Rock Creek Pharmaceuticals
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Novel anti-inflammatory compounds for psoriasis and beyond

Anatabine citrate, a cholinergic small molecule in development at Rock Creek Pharmaceuticals, offers a distinct alternative to existing nonsteroidal anti-inflammatory drugs (NSAIDs), steroids and biologics for the treatment of chronic and acute inflammatory diseases. The company is looking to partner for a phase 2 trial in psoriasis.

Rock Creek Pharmaceuticals is an emerging drug-development company that is focused on the discovery, development and commercialization of innovative therapies for chronic and acute inflammatory diseases.

Existing NSAIDs, steroids and biologics used for treating inflammatory diseases have been associated with high rates of adverse drug reactions, so there is a pressing need for anti-inflammatory therapies with positive safety profiles.

Rock Creek is developing anatabine, a natural alkaloid that was originally identified in various plants and vegetables, including tomato, potato, eggplant and tobacco. Anatabine modulates inflammatory function by a mechanism involving cholinergic receptors and their downstream effectors. Data from a recent phase 1a trial with healthy volunteers show that anatabine has very favorable safety and tolerability profiles.

As proof of concept of the compound's therapeutic utility, the company is focusing on mild to moderate psoriasis. This year, the compound will be entering a phase 1b/2a trial for this indication, and Rock Creek will be looking for co-development partners to launch and complete a phase 2 trial in 2017.

Anatabine mechanism of action

Anatabine, an alkaloid with structural similarity to nicotine, is a cholinergic agonist that binds to cholinergic receptors, including key mediators of the cholinergic anti-inflammatory pathway, such as the α7 nicotinic receptor. *In vitro* mechanism of action (MOA) studies have shown that anatabine triggers downstream inhibition of two signaling pathways that are central to the inflammatory response: the Janus kinase (JAK)–signal transducer and activator of transcription 3 (STAT3) pathway, and the glycogen synthase kinase 3β (GSK3B)–inhibitor of nuclear factor-κB kinase (IKK)–nuclear factor-κB (NF-κB) axis.

Inhibition of these two pathways prevents activation of the transcriptional regulators STAT3 and NF-κB, respectively, which results in suppression of cytokine release triggered by inflammatory stimuli (**Fig. 1**).

Anatabine efficiently crosses the blood–brain barrier, exhibits an excellent bioavailability profile and has the potential to be applied locally as well as systemically, owing to the wide distribution of its target receptors. These characteristics make anatabine and its engineered derivatives strong therapeutic candidates for treating a range of conditions, including psoriasis, atopic dermatitis, osteoarthritis, ulcerative colitis, thyroiditis, Alzheimer's disease and multiple sclerosis.

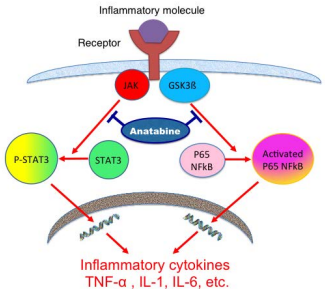

Figure 1: Anatabine, which is being developed by Rock Creek, modulates inflammatory function by a mechanism involving cholinergic receptors and their downstream effectors. Anatabine efficiently crosses the blood–brain barrier, exhibits an excellent bioavailability profile and has the potential to be applied locally as well as systemically owing to the wide distribution of its target receptors.

Preclinical *in vitro* and *in vivo* studies have already shown a strong anti-inflammatory effect of anatabine in models of multiple sclerosis, Alzheimer's disease and autoimmune thyroiditis.

According to Rock Creek's CEO, Michael Mullan, "Much of the scientific excitement about this drug derives from the potentially far-reaching clinical relevance of its mechanism of action, implicated as it is in a wide range of inflammatory and immunological conditions."

Targeting psoriasis

Psoriasis is a chronic inflammatory disease of the skin that affects 2–3% of the general population in developed countries. The skin lesions associated with the condition are a result of epidermal hyperplasia, which is thought to be caused by dysregulated interplay between epidermal keratinocytes and immune cells. NF-κB and STAT3 have a central role in the cross-talk between these two types of cell, making the two transcriptional factors attractive targets for therapeutic intervention in psoriasis and possibly other dermatological conditions.

Anatabine's MOA, which suppresses both NF-κB and STAT3 activation, indicates that the compound is an ideal candidate for testing in psoriasis. The nature and location of the psoriatic lesions allow for visual evaluation of disease progression, providing an avenue for highly simplified protocols. Additionally, surface biopsies can be taken to determine whether STAT3 and NF-κB expression occurs after treatment.

Partnering with Rock Creek

Rock Creek has developed a lead compound, anatabine citrate, and a number of engineered derivatives that have been shown to adequately and safely modulate the cholinergic anti-inflammatory response in preclinical disease models of inflammation. These compounds are protected by a robust and growing patent portfolio that includes issued patents for pharmaceutical composition of matter and for the large-scale commercial synthesis of anatabine, as well as 20 US and foreign pending patents for the use of anatabine and salts thereof, its isomers and its derivatives for inflammatory conditions.

With plans for proof-of-concept studies for psoriasis now under way, the company is looking to identify appropriate partners for a comprehensive phase 2 study. Potential partners include specialist dermatological companies that are focused on treatments that are distinct from steroids, NSAIDs and biologics, as well as mid-size pharma companies that are looking to expand into or complement an existing dermatology program. In addition to mild to moderate psoriasis, anatabine could have therapeutic utility in atopic dermatitis and acne vulgaris, opening the possibility of packaging all three indications into one licensing agreement.

Finally, Rock Creek would also be interested in collaborating on other potential target indications if the right partner were identified. "Finding new ways to fight inflammation, as it applies to dermatological conditions, and subsequently finding new ways to treat other disorders implicating an overexpression of NF-κB and STAT3 has been a focus of the medical and pharmaceutical community for a number of years. Given that our program provides a potential alternative to current anti-inflammatory treatment paradigms, we believe there will be substantial interest in partnering with our company," said Theodore Jenkins, vice president of corporate strategy and development at Rock Creek.

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