APD588, a Novel, Selective S1P Receptor Modulator, Regulates Inflammatory Responses and Attenuates Cardiac Dysfunction Following Experimental Myocardial Infarction in Mice

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BACKGROUND AND HYPOTHESIS

BACKGROUND

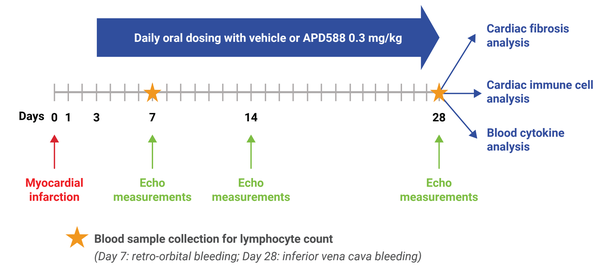
Recent studies have determined that chronic inflammation contributes to left ventricular (LV) remodeling following myocardial infarction (MI) leading to heart failure (HF). Evidence points to a critical role of T lymphocytes in driving the maladaptive inflammatory process associated with adverse tissue remodeling and cardiac dysfunction. FTY720, a non-selective sphingosine 1-phosphate (S1P) receptor modulator, elicits anti-inflammatory effects via inhibition of lymphocyte egress from secondary lymphoid organs and has been reported to improve cardiac remodeling and function post-MI.[1]

HYPOTHESIS

We hypothesized that APD588, a next-generation S1P receptor modulator with optimized $S1P_{1,5}$ receptor selectivity, would prevent cardiac remodeling and dysfunction following MI through modulation of T lymphocyte-mediated inflammatory responses.

METHODS

Figure 1. Experimental Design

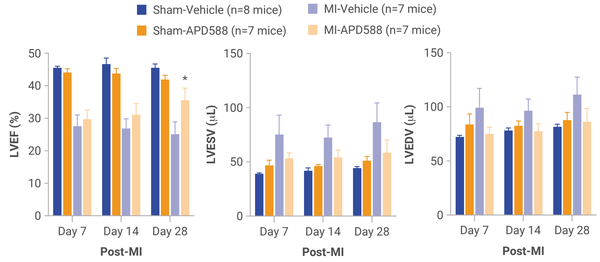


- **Male C57BL/6 mice; 4 groups:**
  - Sham-Vehicle (n=10)
  - Sham-APD588 (n=10)
  - MI-Vehicle (n=11)
  - MI-APD588 (n=13)
- **Key endpoints:**
  - Echocardiographic measurements at 7, 14, and 28 days post-MI
  - Lymphocyte count at 7 and 28 days post-MI
  - Cardiac immune cell infiltration at 28 days post-MI
  - Cardiac tissue fibrosis at 28 days post-MI

* A total of 8 mice survived following MI in both MI-Vehicle and MI-APD588 groups

RESULTS

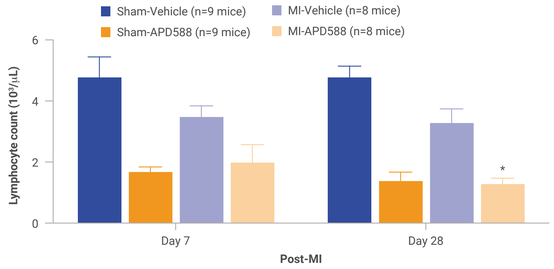
Figure 2. APD588 Treatment Improves Cardiac Function Following MI



Mean ± SEM; *P<0.05 vs MI-Vehicle

- APD588 significantly increased Left Ventricular Ejection Fraction (LVEF) 28 days post-MI compared to MI-Vehicle.
- APD588 treatment showed a trend in improving LV end-systolic and end-diastolic volumes (LVESV and LVEDV) following MI compared to MI-Vehicle.

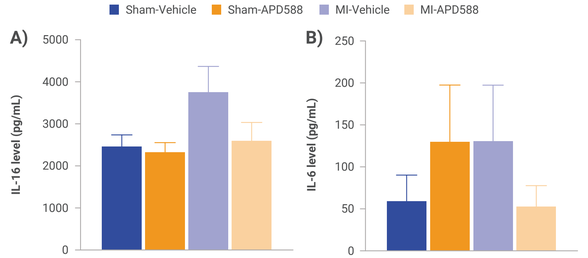
Figure 3. APD588 Treatment Decreases Circulating Lymphocytes Following MI



Mean ± SEM; *P<0.05 vs MI-Vehicle

- APD588 treatment showed a trend in decreasing circulating lymphocyte numbers compared to MI-Vehicle at 7 days post-MI.
- APD588 significantly decreased lymphocyte count 28 days post-MI compared to MI-Vehicle.

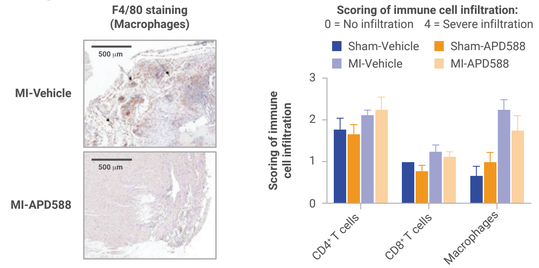
Figure 4. APD588 Treatment Results in a Trend in Reducing Circulating Pro-inflammatory Cytokine Production Following MI



Mean ± SEM (n=9 samples/Sham group and 7 samples/MI group)

- APD588 treatment showed a trend in reducing the concentration of circulating A) IL-16 and B) IL-6 compared to MI-Vehicle 28 days post-MI.
- APD588 also showed a trend in increasing circulating levels of IL-2 and IL-22, but no effect was detected on other cytokines measured (IFN-γ, IL-1β, IL-4, IL-5, IL-10, TNF-α, IL-17, IL-21, IL-23, IL-31).

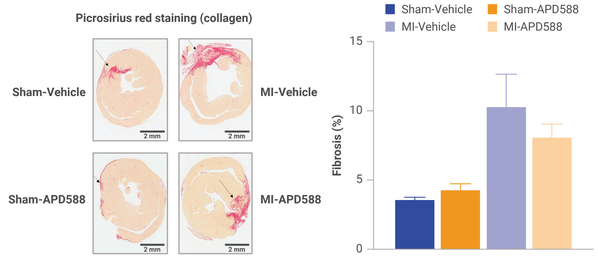
Figure 5. APD588 Treatment Results in a Trend in Reducing Cardiac Tissue Infiltration of Macrophages Following MI



Mean ± SEM (n=9 samples/Sham group and 8 samples/MI group)

- APD588 treatment showed a trend in decreasing cardiac macrophage infiltration 28 days post-MI compared to MI-Vehicle. No differences in infiltration of $CD4^+$ or $CD8^+$ T cells were observed.

Figure 6. APD588 Treatment Results in a Trend in Decreasing MI-Induced Cardiac Fibrosis



Mean ± SEM (n=9 samples/Sham group and 8 samples/MI group)

- APD588 treatment indicates a trend in reducing adverse cardiac remodeling 28 days post-MI compared to MI-Vehicle.

CONCLUSIONS

- The $S1P_{1,5}$ receptor modulator APD588 reduced circulating lymphocyte numbers and improved cardiac functional recovery 28 days post-MI in mice.
- In this small exploratory study examining inflammatory responses only at 28 days post-MI in mice, a trend in decreasing key circulating pro-inflammatory cytokines, infiltration of macrophages in the heart, and cardiac fibrosis was observed with APD588 treatment. Further studies examining these responses at additional timepoints are warranted.
- This study supports the potential of S1P receptor modulation and other T lymphocyte-directed strategies as a targeted immunomodulatory approach in HF.

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REFERENCE: 1. Zhang F et al. Sphingosine 1-phosphate signaling contributes to cardiac inflammation, dysfunction, and remodeling following myocardial infarction. *Am J Physiol Heart Circ Physiol.* 2016;310(2):H250-61.

DISCLOSURES: NN, MZC, JWA are employees of Arena Pharmaceuticals, Inc. LAN, HW, TM, MRG are employees of CorDynamics

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