PROTOCOL 588: OVERALL ASSESSMENT

- Concept is sound, well supported
- Vector is safe
- Transgene product is reasonably safe
- Overall, a phase I study seems acceptable in principle
- Three issues

PROTOCOL 588:
1st Issue

Poor Correlation Between Transgene Expression and Efficacy

- ≤ 50% of SCW rats express transgene in joint

but

- they all seem to improve dramatically.

and

- they all have vector DNA (expression?) outside the joint

- Is extraarticular transgene expression important for the anti-arthritic effect?
- Is this why the effects of i.m. and i.a. injection are equivalent?

PROTOCOL 588:
2nd Issue

Vector DNA appears in the ovaries of SCW rats.

Is this a concern?

PROTOCOL 588: 3rd Concern

Patient Recruitment

- The American College of Rheumatology has issued the following statement:

"We believe that all patients with serious rheumatic disease must have these new "biologic" medications available when clinically appropriate."

- The inclusion criteria of the proposed study state:

"No past or current use of TNF-α antagonists, and no planned use of TNF-α antagonists other than tgAAC94 in the next three months."

How can these two statements be reconciled?

PROTOCOL 588:
3rd Concern (Cont)

- Under what conditions are patients likely to be suited for Enbrel gene therapy but not standard Enbrel therapy?
- A major obstacle to the use of Enbrel is cost (~$12,000 p.a.)
- Need to avoid exploiting poorer patients
- Add language to Consent Form…….

PROTOCOL 588:
3rd Concern (Cont)

Possible additional language to the consent form, in the section "alternative therapy" (Rough Draft)

"It has been explained to me that the genetic medicine I will receive during this study is, in many ways, equivalent to the drug Enbrel. For most patients, Enbrel is very effective in controlling the signs and symptoms of rheumatoid arthritis. It has been explained to me that my rheumatoid arthritis is not suitable for Enbrel treatment. Enbrel is not being denied to me because it is very expensive or in order to encourage me to participate in the study"