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자가면역질환 치료용 NFAT5 저해제

Korea Research Institute of Chemical Technology

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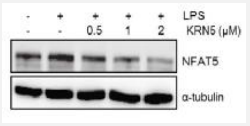
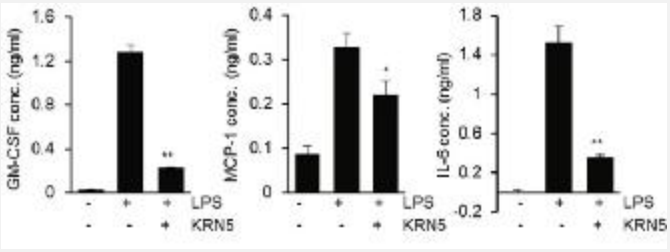
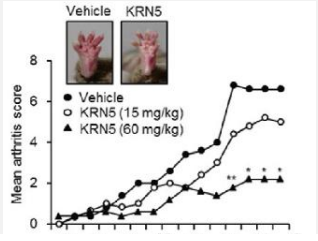
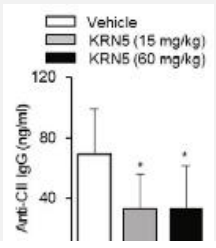
Target	NFAT5
기술개요	• 류마티스관절염 (RA) 치료제는 methotrexate를 비롯한 DAMRDs 계열 약물과 TNF를 저해하는 주사제가 주류를 형성하고 있으나 JAK을 저해하는 경구용 약물이 급성장하고 있고 환자들은 약물에 대한 내성이 생기기 때문에 새로운 기전의 약물이 필요함 • RA 치료제 시장은 2017년 239억달러이었고 2025년에는 378억달러로 성장할 것으로 예측됨 • RA 환자들에게서 과발현되어 있는 NFAT5 전사인자는 TNFα, IL1β 등의 염증성 사이토카인에 의해 활성이 더욱 증가하며, NFAT5 결핍마우스는 RA가 발현되지 않음
주요성과	• KRN5는 NFAT5를 선택적으로 저해하는 경구용 RA 치료 물질 - NFAT5 IC_{50} : 0.75 μM based on FACS reporter assay - 염증성 cytokine 억제능 우수 (*Raw263.7* 세포)

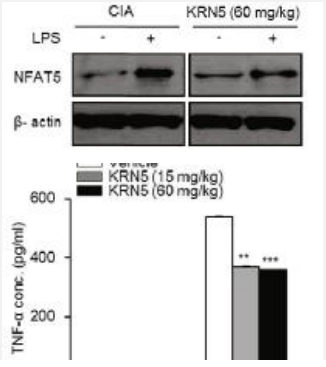




- NaCl에 의한 활성화, p38인산화와 무관 (관련 부작용 없음)
- hERG 저해 IC50 > 10 μM
- 대사안정성 68% 잔류 (투여 30분후, human microsomal fraction)
- PK : BA 15%
- 마우스 CIA 모델 시험에서 우수한 효과를 나타냄







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Target	Target Name
Mechanism of Action	• NFAT5 transcription factor inhibition
Indication - Primary	• Rheumatoid Arthritis (RA)
Indication - Expansion	• Autoimmune diseases
Route of Administration	• PO
Competitive Advantage	• Inhibition of NFAT5 which is crucial in RA pathogenesis. • Novel treatment for the patients relapsed after conventional disease-modifying anti-rheumatic drugs (DMARDs) • KRN5, a derivatives of a natural compound
Data Files	• NFAT5 inhibition IC_{50} = 0.75 μM • Suppression of GM-CSF (>70%), MCP-1 (>30%), IL-6 (>60%) at 1 μM treatment in *Raw267.3* cells • >30% IL-6 and TNF-α suppression in splenocytes isolated from CIA mice (15 and 60 mg/kg) • ED_{50} (PO, DBA/1J) = 15 ~ 60 mpk • DMPK (mouse, 5 mpk) - AUC 3,470 ng·h/mL (po) - F (%) = 15.2
IP Status	• Patent registered in Korea and US
Collaboration Model	• Licensing out
	• EBioMedicine 18 (2017) 261-273