MODULATING OSTEOARTHRITIS PAIN VIA IPSC-DERIVED NOCICEPTOR CELL THERAPY

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1. Introduction

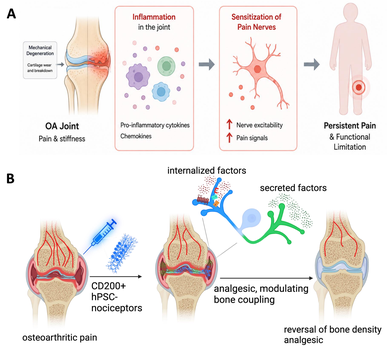


Figure 1. Proposed mechanism of SN101 iPSC-derived nociceptor cell therapy for osteoarthritis pain. **(A)** Mechanical joint degeneration promotes local inflammation and release of pro-inflammatory cytokines and chemokines, leading to sensitization and increased excitability of endogenous nociceptors and ultimately persistent pain and functional limitation. **(B)** SN101 iPSC-derived nociceptors are delivered into the OA joint, where they are proposed to interact with and equester pain- and inflammation-associated mediators through nociceptor receptors, reducing activation of endogenous pain-sensing nerves, and supporting restoration of joint homeostasis.

2. Methods

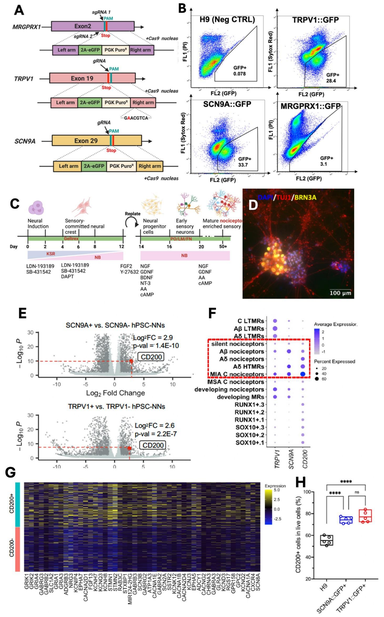


Figure 2. Generation of purified nociceptor from sensory neuronal cells of differentiated human pluripotent stem cells (hPSC). **(A)** CRISPR-mediated knock-in construct for MRGPRX1::GFP, TRPV1::GFP, and SCN9A::GFP cell lines. **(B)** FACS plots of TRPV1::GFP, SCN9A::GFP, and MRGPRX1::GFP iPSC-derived neurons (n=12). **(C)** Timeline of sensory neuron differentiation. **(D)** Representative morphology of iPSC-nociceptors expressing TUJ1 and BRN3A. **(E)** Volcano plot shows CD200 is enriched in TRPV1+ and SCN9A+ hPSC-SNs. **(F)** Dot plots showing the co-enrichment of TRPV1, SCN9A and CD200 in nociceptor clusters. **(G)** Heatmap illustrating the upregulation of nociceptor membrane receptor genes in CD200+ compared to CD200- cells. **(H)** FACS analysis showing the expression of CD200 in H9 parent line, SCN9A::GFP, and TRPV1::GFP lines.

3. Results

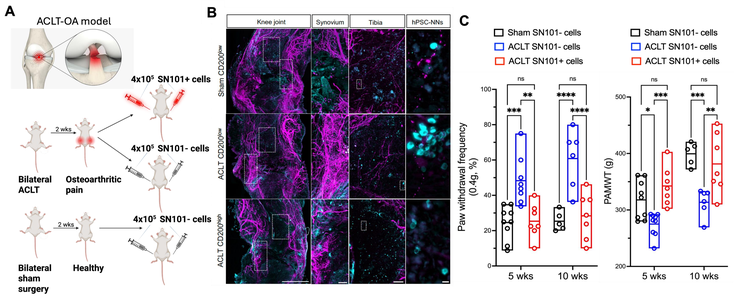


Figure 3. CD200+ hPSC-nociceptors promote healthy bone homeostasis in a mouse model of osteoarthritis (OA). **(A)** Schematic workflow of bilateral intra-articular and tibial bone marrow injections of CD200+ hPSC-nociceptors or CD200- cells into NIH-3 immunodeficient mice. Mice underwent sham or ACLT surgery, with injections administered two weeks after the surgery. **(B)** Representative 3D light-sheet fluorescence microscopy knee joints following CD200+ SN101 or CD200- control cells injection. The spatial localization of innervating nerves at synovium and tibia (magenta) and injected cells (cyan) are shown. Scale bars, 1 mm (left), 100 µm, 100 µm, 10 µm (right). **(C)** ACLT-CD200+ animals showed improved mechanical hypersensitivity demonstrated by Von Frey test.

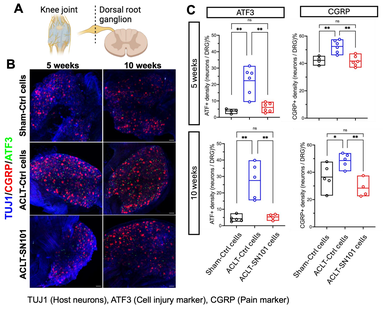


Figure 4. CD200+ SN101 demonstrate therapeutic effects in ACLT-OA mouse model. **(A)** Schematic image of DRG region where the neuronal signals received from knee joint innervated exons. Dashed line indicate the cross-sectional view of (B). **(B)** Representative images of cross-sectional view of dorsal root ganglion (DRG) region stained with TUJ1 (Blue, neurons), CGRP (Red, pain marker), and ATF3 (Green, cell injury marker). Scale bars are 10 µm. **(C)** Quantification of ATF3 and CGRP at 5- and 10-week post SN101 or counter part control cell injection demonstrated reduced pain and injury signals in DRG region.

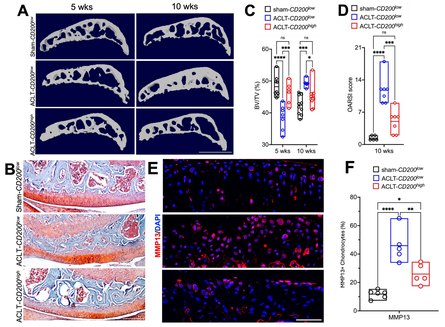


Figure 5. CD200+ SN101 supports bone and cartilage in OA model. **(A)** micro-CT images shown trabecular bone post injection 5 and 10 weeks. **(B)** Safranin O staining of SN101 or control cell injected cartilage sections. **(C,D)** SN101 cell injected animal in OA model demonstrated improved knee joint bone parameters (C) and cartilage degeneration score (OARSI score). **(E,F)** MMP13 staining on subchondral cartilage area and quantification.

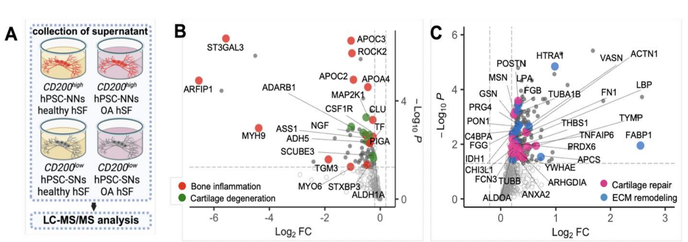


Figure 6. CD200+ SN101 promote healthy joint homeostasis by depleting inflammatory factors and secreting factors that facilitate tissue repair. **(A)** Schematic workflow of proteomic analysis of supernatants from CD200+ and CD200- hPSC-sensory neurons (SN) following overnight incubation with OA human synovial fluid (hSF) or pooled healthy hSF (n = 2 independent OA donors pooled; n = 3 independent differentiations; n = 6 proteomic replicates). **(B, C)** Volcano plots of proteins depleted (B) or enriched (C) in OA hSF following incubation with CD200+ versus CD200- hPSC-SNs (log2 fold change, ≥ 0.2; FDR cutoff < 0.05).

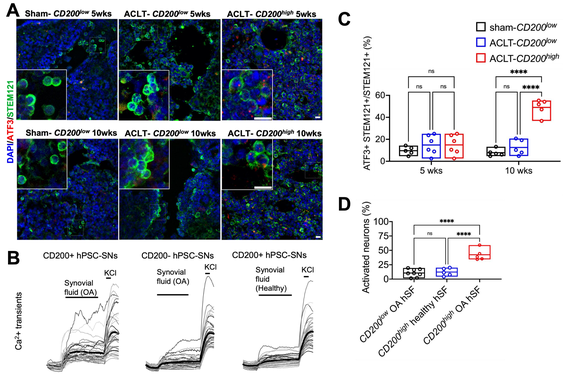


Figure 7. CD200+ SN101 promote healthy bone homeostasis by depleting inflammatory factors and secreting factors that facilitate tissue repair. **(A,C)** CD200high hPSC-NNs displayed more in vivo activation compared to CD200low hPSC-SN. Transplanted cell are stained by human cell marker STEM121 (green), ATF3 is used as activation marker (red). Scale bar, 10 µm. **(B,D)** Representative Ca2+ transients (Ft/F0) demonstrating CD200high hPSC-NNs exhibit heightened activation when stimulated with human synovial fluid from OA patients (OA hSF). This effect is quantified in (B).

4. Summary

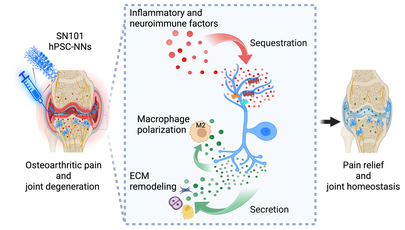
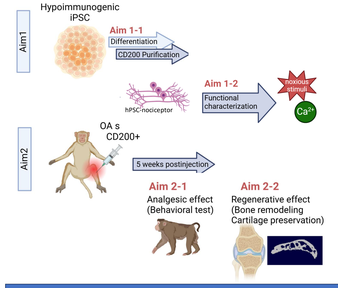


Figure 8. Multimodal mechanism of SN101 in osteoarthritis. Intra-articularly delivered SN101 hPSC-derived nociceptors are proposed to modulate the OA joint microenvironment through sequestration of inflammatory and neuroimmune factors, promotion of M2 macrophage polarization, and secretion-mediated ECM remodeling, collectively contributing to pain relief and restoration of joint homeostasis.

5. Future Study



6. Funding

- Maryland Stem Cell Research Fund (MSCRF) Commercialization Award
- Blaustein Research Pain Foundation (GS Lee)