

T Cell-Targeted Drugs for Treatment of Rheumatoid Arthritis

Efficient and specific inhibition of T cell activation and propagation....

Summary

Indication:

Rheumatoid Arthritis

Development Stage:

Lead identification & optimization

Intellectual Property:

Patent issued and applied in several countries including US

Partnering Interests:

Collaborative R&D and Licensing out

Interested in this technology?

Ask for more information.

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Introduction

For decades, considerable efforts have been made to develop immunosuppressive drugs for the treatment of undesired immune reactions, such as autoimmune diseases. Conventional immunosuppressive drugs, especially anti-metabolite drugs, are associated with severe side effects presumably due to lack of target specificity and there is now increasing demand for the anti-rheumatic agents which specifically attack discrete subpopulations of immune cells.

Lck, a Src family protein tyrosine kinase mostly expressed in T cells and NK cells, plays a principal role in the initiation as well as the propagation of T cell antigen receptor (TCR)-induced signaling, leading to IL-2 expression and T cell proliferation. Therefore, blockage of Lck-mediated signal transduction would give efficient as well as specific inhibition of T cell activation.

RosA also induced apoptosis of human peripheral blood mononuclear cells in an Lck-dependent manner, where RosA kills Lck-expressing T cells and NK cells but not Lck-negative cells such as B cells and monocytes³. Most importantly, RosA-induced apoptosis is limited to actively proliferating T cells and NK cells but not resting cells³. This indicates that activated, pathogenic T cells could be eliminated without disruption of the normal T cell repertoire.

Anti-rheumatic Effects

RosA and its derivatives show strong anti-rheumatic activity in a collagen-induced arthritis (CIA) model⁴. CIA was evaluated by arthritis index based on severity of joint swelling and by histopathologic index based on intensity of immune reaction as well as integrity of bone structure in the joint area.

RosA Derivatives

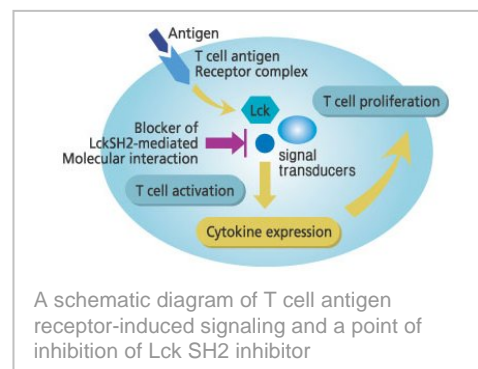
Important functional domains of RosA for anti-T cell activity have been determined. Based on the SAR work, RosA derivatives were generated and they are now under further investigation.

Potential Benefits

- Dual inhibition mechanism
- Early inhibition of T cell activation
- Apoptosis specific to T and NK cells
- Apoptosis specific to actively proliferating pathogenic T-cells, but not to resting normal cells
- No or minimal side effects expected
- Unique ELISA system to screen Lck SH2-mediated molecular interaction

Selected Publications

1. Eur. J. Immunol. 2003, 33: 870-9
2. Blood. 2003, 101(9): 3534-42
3. J. Immunol. 2004, 172(1): 79-87
4. J. Rheumatol. 2003, 30(6): 1203-7



Action Mechanisms

We have focused on the development of T cell-targeted drugs by screening natural products that inhibit Lck SH2-mediated molecular interactions. Screening of thousands of substances identified rosmarinic acid (RosA) from medicinal plant, *Prunella vulgaris*, to have strong T cell inhibitory activities in various *in vitro* assays representing T cell activation^{1, 2}.