# A new anti-inflammatory drug that utilizes the active site of an endogenous NFκB 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). SAIDs have a strong anti-inflammatory effect by directly inhibiting NFκB.
2. Long-term and megadose administrations of SAIDs cause serious side-effects and susceptibility to infection, both make it difficult to continue the therapy. Also, the emergence of steroid-resistance makes it difficult to continue the therapy.
3. An NFκB inhibitory drug that has the strong anti-inflammatory action as SAIDs together with the high safety is highly recommended, but has not yet been developed.

【Superiority of this new drug seed against SAIDs】

A) The investigator found an intrinsic NFκB inhibitor (MTI-II, Fig. 1). The active domain (6A) in MTI-II with cell permeable peptide(CPP; 8R) shows an anti-inflammatory action.

B) As 6A-8R directory inhibits the transcriptional activity of NFκB, it has as strong action as SAIDs.

C) As it has few side-effects (Table 1), it can be used for long-term therapy for fulminant cases.

D) As it inhibits NFκB by a different pathway from SAIDs, it will overcome the steroid-resistance.

E) Table 2 shows the applications of 6A-8R with confirmed therapeutic efficacy in animal models.

Fig 1. Intrinsic NFκB Inhibitor, MTI-Ⅱ

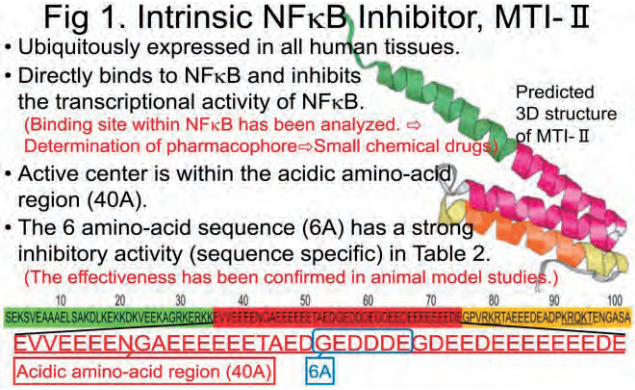


Table 1. Animal POC of MTI Anti-Inflammatory Drugs

| 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 studies.

Results of joint study with the clinical departments of Osaka University School of Medicine (obstetrics gynecology, ophthalmology, orthopedics).

1. Therapeutic agent for Endometriosis that does not affect the hormone balance and is compatible with treatment for pregnancy (confirmed suppression of proliferation of human endometriosis epithelial cell HMOsis).
2. Therapeutic agent for Premature birth (animal tested).
3. Therapeutic agent for Uveitis without glaucoma (safety tested).
4. Therapeutic agent for Rheumatoid arthritis that does not induce osteoporosis (no changes in osteoblasts and osteoclasts).

The connections with other clinical departments are possible.

NextPlans :
(1) Optimization of 6A-8R. (I have done stabilization.)
(2) Pharmacophore of 6A-8R➡Low MW chemicals
＊Evaluation systems for NFκB-binding (Kd) and for in-vitro inhibition activity (HTS) have been built.

Call for Collaborations :
➢Arrangement of non-clinical and clinical tests of 6A-8R.
➢Synthesis of new chemicals that mimic the pharmacophore of 6A peptide. (When you want chemical drugs.)

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 (NFkB inhibition)as SAIDs with few side-effects has not yet been developed. Using endogenous NFkB 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.