RESEARCH FUNDING ANNOUCEMENT:
RFP LJPC-MA001-18

MICROCIRCULATORY FLOW IN PATIENTS WITH SEPTIC OR OTHER DISTRIBUTIVE SHOCK

Sponsor:

La Jolla Pharmaceutical Company
4550 Towne Centre Ct
San Diego, CA 92121

Sponsor Contact:

Antonio E. Civitarese, PhD, MBA
Director of Research - Medical Affairs
858.207.4264; Ext 1175 - Office
acivitarese@ljpc.com

Original RFP
Version 1.0
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FOR QUALIFIED INVESTIGATORS AND THEIR INSITUTIONS ONLY

Date: June 19, 2018

Timing: Close date; August 31st, 2018

Objective of the RFP

La Jolla considers providing research support for assessment of Microcirculatory Flow with GIAPREZA™ (angiotensin II) Injection for intravenous infusion, alone or in combination of other vasopressors, in therapeutic areas where mean arterial pressure-microcirculation association may be altered.

The objective of this initiative is to:

- Assess the effect of GIAPREZA (angiotensin II) on microcirculatory flow in patients prior to, during, and after treatment initiation

The content and/or the format of the RFP initiative and its related materials must be designed in such a way that it addresses the primary objective and improves the understanding on how GIAPREZA alone or in conjunction with other vasopressors regulates the dynamics between microcirculatory flow/variables and health outcomes.

Background:

The microcirculation is a central part of the cardiovascular system consisting of blood vessels with a diameter approximately less than 100 μm. The network of arterioles, capillaries, and venules that compose the microcirculation are the principal site of oxygen and nutrient delivery to underlying tissue, with key exchange occurring in vessels of diameters of 20 μm or less. [1] Normal microcirculation is characterized by networks of perfused capillaries with mostly homogeneous flow. Capillary flow is modulated according to metabolic needs by opening and closing of precapillary arterioles. Fine tuning perfusion is regulated by local factors that include stimulation of endothelial cells through backward communication and local release of nitric oxide by red blood cells under hypoxic conditions.[2] Experimental and clinical studies suggest that the endothelium regulates microcirculatory function, thus providing adequate tissue oxygenation for cellular respiration. [2-9]

The causes of microcirculatory flow alterations during critical illness are multifactorial and include endothelial cell dysfunction, increased leukocyte adhesion, microthrombi formation, rheological abnormalities, altered local perfusion pressure due to regional redistribution of blood flow and low density of perfused capillaries. [1] Several studies demonstrate that persistent sublingual microcirculatory alterations refractory to resuscitation are highly

prognostic of fatal outcome, independent of systemic variables and oxygen derived variables. [2-9]. This RFP will aim to improve the understanding between microcirculatory flow, vasopressor pharmacology and patient outcomes.

Incident Dark-Field illumination (IDF) technology enables the visualization of the microcirculation by using green light that is absorbed by hemoglobin near the isosbestic point so that red blood cells appear dark. This permits direct visualization of blood flow in the sublingual microcirculatory network in human subjects in a non-invasive fashion using a hand-held video microscope. The technique has been validated in both experimental and human studies. [10-12] The sublingual site is used as numerous investigators have demonstrated that impaired sublingual perfusion can track impairment of splanchnic perfusion and detect early systemic perfusion failure in shock states.[13-15] Monitoring sublingual blood flow can yield important information for use in clinical studies of circulatory shock because (1) the sublingual mucosa shares the same embryologic (and therefore anatomic) origin as the splanchnic mucosa, (2) derangements in sublingual perfusion reflect derangements in splanchnic blood flow, [14-18] and (3) the sublingual space is easily accessible. Because splanchnic hypo-perfusion is one of the earliest indicators of systemic hypo-perfusion in circulatory shock, [19] impaired sublingual blood flow can herald the onset of systemic hypo-perfusion. [15]

In human physiology, blood pressure is under tight counterregulatory control. The three main systems the body leverages are the sympathetic nervous system, arginine-vasopressin system, and the renin-angiotensin-aldosterone system (RAAS). Angiotensin II is a peptide hormone naturally produced by the body that regulates blood pressure via vasoconstriction and sodium reabsorption. In numerous clinical studies, angiotensin II has demonstrated significant effects on systemic and renal blood flow. [1] Intravenous (IV) angiotensin II has been studied in patients with hypertension, aortic regurgitation, coronary artery disease, recent myocardial infarction, congestive heart failure, traumatic brain injury, chronic obstructive pulmonary disease, peripheral vascular disease, diabetes mellitus, congenital adrenal hyperplasia, primary hyperaldosteronism, renovascular hypertension, cirrhosis, and adrenal masses. [16-17] Case reports support the use of angiotensin II to treat hypotension in patients suffering from vasopressor-resistant shock. [16, 18-19] In addition, angiotensin II has been reported to restore mean arterial pressure (MAP) in patients who have taken overdoses of angiotensin converting enzyme (ACE) inhibitors who were refractory to catecholamines. [20-21]

Hemodynamic effects of angiotensin II administration have demonstrated significant effects on systemic and renal blood flow. [16-18] However, our understanding of micro-circulatory flow, angiotensin use; alone or in conjunction with other vasopressors, is not well understood. The aim of this RFP is to improve our understanding between micro-circulation, Giapreza, and vasopressor use.

Micro Circulation Image Acquisition and Analysis

The sublingual microcirculation will be visualized with an IDF video microscope (Braedius BV, Huizen, The Netherlands). Images will be recorded and analyzed at the Principle Investigator Site. La Jolla has 10-cameras that can be leased (incorporate into the study budget) in order to perform research.

Upon approval of sponsored project, La Jolla will provide site training on camera use, and instructions on how to perform data acquisition and image analysis. Study team participants will receive instruction on the operation and utilization of the Cytocam device primarily in live training during individualized training sessions provided at their institution. A group session from one of the trainings will be recorded and made available, which will contain all lectures, slides, and examples of device setup and operation.

The training session will consist of:

- An introduction to the Braedius IDF Cytocam device, its setup and operation
- A detailed presentation of the technique for good image acquisition including positioning, lighting, focus, and image recording
- Instruction on image analysis.

All participants will be required to produce several videos to demonstrate competency. The videos will be graded for image quality, and feedback will be provided to the participant. Image quality not meeting predefined standards will be identified (if necessary), and retraining will be provided as needed (online).

Proposal Submission Requirements

In the submission email header, indicate that this is in response to RFP code: RFP LJPC-MA001-18.

Proposals should be submitted on or before August 31st, 2018.

When responding to this RFP, please follow the established guidelines for the La Jolla research grant submission process (see Proposal Format below). All applications and supporting documents must be submitted to MAresearch@ljpc.com.

Grant applications submitted after the deadline will not be reviewed.

Proposal Format Guidelines:

Section 1. General Information (2-page maximum).

- Investigator information (name, email, phone, institution, address, CV)
- Country(s) where study will be conducted
- Products (Drugs of use and source)
- Study title
- Study duration (number of months, estimated start and end dates)
- Resources requested (study drug and/or funding)
- Proposed Budget

Section 2. Study Design

- Study hypothesis (medical/scientific question to be addressed)
- Background & rationale
- Study objectives
- Inclusion/exclusion criteria (if applicable)
- Study design/schedule (including treatments/procedures)
- Patient population
- Study endpoints
- Publication and statistical plan
- References

Proposals should be submitted electronically through the La Jolla MA Research portal at MAresearch@ljpc.com.

Please contact Antonio E. Civitarese at acivitarese@ljpc.com if you have any questions regarding this RFP.

Evaluation Criteria

Submitted proposals will be evaluated according to the following criteria:

- Completeness of the proposal, addressing each of the requested sections in this RFP
- Experience and successful track record of implementing quality improvement initiatives
- Familiarity with the disease area – understanding its pathology, treatment, current issues Proposed initiative structure and delivery options
- Number and type of patients included in the initiative
- Type and setting of disease state
- Length of initiative (feasibility to complete in proposed time)
- Qualifications and credentials of researchers, analysts, statisticians, and other quantitative skills represented in the staffing plan to conduct analysis
- Documentation of program results (i.e. outcomes reported, publication plan of the results, etc.)
- Clarity of proposal and budget
- Fiscal responsibility

- Collaboration with a national society or association, a medical or academic institution, or other non-profit organizations and governmental agencies
- Timely submission

Funding Guidelines
Budget should demonstrate fiscal responsibility and cost effectiveness.

Decision Date and Notification
You will receive an acknowledgement email upon receipt of your application. Once the Committee has reached a decision, a Response Letter will be sent via email, followed by an LOA and CDA if the request is approved.

References:

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8. den Uil, C.A., et al., Low-dose nitroglycerin improves microcirculation in hospitalized patients with acute heart failure. Eur J Heart Fail, 2009. 11(4): p. 386-90.

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function in normal subjects and subjects with primary hyperaldosteronism. Prog Biochem

Pharmacol, 1980. 17:p14–19.

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19. Wray, GM., et al., Severe septic shock unresponsive to noradrenaline. Lancet, 1995. 346(8990):1604.

20. Trilli, LE., et al., Lisinopril overdose and management with intravenous angiotensin II. Ann Pharmacother, 1994. 28(10): p1165–8.

21. Newby, DE., et al., Enalapril overdose and the corrective effect of intravenous angiotensin II. Brit J Clin Pharmaco, 1995. 40(1): p103–4.