

## Recent Advances in Hair Cloning

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New Research

Hair Cloning in 2004, an update in the progress of Article written exclusively for HairlossTalk and its users, Dr. Kevin McElwee provides this three-part review on the current state of hair cloning research, its history, and what you can expect to see in the coming years with this exciting new technology...

The hair follicles we are born with have to last us a lifetime. Like internal organs, we cannot naturally generate new hair follicles in adult life. If hair follicles are damaged or destroyed through disease or trauma, the area of affected skin is permanently depleted of hair follicles. At least that is currently the case, but in the same way that research is being conducted into the possibility of organ regeneration to replace, for example, a diseased liver, scientists have been looking at ways to regenerate hair follicles.

### How Hair Cloning Works

In principle, it is possible to produce new hair follicles from certain cells. At its simplest, a few healthy hair follicles can be excised from an individual by biopsy. The follicles are then dissected to isolate a small ball of cells at the base of each follicle called the dermal papilla. For the average full grown scalp hair there are about 200-400 cells in each dermal papilla. That's not much, but these cells can be cultured in incubators to make several hundred thousand cells within about 6 weeks or so. These cells can then be implanted into bald skin where the dermal papilla cells induce new hair follicles to develop. The process is not fully understood, but we do know that dermal papilla cells send out chemical signals called cytokines that tell the skin to produce a new hair follicle. A new hair follicle is made from epithelial cells, but the \*development and cycling\* of the follicle is determined by dermal papilla cells. You must have both dermal papilla cells and epithelial cells together to form a hair follicle. Just one or the other cannot form a follicle on their own.

### Re-triggering that Fetal Fun...

This process whereby dermal cells communicate with epithelial cells to produce hair follicles occurs naturally during your fetal development. At this time, cells destined to become dermal papilla cells, migrate through the skin dermis and start to cluster together. The initial trigger that causes this to happen is unknown. Each cell cluster tells nearby epithelial cells to make a new hair follicle, but after birth the number and distribution of dermal papilla cell structures are all fixed in place. There is no new dermal papilla structure formation, so there is no new hair follicle formation after birth. However, the above principle shows that all the ingredients necessary to generate brand new follicles \*are\* present in adult skin. The kicker is trying to figure out how to get these cells to restart their communications and do what they did while you were an adorable little fetus.

## **A topical Hair Cloning treatment?**

It might be possible one day to cause new hair follicle formation by applying skin with a chemical signal that triggers the resident dermal cells to return to their embryogenic days, but such a treatment approach is not likely for a long time. We know some of the chemical signals that might be involved, but certainly not all of them. Products such as Lef1 or beta Catenin may be involved, but there must be many more factors involved to induce hair follicle development that we do not know about. Before a chemical treatment can be developed to induce new hair follicle formation, we need to know a lot more about the mechanism of natural hair follicle development.

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Since we don't yet have a convenient topical liquid you can just put on your head to kickstart new follicle development, several academic and commercial groups based in the US, Canada, England, the Netherlands, and Japan have been looking into the method of extracting normal hair follicles, culturing the dermal papilla cells outside the body, and then implanting them, to induce new hair follicles. This basic technique comes in several variations and with a variety of names, but perhaps the most common method of referring to the hair follicle regeneration principle is "hair or follicle cloning". Strictly speaking, the technique does not involve cloning in the true scientific sense (as in Dolly the sheep), but multiple hair follicles can be produced from just one donor follicle, so it is a sort of cloning. Others refer to "follicular neogenesis" or "multiplication". It is all basically the same thing.

## **Hair Cloning is a proven Technology**

Scientists have actually known about the ability to induce new hair follicle development by using existing hair follicles for a long time. As far back as 1944 two scientists, Lillie and Wang, were taking bits of feather follicle (which is basically the same structure as a mammal hair follicle) and implanting them to chicken skin to induce new hair follicles to form. In the 1960's Cohen and Oliver showed the same could be done with rat follicles. This principle was developed greatly by other scientists and particularly Colin Jahoda and Amanda Reynolds who are past students of Oliver. With studies on rodents, Jahoda and Reynolds showed that just the dermal papilla cells could be used to produce new hair follicles, and that these cells could be cultured and then transferred to skin to induce new hair follicles. In a paper published in the top journal "Nature", they showed that cells could be taken from one human donor, (Jahoda) and implanted to another (Reynolds) and induce new hair follicle formation, although no cell culturing was involved in this particular study. So far this is the only study actually published to prove hair cloning would work in humans. Since this publication, there has been a lot of interest in developing the idea of hair and follicle cloning into a practical technique for use in the dermatology/hair transplant clinic. Companies like Aderans (the owners of the hair transplant chain, Bosley International) and Intercytex have set up well funded laboratories

to develop the technique. Dr's Jahoda and Reynolds continue their academic work at Durham University in England and several other academic research scientists have decided to jump on the bandwagon.

## **The Current Roadblocks with Hair Cloning**

### 1 - **Unreliable Quantities**

While the principle of hair cloning is proven, turning it into a practical technique for clinical use is fraught with problems. First, the results of implantation can be very variable. Even if they inject the same quantity of cells, and even if the cells are from the same donor, the number of hair follicles produced in response is extremely unreliable. There have been unofficial reports from two sources (Aderans/Bosley, Dr Jerry Cooley) that they have successfully induced hair growth in humans by using cultured cells. Unfortunately the success rate stated by both sources was poor. Implantation of cultured cells to volunteers by Aderans/Bosley produced just 2 hairs in a single individual. Dr Jerry Cooley implanted cultured cells into himself at fifteen different sites but only managed to promote one hair follicle to grow.

### 2 - **Unreliable Angles**

Second, the new hair follicles induced in studies using rats or mice are usually disorientated. Natural hair follicles grow hair with a "grain", so on your scalp your hair grows in whirl pattern (usually clockwise) about the vertex. On your lower legs your hair grows down towards your feet etc. With hair follicles induced in hair cloning studies on rodents, the follicles can grow hair at all sorts of angles. This gives a cosmetically "scruffy" appearance.

### 3 - **Uneven Distribution / Patchy Growth**

Third, natural hair follicles are evenly distributed over the skin, but in rodent studies hair follicles induced by hair cloning do not have an even distribution over the skin – there can be clumps of hair growth. Again, the cosmetic appearance of this clumpy growth is generally unacceptable.

For hair cloning to become a practical and popular treatment, all these problems must be overcome.

**For Hair Cloning to work, researchers need to be able to (1) produce a consistent number of hair follicles for a given number of injected dermal papilla cells (2) figure out how to control the angle at which the new follicles grow and (3) produce a consistent level of density over the treated area. Currently, these are the 3 main roadblocks to successful hair cloning.**

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New Study of Dermal Papilla & Hair Growth

[IMAGE]

Two very recent studies from academic research groups have added new information to the debate on the future of hair cloning. The first paper by Paus and colleagues in Hamburg, Germany and Bradford England, shows that the ball of cells necessary to make new follicles do not originate only in the dermal papilla. By analyzing follicles in different stages of the hair growth cycle, they found that the dermal papilla structure is filled with cells that have migrated from an adjacent structure around the hair follicle called the “dermal sheath”.

The dermal sheath is an outer sleeve of cells around the epithelial component of the hair fiber-producing part of the hair follicle. Clear as mud? :)

In other words, cells in the dermal sheath were previously thought to only play a minor role, mostly as physical support to the hair follicle. This recent study has shown that cells multiply in the lower dermal sheath and then migrate into the dermal papilla at the start of a new hair growth cycle. At the end of the hair growth cycle the cells migrate out again either back into the dermal sheath or out into the dermis.

This might be one explanation as to how androgenetic alopecia develops. If at the end of each growth cycle the dermal papilla cells migrate away from the follicle never to return, then the dermal papilla structure may get progressively smaller with each growth cycle - but this is a story for another time.

*Figure 1 above: (a)*

*Cross-section view of a hair follicle in growth phase (anagen) and the bulb region*

*(b) the same follicle with the dermal component outlined*

*with an dotted line. The hair follicle dermal component can be subdivided into at least three parts based on morphology and the ability of cells to induce new hair follicles (c) The dermal papilla (DP) sits at*

*the base of the hair follicle in a pear shape structure. The DP is fed by cells of the lower dermal sheath called the dermal sheath “cup” (DSC). The*

*cells of the dermal sheath (DS) away from the hair follicle bulb have no apparent ability to induce new hair follicle development.*

### **How this Study relates to Hair Cloning**

The size of the dermal papilla is known to directly dictate the size of the hair fiber produced. A big papilla promotes the growth of a big hair fiber.

For the purposes of understanding hair cloning, the study shows that the dermal sheath plays an active role in determining the size of the dermal papilla. The dermal sheath provides the cells. The Dermal Papilla is created with these cells.

The two together define the size of the hair fiber produced, and how long that hair will stay in growth phase. This is very important for hair cloning. It shows that to make big, healthy new hair follicles with hair cloning, you need to use cells from a big, healthy donor hair follicle. The cells from the donor follicle apparently retain the instructions for a big follicle and transfer this information to the new follicle in hair cloning.

The second paper from Marburg Germany takes these observations a step further. In these studies the scientists used cells that contained a green fluorescent

protein tag. Under ultra violet (UV) light the cells fluoresce green and this enables the scientists to follow where the cells go and what they do over time. The scientists took dermal papilla cells and dermal sheath cells, cultured them, and then injected them into normal mouse ears and mouse feet.

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### **Alkaline Phosphatase**

Mouse feet do not, in general, have hair follicles in them, just like human palms and soles. However, mouse ears, like humans ears, are covered in tiny hair follicles that produce tiny hair fibers (vellus hair fibers in humans). After about 3 months, the scientists observed visible new hair growth from the injected skin, both with dermal papilla and cells from the lower dermal sheath, next to the dermal papilla, but not the upper dermal sheath. This showed that both cell types, although they came from different structural components of the hair follicle, were functionally similar - both cell populations could induce new hair follicle formation. The scientists also demonstrated that the cells with the ability to induce hair growth were alkaline phosphatase positive. Alkaline phosphatase itself probably has nothing to do with the ability to induce hair growth, but its expression is potentially a useful method of quality control. Conclusion? Those cells with alkaline phosphatase positive expression are the ones you want to take, culture, and transplant. Cells that are alkaline phosphatase negative do not seem to promote new hair growth and should be discarded. This may help improve the success rate with hair cloning.

### **Injected cells merging with existing cells**

[IMAGE]

At 3 and 6 months post cell injection, the scientists shone UV light on the mouse ear and foot tissue. They could see that the implanted fluorescent cells were found within hair follicles and the cells were in the dermal sheath and dermal papilla structures. This suggested the both cell populations were capable of inducing brand new hair follicles to develop. That is not so surprising given the previous work in this field by Jahoda and others. However, what was more intriguing for understanding hair cloning, was that in mouse ears there were “chimeric” hair follicles with dermal papilla and dermal sheath structures containing both fluorescent and non-fluorescent cells combined. The scientists suggested that this was an indicator that the injected fluorescent cells had migrated in and integrated themselves into the tiny natural hair follicles already present in the ears. The new cells had apparently altered the size and growth cycle of the tiny hair follicles to make them much bigger and to make them grow for longer which in turn produced bigger hair fibers.

Fig 2 above: Cultured dermal papilla cells injected into a mouse ear induce new hair follicles and modify natural hair follicles already present to yield tufts of long hair growth 4 months after injection.

### **Using injected cells to reverse Miniaturization?**

This observation makes several important points in terms of using hair cloning to treat androgenetic alopecia. If cells can be implanted that will integrate with resident hair follicles, then men and women in the early stages of androgenetic alopecia could be treated. Hair follicles in the process of miniaturization could be boosted with implanted cells to force them back into a full sized, terminal growth state. By exploiting the resident hair follicle structures as a guide for the implanted cells, the problems of erratic follicle orientation and distribution over the skin, seen in hair cloning studies so far, could be resolved. The damaged, small, natural hair follicles would provide the distribution pattern and angle of orientation, while the injected dermal papilla cells would contribute the characteristics of large, terminal hair follicles. So those in the early stages of baldness with just a little thinning, could significantly benefit from hair cloning. In theory, young men and women in families where the androgenetic alopecia trait is strong and who are likely to develop androgenetic alopecia could be injected with cells in advance of overt hair loss and need never develop any alopecia.

Even men in the late stages of androgenetic alopecia with extensive baldness might still benefit from this observation. Even in apparently bald skin, there are usually tiny vellus hair follicles still present. It is possible these follicles still retain a “memory” of what they once were and their old growth patterns as terminal hair follicles. If so, it may be possible to implant cells such that they integrate with the vellus hair follicles and produce a cosmetically acceptable result even for extensively bald men and women. It remains to be seen whether the perceived problems of follicle orientation and distribution identified in scientific studies with rodents actually prove founded when transferred to the bald human scalp. The process of androgenetic alopecia with gradual miniaturization of hair follicles may actually be ideal for the hair cloning technique to work.

### **The Migrated might continue to Migrate...**

Both studies reinforce the fact that the cultured dermal papilla cells, and also lower dermal sheath cells, retain the characteristics of the donor hair follicle. There has been some concern that the property of large hair follicle induction that is transferred with the implanted cells would gradually dissipate over time. Most recently, in the December 2003 issue of the Journal for Investigative Dermatology, Dr Jahoda has expressed this fear in a commentary on both the above papers. The observation by Paus et al, that cells can disperse from the dermal papilla at the end of the hair cycle raise the question of whether the implanted cells of hair cloning might eventually migrate away leading to a progressive redevelopment of the alopecia. This is an important issue that remains to be resolved. Rodent models have shown hair growth induced by hair cloning to last for at least 18 months with no significant change, but the naturally short life span of rats and mice (around 2 years) means that scientists will not be able to claim induced hair growth survival much beyond this time span. The answer to this question probably won't be elucidated until long term studies are conducted directly on humans.

Overall then, good progress is being made with hair cloning, but there is much more work to be done before hair cloning can become a routine procedure that yields consistent results in humans.

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