Stanford University</td>
</tr>
</tbody>
</table>
Corticotropin Releasing Factor Family of Peptides & Conjugate Receptor
Physiology – Pharmacology – Molecular - Biochemical

Hormones/Peptides

Corticotropin Releasing Factor

Urocortin

Stresscopin
Stresscopin Related Peptide
Urocortin-II
Urocortin-III

CRF-R₁

CRF-R₂

7 TM Receptors

G-Protein Coupling

Second Messengers

Pituitary-Adrenal Axis
Endocrine, Autonomic & Behavioral Response
to stress → "FIGHT OR FLIGHT"

“DEAROUSAL”
CARDIOVASCULAR
  a. Inotrope/Lusitrope
  b. Vasodilation
GI & APPETITE
ANXIOLYTIC
SKELETAL MUSCLE
Amino Acid Sequence & Homology Between Human Stresscopin & Members of the Corticotropin Releasing Factor Peptide Family

TKFTLSLDVPTNIMNLLFNIAKAKNLRAQAAANAHLMQI-NH₂  h-SCP

Human Stresscopin  ~38% homology with h-UCNII
~20% homology with h-UCNI
Ischemia Induced, Progressive Heart Failure in Dogs

A well characterized model that parallels many features reported in patients with the syndrome

• Healthy mongrel dogs (22-26 kg)
• Baseline hemodynamics, angiographic, and neurohormonal measurements
• Multiple-sequential-intracoronary microembolization using polystyrene latex microspheres (77-102mM)
  ➢ Embolizations were performed 1-2 weeks apart
  ➢ Each dog received a total of 7-10 embolizations divided equally between LAD and LCFX CA
  ➢ Embolizations were discontinued when LVEF <30%
• Highly studied, published validated model
  ➢ Cellular, molecular, hemodynamic, neurohormonal, electrophysiological, angiographic changes similar to patients
  ➢ Responds to current HF therapy in a manner similar to patients

Study Design

Healthy Mongrel Dogs → Multiple Sequential Microembolization → Advanced Heart Failure

7-10 Microembolizations

Cross-Over Escalating IV human Stresscopin – time/vol matched vehicle control

2.2 ng/kg/min for 60 min → 4.3 ng/kg/min for 60 min → 7.3 ng/kg/min for 60 min

Hemodynamic, ventriculographic & *MVO₂ measurements:
1. Baseline – prior to drug/vehicle administration in dogs with HF
2. At the end of 60 min drug or vehicle administration

(N= 7)

Effects of Human Stresscopin on Global LV Systolic & Diastolic Function and Myocardial Oxygen Consumption in Dogs with HF
Effects of Human Stresscopin on Global LV Systolic & Diastolic Function and Myocardial Oxygen Consumption in Dogs with HF

*LVEF (%)

Baseline       2.2                 4.3              7.3       
                 ng/kg/min
*
* *

SV, ml

Baseline       2.2                 4.3              7.3       
                 ng/kg/min
*
* *

*p<0.05 vs. time & volume matched vehicle control
**Effects of human Stresscopin on Global LV Systolic & Diastolic Function and Myocardial Oxygen Consumption in Dogs with HF**

<table>
<thead>
<tr>
<th>Time &amp; volume matched vehicle</th>
<th>Human Stresscopin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>2.2</td>
</tr>
<tr>
<td>LVEDP, mmHg</td>
<td>ng/kg/min</td>
</tr>
<tr>
<td>LVESV, ml</td>
<td>ng/kg/min</td>
</tr>
</tbody>
</table>

* p<0.05 vs. time & volume matched vehicle control
Summary

In dogs with advanced HF, acute IV administration of human stresscopin elicited dose- and plasma-concentration dependent:

- ↑ LV ejection fraction (EF)
- ↑ cardiac output (CO)
- ↑ stroke volume (SV)

With NO
- ↑ heart rate (HR) or de novo cardiac arrhythmias
- ↓ aortic BP
- ↑ myocardial oxygen consumption (MVO₂)
Conclusion

- In the current study, the effects of human Stresscopin in dogs with ischemia induced, irreversible HF correlate with hemodynamic changes demonstrated with the peptide in a recent Phase 2a study* in patients with severe systolic HF.
- This finding denotes the translational pharmacology of the peptide between dogs and patients with HF.

*Late Breaking Clinical Trial Session - HFA ESC Meeting, Belgrade, Serbia (19-22 May 2012).
Thank You