A Novel MMP-Inhibiting Wound Dressing Reduces MMP activity in human chronic wounds

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Introduction: Dysregulated MMP activity leading to excessive tissue destruction is a characteristic feature of chronic wounds[1]. To address this problem, a novel MMP-inhibiting wound dressing (MI-Sorb Dressing™, Rimon Therapeutics Ltd.) was developed to promote new tissue formation through localized and selective binding and removal of active MMPs from the wound environment. The dressing contains beads of Rimon's matrix metalloproteinase (MMP) inhibiting Theramer™ (MI Theramer™) contained within a porous pouch. A Theramer™ is a *thera*peutic poly*mer* that combines bioactivity with a broad range of desirable physical properties, but does not contain any drugs.

Here we present in vitro results showing the effect of MI Theramer™ beads on sequestering active MMP, but not pro-MMP and we summarize our experience with the MI-Sorb™ dressing in a clinical study.

Methods: MI-beads were prepared by hydroxamation of crosslinked poly(methacrylic acid-co-methyl methacrylate) (65% MAA) beads, washed thoroughly and characterized by XPS. MMP-8 concentration was determined by ELISA while activity was measured by a chromogenic substrate assay (Biomol International) using catalytic domain (active) MMPs. Dressing efficacy, determined by reduction in wound exudate MMP activity, was evaluated in a 32 patient study with various chronic wound types. After 2 weeks of baseline treatment with practitioner's standard of care, patients were randomized to 4 weeks of treatment with either the MMP-inhibiting dressing or SOC. Dressings were collected weekly and exudates extracted for analysis of MMP activity and concentration. All measurements were normalized for exudate mass and protein concentration.

Results and Discussion: MI Theramers™ elicited bead mass dependent reductions in enzymatic activity for catalytic domain solutions (Figure 1). In contrast, pro-MMP solutions were unaffected by MI Theramer™ incubation. Activation of pro-MMPs resulted in increased binding to MI Theramer™, suggesting a preferential bead affinity for the activated enzyme forms. Similar experiments performed with human chronic wound fluid samples demonstrated that MI Theramer™ treatment elicited large reductions in MMP activity while the concentration (measured by ELISA) of inactive, pro-MMP fraction was unaffected.

The preferential binding of MI Theramer™ beads to active MMPs within the local wound environment is advantageous because it specifically targets one stage in the MMP regulatory cascade, namely that directly preceding matrix degradation. This has been demonstrated with preliminary clinical results that indicate MI Sorb™ treatment significantly reduces chronic wound exudate MMP activity, which correlates with improvements in wound bed quality (Figure 2).

Future prospects: Beyond chronic wound care, MMP inhibition is expected to have broad applicability in a number of inflammatory disease situations and the clinical support for the MI-Theramer™ may enable other novel medical devices.

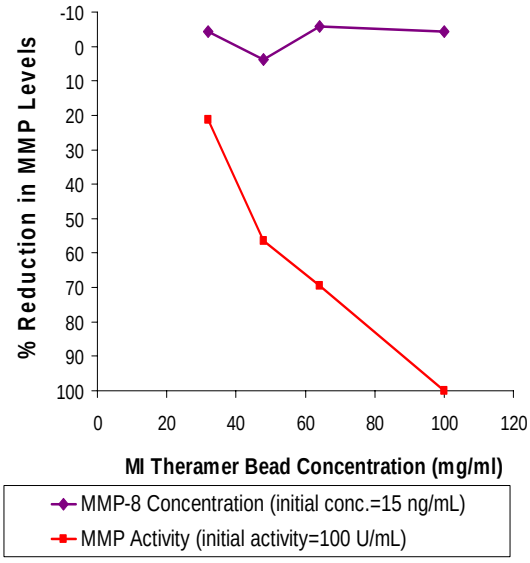
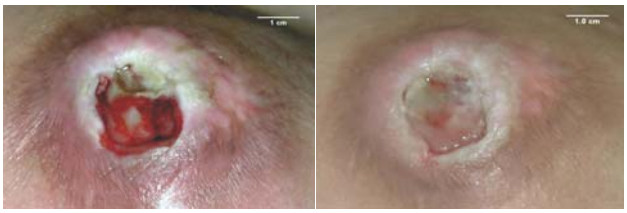


Figure 1. MMP Activity (MMP-8 catalytic domain, chromogenic substrate) but not MMP-8 concentration decreases with increasing amount of MI Theramer™ beads



Prior to treatment with MI-Sorb™ Dressing

After 4 weeks treatment

Figure 2: Wound bed before and after treatment with MI-Sorb™ in one patient

[1]Trengrove N. et al. (1999) Wound Repair Regen., 7(6), 442-52.