MEMORANDUM OF UNDERSTANDING (MoU)

Between

COCHIN UNIVERSITY OF SCIENCE AND TECHNOLOGY (CUSAT)
KOCHI – 682022

&

PUSHPAGIRI RESEARCH CENTRE
Thiruvalla- 689101

This MOU is made and executed on this 18th day of December 2019 at _____ by and between

Cochin University of Science and Technology (CUSAT) established by CUSAT Act 1986 is a leading science and technology University in India, which has three campuses: two in Cochin and one in Kuttanad, Alappuzha, and provides university level education in the field of Engineering, Environmental Studies, Humanities, Law, Marine Sciences, Medical Sciences & Technology, Science, Social Sciences and Technology (hereinafter called "CUSAT" which expression shall where the context so admits include its successors and permitted assignees) party of the one part, represented by its Registrar, Dr.K.Ajitha.

AND

Pushpagiri Research Center(PRC) represented in this MoU by , Pushpagiri Groups of Institutions as the authorized signatory hereinafter referred as the PRC as the second party (hereinafter referred to as **PRC",** which expression, unless it be repugnant to the context shall mean and include its successors and assigns) of the other part,represented by its Drector,Rev,Dr.Mathew Mazhavancheri.

Pushpagiri Research Centre, was established in the year 2009 and it is a recognized centre for Ph. D. under the Kerala University of Health Sciences (KUHS). The centre is a DSIR (Department of Scientific and Industrial Research) recognized Scientific and Industrial Research Organization (SIRO). Situated in the campus of Pushpagiri Institute of Medical Science and Research Centre, PRC features open-plan, multifunctional research laboratories. Focusing on advanced quantitative approaches to specific biotechnology challenges at the interface of medicine and biology, the PRC offers a unique pluralistic and open research culture that is supposed by world-class infrastructure.

Pushpagiri Institute Of Medical Sciences has a multi disciplinary ,ISO 9001:2000 certified, super specialty hospital, is working with the following Departments: General Medicine, Cardiology, Psychiatry, Dermatology, TB & Chest, Gastroenterology, Neuro Medicine, Pediatric Surgery, General Surgery, Orthopedics, Physical Medicine, ENT, Ophthalmology, Pediatric Medicine, Urology, Nephrology, Neuro Surgery, Plastic Surgery, Multi specialty Dental Clinic, Obstetrics & Gynecology, Radio diagnosis, Anesthesiology, Emergency & Trauma care, Diabetology& Endocrinology.

Pushpagiri College of Dental Sciences started in the year 2006 with an annual intake of 50 students in BDS course and also offers PG courses for the Department of Oral and Maxillofacial Surgery, Periodontics, Prosthodontics, Orthodontics and Endodontics

WHEREAS "CUSAT" has been covering all the major engineering, science and humanities disciplines, offering BTech, MSc, MA, MBA, LLB, LLM, MCA, MTech, MFSc, M.Phil and PhD programmes. CUSAT Kochi has world-class infrastructure for carrying out advanced research and has been equipped with a variety of state-of-the-art scientific and engineering instruments. The major thrust of the Department of Biotechnology includes neurobiology, plant biotechnology, nanobiotechnology, computational biology, cancer biology, infectious diseases and proteomics.

AND WHEREAS, both parties have come forward to work together in the area of common interest. Now therefore the parties have decided to sign this MoU to define the scope, roles and responsibilities to implement the project.

1. OBJECTIVE OF THE MOU

In order to promote scientific and cultural co-operation between Pushpagiri Research Center (PRC) and Cochin University of Science and Technology (CUSAT) Kochi, the following general forms of cooperation will be pursued:

- Fostering collaborative research opportunities through academic visits, meetings, lectures, workshops etc.
- Joint research activities, collaborative research projects and publications in areas mutually agreed upon.
- Exchange of scientific materials and information of common interest including data, study reports, books, publications, course information etc.
- Joint training programs for project staff/PhD students pertaining to specific projects undertaken in collaboration.

2. JOINT RESPONSIBILITIES

- To ensure that cooperation as stated under this MoU are accomplished within stipulated time.
- Each Institute shall designate a coordinator to develop and implement specific activities and programs.

RESPONSIBILITIES OF CUSAT

FIRST YEAR

Work I: Development of inherently radiopaque sol – gel bioglass formulations and membranes with superior angiogenesis potential for periodontal bone regeneration

- Design and synthesis and optimization of inherently radiopaque sol – gel bioglass formulations and membranes with superior angiogenesis potential

- Physico-chemical characterizations of the as – synthesized samples such as:
  - Phase purity and crystallinity evaluation by X-Ray diffraction analysis
  - Functional group evaluation by FT-IR spectral analysis
  - Thermal stability studies by Thermogravimetric analysis
  - ICP analysis for finding the elemental composition.
  - Porosity and surface area evaluation by BET analysis
  - Ultrastructural analysis by Transmission electron Microscopy
  - Quantitative Radiopacity evaluation by micro CT Analysis
- Bio-functional evaluation of radiopaque bioglass formulations
  - Determination of Ion dissolution in simulated body fluid by ICP analysis
  - *In vitro* Bio-mineralization assay of radiopaque bioglass formulations in simulated body fluid and evaluation of apatite formation ability SEM/EDAX/ Elemental mapping.
  - Fabrication of electrospun GTR membranes of biodegrable polymers with varying radiopaque sol – gel bioglass content.
- Cell culture and maintenance (MG-63 cell lines)

- Biological evaluations - *In vitro*
    - Cytocompatibility and cell proliferation evaluation by MTT assay
    - Evaluation of nanoparticle uptake by the MG-63 cells
    - Alkaline Phosphatase (ALP) assay: Assessment of osteogenic differentiaition by measuring a time course of ALP activity of **MG-63 cells** grown on radiopaque bioglass formulations.
    - Alizarin red staining study to visualize and quantitative estimation mineral (calcium) deposits.

Work II : Development of biomimetic bone-grafts from collagen/chitosan based formulations/scaffolds for orthopedic applications

- Evaluation of degree of purity of collagen membranes obtained from PRC
- Physicochemical characterizations of as-obtained collagen/chitosan membranes/formulation/scaffolds.
- Density and Porosity of the formulations/scaffolds by Water displacement method and liquid intrusion porosimetry analysis.
- *In vitro* bio-degradation study of the as-synthesized formulations/scaffolds in two biologically related media: phosphate buffered solution (PBS) and simulated body fluid (SBF).
- Development of biomimetic bone grafts by biomimetic modulation of collagen/chitosan scaffolds with intrinsic bone regeneration potential
- *In vitro* Bio-mineralization assay of the newly developed biomimetic bone-grafts in simulated body fluid and evaluation of apatite formation potential by SEM/EDAX/ Elemental mapping.

Work III : Development of Antibacterial wound healing patches

- Isolation and purification of natural antibacterial agents from plant sources for with wound healing potential.

SECOND YEAR

Work I

- Isolation of bone marrow mesenchymal stem cells from Sprague dawley rats, cell culture and maintenance.
- Alkaline Phosphatase (ALP) assay: Assessment of osteogenic differentiaition by measuring a time course of ALP activity of bone marrow cells grown on radiopaque bioglass formulations.
- Determination of the ability of radiopaque bioglass formulations to stimulate the secretion of angiogenic growth factors from bone marrow mesenchymal stem cells and subsequent angiogenesis by the measurement of vascular endothelial growth factor (VEGF) secretion.

Work II

- Evaluation of transformation of collagen based formulations/scaffolds as orthopedic agents
- Bioloical evaluations
    - Isolation of bone marrow cells mesenchymal cells from Sprague dawley rats, culture and maintenance.

- *In vitro* biological evaluations using bone marrow mesenchymal stem cells such as Alkaline phosphatase assay, Alizarin red staining, Von kossa staining etc.

Work III

- Antibacterial susceptibility testing by various assays using different bacterial strains such as E. Coli, S. aureus, S. aeroginosa etc.
  - Minimal inhibitory concentration (MIC) test to find out the minimal concentration of an antimicrobial agent required to inhibit the growth of a given bacterial strain.
  - Agar disc diffusion assay to find out the diameter of zone of inhibition.
  - Time kill test to reveal the time-dependent or concentration-dependent antimicrobial effect.
  - Antimicrobial gradient method (E test) to find out the minimal inhibitory concentration.
- *In vitro* biological evaluations of the extracted antibacterial agents from natural plant sources.
  - Cytocompatibility evaluation by MTT assay
  - Nanoparticle uptake study etc.

- *In vitro Wound healing assays*

THIRD YEAR

Work I

- Assisting clinical trials/ Product development activities of inherently radiopaque sol – gel bioglass formulations/membranes with superior angiogenesis potential.

Work II

- Assisting clinical trial/Phase III of Product development activities of collagen based formulations/ scaffolds for orthopedic applications.

Work III

- Assisting clinical trial/Phase III of Product development activities of antibacterial wound healing patches from natural plant sources.

RESPONSIBILITIES OF PRC

FIRST YEAR

Work II

- *In vitro* cell culture studies
    - Cell culture and maintenance
    - Biological evaluations - cytocompatibility evaluation by MTT assay, BrdU assay, cell adhesion evaluation etc.

SECOND YEAR

Work I

- Animal experiments according to standard implantation procedures of animal ethics committee - Creation of defects of 2mm x 6mm diameter on the femur of the Wi star rats followed by implantation of both test as well as control samples into the defect site and subsequent physical observation of the animals during the particular time period of implantation by micro CT evaluation.
- Biochemical analysis for the evaluation of serum and blood parameters.
- Molecular evaluations – Identification of biomarkers and gene expression studies
- Periodical sacrifice of the animals and retrieval of the implants
- Biofunctional evaluations –

  (a) Histopathological evaluation by H&E staining

  (b) New bone bone formation V-P staining

  (c) Mason trichrome staining assay

  (b) Immunohistochemistry analysis.

Work II

- Purification of collagen membranes
- *In vitro* analysis of the collagen membranes
- *In vitro* biofunctional analysis of biomimetically modulated collagen membranes

- Animal experiments according to standard implantation procedures of animal ethics committee - Creation of defects of 2mm x 6mm diameter on the femur of

the Wi star rats followed by implantation of both test as well as control samples into the defect site and subsequent physical observation of the animals during the particular time period of implantation by micro CT evaluation.

- Biochemical analysis for the evaluation of serum and blood parameters.
- Molecular evaluations – Identification of biomarkers and gene expression studies
- Periodical sacrifice of the animals and retrieval of the implants
- Biofunctional evaluations –

  (a) Histopathological evaluation by H&E staining

  (b) New bone bone formation V-P staining

  (c) Mason trichrome staining assay

  (b) Immunohistochemistry analysis.

Work III

- Animal studies according to standard excision wound model procedures of animal ethics committee – Using toothed forceps and pointed scissors circular excision wound of 300 - 400 mm^2 and 2 mm depth will be made by cutting outer layer of skin from the shaven area. In the control group, the wound would be left open, whereas, the developed wound healing patches will be applied topically on excised wound. Percentage reduction in wound area with respect to initial wound area will be calculated during several time periods.
- Evaluation of biochemical parameters such as hydroxoproline, collagen and hexosamine etc.
- Histopathological evaluation by haematoxylin and eosin staining.

THIRD YEAR

Work I

- Clinical evaluation of inherently radiopaque sol – gel bioglass formulations/membranes with superior angiogenesis potential.

Work II

- Clinical evaluation of biomimetic bone-grafts from chitosan and collagen based formulations/ scaffolds for orthopedic applications.

Work III

- Clinical evaluation of antibacterial patches for wound healing applications.

3. FINANCIAL ASPECTS

Research student/Project staff exchange: Unless otherwise agreed upon in writing for some particular case, travelling expenses will be borne by the visitor's own institute/university as per their rules.

Faculty exchange: Unless otherwise agreed upon in writing for some particular case, expenses like traveling, stay, food etc. will be borne by the visitor's own institute/university as per their rules.

4. CONFIDENTIALITY AND NON-DISCLOSURE

Any software/hardware material, product specifications, designs, financial, technical information, documents etc. shall be deemed to be in private domain and it shall not be made public or shared with any other party without the prior written consent of the party which owns it.

5. INTELLECTUAL PROPERTY RIGHTS SHARING

5.1 Pre-existing IP shall be owned by respective owner.

5.2 All existing IP of PRC shall be owned by PRC and existing IP of CUSAT shall be owned by CUSAT.

5.3 For new IP generation, a separate agreement shall be initiated with mutual consent by both the parties, for each project/program.

5.4 The projects proposed in this MoU will be leading to clinically significant products for orthopeadic, periodontal and wound healing applications. Both CUSAT and PRC organizations will be equally benefited in terms of technology transfer by the MoU through the successful conduct of the projects and present opportunities for the development and growth of biomedical industries in India

6. ENTIRE MOU AND AMMENDMENTS

6.1 This MOU represents the entire understanding between CUSAT and PRC and supersede any and all understanding either oral or written hitherto with respect to the subject matter of the MOU.

6.2 No amendments or modification of the MOU shall be valid unless same is made in writing and signed by the parties. The modifications/changes shall become part of the MOU from the date on which they are made / executed, unless otherwise agreed to.

6.3 The terms of cooperation under this MoU shall be mutually discussed and agreed upon in writing by both parties prior to the initiation of that activity. Details of the implementation of any particular/further collaboration agreement shall be negotiated between the two Institutions as and when a specific case arises. Such agreement will be legitimized by the completion of a specific Memorandum of agreement.

7. FORCE MAJEURE

Neither the party shall be responsible or liable for any failure to perform any of the terms and conditions of the present agreement, due to unforeseen circumstances or causes beyond the reasonable control of either party, including but not limited to acts of God, war, riot, embargoes, acts of civil of military actions, fires, floods, accidents, terrorist activities, strike, quarantine, civil commotion, action of government in its sovereign capacity or shortage of transportation, facilities, fuel,

energy, labour or materials. In the event of any such delays, delivery date for a period equal of the time of such delay may be decided on mutual understandable basis. If force majeure continues beyond six months the parties will then decide the future course of action.

8. EFFECTIVE DATE AND DURATION OF THE MOU

8.1. This MOU shall be effective from the date of signing and remain valid for a period of 3 years.

8.2. The validity of the MOU may be extended by an agreement in writing and signed by both the parties.

9. ARBITRATION

9.1. In the event of any dispute or difference between the parties hereto, such disputes or differences shall be resolved amicably by mutual consultation. If such dispute or difference is not resolved then such difference shall be referred to an Arbitrator as the proceedings shall be as per **the Arbitration and Conciliation (Amendment) Act, 2015**. The decision of the Arbitrators shall be final and binding upon parties to the dispute. The arbitration proceeding shall be held at Kochi. This MoU shall be governed and interpreted in accordance with the Indian Laws.

In witness whereof, the parties hereto have signed this MOU on the day, month and year mentioned herein before.

Parties:

For and on behalf of
Cochin University of Science
And Technology (CUSAT)

Name: Dr. K. Ajitha

Designation: REGISTRAR

For and on behalf of
Pushpagiri Research Centre

Name: Rev. Dr. Mathew Mazhavancheril

Designation: DIRECTOR

Witnesses (Name & address)

Name: Mr. Vinod Kumar P.
Designation: Director IRAA

Witness (Name and Address)

Name: Dr. Yogesh Dalvi
Designation: Scientist & Research Coordinator

Witnesses (Name & address)

Name: Dr. Sailaja G. S.
Designation: Associate Professor
PS &RT
Cochin University of Science and Technology (CUSAT)

Witness(Name and Address)

Name: Dr. Nebu George Thomas
Designation: Professor in Periodontics Department & Scientist
Pushpagiri Research Centre
Thiruvalla