

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 directly 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

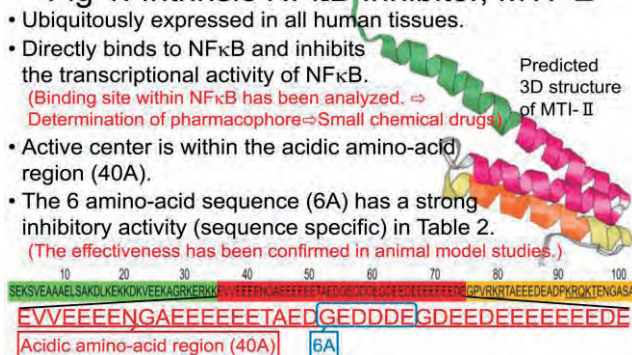


Table 1. Animal POC of MTI Anti-Inflammatory Drugs

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
Mite antigens induced atopic dermatitis	binocularly instilled	6A with CPP 6A-8R (1928 Da)	330 nmol/ drop	Dexamethasone 13 nmol/ drop
Collagen-induced arthritis	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.
	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 HMOs).
2. Therapeutic agent for **Premature birth** (animal tested).
3. Therapeutic agent for **Uveitis** without glaucoma (safety tested).
4. Therapeutic agent for **Postmenopausal osteoporosis**.
(JCI Insight. 2023;8(22):e171962.)

The connections with other clinical departments are possible.

Next Plans :

- (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 (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.