Research is seeing what everybody else has seen,
and thinking what nobody else has thought

- Albert Szent-Györgyi

Ganga Orthopaedic Research and Education Foundation

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GOREF

Ganga Orthopaedic Research and Education Foundation

" Research for Humanity"

Three Arms of Translational Research at Ganga

Ganga Orthopaedic Research & Education Foundation (GOREF) was established in 2002, to facilitate and conduct research in all aspects of orthopaedic surgery, in both clinical and basic sciences. GOREF is recognized by Scientific and Industrial Research Organization (SIROs), Ministry of Science & Technology, New Delhi. It directs and funds the research in both clinical and basic science divisions in musculoskeletal pathology. The strength of GOREF is its focus on translational research and its ability to harness the strength of Ganga Hospital, one of the largest clinical orthopaedic units in the country and Ganga Research Centre, a unit of basic science specialists skilled in genomics, proteomics and bio-informatics. The entire work of GOREF is thus oriented to the need of the hour – translational research focused on solving more than 50 million patients with musculoskeletal problems worldwide.

Ganga Hospital, Coimbatore, with 450 beds and 21 operating theatres is one of the largest orthopaedic clinical units in South Asia. Annually, more than 25,000 major surgeries are performed and has an out-patient strength in excess of 50000 new patients and total outpatient attendance of 1, 50,000 every year. The strongest feature of the hospital has been the proper blend of clinical, academic and research activities, all focussed towards better patient care.

Ganga Research Centre (GRC) was founded in 2015 as the basic science research wing of GOREF to seek solutions for musculoskeletal diseases at molecular level through OMICS approach. The ultimate aim is to unravel the etiology of ageing and degeneration of musculoskeletal tissues and seek solutions at molecular level. Cutting-edge technologies of genomics and proteomics will be utilized to identify biomarkers and probe possibilities of prevention and reversal of diseases.

Ganga Orthopaedic Research and Education Foundation

Vision

To understand, treat and prevent musculoskeletal diseases at molecular level

Mission

Harnessing translational research for patients benefit

As infectious diseases are being controlled, non communicable diseases exert a significant influence on the health and well being of the society. Musculoskeletal disorders play a lead role with low back pain and joint diseases crippling more than 50 million patients worldwide. The incidence of these diseases continue to increase in alarming proportion irrespective of whether it is a under-developed or developed country.

While there is an urgent need to prevent these diseases, a complete understanding of the etiology and preventive aspects are still elusive. This is mainly because clinical and basic science research have been compartmentalised and translational research in this field is sparse. GOREF was set up to overcome this deficiency and is uniquely poised to perform high quality translational research by bringing together the clinical wealth of Ganga Hospital and the basic science capabilities of Ganga Research Centre. The knowledge gaps arising out of the treatment of more than 50,000 new patients with musculoskeletal diseases every year is addressed by a group of focused basic science specialists and this unique strength has already produced quality research which has won many international awards and numerous highly cited publications.

We look forward to focused research that will solve patient's problems and place India on a place of pride in the world map of musculoskeletal research.

Prof. S. Rajasekaran PhD.,
Chairman, GOREF

Half of science is putting forth the right questions.
- Sir Francis Bacon

Huge Clinical load with the entire spectrum of musculoskeletal disorders

Out-patient strength in excess of 50000 new patients

Total outpatient attendance of 1,50,000 every year.

20000 major surgeries per year

Knowledge Gaps from Clinical Practice

Addressed by Translational Research

Ganga Research Centre

Ganga Research Centre (GRC) was founded in 2015 as the basic science research wing of GOREF to seek solutions for musculoskeletal diseases at molecular level through OMICS approach. It has excellent infrastructure and human resource for performing the basic science component of the research through protomics and genomics with high quality bioinformatics support.

Infrastructure

Proteomics

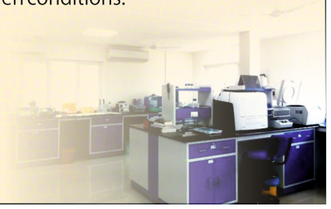
Proteomics Laboratory is equipped with the impedimentum necessary for sample quantification (Varioskan Lux), sample pre-fractionation device (MiniVE, BioRad), isoelectric focusing (IEF) units (Ettan™ IPGphor III, GE), Two-dimensional gel separation units (Ettan™ DALTsix, GE), SpeedVac™ Concentrator, Chemi-Doc It for imaging gels. This state-of-the-art equipment allows us to conduct and provide various proteomics analysis such as separation, identification, characterization and quantification of proteins expressed in biological samples. LC-MS/MS services are outsourced from the national DBT facilities. The Proteomics Laboratory is also equipped with various devices for downstream validation study (ELISA, Western blot and immunohistochemistry).

Genomics

Our recent findings of bacterial presence and host defence response has urged us to probe deeper into the question of whether sub clinical infection by commensal organisms can be the main initiating factor for disc disease. The research centre has facilities for isolating DNA using LN2 and quantifying the DNA with Nanodrop which will be subjected to metagenomics using Nextgen Sequencing (NGS) and shot gun technology which will be outsourced.

Bioinformatics

For big data analysis obtained from OMICS, the research centre is equipped with a high end server Power Edge™ R740 with Intel® Xeon® Silver 4114 2.2G, with appropriate 128GB LRDIMM memory capacity and RAM expandable up to 3TB. All open source Metagenomic softwares like QIIME, Mothur, Alignment tools(Bowtie, MetaVelvet, BWA) & Proteomics software such as Proteome Discoverer (version2.2), Cytoscape (Version 3.6.1), STRING (Version 10.5), MAXQuant allows us to apply rapid, objective and reliable statistical analyses using STATISTICA assist us in identifying molecules of interest involved in normal and altered disc biology under any given conditions.



Ganga Research Team

Prof. S. Rajasekaran
Principal investigator & Director (Clinician)

Dr. Chitra Tangavel
Co-Principal investigator &
Research Coordinator (Biotechnology)

Dr. K. S. Sri Vijay Anand
Senior Research Fellow (Clinician)

Dr. S. Dilip Chand Raja
Senior Research Fellow (Clinician)

Ms. Sharon Miracle Nayagam
Junior Research Fellow (Biotechnology)

Ms. Monica Steffi Matchado
Junior Research Fellow (Bioinformatics)

The research team is lead by Prof S Rajasekaran who directs and co-ordinates the translational research of the clinical team at Ganga Hospital and the basic science team of the Ganga Research Centre. He had his PhD in the field of spinal tuberculosis from the Tuberculosis Research Centre, Chennai and subsequently has focused on clinical and basic science research in the field of disc degeneration and low back pain. Dr Chitra Tangavel, Research Co-ordinator, Ganga Research Centre is a PhD in proteomics and heads the basic science team. Dr Sri Vijay Anand and Dr Dilip Chand Raja form the clinical team and Ms. Sharon MIracle Nayagam (Biotechnology) and Ms. Monica Steffi Matchado (Bioinformatics) fulfill the rest of the basic science team.

"As a young citizen of India, armed with technology and love for my nation,
I realize, a small aim is a crime."
- A. P. J. Abdul Kalam

NATIONAL ADVISORY BOARD

Prof. K Dharmalingam
Director of proteomics research,
Aravind Eye Care System
Madurai

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Tamilnadu Agricultural University
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Prof. Bjorn Rydevik
Department of orthopaedic
surgery at Göteborg University
and Sahlgrenska University,
Gothenburg, Sweden

The art and science of asking questions is the source of all knowledge.
- Thomas Berger

Study Protocol

GOREF (DSIR Approved Centre)

Clinical

Spine Surgery Unit, Ganga Hospital
(approved for PhD studies)
The Tamilnadu Dr MGR Medical University

- 30,000 new outpatients
- >2500 major surgeries
- Highly advanced Radiology service

Elaborate clinical and
Radiological records and follow up

Segregate and identify
Different clinical phenotypes

Spontaneous resolution | Progressive disease | Suspicion of sub clinical infection

Diseased Disc

Approved by
Govt of Tamilnadu under
Transplant act for retrieval of
MSK organs for brain dead patients

Harvest of Lumbar Spine after
Removal of Heart, Lungs Kidney & Liver

Removal of Discs
under Sterile condition

Radiological investigation
to confirm MRI normal Disc

Control Disc

Basic Science

Research Methodology

Patients with Low Back Pain

Clinical and Radiological

- Clinical examination
- History
- Plain radiograph
- MRI
- CT
- DEXA

→ Identify the various radiological patterns

→ Describe the radiological phenotypes at risk for Low Back Pain

Biochemical

- Blood investigations
  - ESR
  - CRP
  - CBC
  - VITAMIN D
  - RBS
  - HbA1c
- Cytokine analysis

→ Identify inflammatory pathways

→ Develop biomarkers for early diagnosis of disc disorders

OMICS

- Proteomics
- Metagenomics

→ Identify the protein profile of normal and diseased disc

1. Understand the differences in process of ageing and degeneration
2. Probe the initiating factors of degeneration at proteomic level
3. Document host defence response to infection

→ Identify the microbiome of disc

1. Does normal disc contain bacteria?
2. Document the entire bacterial spectrum in disc tissue
3. Do these bacteria proliferate & initiate inflammation?

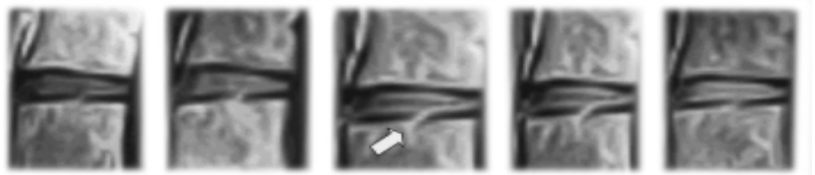
International Awards for Research in Low Back Pain

1) Non -invasive evaluation of intervertebral disc/ Endplate

2004-ISSLS prize winner: Spine (Phila Pa 1976)2004 Dec 1;29(23):2654-67.

A study of diffusion in human lumbar discs: a serial magnetic resonance imaging study documenting the influence of the endplate on diffusion in normal and degenerate discs.

Diffusion studies in MRI as a non-invasive method to assess the physiologic status of disc and endplate was introduced for the first time. The study described reliable signs by which end plate cartilage damage can be identified and the method claimed to be beneficial in studying the effect of drugs, smoking, loading and exercise on physiology of disc.



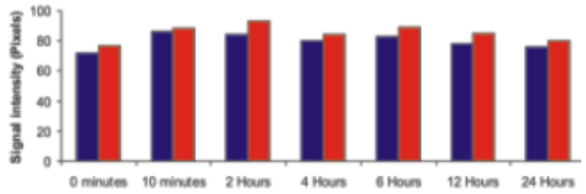
Serial post-contrast MRI study depicting an endplate break by virtue of the absence of endplate delay and diffusion march. The dye directly enters the nucleus pulposus within 10mins of injection.

2) Pharmacological alteration of disc biology

2008-ISSLS-Sofamer Danek Award: Eur Spine J.. 2008 May;17(5):626-43.

Pharmacological enhancement of disc diffusion and differentiation of healthy, ageing and degenerated discs: Results from in-vivo serial post-contrast MRI studies in 365 human lumbar discs.

First study to document a pharmacological enhancement of disc diffusion to improve disc nutrition. It also proposed an Endplate damage score and correlated it with disc degeneration. It is now a widely used scoring system in world to assess severity of disc degeneration.



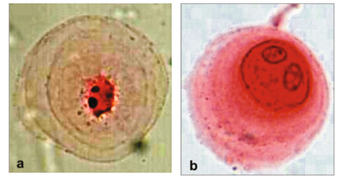
Bar diagrams depicting the enhancement of dignal intensity at all the stages of disc diffusion namely the subchondral bone, endplate and nucleus pulposus. (Blue - precontrast, Red - Postcontrast)

3) Influence of mechanical loading on disc degeneration

2010-ISSLS prize winner: Spine (Phila pa 1976). 2010 Oct 1;35(21):1930-43.

A study of effects of in vivo mechanical forces on human lumbar discs with scoliotic disc as a biological model: results from serial post contrast diffusion studies, histopathology and biochemical analysis of twenty-one human lumbar scoliotic discs.

The study demonstrated the influence of mechanical loading in decreasing nutrition and leading to degeneration on scoliotic disc model by non invasive diffusion studies much earlier stage and discussed its usefulness on timing and choice of surgery.



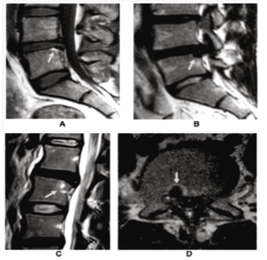
Cell viability was assessed by eosin exclusion method. Viable cells were identifiedby their ability to exclude eosin and maintain clear cytoplasm (a). The cytoplasm of the dead cells accumulated eosin (b).

4) Understanding pathoanatomy of disc herniation

2013-ISSLS prize winner: Spine (Phila Pa 1976) 2013 Aug 1;38(17):1491-500

The anatomy of failure in lumbar disc herniation – an in-vivo, multi-modal, prospective study of 181 subjects.

Our study was the first to show in vivo evidence that LDH in humans is more commonly the result of endplate junction failure than Annulus fibrosus rupture in patients requiring disc surgery. Our results offered clinical validation of previous in vitro mechanical disruption studies.



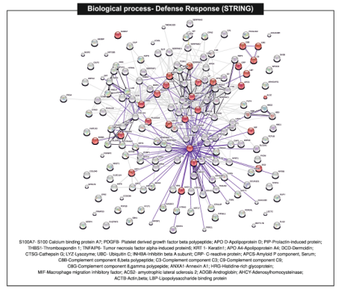
Four types of end plate junction failure in lumbar disc herniation

5) Infection as a cause for disc degeneration

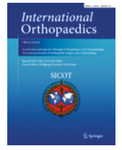
ISSLS PRIZE IN CLINICAL SCIENCE-2017: Eur Spine J.. 2017 May;26(5):1384-1400

Is infection the possible initiator of disc disease? An insight from proteomic analysis.

The Proteomic and 16S rDNA analysis of disc tissues obtained in vivo demonstrated bacterial specific proteins and host defense proteins to infection strengthened the hypothesis of infection as a possible initiator of disc disease. These results can lead to a paradigm shift in our understanding and management of disc disorders.



Other Publications From GOREF



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Research Collaborations & Support

Department of Biotechnology Government of India
Diffusion tensor imaging of the spinal cord and its clinical applications

The University of Hong Kong
Selective Nucleotide Polymorphism analysis for genetic study

Department of genomics and proteomics, TNAU- Coimbatore
Molecular Biology Analysis - Isolation of DNA from blood samples and proteomic analysis of disc specimens

Rush University, Chicago
Functional Element Model Analysis of Post Tubercular Deformity

Department of Biochemistry, University of Delhi
Biochemical analysis for apoptosis and pro-inflammatory cytokines in Disc Degenerative Disease.

Cotrel Foundation, Paris
Role of Mechanical stress on the causation of disc degeneration - scoliotic disc study

Department of Biochemistry and Biotechnology,
Central Leather Research Institute, Adyar, Chennai
Biochemical and collagen alterations in scoliotic discs subjected to abnormal mechanical forces.

AO Spine - Effectiveness and Safety of Batroxobin, Tranexamic Acid and a Combination in Reduction of Blood Loss in Lumbar Spinal Fusion Surgery. The role of Preemptive analgesia in spine surgery

Siemens India
Diffusion Tensor Imaging studies of Spinal cord, Functional MRI studies and Disc diffusion Analysis.

Department of Biotechnology, CMC, Vellore
Electron microscopic analysis of disc specimens with respect to mechanical stress on the concave and convex side of scoliotic discs were analyzed.

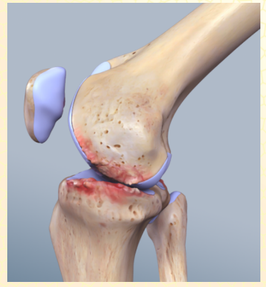
Other Focus of Research

Spinal cord injury (SCI)

- Around 5, 00, 000 individuals suffer a SCI yearly.
- Young males belonging to the most productive age group are most affected.
- SCI is the leading cause of irreversible disability, due to the poor regenerative capacity of the mammalian central nervous system (CNS).
- Paralysis creates a high socio economic burden and results in a minimal annual cost of 42,000$.
- There are no FDA-approved therapeutic interventions in SCI

Potential of proteomics in SCI

1. Identify clinically useful "biomarkers" from CSF or plasma to prognosticate outcomes.
2. Discover the distinct molecular pathways involved in primary and secondary injury to the spinal cord.
3. Prevent secondary injury to the traumatized spinal cord by identifying new therapeutic intervention targets.
4. Explore the possibilities of inducing regeneration in human spinal cord.
5. Modulation of inflammatory and neurotrophic responses to promote recovery after SCI.



Proteomics in other Musculoskeletal (MSK) pathologies

1. Early detection of Osteoarthritis (OA), before the appearance of radiographic changes through biomarkers from blood, serum, synovial fluid, and/or urine to diagnose sub-clinical OA.
2. Enhancement of Bone healing to achieve faster union in fractures.
3. Modulation of Bone remodeling to prevent or manage osteoporosis.
4. Promote healing or repair in soft tissue pathologies such as sarcopenia, articular cartilage, meniscus, ligament and tendon injuries.