

Protein kinase Inhibitors for the Treatment of Inflammatory and Autoimmune Diseases

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Protein kinases form an integral part of the enzyme machinery of all cells and play an important role in a large number of cell functions and processes from cell signaling, metabolism and DNA damage response to cell adhesion and proliferation, these enzymes regulate numerous key molecules and constitute one of the largest and most diverse families of enzymes known. While the importance of these molecules has been known for a while now, their potential as therapeutic targets has only recently begun to be explored.

In recent years a number of inhibitors that inhibit one or several functions of protein kinases have been developed. Their most successful application has been in the field of hematologic cancers. Imatinib (Gleevec), a tyrosine kinase inhibitor, is now licensed to treat a number of malignancies, including acute lymphoblastic leukemia, chronic myeloid leukemia, gastrointestinal stromal tumors

and myelodysplastic disorders [1]. This success has been followed by an explosion of studies on solid tumors as well including breast, lung and colorectal tumors [2].

Most recently, the application of protein kinase inhibitors to Sciatic Inflammatory Neuritis (SIN) inflammatory and autoimmune disorders have started to be explored. Currently only a few therapeutic modalities are available for these disorders; most of which entirely non-specific for the disease process in target. Protein kinase inhibitors promise to offer a much more selective approach while, at the same time, minimizing potential side effects.

For example, imatinib, has been tested in various models of autoimmune disease with promising results. Experiments in mice have shown that imatinib attenuates the disease process in autoimmune arthritis, autoimmune diabetes and multiple sclerosis [3-5]. Another example are spleen tyrosine kinase (Syk) inhibitors. Syk contributes significantly to the abnormal T cell function found in autoimmunity [6] and a number of Syk inhibitors are now being tested in both pre-

clinical and clinical trials with varying degrees of success [7-9].

Another protein kinase that has been of great interest recently is Bruton's tyrosine kinase (Btk). Btk is a key component of both B cell receptor and Fc-gamma receptor signaling processes and Btk inhibitors are currently being tested in mouse-models of arthritis [10,11]. Also, inhibitors of janus kinases (JAKs), which mediate cytokine signaling, are found to be efficacious in treatment-resistant patients with rheumatoid arthritis [12]. Studies in systemic lupus erythematosus, psoriasis, inflammatory bowel disease and transplantation are also currently under way [13,14]. Finally, IKK-2 inhibitors (a serine-threonine kinase that activates the transcription factor NF- κ B) were found to be of benefit in preclinical trials of allergy, inflammation and edema [15].

Although just a few examples, these molecules clearly illustrate the vast potential this novel group of compounds has. Such highly targeted therapeutic approaches have dominated the pharmaceutical landscape recently and are expected to be able to transform the field of autoimmune disease therapeutics as well.

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