# A new anti-inflammatory drug that utilizes the active site of an endogenous NFkB direct inhibitory protein


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## Project Outline

**【Unmet Medical Needs】**

1. In severe or fulminant cases, there is no effective drug other than steroid anti-inflammatory drugs (SAIDs).
2. SAIDs have a strong anti-inflammatory effect by directly inhibiting NFκB, however, long-term administrations of SAIDs cause serious side-effects and susceptibility to infection. Also, the emergence of steroid-resistance makes it difficult to continue treatment.
3. An NFκB inhibitor that has the strong anti-inflammatory action as SAIDs together with the high safety is highly recommended, but has not yet been launched.

**【Superiority of this new drug seed against SAIDs】**

① The investigator found a new intrinsic NFκB inhibitor (MTI-II, Fig. 1).
② The active domain (6A) in MTI-II with cell permeable peptide (CPP; 8R) shows an strong anti-inflammatory action.
③ As 6A-8R directly inhibits the transcriptional activity of NFκB, it has as strong action as SAIDs.
④ As it has few side-effects (Table 1), it can be used for long-term therapy for fulminant cases.
⑤ As it inhibits NFκB by a different pathway from SAIDs, it will overcome the steroid-resistance.
⑥ Table 2 shows the applications of 6A-8R with confirmed therapeutic efficacy in animal models.

**【How easy this peptide drug (6A-8R) can be used.】**

A) It is easily soluble in saline/TBS/PBS/water and can be administered locally in small volumes at high concentrations (1 g/mL). No viscosity was observed even at a concentration of 1 g/mL.
B) It does not denature, inactivate, or decompose even when heated in aqueous solution (100°C, 5 minutes), or under acidic conditions (approx. pH 2) or alkaline conditions (approx. pH 11).
C) It can be administered topically because it does not denature or become inactive when mixed with an ointment base. Its effectiveness has been confirmed in an experimental atopic dermatitis model.
D) It is not antigenic. (Confirmed by the IEDB (Immune Epitope Database) Analysis Resource.)
E) It can be embedded in enteric-coated tablets, allowing localized delivery to the small intestine, and can also be used as an oral medication.
F) It can be synthesized in accordance with GMP standards.

Fig 1. Intrinsic NFκB Inhibitor, MTI-Ⅱ

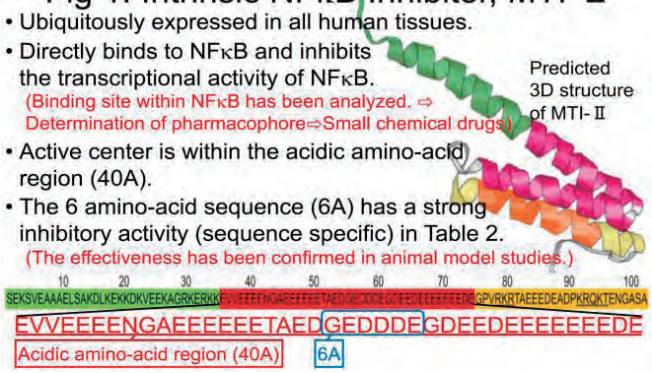


Table 1. Animal POC of MTI Anti-Inflammatory Drugs

| Animal Tests | Routes | MTI Anti-Inflammatory Drug | Dose | Control |
|---|---|---|---|---|
| Carrageenan-induced foot edema | intra-peritoneal | MTI-Ⅱ with CPP* (14.17 kDa) *cell permeable peptide | 0.4 μmol/ injection | Indomethacin 1.1 μmol/ injection |
| Croton oil-induced conjunctival inflammation | binocularly instilled | MTI-Ⅱ with CPP (14.17 kDa) | 14 nmol/ drop | Dexamethasone 13 nmol/ drop |
| | binocularly instilled | 6A with CPP 6A-8R (1928 Da) | 330 nmol/ drop | Dexamethasone 13 nmol/ drop |
| Mite antigens induced atopic dermatitis | mixed with ointment base and applied | 40A with CPP 40A-8R (5.88 kDa) | 170 nmol/ $cm^2$ (without skin atrophy) | Betamethasone (140 nmol /$cm^2$) Show severe skin atrophy. |
| Collagen-induced arthritis | intra-peritoneal (The 28 days consecutive dosage) | 40A with CPP 40A-8R (5.88 kDa) | 0.6 μmol/ injection | |

Do not show the side effects of SAIDs.
No toxicity after repeated injection.

1. No swelling, hypertrophy or atrophy is observed in the internal organs.
2. No bleeding, erosion, nor ulcer was found in the gastrointestinal tract.
3. Blood biochemical test showed no significant difference from NC group → No increase in blood glucose level.
4. White blood cell count and fraction showed not significantly different from NC group → No decrease in neutrophil migration ability.

**Table 2. Applications of MTI anti-inflammatory drug (6A-8R) with confirmed therapeutic efficacy in animal model.**
Results of joint study with the clinical departments of Osaka University School of Medicine (ophthalmology, orthopedics).

1. Therapeutic agent for Uveitis without glaucoma (safety tested).
2. Therapeutic agent for Rheumatoid arthritis that does not induce osteoporosis (no changes in osteoblasts and osteoclasts).
3. Therapeutic agent for Osteoporosis.

The connections with other clinical departments are possible.

Call for Collaborations : Arrangement of non-clinical and clinical tests of 6A-8R.

Target diseases: osteoarthritis, rheumatism, uveitis, endometriosis, preterm birth and target diseases of SAIDs.

Patents: Patent No.6830651, Patent No. US7,932,226 B2, Patent No.4874798.

Characteristics: An anti-inflammatory drug which has the same actions (NFκB inhibition) as SAIDs with few side-effects has not yet been developed. Using endogenous NFκB inhibitor, we have developed a new drug.

Market Superiority: This drug will replace SAIDs, and help many patients suffering from side effects of SAIDs.

Desired Collaboration: Arrangement of non-clinical and clinical tests for 6A-8R. Synthesis of new chemicals.