# 85. Small molecule promoting nerve regeneration

**(Oregon Health and Science University)**

5TH KDDF GLOBAL C&D TECH FAIR

## Asset Overview

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|---|---|
| **Product Type** | Small Molecule |
| **Disease Area** | Others |
| **Indication** | Nerve Damage |
| **Current Stage** | Lead Optimization |
| **Target** | the PTPσ signaling pathway |
| **MoA** | CSPGs bind to monomers of receptor protein tyrosine phosphatase sigma (PTPσ) on the surface of neurons, enhancing the ability of PTPσ to bind and dephosphorylate Trk tyrosine kinases, inhibiting their activity and preventing axon outgrowth. |
| **Brief Description** | • Protein tyrosine phosphatase receptor sigma (PTPσ), expressed on sympathetic nerves, is a major receptor for CSPG; therefore, novel compounds were designed to disrupt the PTPσ signaling pathway and tested for restoring axon growth in the presence of CSPG.<br>• The novel compounds increased axon outgrowth over culture plates containing CSPG in a dose dependent manner, with full restoration achieved at concentrations in the range of 100 nM. In vivo testing 3 days following myocardial infarction in mice found that these compounds restored normal nerve density within the infarct, without signs of toxicity or widespread non-specific binding.<br>• These compounds were capable of reducing isoproterenol-induced arrhythmias post-infarction and also restored cardiac output to levels observed in sham uninjured mice.<br>• These compounds have demonstrated efficacy in vitro and in vivo to promote nerve regeneration through injury and CSPG expression and could improve outcomes for a wide range of injuries that cause permanent nerve damage. |
| **Intellectual Property** | WO2022051233A1 |
| **Publication** | • Therapeutics That Promote Sympathetic Reinnervation Modulate the Inflammatory Response After Myocardial Infarction. JACC Basic Transl Sci. (2022)<br>• Small Molecules Targeting PTPσ-Trk Interactions Promote Sympathetic Nerve Regeneration. ACS Chem Neurosci. (2022) |
| **Inventors** | Michael Cohen, Beth Habecker, Haihong Jin, Ryan Gardner, Matthew Blake |

## Highlights

- Quantitative multiplex immunohistochemistry employing 23 antibodies was used to identify the immune cells present in the left ventricle 2 weeks after ischemia-reperfusion.
- Two therapeutics (ISP and HJ-02), administered on days 3-10 after ischemia-reperfusion, restored sympathetic innervation throughout the left ventricle and decreased arrhythmia susceptibility.
- Treatment with ISP and HJ-02 shifted the immune response from inflammatory to reparative, with fewer pro-inflammatory (M1-like) macrophages and increased numbers of regulatory T cells and reparative (M2-like) macrophages in reinnervated hearts.
- HJ-02 stimulated a significantly greater shift from pro-inflammatory to reparative cell types compared with ISP, which coincided with decreased infarct size and normal cardiac output and ejection fraction.
- Neither ISP nor HJ-02 altered macrophage phenotypes in cultured peritoneal macrophages, which suggested that reinnervation contributes to the M1 to M2 shift in vivo.

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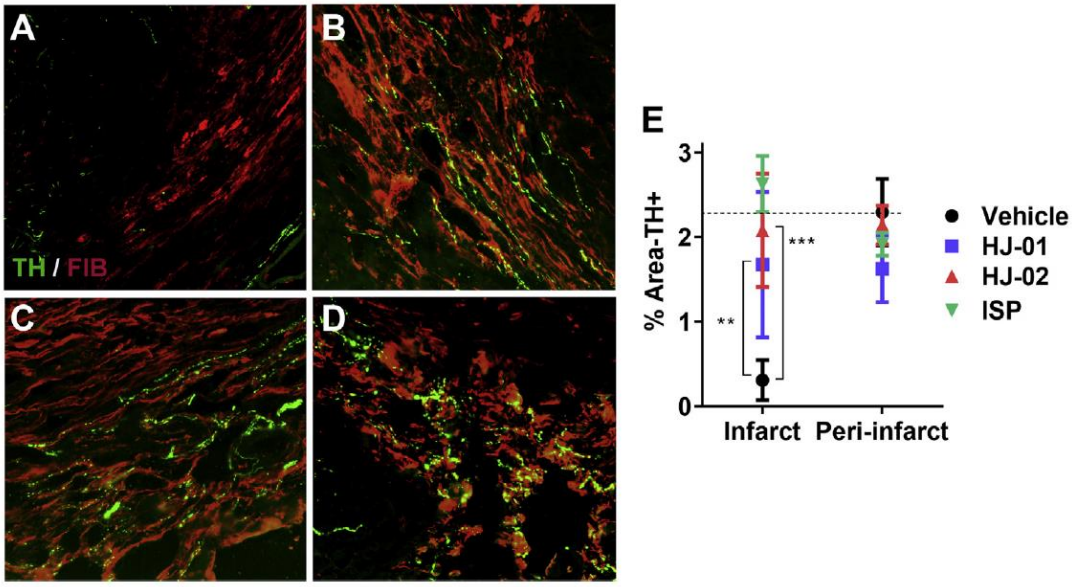
## Key Data

### ISP, HJ-01 and HJ-02 Injections Promote Sympathetic Reinnervation of the Infarct




(A-D) Representative images of infarcted left ventricles from mice treated with (A) VEH, (B) HJ-01, (C) HJ-02, and (D) ISP 14 days after MI. Sections were stained for tyrosine hydroxylase (TH) to identify sympathetic nerve fibers and fibrinogen to identify the infarct. HJ-01, HJ-02, and ISP treatment resulted in extensive sympathetic reinnervation of the infarct. (E) Quantification of THþ fiber density within the infarct 14 day post-MI (mean SD; n ¼ 5/group; **P < 0.01; ***P < 0.001; 2-way ANOVA with Tukey's multiple comparisons post-test). Dotted line denotes innervation density in sham animals.

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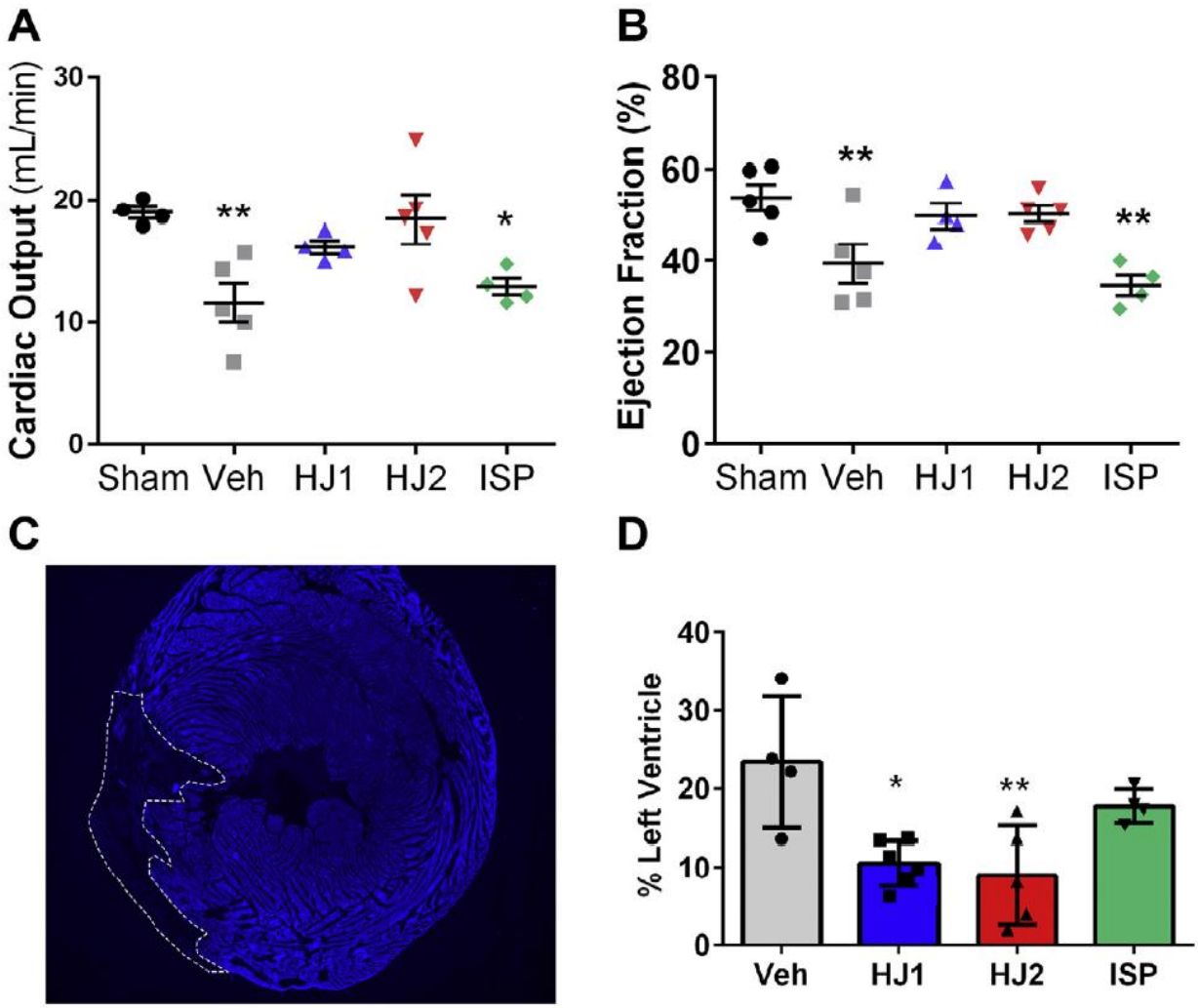
## Key Data

### HJ-01 and HJ-02, But Not ISP, Reduce Infarct Size and Preserve Cardiac Function




(A and B) Quantification of cardiac output and ejection fraction in mice following sham or myocardial infarction (MI) procedures, then treated with vehicle, HJ-01, or HJ-02. (C) Example image of a heart after MI depicting the loss of autofluorescence in the infarct. (D) Quantification of infarct size as a percentage of left ventricle in mice treated with HJ-01, HJ-02, or intracellular sigma peptide (ISP). Data are mean SD; n ¼ 5/group except sham (n ¼ 4); *P < 0.05; **P < 0.01; 1-way analysis of variance (ANOVA) with Dunnett's multiple comparison post-test. (control group ¼ sham mice in A and B.)