Issue 6, June 2014

BIOWATCH™

Your independent Biotech News Source

In This Issue:

- Male Pattern Baldness & Female Pattern Hair Loss
- RepliCel Life Sciences Interview With a Specialist

With Updates On:

- KinDex Pharmaceuticals
- Ambit Biosciences
- Evoke Pharma
- Seattle Genetics

Sample Issue

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Letter From Our CEO

Alan Leong

The topic of “male pattern baldness” (AKA androgenetic alopecia) was planted several months ago.

I believed there was a profitable yet boutique market for medical hair restoration. I also wondered about the lesson of NASA spinoffs: the effort to travel into space has resulted in the creation of commercially successful inventions. Would the effort to rejuvenate the hair follicle yield similar successes?

We might have found it with RepliCel Life Sciences of Vancouver, BC. The company’s special cell therapy uses the patient’s own hair follicle cells, to rejuvenate dormant follicles and create new ones. RepliCel will also be testing it to heal tennis elbow and Achilles tendinosis, as well as skin wrinkles.

When talking to colleagues about hair restoration, I was also struck by the breadth and depth of their desire.

The following quote is almost urban legend: *30% of men with hair loss would give up sex to get back their hair.*

Although I was initially skeptical of the quote, I now see its validity. Multiple surveys show that many men are willing to go to extraordinary lengths to regain scalp hair. I also saw the reactions of my acquaintances.

A large market is ready for a new and improved hair restoration solution. This medical area is worth monitoring.

This issue also features a wonderful interview with Dr. Tony Mangubat. Dr. Mangubat is a cosmetic surgeon who was also President of the International Society of Hair Restoration Surgery, among other very notable positions in the industry. He discusses his thoughts about the current art of hair restoration as well as its professional context. Did you know that Cosmetic Surgeons and Plastic Surgeons are distinct professions with different training requirements?

For last month’s feature on metabolic disease, we briefly mentioned a small private company called Kindex Pharmaceuticals. For this issue, Erik Richardson took the lead in writing an expanded report on Kindex.

We also included small updates on Ambit Bioscience and Evoke Pharmaceuticals. There will be an update on Medivation but it will be placed in Notable News after this issue is published.

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There is a lot of ground to cover with Medivation, but our conclusion remains the same. The presentations at the recent ASCO (American Society of Clinical Oncologists) conference confirm that Medivation's Xtandi (enzalutamide) is best-in-class as a prostate cancer drug. The stock price has been steadily climbing and the ASCO conference did nothing to deter it.

SENS Research Foundation hosts Rejuvenation Biotechnology 2014:

As you have probably seen by now, we sent out a special invitation to all of you for the SENS Rejuvenation Biotechnology 2014 conference (RB2014) in Santa Clara, CA, on August 21 – 23rd.

The full announcement—with discount code—is located in Notable News and offers our subscribers an exclusive 50% off of the regular price of admission. Also, SENS is offering an early bird discount until June 30th, which makes this offer an incredible deal at $898 for three days of the conference, which includes a few meals and a party with world-class entertainment.

RB2014 will be notable considering it will only be the second time SENS has sponsored an event on American soil; and the lineup of speakers is impressive to say the very least. Additionally, the panel will place a special focus on combinatory strategies for Rejuvenation Biotechnology as a possible industry sector of the future.

We, at BioWatch News, are also proud to announce we are a sponsor of the event and will be hosting a special dinner for our subscribers in attendance. Please watch your email for additional announcements on the up-coming evening sometime mid-July.

We hope this finds all of you well and enjoying the summer.

All the best as always,

Alan Leong, CEO

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Male Pattern Baldness & Female Pattern Hair Loss

Alan Leong

Introduction

Did you know that hair loss treatment is a $2B business in the United States? This includes oral and topical medications, hair transplants, and laser treatments.[1]

Although the exact figure is hard to document, the total hair loss treatment industry is a multi-billion dollar business in the United States. In most instances, hair loss treatments are not covered by insurance. It is largely paid out-of-pocket and it is still growing.[2]

There is an appetite for cosmetic surgery procedures that make us look better. Hair loss treatments are part of it.

Did you know that in 2013, over 14.3M cosmetic surgical procedures were performed in the USA? This includes over 290,000 breast augmentations, and 220,000 nose reshapings (rhinoplasty).

3

Male Pattern Baldness & Female Pattern Hair Loss

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[1] We saw a wide range of estimates from $1.3B to over $7B. It is difficult to document revenues from unapproved, generic, or over-the-counter treatments. The $7B could include all stages of the supply chain. We estimate that the actual figure for end-user sales is closer to $2B for the USA. Hair restoration surgeries alone account for about $550M.

[2] By all estimates, hair loss treatment revenues showed slight growth or decline during the financial crises. Nevertheless, a slight decline during the crises signals underlying robust demand.

[3] 2013 Cosmetic Surgery Gender Distribution. Published by the American Society of Plastic Surgeons. Retrieved June 8, 2014, from http://www.plasticsurgery.org/Documents/news-resources/statistics/2013-statistics/cosmetic-procedures-men.pdf

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Male pattern baldness is better known as *androgenetic alopecia* in the medical journals. Its prevalence is quite high among the elderly although it can begin with puberty.

> *Did you know that in a recent survey, over 60% of men believe that having more hair will advance their career or help them get a job?*
>
> [4]

The social and psychological impact of hair loss can be high. It is intertwined with perceptions of personal and professional attractiveness. It is no surprise that most consumers of hair loss treatments are men.

Androgenetic Alopecia

Alopecia generically refers to the loss of hair. Although there are different causes, androgenetic alopecia comprises 95% of this category. As stated before, this is commonly referred as "male pattern baldness." In some of the older articles, "male pattern baldness" is generically applied to male and female hair loss.

Men vs. Women

> *Did you know that over 2/3 of hair restoration patients are male?*
>
> [5]

The hair loss patterns are different. Men typically display receding hairlines and thinning at the top. Women typically have thinning distributed through the crown and are spared the hairline.[6] While a large proportion of men experience thinning hair in their 20s, only 3% of women experience it by age 29.

There appear to be distinct differences in the underlying genes that drive female pattern hair loss (FPHL) versus male pattern baldness (MPB).[7] It is, therefore, not surprising that there are gender differences for the age of onset and rate of progression.

Mechanism

> *Did you know that male baldness isn't inherited just through the mother? The risk increases with the percentage of bald family members. Bald men are more likely to have bald fathers too.*
>
> [8]

While androgenetic alopecia is a very complex phenomena, there are a few commonly accepted key concepts.

The Hair Follicle Cycle

The follicle is a cavity or pit in the skin that envelopes the hair root. The follicle shrinks over time and if it becomes too small, then the follicle ceases to grow hair.

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[4] 2010 Hair Transplant Challenge Survey Results Summary. Published by the International Society of Hair Restoration Surgery Retrieved June 8, 2014 from http://www.ishrs.org/sites/default/files/users/user3/SummaryReport_ISHRS-HTChallenge%209.21.10.pdf

[5] Men comprise 66% to 81% of hair loss patients. Sources include the International Society of Hair Restoration Surgery and the American Society of Plastic Surgeons.

[6] Levy, L.L., & Emer, J.J. (2013). Female pattern alopecia: Current perspectives. *International Journal of Women's Health, 5,* 541-556.

[7] E.g. Nuwaihyd, R., Redler, S., Heilmann, S., et al. (2014). Investigation of four novel male androgenetic alopecia susceptibility loci: no association with female pattern hair loss. *Archives of Dermatology Research, 306*, 413-408.

[8] Rathnayake, D. & Sinclair, R. (2010). Innovative Use of Spironolactone as an Antiandrogen in the Treatment of Female Pattern Hair Loss. *Dermatology Clinics, 28,* 611-618.

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Our hair follicles go through continuous cycles of hair growth, regression, and rest. These three phases are described as follows:

- Anagen (growth) stage – This is the active growth phase in which root hair cells are rapidly created. The healthy follicle thus grows hair during the anagen phase and this should last about 2 to 6 years, before it receives a signal to move to the catagen stage.

- Catagen (regression) stage – Over 1 to 2 weeks, the follicle sheds and cells undergo apoptosis (cell death).[9] During this transition stage, the follicle receives a variety of signals to induce apoptosis.

- Telegen (resting) stage – This lasts about 5 to 6 weeks. The hair dies and falls out.

At the end of the telegen phase, the dermal papilla reaches out to meet the hair follicle once again and the follicle returns to the anagen stage. The dermal papilla cells are essential for nourishing the hair follicles and especially the hair root. It is believed to be a key regulatory element for enabling hair cell proliferation and growth.

In normal adults not experiencing hair loss, about 85% of the follicles are in the anagen phase, only 1% are in the catagen phase undergoing a transition to the telegen phase (about 15%).

Dihydrotestosterone (DHT)

DHT is an especially potent sex hormone. A small portion of testosterone is converted to DHT through interaction with 5α-reductase enzymes. In men, DHT is the primary *known* factor for fueling male pattern baldness. Propecia (finasteride) and Avodart (dutasteride) are 5α-reductase inhibitors: they block the production of DHT and prevent hair loss in men. DHT disrupts activation of the hair stem cells and hair cell proliferation. It thus shortens the anagen phase and lengthens the telegen phase. Worse, it also shrinks the follicle, forcing hairs to become finer and shorter before the follicle becomes inert.

In women, the picture is different.

> *"In contrast, the role of androgens in Female Pattern Hair Loss has not been clearly established and it does not seem to be as essential…mechanisms other than androgens may be involved."*[10]

FPHL may be far more impacted by (low) levels of estrogen rather than testosterone and its derivatives. It also is impacted by glucose tolerance (diabetes), insufficient blood flow through fine blood vessels, and inflammation.

Non-Androgenetic Alopecias

Non-androgenetic alopecias comprise only 5% of the overall category. Some of these are mentioned below.

Alopecia Areata

Alopecia areata: This is viewed as an autoimmune disorder in which the hair follicle is attacked.[11] It can occur at any age, even children and otherwise healthy people can be affected. About 20% are

[9] Botchkareva, N.V., Ahluwalia, G., & Shander, D. (2006). Apoptosis in the hair follicle. *Journal of Investigative Dermatology, 126,* 258-264.

[10] Mesinkovska, N.A., & Bergfeld, W.F. (2013). Hair: What is new in diagnosis and management? Female pattern hair loss update: Diagnosis and treatment. *Dermatology Clinics, 31,* 119-127.

[11] There Is still some doubt whether this is an autoimmune disease, as the exact process is still unclear. For a discussion, see McElwee, K.J., Gilhar, A., Tobin, D.J., et al. (2013). What causes alopecia areata? *Experimental dermatology, 22,* 609-626.

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aware of a relative that experienced the disorder. Areata patients may also be at higher risk for allergies, rashes, and hay fever.

34% to 50% of areata patients recover within one year. About 20% will lose all the scalp hair (**alopecia totalis**) or become hairless over the entire body (**alopecia universalis**); these patients are unlikely to make a full recovery.[12] The disease progression is unpredictable. The patient may recover but also have a recurrence.[13]

Areata Treatment

The areata patients are typically treated with topical or injected steroids into the affected scalp. There appears to be some efficacy although the therapeutic response varies widely.[14, 15]

Anthralin (dithranol) is a salve applied to the skin for up to an hour per treatment. The treatment is relatively safe and can be combined with other treatments. Originally used for treating psoriasis, new hair growth may be seen in 10 to 24 weeks in about 30% of patients.

"Contact immunotherapy" involves the application of special solutions to the affected skin, namely diphencyprone (DPCP) or squaric acid dibutylester (SADBE). This causes an allergic reaction: itching, swelling, and redness.[16] It is reasonably effective in about 30% of patients after 6 months of treatment; longer treatment periods are associated with even greater success. It is seen as a safe option for children although recurrence rates after hair regrowth may be high (in almost 2/3 of the patients!).[17]

Other treatments include low-intensity laser and photochemical therapy (PUVA) which appear to have similar outcomes to Minoxidil (Rogaine). Lastly, a number of immunosuppressant antibodies are in clinical testing.

Traction and Effuviums

Traction alopecia: Hair loss caused by tension on the hair such as prolonged hair weaving. This tension may unveil a genetic predisposition to "weak hair." This may result in permanent hair loss.

Effiuvium: Medications, hormones, or emotional and physical stress may push hair follicles into the **telogen** phase in which it "rests" and sheds hair. This is usually temporary until the stressor is removed. Toxic chemotherapy and radiation therapy may also poison the follicle's capacity to grow hair.

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[12] Miteva, M., & Tosti, A. (2012). Treatment options for alopecia: An update, looking to the future. *Expert Opinion on Pharmacotherapy, 13,* 1271-1281.

[13] Alkhalifah, A., Alsantali, A., Wang, E., McElwee, K.J., Shapiro, J. (2010). Alopecia areata update: part I. Clinical picture, histopathology, and pathogenesis. *Journal of the American Academy of Dermatology, 62,* 177-188.

[14] Tosti, A., Iorizzo, M., Botta, G.L., Milani, M.(2006). Efficacy and safety of a new clobetasol propionate 0.05% foam in alopecia areata: a randomized, double-blind placebo-controlled trial. *Journal of the European Academy of Dermatology and Venereology, 20*, 1243-1247.

[15] Alsantali, A. (2011). Alopecia areata: a new treatment plan. *Clinical, Cosmetic and Investigational Dermatology, 4,* 107-115.

[16] Rokhsar, C.K., Shupack, J.L., Vafai, J.J., Washenik, K. (1998). Efficacy of topical sensitizers in the treatment of alopecia areata. *Journal of the American Academy of Dermatology*, *5*, 751-761.

[17] Ohlmeier, M.C., Traupe, H., Luger, T.A., Bohm, M. (2012). Topical immunotherapy with diphenylcyclopropenone of patients with alopecia areata -- a large retrospective study on 142 patients with a self-controlled design. *Journal of the European Academy of Dermatology and Venereology, 26*, 503-507.

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Current Treatments

In terms of prolonged efficacy, surgical hair transplants remain the only treatment with durable outcomes. Possible competitors (e.g., cloning or gene therapy) have yet to be proven viable, and are still years into the future.

The market for non-invasive, non-surgical androgenetic hair loss treatments is expected to grow. Growth estimates range from 3% to 5% annual growth for the next five years.

Propecia brought sales of $380M in 2013. Rogaine had only $57M in revenues but it has also gone generic. The patent expired in 1996. Pfizer sold Rogaine to J&J in 2006. J&J introduced a foam version of Rogaine and sales increased 25% in 2007 to $42M.

GlaxoSmithKline's Avodart is the major drug currently in the pipeline. It enjoys certain advantages over Propecia and is already prescribed off-label for alopecia.

By most estimates, hair treatment industry revenues remained flat during the financial crisis and are now experiencing steady growth. This suggests an underlying market demand that is robust. Furthermore, if something markedly better is introduced, it should have a rapid uptake and the overall market would expand.

Shocking Facts and Statistics about Hair Loss

30% of hair loss sufferers said they would give up sex if it meant they would get their hair back. When respondents were asked if they would rather have more hair, more money, or more friends, about two-fifths of respondents replied either 'more hair' (43.2%) or 'more money' (39.9%).

Hair Club for Men generated over $70M in 2010 by selling patches of human hair? The Club was subsequently acquired for $268M.

Among members of the International Society of Hair Restoration Surgery, over 88,000 surgical hair procedures were accomplished in the USA with over 310,000 worldwide in 2012. Did you know that about 86% of these surgical patients were men?

18, 19,20

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[18] Regis Corporation 2010 Annual Report

[19] International Society of Hair Restoration Surgery: 2013 Practice Census Results. Published by the International Society of Hair Restoration Surgery. Retrieved June 8, 2014, from http://www.ishrs.org/press-release/ishrs-2013-practice-census-facts-and-figures.

[20] 2010 Hair Transplant Challenge Survey Results Summary. Published by the International Society of Hair Restoration Surgery.

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Current Treatments for Androgenetic Alopecia				
Treatment Class	**Notable Products**	**Sales**	**Pros**	**Cons**
Hair Transplants	Follicular Unit Transplantation (FUT), Follicular Unit Extraction (FUE)	$1.9B World (2013)	Only relatively permanent solution	Long surgical procedure requiring deep skills, expensive
Hair transplantation moves individual hair follicles from one part of the body called the 'donor site' to a bald or balding part of the body known as the 'recipient site'. These transplanted grafts contain hair follicles that are resistant to balding and placed onto the bald scalp. It is primarily used to treat scalp hair but can also be used for restoring eyelashes, eyebrows and chest hair. With the advent of FUT in the 90s, transplantation focused on the harvesting of naturally occurring units of follicles. In this method, a strip is harvested and then divided into individual units. It is then sutured or stapled into the recipient area. The units involve groups of 1 to 4 hairs and include oil glands, muscle, and nerves. FUE involves small extractions from the donor area of one follicle unit at a time; each extraction is approximately 0.6 to 1.2 millimeter in diameter. This is very small and may limit visible scarring in the recipient area. The skilled FUT practitioner, however, will limit scarring and the skilled FUE practitioner can implant more than a thousand grafts in a single day.[21] The cost is variable often depending upon the number of grafts. We've heard ranges from $6,000 to $28,000 for the USA.				
Robotic Restoration	ARTAS, NeoGraft	-	Increase speed and lower physician fatigue	May enlist unskilled medical practitioners
The ARTAS and NeoGraft systems help to automate a portion of the hair transplantation routine - especially for FUE procedures. A single session can take hours and involves repetitive strain. The ARTAS system is designed to work with cosmetic surgeons and charges "by the motion to harvest" and not the actual successful harvest. The NeoGraft business model involves the adoption of its robotic system into the physician practice but is deployed by a technician or assistant. One clinical researcher stated that graft quality can still vary dramatically in the hands of an inexperienced team.[22]				
Nonsurgical Medical	Minoxidil (Rogaine), Finasteride (Propecia), Dutasteride (Avodart)	$320M USA	Generic, neuroprotective	Lifetime costs are high

[21] According to the International Society of Hair Restoration Survey, the average number of grafts per session to "achieve the desired result" was 2,016.

[22] Rashid, R.M. (April, 2014). Follicular unit extraction with the ARTAS robotic hair transplant system: an evaluation of FUE yield. *Dermatology Online Journal, 20, Accessed on June 8, 2014 at http://escholarship.org/uc/item/0w5620q5*

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Minoxidil appears to restore some dormant follicles to the anagen phase and helps reduce apoptosis signaling to prevent follicles from going into the catagen phase. It thus reduces hair loss and may encourage some seemingly dormant follicles to grow hair. [23]

Finasteride (Propecia) and Dutasteride (Avodart) are 5-α reductase inhibitors that prevents the conversion of testosterone to DHT. Finasteride is generic while Dutasteride is made by GSK. Both drugs are approved to treat benign prostatic hyperplasia. However both increase the risk of erectile dysfunction and decreased sexual desire.

Dutasteride is currently prescribed off-label and appears to be more effective than Finasteride. Dutasteride inhibits two of the three isoforms of 5-alpha reductase, types I and II, whereas finasteride only inhibits type II, and has a much shorter half-life. Dutasteride has a warning for an increased risk of high-grade prostate cancer.

Alfatradiol (17α-estradiol, trade names Ell-Cranell Alpha and Pantostin in Germany) is also a 5α-reductase inhibitor but is applied topically for treating German men and women.

Dandruff Shampoos	Ketaconazole (Nizarol), Zinc Pyrithione, Piroctone Olamine	-	Inexpensive, Works for many	May not synergize with Minoxidil

There are two studies that document the benefit of zinc pyrithione (e.g. Head & Shoulders) in reducing alopecia. In one study, shampoos containing ketoconazole, zinc pyrithione, and piroctone olamine were compared.[24] All three reduced hair shedding and increased anagen stage hair percentage. Mean hair diameter increased only for ketoconazole and piroctone olamine. It only requires 2x-3x weekly use for six months before results are seen.

In other articles, however, Selenium Disulfide (Selsun Blue) is implicated in hair loss. In a separate study, there were no advantages with stacking zinc pyrithione to Minoxidil.

Laser	HairMax Lasercomb, IGrow (TopHat) System	-	Relatively non-invasive. Can be expensive.	

Laser light is emitted at a specific wavelength and the target tissue molecules respond with adaptive biological changes.

Laser therapy appears to shift some dormant follicles to the anagen phase. It is also hypothesized to stimulate epidermal stem cells in the hair follicle. Laser therapy is effective with minimal to moderate hair loss. As with other nonsurgical hair treatments, individual results widely vary.
TopHat 655 (IGrow) system is an in-home device and sells online and in stores for $695. The laser device is worn “like a hat.”

[23] Minoxidil stimulates hair follicles and growth, but does not reduce DHT or the enzyme responsible for its accumulation around the hair follicle. Therefore, when treatment is stopped, the DHT has its expected effect of shrinking and ultimately destroying the hair follicles.

[24] Pie¤rard-Franchimont, C., Goffin, V., Henry, F., et al. (2002). Nudging hair shedding by antidandruff shampoos. A comparison of 1% ketoconazole, 1% piroctone olamine and 1% zinc pyrithione formulations. *International Journal of Cosmetic Science*. *24,* 249-256.

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Female Treatments

Given that the underlying physiology and genetics differ between men and women, it's not surprising that the female response to therapy also differs.[25]

For example, *"…the response to treatment with 5a-reductase inhibitors is unpredictable."*[26]

Furthermore, Avodart and Propecia should not be used in women of childbearing age. A recent study on comparing Alfatradiol, a topical 5a-reductase inhibitor, versus Minoxidil was conducted on women: Minoxidil was effective at increasing hair density, while the hair metrics were unchanged with Alfratradiol.

Women (and rarely men) may receive oral anti-androgen medications. Spironolactone reduces testosterone and also blocks androgen receptors. Prescribed off-label, it appears to help almost half of FPHL patients.

Women have also used hair transplants although men are currently the main consumers. It is estimated that 71% to 86% of hair restoration surgical patients are male.[27]

Clinical Development

If we screen out the trials involving nutritional supplements, the list of treatments is indicative of a slow steady growth. Outside of cell therapies from Aderans and Replicel, these represent incremental advances.

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[25] Rathnayake, D. & Sinclair, R. (2010). Innovative Use of Spironolactone as an Antiandrogen in the Treatment of Female Pattern Hair Loss. *Dermatology Clinics, 28,* 611-618.

[26] Mesinkovska, N.A., & Bergfeld, W.F. (2013). Hair: What is new in diagnosis and management? Female pattern hair loss update: Diagnosis and treatment. *Dermatology Clinics, 31,* 119-127.

[27] International Society of Hair Restoration Surgery: 2013 Practice Census Results. Published by the International Society of Hair Restoration Surgery. Retrieved June 8, 2014, from http://www.ishrs.org/press-release/ishrs-2013-practice-census-facts-and-figures. Also the 2013 Cosmetic Surgery Gender Distribution. Published by the American Society of Plastic Surgeons. Retrieved June 8, 2014, from http://www.plasticsurgery.org/Documents/news-resources/statistics/2013-statistics/cosmetic-procedures-men.pdf

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Androgenetic Alopecia Treatments in Clinical Development has been removed for the purpose of providing this sample issue.

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Did you know that 53% of hair treatment physicians specified "cell therapy / stem cells / tissue engineering" as the next leap forward in hair restoration? Surgical automation and robotics came second (35%) and a distant third (2.6%) was "growth factors."

[28]

Cell Therapy

Cell therapies for curing alopecia are early in their clinical development. These must still show evidence of durable and robust efficacy. Nevertheless, it bears watching. Regenerative cell therapies are making swift, genuine strides in treating specific human organs such as the heart. We expect these gains to extend towards rejuvenating hair follicles.

The science behind regenerative cell therapies is currently being advanced by a number of small companies and academic centers. If you examine the current efforts behind commercialization and intellectual property, it's a wide open field with key components owned by individuals, universities, and small companies. This is unlike targeted cancer therapies, which are currently dominated by Big Pharma. Having carved out its intellectual property and commercial turf, Seattle Genetics (Nasdaq: SGEN) is a notable exception. It's a small biotech that commands significant reach. We are looking for future SGENs, albeit smaller ones.

Among cell therapy companies in the alopecia space, tiny RepliCel Life Sciences in Vancouver, BC, is furthest into human testing. RepliCel originally started trading on the OTC bulletin board (OTCQB: REPCF) and was recently added to the Toronto Stock Exchange (TSXV: RP).

Wonder Drugs

Every other year, we also hear about a wonder drug or lotion that will magically restore hair. It's easy to be cynical. Nevertheless, it would only be a mild surprise if something arises that works better than Minoxidil or is an effective additive. Even a moderate improvement would translate into good revenues.

Featured later in this report, we'll recap the hype around "prostaglandin D2" (PGD2), which created a stir in the summer of 2012 as an upcoming "baldness cure." The scientists behind it include George Cotsarelis, head of dermatology, at Pennsylvania University and his crew. It is actually some interesting science although there was some hype in the traditional media.

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[28] International Society of Hair Restoration Surgery: 2013 Practice Census Results. Published by the International Society of Hair Restoration Surgery. Retrieved June 8, 2014, from http://www.ishrs.org/press-release/ishrs-2013-practice-census-facts-and-figures.

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Replicel

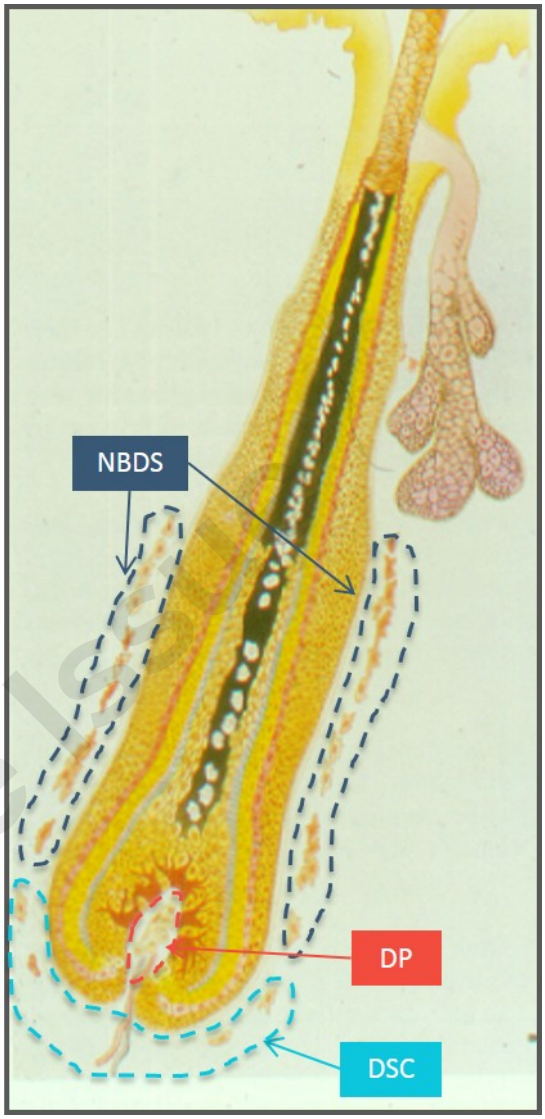
Replicel Life Sciences is developing its proprietary cell therapy approach designated **RCH-01.** It aims to rejuvenate damaged, miniaturized hair follicles in balding scalp skin. It focuses on correcting a deficit of healthy dermal sheath cup cells (DSCs) in the follicle.

The DSCs regulate the volume of DP cells. *Increase the number of healthy DSCs and it increases the DP cells*. As mentioned before, the dermal papillae (DP) cells fuel hair growth and push the follicle into the anagen or growth phase.

The DSCs in the bald area are compromised by DHT and other androgens.

> *Our therapies are designed to simply multiply a patient's particular cells that are in deficit and then deliver it to the area of deficit.*[29]
>
> *The mechanics of our technology involve the extraction of as few as 10 to 20 hair follicles from a patient.*
>
> *The dermal sheath cup cells are then replicated in a laboratory through our cellular replication process and injected back into the patient's bald scalp. The implanted cells help rejuvenate inactive hair follicles. Our anticipated long-term result is rejuvenation of existing quiescence hair follicles on the scalp.*[30]

Figure: Parts of a Hair Follicle



Figured used with permission of RepliCel

[29] RepliCel Life Sciences. (2014). RepliCel — Treating Functional Cellular Deficits. An Interview with CEO, David Hall. [news release]. Retrieved from http://www.replicel.com/replicel-treating-functional-cellular-deficits-an-interview-with-ceo-david-hall/

[30] Research Findings: RCH-01 – Treatment for Pattern Baldness. (n.d.). RepliCel. Retrieved June 12, 2014, from http://www.replicel.com/technology/research-findings/

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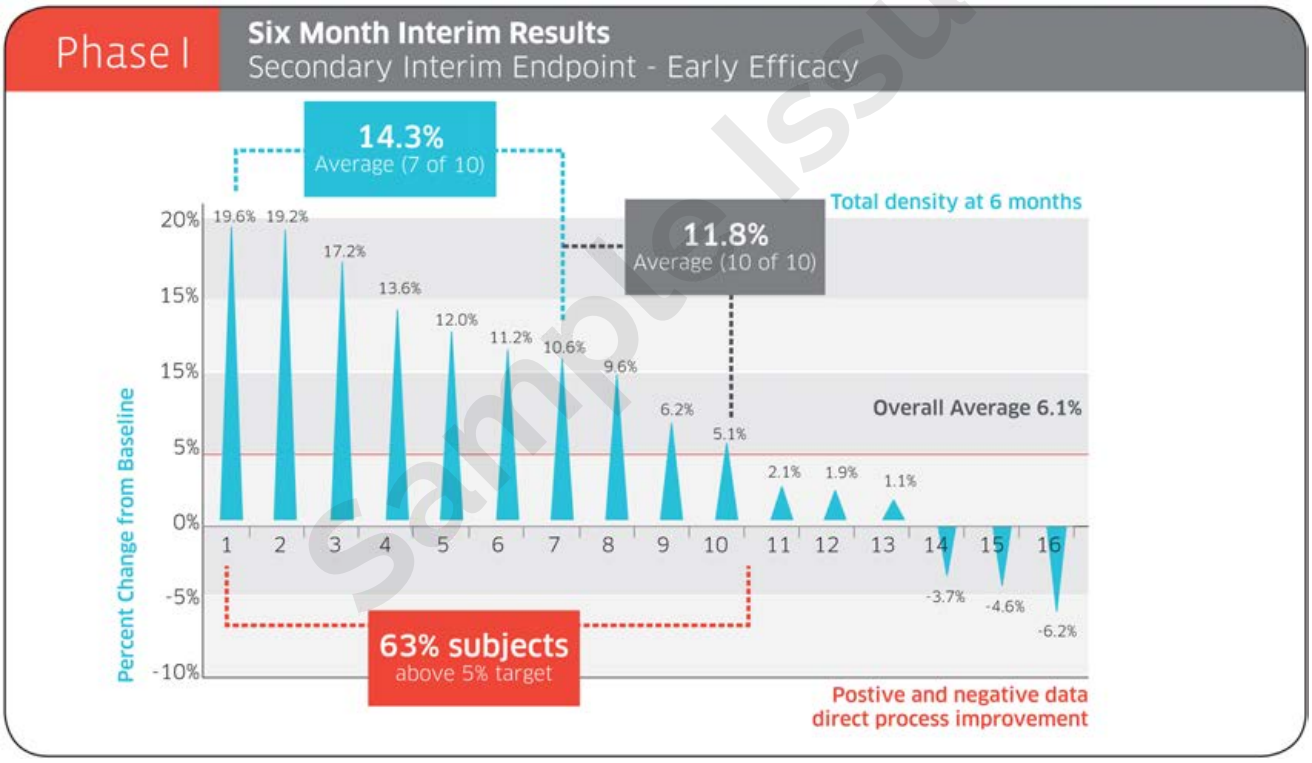
Phase I/IIa Results

19 subjects (10 male, 9 female) with mild to moderate androgenetic alopecia were given a single set of injections. On one part of the scalp, they were injected with their own replicated DSCs. On another part, subjects were injected without DSCs (placebo) to assess safety and efficacy.

During May 2012, RepliCel released positive interim results from this early trial.

- 63% of patients achieved increases in density > 5% target
- Mean change in total hair density = 6.1% vs. 5.0% target
- 70% of responders were above 10% with an average increase of 14.3%.

In contrast, Minoxidil gives an average 8% to 16% increase in density while finasteride (Propecia) gives a 7% to 14% increase. Women, however, are excluded from using finasteride. Hair transplant, however, remains the current gold standard.



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RepliCel Life Sciences Proposed PhaseIIb Study, competitive profile and Prostanglands D2 (PGD2) has been removed for the purpose of providing this sample issue.

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Summary Thoughts

The hair restoration industry has robust underlying demand with steady growth. Although a new and effective treatment could bring decent revenues and expand the market, none are on the immediate horizon.

There are, however, some tantalizing possibilities.

1) RepliCel Life Sciences – Three clinical trials launch in 2014. The results don't return until 2015 and 2016. It defines itself as the hair follicle company. Will its hair follicle cells provide superior results? These trials will make or break the company. More importantly, the results may spur other cell therapies to step forward into treating alopecia.

2) Surgical Automation – A small but growing proportion of hair treatment surgeons employ devices to automate part of their repetitive work. The ARTAS robotic system has an interesting business model in which it charges per motion (not by successful graft). As automation tools improve and also expand to include more of the hair transplant procedure, this should result in greater adoption.

3) "Wonder Drugs" – While there is considerable snake oil being marketed for curing baldness, we're also seeing some credible scientists swing for the fences. In an unconventional article, Ashley Nieves and Luis Garza simply outline their multiple reasons for pursuing PGD2 inhibition as a hair restoration treatment. As we noted before, newspapers trumpeted PGD2 inhibition as the latest cure for baldness. Nieves and Garza end their article with these two phrases: *the possibilities are vast for identifying bioactive lipids, which will inhibit or promote hair growth. The tools are limited, but the task is simple: just find the needle in the haystack.*[39]

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[39] Nieves, A., & Garza, L.A. (2014). Does prostaglandin D_2 hold the cure to male pattern baldness? *Experimental Dermatology, 23,* 223-227.

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Interview with a Cosmetic Surgeon

Alan Leong, Corinne Jordan, Mike Hoak, Chris Baker

Introduction

In support of our June issue on hair restoration, the team recently met with Dr. E. Antonio Mangubat, a private practice cosmetic surgeon who specializes in cosmetic reconstruction and hair restoration surgery here in the Northwest.

As you will see with one glance of his bio on his company website at La Belle Vie, Dr. Mangubat isn't just any ordinary specialist in hair restoration; he is a strong industry supporter, inventor and advocate on regulatory standards since entering the field in the 80's.

Interview

BioWatch News: Can you share a little about your background?

Dr. Tony Mangubat: My entry into cosmetic surgery started many years ago when I met Dr. Richard Webster at a meeting on hair transplantation. I was fascinated by his take on cosmetic surgery in general. I attended the conference to learn about hair restoration; but I gained a much broader view on not just one procedure, but also everything about making a person look better.

After the conference, I contacted Dr. Webster and made arrangements for my wife and I to fly to Boston to have dinner with him. That evening we spoke about cosmetic surgery in general; how it really differed from plastic surgery and Dr. Webster said, "You know, plastic surgery is about reconstruction; if you want to learn cosmetic surgery, you'll never get there in plastic surgery." So I asked him, "Where do I learn this craft?" and he said, "From me." So that was my introduction into cosmetic surgery and how Dr. Webster became my mentor.

I spent approximately 18 months with Dr. Webster, and in that time, he taught me everything he could about the cosmetic surgeries that he performed. Interestingly enough, he didn't do a single hair transplant the entire time I was there. I ended up going to other places to shore up my knowledge on hair restoration; but Dr. Webster did teach me about everything else: rhinoplasty, face-lifts, eyelids, breast augmentations, breast reductions, tummy tucks, and liposuction.

As the founder of the American Academy of Cosmetic Surgery, Dr. Webster is very well respected in our organization. As my mentor, he fueled my passion for cosmetic surgery.

BioWatch News: You are fairly noted in hair restoration and known for pioneering some of the tools and methods in the field. Could you share a little about that?

Dr. Tony Mangubat: In all honesty, many of the things that I pioneered back then are no longer used because current methods have exceeded what we could do in those days. But let's step back to around 1987...one of the most popular procedures that was done in hair loss was to do a scalp reduction, or a scalp lifting operation.

The procedure basically involved making an incision between the hair and the bald scalp; we would free up the entire hair-bearing scalp as much as we could - even as far down as onto the neck - and then we would lift it up as high as we could.

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The remaining section on “Interview with a Cosmetic Surgeon” has been removed for the purpose of providing this sample issue.

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KinDex Pharmaceuticals

Erik Richardson

Overview

KinDex Pharmaceuticals is a privately held, venture-backed company, focused on developing a drug platform for treatment of metabolic syndrome. CEO, Dr. Jeffery Bland, the captain of KinDex, is poised at the helm. He is backed by twelve years of tenured research experience at the University of Puget Sound and is former CSO of Metagenics. KinDex was created as a carve-out when, in 2009, Metagenics was acquired by Altacorp. Dr. Bland saw the potential for a platform of molecules derived from beer hops, and chose to continue developing that intellectual property. Since AltaCorp is a nutrition and lifestyle company, and not a pharmaceutical development company, Dr. Bland recognized the opportunity to carve out the technology and associated patents that were developed around the hops molecules. KinDex Pharmaceuticals, now holds the perpetual license for those patents.

That development led to KDT-501; the lead product at KinDex. In scientific terms this molecule is a 1,3-cyclopentadione derived from the humulone of the *humulus lupulus or hops* plant[40]. It provides a multi-faceted mechanism[41] that hits multiple targets for the regulation of a bio network involved in metabolic conditions. Translated, this means that KinDex has taken a molecule commonly found flavoring the beverages of beer aficionados and altered it to modulate a few of the body's pathways involved with diabetes, inflammation, hypertension, and even weight gain. KDT-501 successfully completed Phase Ia and Ib trials and awaits additional Series A funding to move into Phase II.

KDT-501 piqued our interest with its novel approach of abating weight gain, in an obesity-linked diabetic market that has the potential for rapid expansion. It is true that KinDex is entering congested pharmaceutical space, but the commitment of Polaris to their Series A lends confidence since Polaris has backed a number of successful life science companies. The Series A round is not over, and KinDex is prepared to entertain investment offers for additional funding. Given satisfactory answers to questions regarding the efficacy of the mechanism and Phase I details,

KinDex Pharmaceuticals

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[40] Urban, J., Dahlberg, C. J., Carroll, B. J., & Kaminsky, W. Absolute Configuration of Beer's Bitter Compounds. *Angewandte Chemie International Edition*, *52*, 1553-1555.

[41] Also known as pleiotropic - Pleiotropic is a term borrowed from genetics wherein it describes a gene's ability to affect multiple, seemingly uncorrelated responses. In this context, its meaning is appropriated to the multifaceted effects of KDT-501. This molecule interacts with multiple upstream targets eliciting downstream responses in a variety of capacities. This differentiates it from more traditional drugs that have an individual target with the goal of eliciting an individual, homologous response.

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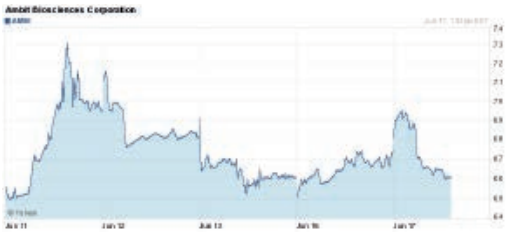
Ambit Biosciences Corporation

Introduction:

Ambit Biosciences Corporation (AMBI) focuses on the discovery, development, and commercialization of drugs for the treatment of oncology, autoimmune, and inflammatory diseases.

The company's products include Quizartinib, an orally administered FMS-like tyrosine kinase 3 inhibitor that has completed Phase II clinical trials; AC410, a small molecule inhibitor of Janus kinase 2, which is in Phase 1 clinical trials; and AC708, a receptor tyrosine kinase inhibitor that is in pre-clinical studies for the treatment of oncology, autoimmune, and inflammatory diseases.



Why Pay Attention:

Quizartinib is a state-of-the-art FLT3 inhibitor. Before Quizartinib, FLT3 inhibitors had disappointing, almost non-existent response rates; but Quizartinib is different. In a recent Phase II trial, Quizartinib displayed a 50% remission rate with FLT3-ITD+ Acute Myeloid Leukemia (AML) patients.

Ambit recently launched a large, randomized, open-label, comparison trial of Quizartinib vs. chemotherapy in the USA, Australia, and the European Union. If successful, the company hopes to file with the FDA and then later with the foreign regulatory bodies. Ambit may have a partner(s) outside the USA.

Executive Team:

Mr. Michael A. Martino
CEO, Pres. & Director
Mr. Alan Fuhrman
CFO & PAO
Dr. Athena Countouriotis M.D.
Chief Medical Officer
Mr. Kevin J. Kinsella
Founder
Dr. David J. Austin Ph.D.
Co-Founder, Chairman of Scientific Advisory Board

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Recent Highlights:

	Date
Results from multiple Phase II studies of Quizartinib to treat acute myeloid leukemia (AML)	6/2/14
Launch Phase 3 Trial (Quantum) of Quizartinib in relapsed or refractory AML Patients with FLT3-ITD+ Mutation.	4/8/14
Launch Phase 2 Trial of Quizartinib added to frontline chemo to treat AML and myelodysplastic syndrome.	4/7/14

Upcoming Events & Milestones:

	Date
Launch Phase III Trial with Quizartinib addition to frontline chemo to treat Fit elderly AML patients.	2H-2014
Interim Results from trial of Quizartinib added to frontline chemo to treat Unfit elderly AML patients.	2H-2014
Conduct 13-week Chronic Toxicology Animal Study of AC410 (Autoimmune Diseases).	2014
Interim Analysis Phase III Trial (Quantum) of Quizartinib in relapsed or refractory AML Patients with FLT3-ITD+ Mutation	2H-2015

Financial Position:

Quarter Ending March 31, 2014	Q1-2014	Q4-2013	Q1-2013
Revenues	-	$1.3M	$6.6M
R & D Expense	6.3M	6.1M	9.0M
SG & A Expenses	3.3M	3.3M	10.8M
Total Operating Expenses	9.6M	9.4M	332K
Net Loss**	(9.0M)	(2.0M)	(4.2M)
Basic & Diluted Loss Per Share	(0.50)	(0.11)	(3,019.30)
Weighted Avg. Shares Outstanding	17.9M	17.9M	4.0K
Recent Price (Per Share)***	6.61(6/13/14)	9.97(3/15/14)	n/a
Market Capitalization***	119M	61M	n/a
Cash & Short-term Investments	61.9M	71.2M	-

*The decrease of 6.6M in revenues is mostly due to the termination of the partnership with Astellas Pharma.
** For Q4-2013, there was "other income" which netted $6.1M. This improvement was primarily due to the change in fair value (FV) of the Company's stock warrant liabilities, which was driven by the change in FVof the underlying securities.
***The company IPO commenced on May 15, 2013.

Ambit Biosciences Update

Alan Leong

Ambit Biociences (Nasdaq: AMBI) is a small San Diego biotechnology company that is developing small molecules for treating cancer and autoimmune disease. Its lead drug, Quizartinib, is in a Phase III trial to treat acute myeloid leukemia patients that have relapsed or are refractory to treatments (RR AML).

Ambit Biosciences Update

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Acute Myeloid Leukemia (AML)

AML is a catch-all category for cancers that involve special cells that reside in the bone marrow. These are parent cells from which blood cells develop.[60] With AML, these parent cells mutate and experience abnormally vigorous and unrestrained proliferation. The resulting cells remain immature and do not become useful, normal red and white blood cells and platelets in the blood. These useless immature cells crowd out the useful cells until normal functions cease.

Younger AML patients may respond well to chemotherapy and stem cell transplants. The remission rates are dim for those over 60; furthermore the side effects are difficult for the elderly.

In 2013, about 14,500 AML patients were diagnosed in the USA and 15,000 in Europe.[61] Most were over 60 years old. The five-year survival rate for those over 60 is only 5% to 10%; while remission rates after chemotherapy are often less than 10%.

The survival and remission rates are especially wretched for those who have a mutation in the FLT3 receptor (termed FLT3-ITD+). 80% of FLT3-ITD+ patients will relapse and die within 2 years of their initial diagnosis. This mutation is present in 35% of AML patients.

Phase III Program Update

Quizartinib is a state-of-the-art FLT3 inhibitor. Before Quizartinib, FLT3 inhibitors had disappointing, almost non-existent response rates; but Quizartinib is different. In a recent Phase II trial, Quizartinib displayed a 50% remission rate with FLT3-ITD+ AML patients.

Ambit recently launched a large, randomized, open-label, comparison trial of Quizartinib vs. chemotherapy in the USA, Australia, and the European Union. If successful, the company hopes

[60] These parent cells are called hematopoietic progenitor cells.

[61] Quizartinib is designated as an Orphan Drug for treating AML in the USA and the European Union (EU). The orphan designation waives the filing fees and allows for research expenditures to be applied as tax credits against future Quizartinib revenues. Ambit may receive special guidance for designing clinical development. It also guarantees marketing exclusivity for using Quizartinib to treat AML for 7 years in the USA and 10 years in the EU - this may be moot, as composition of matter patents apply until 2028 and extensions may lengthen it.

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