



IDENTIFICATION OF PHOSPHODIESTERASE 3A POLYMORPHISM WITH POTENTIAL TO INCREASE EFFECTIVENESS OF PDE3 INHIBITORS PUBLISHED IN THE JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Westminster, CO, March 18, 2019 – [ARCA biopharma, Inc.](http://www.arcabio.com) (Nasdaq: ABIO), a biopharmaceutical company applying a precision medicine approach to developing genetically-targeted therapies for cardiovascular diseases, today announced that the paper “*PDE3A Promoter Polymorphism Regulates cAMP-Induced Transcriptional Activity in Failing Human Left Ventricles*” was recently published in the *Journal of the American College of Cardiology* (JACC) (<http://www.onlinejacc.org/content/73/10/1173>).

The lead author on the paper is University of Colorado molecular biologist Carmen Sucharov, PhD and the senior author is Michael R. Bristow MD, PhD, ARCA’s Chief Executive Officer, who is also the Director of the University of Colorado Cardiovascular Institute (CU CVI) Section of Pharmacogenomics. The work was sponsored by a Leducq Foundation Transatlantic Networks of Excellence grant awarded to Dr. Bristow and to Matthew Movsesian, MD of the University of Utah, who is also an author on the paper.

The paper describes the discovery and characterization of a polymorphism in the promoter region of the phosphodiesterase 3A (PDE3A) gene, which encodes the target of Type 3 phosphodiesterase inhibitors (PDE3Is). Members of this drug class (milrinone, enoximone) are used intravenously to treat acutely decompensated heart failure, to provide short-term circulatory support in other settings, and in selected patients as a bridge to cardiac transplantation. These agents uniformly have favorable short-term hemodynamic effects, but when oral forms were used long term to treat advanced chronic heart failure there was either a safety concern or a lack of effectiveness. The JACC paper investigators identified a high frequency polymorphism in the PDE3A gene that may explain the heterogeneity of patient response to PDE3Is.

The 29 nucleotide (nt) insertion/deletion (indel) polymorphism is 2214 nts upstream from the PDE3A1 translation start site that regulates transcriptional activity in response to cyclic adenosine monophosphate (cAMP) levels, with the insertion (INS) allele having a frequency of 0.41. When a cAMP analogue or a PDE3I was administered to cultured cardiac myocytes transfected with promoter-reporter constructs containing one of the alleles, PDE3A transcription increased with the deletion (DEL) variant. In contrast, the INS form of the polymorphism acted as a repressor, and a pharmacologic increase in cAMP did not result in increased gene transcription. The investigators then measured PDE3 activity and PDE3A1 mRNA abundance in failing explanted left ventricle tissue samples from patients who had or hadn’t been treated with milrinone or enoximone prior to cardiac transplantation, and found that enzyme activity and mRNA abundance were higher in DEL compared to INS homozygotes who had been treated with PDE3Is. This indicated that the favorable hemodynamic effects of restoring cAMP levels towards normal were blunted in DEL

genotype patients by up-regulation in PDE3A enzyme activity and subsequent increased hydrolysis of cAMP, through a functionally negative feedback loop.

In an accompanying editorial, Dr. Arthur M. Feldman of Lewis Katz School of Medicine at Temple University remarked, "The approach that Sucharov et al. used to interrogate the biology of the PDE3A genetic variant, including expression screening, DNA sequencing, and microsomal fractions from failing human heart, is novel. This in vitro approach may prove useful for evaluating what will undoubtedly be an increasing number of genetic variants as studies such as the National Institutes of Health-sponsored "All of Us," which plans to genotype 1 million Americans, gain traction."

Dr. Bristow commented: "One of the first molecular defects identified in failing human hearts was a decrease in myocardial cAMP levels, which should be restorable towards normal with PDE3Is. However, when PDE3Is were administered in higher doses there was either loss of initial effectiveness and subsequent progression of heart failure, or an increase in mortality. Subsequent lower dose long term treatment approaches were safe but lacked effectiveness. The data in the JACC publication suggest that loss of effectiveness with PDE3Is may have a pharmacogenetic basis and could be avoided in INS genotypes. This hypothesis can be readily tested in a small hemodynamic and exercise tolerance trial with genotyping for this polymorphism."

ARCA biopharma has licensed from the University of Colorado the intellectual property around the use of the PDE3A indel for guiding PDE3I therapy and a U.S. patent has been issued.

About ARCA biopharma

ARCA biopharma is dedicated to developing genetically-targeted therapies for cardiovascular diseases through a precision medicine approach to drug development. ARCA's platform approach is to identify functionally important genetic variation in drug targets using human cardiovascular tissues or cells, and then screen for and identify compounds whose action is uniquely enhanced in a particular variant. ARCA's lead product candidate, GencaroTM (bucindolol hydrochloride), is an investigational, pharmacologically unique beta-blocker and mild vasodilator being developed for the potential treatment of atrial fibrillation in heart failure patients with mid-range ejection fraction. ARCA has identified common genetic variations that it believes predict individual patient response to Gencaro, giving it the potential to be the first genetically-targeted AF prevention treatment. The Gencaro development program has been granted Fast Track designation by FDA. ARCA is also developing AB171, a thiol-substituted isosorbide mononitrate, as a potential genetically-targeted treatment for heart failure and peripheral arterial disease (PAD). For more information, please visit www.arcabio.com.

Safe Harbor Statement

This press release contains "forward-looking statements" for purposes of the safe harbor provided by the Private Securities Litigation Reform Act of 1995. These statements include, but are not limited to, statements regarding the ability of ARCA's financial resources to support its operations through the end of the second quarter of 2019, potential future development plans for Gencaro, the expected features and characteristics of Gencaro or AB171, including the potential for genetic

variations to predict individual patient response to Gencaro, Gencaro's potential to treat AF, AB171's potential to treat HF, future treatment options for patients with AF, and the potential for Gencaro to be the first genetically-targeted AF prevention treatment. Such statements are based on management's current expectations and involve risks and uncertainties. Actual results and performance could differ materially from those projected in the forward-looking statements as a result of many factors, including, without limitation, the risks and uncertainties associated with: ARCA's financial resources and whether they will be sufficient to meet its business objectives and operational requirements; ARCA may not be able to raise sufficient capital on acceptable terms, or at all, to continue development of Gencaro or to otherwise continue operations in the future; results of earlier clinical trials may not be confirmed in future trials; the protection and market exclusivity provided by ARCA's intellectual property; risks related to the drug discovery and the regulatory approval process; and, the impact of competitive products and technological changes. These and other factors are identified and described in more detail in ARCA's filings with the Securities and Exchange Commission, including without limitation ARCA's annual report on Form 10-K for the year ended December 31, 2018, and subsequent filings. ARCA disclaims any intent or obligation to update these forward-looking statements.

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