Anti-aging Cosmetics
FGF-1 Formulation

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Executive Summary

Phage Pharmaceuticals, Inc. (“Phage”) is developing a high-value “cosmeceutical” for the U.S. and European markets as an anti-aging treatment for wrinkles and rejuvenation of skin. The active ingredient of the formulation is the FGF-1 protein, which is already used in various pharmaceutical indications and is becoming popular in the deluxe anti-aging cosmetic market.

Aging of the skin is mediated by a combination of the effects of time (intrinsic aging) and environmental factors (extrinsic aging) on cellular and extracellular infrastructure. These are two independent, clinically and biologically distinct processes that affect the skin structure and function simultaneously. Both of these aging processes can be reversed by aiding the body in its natural biology of skin repair.

Phage maintains a licensed cGMP (current Good Manufacturing Practice) facility and utilizes its patented manufacturing process to produce pharmaceutical grade soluble, active proteins that are purely recombinant (i.e., no animal or human products are used).
Cosmetic FGF-1 Product

Growing evidence now suggests that the two aging processes (intrinsic and extrinsic) have converging biochemical and molecular pathways that lead to photo-aging of the skin. Recent advances in understanding the role of endogenous growth factors in the aging process provide one such opportunity to develop novel anti-aging cosmeceutical products.

Since cosmetics that include growth factors are considered "deluxe" products, they should be targeted at the high end cosmetics niche, which is growing in popularity in both the EU and the U.S.

The FGF-1 anti-aging serum would be an ideal product to pursue for a company that already has access to the cosmetic market in the EU or U.S., but wants to diversify and enter the luxury cosmetics niche that is less competitive and allows selling products at a higher profit. An advantage for partnering with Phage Pharmaceuticals is the fact that we already produce the active ingredient of the formulation (FGF-1) in-house in a cGMP certified facility (located in San Diego, CA). Phage uses a unique and patented recombinant technology (i.e., no animal products) to efficiently produce FGF-1 with consistent quality and at low cost. Phage Pharmaceuticals runs the only facility in the world that produces pharmaceutical grade FGF-1 approved and used for clinical trials by the FDA.

Phage’s anti-aging serum is currently under development: a cosmetically soothing formulation for topical delivery of an active dosage of FGF-1 through the skin. It is projected that the development will be finished in Q4 of this year. The product will not need regulatory approvals for the U.S. or EU cosmetic markets.
**Background Information on FGF-1**

Fibroblast growth factor 1 is a protein that is encoded by the *FGF-1* gene. The protein encoded by this gene is a member of the fibroblast growth factor (FGF) family. FGF family members possess broad mitogenic and cell survival activities, and are involved in a variety of biological processes, including embryonic development, cell growth, morphogenesis, tissue repair, and cellular regeneration\(^1\). This protein also functions as a modifier of endothelial cell migration and proliferation\(^2\), as well as an angiogenic factor\(^3\).

**FGF Families**

In humans, 22 members of the FGF family have been identified, all of which are structurally related signaling molecules (**Figure 1**). Members FGF-1 through FGF10 all bind fibroblast growth factor receptors (FGFRs)\(^1\). FGF-1 is also known as *acidic*, and FGF-2 is also known as *basic fibroblast growth factor*\(^4\).

**Receptors**

The mammalian fibroblast growth factor receptor family has 4 members, FGFR1, FGFR2, FGFR3, and FGFR4. Alternate mRNA splicing gives rise to 'b' and 'c' variants of FGFRs 1, 2 and 3. Through this mechanism seven different signaling FGFR sub-types can be expressed at the cell surface. FGF-1 is sometimes referred to as the 'universal ligand' as it is capable of activating all 7 different FGFRs\(^1\).

**Function**

FGFs are multifunctional proteins with a wide variety of effects; they are most commonly mitogens but also have regulatory, morphological, and endocrine effects\(^1\). They have been alternately referred to as pluripotent growth factors and as "promiscuous" growth factors due to their multiple actions on multiple cell types. Promiscuous refers to the biochemistry and pharmacology concept of how a variety of molecules can bind to and elicit a response from a single receptor. One important function of FGF-1 and FGF-2
is the promotion of endothelial cell proliferation and the physical organization of endothelial cells into tube-like structures. They thus promote angiogenesis from the pre-existing vasculature. FGF-1 and FGF-2 are more potent angiogenic factors than VEGF (vascular endothelial growth factor) or PDGF\(^5\) (platelet-derived growth factor).

As well as stimulating blood vessel growth, FGFs are important players in wound healing\(^6\). FGF-1 and FGF-2 stimulate angiogenesis and the proliferation of fibroblasts that give rise to granulation tissue, which fills up a wound space/cavity early in the wound healing process. FGF7 and FGF10 (also known as keratinocyte growth factors KGF1 and KGF2, respectively) stimulate the repair of injured skin and mucosal tissues by stimulating the proliferation, migration and differentiation of epithelial cells, and they have direct chemotactic effects on tissue remodeling\(^7,8\).
FGF-1 Cosmetics

Summary

*Cosmetic Anti-aging Serum* – Phage is currently developing a cosmetic formulation containing FGF-1 for use as an anti-aging product. FGF is well known as a stimulant of keratinocytes, collagen, and epidermal stem cells. This cosmetic product is targeted to launch in the U.S. and Europe in the next 12 months and in Asia within 24 months.

Market Opportunity

The U.S. is the largest cosmetic market among individual countries - $53.7 BB in 2011 with 3.1% annual growth rate estimated from 2011 till 2016. Skin care products constitute 23.7% of the market ($12.7 BB). The anti-aging facial skin care segment constitutes a large part of the skincare market ($2.1 BB in sales), and is the fastest growing with a predicted 8% growth rate, with leading brands focusing on this sector. The industry is characterized as mature, with a saturated market and a slow growth rate, but steady growth in exports, now accounting for 12% of production. The largest companies are multinationals; however, none is dominant, with the largest one, P&G, controlling approximately 16% of the market, and the top 4 companies controlling only 28%.

As a group, EU27 is the largest cumulative market with estimated sales of €63.5 BB. Skincare cosmetics occupy 25% of the market, with a CAGR (compound annual growth rate) of 5.6%. The European cosmetic market shares similar trends with the U.S. market, and anti-aging products are in focus as a fast growing segment, with UK, Finland and Denmark showing double digit growth rates.

Asian countries, such as Japan, China and Korea, traditionally show even more interest in skincare products than both the U.S. and the EU, with market share of skincare products reaching 40%. Anti-aging products are also the leaders with a high growth rate in the skincare market.
Similar trends can be observed in Brazil, with anti-aging products becoming increasingly more popular and the local cosmetic market having the highest CAGR in the world\textsuperscript{12}.

**Competitive landscape.** Top anti-aging facial brands had the following market share in the U.S.\textsuperscript{13}:

<table>
<thead>
<tr>
<th>Brand</th>
<th>Market Share</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Olay Regenerist</strong></td>
<td>9.84%</td>
</tr>
<tr>
<td><strong>L’Oréal DermoExpertise Advanced ReVitaLift</strong></td>
<td>6.94%</td>
</tr>
<tr>
<td><strong>RoC Retinol Correxion Deep Wrinkle</strong></td>
<td>3.82%</td>
</tr>
<tr>
<td><strong>Olay Professional X</strong></td>
<td>3.63%</td>
</tr>
<tr>
<td><strong>Olay Definity</strong></td>
<td>3.17%</td>
</tr>
<tr>
<td><strong>Garnier Nutritioniste Skin Renew</strong></td>
<td>2.95%</td>
</tr>
<tr>
<td><strong>Olay Age Defying</strong></td>
<td>2.89%</td>
</tr>
<tr>
<td><strong>Olay Regenerist Micro Sculpting</strong></td>
<td>2.79%</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>63.97%</td>
</tr>
</tbody>
</table>

All currently dominant brands are traditional cosmetic formulations in the low to medium price range. However, the particularly interesting segment of deluxe anti-aging skincare products tends to use bio-tech formulations, including growth factors, to promote skin growth and regeneration. This segment is expected to grow at the same or higher rate than the luxury cosmetics market, which showed double digit growth in 2011. Three leading products in the deluxe anti-aging skincare segment include:

- **RéVive** Serum Pressé, which contains both FGF and EGF, is distributed online as well as through major deluxe retail stores (Nordstrom, Neiman

Figure 2. One of the ReVive EGF products (anti-aging serum 3x3ml)
Marcus) in the U.S. Price range, depending on the product, is in the $350-$1500 range\textsuperscript{14}.

- **BioEffect** Serum, which contains EGF, is distributed online as well as in stores in the EU. The company (SIF Cosmetics) uses EGF as the active ingredient. Price point is ~£125\textsuperscript{15}.

- **E’shee** Clinical Esthetics, contains FGF, and is sold mainly on-line at $120-180 for a 10 ml vial\textsuperscript{16}.

There seems to be a lucrative niche market for deluxe anti-aging cosmetics in the U.S., the EU and Asia: A market which is neither saturated nor fiercely competitive.

**Scientific Background**

The use of growth factors and cytokines in skin rejuvenation and the reversal of photo-aging is emerging as a novel anti-aging treatment. A number of important growth factors, such as FGF-1 and cytokines, affect the proliferation of dermal fibroblasts, stimulation of hair growth, keratinocyte growth and extracellular matrix production\textsuperscript{1}.

![Figure 5. FGF-1 stimulates production of other growth factors.](image-url)

![Figure 3. BioEffect product (15ml vial)](image-url)

![Figure 4. E’shee Clinical Esthetics line of products](image-url)
FGF-1 is a premiere growth factor as it activates a number of other growth factors essential to skin repair (Figure 5).

Providing some of these agents to cells responsible for extracellular matrix production and remodeling seems to help rejuvenate aging skin. Several cosmeceutical products containing either a single human growth factor or a combination of multiple human growth factors and cytokines are currently marketed for skin rejuvenation\(^{17}\).

Compared to young skin, older skin is thinner and has less subcutaneous tissue\(^{18}\). It is believed these growth factors can increase skin thickness and improve collagen matrix formation (Figure 6)\(^ {19}\). Clinical results are now available for some of these products and the results show that human growth factors, when applied topically, provide beneficial effects in reducing the signs of facial skin aging.

In one clinical study, 14 patients with Fitzpatrick class II or greater facial photo damage applied an FGF-based complex twice daily for 60 days\(^ {20}\). The patients were evaluated for clinical grading of photo-damage on a nine-point scale: optical profilometry and punch biopsy for collagen measurements. The results showed a statistically significant reduction in fine lines and wrinkles and reduction in periorbital photo damage. Clinical grading showed a 12.2% improvement (p = 0.0003) in the periorbital area after 60 days compared to baseline. A reduction in fine lines and wrinkles measured by optical profilometry showed a 14.1% decrease in roughness measurement (p = 0.008) and a 36.2% decrease in shadow measurements (p = 0.02). Measurements of collagen and epidermal thickness measured from the biopsy exhibit a 37% increase in collagen and a 30% increase in epidermal thickness. Studies of longer durations demonstrate dramatic improvement in visible signs of aging.
Transdermal Studies of Skin Penetration of FGF-1

Studies have been performed to assess the penetration of FGF-1 through intact skin. In these experiments, skin penetration using a Franz Cell device was performed. In this model, drug (donor) sample is placed above a sheet of intact pigskin. The skin is sandwiched to a collection container and the donor sample (Figure 7).

Samples from the receiving compartment were collected over 24 hours. These samples were assayed (using the ELISA method) for the presence of FGF. In the case of FGF-1, nearly 1% of the protein load was detected beneath the skin layer at 1 and 2 hours, with little additional effect seen after 24 hours (Figure 8).

These data demonstrate that FGF-1 can penetrate intact skin in sufficient quantity to produce cosmetic effects.
A Single Dose Pharmacokinetic Study of Recombinant Human FGF-1 Applied Topically in Rats

Studies of the safety of FGF-1 in animals have been performed. A pharmacokinetic study was performed to determine the absorption and distribution of FGF-1 following dermal administration.

A total of 14 male and 13 female rats were randomized into three dosing groups (0, 2, and 20 \( \mu \)g). A punch biopsy was made in the intrascapula area of the neck of each animal and either FGF-1 or vehicle control was applied directly into the open wound.

**Results**

FGF-1 was virtually undetectable in serum 24 hours post-dosing in all three dosing groups. Details of the study are available under a nondisclosure agreement.

A 4-Week Dermal Toxicity Study of Recombinant Human FGF-1 in Rats

A study of the safety of FGF-1 was performed to evaluate the immunogenicity and dermal tolerance of FGF-1. The objective of the study was to evaluate the initial toxicity of the test article, recombinant human FGF-1 at a dose of 0, 2, and 20 \( \mu \)g, following its application to a punch skin biopsy in the intrascapular area of the neck of CD-1 rats.

Two treatment groups of six male and six female rats were administered the test article at respective dose levels of 2 and 20 \( \mu \)g. One group of six animals/sex served as the vehicle control. One additional group of six animals/sex served as the untreated control. Either FGF-1 or vehicle control were topically administered into 6 mm diameter full-thickness skin punch biopsies.

**Results**

Based upon the various endpoints evaluated during this 4-week study, no observable acute toxicity was noted. The immunoassay samples suggest no overall antigenicity between the untreated, control, and treated test groups. The data obtained during the course of this study indicate no increase in acute toxicity following the dermal application of either the 2 or 20 \( \mu \)g test article formulations. Details of the study are available under a nondisclosure agreement.
References

15. http://www.bioeffect.co.uk/