

RDP58 (delmitide) Partnering Overview

August 2009

Executive Summary

- Rationally designed decapeptide with anti-inflammatory activity
- Proof of concept established in Inflammatory Bowel Disease
 - Potential use in a wide range of other indications
- Clinical experience in ~400 patients and volunteers
- Clear development and regulatory pathway
- Strong IP position
- Material available for transfer
 - 3.5 Kg of RDP58 GMP drug substance
 - 47.6 Kg intermediate (GMP)

A Rationally Designed Peptide

- **Derived from heavy chain of HLA class 1 molecules**
 - HLA B2702 potent immunomodulator
 - Activity based, statistical modeling through *in silico* screening
 - Peptide from amino acids 75-84 (Allotrap 1258)
 - 100x increased activity
- **Novel peptide synthesised**
 - More potent inhibition of T-cell differentiation & cytotoxicity
 - Prolonged murine heart allograft survival

Grassy et al Nat Biotechnol 1998;16:748

Iyer S, Lahana R, Buelow R Curr Pharm Des 2002; 8:2217-29

H₂N-r-nle-nle-nle-r-nle-nle-nle-g-y-CONH₂

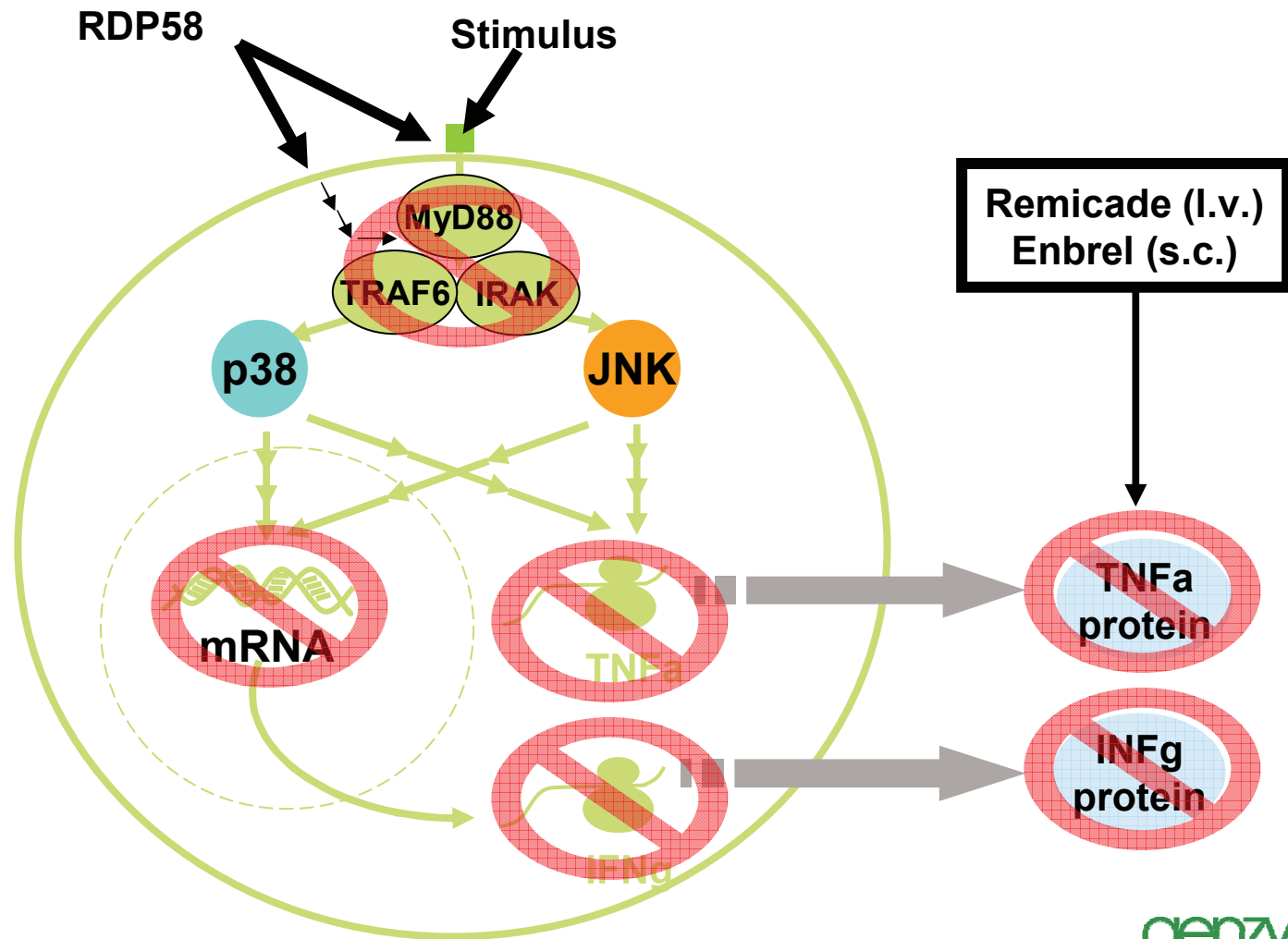
- 10 D-amino acids
 - Stable
 - Highly protease resistant
- Activity of L- and D-isomers independent of presentation by MHC
 - No binding to T cell receptors
 - No direct interaction with NK cell receptors
 - No binding to Hsc/Hsp70
- Not systemically bioavailable

Willis et al *Nat Med* 1996;2:87

Mechanism of Action

- **Overview**
 - Cytokine mRNA levels
 - Signal transduction pathways
 - Transcription factors
 - Internalisation
- **RDP58 targets TRAF6/IRAK4/MyD88 complex**
 - Inhibits phosphorylation of SAPKs (p38 & JNK)
 - Inhibits AP1 and NF κ B activation

RDP58 blocks TRAFYK



Inhibition of phosphorylation and activation of p38MAPK and JNK 1,2

- Northern blots
 - No effect of RDP58 on cellular TNF α mRNA
 - Although TNF α synthesis completely inhibited
 - Similar in cell extracts and supernatant
 - RDP58 acts at translational level
- Regulation of TNF α mRNA translation modulated by stress-activated protein kinases (p38/JNK)

In vitro activity

- RDP58 inhibits the production of
 - $\text{TNF}\alpha$, $\text{IFN}\gamma$, IL-12, and IL-2
 - in different cell types
 - and mucosal biopsies from Crohn's disease
- No effect on
 - IL-1b, IL-4, IL-6, IL-8, IL-10
- RDP58 inhibits the response to various stimuli
 - LPS, PMA/PHA, dsRNA, $\text{TNF}\alpha$, IL-1b, IL-18
- Upregulates heme oxygenase (HO-1) activity

Intracellular Target

- **Pathway 'walk through'**
 - Stratagene's Pathdetect system for cytokine regulation, using active mutants of proteins for each step of pathway distal to MAPKK,
 - No effect of RDP58
 - Therefore target of RDP58 upstream of MAPKK
 - Most upstream level of complex formation on receptor activation is MyD88-IRAK-TRAF6
- **Disruption of MyD88-IRAK-TRAF6 confirmed by co-immunoprecipitation**

Human Studies Completed

- Phase I safety in normal volunteer (SangStat)
- Phase II Mild-moderate active ulcerative colitis (SangStat)
- Phase II Moderate active ulcerative colitis (P&G)
- Phase II Crohn's disease (SangStat)

RDP58 Clinical Overview

- ~400 subjects have been dosed with RDP58 in 6 clinical trials
 - Phase I safety in normal volunteers
 - 2 Phase II mild-moderate active ulcerative colitis
 - Phase II moderate active ulcerative colitis vs. Asacol 4.8
 - 2 Phase II Crohn's disease
- UC studies suggested that
 - RDP-58 200/300mg is safe and effective in the treatment of mild-moderate active UC
 - RDP-58 200mg + Asacol 2.4g has similar efficacy to Asacol 4.8g
 - Improved efficacy may be achievable if a formulation can be created that ensures that the active ingredient reaches site of action

Available for Transfer

- Multiple Kg of intermediate (GMP)
- 3.5 Kg of drug substance

RDP58 Intellectual Property

- **Allotrap patent estate**
 - Licensed exclusively from Stanford
- **RDP58 core patent claims**
 - 9+ a.a. peptides within wide range of physical-chemical values
 - Combinations with carriers, antibodies and other molecules
 - Peptides with broad immunomodulatory properties
 - Peptides capable of inhibiting inflammatory molecules
 - Peptides capable of modulating heme-containing enzymes
 - Peptides with applications in various autoimmune a/o diseases
- **Know-how**
 - Process
 - Formulation

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