The modern era of soft-tissue augmentation with dermal fillers began in the latter half of the 19th century with the use of autologous transplanted fat to correct facial and body contour deformities. Since that time, physicians have worked with many different “filling” agents in a quest to identify and utilize the ultimate substance to enhance facial appearances. Nowadays, the challenge for cosmetic dermatologists is to tailor the use of specific fillers to a patient’s specific needs. With an ever-expanding list of fillers coming to market and more of an appreciation for superficial and deeper volumetric facial augmentation, there are more choices than ever before.

Most fillers on the market are indicated for temporary improvement of lines and folds. In recent years, innovations in dermal filler technology have generated a bevy of products that are designed to minimally stimulate an inflammatory response when injected in the skin, yet stimulate a biological response and occupy space in the dermis, causing gradual, longer lasting dermal thickening. Because most static wrinkles are caused, in part, by defects in the dermis, these products can be highly effective.

Moving Forward
Cosmetic treatment with dermal fillers is moving beyond a focus on the treatment of individual lines and wrinkles to efforts to achieve a “field effect” whereby the treated area is rejuvenated in the most natural way. This involves recreation of the actual structure of the collagenous matrix or scaffolding in the normal dermis, such that the dermal thinning and loss of elasticity are rectified. What better way to do this, than to re-introduce fibroblasts, the collagen-producing cells, back into the dermal environment from which they have become lost or inactivated over time in the process of aging?

Research in this arena began back in the early 1990’s, when cell biologist Olga Marko began...
investigating the use of technology for stimulating a patient’s own cells to produce collagen. Research of this nature was then not yet regulated by the FDA. Through her research, Ms. Marko developed a scientific process of mining a patient’s own collagen-producing cell dermal fibroblasts, growing and expanding those cells in a controlled environment, and then re-introducing the fibroblasts by injection into the skin of the patient’s face. Once injected, it was believed that the fibroblasts produced collagen which could prove beneficial in the repair of dermal defects. This research led to the development of the Isolagen Process. At that time, the process could be legally utilized worldwide.

In December 1995, with the support of William K. Boss, Jr., MD, a board certified plastic surgeon, Isolagen Technologies was formed for the purpose of researching, developing, marketing, and commercializing the autologous fibroblast injection process for cosmetic applications. During 1995, Dr. Boss began treating dermal defects (e.g., wrinkles, depressions, and scars) in a limited number of his patients with success. Dr. Boss and Ms. Marko soon solicited the clinical support of Gregory Keller, MD, Associate Chief, Head and Neck Plastic Surgery at the University of California, Los Angeles Medical School and W. Gregory Chernoff, MD, a plastic surgeon with practices in California and Indiana. Between 1995 and 1999 Drs. Boss, Keller and Chernoff, together with about 200 other doctors, used autologous fibroblast injection process for cosmetic applications. In 1999 the FDA began to more strenuously regulate the injectables in the US market, including the use of autologous and non-autologous filler products. In the interim, Isolagen reorganized as Fibrocell Technologies and through expanded research efforts from 2000 to 2010 designed and concluded a series of randomized multi-site, placebo controlled Phase III US-based clinical trials that met the stringent FDA requirements to become the first and only FDA-approved autologous cell-based therapy (Table 1).

This approval, which occurred in mid 2011, resulted in rebranding of the product as what is now known as LaViv. LaViv is an autologous cellular product composed of fibroblasts that are grown from a patient’s own cells to produce collagen. As a cell-based treatment injected into the dermal layer of the skin, it is not intended just to “fill” the wrinkles. LaViv is intended to place a patient’s own living cells into the treatment area, rebuilding the dermis and improving the remodeling appearance of nasolabial fold wrinkles. The exact mechanism of action of injected autologous fibroblasts is unknown.

Fibrocell’s patented autologous living cell therapy or LaViv therapy, begins with the injection of a local anesthetic to numb a small section of skin behind the ear. This area was chosen because of its vascularity, lack of sun exposure, and the invisibility behind the ear. This area is then prepared for injection with a local anesthetic to numb a small section of skin behind the ear. The worst reported reactions observed at that time were redness at the injection process approximately 3,400 times on approximately 1,100 patients. In clinical trials with LaViv, side effects were usually mild to moderate and went away within 1 week. The most common side effects were redness, bruising, bleeding, swelling, and pain at the sites of injection.

Patients with skin infections on the face, and patients with certain allergies, should not receive LaViv. Other kinds of reactions have been reported following treatment with LaViv. LaViv (adcell-T) is an autologous cellular product indicated for improvement of the appearance of moderate to severe nasolabial fold wrinkles in adults. The safety and efficacy of LaViv for areas other than the nasolabial folds have not been established.

The efficacy of LaViv beyond six months has not been established. That being said, anecdotal observations by many of the investigators shows longevity of the LaViv effect to be last for several years. (Figs. 3-6)

Generally, three sets of injections will be performed within a 12-week period, six weeks apart, with tens of millions of collagen-producing cells being injected during each visit. Within the patient’s skin, it is believed that the injected fibroblasts will survive and continue to multiply and create new collagen that will fill dermal imperfections by restructuring the dermis to its earlier undamaged state, thus reducing the signs of cutaneous aging. Unlike other fillers currently on the market, this can potentially lead to long-lasting results. (Figs. 1, 3-6).

Cryogenic storage of cultured cells permits patients to receive future treatments with cells that are still in the process of being cultured. (Fig. 4).

Table 1. Pivotal Study Data

<table>
<thead>
<tr>
<th>Primary Endpoint: Percentage (%) of Physicians Reporting a 1-Point Improvement</th>
<th>Study Results</th>
<th>p-Value</th>
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<tbody>
<tr>
<td>LaViv</td>
<td>Vehicle</td>
<td>p-Value</td>
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<tr>
<td></td>
<td></td>
<td>38%</td>
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</table>

Secondary Endpoint: Percentage (%) of Physicians Reporting a 1-Point Improvement

<table>
<thead>
<tr>
<th>LaViv Vehicle</th>
<th>p-Value</th>
<th>Study Results</th>
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<tr>
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<td></td>
<td>64%</td>
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<tr>
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<td>36%</td>
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The effectiveness of LAVIV was demonstrated in a multi-center, randomized, double-blind, vehicle-controlled study. The study population consisted of subjects with moderate-to-severe bilateral nasolabial fold wrinkles. A total of 372 subjects, aged 23 to 79 years, were randomized to receive LAVIV (n=181) or vehicle-control (n=191). The evaluating physicians used a 6-point Evaluator Wrinkle Severity Assessment scale that ranged from 0 to 5 (Lemperle scale). Evaluation with the Lemperle scale was aided by a photograph, which correlated wrinkle appearance with a specific numerical score:

- Class 0: No wrinkles
- Class 1: Just perceptible wrinkles
- Class 2: Shallow wrinkles
- Class 3: Moderately deep wrinkles
- Class 4: Deep wrinkles, well-defined edges
- Class 5: Very deep wrinkles, redundant fold

Figure 1. Study subject shown at Baseline (left) and six months (right).

Figure 2. The LaViv Process

- Extraction: A small cell sample is removed behind the ear from a small skin punch biopsy with the use of a vacuum aspirator
- Purification & Culturing: A proprietary manufacturing process expands fibroblasts from the sample into billions of new cells in 7-10 days
- Injection: Cells are frozen for use in potentially multiple applications and shipped to the treatment center
- LaViv: Cells are injected at the treatment site lasting about a week.

Table 2. Important Safety Information

- In clinical trials with LaViv, side effects were usually mild to moderate and went away within 1 week. The most common side effects were redness, bruising, bleeding, swelling, and pain at the sites of injection.
- Patients with skin infections on the face, and patients with certain allergies, should not receive LaViv.
- Other kinds of reactions have been reported following treatment with LaViv.
- LaViv (adcell-T) is an autologous cellular product indicated for improvement of the appearance of moderate to severe nasolabial fold wrinkles in adults. The safety and efficacy of LaViv for areas other than the nasolabial folds have not been established.
- The efficacy of LaViv beyond six months has not been established. That being said, anecdotal observations by many of the investigators shows longevity of the LaViv effect to be last for several years. (Figs. 3-6).

The minimal incision is closed with an adhesive or single absorbable suture.

At Fibrocell, the tissue is cultured utilizing a patented process. This process separates collagen-producing cells or fibroblasts from the rest of the tissue, then stimulates them to multiply into tens of millions of new cells in the laboratory, in an FDA-approved process. After approximately 60 days, 1 to 1.5ml of cultured fibroblasts are sent back to the doctor for injection into the patient’s wrinkles, lines, and scars. (Fig. 2)

Generally, three sets of injections will be performed within a 12-week period, six weeks apart, with tens of millions of collagen-producing cells being injected during each visit. Within the patient’s skin, it is believed that the injected fibroblasts will survive and continue to multiply and create new collagen that will fill dermal imperfections by restructuring the dermis to its earlier undamaged state, thus reducing the signs of cutaneous aging. Unlike other fillers currently on the market, this can potentially lead to long-lasting results. (Figs. 1, 3-6).

Cryogenic storage of cultured cells permits patients to receive future treatments with cells that are still in the process of being cultured. (Fig. 4).
were harvested when the patient was younger. Thus, a patient can have access to a virtually unlimited supply of their own collagen-producing cells to have treatment on-demand. The process of sample harvesting is simple, and will pose no significant challenges for the dermatologist. Similarly, injection of the cultured fibroblasts is also relatively straightforward, although proper placement of the autologous material is imperative. Fibrocell is providing comprehensive education and training on the entire procedure for clinicians as well as staff who may be involved in packaging, shipping, receiving, and preparing materials.

Benefits of facial rejuvenation
Since LaViv is an autologous system (exclusively using a patient’s own cells), it is expected that minimal allergic reactions would occur, as compared to bovine collagen and other non-autologous, Non-NASHA fillers. Fibrocell hopes to demonstrate that the use of autologous cells will result in prolonged beneficial effects, as the immune system should not reabsorb or reject them as it might with foreign materials and proteins. Patients may experience gradual and continued improvement as a result of the natural activity of the re-introduced cell structure.

A New Approach
In the expanding dermal filler market, LaViv is a unique treatment option. It is an autologous cellular product indicated for improvement of the appearance of moderate to severe nasolabial fold wrinkles in adults. In keeping with current approaches to rejuvenation, it is thought to contribute to a field effect, rather than simply “fill” specific defects. In clinical trials with LaViv, side effects were usually mild to moderate and went away within one week. The most common side effects were redness, bruising, bleeding, swelling, and pain at the sites of injection. LaViv is manufactured specially for each patient and is injected by trained and authorized practitioners.

Clinicians and potential patients are interested in possible future indications for LaViv, including the treatment of distensible acne scarring, which has been investigated in positive Phase III trials. Currently, it is not recommended for LaViv treatments to be performed simultaneously with other laser/light therapies, aesthetic treatments, such as chemical peels, or along with other fillers. There should be at least a four to six week window between treatment with LaViv and other aforementioned therapies.


Figs. 3-6. Patients before (left) and two years after (right) treatment with LaViv.

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Dr. Munavalli was an investigator for LaViv.

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