

Isolagen BLA 125348 Review Team Meeting Minutes (10-20-09 and 10-23-09)

Participants: Donald Fink, John Thomas, Yao-Yao Zhu, Gang Wang, Stephanie Simek, Shiojjen Lee, Changting Haudenschild, Raj Puri, Lisa Stockbridge, Craig Zinderman, Atm Hoque, Keith Wonnacott, Kimberly Benton, Lori Tull, Celia Witten

1. Product Name

- Proposed product proprietary name - Laviv™ (under review). The Advertising and Promotional Labeling Branch (APLB) asked if there were any objections to the use of the name because it meant "alive." If "alive" is not an accurate description of the product, then the name could be considered fanciful, and we could object.
- USAN – azfibrocel-T changed to azficel-T on 10-9-09 due to the original name being too similar to the company's new name (Fibrocell Sciences, Inc) which may provide an unfair advantage in the marketplace.

2. Advisory Committee (CTGTAC) – Discussion of Issues Raised

- **Clinical Consult with Dr. Drake – 10-20-09**

Participants:

AC Panel member-Lynn Drake, MD (Dermatologist/Dermatopathologist)
FDA-Changting, Bruce, Yao-Yao, Agnes, Mercedes

Dr. Drake's responses/comments:

- We do not know what is going on with the injected cells. From a safety standpoint, we want to know that something bad is not going to happen. For example, scarring and granulomas may form at injection sites. We want to know about the tissues/cells after injection. The sponsor did not look, therefore we do not know. This should be the minimum standard, and the sponsor failed to meet it.
- A post-injection biopsy study (up to 6 months) may provide some answers as to what the injected cells have done and what tissues are found at the injection sites.
- **Proposed Clinical Study:**
 - Facial biopsies have been done before, e.g. photoaging studies. The alternative is the forearm (antecubital), while not the same as the face, it is acceptable.
 - Recommendation - forearm (antecubital) biopsies
 - Follow the "3/3/3/6 phase rules" of wound healing would be acceptable
 - Small sample size study, ~ 20 subjects
 - Multiple biopsies. No more than 3 biopsies in a patient
 - 10 subjects: day 3, week 3
 - 10 subjects: mo 3, mo 6
 - Biopsies @ 3 or 6 mo would be adequate for safety concerns; OK to do in different subjects
 - Recommendation - biopsy evaluations be performed by a dermatopathologist

- Histologically, collagen and elastin in scars can be distinguished from normal collagen and elastin due to their altered architecture (curled, clumped, acellularity)
 - Dr. Drake was not concerned whether the fibroblasts persist at the injection site or not
 - Recommendation – focus on biopsies in subjects < 65 years because younger patients will have more robust reactions
 - Would not specifically perform biopsies in racial subgroups
 - Location matters
 - o The face heals well whereas chest scars are very prominent
 - o Different kinetics between face and arm; could affect results
 - Difference between wrinkles vs folds vs contour. Once approved, product will be used for other indications, and Tx around the eyes and glabella could lead to additional potential AEs. For the post-injection biopsy study, recommend keeping it to wrinkles
- o **Use of Animal Models:**
- Xenograft models could provide guidance for the time points to do the biopsies.
 - Markers could be used in animal models to
 - o Check cell fate
 - o To study how long injected fibroblasts last and what they secrete.
 - o Address the mechanism of action issue by labeling studies in animals
 - While animal studies may be informative, Dr. Drake would also be in favor of not doing them and conducting a “3(days), 3 (weeks), 3 (months)” clinical study only.

Additional issues:

- o What are the residual components in the final product?
- o Suggested asking cell experts regarding how long injected fibroblasts may persist

• **Product Consult with Dr Dubinett – 10-23-09**

Following presentation of the product-related issues raised at the AC meeting and possible solutions at the Review Team meeting on 10-20-09, Dr. Witten suggested a consult with a CTGTAC member for clarification.

Participants: Terrig Thomas, Kim Benton, Keith Wonnacott, Raj Puri

Tumorigenicity

A number of different assays were discussed that may contribute to our understanding of the potential for tumorigenicity. These include karyotype analysis, histopathology, protein profiles, and anchorage independent growth. Please discuss the advantages and disadvantages of testing fibroblasts using one or more of these tests and how well these tests correlate with in vivo tumor formation.

- *Dr Dubinett's primary concern on the safety of the product was that the follow-up on the subjects in the clinical trials had been too short to capture any late adverse events. His primary recommendation was increased length of follow-up from subjects in the pivotal trials. Each aspect of the above question was discussed and Dr. Dubinett's opinion was that the anchorage-independent growth assay would be the preferred choice as an indicator of tumorigenicity. However, he does not know the feasibility to adapt this assay to primary fibroblasts, or the potential to validate the assay to use for lot release. He thought that karyotyping, histopathology of the biopsy and protein profiling may or may not provide useful information.*

Product Characterization

The committee had some concerns about the characterization of the final product with regard to other cell types that may be present in addition to fibroblasts and keratinocytes.

- The presence of mast cells in the final product and a possible correlation to keloid formation was a concern. Please describe the correlation between mast cells and keloid formation. Is there a direct link between mast cell number or mast cell percentage and keloid formation?
 - *Dr. Dubinett said that as this was not his field he could not answer this question. However he thought that patients with a history of keloid formation should not receive the product, due to potential keloid formation at the biopsy site.*
- What are the cell types obtained from a skin biopsy that are likely to be expanded in culture? Are there other cell types that would raise a safety concern for this product?
 - *Having cultured cells from other tissue sources it has been his experience that fibroblasts have the growth advantage and it is difficult for other cell types to grow in the presence of proliferating fibroblasts. He considered the presence of inflammatory cells or mast cells in the final product to be a theoretical concern. He suggested literature search to confirm the conditions that mast cells require for growth. He suggested that the company could perform marker analysis on a subset of retention lots to confirm their absence.*
- The current collagen assay measures total collagen content in the final product -----(b)(4)----- . It was suggested that the collagen type I/III ratio produced may provide useful information regarding mechanism of action (scar or normal tissue). Is there a safety concern associated with either collagen type I or collagen type III? Is there any evidence that efficacy will be different if

the ratio of collagen type I/III is different? Would you expect the ratio of collagen type I/III secretion by the product to be different in vitro and in vivo?

- *Dr. Dubinett said that while the amount and ratio of type I/III collagen could be determined in vitro he did not know how this may or may not correlate with what the cells made in vivo. The knowledge in the field is not sufficiently advanced to support a requirement for collagen type I/III ratio specification for this product. Pre-clinical studies could be done, but he did not know if they would provide relevant information in the human setting.*

3. Control of Excipients – DMEM

DMEM is used as the vehicle for final formulation of the product. Dr. Witten wanted to know how this is qualified for use in humans and what is the process for change control if the vendor modifies something in their process of producing the DMEM.

- DCGT (Terrig, Kim and Keith) and Bob Yetter addressed the above questions
 - Dulbecco's Modified Eagles Medium is a commercially available media manufactured by a number of different companies to the same formulation
 - DMEM is obtained from (b)(4), for which a certificate of analysis is provided in the BLA indicating it is produced aseptically under cGMP
 - The CoA indicates the test methods, specifications and results for -----
----- (b)(4) -----
 - Each lot of DMEM is also subjected to in-house testing at Isolagen for -----
----- (b)(4) -----
-----.
 - Safety for use in humans is determined during the clinical trials for a particular cell product. The fact that it is used in Carticel for use in cartilage repair cannot be generalized to other indications.
 - In the event that (b)(4) ceases to produce DMEM, the sponsor has also qualified lots manufactured by ----(b)(4)---- for growth of autologous fibroblasts.
 - DMEM is a standard formulation and will contain the same components at the same concentrations regardless of the manufacturer.
 - Dr. Witten may follow-up with DCGT to better understand the reagent qualification process

4. Other Review Updates

- a. -----
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- -----Withheld per Privacy Act-----

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- ----- Withheld per Privacy Act -----

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b. DMPQ Outstanding Facility Inspection Issues

- Validation of aseptic processing and other 483 citations have still not been submitted
- Validation of Mycoplasma testing by --(b)(4)-- – T-con held with --(b)(4)-- and DCGT/DMPQ on 10-23-09
 - o The consensus opinion was that when an assay is purported to conform to 21 CFR requirements and/or other guidance such as Points to Consider for mycoplasma testing, sponsors aren't required to "validate" the assay, rather, verify they are in compliance with regulatory specifications.
 - o --(b)(4)-- needs to provide information about the protocol executed to evaluate the final formulated product for mycoplasma testing together with results of testing performed with the final formulated product.
 - o -(b)(4)-, the company currently proposed as the contract laboratory for performing mycoplasma testing, has provided a -----(b)(4)----- protocol and test result obtained using the Fibrocell product, but did not provide a protocol document for the mycoplasma test. The sponsor needs to provide a copy of the SOP describing the mycoplasma testing protocol performed at -(b)(4)-.

5. PVP/REMS

- Next meeting with FDAAA SWG 11-03-09, if needed

6. Action Items

- At the next review team meeting to be held on 10-30-09 recommendations for the next steps to be taken for the Fibrocell BLA will be discussed.

- If approval is to be granted then according to PDUFA guidelines the first labeling discussions with the sponsor should take place not less than 60 days before the action date. This would be November 1.