All-Trans Retinoic Acid (ATRA) to Prevent and Treat Atrial Fibrillation

A safe and effective disease-modifying treatment to prevent and treat atrial fibrillation (AF).

Technology

The Park Lab at NYU Langone Health has discovered a surprising and unexpected application of natural all-trans retinoic acid (ATRA) in preventing or reversing pathological atrial remodeling underlying AF. ATRA is an intracellular metabolite synthesized from Vitamin A (retinol) that is a master regulator of transcription programs. It is currently approved to treat acute promyelocytic leukemia (APL) under the name tretinoin; however, its role in LA remodeling, both electrical and structural, was previously unrecognized. In proof-of-concept studies (unpublished), using transverse aortic constriction (TAC) banding as a model for rodent AF, the Park Lab showed that ATRA administration during TAC onset normalizes LA electrical activity (activation time and conduction velocity) in a dose-dependent manner, and also normalizes structural properties (fibrosis and gap junction integrity) without adversely affecting heart rate, left ventricular function, or repolarization times. Similar results were also observed following delayed ATRA administration in rodents (2 weeks post-TAC). Together, these results demonstrate that ATRA treatment can both prevent and reverse pathological LA remodeling underlying AF. Furthermore, transcriptomic analysis of LA samples from TAC + ATRA group hearts revealed that ATRA regulates transcription programs that protect against electrical and structural remodeling by normalizing adversely expressed genes; particularly, acting to downregulate key inflammatory and fibrotic signaling pathways, as well as signaling cascades driving gap junction remodeling. Lastly, in a retrospective study of 24 patients taking Vesanoid (tretinoin) for APL, electrocardiogram data revealed a significant decrease in LA activation time (P wave) over 1 month. This human data provides strong initial POC that ATRA can correct the pathological LA remodeling underlying AF in man. Taken together, these data demonstrate that ATRA supplementation can both prevent and treat AF by blocking and reversing pathological LA remodeling, respectively. ATRA, therefore, represents a new therapeutic option to treat AF that is non-invasive, low-risk, preventative, and disease-modifying.

Development Status

The Park Lab has a robust pre-clinical data package (transcriptomic data on ATRA-mediated gene expression; in vivo mouse efficacy data (including dose-response curves); and retrospective human efficacy data from an APL clinical trial) which establishes clear animal POC and initial POC in man. The program is ready for additional pre-clinical, CMC, and clinical/regulatory development efforts.

Partnership Opportunity

NYU is seeking a commercial partner (via IP licensing or other arrangements) to advance the ATRA program into clinical trials.

Technology ID

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Category

Life Sciences/Therapeutics/Cardiovasc Disease

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Background

AF is the most common cardiac rhythm disorder encountered in clinical practice, with an estimated worldwide prevalence of 37.6 million cases (as of 2017) that has increased sharply by 33% over the last 20 years. The occurrence of AF is strongly correlated to age; its prevalence is very low among young < 40 year-old individuals, but raises to 10-17% in those > 80 years of age. AF negatively impacts all cardiovascular outcomes; namely, it increases stroke risk, morbidity, mortality, and hospitalizations. The economic burden associated with AF hospitalizations in the U.S. is estimated at $6.65 billion annually. Presently, there are two main options for AF treatment: anti-arrhythmic drugs (AADs) and catheter ablation therapy. AADs have low efficacy in maintaining sinus rhythm and often carry lethal proarrhythmic side effects. Catheter ablation is more effective at maintaining sinus rhythm, but is an invasive procedure and carries risk for major adverse events. Importantly, neither therapy addresses the underlying left atrial (LA) myopathy that gives rise to AF and promotes its progression to a persistent form. Given our aging global population and the current lack of preventive or low-risk, disease-modifying treatments, there is an urgent need to develop innovative and efficacious therapies to prevent or treat AF.

Applications

ATRA can be used to prevent or treat patients with AF, including those already diagnosed with heart failure and/or hypertension.

Advantages

- **Clinically safe:** ATRA (Tretinoin) and a closely related retinoid have already been FDA approved for the treatment of APL and acne
- **Abbreviated regulatory pathway:** The U.S. 505(b)(2) new drug application pathway (and the European equivalent) could be leveraged
- **Well characterized pharmacokinetics and pharmacodynamics:** There are numerous basic and clinical studies on ATRA in non-left atrial contexts
- **Restorative or supplemental treatment:** Modulates natural ATRA levels; no foreign chemicals are needed
- **Biomarker compatible:** patient ATRA levels could be used to inform treatment applicability and/or tailor personalized therapies

Intellectual Property

NYU has filed a PCT patent application covering the method of using endogenous ATRA and other retinoids to prevent or treat AF.