Neural EGFL Like 1, a New Dual-Functioning Disease-Modifying Osteoarthritis Drug

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INTRODUCTION

Arthritis

- Arthritis is the leading cause of disability in adults
- The prevalence of arthritis is expected to increase sharply in the near future
- Osteoarthritis (OA) is the most common form of arthritis
- There are no currently approved disease-modifying osteoarthritis drugs (DMOADs) that can prevent, stop, or even restrain the progression of OA

Neural EGFL-like 1 (NELL-1)

- a novel pro-chondrogenic molecule
- an ECM molecule expressed in articular cartilage
- NELL-1 → NFATc1 → RUNX3 → IHH is essential for NELL-1's pro-chondrogenic bioactivities
- single nucleotide polymorphisms (SNPs) within the NELL-1 gene are associated with ankylosing spondylitis and psoriatic arthritis

METHODS

In vivo

All the experiments on live mice were performed under an institutionally approved protocol provided by the Chancellor's Animal Research Committee at UCLA.

- Spontaneous OA model
  Nell-1$^{+/6R}$ mice vs. WT counterparts
  1-month (a prepubescent stage)
  3-month (a mature young adult stage)
  18-month (a senescent stage)
- Induced OA model -- direct intra-articular injection
  Nell-1$^{+/6R}$ mice vs. WT counterparts

Group	Treatment	
Control	6 μl PBS for 7 days	6 μl PBS for 7 days
NELL-1	6 μl PBS for 7 days	2 μg NELL-1 in 6 μl PBS for 7 days
IL1β	100 ng IL1β in 6 μl PBS for 7 days	100 ng IL1β in 6 μl PBS for 7 days
IL1β + NELL-1	100 ng IL1β in 6 μl PBS for 7 days	100 ng IL1β + 2 μg NELL-1 in 6 μl PBS for 7 days

Fig 1. Schematic depicting the intra-articular injection animal model.

In vitro

- chondrogenic cell line or primary chondrocytes
- RNAi technology was used to identify the transcriptional factors that mediate the anti-arthritic effects of NELL-1

All statistical analyses were conducted with OriginPro 8 (Origin Lab Corp.) in consultation with the UCLA Statistical Biomathematical Consulting Clinic. P < 0.05 (*) was considered a suggestive difference, while P < 0.005 (**) was recognized as a statistically significant difference

DISCLOSURE

CL, ZZ, XZ, KT, and CS are inventors of NELL-1 related patents. XZ, KT, and CS are also founders and/or past board members of Bone Biologics Inc./Bone Biologics Corp., who sublicense NELL-1 patents from the UC Regents, who also hold equity in the company. CTC is an inventor of NELL-1 related patents filed from Oak Ridge National Laboratory (ORNL) and a founder of NellOne Therapeutics, Inc., which licensed NELL-1 related patent applications from ORNL. Bone Biologics Inc./Bone Biologics Corp. and NellOne Therapeutics, Inc. did not provide financial support for the current study. All of the other authors declare no conflict of interest.

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RESULTS

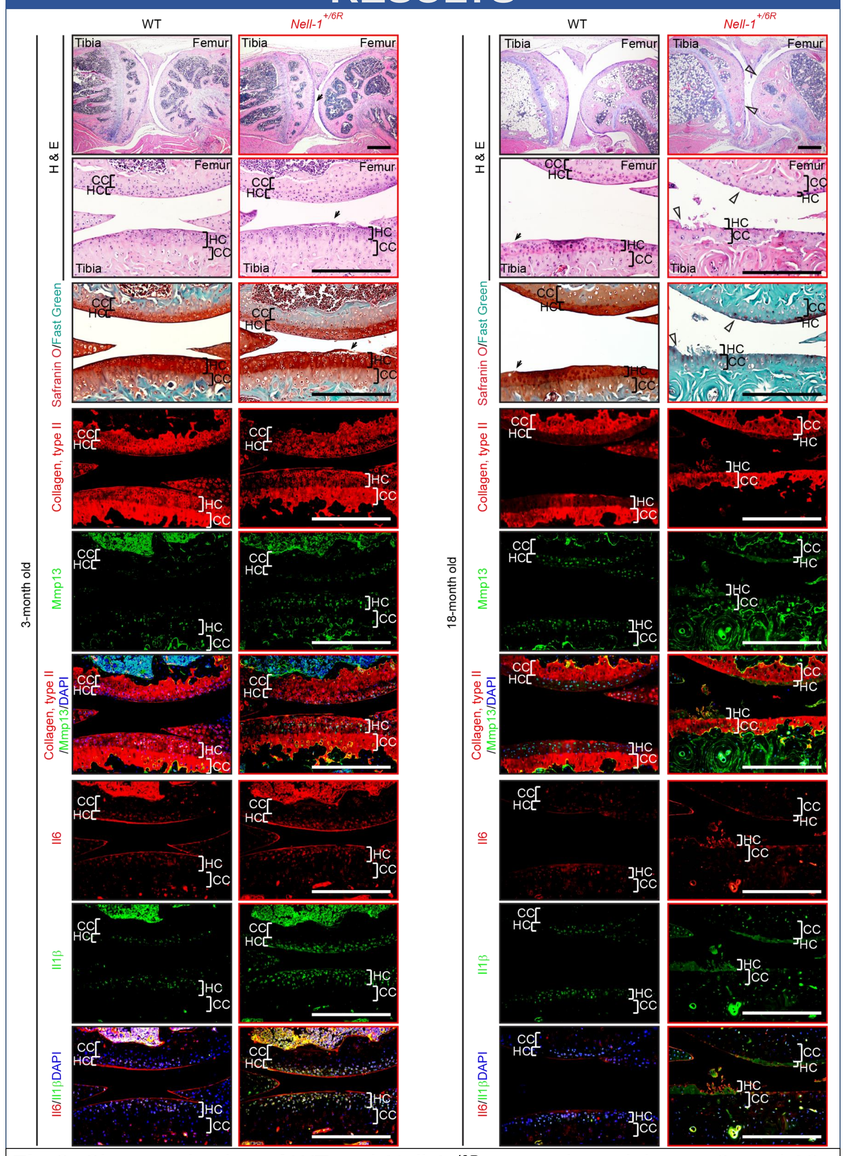


Fig 2. Characterization of WT and *Nell-1*$^{+/6R}$ mouse knee joints at 3- and 18 -months of age. Bar = 500 μm.

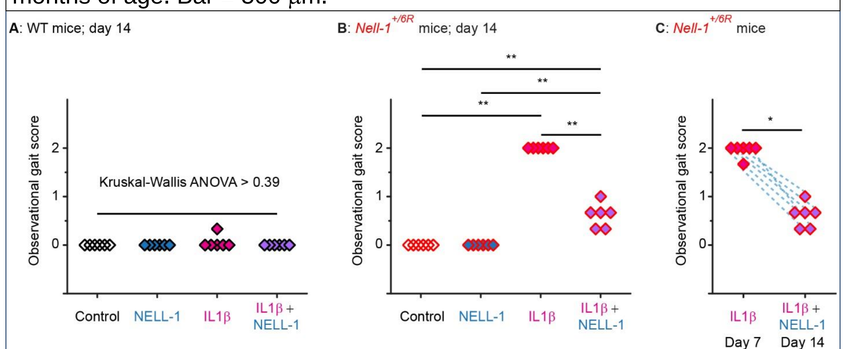
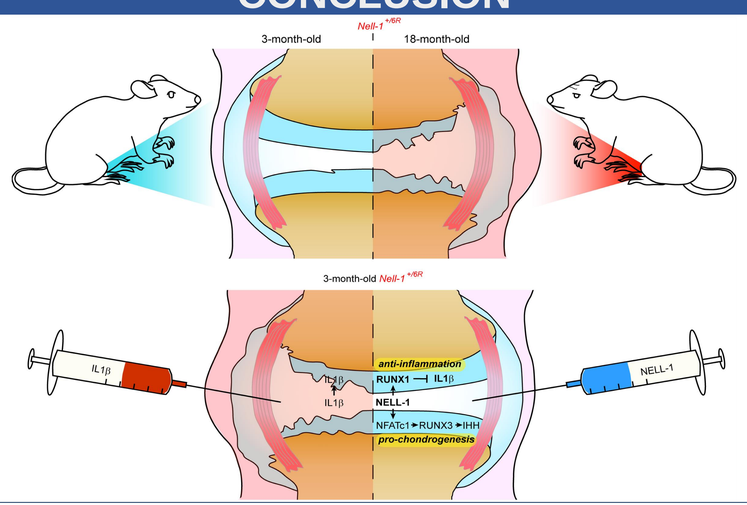


Fig 3. Observational gait scoring of WT and *Nell-1*$^{+/6R}$ mice after intra-articular injections.

CONCLUSION



RESULTS

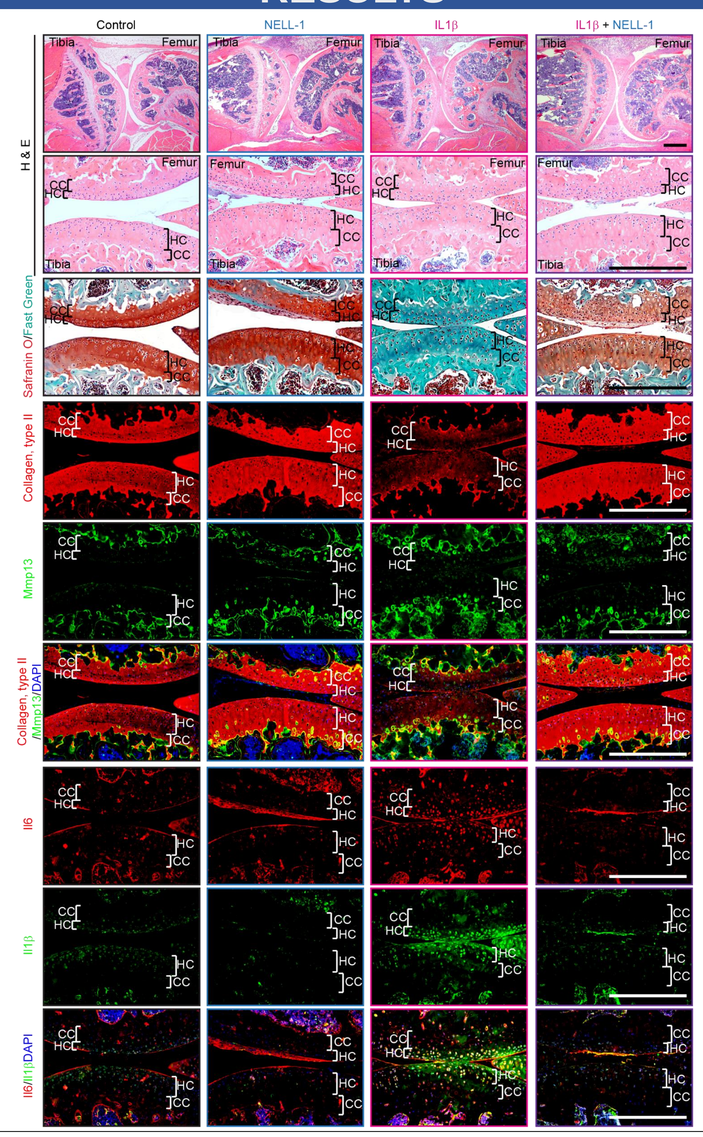


Fig 4. 2.5-months-old female WT mouse knee joints after 14 days of intra-articular injections (3-months-old at the end of treatment). Bar = 500 μm.

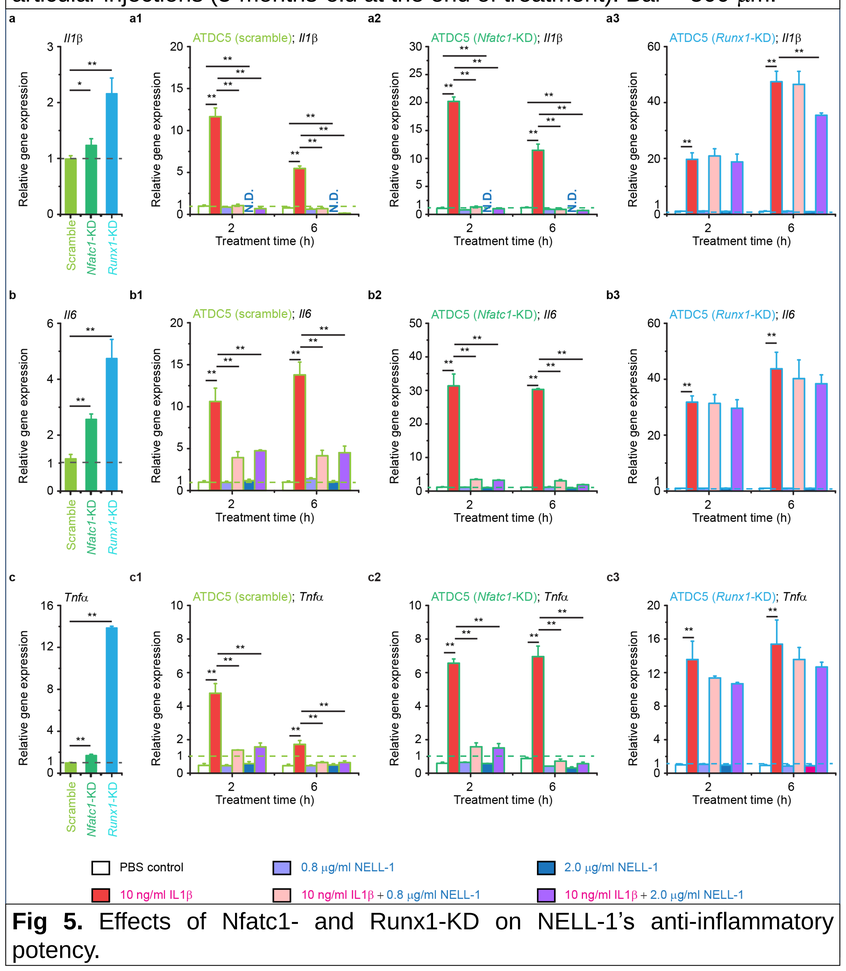


Fig 5. Effects of Nfatc1- and Runx1-KD on NELL-1's anti-inflammatory potency.