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Retrometabolic Drug Delivery in Dermatology

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A fundamental aspect of dermatologic diagnosis and treatment is our visibly ready access to the site of skin disease. Just as we can often render a diagnosis based on visual assessment of a lesion or rash, so can we often prescribe topical therapies that can be applied directly to the site of involvement. The complex and efficient stratum corneum generally facilitates localized treatment. It is usually possible to deliver therapeutically effective doses of active drugs in topical formulations such as: ointments, creams, lotions, gels, foams, and sprays that will act locally in the skin, being metabolized at the site of the disease and posing the potential for little or no resultant systemic exposure. Of course, there are no absolutes in medicine, and the inverse is also true: it is possible for some drugs to bypass the epidermal barrier to provide an action systemically. Unfortunately, percutaneous absorption of drugs can be associated with undesirable systemic effects. The ability of a topically applied drug to work locally or be absorbed percutaneously may be a function of multiple factors, including the total dose applied, the chemical entity itself, and/or the chemical delivery system.[1] Interestingly, chemical delivery systems can be designed to encourage local metabolism of active drug while minimizing or preventing systemic exposure.

Just as the chemical delivery system can be modified for targeted drug delivery, in some cases the chemical structure of the drug itself can be modified. Retrometabolic drugs are designed to be quickly metabolized to inactive moieties, or they are designed with sequential metabolic activity that leads to rapid metabolism after the drug has performed its desired local pharmacological activity in the target organ.[2] Also known as soft drugs, retrometabolic drugs have been used in other fields of medicine for some time, and they are finally poised to make an entrance into the field of dermatology. This represents an exciting new direction in the development of topically applied therapies for dermatologic diseases.

A leading investigational soft-drug candidate for dermatologic application is sofpironium bromide, a derivative (analog) of glycopyrronium, that is in development for the topical management of primary axillary hyperhidrosis (PAH). The chemically modified structure of sofpironium bromide facilitates rapid hydrolytic deactivation upon application to the skin. This minimizes the potential for clinically significant systemic side effects associated with traditional anticholinergic drugs. As described in the pages ahead, sofpironium bromide has demonstrated efficacy and safety for treatment of PAH in Phase II and Phase III clinical trials in the United States and Japan.[3,4] For the nearly 5% of adults estimated to suffer from PAH, an effective treatment with limited systemic risks is highly desirable. A more recent development in the treatment space for PAH is glycopyrronium cloth, which is designed for targeted, local deposition of active drug. While this delivery system has benefited many patients, treatment is nonetheless associated with risk for systemic side effects.[3,4]

Results of Phase II and III trials demonstrate the efficacy of topically applied sofpironium bromide at various concentrations, as reviewed in the following pages of this publication. Of particular significance, treatment was well-tolerated. Observed side effects of treatment were deemed to be mild-to-moderate in severity and many were local application site reactions.[3]

In addition to sofpironium bromide, other retrometabolic designed molecules under investigation include soft JAK inhibitors, soft PDE-4 inhibitors, and soft estrogens among others.

The science of retrometabolic drug development is well-established, and soft drugs have already been adopted into other fields of medicine. The potential to apply soft-drug development to the dermatology space holds the promise to permit the

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use of many potentially effective drugs whose use has, until now, been limited by risks of excessive systemic exposure and associated unwanted adverse effects.

This is truly an advancement in the field of drug designing and targeted delivery that is so close to my heart.

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DISCLOSURE

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