RAC PROTOCOL 0401-622 OVERALL ASSESSMENT

- Definite need for improved therapeutic options in CHF
- AC_{VI} appears to be a novel target and represents innovative treatment
- Vector (Ad5) and transgene product should be reasonably safe
- Overall, this proposed trial appears acceptable

Four Areas of Potential Concern

- Coronary catheterization risks and patient population
- Complexities of concurrent medications with AC gene transfer
- Overall statistical analysis
- Pre-clinical data

1. Coronary catheterization risks and patient population

- Overall risks in patients with LV dysfunction
- Added risk of ischemia during delivery
- Placebo issues

1. Coronary catheterization risks and patient population

Overall risks in patients with LV dysfunction

In his response, the PI stated that highest risk for adverse events with coronary catheterization is with unstable angina (patients excluded from trial). Did acknowledge some risks in CHF patients. To further reduce the risks, they would try to simultaneously enroll subjects where physicians had already recommended a Cath. procedure (Class I indication), however doesn't appear that this will be that many patients, so original question may remain.

Worthy of further discusssion.

1. Coronary catheterization risks and patient population

Added risk of ischemia during delivery

The PI stated that there will be no ischemia based on a slow infusion of virus through an infusion catheter.

1. Coronary catheterization risks and patient population

Placebo issues

From PI's response:

"The issue of enrolling placebo-treated patients is important. My belief is that clinical trails of this nature should be double-blinded so that the data collected will be meaningful. I cannot assure that the treatment will be effective — in this regard patients receiving placebo or active treatment are similar. The important question, it seems to me, is whether the trial should be done at all. If the answer is yes, then it should include a placebo group. Others may have a different view, and I would be happy to discuss this in more length at the meeting."

2. Complexities of concurrent medications with AC gene transfer

- How will AC overexpression be in combination with current therapies.
- Will β-AR blockade be given any special consideration.
- How to test potential efficacy in exercise during potential β-AR blockade.

2. Complexities of concurrent medications with AC gene transfer

How will AC overexpression be in combination with current therapies

The PI stated that no data as of yet. Pig model cannot tolerate β-AR blockade. ACE Inhibition in model led to positive findings in regard to cAMP generation. Could be additive as β-AR antagonists do increase efficiency of the β-AR system.

2. Complexities of concurrent medications with AC gene transfer

How to test potential efficacy in exercise during potential β-AR blockade and β-AR antagonist consideration.

This question arose due to my assessment of pre-clinical data that most positive effects seen after β-AR stimulation and thus, if patients are on β-AR antagonists treadmill test may be hard to interpret. Possibility of doing stress test ? Or withhold β-AR blockers during test ? Will presence of β-AR blockers be part of inclusion/exclusion ?

PI stated also basal effects seen with AC overexpression including LV geometry. Didn't comment on stress test or β-AR blockers.

3. Statistical Analysis

- Overall Power analysis
- Specific tests for effect of treatment should be included

3. Statistical Analysis

Power Analysis and Sample Size

From PI's response:

"The proposed dose escalation design begins at a dose, which is 2 log units below what we have shown to be effective in preclinical studies. Escalation is 0.5 log units per dose, and we will treat 4 patients per dose at the two lowest doses, then 12 patients at subsequent doses. Based on our preclinical data, we anticipate that a treatment effect will not be likely until dose 4 or 5 are reached. To increase the power of this first trial we wish to provide a means for the DSMB to recruit additional patients if there are trends for increases in exercise capacity, maintaining the 3:1 randomization ratio, and maintaining the blindedness of the trial.
The coefficient of variation of exercise testing in this patient population is 25%. We wish to detect a 20% treatment effect. Assuming a ß-error of 0.10 and an α-error of 0.05 (standard criteria), the study would require a group size of 20. This is derived by simple power calculation. "

3. Statistical Analysis

Specific Statistical Tests

Not specifically answered. Was also an issue also raised by members of the RAC committee. For example, what statistical test will be used to compare exercise tolerance?

Worthy of further discusssion.

4. Pre-Clinical Data

- Reproducible and reliable global cardiac transgene expression.
- Details of cAMP-independent effects.
- Cardiac inflammation.
- Extra-cardiac expression.

4. Pre-clinical Data

Global Transgene Expression

PI's response was to refer to figures in Lai et al., 2000 and also in unpublished manuscript on CHF rescue in pig. There is evidence for transgene overexpression but would have liked to see expression in representative sections throughout the heart. Are western blots a single LV section ? How about X-Gal staining of more areas of heart ?

4. Pre-clinical Data

cAMP-Independent Effects of AC Overexpression

PI's response was to show added data from the briefly mentioned report on this in the protocol. Nice data indicating that AC overexpression decreases PLB expression but was not in the presence of a cAMP inhibitor. Certainly could play a role in a functional rescue in the heart and begs for future experimentation. Are calcium transients increased ?

4. Pre-clinical Data

Cardiac Inflammation and Extra-Cardiac Expression

PI's response was that at the doses to be tested they have seen no cardiac histopathology or expression of virus outside of the heart is not typically seen until higher doses. Thus, to the PI this is not a large concern.

Still a potential risk that should be appreciated in this trial

SUMMARY

- Definite need for improved therapeutic options in CHF.
- Can be considered pioneering.
- Just a few areas for further discussion.