Review of the available literature

regarding the use of 'Dermaroller MC'

as of December 1st 2010

Application fields:

1. Transdermal delivery of active substances into the skin
2. Treatment of skin alterations by means of neocollagenesis

Application field 1: Transdermal delivery of active substances into the skin

These results also apply to the Dermaroller HC models

Regarding this field of application, **thirteen studies of the years 2001-2010** have been evaluated. The topic of all these studies was to find out if the Dermaroller (or a comparable instrument) is suited to breach the *stratum corneum* barrier and deliver active substances into the epidermis and/or deeper layers of the skin. In a first step, the literature itself was evaluated regarding the scientific quality, the qualification of the authors etc. The findings are summarized in table 1. All studies were found suitable to be used for this literature evaluation.

The first of the studies (Verma & Fahr 2001a) was carried out on behalf and at the expense of Dermaroller SARL. For six studies the Dermarollers were provided free of charge on request of the performers.

Nine of the studies were published in renowned scientific journals, two were presented as a talk resp. poster presentation at a congress and the two oldest studies were published online. In nine of the thirteen studies, the original Dermaroller® resp. Dermastamp® was used. The instrument used by Bal *et al.* 2008 is similar to the Dermaroller as regards material (stainless steel) and diameter. The model used by Clementoni *et al.* 2010 and Zhou *et al.* 2010 closely resembles the Dermaroller with respect to the construction (round needle arrangement), material (stainless steel), needle tip (conical) and needle length (200 - 1000 µm).

In six of the studies, the effectiveness of the Dermaroller was studied *in vitro* employing human skin, porcine skin or hairless rats. Two studies were carried out both *in vitro* and *in vivo* using mice or rats. Five studies are *in vivo* studies employing rats or humans (table 1).

Following table 1, the studies evaluated and their main findings are briefly summarized.

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To prove the ability of the Dermaroller to increase the amount of active substances passing through the *stratum corneum* into the skin, Dermaroller SARL initiated a study in the year 2000 with Prof. Dr. Alfred Fahr (Phillips-University Marburg, Germany). The results were published online in 2001 (**Verma & Fahr, 2001a** and **2001b**). In the first part, the effect of different Dermaroller models (C-8, needle length 0.13 ± 0.02 mm and M8, needle length 1.5 ± 0.02 mm) was investigated using a lipophilic (retinol) and a hydrophilic (flufenamic acid) model drug. After Dermaroller pre-treatment the model drugs were applied in liposomal formulation on human skin *in vitro*. After 6 hours the *stratum corneum* and deeper layers of the skin were investigated using HPLC to check for the amount of drug present. The results demonstrate that both Dermaroller models are efficient in delivering hydrophilic as well as lipophilic drugs into the *stratum corneum* and deeper layers of the skin. The depth of maximum drug deposition depends on the needle length.
The second part of the study (2001b) is identical in general, but uses a fluorescent dye to illustrate the drug deposition by images taken with a confocal laser scanning microscope. The results confirm the findings of the first part study. The authors emphasize the simplicity and high reproducibility of the results.

The effectiveness of the Dermaroller was confirmed by **Kolli *et al*. (2007a)**, who also showed that the Dermaroller efficiently creates microchannels in the skin. It thus offers an alternative means to breach the *stratum corneum* barrier. The authors also addressed the question of micropore closing under different conditions for the first time (**Kolli *et al*., 2007b**). Using hairless rats they could show that the micropores can be kept open for up to 72h *in vitro* when they are occluded or covered by a buffering solution. This effect may be desirable, e.g. when active substances have to be applied repeatedly over a longer period of time (see Li *et al.* 2009).

Microchannels caused by microneedles made of sugar resp. of metal were characterized *in vitro* and *in vivo* by **Li *et al.* (2009)** using hairless rats. The metal needle instrument used was a Dermaroller CIT 8. Human immunoglobin G (IgG) was employed as model drug. Microchannels were characterized using methylen blue staining, calcein imaging, confocal laser microscope images and histological findings. The *in vivo* uptake of the model drug into the metabolism was analyzed using ELISA.
Results show that the Dermaroller breaks the *stratum corneum* and creates uniform microchannels of about 150 µm depth. Through these microchannels the transdermal delivery of human IgG was increased both *in vitro* and *in vivo*. When occluded, the microchannels could be kept open for 24 hours.

The geometry of microchannels over time was investigated by **Bal *et al*. (2010a and b)**. For this study six healthy volunteers were treated on the forearm using the DermaStamp (needle length 300 µm). The model drug used was a fluorescent dye that was applied either before or after the treatment. Confocal laser scanning microscopic images were used to analyze the amount of dye at the skin surface, the volume of the microchannel, and the maximum depth of diffusion at time points 5, 10, and 15 minutes after application. The treatment was not perceived as painful. There were no bleedings. The dye was delivered into the skin at a depth that would be sufficient to channel macromolecules into the viable epidermis. The most important result of this study is that without occlusion, micropores were found to be closed after 10-15 minutes. Therefore the risk of infections following a microneedling treatment is very low (see also section 3). The authors conclude that the Dermastamp is a promising tool for transcutaneous vaccination (Bal *et al*. 2010b).

The dependance of the transdermal delivery on needle length and drug to be delivered was studied by **Badran *et al.* (2009)**. The authors employed Dermaroller models of needle length 150, 500 resp. 1500 µm. The treatment was carried out *in vitro* using human skin. The authors investigated the influence of the treatment on the skin surface, the transepidermal water loss (TEWL), as well as on the penetration and permeation of different hydrophilic model drugs. Alternatively, they delivered invasomes with the Dermaroller to evaluate the potential of combining these two approaches.
The different Dermaroller models created micropores of 50-200 µm diameter, the pore diameter being a function of the needle length. Also the TEWL increased with increasing needle length. The TEWL suggested pore closure after 2 hours. The authors stress, however, that *in vivo* pore closing should be faster (see above, Bal *et al.* 2010).

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Depending on the needle length, the different Dermaroller models show characteristic distribution profiles of the model drug delivered into the skin. The shorter the needles, the more of the active substance remains in the *stratum corneum* resp. in the immediately underlying layers of skin. With long needles (1500 µm) the biggest part of the active substance is found in the receptor compartment. The amount of active substance delivered into the skin could be increased additionally by using invasomes. According to the authors, the Dermaroller model with 500 µm long needles is best suited for transdermal delivery purposes. Using 150 µm long needles mainly results in creating a depot of the active substance in the *stratum corneum*. From here, however, the active substance can diffuse into the (epi)dermis. The authors point out the advantage of the cylindrical needle arrangement that results in much lower penetration forces compared to a flat needle arrangement.

Yoon *et al.* (2008) used the Dermaroller to increase the transdermal delivery of an optical clearing agent, glycerol. Using porcine skin they could demonstrate that a Dermaroller pre-treatment results in an increased delivery of glycerol into the skin and an increased optical clearing efficiency. A combination of microneedle pretreatment and sonophoresis resulted in an even further increase of the transdermal diffusion rate of 70% glycerol (Yoon *et al.*, 2010).

In a clinical study employing 18 healthy volunteers, **Wermeling *et al.* (2008)** compared the effect of a microneedle pretreatment on the transdermal delivery of Naltrexone by means of a NTX-patch. For this purpose they employed flat microneedle arrays, each consisting of 50 stainless steel microneedles (620 µm length) in a 5x10 pattern. These arrays were pressed into the skin of the upper arm before the NTX-patch was put on. Results show that no NTX was delivered into the skin without pretreatment. With a microneedle pretreatment, however, NTX could be detected in the blood already two hrs after patch application and remained constantly detectable for at least 48 hrs. The pretreatment was considered painless by the volunteers.

The potential of microneedle rollers for the transdermal delivery of insuline was studied by **Zhou *et al* (2010)**. The authors used stainless steel needle rollers with a needle length of 250, 500 resp. 1000 µm. Hairless rats were taken as animal model. Results show that microneedle pretreatment followed by applying an insuline patch resulted in a significant reduction of blood sugar levels of the test animals, prooving that insuline was successfully delivered. In conclusion, the authors state that "this delivery method is easy to handle, applicable to many other vaccines and holds great potential for future applications".

A new field of aplication is the use of the Dermaroller in photodynamic therapy (PDT). PDT is a method for the treatment of tumors and other tissue changes with light in combination with a light-activated substance (photosensitizer) and oxygen present in the tissue. For this purpose, a not primarily toxic photosensitizer or its metabolic precursor is administered to the patient which selectively accumulates in the tumor. After a certain amount of time the tumor is irradiated with light of suitable wavelength. This initiates a photophysical process which generates a toxic substance(s) that are harmful to the tumor.
PDT is widely used in dermatology to treat various forms of skin cancer and their precursors. One admitted drug for the treatment of actinic keratoses and certain forms of basal cell carcinoma is 5-aminolevulinic acid ("ALA"), a metabolic precursor of the photosensitizer protoporphyrin IX (PpIX). Promising studies and case reports also suggest efficacy in circumscribed scleroderma, acne, psoriasis vulgaris, various hyperkeratosis, viral warts and other chronic skin diseases.

An overview of the effect of PDT is given e.g. by Park *et al.* (2009). **Donnelly *et al.* (2008)** reported for the first time the use of microneedle arrays - in this case made from silicone - to increase ALA penetration into the skin (*in vitro* and *in vivo*). The authors could show that *in vivo* microneedle pretreatment clearly reduced both the application time and the ALA dose needed. These positive effects have no negative side effects, as was proven by the same group (Mikolajewska *et al.* 2010). Employing a group of healthy human volunteers they could show that the microneedle pretreatment neither increased pain sensation during irradiation nor the number or amount of erythema resulting from the treatment.

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The positive effect of a microneedle roller on the efficiency of PDT was shown **Clementoni *et al.* (2010)**. The authors used a cylindrical roller closely resembling the Dermaroller (stainless steel needles, needle length 300 µm). Their goal was a photorejuvenation of the skin by doing a full face treatment on 21 patients. After pretreating with the microneedle roller, ALA was applied and concurrently activated by a combination of red light and pulsed light. Three and six months after treatment, three independent physicians found a statistically significant improvement of the global 'Photoaging-score' und its components (small wrinkles, mottled pigmentation, surface roughness, telangiectasia). Also 90% of the patients treated judged the results as ‚more than 50% compared to the initial situation'. The use of the needle roller was well tolerated and lead to a more uniform and deeper absorption of ALA into the skin.

The use of PDT for the treatment of *alopecia totalis* was not successful, however, even if a microneedle pretreatment was carried out (Yoo *et al.* 2010).

Summary 'Transdermal delivery':

All of the studies evaluated here clearly confirm the efficiency of the Dermaroller for the transdermal delivery of different active substances (hydrophilic, lipophilic, macromolecules) into the skin. This finding holds true already for a needle length of 150 µm. As a result, there is a wide range of possible applications for the instrument (e.g. transdermal delivery of insulin or other drugs, transcutaneous vaccination, PDT). The treatment is painless up to a certain needle length and causes only minimal skin irritations. The cylindrical arrangement of the needles is very positive because it minimizes the penetration forces needed.

No studies are known that report on a failure of the method with respect to transdermal delivery or on adverse effects or risks of the treatment.

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2: Treatment of skin alterations by means of neocollagenesis

Regarding this field of aplication, **fourteen studies of years 2002-2010** were evaluated. All of them investigate the potential of the Dermaroller (or a comparable instrument) to treat skin alterations, especially scars and wrinkles, by activating the body-own formation of collagen (neocollagenesis).

In a first step, the literature itself was evaluated regarding the scientific quality, the qualification of the authors etc. The findings are summarized in table 2. Following table 2, the studies evaluated and their main findings are briefly summarized.

Eleven of the studies were published in scientific journals, one is accepted for publication, one was presented as a poster on a congress, one is unpublished. Half of the studies used the original Dermaroller®, the others used the Medical Roll-CIT (Environ, S. Africa). This instrument is similar to the Dermaroller® with regard to the general principle of function and the arrangement of the needles. The results of these studies were therefore transferable to the Dermaroller and could be used for this literature evaluation.

All studies were carried out with humans (table 2).

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In 1995, **Orentreich & Orentreich** published a pioneering report on a new method to treat atrophic scars, the so-called 'subscision'. They showed that repeated piercing of a scar with a needle activated the wound healing process. A similar approach was chosen by **Camirand & Doucet (1997)**, who used a tattoo gun (without pigment) to treat scars. These are the first publications that point towards the potential of 'needling' to treat scars and wrinkles. They formed the basis for investigations of the effect of the Dermaroller on collagen induction.

Starting around the year 2000, first studies regarding the therapeutic effect of the Dermaroller were initiated by collaborating with plastic surgeons. These were mainly Dr. Philippa McCaffrey, Australia (focus: scars/acne scars), Dr. Norman Leaf, USA (focus: wrinkles of the upper lip), and Dr. Martin Schwarz, Germany. Dr. McCaffrey and Dr. Rusher personally reported good to excellent results. Their results were never published, however.

First results of Dr. Schwarz were finally accepted for publication by the journal 'Plastic Reconstructive Surgery'. They await publication in 2011 (**Schwarz und Laaff, acc**). The results refer to a study in which ten patients with posttraumatic or acne scars were treated with Dermaroller MF8 (needle length 1.5 mm). Before and 6-8 weeks after the treatment, small skin samples were punched out, stained and fixated in paraffin. Evaluation was carried out in a blind study by an independent dermatologist / pathologist. Histological findings showed a significant increase in the amount of elastic fibers in the treated biopsies. Skin thickness had increased, too. The treatment was well tolerated and all the patients were content with the treatment results. Adverse effects were not observed except for a slight redness of the skin and occasionally slight hematoma. All patients could go to work or take part in social life normally. Good prospects of success are also attested to the Dermaroller for the treatment of stretch marks. On this subject, further investigations are in progress.

Fernandes (2002) was the first to publish results on the use of microneedles for the treatment of scars and wrinkles in a scientific paper. In this and two more detailed papers **(Fernandes, 2005; Fernandes & Signorini, 2008)** the author describes the effect of the collagen induction method, its indications, advantages and shortcomings in general, but does not present results from a specific study. Fernandes did not use the Dermaroller®, but the Medical Roll-CIT (Environ, South Africa). This microneedle roller resembles the Dermaroller® as regards the general principle of function, the cylindrical needle arrangement, and the materials used. The resemblance is sufficient to incorporate the results into this literature evaluation.

Fernandes (2005) gives a detailed description of the physiological bases of collagen induction by means of microneedle treatment. The microinjury induces the wound healing cascade and thus leads to the release of a number of different growth factors which induce cell proliferation. Collagen and elastin are formed as well as new capillaries. In the final remodeling phase, collagen III is converted into collagen I resulting in an increased firmness of the tissue. The author reports on the successful application of collagen induction therapy in the treatment of wrinkles, scars (esp. acne and burn scars), and stretch marks. However, he gives neither case numbers nor success rates. As advantages of the method he names the constructive instead of destructive nature of the method, the possibility of using it repeatedly on all body parts, and the short healing phase. Disadvantages are bleedings during and shortly after the treatment. Adverse effects are also bleedings, swelling and redness of the skin that can last for a few days.

Adverse effects of this severity have not been observed during or after a Dermaroller® treatment (see below). This is caused partly by the longer needles used by Environ (3 mm, relating to a penetration depth of 1.5-2 mm into the skin). In addition, Dr. Fernandes sees the cause for triggering the wound healing cascade in the release of blood cells and serum into the surrounding tissue (see Fernandes 2005, p. 57). The initiation of bleedings is thus a desired effect and 'energetic' rolling across the skin recommended. In contrast, Dermaroller SARL is convinced that already the change in the electrical resting potential of the cells - caused by the penetration of the needles - sets this process in motion (Liebl 2008). The release of blood is not necessary for this. Consequently, Dermaroller® treatment is carried out applying a minimum amount of pressure. An even formation of microbleedings on the skin surface (total blood volume 3-4 drops) is considered sufficient evidence of proper execution.

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A retrospective analysis of 480 patients from Germany and South Africa who had undergone collagen induction with the Environ Medical Roll-CIT (needle length 1-3 mm) was published by **Aust *et al.* (2008)**. The treatments were carried out in years 1997 to 2006. Indications were wrinkles (350/480), lax skin (58), scars and stretch marks (72). Before and 6 months after treatment, biopsies were taken from 20 patients to compare pre- and postoperative collagen and elastin. Different staining methods were used for this purpose. Evaluation of the biopsies showed a significant increase of the amount of collagen and elastin 6 months after treatment. The collagen formed showed a normal lattice pattern and not the parallel pattern typical of scar tissue. The *stratum corneum* was normal, the epidermis had thickened by 40%. These results are in good agreement with the findings of Schwarz & Laaf (acc.).
In 50 patients (15 with scars / stretch marks, 35 with wrinkles), patient satisfaction was evaluated before and 12 month after treatment. In this, the patients rated their appearance on a visual scale from 0 (=completely dissatisfied) to 10 (= completely satisfied). In the group with wrinkles, satisfaction increased significantly ($p \leq 0,05$) from 4.5 to 8.5. In the group with scars, satisfaction increased also significantly from 3.0 to 7.5. In this group, two additional objective methods for assessing scars were used: ‚Vancouver Scar Scale, VSS' and ‚Patient and Observer Scar Assessment Scale, POSAS'. Both of these scales demonstrated a significant success of the treatment. None of the patients reported on scarring, hyper- or hypopigmentation or photosensitivity after the treatment. Two patients developed a *herpes simplex* infection that could be successfully treated.
In summary, the authors see collagen induction as a safe and fast method for the treatment of wrinkles and scars, which leaves the epidermis intact instead of damaging it.

A study regarding the efficiency of the Dermaroller® to treat acne scars was published by **Fabbrocini *et al.* (2009)**. In this, 32 patients with acne scars received two treatments with Dermaroller model MS4 (needle length 1.5mm). The interval between treatments was 8 weeks. Before the first treatment, scar severity was scored by a dermatologist on a visual 1-10 scale. Afterwards patients were divided into three groups: severe, moderate, and mild scars. Additionally, ≥ 3 photos were taken of each patient and evaluated digitally. These steps (scoring, photos) were repeated before and 8 weeks after the second treatment. For 5 of the patients, also a microrelief impression of the skin surface was made that was evaluated by image processing and also served as an objective measure of treatment success.
Eight weeks after the second treatment, a significant treatment success was evident. Scar depth was significantly reduced, irrespective of the initial scar grading. Scar severity was significantly reduced, too. The microrelief impressions showed a reduction of skin irregularities and a great reduction of scar severity. There were no (negative) signs of the treatment and no hyperpigmentation. Patients reported redness and swelling after the treatment, but stated that they disappeared within 2-3 days.

A similar study was undertaken by **Majid (2009)**. He treated 36 patients suffering from atrophic facial scars caused mainly by acne, but also by chicken pox. The instrument used is very likely the original Dermaroller®, even if this is not explicitely stated in the publication. The needle length used was 1.5mm. Patients were treated three or four times with a treatment interval of 4 weeks. Final evaluation was carried out 8 weeks after the last treatment. Also in this study, scar severity was scored on a visual scale (Goodman & Baron; grade 1 - grade 4 = severe) and photos were evaluated by image processing. Only patients with scars of grade 2-4 were included in the study. In the final evaluation, an improvement of scarring by two grades or more was labelled as 'excellent' response, improvement by one grade as 'good', and no improvement as 'poor'. The patients themselves rated their improvement on a 1-10 scale. In this, rating above 6 was graded as 'excellent' response, 4-6 as 'good' and <4 as 'poor'. Adverse effects were also noted down.
The objective assessment showed that Dermaroller treatment resulted in an excellent response in 72% of the patients treated (26 of 36). Especially scars of grade 2 and 3 showed mainly excellent response while severe scars showed a somewhat lower response. Of the scar types mainly 'rolling' and 'boxcar' types showed good to excellent response. Also the patients labelled the treatment response predominantly as excellent (80%). The treatment was well tolerated by all patients. No adverse effects were observed except for a temporary erythema. Hyperpigmentation was observed in one patient. All patients were able to attend their daily duties on the same day or the day after the treatment.

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The results of the treatment of 31 Thai patients suffering from atrophic acne scars are reported by **Polnikorn (2009)**. All patients were medium to dark skin types (Fitzpatrick-scale III - V) and showed medium to severe acne scarring. The management of acne scars is generally more difficult in darker than in light skin types due to hyperpigmentation problems. For collagen induction the Dermaroller model MF8 (needle lenght 1.5 mm) was used. One to four treatments were carried out with a treatment interval of one month. Clinical evaluation was done by two independent experts comparing standard photographs using a 0-6 (6 = severe) scarring scale. Six months after the last treatment, average scar severity had declined from 4.24 to 2.33. A reduction > 50% was observed in more than two thirds of the patients. The author concludes that the Dermaroller treatment is an efficient and safe method for the treatment of atrophic acne scars in darker skin types.

On the 68th meeting of the American Academy of Dermatology, **Fabbrocini et al. (2010)** presented results of a study on 60 patients representing skin types I (white) to VI (afor -carribean) who were suffering from acne scars. The patients received three treatments with a treatment interval of 4-12 weeks. Results were scored on the basis of digital photographs. In a selected group of patients, scar depth was measured before and three month after the third treatment using Visioscan. The aesthetic improvement of all patients was assessed using the Global Aesthetic Improvement Scale, GAIS. In most patients, the treatment reduced scar severity and improved the overall appearance of the skin. Aesthetic improvements were significant. Side effects like hyper- or hypopigmentation were not observed. The authors condlude that 'skin needling is a simple and safe method to treat acne scars in all skin types from I to VI'.
In a review article on acne scarring (**Fabbrocini et al. 2010 b**) the authors draw the conclusion that "skin needling can be safely used in all skin colors and skin types; the risk of postinflammatory hyperpigmentation is lower than in other methods like dermabrasion, chemical peelings, and laser treatments."

Successful acne scar treatments with the Dermaroller® are also reported by Dr. Tony Chu (reference below). However, he gives no case numbers etc. but only states that '75% of the patients treated show good to excellent results'.

The potential of the Dermaroller for the treatment of melasma, an aquired pigmentation disorder, was studied by **Co & Abad-Casintahan** (unpublished). In a randomized blind study, ten Filipino women were treated using a split-face approach, i.e. both halves of the face were treated separately with the Dermaroller MF8 (1.5 mm needle length). After Dermaroller pre-treatment, tranexamic acid was applied on one side of the face, the other received saline solution as a placebo (which side received which treatment remained unknown to the patients). Afterwards, another round of needling was carried out. This treatment was carried out thrice with a treatment interval of 4 weeks. Results were assessed on the basis of skin pigmentation changes (melanin and erythema index), on the basis of the MASI-index, and as a final criterion a 'physician's global assessment, PGA'. The patients were also asked for their opinion regarding the success of the treatment.
Assessment of the results revealed a statistically significant reduction of the melanin and erythema index for both treatment variants (tranexamic acid / placebo) over the treatment period. The two treatment variants were statistically not significantly different from each other, meaning that the treatment with the Dermaroller alone already had a therapeutic effect. Evaluation of the MASI index as well as of the PGA showed no consistent trend. The patients themselves judged their results after 12 weeks as follows: on the side treated with tranexamic acid, 3 patients noted a slight improvement, 2 patients a clear improvement, 1 patient an almost perfect and one a perfect result, i.e. the melasma had vanished. On the placebo side, i.e. only Dermaroller treatment, one patient rated the improvement as mild, 6 patients as clear and 1 patient as almost perfect.

The improvement of pigmentation disorders (hyper- / hypopigmentation) after microneedle treatment is also described in other studies. Already **Fernandes (2002)** pointed out that 'white' scars approach the surrounding skin colour again after microneedle treatment. The reason for this is a revascularization and repigmentation of the skin, the exact causes of which are not thoroughly investigated, yet. An improvement of the skin colour was also reported following the microneedle treatment of burn scars (Cho et al., 2009, see below, Safonov, pers. communication). Moreover,

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Fernandes (2005) reports on an improvement of telangiectasia "probably because the tiny blood vessels are punctured in so many places that they can not be repaired."

A new focus for Dermaroller use is the treatment of burn scars. **Aust *et al.* (2009)** report on a study on 16 patients suffering from burn scars after 2nd degree burnings. Patients were treated with the Environ Medical Roll-CIT with 3mm long needles. Also in this study, patient satisfaction was evaluated and histological examinations carried out (compare Aust *et al.* 2008). Twelve months after treatment, patients rated the improvement as mean of 80% better than before the treatment. Histological examination demonstrated a considerable normalisation of the extracellular collagen-elastin matrix, a significant increase in collagen deposition, and thickened epidermis (*stratum granulosum* +45%). However, a complete restoration of the skin structure as in normal, healthy skin could not be achieved. Pigmentation problems that are often seen with ablative methods were not observed after collagen induction. Also the number of melanocytes was found to be normal. In summary, medical needling is seen as very promising for the improvement of burn scars.

A chapter of the current **Color Atlas of Burn Reconstructive Surgery** is also dedicated to 'Medical Needling' as a new therapeutic option for the treatment of burn scars (Rennekampff *et al.* 2010)

The management of hypertrophic burn scars is the topic of a publication by **Kim *et al.* (2009)**. The authors report on a study in which 51 patients were treated with the Dermastamp® The results were evaluated using the Vancouver Scar Scale, VSS, and in one group also histological examinations. The clinical improvement of scar severity was 1-6 points on the VSS. Scar depth was reduced by 0.8 to 3.6 mm. Histological examination showed an increase of collagen and a more normal orientation of the collagen fibers. A disadvantage of this study is the extremely short treatment interval of 1-2 weeks. An interval of 4-6 weeks is recommended so that the newly formed collagen can 'mature'.

Another publication regarding burn scar treatment is also from Korea (**Cho *et al.*, 2009)**. The authors report on a 50 year old woman who was treated with the Dermaroller in combination with a laser. The treatment was rated as successful. Since it is only a case report, however, this study is listed here only for completeness.

Another field of application for the Dermaroller is the treatment of stretch marks (striae distensae). Literature findings for this field are not as numerous as for other applications, though.

The study of **Aust et al. (2008)** comprised 72 patients with scars / stretch marks (see above). Patient satisfaction was rated before and 12 month after microneedle treatment by a subgroup of 15 of these patients on a visual scale ranging from 0 (= completely dissatisfied) to 10 (= completely satisfied). Patient satisfaction in this group increased significantly from 3.0 to 7.5. The significant improvement resulting from the treatment was also confirmed by two objective measurements.

Fernandes & Signorini (2008) also recommend percutaneous collagen induction for the treatment of stretch marks. They advise to use 1-3 mm long needles, depending on the severity of the marks.

In a short communication, **Aust et al. 2010 b** report on a study on 22 female patients suffering from stretch marks who were treated once with a microneedle roller. Six months after treatment, the authors observed an improvement of the skin structure, a tightening of the skin, and a formation of new blood vessels without a change of pigmentation. Biopsies revealed an increase of collagen I and elastin.

Significant improvements in 5 out of 6 stretch mark patients were also achieved by **Rezai (2009)** after multiple treatments with the Dermaroller MF4 (1.5 mm needle length).

The successful treatment of wrinkles is documented mainly through the studies of Fernandes (2005), Aust et al. (2008) and Fernandes & Signorini (2008).

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Summary 'Treatment of skin alterations by neocollagenesis':

All publications evaluated demonstrate the efficiency of the Dermaroller for the treatment of skin alterations by means of neocollagenesis. Scars, esp. acne and burn scars, respond well to Dermaroller treatment. The clinical improvement of scars (reduction of scar depth, normalization of skin structure) resulting from the treatment was confirmed by objective measures. Histological findings prove an increase in the amount of collagen as well as a re-orientation of collagen fibers that is similar to that in normal skin. A thickening of the epidermis was also observed. The *stratum corneum* is normal after the treatment.

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Table 1: Short description of the studies evaluated for application ‚Transdermal Delivery' (chronological order)

Study	Authors	Published	Quality Journal	DR® used?	Needle length (mm)	Evaluation system	Stat. Ana.	DR effective ?	Short conclusion
Verma & Fahr 2001a	+	online	./.	yes**	0.13 / 1.5	in vitro, human skin	./.	yes	DR ist suitable for transdermal delivery
Verma & Fahr 2001b	+	online	./.	yes*	0.13 / 1.5	in vitro, human skin	ok	yes	High reproducibility of the results +
Kolli *et al.* 2007a	+	Congress	./.	yes*	0.5	in vitro, rat	./.	yes	DR is alternative means of microporation
Kolli *et al.* 2007b	+	Congress	./.	yes*	0.5	in vitro, rat	./.	yes	Occluded, micropores stay open 72 hrs
Li *et al.* 2009	+	Journal	+	yes*	0.7	in vitro/in vivo, rat	+	yes	DR suitable for delivery of macromolecules
Bal *et al.* 2010 a	+	Journal	+	yes*	0.3 (DS)	in vivo, human	+	yes	Pores are closed after 10-15 min. *in vivo*
Bal *et al.* 2010 b	+	Journal	+	yes*	0.3 (DS)	in vivo, human	+	yes	DS suitable for transdermal vaccination
Badran *et al.* 2009	+	Journal	+	yes*	.15/0.5/1.5	in vitro, human skin	./.	yes	DR promising for transdermal delivery
Yoon *et al.* 2008	+	Journal	+	yes	0.5	ex vivo, pig	ok	yes	DR suitable for transd. delivery of glycerol
Wermeling *et al.* 2008	+	Journal	+	no	0.6	in vivo, human	+	yes	Suitable for transd. delivery of naltrexon
Zhou *et al.* 2010	+	Journal	+	no	0.2/0.5/1.0	in vivo, rat	-	yes	Suitable for transd. delivery of insuline
Donnelly *et al.* 2008	+	Journal	+	no	0.3	in vitro/in vivo, mice	+	yes	MN reduce ALA-dose & application time
Clementoni *et al.* 2010	+	Journal	+	no	0.3	in vivo, human	+	yes	Microneedling increases efficiency of PDT

./. = non applicable; ** carried out on behalf & at the expense of Dermaroller SARL/ * Dermarollers provided free of charge; Stat. Ana. = statistical analysis

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Table 2: Short description of the studies evaluated for application ‚Skin alteration treatment by neocollagenesis' (chronological order)

Publication	Authors	Published	Quality Journal	Goal / treated	DR® used?	Needle length	Stat./ Study	Effect confirmed	Short summary
Schwarz& Laaff *2011*	+	(Journal)[§]	./.	Scars	yes	1.5 mm	blind	yes	Increase of amount of elastic fibers and skin thickness
Fernandes 2002	+	Journal	+/-	PCI[$]	no	?	./.	(yes)	Microneedling offers soft alternative to laser treatment
Fernandes 2005	+	Journal	+/-	PCI[$]	no	?	./.	yes	Non ablative, short healing phase, skin thickness increases
Fernandes & Signorini 2008	+	Journal	+	PCI[$]	no	1-3mm	./.	yes	Method suitable for the treatment of scars resulting e.g. from acne or burn injuries, wrinkles, lax skin, striae
Aust *et al.* 2008	+	Journal	+	Scars, wrinkles	no	1-3 mm	+	yes	Easy and safe method for the improvement of wrinkles and scars
Fabbrocini *et al.* 2009	+	Journal	+	Acne scars	yes	1.5 mm	+	yes	Dermaroller treatment clearly improves acne scars ; Method is advantageous over other treatment options
Majid 2009	+	Journal	+	Atrophic scars	(yes)	1.5 mm	+	yes	Scars of grade 2 and 3 are reduced significantly; method is simple, safe and free of adverse effects
Polnikorn 2009	+	Journal	-	Acne scars	yes	1.5 mm	+	yes	Efficient and safe method for the treatment of atrophic acne scars in darker skin types
Fabbrocini et al. 2010	+	Poster	./.	Acne scars	yes	1.5 mm	+	yes	Treatment improves appearance of the skin without risk of hypo- / hyperpigmentataion in all skin types (I-VI)
Co & Abad-Casintahan	+	./.	./.	melasma	yes	1.5 mm	+	yes	Dermaroller treatment clearly reduces hyperpigmentation
Aust *et al.* 2009, Aust *et al.* 2010a	+	Journal	+	Burn scars	no	3 mm	+	yes	Method is very efficient to treat burn scars
Kim *et al.* 2009	+	Journal	+	Burn scars	yes (DS)	2.1 mm	+	yes	Dermastamp very well suited to treat hypertrophic scars; Scar depth is reduced
Aust et al. 2010b	+	Journal	+	Striae distensae	no	?	?	yes	PCI ist a promising technique for the treatment of stretch marks

[$]Accepted for publication; [$] Percutaneous Collagen Induction ; Stat. = Statistical analysis

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