Herpes labialis, or cold sores, is one of the most common and bothersome recurrent infectious disorders in the US. Up to 80% of the general population has been infected with the Herpes Simplex Virus (HSV-1) that causes this disease. Despite the availability of a variety of topical agents to combat oral herpes, none is particularly effective at controlling the infection and shortening the duration and severity of outbreaks. The reason: available topical anti-viral agents cannot penetrate the skin in sufficient doses in a timely enough manner to be effective.

Similarly, medications shown to be active against other types of dermal lesions, such as those associated with eczema or psoriasis – two common skin ailments – are less than optimally effective when applied as topical formulations to the skin surface. The reason is the same – the drug has difficulty breaching the barrier created by the stratum corneum, the outer layer of the skin. The same barrier that serves as the immune system’s natural first line of defence – protecting the underlying dermal layers, organs and blood supply – also prevents topically applied drugs from effectively reaching their target.

Iontophoresis, a technique that increases the movement of drugs through the stratum corneum, expediting the transport of charged drugs to the dermis, is a safe and effective transdermal strategy for overcoming the challenges inherent in topical drug therapy for dermal diseases. This broadly applicable technology offers a non-invasive, patient-friendly means of delivering an effective dose of drug directly to the site of a dermal lesion, thereby sparing other critical organs from exposure to high levels of systemic medications. Instead, a smaller quantity of drug can be applied to rapidly achieve therapeutic doses directly at the site of the dermal pathology.

Transport Pharmaceuticals, Inc is initiating a Phase III clinical trial of its iontophoretic drug delivery system in the lead indication of herpes labialis. The technology merges a sophisticated delivery device with an existing drug to create a combination product that can be adapted for use in a wide range of dermal indications. A key advantage of this product platform is the ability to deliver a powerful therapeutic punch in a timely manner, for example, to disrupt an infectious process early in the natural course of disease, or to interrupt a cascade of events that may trigger or worsen an inflammatory, malignant, or other type of pathological process.

THE PROMISE AND THE PRESENT

The promise of topical transdermal drug delivery technology lies in the ability to deliver a safe and effective dose of a therapeutic compound directly to the problem site. The key advantages are two-fold: a potent drug dose rapidly and painlessly makes a concentrated assault on the affected dermal tissue, and the patient avoids the potential toxicity and adverse effects associated with systemic exposure to a drug intended to act only on the skin. An equally significant benefit of transdermal drug delivery is the ability to revive the commercial potential of a topical agent known to be effective in vitro against the disease target, but unable to bring about an adequate clinical response because an insufficient amount of active drug is able to reach the affected tissue.
Although the promise is evident and, historically, transdermal drug delivery technologies – such as adhesive patches and injectable drug delivery systems – have evolved to enable efficient delivery of certain drug classes, there remains a large unmet medical need for safe and effective therapies for a broad spectrum of dermatological conditions. Prime examples include oral herpes, onychomycosis (a fungal infection of the skin surrounding the toenails or fingernails that affects more than 37 million people in the US alone), and psoriasis (a life-long skin disease that afflicts more than 4.5 million people in the US). These disorders and others represent a significant commercial opportunity. For example, the estimated current market for available oral herpes treatments – most of which are only modestly effective – exceeds $400 million.

Commercially available transdermal drug delivery systems are primarily represented by the adhesive patch, which allows for steady-state systemic drug delivery to treat conditions such as nicotine addiction, motion sickness and hypertension, and to deliver a variety of sex hormones for both contraceptive and therapeutic purposes. Innovative transdermal technologies take advantage of electrical currents, sound waves and thermal energy to drive drug molecules through the outer skin layer and alter the permeability of the dermal environment, creating transient portals for drug passage. Other mechanisms of transdermal drug delivery in development rely on needleless microinjection systems that create small holes in the skin surface and propel a drug through those openings.

Complicating the development of some of these experimental delivery strategies is the need for modified drug formulations that can be incorporated into a patch or propelled in a micro-injected spray. Other challenges include the delivery of drug to parts of the body that are not amenable to the use of a patch or injectable – such as highly sensitive or exposed areas of the skin. Finally, there is the burden of delivering a large enough dose of drug to the target site to bring about a satisfactory clinical response. Ideally, treatment of an acute infection or an outbreak of a chronic, recurrent condition should require only a single transdermal application of a therapeutic drug dose. The ability for patients to self-administer the drug would further enhance the convenience, cost efficiency and widespread applicability of a transdermal delivery device.

**IMPROVING DRUG PENETRATION**

The theory behind electrokinetic drug delivery is that application of a low voltage electrical current to the skin enhances drug transport via a dual mechanism of action. An electromotive force induces active transport of charged drug molecules as ions move through the electric field and are driven or repelled across the stratum corneum and into the dermis (iontophoresis). Passive transport of drug that rides the bulk flow of water brought about by ion movement within the electrical field contributes to the enhanced permeability of the skin to ionic agents (electroosmosis).

In electrokinetic drug delivery, two electrodes are placed in contact with a patient’s skin, creating a closed circuit through which an electrical charge flows, driving or repelling oppositely charged ions. Positively charged ions are driven through the stratum corneum at the anode, whereas negatively charged ions are absorbed into the skin at the cathode. The charge of the drug being delivered will determine
the polarity setting of the electrokinetic device to ensure maximal permeation.

Transport Pharmaceuticals’ iontophoretic system is based on an innovative drug delivery device that generates a low-voltage electrical charge to increase skin permeability at the site of targeted medication delivery. Comprising a re-usable control unit and a disposable, single-use medicated cartridge with fingertip sub-assembly, the device is easy to use and allows patients to self-administer a single dose of topical drug for a variety of indications. The control unit – which contains small, wireless, microprocessor-controlled electrodes – couples to a disposable medicated cartridge pre-filled with a unit dose of drug. Patients first wash the affected area of the face with soap and water, and snap the fingertip containing the medication onto the control unit. They then remove the foil cover from the fingertip exposing the acyclovir cream, and gently press the cream against the centre of the cold sore, holding it there for 10 minutes. A flashing indicator light on the control unit signals the end of the treatment period.

**TARGETING UNMET MEDICAL NEED**

The company will initially apply its iontophoretic technology to three critical disease areas: herpes labialis, onychomycosis and psoriasis. The lead indication, herpes labialis – also called orofacial herpes – is a viral infection that causes recurrent outbreaks of cold sores in about 20-40% of infected individuals. Outbreaks occur with no predictable pattern; they cause painful, visible lesions on and around the lips and mouth area.

Early treatment with an effective antiviral medication is crucial for reducing the healing time of herpes lesions. Typically, a cold sore outbreak will last seven to 14 days, and begins with a tingling sensation or pain at the affected site. Cold sores tend to recur in the same locations, and patients can often detect an oncoming sore before it actually appears. It is at this earliest point in the life-cycle of the lesion that treatment can have its greatest impact on shortening the duration of the outbreak.

Currently available topical antiviral medications are not as effective as they could be because adequate concentrations of drug are not able to penetrate the skin and reach the source of the infection in a timely manner. Acyclovir cream is a leading antiviral drug prescribed to combat outbreaks of herpes labialis. Transport Pharmaceuticals has developed an iontophoretic device that delivers a therapeutic dose of acyclovir to the affected site.

A Phase IIb, double-blind, placebo-controlled clinical study involving 200 patients provided proof-of-concept, demonstrating that the device/acyclovir combination reduced healing time in herpes labialis by approximately 50 hours and also lessened the severity of the outbreak. Each patient in the treatment group received a single, 10-minute application. This compared with the results of previous studies in which topical administration of an acyclovir cream five times a day for four days yielded a 12 to 14 hour reduction in mean healing time.

The iontophoretic system may deliver as much as 40 times more acyclovir directly to the affected skin area than currently available topical formulations of the drug. An added advantage is that the patients’ fingers need not come in direct contact with the cold sore during drug
application. By not touching the lips, the patient is less likely to spread the virus to other sites. Earlier this year, the company signed a collaborative licensing agreement with GlaxoSmithKline (GSK) for the iontophoretic device/acyclovir 5% cream system. The agreement granted GSK exclusive rights to market and sell the product over-the-counter in Europe, Australia, Latin America and South Africa. Transport Pharmaceuticals has completed the successful design and manufacture of a prototype device, readying the product for large-scale testing and marketing.

Two Phase III multicentre trials will evaluate the safety and efficacy of a single electrokinetic application of acyclovir 5% cream compared with placebo or conventional therapy for episodic treatment of recurrent herpes labialis. Each treatment arm will include about 200 subjects. As acyclovir is also an effective treatment for recurrent genital herpes, the company plans to launch a clinical programme aimed at demonstrating the efficacy of the iontophoretic delivery of acyclovir in genital herpes. Successful transdermal treatment could supplement the continuous oral acyclovir regimen required for treating this form of herpes, as the genital area is too sensitive for topical application of acyclovir cream, which causes skin irritation with repeated application.

**ADDITIONAL DERMAL INDICATIONS**

Psoriasis, an immune-mediated genetic disease that affects the skin and joints typically causes life-long outbreaks in which overgrowth of skin cells causes patches of thick, rough skin to accumulate on the surface of affected regions of the body. Once again, effective treatment is challenged by the inability of anti-psoriatic drugs to penetrate the outer skin layers and exert their effects in the dermal layers where the aberrant skin cells originate.

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**A MODEL OF VIRTUAL DRUG DEVELOPMENT**

Paralleling the innovative concept behind combination electrokinetic-based drug delivery is the business model of Transport Pharmaceuticals – a virtual drug development firm – devised to maximise corporate value before building a bricks-and-mortar corporation. Harnessing the innovative spirit that thrives in the biotechnology industry, the company developed a broadly applicable platform technology. All work is done by contract vendors under the management of neXus therapeutics, inc, a biopharmaceutical management firm.

Backed by private investors, Transport has built an iontophoretic system that delivers an existing drug, demonstrated clinical proof-of-principle, and completed Phase II clinical testing. The company has also amassed sufficient clinical safety and efficacy data to attract the interest and collaborative and financial backing of a major pharmaceutical partner, which will now support it as it guides the product through large-scale trials and regulatory review and approval, and applies its longstanding expertise in marketing and product support to move toward commercial launch.

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