**SUBMITTED BY:** **STEPHEN M. LANIER, VICE PRESIDENT FOR RESEARCH**

**UNIVERSITY CONTRACT FOR RESEARCH**
**AND SERVICES FROM QPATHOLOGY**
**A COMPANY CO-OWNED BY A SCHOOL OF MEDICINE**
**FACULTY MEMBER**

**RECOMMENDATION**

The Administration recommends that the Board of Governors authorize the President or his designee to enter into three (3) multi-year contracts with QPathology (QP). The contracts are for evaluation and elucidation of the role of zinc in different human pathologies, and will initially focus on: (1) the ability of thymulin (a zinc-controlled peptide) to modulate T cell maturation and improve cancer immunotherapy; (2) the ability of zinc to decrease inflammation and chronic illnesses in the elderly; and (3) the ability of zinc to improve cardiovascular reactivity and reduce stroke in patients with type 2 diabetes (please see Appendix for synopses, proposed budgets and timelines). Importantly, all of the techniques and expertise necessary to complete these projects are available in the WSU laboratories of Ananda Prasad, MD, PhD and Andrew Fribley, PhD (Elliman and Lande), Warren Lockette, MD (Scott Hall and IBio), and Steven Firestine, PhD (Eugene Applebaum School of Pharmacy).

**BACKGROUND**

Dr. Ananda Prasad, MD, PhD is a Distinguished Professor, Department of Oncology, School of Medicine. He was the first person to show that zinc is essential to humans and that zinc deficiency occurred in the Middle East. He also noted that many of these early-onset zinc deficient individuals died in their mid-20s from pneumonia or parasitic infections and he interpreted this to indicate that zinc affected the immune system. He also reported that zinc deficiency decreased thymulin activity and the generation of Th-1 cytokines. In 1974 his reports led the National Research Council to declare that zinc was essential for humans; his recommendations were adopted by the US Congress.

QPathology (QP) was founded in 2018 by Drs. Octavian Bucur, MD, PhD, Co-Founder and CEO, and Bhanu P. Jena, PhD, Co-Founder and President. QP is a next generation medical services company and is also registered with the National Institutes of Health as a Contract Research Organization. QP seeks to become the world leader in characterizing the role of zinc and zinc-binding agents and their analogues in biology. QP has reached out to Professor Prasad to invite him to assist with the design and development of experimental procedures that can better characterize how zinc regulates the immune system and, specifically, the role in regulating cytokine production. Drs. Prasad and Fribley have provided results from QP sponsored preliminary studies that have now led to additional and substantial investments by QP in their research program.

Michigan Conflict of Interest law requires specific sunshine procedures in order for a University employee, or a company owned by a University employee, to contract directly or indirectly with the University:

(A) The employee must disclose any pecuniary interest in the contract to the Board and the disclosure must be made a matter of record in the Board's proceedings.

(B) The contract must be approved by a vote of not less than two-thirds of the full membership of the Board in open session.

(C) The Board's minutes must report:

(i) The name of each party involved in the contracts.

(ii) The terms of the contract, including duration, financial consideration between the parties, facilities or services of the public entity included in the contract, and the nature and degree of assignment of employees of the public entity for fulfillment of the contract.

(iii) The nature of any pecuniary interest.

If the Board of Governors approves this Recommendation, the minutes will report as follows:

The Board of Governors authorized the President or his designee to enter into three (3) agreements to provide up to $7,615,977 in services with QPathology beginning with the approval of this contract and ending in July, 2025.

(i) The parties involved in the contract are Wayne State University and QPathology.

(ii) The contracts will provide:

(a) These contracts are for the generation of data during these multi-year research studies. The contracts allow for the retention of key research personnel in the Prasad-Fribley lab, individuals who, combined, have many years of experience with the procedures to be used in this study and for the purchase of necessary equipment ,reagents, supplies computers, publication and travel as described in the PI's budgets and budget justifications.

(b) Duration: The contracts will be for 60 months.

(c) Financial Consideration: The amount of the contracts will not exceed $7,615,979 which includes QP's indirect cost rate of 20%. Semi-annual payments by QP are contingent upon QP's receipt of a semi-annual Progress Report which will be due 30 days prior to the semi-annual payment.

- Project 1: The role of zinc and synthetic thymulin analogs in the development of natural killer cells and cancer immunotherapy
    - January 1, 2020 – December 31, 2025
    - $3,308,666 includes IDC at 20%
- Project 2: Clinical study to determine if zinc supplementation can improve insulin resistance, inflammation and immunity in the elderly

- January 1, 2020 – December 31, 2025
- $1,917,578 includes IDC at 20%

- Project 3: Zinc improves cerebrovascular morbidity in patients with diabetes

  - January 1, 2020 – December 31, 2025
  - $2,389,733 includes IDC at 20%

(d) University facilities to be utilized include the laboratory of Drs. Ananda Prasad and Andrew Fribley in the Elliman Building and Lande Buildings on the SOM campus, and also ancillary facilities at Scott Hall, the Karmanos Cancer Center, and the Integrative Biosciences Building, and the Eugene Applebaum College of Pharmacy, all at WSU.
(e) Employees Assigned to the Services: Ananda Prasad, MD, PhD, Distinguished Professor, Department of Oncology and Andrew Fribley, PhD will be the Co-Principal Investigators for these services to prevent any conflicts of interest, real or perceived, that may arise in the conduct of the laboratory services.

(iii) Dr. Jena's pecuniary interest consists of co-ownership of QPathology. He receives no compensation from this contract. As a co-founder of QPathology he has the potential to financially benefit from the commercial success of the company.

**Appendix**
**Projects and Abstracts**

1. **THE ROLE OF ZINC AND SYNTHETIC THYMULIN ANALOGS IN THE DEVELOPMENT OF NATURAL KILLER CELLS AND CANCER IMMUNOTHERAPY**

   Principal Investigators: Ananda S. Prasad, MD and Andrew M. Fribley, PhD; Steven M. Firestine, PhD (Co-I).

   Thymulin is a thymic hormone that is secreted by two distinct epithelial populations in the thymus; it is a nonapeptide, with the sequence H-Pyr-Ala-Lys-Ser-Gln-Gly-Gly-Ser-Asn-OH, that requires ionic zinc (Zn2+) for its biological activity. Thymulin is well known for its ability to modulate immune system function. The production of thymic hormones naturally decreases with age and thymulin is often seen at lower levels in cases of autoimmune diseases, chronic infection illnesses, diabetes, Lyme disease and cancer. A recent focus by our group and others has been to elucidate the role of thymulin as an effector on proinflammatory mediators/cytokines. ***We hypothesize that synthetic thymulin peptides can be used to increase the generation of T cytotoxic and natural killer (NK) cells in vitro and in vivo to improve anticancer immunotherapy.*** In **Specific Aim #1** we will characterize the ability of a zinc-dependent synthetic thymulin peptide/s (STP) to generate T cytotoxic cells in vitro. In **Specific Aim #2** we will elucidate the ability of STPs to increase T cytotoxic and NK cells in vivo and to overcome limitations associated with current immunotherapy approaches in cancer. In **Specific Aim #3** we will generate novel thymulin analogs that: (i) more tightly bind zinc; (ii) mimic the three-dimensional active (zinc bound) thymulin in the absence of zinc.

**Budget**

03/01/2021 – 07/31/25

**Semi-annual funding for this project: $330,814 ($275,678 direct costs + $55,136 indirect costs)**
Release of each semi-annual funding is conditioned by the submission of satisfactory detailed quarterly Research Reports by the PI. Research Reports have to be submitted no later than the 26$^{th}$ day of the 3$^{rd}$, 6$^{th}$, 9$^{th}$ and 12$^{th}$ month of each year.

2. **CLINICAL STUDY TO DETERMINE IF ZINC SUPPLEMENTATION CAN IMPROVE INSULIN RESISTANCE, INFLAMMATION AND IMMUNITY IN THE ELDERLY**

   Principal Investigators: Ananda S. Prasad, MD and Andrew M. Fribley, PhD

   The study will consist of up to 100 elderly patients randomized to 50mg zinc gluconate supplement per day or placebo control over the course of one year in a double-blind fashion. At the current time, there are no plans for a cross-over of the study groups. W will obtain 20ml of freseh whole blood from each subject every three months over the course of the study; the plasma will be archived at -80C at WSU in two ~5ml aliquots to complete the studies outlined below. ***We hypothesize that inflammatory and oxidative stress cytokine expression will be***

***higher in subjects with low zinc levels.*** In **Specific Aim #1** we will determine endogenous thymulin and zinc levels in zinc-supplemented and placebo treated elderly subjects in southeast Michigan. In **Specific Aim #2** we will define the level of expression of a panel of ~20 cytokines and other markers of inflammation and oxidative stress in the same patients in Specific Aim 1. **In Specific Aim #3** we determine the level of inflammatory and oxidative stress mRNA from primary cultures of lymphocytes and monocytes from whole blood from zinc supplemented and placebo controlled elderly subjects. These assays have been routinely performed by our group and are included and further described in our previously approved WSU IRB protocol (065013 M1E).

**Budget**

03/01/2021 – 07/31/25

**Semi-annual funding for this project: $191,727 ($159,773 direct costs + $31,954 indirect costs).** Release of each semi-annual funding is conditioned by the submission of satisfactory detailed quarterly Research Reports by the PI. Research Reports have to be submitted no later than the 26th day of the 3rd, 6th, 9th and 12th month of each year.

**3. ZINC SUPPLEMENTATION IMPROVES CEREBROVASCULAR MORBIDITY IN PATIENTS WITH DIABETES**

Principal Investigators: Ananda S. Prasad, MD, PhD, Warren Lockette, MD and Andrew M. Fribley, PhD

Diabetes mellitus causes adverse microvascular and macrovascular changes than can culminate in stroke or myocardial infarction. Also, when compared to well controlled patients, poor glucose control in men and women with diabetes mellitus confers a much greater risk of stroke and myocardial infarction. For these reasons, it is important to maintain euglycemia in patients with diabetes mellitus. Several studies have consistently shown *supplemention with oral zinc improves glycemic control in patients with diabetes mellitus*. Zinc supplementation has been associated with an absolute fall in glycosylated hemoglobin (HgbA1c), a measurement of metabolic control, by 0.5 percentage points. This is a meangful finding—for every 1% incremental increase in HbA1c concentration, in both diabetes mellitus and non-diabetes mellitus cohorts, there are significantly higher risks for first-ever ischemic stroke with an average hazards ratio of 1.49 and 1.24, respectively. Although zinc supplementation improves glycemic control, *it is unknown* whether this dietary manipulation improves the intermediate phenotypes of cardiovascular reactivity that contribute to ischemic stroke or myocardial infarction. ***We postulate that zinc supplementation, when compared to placebo, will significantly reduce the increased cardiovascular reactivity associated with thrombotic stroke or myocardial infarction in men and women with diabetes mellitus.*** We will conduct a randomized, double-blinded, cross-over study in forty patients with diabetes mellitus in which subjects receive either three months of placebo or oral zinc acetate (11 mg elemental zinc/day). In **Specific Aim #1**, we will show that zinc supplementation, when compared to placebo, enhances flow mediated endothelium-dependent vasodilation in the peripheral vasculature. In **Specific Aim #2**, we will show that zinc supplementation, when compared to placebo, improves *dynamic cerebrovascular autoregulation*. Dynamic cerebrovascular autoregulation refers to the inherent ability of cerebral blood vessels to maintain blood flow in response to a rapid change in arterial blood pressure via rapid counter-

regulatory changes in the vascular resistance of the cerebral arteries. In **Specific Aim #3**, we will show that zinc supplementation, when compared to placebo, improves *cerebrovascular reactivity*. Cerebrovascular reactivity is measured by assessing the intracerebral vascular responses to agonists that selectively relax the cerebral vasculature relative to the peripheral vasculature; acetazolamide and inhaled $CO_2$ directly act upon cerebral resistance vessels. In **Specific Aim #4**, we we will show that zinc supplementation, when compared to placebo, does not adversely affect stress-induced platelet aggregaton. Others have shown that zinc-deficient states increase the potential for hemorrhage.[4] And we have previously shown that both vascular reactivity and platelet reactivity are dependent upon the activity of the zinc-dependent enzyme, carbonic anhydrase, in blood vessels and in platelets. Accordingly, *it is necessary to determine whether the improvement in glucose metabolism induced by zinc supplementation is accompanied by a salutary effect on the intermediate phenotypes that predisose men and women with diabetes mellitus to greater cardiovascular morbidity*.

**Budget**

03/01/2021 – 07/31/25

**Semi-annual funding for this project: $238,935 ($199,113 direct costs + $39,822 indirect costs)**
Release of each semi-annual funding is conditioned by the submission of satisfactory detailed quarterly Research Reports by the PI. Research Reports have to be submitted no later than the 26th day of the 3rd, 6th, 9th and 12th month of each year.