Does understanding the biology of cardiac injury from cancer therapy lead to new cardiac therapy?

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Disclosures

• No financial disclosures

• Funded by:
  – VCTRS career development award

• Research
  – Co-investigator for Phase Ia study of GGF2 (Acorda Therapeutics)
Reverse Translation: Cardiotoxicity to Cardiac Repair

Historical observation from chemotherapy cardiotoxicity

Discovering importance of NRG/ErbB biology

Harnessing NRG/ErbB biology for cardiac repair

Reverse translation – turning biology of injury into therapy of cardiac repair.
Insight into the biology of cardiotoxicity

- Four fold increase in cardiotoxicity with concurrent administration.
- Why is the combination AC + Her2/ErbB2 antibody so cardiotoxic?

Peng et al. Molec Intv 2005
Slamon et al. NEJM 2001
ErbB2 Inhibition Increases AC toxicity

Sawyer et al. Circ. 2002
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ErbB Receptor Biology

ErbB2 Receptor Biology

Hynes et al. Nat Rev Cancer 2005
What is Neuregulin?

- NRG belongs to family of proteins that are part of the EGF family
- Expressed in various tissues
- These proteins have diverse functions:
  - growth
  - differentiation
  - survival

Cote et al. Exp Cell Research 2005
Activation of NRG in the heart

Survival

Growth

Peng et al. Molecular Interv 2005
Is NRG needed for cardiac development?

- Mice in utero begin to develop valves and trabeculation days 9-10.5.
- NRG1, ErbB 2 or 4 are needed for trabeculization.
- NRG1, ErbB 2 or 3 needed for endocardial cushion formation.

Without NRG/ErbB signaling cardiac development is not possible.

What is role NRG / ErbB2 signaling in post-natal heart?

- Conditional knock out mice exhibit dilated LV and thin walls similar to that seen in trastuzumab

- EM - shows increased mitochondria and vacuoles

- NRG helps maintain normal myocyte integrity

Can NRG treatment be protective?

- Myocytes exposed to AC for 24 hrs +/- 30 min pre tx with NRG

- NRG protects myocytes against cardiotoxicity.

Fukazawa et al. J of Molec Cell Cardiology 2003
## Biological Effects of NRG in the Heart

<table>
<thead>
<tr>
<th>Cell type</th>
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<td>PI3-kinase/Akt</td>
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How does NRG promote cardiac repair?

• **Postulated:** Cardiomyocytes have proliferative potential and may regenerate in response to growth factors:

• Screened certain GF’s to see what promoted DNA synthesis.

Bersell et al. Cell 2009
NRG promotes repair through regeneration of myocytes

Bersell et al. Cell 2009
Proliferation / Differentiation Potential of NRG

- NRG promotes in vitro proliferation of EC’s, independent of VEGF levels.

- Embryo hearts develop conduction system cells from CM.

- NRG promotes in vitro differentiation of CM into cardiac conduction cells in a time specific window.

Russell et al. AJP 1999
Rentschler et al. PNAS 2002
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Reverse translation – turning biology of injury into therapy of cardiac repair.
Can NRG be used therapeutically for HF?

- Investigated effects of short term IV recombinant NRG in various animal models of HF.
  - Ischemic CM (rats - ligated LAD)
  - Drug Induced CM (rats tx w/ Doxorubicin)
  - Viral CM (Coxsackie virus)

Liu et al. JACC 2006
NRG improves LV function and Survival

Liu et al. JACC 2006

Survival %

Ischemic Induced CM

Days of Treatment

Dox Induced CM

Days of Treatment

Viral Induced CM

Days of Treatment

EF %

Early MI Rx.

Black sham n=10
Red vehicle n=12
Blue NRG n=13

Dox

Dox+NRG

Cox

Cox+NRG
Translation to clinical trial

We've run out of lab rats, Henderson... Put this on and come with us.
First studies of Rh-NRG in humans

Phase I
- Single center, prospective, open label study 15 chronic HF patients.
- Investigating tolerability & hemodynamics
- Daily infusion 12 hrs.
- F/u 4, 8, 12 wks

Conclusions
- Small increase in LVEF
  - 32 ±2% to 36 ±2%
- Small decrease in LVESV
  - 9% reduction
- Generally safe and well tolerated
  - No lasting HD effects
  - N/V

Jabbour et al. European Heart J. 2010
Safety

- SAE - 2 pts.
- N/V drug stopped on D9.
- N/V requiring CT, US, EGD, and mild EKG and Tp elevation
- One skin cancer noted during course of treatment

**Table 3** Adverse events reported during the 12-week course of the study

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Incidence, n (%)</th>
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<tr>
<td>Cardiovascular</td>
<td></td>
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<tr>
<td>Chest pain</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Postural hypotension</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Postural syncope</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Pericardial effusion (small, asymptomatic)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Second degree type 2 heart block</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Cardio-respiratory</td>
<td></td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Stomach cramps</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Neurological</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Oncological</td>
<td></td>
</tr>
<tr>
<td>Localized squamous cell carcinoma of the skin</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Localized basal cell carcinoma of the skin</td>
<td>1 (7)</td>
</tr>
<tr>
<td>General</td>
<td></td>
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<tr>
<td>Lethargy</td>
<td>2 (13)</td>
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<tr>
<td>Polyuria</td>
<td>1 (7)</td>
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Jabbour et al. European Heart J. 2010
Phase II RCT Rh-NRG in Chronic HF

- 44 NYHA II-III, LVEF <40%, randomized treatment or placebo for 10 days:
  - 0.3, 0.6, 1.2 µg/kg vs. placebo (infusion for 10 hrs)
- 1º Endpoints - change LVEF, ESV, EDV by MRI at 11, 30, 90 days.
  - Conclusions were small improvements in LVEF and LV volumes (0.6 µg/kg) suggesting improved cardiac remodeling
- 2º Endpoints - NYHA, 6MWT, BNP, QOL
  - No significant improvements
- ? Reasons for modest changes is the short $T_{1/2}$

Gao et al. JACC 2010
Phase Ia Rh-NRG in HF

- Different recombinant NRG molecule
- EGF + Kringle domain ~ natural NRG-1
- The effects of Rh-NRG-1 (aka GGF2) longer

Are you worried about a growth factor therapy causing cancer?
NRG1 gene may be a tumor suppressor gene

- Loss 8p is one of the most frequent events in epithelial cancers: breast, colon, prostate, bladder.

- Most breast cancer cell lines had reduced / undetectable NRG1 expression.

Chua YL et al. Oncogene 2009
Trial Design Considerations for Phase Ia Safety Study

• Phase Ia – Study is in NYHA II-III chronic HF patients.
• Participants are required to have up-to-date age-appropriate cancer screening prior to enrollment. No hx of cancer.
• Stable HF symptoms for the last 3 weeks and ICD.
• DSMB committee:
  – Phase I Oncologist
  – Clinical Trial Cardiologists
Phase Ia - Single dose, randomized, controlled double blinded, dose escalation of GGF2

- Plans to complete Phase Ia study this fall and launching multi-center study in the near future.
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Never to macho to wear pink

- Remember October is National Breast Cancer Awareness Month.

Thank You
Many Thanks

- Doug Sawyer
- Dan Lenihan, David Slosky
- Clinical Team from Acorda Therapeutics
- Research Nurses
  - Brenda White, Darla Freehardt, & Sarah Anderson
- Sawyer Lab
  - Xu-Yang Peng, Laura Pentassuglia, Holly M. Smith, Queen Henry-Okafor, Abby Murphy, Jijun Hao, Rashad Harris
- VICTRS Grant Support
Cardio-Oncology – Collaboration to Impact Outcomes and Treatment

“ A success story for cancer, who suffered sudden cardiac death at the age of 51”

• Can we improve cancer survival by preventing carditoxicity?

• Can we learn from mechanisms of cardiac injury and find ways to promote cardiac repair?