Combination Therapy
A New Approach to the Treatment of Myocardial Reperfusion Injury?

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Company name(s): Genesis Pharma S.A.

I declare competing financial interest because of patent application.
AMI and PPCI

- Acute myocardial infarction (AMI) is a major cause of mortality and morbidity worldwide.

- Primary percutaneous coronary intervention (PPCI) is the choice therapy for acute ST-segment elevation myocardial infarction (STEMI) patients.

- However, extensive areas of myocardial necrosis still occur in a high proportion and result in substantial mortality and incidence of heart failure and arrhythmias.
**Ischemia and Reperfusion Injury**

- **Reperfusion** itself can induce myocardial injury and cardiomyocyte death.

- Reperfusion injury is considered a multi-factorial pathology which is responsible for approximately 50% of the final infarct size.

- **Infarct size** is a major determinant of myocardial remodelling and subsequent development of heart failure.
Reperfusion Injury Therapy

- A plethora of experimental studies have suggested many therapeutic strategies and pharmacological targets.

- However, clinical implementation of these strategies has not been very successful to date.

- So far there is no approved effective treatment – an unmet medical need.
**Exenatide**

- A glucagons-like peptide 1 receptor agonist with anti-diabetic effects

- **Preclinical studies** provide strong evidence for cardiovascular protective effects
  - Reduced infarct size and improved cardiac function in a porcine model (J Am Col Cardiol, 2009, 53:501-510)

- **In clinic,**
  - Negative: no benefit of additional treatment with exenatide in patient (91) with an AMI (STEMI) (Int J Cardiol, 2016, 220:809-814)
**Cyclosporine**

- **Immunosuppressant**, which binds to cyclophilin and inhibits calcineurin and IL2

- **Affects mitochondria by preventing MPTPs from opening**

- **Preclinical studies**: able to reduce infarct size in many experimental models

- **In clinic,**
Aldosterone Antagonists

- K-sparing diuretics (spironolactone, eplerenone, potassium canrenoate)
- **Reduce mortality in the setting of HF**
  - High aldosterone plasma levels early after STEMI or NSTEMI are associated with mortality, sudden cardiac death and HF
- **Preclinical studies,**
  - reduce myocardial infarct size from ischemia and reperfusion by 40-50% in murine, rat and rabbit MI models (Eur Heart J, 2010, 31:1655-1662)
- **In clinic,**
  - The addition of eplerenone to standard therapy within 24h of symptom onset is safe and reduces brain natriuretic peptide levels of STEMI patients (1012) (Eur Heart J, 2014, 35:2295-2302)
  - ALBATROSS failed to show the benefit of early MRA (potassium canrenoate and spironolactone) use in addition to standard therapy in patients (1603) admitted for MI (J Am Coll Cardiol, 2016, 67:1917-1927)
Our Proposal: Combination Therapy

- Several advantages when compared with single interventions:
  - An additive or synergistic effect
  - Effective in more patients
Acute Myocardial infarction and Reperfusion injury Model

- It has been used in mice, rats, and rabbits.
- Four series of experiments.
- Approved protocols.
- Coronary artery (LAD) occlusion and release – 30-40 min of ischemia and 2-3 h of reperfusion.
- Estimation of left ventricular area (LV), ischemic area (AAR), necrotic area (infarct size, IF).
- Results are expressed as AAR/LV% and IF/AAR%.
- cTnI measurement.

**Diagram:**
- Thoracotomy
- Intubation
- Dissociative anesthesia
- Catheterization
- Onset of ischemia
- Treatment (10-15 min before)
- Initiation of reperfusion
- 30-40 min
- 120-180 min
- Animal sacrifice and heart isolation.
Effects of Combined Exenatide and Cyclosporine Treatment in a Rabbit Model

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<tr>
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<th>Sham</th>
<th>Control</th>
<th>Exe</th>
<th>CsA</th>
<th>Exe + CsA</th>
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<tbody>
<tr>
<td>IF/AAR</td>
<td></td>
<td></td>
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<tr>
<td>% of control</td>
<td>-94</td>
<td>-</td>
<td>-37.7</td>
<td>-39.8</td>
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<tr>
<td>cTnI</td>
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<tr>
<td>% of control</td>
<td>-93.4</td>
<td>-</td>
<td>-48.1</td>
<td>-36.1</td>
<td>-60.7</td>
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Cardiac Troponin I release

Infarct Size/Area at Risk

Cardiac Troponin I release

N 4 18 18 18 22

IF/AAR % of control -94 - -37.7 -39.8 -55.4

cTnI % of control -93.4 - -48.1 -36.1 -60.7
Dose-dependent Effects of Combined Exenatide and Cyclosporine Treatment in a Rat Model

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<td>-2.2</td>
<td>-3</td>
<td>-6.5</td>
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**Effects of Combined Exenatide, Cyclosporine and Potassium Canrenoate Treatment in a Rabbit Model**

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<td>% of control</td>
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<td>-36.2</td>
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![Graph showing effects of combined treatments](image)

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<td>-50</td>
<td>-70.6</td>
<td>-74.8</td>
<td>-46.5</td>
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Effects of Exenatide, Cyclosporine and Potassium Canrenoate and their double or triple combined therapies in a Murine Model
Conclusions

- Myocardial reperfusion injury is the result of many pathogenic factors, therefore it seems that interfering with therapeutic agents targeting different pathogenic factors involved may have advantageous therapeutic outcome.

- The combined administration of exenatide with cyclosporine and/or potassium canrenoate is more beneficial and advantageous and provides superior outcome against therapies with either agent alone.

- Interestingly, the combination of exenatide and potassium canrenoate is the most promising, providing synergistic cardioprotective effects and as such may be exceptionally useful in methods at preventing and treating ischemia-reperfusion injury in mammalian subjects.
Thank you for your attention