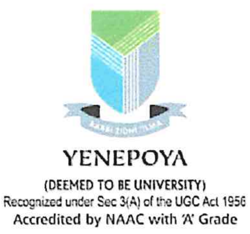

Details of the Collaborative Activity

2016-2021

Name of the Collaborating Institute: Institute of Bioinformatics, International Technology Park, Bangalore, Karnataka, India

Activities:

- Various collaborative research projects were carried out between the Institutes. The activities included:-
- Establishment of the Center for Systems Biology and Molecular Medicine for Proteomic studies
- Joint research projects and publications on mass spectrometry-based Proteomics and Metabolomics
- Student visits for training
- Faculty visits for training

List of Faculty:

- Dr. T.S. Keshava Prasad
- Dr. Aditi Chatterjee
- Dr. Harsha Gowda
- Dr. Sneha M. Pinto
- Dr. Yashwanth Subbannayya
- Dr. Pratigya Subba
- Dr. Prashant Modi

Student/ Faculty Training/Exchange:

1. Mr. Chinmaya Narayana K., Junior Research Fellow, YRC visited Institute of Bioinformatics for Training for Mass Spectrometry during 27.08.2019 to 30.08.2019.
2. Mr. Ajay Balakrishnan, Research Scientist from Institute of Bioinformatics, visited Yenepoya (Deemed to be University) on 25.03.2019 for demonstration and training in the new methodology for the isolation of CTCs.
3. Dr. Prashant Kumar Modi, Assistant Professor, YRC visited Institute of Bioinformatics to use HPLC facility for research work during 17.11.2017 to 18.11.2017.

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4. Mr. Ankur Tayagi, Senior Research Fellow, YRC visited Institute of Bioinformatics on 26.08.2017 for sample processing for his Ph.D. work.

5. Students MS. Oishi Chatterjee, Ms. Lathika Gopalakrishnan, and Mr. Gaurav Dey visited Yenepoya (Deemed to be University) during their Ph.D study from Institute of Bioinformatics.

Joint research publication: 58 research publications and a few significant publications are as follows;

1. Jain A, Patel K, Pinto SM, Radhakrishnan A et al. MAP2K1 is a potential therapeutic target in erlotinib-resistant head and neck squamous cell carcinoma. *Scientific Reports*. 2019; 9(1):18793
2. Sunitha B, Kumar M, Gowthami N, et al. Human muscle pathology is associated with the altered phosphoprotein profile of mitochondrial proteins in the skeletal muscle. *Journal of Proteomics*. 2019; 211:103556.
3. Datta KK, Patil S, Patel K, et al., Chronic exposure to chewing tobacco induces metabolic reprogramming and cancer stem cell-like properties in esophageal epithelial cells. *Cells*. 2019; 8, 949.
4. Patil K, Yelamanchi S, Kumar M, et al., Quantitative mass spectrometric analysis to unravel glycoproteomic signature of follicular fluid in women with polycystic ovary syndrome. *PLoS ONE*. 2019; 4, 14.
5. Sinha S, Ray A, Abhilash L, et al. Proteomics of Asrij perturbation in Drosophila lymph glands for identification of new regulators of hematopoiesis. *Molecular & Cellular Proteomics*. 2019; 8, 1171-1182.
6. Advani J, Verma R, Chatterjee O, et al., Whole genome sequencing of Mycobacterium tuberculosis clinical isolates from India reveals genetic heterogeneity and region specific variations that might affect drug susceptibility. *Frontiers in Microbiology*. 2019; 10:309.
7. Menon D, Singh K, Pinto SM, Nandy A, Jaisinghani N, Kutum R, Dash D, Prasad TSK, Gandotra S. Quantitative lipid droplet proteomics reveals Mycobacterium tuberculosis induced alterations in macrophage response to infection. *ACS Infectious Diseases*. 2019; 5(4):559-569.
8. Subbannayya T, Leal-Rojas P, Zhavoronkov A, et al. PIM1 kinase promotes gallbladder cancer cell proliferation via inhibition of proline-rich Akt substrate of 40 kDa (PRAS40). *Journal of Cell Communication and Signaling*. 2019; 2, 163-177.
9. Nanjappa V, Raja R, Radhakrishnan A, et. al., Testican 1 (SPOCK1) and protein tyrosine phosphatase, receptor type S (PTPRS) show significant increase in saliva of tobacco users with oral cancer. *Translational Research in Oral Oncology*. 2018; 3: 1–11.
10. Sahu A, Gopalakrishnan L, Gaur N, et al., The 5-Hydroxytryptamine signaling map: an overview of the serotonin-serotonin receptor-mediated signaling network. *Journal of Cell Communication and Signaling*. 2018; 12(4):731-735.
11. Selvan LDN, Danda R, Madugundu AK et al., Phosphoproteomics of Retinoblastoma: A pilot study identifies aberrant kinases. *Molecules*. 2018; 23(6):1454.

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12. Pinto SM, Verma R, Advani J. et al., Integrated multi-omic analysis of *Mycobacterium tuberculosis* H37Ra redefines virulence attributes. *Frontiers in Microbiology*. 2018; 9:1314.

13. Rajagopalan P, Patel K, Jain AP, et al., Molecular alterations associated with chronic exposure to cigarette smoke and chewing tobacco in normal oral keratinocytes. *Cancer Biology & Therapy*. 2018; 19(9):773-785.

14. Dhandapani G, Sikha T, Pinto SM, et al. Proteomic approach and expression analysis revealed the differential expression of predicted leptospiral proteases capable of ECM degradation. *BBA - Proteins and Proteomics*. 2018; 1866, 712-721.

15. Kumar M, Varun CN, Dey G, Ravikumar R, Mahadevan A, Shankar SK, Prasad TSK. Identification of host-response in cerebral malaria patients using quantitative proteomic analysis. *Proteomics - Clinical Applications*. 2018; 12(4):e1600187.

16. Babu N, Advani J, Solanki HS, et al, miRNA and proteomic dysregulation in non-small cell lung cancer in response to cigarette smoke. *MicroRNA*. 2018; 7, 38-53.

17. Prasad TSK et al. Integrating transcriptomic and proteomic data for accurate assembly and annotation of genomes. *Genome Research*. 2017; 27, 133-144.

18. Solanki HS, Babu N, Jain AP, et al. Cigarette smoke induces mitochondrial metabolic reprogramming in lung cells. *Mitochondrion*. 2017; 306: L840-L854.

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(Recognized under Sec 3(A) of UGC Act 1956)

MEMORANDUM OF UNDERSTANDING

Between

YENEPOYA UNIVERSITY
Mangalore -575018
India

And

INSTITUTE OF BIOINFORMATICS
Unit-1, Discoverer-7th Floor
International Tech Park
Whitefield,
Bangalore-560066
India

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Collaborative Research and Academic Programme

This memorandum of understanding (MOU) sets down the mutually agreed broad framework fo joint research and academic activities in various fields of interest between Yenepoya Universit (YU) and Institute of Bioinformatics (IOB). It also incorporates the modalities of collaboration.

1. Preamble:

1.1 Yenepoya University is a deemed to be university, mainly engaged in health care delivery an research in health sciences. It has developed a strong basis for patient care, training programme and research activities. YU is also the first unaided Deemed University in the district of Dakshir Kannada, Karnataka. Yenepoya University has four constituent colleges; Yenepoya Dent College, Yenepoya Medical College, Yenepoya Nursing College and Yenepoya Physiotherap College. Yenepoya University has a well-established hospital, Yenepoya Medical College Hospit with 1250 beds with an additional state-of-the-art infrastructure. It offers secondary and tertia health care (super specialty) and treatment free of cost or at highly subsidized rates to all tl needy. It has Intensive care Units, Modern Operation theaters, 24 h Radiology with CT, MR Color Doppler, Echo Cardiograph, Endoscopy Units, Blood Bank, 24x7 Central Clinical La Pharmacy, Dialysis Unit, Physiotherapy, Nutrition and Dietetics services, Casualty and Emergen services and thousands of poor patients from Karnataka and neighboring states avail the benefi of health care offered by us. Approximately 75-80 % of the patients visiting the hospital are fro Minority and Backward Communities. The food (costing Rs. 65/person/day), bed charges a drugs (more than 150 prescriptions) are provided free of cost to all. Most of the Govt. heal care plans and schemes available for the poor, backward and general public are implement by the hospital. Mortuary services, cold storage and medico legal autopsies are also part of t service provided by the hospital. The Hospital works in association with at least twenty servi organizations including orphanages, old age homes, palliative care centers, HIV/AIDS care a support centers, Endosulphan Rehabilitation centers etc. to extend timely free health care servi and support. Quality of education is maintained by trained and experienced teaching faculty unc the leadership of the Deans of the respective faculty. Best and highly qualified (>90%) facu with MCh. DM, MD/MS, MDS, Ph.D and MSc. degrees are recruited for teaching and researc Several faculty members enjoy wide national and international recognitions for their exempl and extraordinary service in their respective areas of specialization.

1.2 The Institute of Bioinformatics (http://www.ibioinformatics.org) is a non-profit resea institute that was established by Dr. Akhilesh Pandey, who is the Director and Scientific Advi of IOB and also an Professor at Johns Hopkins University, Baltimore, USA. The instit currently has a research staff of 50 scientists including 9 Ph.D level faculty scientists. **IOB l been recognized as a Scientific and Industrial Research Organization (SIRO) by DS (Department of Scientific and Industrial Research) since 2004.** Institute of Bioinformat is recognized as full time research center to carry out Ph.D. studies by Manipal Universi Pondicherry University, Amrita University, KIIT University and Kuvempu University. Curren 30 students are carrying out their doctoral work at IOB. Because of the close collaboration of I with Johns Hopkins University, 5 Ph.D. students are carrying out research work in Dr. Akhil Pandey's Laboratory at McKusick-Nathans Institute of Genetic Medicine at Johns Hopk University, Baltomore, USA. In the last five years, IOB has established state-of-the-art hi resolution tandem mass spectrometry facility for proteomic and metabolomic investigations an associated wet lab and animal cell culture facility to carry out molecular biology and genon oriented research. IOB has also collaborated over 50 National and International research institu particularly on clinical research in the area of human diseases including cancers, infections neurological disorders. In a short span of twelve years, the scientists from IOB have been a

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of more than 210 publications in the journals of international repute including *Nature, Nature Biotechnology, Nature Genetics, Nature Methods, Nature Protocols, PNAS* and *Genome Research*. IOB investigators in collaboration with Johns Hopkins University, Baltimore, USA and National Institute of Mental Health and Neuroscience (NIMHANS), Bangalore, have led a landmark investigation on proteomic profiling of 30 human organs/tissues and published a draft map of human proteome for the first time in the world. It was featured on the cover of *Nature*.

1.3 The Institute of Bioinformatics has already established itself as a leading center for genomics, proteomics and bioinformatics research. In addition, Scientists at IOB are poised to strengthen further the genomics, proteomics and proteomics-related bioinformatics in India through establishment of collaborative research.

Thus, the activities of YU and IOB are complementary in several ways and it is felt that initiating collaborative research and academic programs would be of considerable mutual benefit. The samples provided by YU for collaborative research studies will strictly be handled by IOB and will not be allowed to leave India under any circumstances. The collaboration will be only for research purposes and will be shared between IOB and YU and joint manuscripts will be written up for submission to international journals. It is also expected that collaborations will result in transfer of such technologies used in the project to YU.

2. Purpose

YU and IOB would like to initiate cooperative and collaborative activities, which would address scientific, technological and educational problems of relevance to the country. The instrument of this MOU, elements of which, facilitates this as follows:

Article-1

Consistent with the goals and purpose of the collaboration, YU and IOB have proposed the following areas of joint research and academic activities:

Investigating clinical genomics/proteomics/metabolomics of different diseased conditions using global genomic, proteomic and metabolic profiling will be one of the core areas for collaborative research. Applications of bioinformatics in data analysis and database management will be another preferred subject for collaboration.

Additional areas to be identified from time to time in future.

Article-2

The faculty of YU and IOB will hold regular scientific meetings on problems of mutual interest. The faculty and research scholars of YU and IOB will have access to the appropriate facilities of both the institutes, subject to their respective rules and regulations.

Article-3

Provision is hereby made for the:

1. Exchange of faculty, research scholars and students between YU and IOB
2. Joint organization of symposia, seminars and workshops and lectures
3. Mutual sharing of research material, and data and scientific knowledge on

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collaborative projects, ensuring the material is not transported outside India.

4. Offer joint academic programmes (Ph.D, MSc., Diploma, Certificate and Short term Certificate courses)

Article-4

Intellectual property:

1. Important research findings arising out of the activities covered under this MOU may be published in national and international journals, and presented at national and international scientific meetings reflecting collaboration.
2. Knowledge developed, which can result in commercial exploitation, shall be covered by patents filed jointly by YU and Institute of Bioinformatics involved in the collaborative research work.
3. YU and IOB can make use of, for their internal purposes, all the information and data generated during collaborative research programs. However, neither of them shall reveal intellectual property belonging to the other institute, to any third party without the prior written concurrence of the scientists involved from the other institute.
4. The benefits of all IPR developed from the collaborative projects between YU and IOB shall be shared equally between these two institutions.

Article-5

Non–exclusivity of the MOU:

Notwithstanding anything contained in the provisions, excepting Articles of the MOU, both institutes have the unrestricted right to seek additional funding for and to co-operate with any agency or institute, ensuring that it is outside the purview of the collaboration agreed upon.

Article-6

Changes and Modifications:

Any article of the MOU may be modified or changed by mutual agreement of the parties hereto in writing. The modifications and changes shall be effective from the date on which they are made unless otherwise agreed to.

Article-7

All disagreements, difference of opinion, disputes regarding the interpretation of the provision of this MOU shall be resolved by mutual consultation of the heads of the institute or their authorized representatives.

Article-8

The tenure of the MOU shall be three years from the date of signing this MOU. The MOU can be extended for a further period of three years by mutual consent.

ATTESTED

1. YU and IOB will together establish **IOB-YU Center for Systems Biology and Molecular Medicine** at Yenepoya University.

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2. All the parties decided initially to work closely on the research projects in the areas entitled, clinical genomics, proteomics and metabolomics of different diseased conditions. This study will be an attempt to enhance the knowledge in the field of OMICs with particular reference to cancers and infectious diseases.
3. All participating researchers will be co-authors in research articles that emanate from the proposed work.

Project Investigators and Research Staff involved in the project from both the Institutes-

YU investigators-

Faculty /Investigators and Principal Coordinators of the Constituent Centers/Departments/ Colleges from YU will be involved in the research activities.

IOB Investigators-

The Director and Faculty Scientists of the Institute of Bioinformatics, Bangalore, India, who are carrying out research in genomics, proteomics and bioinformatics, will be involved in the collaborative research projects.

In witness whereof the undersigned, duly authorized thereto, have signed this at Mangalore on the ………………., 2014

Signing Date 20/11/2014

Dr. P. Chandramohan, MD. MCh. Vice-Chancellor Yenepoya University Deralakatte, Mangalore-575018	**Dr. Keshava Prasad, Ph.D** Director I/C Institute of Bioinformatics International Technology Park, Bangalore Whitefield, Bangalore-560066
Prof. (Dr.) C. V. Raghuveeer, MD Registrar, Yenepoya University Deralakatte, Mangalore-575018	Dr. Akhilesh Pandey, MD, Ph.D International Technology Park, Bangalore Whitefield, Bangalore-560066

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YENEPOYA
UNIVERSITY

University Road,
P.O.Nithyananda Nagar
Deralakatte
Mangalore - 575018
Ph: 0824-2204676/68/69
Fax: 0824-2203943

No.YU/REG/Cir/Nov 2014

Date: 26.11.2014

CIRCULAR

Sub: MoU entered into between Yenepoya University & Institute of Bioinformatics.

In order to generate knowledge in the area of genomics & proteomics relevant to human diseases & advanced molecular diagnostics in the clinical community, Yenepoya University signed a MoU on 20th of November, 2014 with the Institute of Bioinformatics (http://www.ibioinformatics.org), started by Dr. Akilesh Pandey, Prof of Pathology at Johns Hopkins, USA. IOB is carrying out research in the area of genomics & proteomics in India. Through this MoU, the University intends to start a Centre for Systems Biology & Molecular Medicine (CSBMM), with intentions i) to establish a state of the art high-resolution mass spectrometry-based proteomics facility ii) to provide exposure & hands-on training in proteomics, genomics, transcriptomics and bioinformatics to students, young researchers, clinicians and scientists at YU & iii) to enable exchange of students & faculties between YU & IOB.

In continuation of this association, a 2-day workshop has been planned on 8th & 9th December 2014 at YU to generate ideas for Research Projects & prepare at least 2 concept proposal from each department (one departmental project & one inter-departmental project) in the area of prevalent diseases based on availability of samples in the constituent colleges. A senior Professor will be the Principal Investigator & the other faculty members contributing to the project will be Co-Investigator. The intellectual property & publications generated out of this research shall be shared equally between the investigators & IOB.

Principals of constituent colleges are requested to nominate 2 team members from each department before 5th December 2014, to attend the meeting with short proposals or relevant ideas envisaging genomics, proteomics & metabolomics approach to management of human diseases. The ideas will be developed & fine-tuned to a full research proposal after discussion. A short confirmation message and a write up on the topic should be mailed by the prospective investigator to registrar@yenepoya.org with a copy marked to dydirectoryrc@yenepoya.edu.in latest by 5th December, 2014.

Registrar

To:
The Principals of all the constituent colleges – also with a request to circulate among all HODs.

Cc to:
All the Statutory Officers, Dy.Director, YRC
The Notice Boards of all the colleges & Library.

Office of the NAAC Co-ordinator
No. 254
Received on 26/11/14
Despatched on

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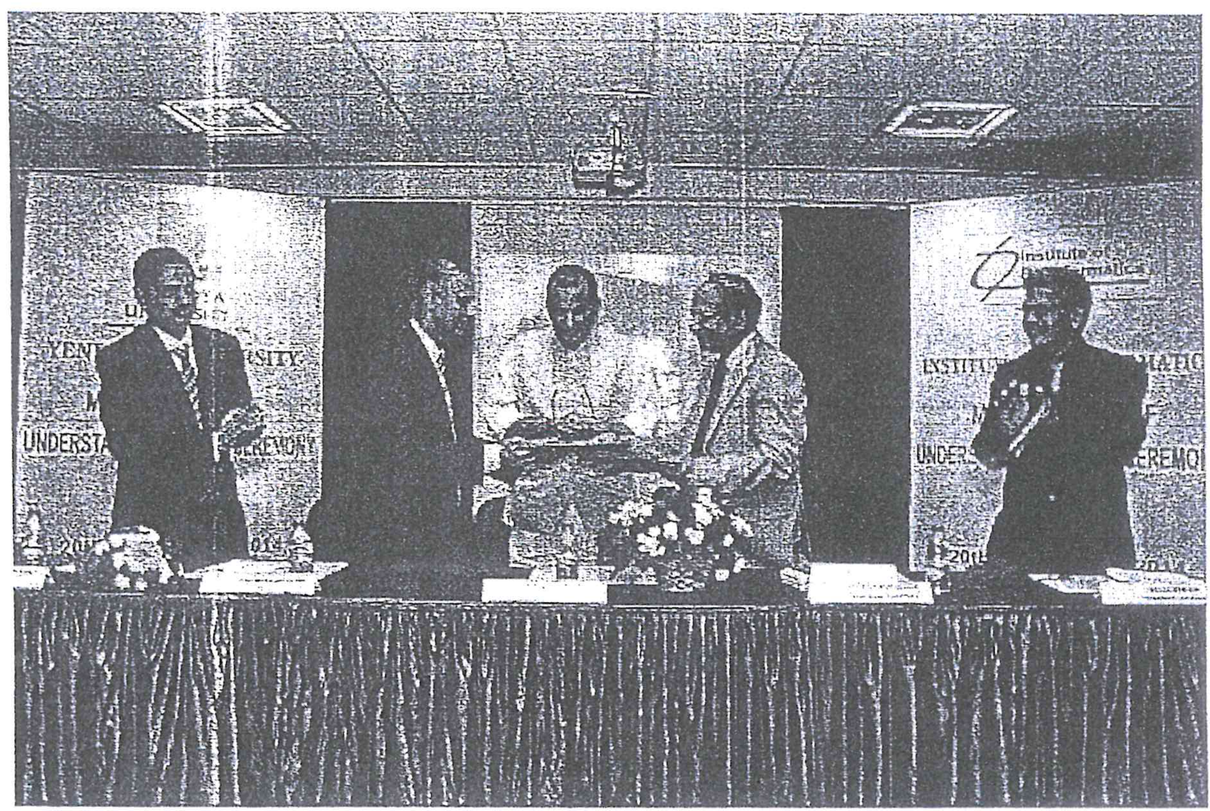
Yenepoya University, Mangalore and Institute of Bioinformatics, Bangalore signed a Memorandum of Understanding to establish a joint YU-IOB Center for Systems Biology and Molecular Medicine at Yenepoya University.

Yenepoya University is a deemed to be University engaged in health care delivery and research in health sciences. It has developed a strong basis for patient care, training programmes and research activities. In order to generate knowledge in the area of genomics and proteomics relevant to human diseases and advanced molecular diagnostics in the clinical community, Yenepoya University signed a memorandum of understanding on 20th of November, 2014 with the Institute of Bioinformatics (http://www.ibioinformatics.org), Bangalore, a premier institute carrying out pioneering research in the area of genomics and proteomics in India that was established by Dr. Akhilesh Pandey, who is also a Professor at Johns Hopkins University, Baltimore, USA. The major goals of this new center will be: i) to establish a state of the art high-resolution mass spectrometry-based proteomics facility at YU; ii) to provide exposure and hands-on training in proteomics, genomics, transcriptomics and bioinformatics to students, young researchers, clinicians and scientists at YU; and, iii) to enable exchange of student and faculties between YU and IOB. Mr. Yenepoya Abdulla Kunhi, Chancellor, Yenepoya University, presided over the function.



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Annual Progress Report of

YU-IOB Center for Systems Biology and Molecular Medicine

(Date of Establishment: June 01, 2015)

Yenepoya Research Centre
Yenepoya University, Mangalore

Progress Report from June 01, 2015 to May 31, 2016

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YU-IOB Center for Systems Biology and Molecular Medicine

YU-IOB CSBMM Annual Progress Report (June 01, 2015-May 31, 2016)

Preamble

The YU-IOB Center for Systems Biology and Molecular Medicine (YU-IOB CSBMM) is an academic research center jointly established by the Yenepoya University, Mangalore and Institute of Bioinformatics, Bangalore, India. YU-IOB CSBMM is a part of Yenepoya Research Center, which started its operation on 1 June, 2016 for carrying out multidisciplinary science. YU-IOB CSBMM is equipped with experimental and data analysis platforms for state-of-art proteomic and metabolomic investigation in the area of discovery and validation of biomarkers and therapeutic targets in human diseases.

Summary of achievements:

1. Establishment of infrastructure, work flow and successful running of mass spectrometry platforms
2. Putting together a group of highly talented, dedicated young faculties and attracting Ph.D. students with research fellowships
3. A total of 17 international publications in reputed journals in the first year of inception
4. Two discoveries in diagnostics and therapeutics of malaria is being prepared for two separate provisional patents
5. Secured two prestigious grants – DST-INPIRE Faculty grant for Dr. Sneha Pinto and SERB Young Investigator for Pratigya Subba
6. Generation of pilot phase mass spectrometry data for several future research collaborations
7. Ready for submission of National Facility grant proposals on molecular targets of ayurvedic preparations
8. Application submitted for Biotechnology Skill Enhancement program of Karnataka Government on OMICs technologies
9. Conducted the Symposium on "Genomics in clinical practice: Future of precision medicine", which was highly successful

Augmentation of Research Faculty and Staff Strength

In the last year, several faculty members with immense academic and postdoctoral experience from leading research institutes were recruited to expand the research activities into the emerging disciplines such as proteomics, genomics and bioinformatics. The names and designations of these faculty members are listed below:

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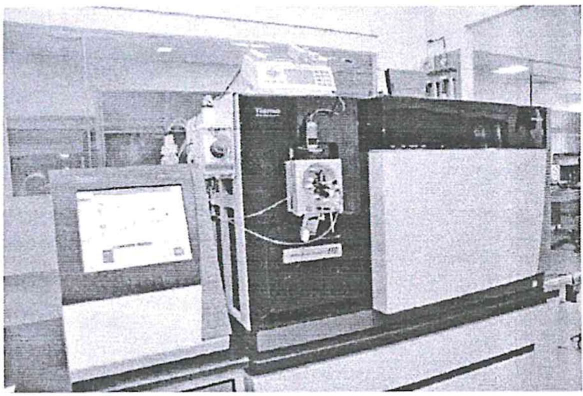
	Name	Designation
1	Dr. T. S. Keshava Prasad	Professor & Deputy Director
2	Dr. Aditi Chatterjee	Professor & Associate Director
3	Dr. Harsha Gowda	Associate Professor & Associate Director
4	Dr. Sneha M. Pinto	DST-INSPIRE Faculty & Assistant Professor
5	Dr. Yashwanth Subbannayya	Faculty Scientist
6	Dr. Pratigya Subba	Scientific Officer (AP stage -1)
7	Dr. Prashant Kumar Modi	Senior Scientific Officer
8	Dr. Sreekala K. Nair	Senior Scientific Officer

During this period, YU-IOB CSBMM team was able to attract highly qualified research scholars with fellowships from various geographical locations in India. These include, Ms Roopna Ravindran (DST INSPIRE JRF Fellow) from Gujarat, and Mr. Altaf Mohammed Najar (UGC Junior Research Fellow) from Kashmir. Mr. Saketh Kapoor, a SRF who joined our team in July has over 4 years research experience in Indian Institute of Science and Ms. Varshasnatha Mohanty who has 2 years of experience working in the quality control division of dairy industry in UK.
These students have already registered for Ph.D. program at Yenepoya University. The names and designations of the research scholars are listed below:

	Name	Designation
1	Mr. Saketh Kapoor	Senior Research Fellow
2	Mr. Ankur Tyagi	Senior Research Fellow
3	Ms. Roopna Raveendran	DST-INSPIRE Junior Research Fellow
4	Ms. Varshasnata Mohanty	Junior Research Fellow
5	Mr. Sandeep Kasaragod	Junior Research Fellow
6	Mr. Altaf Mohammed Najar	UGC Junior Research Fellow

Procurement of Equipments

The center is currently equipped with state-of-the-art mass spectrometers to carry out proteomic and metabolomic investigation to enable discovery and validation of biomarkers and therapeutic targets for human diseases. The major procured equipments in this center include Orbitrap Fusion Tribrid (Thermo Scientific) and QTRAP 6500 (SCIEX) mass spectrometers. These mass spectrometers are used for global as well as targeted proteomic, phosphoproteomic, acetylomic and glycoproteomic analyses of cancers, human pathogens, body fluids and experimental model systems. The data obtained through these high-throughput platforms is providing us insights into
altered patterns of protein expression and modifications and thereby identification of



Orbitrap Fusion Tribrid mass spectrometer (Thermo Scientific)

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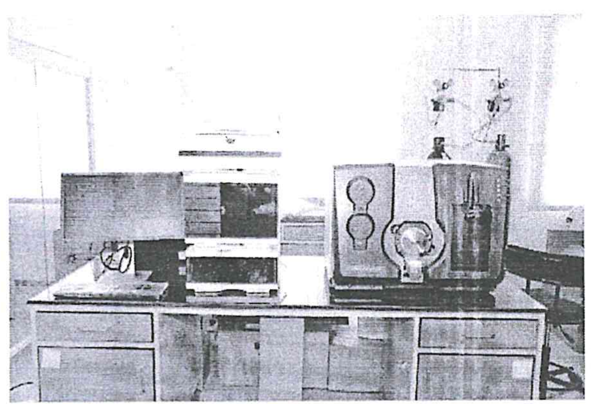
activated or altered signaling pathways. Similarly, using advanced quantitative phosphoproteomic analysis, we are focusing on identification of molecular targets of traditional medicines to allay the criticism on mode of action of these ayurvedic principles obtained from plants to make them globally acceptable. The installation of Orbitrap Fusion Tribrid (Thermo Scientific) was completed on March 2, 2016. The installation of QTRAP 6500 (SCIEX) was completed on April 28, 2016 followed by a software demonstration by the SCIEX application scientist from May 2-4, 2016.



QTRAP 6500 mass spectrometer (SCIEX)

Research Grants

The Faculty members of YU-IOB CSBMM successfully obtained extramural grants from DST worth Rs 84 lakhs and extramural grants worth Rs. 4.70 crores are under review with various funding agencies.

	Name of the Project	**Investigators (Role)**	**Proposed share of YU in the grant amount**	**Funding Agency**	**Current status**
1	Delineating the role of IL-33 in COPD	Dr. Sneha Pinto (PI)	Faculty Award INR 12,00,000 (sanctioned for Year 1) Grant amount INR 35,00,000	DST-INSPIRE	Sanctioned under progress
2	Phosphorylation-mediated induction of salt stress signaling in primary root growth of model plant	Dr. Pratigya Subba (PI) Dr. Sneha M. Pinto (Co-I)	INR 49,20,000	SERB ECRA	Project proposal approved

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	Arabidopsis thaliana				
3	Proteomic approaches to delineate molecular mechanisms of cannabis signaling	Dr. Sneha Pinto (PI)	INR 50,00,000	DST in collaboration with BOHECO	Submitted (under review)
4	Delineating Calcium/calmodulin-dependent protein kinase kinase 2 (CaMKK2)-induced signaling mechanisms using phosphoproteomic approaches	Dr. Yashwanth Subbannayya (PI) Dr. Aditi Chatterjee (Co-I) Dr. Sneha M. Pinto (Co-I)	INR 48,39,439	SERB Early Career Research Award	Not funded
5	Protein post translational modifications mediated induction of salt stress signaling in primary root growth of modern plants *Arabidopsis thaliana*	Dr. Pratigya Subba (PI) Dr. Sneha M. Pinto (Co-I)	INR 57,34,995	DBT	Submitted (under review)
6	Role of inflammatory cytokine Il-17A and p53-fibrinolytic systems in smokers with or without COPD.	Dr. Sneha M. Pinto (Co-I) In collaboration with Dr. Yashodhar Bhandary, YRC		DBT	Submitted (under review)
7	Development of molecular diagnostics for simultaneous identification of Mycobacterium tuberculosis infection and drug resistance pattern in adult and pediatric pulmonary and extra pulmonary tuberculosis	Dr. T. S Keshava Prasad (Collaborator PI) Dr. Harsha Gowda (Collaborator PI) Dr. Sneha Pinto (Co-I)	INR 41,24,000	DBT	Submitted (under review)

8	Expression of Interest for Establishment of Biotechnology Skill Enhancement Programme-BiSEP	Dr. T. S Keshava Prasad (BiSEP course coordinator)	INR 200,00,000 for infrastructure INR 10,00,000/annum as student fee INR 10,00,000/annum as consumables	Karnataka Biotechnology & Information Technology Services (KBITS)	Submitted (under review)
9	Therapeutic potential of marine bacterial biosurfactant against *Trichophyton rubrum*, a dermatophytic fungus	Dr. T. S. Keshava Prasad (Co-I) in collaboration with Dr. Kishor Keekan, YRC	INR 18,00,000	DBT	Submitted concept note on marine natural products development under the programme area Aquaculture & Marine biotechnology
10	Identification of pathogenic effectors and host defensive molecules through multipronged OMICS (transcriptomic, proteomic and metabolomics) analyses during rice-Magnaporthe interactions	Dr. Pratigya Subba (PI) Dr. Sneha M. Pinto (Co-I) Dr. T. S. Keshava Prasad (Co-I) in collaboration with Dr. Malali Gowda, Transdisciplinary University, Bangalore	INR. 55,20,000	DBT	Submitted concept note on plant microbe interactions
11	Diagnosing survivability in early stages of bacterial sepsis based on acute phase response – designing a cost effective nanoprobe immunoassay	Dr. Sneha M. Pinto (PI)	INR 13,95,000	DST	Submitted (not approved)

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12	Assessing the predictive value of Lactate dehydrogenase isoenzymes in neonatal birth asphyxia	Dr. Yashwanth Subbannayya (Co-PI), Dr. Sneha M. Pinto (co-I) in collaboration with Dr. Sahana K S, Dept of Pediatrics, YMC	INR 48,80,000	DBT-ICMR	Submitted
13	Identification of urinary markers using high resolution mass spectrometry to predict neonatal birth asphyxia	Dr. Yashwanth Subbannayya (PI), Dr. Sneha M. Pinto (co-I) in collaboration with Dr. Sahana K S, Dept of Pediatrics, YMC	INR 55,80,000	DBT-ICMR	Submitted
14	Identification of candidate markers using predictive of preeclampsia using an integrated OMICs approach	Dr. Sneha M. Pinto (PI), Dr. Yashwanth Subbannayya (co-I) in collaboration with Dr. Sharon Rasquinha, Dept. of OBG, YMC		DBT	Submitted
15	Identification of molecular markers for predicting therapy response in oral cancer using an integrated omics-based approach	PI: Dr. M. Vijayakumar, co-ordinator: Dr. Yashwanth Subbannayya	4,47,00,000	DBT (GLUE grant)	Submitted letter of Intent (LOI) for the Glue grant
16	Novel approaches to colorectal cancer through a basic, clinical	(Co-PI: Dr. Sneha Pinto, Dr. Yashwanth	7,50,00,000 (CSBMM	DBT	Under review Letter of Intent

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	and translational partnership	Subbannayya) in collaboration with Dr. Shaida Andrabi, University of Kashmir	component: 65, 00,000)		(LOI) for the Glue grant
17	Immunomodulation by parasitic Macrophage migration Inhibitory Factor (MIF) in Type 1 and Type 2 diabetes	(Co-PI: Dr. Sneha Pinto, Dr. T. S. Keshava Prasad) in collaboration with Dr. S. L. Hoti, RMRC, Belgavi	INR 25,00,000	ICMR	Under review
18	Proteomics approach for rapid identification of clinically important bacterial species	Centers of Excellence in Science, Engineering and Medicine (CESEM)	INR 60,00,000	VGST	Under review

Publications

1. Sathe, G. J*., Pinto, S. M*., Syed, N., Nanjappa, V., Solanki, H. S., Renuse, S., Chavan, S., Khan, A. A., Patil, A. H., Nirujogi, R. S., Nair, B., Mathur, P. P., Prasad, T. S. K., Gowda, H and Chatterjee, A. (2016). Phosphotyrosine profiling of curcumin-induced signaling. *Clinical Proteomics*. 13:13. (*The authors contributed equally)

2. Sunitha, B., Gayathri, N., Kumar, M., Prasad, T. S. K., Nalini, A., Padmanabhan, B., and Bharath, M. M. S. (2016). Muscle biopsies from human neuromuscular diseases with myopathic pathology reveal common alterations in mitochondrial function. *Journal of Neurochemistry* . 138(1):174-91.

3. Anand, A., Sharma, K., Sharma, S. K., Singh, R., Sharma, N. K. and Prasad, T. S. K. (2016). AMD genetics in India: The missing links. *Frontiers in Aging Neuroscience*. 8, 115.

4. Subbannayya, T., Variar, P., Advani, J., Nair, B., Shankar, S., Gowda, H., Saussez, S., Chatterjee, A. and Prasad, T. S. K. (2016). An integrated signal transduction network of macrophage migration inhibitory factor. *Journal of Cell Communication and Signaling*. 10(2):165-70.

5. Barua, P., Subba, P., Lande, N.V., Mangalaparthi, K.K., Prasad, T. S. K., Chakraborty, S., Chakraborty, N. (2016). Gel based and gel-free search for plasma membrane proteins in chickpea

(Cicer arietinum L.) augments the comprehensive data sets of membrane protein repertoire. *Journal of Proteomics*. pii: S1874-3919(16)30137-3.

6. Datta, K. K., Patil, A. H., Patel, K., Dey, G., Madugundu, A. K., Renuse, S., Kaviyil, J. E., Nirujogi, R. S., Arunima, A., Daswani, B., Kaur, I., Mohanty, J., Sinha, R., Jaiswal, S., Sivapriya, S., Sonnathi, Y., Chattoo, B. B., Gowda, H., Ravikumar, R. and Prasad, T. S. K. (2016). Proteogenomics of Candida tropicalis - an opportunistic pathogen with importance for global health. *OMICS:* 20(4):239-47.

7. Subbannayya, Y., Pinto, S. M., Gowda, H and Prasad, T. S. K. (2016). Proteogenomics for understanding oncology: Recent advances and future prospects. *Expert Review Proteomics*. 25, 1-12.

8. Radhakrishnan, A., Nanjappa, V., Raja, R., Sathe, G. J., Chavan, S., Nirujogi, R. S., Patil, A., Solanki, H., Renuse, S., Sahasrabuddhe, N. A., Mathur, P. P., Prasad, T. S. K., Kumar, P., Califano, J. A., Sidransky, D., Pandey, A., Gowda, H. and Chatterjee, A. (2016). Dysregulation of splicing proteins in head and neck squamous cell carcinoma. *Cancer Biology and Therapy*. 17, 219-29.

9. Yelamanchi, S. D., Jayaram, S., Thomas, J. K., Gundimeda, S., Khan, A. A., Singhal, A., Prasad, T. S. K., Pandey, A., Somani, B. L. and Gowda, H. (2015). A pathway map of glutamate metabolism. *Journal of Cell Communication and Signaling.* 10(1):69-75.

10. Subbannayya, T., Leal-Rojas, P., Barbhuiya, M., Raja, R., Renuse, S., Sathe, G., Pinto, S. M., Syed, N., Nanjappa, V., Patil, A. H., Garcia, P., Sahashrabuddhe, N. A., Nair, B., Guerrero-Preston, R., Navani, S., Tiwari, P. K., Santosh, V., Sidransky, D., Prasad, T. S. K., Gowda, H., Roa, J. C., Pandey, A. and Chatterjee, A. (2015) Macrophage migration inhibitory factor – a therapeutic target in gallbladder cancer. *BMC Cancer.* 15, 843.

11. Nanjappa, V., Renuse, S., Sathe, G. J., Raja, R., Syed, N., Radhakrishnan, A., Subbannayya, T., Patil, A., Marimuthu, A., Sahasrabuddhe, N. A., Guerrero-Preston, R., Somani, B. L., Nair, B., Kundu, G. C., Prasad, T. S. K., Califano, J. A., Gowda, H., Sidransky, D., Pandey, A. and Chatterjee, A. (2015). Chronic exposure to chewing tobacco selects for overexpression of stearoyl-CoA desaturase in normal oral keratinocytes. *Cancer Biology and Therapy*. 16(11):1593-603.

12. Verma, R., Balakrishnan, L., Sharma. K., Khan A. A., Advani, J., Gowda, H., Tripathy, S.P., Suar, M., Pandey, A., Gandotra, S., Prasad, T. S. K., Subramanian, S. (2015). A network map of Interleukin-10 signaling pathway. *Journal of Cell Communication and Signaling.* 10(1):61-7.

13. Selvan, L. D. N., Sreenivasamurthy, S. K., Kumar, S., Yelamanchi, S. D., Madugundu, A. K., Anil, A. K., Renuse, S., Nair, B. G., Gowda, H., Mathur, P. P, Satishchandra, P., Shankar S. K., Mahadevan, A. and Prasad, T. S. K. (2015). Characterization of host response to Cryptococcus neoformans through quantitative proteomic analysis of cryptococcal meningitis co-infected with HIV. *Molecular BioSystems*. 11, 2529-2540.

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Awards and recognition

- Dr. Aditi Chatterjee was awarded the "Bharat Ratna Mother Teresa Gold Medal Award" from the Global Economic Progress and Research Association for the year 2016 for her outstanding service in Health.
- Dr. Harsha Gowda was awarded the Sir C.V. Raman Young Scientist Award from Karnataka State Council for Science and Technology for the year 2013.
- Dr. Sneha Pinto and Dr. Yashwanth Subbannayya received awards for excellence in performance in the Targeted proteomics workshop held at IIT Bombay, Mumbai.
- Dr. Shyama Prasad Rao, YRC, won a "Best Poster prize" for his poster entitled "Expression pattern of protein kinases across human tissues" at NextGen Genomics, Biology, Bioinformatics and Technologies (NGBT) Conference, Hyderabad. The work was done in collaboration with Dr. Harsha Gowda and Dr. Yashwanth Subbannayya, YU-IOB CSBMM.
- Mr. Saketh Kapoor won the first prize in the event "Budding Scientist- Best Hypothesis Award" organized by Yenepoya Research Centre, Yenepoya University on the occasion of celebration of National Science day on February 24, 2016.
- Mr. Saketh Kapoor, Mr. Sandeep Kolya and Ms. Roopna Raveendran won third prize in the General Knowledge Quiz Competition organized by Yenepoya Research Centre, Yenepoya University, on the occasion of celebration of National Science day on February 25, 2016.
- Ms. Varsha Mohanty and Ms. Roopna Raveendran won the third prize in the event "Sci-Cartoon: Drawing of Scientific Cartoon" organized by Yenepoya Research Centre, Yenepoya University, on the occasion of celebration of National Science day on February 23, 2016.

Conferences/Seminar/Symposia/CME/Workshops organized

1. Workshop on mass spectrometry-based proteomics for beginners

The faculty members of YU-IOB Center for Systems Biology and Molecular Medicine, Yenepoya University conducted a workshop on "Mass Spectrometry-based Proteomics for Beginners" from February 09-10, 2016 at the seminar hall, Yenepoya Research Centre, Yenepoya University. The theme of the workshop was to provide basic concepts of mass spectrometry-based proteomics to the participating post-graduate students from various departments of Yenepoya University. The workshop was attended by M.D.S. and M.D. students of Yenepoya Dental College and Yenepoya Medical College respectively.

The event was coordinated by Dr. Sneha Pinto, Dr. Yashwanth Subbannayya and Dr. Pratigya Subba along with the assistance of the students of YU-IOB-CSBMM and staff of YRC. The technical aspects of the mass spectrometry instrumentation were demonstrated by Dr. Sneha Pinto at the CSBMM laboratory. The demonstrations for the proteomics experiments were conducted by Dr. Sneha Pinto and Dr. Yashwanth Subbannayya.

Participants

The following students attended the workshop

1. Dr. Sameera Begum, Department of Oral Pathology and Microbiology

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2. Dr. Umme Amarah, Department of Oral Medicine and Radiology
3. Dr. Anu Babu, Department of Oral Medicine and Radiology
4. Dr. Chandhini Begum N., Department of Oral Medicine and Radiology
5. Dr. Nimi Susan Mathew, Department of Oral Medicine and Radiology
6. Dr. Sithara Rathan, Department of Oral Medicine and Radiology
7. Dr. Tariq Ahmed, Department of Ophthalmology
8. Mr. Sandeep Kasargod, YU-IOB CSBMM
9. Mr. Saketh Kapoor, YU-IOB CSBMM
10. Ms. Varsha Mohanty, YU-IOB CSBMM
11. Ms. Roopna Raveendran, YU-IOB CSBMM
12. Ms. Faraz, Yenepoya Research Center
13. Mr. Muhammed Manzoor, Yenepoya Research Center

Outcomes of the workshop-training

Feedback forms were distributed among the participants at the end of the session. The overall feedback received was positive.

2. Symposium on "Genomics in clinical practice: Future of precision medicine" organized by YU-IOB Center for Systems Biology and Molecular Medicine and Yenepoya Research Centre

YU-IOB Center for Systems Biology and Molecular Medicine and Yenepoya Research Centre organized the first symposium on **"Genomics in clinical practice: Future of precision medicine"** at Yenepoya University on June 1-2, 2016. The symposium was of a scientific and technical nature highlighting the advances and applications of Next Generation Sequencing (NGS) to medicine. It covered various aspects of NGS - including oncology applications, non-invasive prenatal testing, inherited disease diagnosis, traditional medicine, microbiological applications, diagnostic and research applications. The symposium was well received by both the student and faculty participants. The resource persons included 16 individuals from various academic organizations as well as industry. The symposium was attended by 218 participants from 24 institutions around India. The inaugural session was presided over by Mr. Farhad Yenepoya, Director (Finance), Yenepoya University, Dr. C.V. Raghuveer, Registrar, Yenepoya University, Dr. M. Vijayakumar, Vice-Chancellor, Yenepoya University, Dr. Keshava Prasad, Professor and Deputy Director, YU-IOB Center for Systems Biology and Molecular Medicine.

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The talks at the symposium were delivered by 16 speakers from various organizations across India. The talks delivered at the symposium were as follows:

Title of the Talk	Speaker name and affiliation
Impressive advances in technology and understanding disease biology propels change from GATC to genomic medicine	Dr. B. K. Thelma University of Delhi, New Delhi
The role of genomics in evidence based medicine	Dr. Harsha Gowda Institute of Bioinformatics/ YU-IOB CSBMM
Advances in genetic testing- "what to offer and when"	Dr. S. Chikara Eurofins
Translational applications of Next Generation Sequencing in oncology	Mr. Rajendra Tari Illumina
Translating cancer genomics to medicine	Dr. Amit Dutt ACTREC, Navi Mumbai
Ion Torrent: Semiconductor based Next Generation Sequencing technology- Introduction and Applications	Dr. Sreejayan Nambiar Thermo Fisher Scientific
Pathogen signatures in the blood and the brain- an investigation using genomic tools	Dr. Chitra Pattabiraman National Centre for Biological Sciences, TIFR, Bangalore
Genomic diversity in the host-pathogen interacting genes and its association with human microbiome dysbiosis in chronic diseases	Dr. Souvik Mukherjee BMGC, NIBMG, Kolkata
Population genomic inferences indicate possibility of personalized medicine for malaria in India	Dr. Aparup Das NIMR, New Delhi
Non-invasive prenatal screening for chromosomal abnormalities	Dr. Priya Kadam MedGenome Laboratories, Bangalore
Genetic testing as tool for Beti Bachao: recipe for lawmakers	Dr. Akshay Anand PGIMER, Chandigarh
Genomics of medicinal plants and traditional	Dr. Malali Gowda Transdisciplinary University Foundation of Revitalization of

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formulations	Local Health Traditions, Bangalore
Single molecule real time sequencing - beyond a single human reference genome	Dr. Stephen Rudd PacBio, Singapore
Droplet Digital PCR: Way forward for liquid biopsy	Ms. Niyati. S. Dave Bio-Rad Laboratories
A gene expression array for predicting chemotherapy response in cancer patients	Dr. Shaji George BioPharm Laboratories, New York/Bangalore
Monogenic diabetes – from bench to bedside	Dr. Radha Venkatesan Madras Diabetes Research Foundation, Chennai

Panel Discussion

The post-lunch session on Day 2 of the symposium also consisted of a panel discussion. Radha Venkatesan, Executive Scientific Officer, Madras Diabetes Research Foundation, Dr. Stephen Rudd, PacBio, Singapore, Dr. Malali Gowda, Professor, School of Conservation, Life Science and Health Science, Transdisciplinary University, Dr. Priya Kadam, Medical Officer, MedGenome Labs Private Ltd, Dr. Chitra Pattabiraman, Postdoctoral Fellow, NCBS, Dr. Shaji George, Director and Chief Scientific Officer, Mir Lifescience Pvt Ltd, Bangalore were the members of the panel and Dr. T. S. Keshava Prasad served as the moderator for the panel discussion. Several students participated in this panel discussion and asked there queries regarding genomics in clinical practice.

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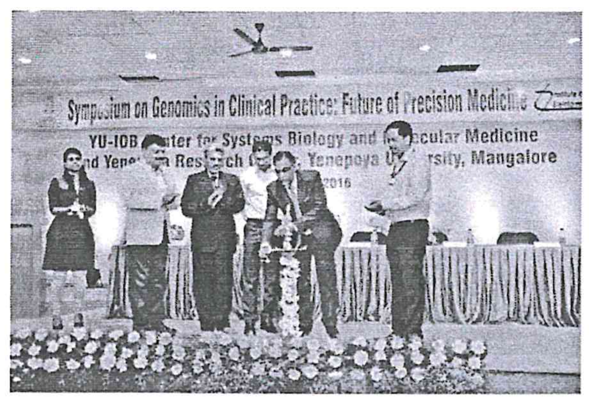

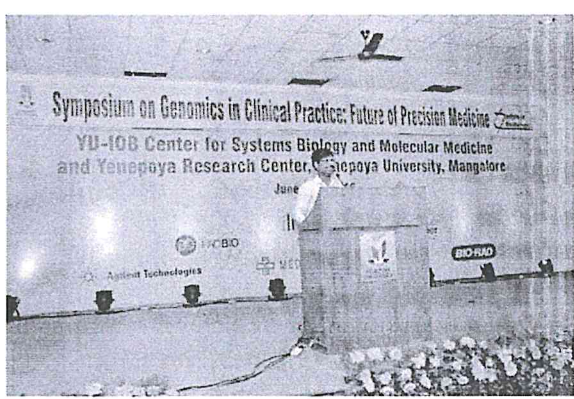

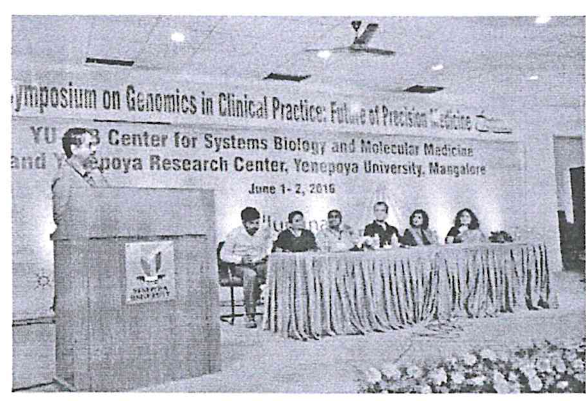

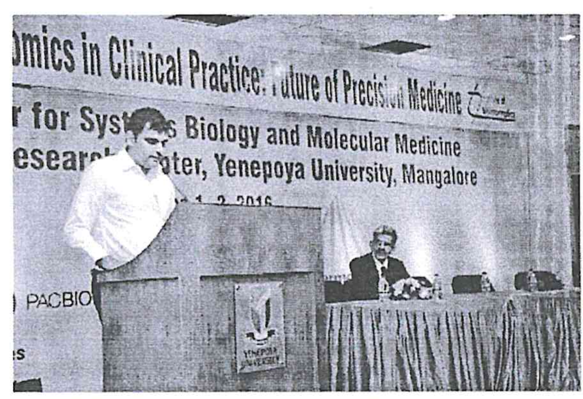

Guest lectures

1. Guest lecture on 'Taking comprehensive eye care to rural India: Focus on retinopathy of prematurity and diabetic retinopathy' was delivered by Dr. Krishna R. Murthy, Faculty scientist, Institute of Bioinformatics, Bangalore; Medical Director of Prabha Eye Clinic and Research Centre, Bangalore; Consultant Vitreoretinal Surgeon, Vittala International Institute of Ophthalmology, Bangalore; Consultant for Pediatric ROP clinic, Indira Gandhi Institute of Child Health Sciences, Bangalore on March 2, 2016.

2. Guest lecture on 'A System Biology approach to elucidate Epithelial-Mesechymal Transition (EMT) in cancer' was delivered by Dr. Shivashankar Nagaraj, Vice Chancellor's Research Fellow, Queensland University of Technology, Australia on March, 24 2016.

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Invited talks and conferences

- The following posters were presented with the YU-IOB affiliation at the 7th annual meeting of Proteomics Society, India at Vellore Institute of Technology, Vellore between December 3-6, 2015
  - Rapid processing of biological samples for proteomic analysis using pressure-cycling technology
  - Cigarette smoke induced molecular alterations in esophageal cells
  - Mapping protein coding regions in the human genome
  - Chewing tobacco and cigarette smoke-induced molecular alterations in oral cancer
  - SILAC-based proteomic analysis to delineate mechanisms underlying erlotinib resistance in head and neck squamous cell carcinoma
  - Proteomic profiling to identify tobacco-induced signaling in esophageal cells
  - Quantitative proteomics of cerebrospinal fluid from tuberculous meningitis co-infected with HIV
  - Expression dynamics of protein kinases and phosphatases across human tissues
  - Identification of differential host responses to infections in cryptococcal meningitis, toxoplasma encephalitis and tuberculous meningitis co-infected with HIV
  - Human brain proteome: molecular insights into regional heterogeneity
  - A proteome map of the human eye
  - Proteomic profiling of brain regions reveals complex biological basis for schizophrenia
  - Repertoire of differentially expressed proteins in cases of acute rabies encephalitis (<5 days) and sub-acute cases who succumbed late (>3 weeks)
  - Quantitative proteomic analysis of serum from paralytic rabies and Guillain–Barré syndrome
  - Phosphoproteomic analysis of gallbladder cancer
  - Proteogenomic analysis of Mycobacterium tuberculosis H37Ra strain
  - Identification of host response in cerebral malaria brain proteome using quantitative proteomic analysis
  - Quantitative proteomic and phosphoproteomic analysis of H37Ra and H37Rv strains of Mycobacterium tuberculosis

- Dr. Keshava Prasad chaired a session and judged posters at 7th annual meeting of Proteomics Society, India held at Vellore Institute of Technology, Vellore from December 3-6, 2015.
- Dr. Harsha Gowda chaired a session at 7th *annual meeting of Proteomics Society, India* held at Vellore Institute of Technology, Vellore from 3-6 December 2015.
- Dr. Harsha Gowda was an instructor for the HR-LC-MS/MS workshop held at IIT Bombay, Mumbai from December 10-12, 2015.
- Dr. Harsha Gowda gave a talk on "Quantitative Proteomics using MS-based iTRAQ" at the Education Day programme of the Targeted Proteomics International Symposium, IIT Bombay, Mumbai held on December *12, 2015*.
- Dr. Harsha Gowda was an invited speaker at the Targeted Proteomics International Symposium, IIT Bombay, Mumbai held from December 13-14, 2015. He spoke on "Targeted proteomics and metabolomics approaches for validating cancer biomarkers". Dr. Harsha Gowda also chaired a session at the Targeted Proteomics International Symposium during the same time.

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- Dr. Keshava Prasad was an invited speaker at the International Conference on Frontiers of Mass Spectrometry (ICMS-2015), Mahatma Gandhi University, Kottayam, Kerala on December 14, 2015. He spoke on the "Proteogenomics analysis for accurate assembly and annotation of newly sequenced genomes".
- Dr. Keshava Prasad spoke at the Tamil Nadu Agricultural University, Coimbatore on December 15, 2015. He spoke on the "Applications of mass spectrometry for biological research" followed by collaborative discussions with the faculties of Center for Plant Molecular Biology and Department of Biotechnology
- Dr. Keshava Prasad was an invited speaker at the meeting between Ohio State University and Avinashilingam University, Coimbatore on December 16, 2015. He spoke on the "Functional proteomic approaches to identify biomarkers and therapeutic targets in cancers".
- Dr. Keshava Prasad was a Key Note Speaker at MS Ramaiah Institute of Technology, Bangalore on January 19, 2016.
- Dr. Keshava Prasad was a Key Note Speaker at Bapuji Institute of Engineering and Technology, Davanagere on January 20, 2016.
- Dr. Keshava Prasad participated in an invited meeting and delivered a lecture on "Phosphoproteomics as a novel approach to detect molecular targets of herbal medicines" at RMRC, Belgavi on February 25, 2016.
- Dr. Keshava Prasad delivered an invited lecture at Amrita University on "Proteomics and Phosphoproteomics approached to investigate human diseases". Host- Dr. Bipin Nair on February 3, 2016.
- Dr. Keshava Prasad was invited to deliver a lecture as the keynote speaker for Symbiot 2016 at Manipal Institute of Technology on April 8, 2016.
- Dr. Yashwanth Subbannayya, Dr. Pratigya Subba, Mr. Saketh Kapoor, Ms. Varshasnata Mohanty and Mr. Ankur Tyagi attended the workshop on "Stem Cell Characterisation and Sorting" from April 26-28, 2016 organized at Yenepoya Research Center, Yenepoya University

Short term research training

Several students from various academic institutions undergo short term trainings at YU-IOB CSBMM for proteomics and bioinformatics.

Sl.No	Name & designation of the student	Training
1	**Ms. Aditi Shenoy**, B.Tech.(Biotechnology), Department of Biotechnology, Manipal Institute of Technology, Manipal University	Analysis of potential bio-markers for the development of novel molecular diagnostics of Dengue and Chikungunya"
2	**Ms. Sruthi E**, M.Tech.(Computer Science and Engineering) from Canara Engineering College, Mangalore	Computational approach in proteogenomics analysis.
3	**Dr. Chandhni Begum**, pursuing post graduation from the Department of Oral Medicine and Radiology, Yenepoya Dental College, Mangalore	Proteomic technique and data analysis.
4	**Dr. Nimi Susan Mathew**, pursuing post graduation from the Department of Oral	Proteomic technique and data analysis.

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	Medicine and Radiology, Yenepoya Dental College, Mangalore.	
5	**Dr. Sitara Rathan**, pursuing post graduation from the Department of Oral Medicine and Radiology, Yenepoya Dental College, Mangalore.	Proteomic technique and data analysis.
6	**Dr. Umme Amarah**, pursuing post graduation from the Department of Oral Medicine and Radiology, Yenepoya Dental College, Mangalore.	Proteomic technique and data analysis
7	**Dr. Anu Babu**, pursuing post graduation from the Department of Oral Medicine and Radiology, Yenepoya Dental College, Mangalore.	Proteomic technique and data analysis
8	**Mr. Vinuth N. Puttamallesh**, pursuing Ph.D. (Biotechnology) at Institute of Bioinformatics, Bangalore	Attended the training session on handling QTRAP mass spectrometer and its application for Multiple Reaction Monitoring (MRM) based quantitative proteomic and metabolomic analysis.
9	**Mr Firdous Ahmad Bhat**, pursuing Ph.D. at Institute of Bioinformatics, Bangalore	Attended the training session on handling QTRAP mass spectrometer and its application for Multiple Reaction Monitoring (MRM) based quantitative proteomic and metabolomic analysis.
10	**Dr. Sreekala K. Nair**, Assistant Professor (Botany) Bharathiar University, Coimbatore	Exposure to mass spectrometry- based proteomic analysis
11	**Dr. Catherine S. Manohar**, Senior Scientist at CSIR-National Institute of Oceanography, Dona Paula, Goa.	Provided with an exposure to mass spectrometry-based phosphoproteomic analysis and signaling pathways.
12	**Mr. Gunasekaran Dhandapani**, DST-JRF in RMRC (ICMR), Port Blair.	At YU-IOB CSBMM, he analyzed proteomic data from collaborative projects between YU-IOB CSBMM and RMRC proteomic data analysis and manuscript writing.
13	**Ms. Pragya Barua**, pursuing Ph.D. from National Institute of Plant Genome Research.	At YU-IOB she is being trained in labelling-based differential proteomic analysis using mass spectrometry.
14	**Mr. Nilesh Vikram Lande**, pursuing Ph.D. from National Institute of Plant Genome Research.	At YU-IOB he is being trained in mass spectrometry-based proteomic analysis of chloroplast.
15	**Dr. Sandhya Sanand** obtained her Ph.D. degree from NDRI, Karnal. She is currently working as a Scientist at ICAR-National Research Centre on Plant Biotechnology, New Delhi.	At YU-IOB CSBMM, she is being trained in mass spectrometry-based proteomics and data analysis.

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Progress of existing projects:

Progress of *Mycobacterium tuberculosis* genome sequencing project

Scientists at IOB and YU-IOB CSBMM in collaboration with JALMA and PGIMER, Chandigarh are carrying out whole genome sequencing of Indian clinical isolates of *M. tuberculosis* as an effort to investigate a panel of mutations associated with drug resistance. This will provide candidates for the early detection of MDR and XDR *M. tuberculosis*, which will help TB control programs in India.
We have obtained DNA samples from 206 clinical isolates of *M. tuberculosis* from JALMA, Agra. These include 198 samples of pulmonary TB and the remaining extra pulmonary TB. From Genome sequencing is being outsourced to MedGenom. In all, we have already received the sequencing data for 107 samples. Out of these, alignment and analysis of data has been completed for 100 clinical isolates. We have identified mutations associated with drug resistance in ~30% of the clinical isolates that have been labeled as drug sensitive isolates. In addition, we also identified mixed infection in some of the clinical samples. The phylogenetic analysis performed using whole genome sequencing data have identified distribution among 4 lineages - East-African Indian (87%), Indo-Oceanic (21%), Euro-American (16%) and Beijing (6%). Strain-to-strain variability in MTB can have important phenotypic consequences. Phylogeographical strain variation might affect the development of new diagnostics, drugs, and vaccines. Data on genotypic diversity of MTB is important to understand its epidemiology, clinical phenotypes, and drug resistance. Further, we have received sequencing data of 90 pulmonary M Tb samples from MedGenom. Currently initial QC check is being performed on the received sequences. We have received sequencing data for 85 of the 90 pulmonary samples and data analysis is currently on-going. Also we have standardized the protocol for drug susceptibility testing (DST) profiling for the clinical strains sequenced thus far and have subcultured close to 200 clinical isolates for initiating DST profiling in these samples

Progress of *M. tuberculosis* proteomics and phosphoproteomics analysis project

Protein phosphorylation is an important post-translational modification in *Mycobacterium tuberculosis*. The two laboratory strains H37Rv and H37Ra of *Mycobacterium tuberculosis* show different pathogenic phenotypes. Alterations in the protein expression and phosphorylation status among the two strains could be an important factor for the virulence attenuation in H37Ra strain. To this end, we carried out tandem mass tag based quantitative proteomic and phosphoproteomic analysis of the two strains at log and stationary phase. We identified 2,793 proteins and 522 phosphorylation sites. Comparative proteomic analysis revealed upto 20 fold overexpression of several proteins associated with virulence. Data analysis and manuscript writing was carried out by faculty of YU-IOB CSBMM. The manuscript has been finalized for submission to *Journal of Proteome Research.*

Progress of "MyKINOME- a compendium of protein kinases and phosphatases in *Mycobacterium tuberculosis*." Project

Mycobacterium tuberculosis (MTB) expresses various serine/threonine and tyrosine protein kinases that play essential roles in the fundamental biological processes. However the biological

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functions of these systems are largely unknown. Various studies have reported the roles of these signaling molecules in the pathophysiology of tuberculosis. The MTB genome contains 11 serine/threonine protein kinases (STPKs) namely; *pknA* to *pknL* and here we present the current knowledge on their substrates. We catalogued substrates of known Ser/Thr kinases using a manual literature-based curation strategy and compiled a list of 255 substrates with 701 threonine and 144 serine phosphorylation sites. Majority of the proteins are substrates for multiple kinases. This compendium will foster the development of information networks which will provide novel insights into MTB pathogenesis. The data is being reviewed and the manuscript is being prepared by faculties and students of YU-IOB CSBMM.

Progress of Head and Neck cancer project

Using a cell line model chronically treated with chewing tobacco, Stearoy-CoA desaturase (SCD) was identified as a potential therapeutic target in head and neck squamous cell carcinoma, especially in patients who are users of tobacco. This data was recently published in the journal "*Cancer Biology and Therapy*". Currently, using the cell secretome of the same model, we identified Sparc/osteonectin, cwcv and kazal-like domains proteoglycan (testican) 1 (SPOCK1) and Prosaposin (PSAP) which is being validated using ELISA based validation on saliva samples from oral cancer patients to serve as potential early detection biomarkers in oral cancer patients, especially in tobacco users. We have performed phosphotyrosine analysis of HNSCC cell lines and dual-specificity tyrosine- (Y) - phosphorylation regulated kinase 1A (DYRK1A) was identified to be hyperphosphorylated in all HNSCC cell lines. We have evaluated the therapeutic potential of targeting DYRK1A using *in vitro* and mouse models. The study is currently submitted to *BMC Cancer* and is under review. p-Ser/Thr analysis of all HNSCC cell lines was also carried out and the data revealed significant enrichment of molecules involved in RNA splicing. We validated the role of serine arginine rich protein kinase 2 (SRPK2) in HNSCC cells. The manuscript is accepted for publication in *Cancer Biology and Therapy*.
Using the untreated normal oral keratinocytes, OKF6/TERT1 and the derivative cell line chronically treated with chewing tobacco, we carried out mass spectrometry-based secretome analysis to identify the proteins that secreted at higher or lower abundance in response to chewing tobacco. A total of 2,873 proteins were identified among which 360 and 184 proteins were shed at higher and lower abundance, respectively by the tobacco treated cells compared to untreated OKF6/TERT1 cells. Among the proteins that are abundantly secreted, immunohistochemistry-based validation further revealed the overexpression of Prosaposin (PSAP) and Testican-1 (TIC1) in HNSCC tissues compared to normal tissues, thus, showing the probable role of PSAP and TIC1 in inducing transformation of normal oral keratinocytes in response to chewing tobacco. Further, ELISA-based validation of TIC1 and PSAP in saliva from oral cancer patients and healthy individuals will be carried out.

Mechanisms of erlotinib resistance in head and neck squamous cell carcinoma

Epidermal growth factor receptor (EGFR) plays an important role in the pathogenesis of HNSCC. Overexpression of EGFR is observed in about 90% of HNSCC cases and has been implicated in more aggressive phenotypes. Tyrosine kinase inhibitors (TKIs) such as erlotinib and gefitinib among several other drugs are currently under Phase III investigations as treatment options. However, most of these TKIs have shown a modest activity in recurrent or advanced

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HNSCC in clinical trials. One of the major reasons for acquired resistance over relatively short periods being development of intrinsic mechanisms by these tumors to circumvent blockade of EGFR signaling. Elucidating the molecular mechanism of resistance to EGFR-targeted therapies is therefore essential to identifying potential therapeutic targets. Drug resistant cell lines (SCC-R) were generated via a process of slowly escalating exposure of UM-SCC1 cells to erlotinib. SCC-S is used to designate the parental UM-SCC1 cells exposed to DMSO.SILAC-based global quantitative proteomic analysis was carried out to gain insights into the mechanism of erlotinib resistance in these cell lines. SCC-S cells were grown in heavy SILAC media whereas SCC-R cells were grown in light SILAC media. The lysates were mixed in equal amounts and subjected to in-solution tryptic digestion and fractionated. The fractions were analyzed on high resolution Fourier transform Orbitrap Fusion Tribrid mass spectrometer.
SILAC-based quantitative proteomics experiment led to identification of 5,427 proteins of which 509 proteins were overexpressed and 504 proteins were down regulated by more than 2 fold in SCC-R cells with respect to SCC-S cells. We observed overexpression of several signaling molecules downstream of EGFR such as, breast cancer androgen receptor 1(BCAR1) and paxillin (PXN). In addition, we also observed overexpression of AXL which have been previously implicated in mediating erlotinib resistance in HNSCC. Furthermore, we identified 6.4 fold overexpression of Cub-domain containing protein 1(CDCP1), a transmembrane protein involved in cell adhesion and cell matrix association and a known interactor of integrin β1 in SCC-R cells implicating its role in erlotinib resistance. Additionally, we also observed 12 fold overexpression of vimentin in SCC-R cells and loss of E-cadherin and dysregulation of proteins involved in actin-cytoskeleton remodeling indicating epithelial to mesenchymal transition (EMT).

Progress of Lung cancer project

Epidemiological data clearly establishes cigarette smoking as one of the major cause for lung cancer worldwide. Though certain targeted therapies such as anti-EGFR are in clinical practice, they have shown limited success in the smokers suffering from lung cancer. This demands discovery of alternative drug targets through systematic investigation of altered signaling mechanisms. To study dysregulated signaling pathways due to chronic cigarette smoke exposure, we carried out SILAC-based phosphoproteomic analysis of lung cell line H358 chronically exposed to cigarette smoke. We identified 1,812 phosphosites, of which 278 phosphosites were hyperphosphorylated (≥ 3-fold) in lung cells chronically exposed to cigarette smoke. Our data revealed hyperphosphorylation of Ser560 which is conserved in the kinase domain of group II PAKs (PAK4/5/6). Activation of PAK6 is associated with various processes in cancer including metastasis. We further assessed the role of PAK6 in non-small cell lung cancer cells. Inhibition of PAK6, leads to reduction in cell proliferation and invasive ability of lung cancer cells. Further, in vivo studies have shown that PAK6 inhibitor could significantly reduce tumor burden in mouse tumor xenograft model. Our study indicates that PAK6 is a promising novel therapeutic target for NSCLC especially in smokers. We are currently working on addressing the reviewer's comments and have initiated mice tumorigenicity experiments to evaluate the effect of PAK6 inhibitor on H358 smoke treated cells (**Manuscript under revision, Oncotarget, 2016**).

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Phosphotyrosine profiling of lung cancer cells chronically exposed to cigarette smoke

Tyrosine phosphorylation accounts for a minority of total phosphorylation; however it is critical for activation of signaling pathways and plays a disproportionately large role in diseases, especially cancer. We have compared phosphotyrosine profile of H358 cells (bronchioalveolar carcinoma cells) chronically treated with cigarette smoke condensate with the parental H358 cells. We have employed SILAC based quantitative approaches where H358 cells were metabolically labelled with heavy isotopes of amino acids (K6R6). The H2358 cells chronically exposed to cigarette smoke were maintained in media containing natural isotopes of amino acids. Protein lysates obtained from untreated and treated cells were normalized, pooled, fractionated by in-gel and SCX and subjected to LC-MS/MS analysis using LTQ-Orbitrap Velos. The protein mixture was then digested by trypsin, desalted with C18 reversed phase column and enrichment of phosphotyrosine containing peptides were carried out using anti-phosphotyrosine antibodies. The fractions are then analyzed on LTQ-Orbitrap Velos mass spectrometer. Data was searched using Mascot and Sequest and after application of 1% FDR, phosphosites passing 75% PhosphoRS probability score were considered. With these criteria, 322 phosphosites were identified (278 pY, 24 pT and 20 pS) of which 123 were hyperphosphorylated and 49 hypophosphorylated.

Progress of ESCC proteomics projects

We have performed phosphoproteomic and proteomic analysis of non-neoplastic esophageal cell line model chronically treated with chewing tobacco. Phosphoproteomic analysis of Het1A-parental and tobacco treated cells resulted in the identification of 2029 phosphopeptides corresponding to 1142 proteins. Among them 263 and 264 proteins were found to be hyper- and hypo-phosphorylated respectively in response to chewing tobacco in Het1A cells. Currently, data is being analyzed for significantly altered molecular pathways which will be further validated using cell line and mouse models. In addition, we have performed temporal proteomic analysis of esophageal cells treated with chewing tobacco. We will now analyze the data to identify molecules which display progressive expression trends with increasing treatment period. We have currently harvested the temporal treated cells for metabolomics analysis.

We have also performed several phenotypic assays including proliferation and invasion assays to determine the effect of chewing tobacco on esophageal (Het1A) cells. The results show that tobacco treated Het1A cells have increased proliferation and invasive properties. Using western blot, we have screened for levels of apoptotic and anti-apoptotic molecules such as BCl2, BCL-XL and BAX in chewing tobacco treated esophageal cells. Our data reveals that chewing tobacco treated Het1A cells have elevated anti-apoptotic molecules contributing to enhanced survival of the cells. Further, we assayed for EMT markers and our data showed increased expression of mesenchymal markers such as N-Cadherin and vimentin whereas E-cadherin was downregulated in Het-1A-Tobacco cells. We also find significant upregulation of MAPK signaling (ERK and JNK pathways), however AKT signaling remained unaffected in Het1A-Tobacco cells. Next we evaluated the effect of JNK inhibitor on ESCC cell proliferation and invasion. We performed colony formation assay and our results indicate significant reduction in ESCC cell proliferation upon treatment with JNK inhibitor. We also performed invasion assay using ESCC cell lines in the presence of JNK inhibitor (10 μM) and we observed reduced

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invasive properties in ESCC cell lines treated with JNK inhibitor compared to the corresponding vehicle treated control.

Progress of gallbladder cancer projects

We have performed total proteomic analysis of GBC cell lines. We identified 3,653 proteins, of which, more than 1,000 proteins were found to be differentially regulated. Of these, macrophage migration inhibitory factor (MIF) was identified to be overexpressed in the invasive GBC cell lines when compared to the non-invasive GBC cell line, TGBC24TKB. Immunohistochemical studies revealed that MIF was found to be overexpressed in GBC tissues. The therapeutic potential of targeting MIF in GBC was evaluated through *in vitro* assays using siRNA-mediated silencing as well as pharmacological MIF inhibitors. MIF was found to have a potential as a therapeutic target for GBC. This study has been published in *BMC Cancer* (November 2015). We have in addition done pSer/Thr enrichment from GBC cell lines, following TMT labelling. The labelled fractions were run on M/S. We identified 2,418 phosphopeptides corresponding to 2,665 proteins. In this study, we have identified Thr 246 of AKT1S1 to be hyperphosphorylated greater than 2-fold in all the four gallbladder cancer cell lines used in the experiment. This molecule is a substrate of AKT and PIM1. We have observed significant decrease in cell survival following treatment with PIM inhibitor in GBC cell lines. At present, we are checking the effect of PIM inhibitor on downstream signaling through Western blot.

Progress of bladder cancer proteomics project

Prior to harvesting the bladder cancer cell lines for proteomic studies, we analyzed classical indicators of epithelial or mesenchymal cell status in seven human bladder cancer cell lines and two non-neoplastic bladder cell lines. As epithelial marker we measured E-cadherin and as mesenchymal markers we measured N-cadherin and vimentin by Western blot. E-cadherin was expressed strongly in non-neoplastic bladder cell lines and bladder cancer cell lines derived from female patients (RT-112 and SW-780). All the bladder cancer cell lines derived from male patients did not express E-cadherin but was positive for N-cadherin expression. As expected non-neoplastic cell lines SV-HUC1 and TERT-NHUC did not show any expression of N-cadherin reconfirming their epithelial origin. We performed TMT- based quantitative proteomic data analysis on the panel of bladder cancer cells. The LC-MS/MS data was acquired in triplicates with MS3 quantitation. We identified a total of 5,527 proteins across 7 cancer cell lines among which 3,982 has triplicate quantitative values. Presently, analyzing the differentially regulated proteins in comparison with the two normal bladder cell lines.

Data acquisition for the human brain proteome map project

We are currently acquiring data on different regions of the human brain. These samples were received from Dr. Keshava Prasad's team at NIMHANS, Bangalore. We have carried out a part of the sample preparation here and completed acquisition of 3 human brain regions on Thermo Orbitrap Fusion Tribrid mass spectrometer namely- caudate nucleus, striate cortex and Thalamus. We have identified 5306, 6094 and 5081 proteins respectively in each of these regions. We also received in-gel digested fractions of orbito prefrontal cortex (OPFC), globus pallidus (GP) regions and bRPLC fractions of dorsolateral prefrontal cortex (DPFC) samples and

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identified 6229, 5119 and 5943 proteins respectively in each of these regions. This is by far the largest number of proteins identified to date.

Proteogenomic analysis of *Mycobacterium tuberculosis* H37Ra

Dr. Keshava Prasad has an ongoing collaboration with Dr. Sheetal Gandotra, IGIB, New Delhi. In continuation of their collaboration, we received protein pellet for H37Ra from Dr. Sheetal Gandotra. *Mycobacterium tuberculosis* H37Ra is an avirulent strain closely related to the virulent type strain H37Rv. The genome sequencing of H37Ra strain of *Mycobacterium tuberculosis* was completed in 2008. However, annotation of its genome remains challenging because of high GC content and dissimilarity to other model prokaryotes. To this end, we plan to carry out an in-depth proteomic analysis of *M. tuberculosis* H37Ra strain using high resolution Fourier transform mass spectrometry.
Currently, we have estimated the protein amount in the samples provided and also ran a SDS-PAGE gel. One mg of protein lysate was taken for in-solution trypsin digestion and the peptides were further fractionated using bRPLC. Equal amount was taken for in-gel digestion. The peptides from each fraction were analyzed using reversed phase nano scale liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) on Orbitrap Fusion Tribrid mass spectrometer (Thermo Scientific, Bremen, Germany) interfaced with Easy-nLC nano flow liquid chromatography system (Thermo Scientific, Odense, Denmark). After LC-MS/MS we have identified a total of 3,076 *Mycobacterium tuberculosis* H37Ra proteins by bRPLC and in-gel method (76.4%). The search is performed in PD 2.0 against H37Ra protein database using only SEQUEST.

Proteomic investigation of clinically relevant microorganisms

Scientists at YU-IOB CSBMM in collaboration with Dr. Prakash P.Y, Assistant Professor, Mycology lab, KMC, Manipal, carried out experiments on the proteomic analysis of *Rhodotorula mucilaginosa,* an emerging opportunistic pathogen. The fungi were cultured and processing of cell proteome and secretome was carried out. We have now analyzed the samples on the mass spectrometer. We are currently analyzing the data.
Fungal cultures of three bio-medically important fungi *Aspergillus flavus*, *Aspergillus niger* and *Rhizopus oryzae* were cultured by Dr. Prakash PY at Department of Microbiology, Manipal Institute of Technology, Manipal. The cultures were centrifuged to obtain the pellets of the fungi. The samples were then transported to YU-IOB CSBMM and are currently stored at -80°C.

Proteomic analysis of *Elizabethkingia meningoseptica*

Scientists at YU-IOB CSBMM in collaboration with NIMHANS, Bangalore carried out experiments on the proteomic analysis of an emerging opportunist pathogen, *Elizabethkingia meningoseptica.* This fungi is known to cause meningitis in newborn babies and meningitis or bloodstream and respiratory infections in people with weakened immune systems. We carried out bRPLC fractionation of this fungus here at YU-IOB CSBMM and identified 1634 proteins.

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Proteomic analysis of *Mycobacterium fortuitum*

We acquired data on *Mycobacterium fortuitum* which were received from Dr. Ravi Kumar, NIMHANS, Bangalore. We have carried out a part of the sample preparation here and completed the data acquisition on Thermo Orbitrap Fusion Tribrid mass spectrometer. We identified 594 proteins from the bRPLC fractions of *Mycobacterium fortuitum.*

Proteomic analysis of urine samples from *Plasmodium vivax* infected malaria patients

We acquired data on three urine samples from *Plasmodium vivax* infected malaria patients. These samples were received from National Institute of Malaria Research (NIMR), Goa. We carried out sample preparation here and completed acquisition of 3 urine samples on Thermo Orbitrap Fusion Tribrid mass spectrometer labeled- Goa_37, Goa_55 and Goa_08. We identified 321, 864 and 1045 proteins respectively in each of these samples of which 2, 21 and 56 were *Plasmodium vivax* proteins. These data of these samples were already acquired in NIMHANS, Bangalore and were carried out here to do the reproducibility check.

Chickpea nuclear phosphoproteomics

In order to gain a better understanding of the signaling mechanisms under dehydration stress in plants, we plan to generate differential nuclear phosphoproteome of chickpea (*Cicer arietinum* L.) cv. JG-62. Nuclei enriched fractions were isolated from three-weeks old seedlings subjected to water-deficit stress (Control, 72 h, 144 h). The nuclear pellets were received from Dr. Niranjan Chakraborty, National Institute of Plant Genome Research, New Delhi by Dr. Keshava Prasad and Dr. Pratigya Subba.
Nuclear proteins were extracted using 4% SDS solution and ~2 mg of the proteins were precipitated using acetone. The proteins were then digested using trypsin followed by TMT labeling. These processes were carried out by Mr. Kiran Kumar at the Institute of Bioinformatics, Bengaluru. At YU-IOB-CSBMM, the TMT labeled peptides were pooled and fractionated into 12 bRPLC fractions. Mass spectrometric analysis led to the identification of 5010 protein groups. Quantitative proteomic analysis is currently being carried out.

Optimization of metabolomics analysis using QTRAP 6500 mass spectrometer

After the installation of QTRAP 6500, the data for a mixture of TCA cycle metabolite standards were acquired. Parameters like Declustering Potential (DP), Entrance Potential (EP) and Collision Energy (CE) were optimized using various scan modes viz., Q1MS, EPI, Q1MI and MRM. Some of the expected m/z values were observed after which the data for each metabolite was acquired individually using Q1MI scan mode. Expected m/z values for some of the metabolites without any adducts were observed. The six point calibration curve of the TCA metabolite standard mix was generated using MRM scan type. A three-point calibration curve for all the metabolite was observed and the lower limit of detection was found to be 200 nmol.

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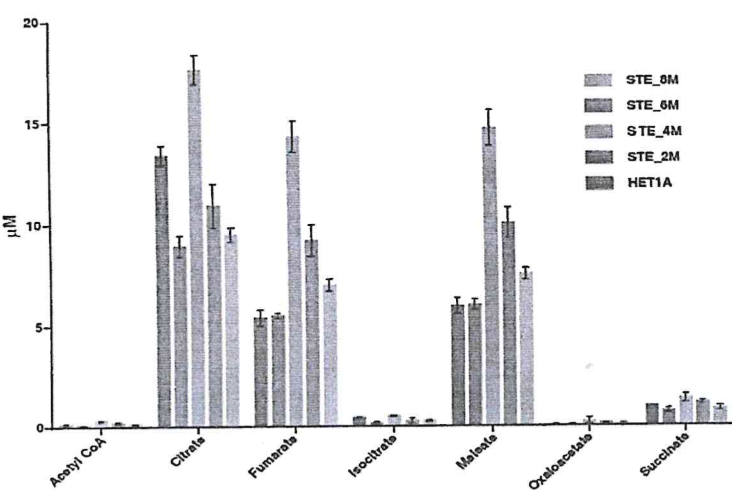
Metabolomic analysis of smokeless tobacco extract treated HET1A and STE cell lines

The data for metabolite extract samples derived from HET1A and cell lines treated with smokeless tobacco (STE cell lines; time-points 2, 4, 6, 8 months after treatment) were acquired using the MRM scan mode. The transitions for most of the metabolites present in the metabolite extracts were observed and the data was also used to generate a metabolic profile graph. In addition, a spike-in experiment was also conducted wherein 100 nmol Acetyl CoA was spiked into one of the STE sample (6 months after treatment) to test if it can be observed in the complex matrix. Data for these metabolite extracts derived from HET1A and STE cell lines has been acquired using EMS (Enhanced MS) type scan mode and will be analyzed using the MarkerView software.



National facility for proteometabolomic characterization of Ayurvedic and traditional medicinal plants

With an aim to characterize metabolites and proteins involved in the production of secondary metabolites, YU_IOB investigators are planning to prepare a dossier and submit it to Ministry of AYUSH. We expect to receive huge support from the ministry for such an endeavor. We seek PACBIO genome sequencer and three different types of mass spectrometers which will be used to carry out screening of global genomic, proteomic and metabolomics profile of Ayurvedic plants and formulations. We intend to provide this data freely to the international community by developing public databases. For this, we have already procured Triphala preparations and extracted metabolites and we have acquired the data in the mass spectrometer and generated untargeted metabolomics profile. Now, we are in the process of preparing the dossier and project proposal.

Visitors at YU-IOB CSBMM

Several eminent scientists visited YU-IOB CSBMM in past year. They interacted with the faculty members and research students at YU-IOB CSBMM.

1. Dr. Malali Gowda, Professor, School of Conservation, Life Science and Health Science, Transdisciplinary University, Bangalore visited YU-IOB CSBMM laboratory on June 2, 2016.
2. Dr. Shaji George, Director and Chief Scientific Officer, Mir Lifescience Pvt Ltd, Bangalore, Dr. Priya Kadam, Medical Officer, MedGenome Labs Pvt Ltd, Bangalore and Dr. Stephen Rudd, Pacific Biosciences, Singapore visited YU-IOB CSBMM laboratory on June 2, 2016.

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3. Dr. Akshay Anand, Additional Professor, PGIMER, Chandigarh visited YU-IOB CSBMM laboratory on June 2, 2016.
4. Dr. B. K. Thelma, Professor, Department of Genetics, University of Delhi, New Delhi visited YU-IOB CSBMM laboratory on June 1, 2016
5. Dr. Anurag Bhargava, Dept of Medicine, YMC, Yenepoya University visited YU-IOB CSBMM laboratory on June 1, 2016.
6. Dr. Chitra Pattabiraman, Postdoctoral Fellow, NCBS, Bangalore visited YU-IOB CSBMM laboratory on June 1, 2016.
7. Dr. Veena Shetty, Associate Professor, Department of Mocrobiology, K S Hegde Medical Academy, Mangalore visited YU-IOB CSBMM laboratory on May 25, 2016.
8. Dr. Rajendra B. Surpam, Professor and Head, Department of Mocrobiology, Government Medical College and Hospital, Nagpur, visited YU-IOB CSBMM laboratory on May 23, 2016.
9. Mr. Syed Sajjad Ahmed, Inspiring authority, Maulana Azad Education Foundation, Ministry of Minority Affairs, Government of India, New Delhi, visited YU-IOB CSBMM laboratory on May 10, 2016.
10. Dr. Rajashekhar, Professor, Department of Bioscience, Mangalore University, visited YU-IOB CSBMM laboratory on May 5, 2016.
11. Dr. Ajeet Mohanty, Scientist, National Institute of Malaria Research, Goa, visited YU-IOB CSBMM laboratory on May 5, 2016.
12. Honorable Chancellor Dr. S. Kumar, Registrar Dr. A. V. Moideen Kutty, Director of Academics Dr. Mohan Kumar and Executive Engineer Mr. Hanumantha Rao from Sri Devaraj Urs Academy of Higher Education and Research, Kolar, visited YU-IOB CSBMM laboratory on May 2, 2016.
13. Dr. Shivashankar Nagaraj, Vice Chancellor's Research Fellow, Queensland University of Technology, Australia visited YU-IOB CSBMM laboratory and delivered a talk on 'A System Biology approach to elucidate Epithelial-Mesechymal Transition (EMT) in cancer' on March 24, 2016.
14. Dr. Krishna R. Murthy, Faculty scientist, Institute of Bioinformatics, Bangalore; Medical Director of Prabha Eye Clinic and Research Centre, Bangalore; Consultant Vitreoretinal Surgeon, Vittala International Institute of Ophthalmology, Bangalore; Consultant for Pediatric ROP clinic, Indira Gandhi Institute of Child Health Sciences, Bangalore visited YU-IOB CSBMM laboratory and delivered a talk on 'Taking comprehensive eye care to rural India: Focus on retinopathy of prematurity and diabetic retinopathy' on March 2, 2016.
15. Dr. A. S. Kiran Kumar, Chairman, Indian Space Research Organization (ISRO), visited YU-IOB CSBMM laboratory on February 28, 2016.
16. Honorable Chancellor Mr. Yenepoya Abdulla Kunhi visited YU-IOB CSBMM Laboratory along with other dignitaries of Yenepoya University on February 2, 2016

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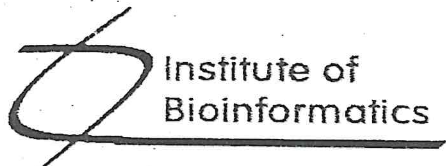

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March 31, 2016

To,
Dr. Arun Bhagwath,
Deputy Director,
Yenepoya University, Mangalore

Subject: Student exchange and deputation to YU-IOB Center for Systems Biology and Molecular Medicine- Mr. Vivek Todur

Dear Dr. Bhagwath,

Mr. Vivek Todur is currently working as research student at Institute of Bioinformatics, Bangalore. He has several years of experience in NextGen sequencing data analysis. Prior to joining IOB, he was working with MedGenome Labs Pvt. Ltd., Bangalore. He will train our students in NextGen sequencing data analysis and set up genomics data analysis pipelines. In addition, he will also be trained in proteomic and integrated data analysis pipelines.Therefore, I have asked him to work with Dr. Pinto and Dr. Subbannayya at CSBMM from April 4, 2016 to May 7, 2016. Please permit IOB-CSBMM to reimburse him travel bills and other logistics against invoices. I request you to also provide him free hostel accommodation.

Sincerely,

Keshava Prasad, Ph.D.
Faculty Scientist,
Institute of Bioinformatics,
Bangalore

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NUTS AND BOLTS

Molecular alterations in oral cancer using high-throughput proteomic analysis of formalin-fixed paraffin-embedded tissue

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Abstract
Loss of cell differentiation is a hallmark for the progression of oral squamous cell carcinoma (OSCC). Archival Formalin-Fixed Paraffin-Embedded (FFPE) tissues constitute a valuable resource for studying the differentiation of OSCC and can offer valuable insights into the process of tumor progression. In the current study, we performed LC–MS/MS-based quantitative proteomics of FFPE specimens from pathologically-confirmed well-differentiated, moderately-differentiated, and poorly-differentiated OSCC cases. The data were analyzed in four technical replicates, resulting in the identification of 2376 proteins. Of these, 141 and 109 were differentially expressed in moderately-differentiated and poorly differentiated OSCC cases, respectively, compared to well-differentiated OSCC. The data revealed significant metabolic reprogramming with respect to lipid metabolism and glycolysis with proteins belonging to both these processes downregulated in moderately-differentiated OSCC when compared to well-differentiated OSCC. Signaling pathway analysis indicated the alteration of extracellular matrix organization, muscle contraction, and glucose metabolism pathways across tumor grades. The extracellular matrix organization pathway was upregulated in moderately-differentiated OSCC and downregulated in poorly differentiated OSCC, compared to well-differentiated OSCC. PADI4, an epigenetic enzyme transcriptional regulator, and its transcriptional target HIST1H1B were both found to be upregulated in moderately differentiated and poorly differentiated OSCC, indicating epigenetic events underlying tumor differentiation. In conclusion, the findings support the advantage of using high-resolution mass spectrometry-based FFPE archival blocks for clinical and translational research. The candidate signaling pathways identified in the study could be used to develop potential therapeutic targets for OSCC.

Keywords Cancer pathology · Pressure cycling technology · Molecular medicine · Cancer grade · Quantitative proteomics · Tumor differentiation

Abbreviations

DTT	Dithiothreitol
FDR	False Discovery Rate
FFPE	Formalin-Fixed Paraffin Embedded
GO	Gene Ontology
IAA	Iodoacetamide
MS/MS	Tandem Mass Spectrometry
OSCC	Oral Squamous Cell Carcinoma
PCT	Pressure Cycling Technology
PSM	Peptide Spectrum Match
SDS	Sodium Dodecyl Sulfate
TEABC	Triethyl Ammonium Bicarbonate
TMT	Tandem Mass Tags

Varshasnata Mohanty and Yashwanth Subbannayya contributed equally to the manuscript.

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Introduction

Cancers of the lip and oral cavity arise primarily from epithelial cells, and 90% of these are composed of oral squamous cell carcinoma (OSCC) by origin (Miranda-Filho and Bray 2020). OSCC arises in various anatomical locations

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Molecular alterations in oral cancer between tobacco chewers and smokers using serum proteomics

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Abstract.
BACKGROUND: Tobacco exposure (through smoking or chewing) is one of the predominant risk factors associated with the development of oral squamous cell carcinoma (OSCC). Despite the growing number of patients diagnosed with OSCC, there are few circulating biomarkers for identifying individuals at a higher risk of developing the disease. Successful identification of candidate molecular markers for risk assessment could aid in the early detection of oral lesions and potentially be used for community screening of high-risk populations.
OBJECTIVE: Identification of differentially expressed proteins in the serum of oral cancer patients which can serve as biomarkers for the diagnosis of the onset of oral cancer among tobacco users.
METHODS: We employed a tandem mass tag (TMT)-based quantitative proteomics approach to study alterations in the serum proteomes of OSCC patients based on their tobacco exposure habits (chewing and smoking) compared to healthy individuals with no history of using any form of tobacco or any symptoms of the disease.

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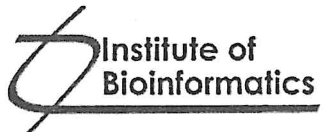

Annual Progress Report of

YU-IOB Center for Systems Biology and Molecular Medicine

(Date of Establishment: June 01, 2015)

Yenepoya Research Centre
Yenepoya University, Mangalore

Progress Report from June 01, 2015 to May 31, 2016

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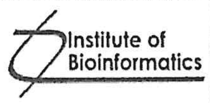
YU-IOB Center for Systems Biology and Molecular Medicine



YU-IOB CSBMM Annual Progress Report (June 01, 2015-May 31, 2016)

Preamble

The YU-IOB Center for Systems Biology and Molecular Medicine (YU-IOB CSBMM) is an academic research center jointly established by the Yenepoya University, Mangalore and Institute of Bioinformatics, Bangalore, India. YU-IOB CSBMM is a part of Yenepoya Research Center, which started its operation on 1 June, 2016 for carrying out multidisciplinary science. YU-IOB CSBMM is equipped with experimental and data analysis platforms for state-of-art proteomic and metabolomic investigation in the area of discovery and validation of biomarkers and therapeutic targets in human diseases.

Summary of achievements:

1. Establishment of infrastructure, work flow and successful running of mass spectrometry platforms
2. Putting together a group of highly talented, dedicated young faculties and attracting Ph.D. students with research fellowships
3. A total of 17 international publications in reputed journals in the first year of inception
4. Two discoveries in diagnostics and therapeutics of malaria is being prepared for two separate provisional patents
5. Secured two prestigious grants – DST-INPIRE Faculty grant for Dr. Sneha Pinto and SERB Young Investigator for Pratigya Subba
6. Generation of pilot phase mass spectrometry data for several future research collaborations
7. Ready for submission of National Facility grant proposals on molecular targets of ayurvedic preparations
8. Application submitted for Biotechnology Skill Enhancement program of Karnataka Government on OMICs technologies
9. Conducted the Symposium on "Genomics in clinical practice: Future of precision medicine", which was highly successful

Augmentation of Research Faculty and Staff Strength

In the last year, several faculty members with immense academic and postdoctoral experience from leading research institutes were recruited to expand the research activities into the emerging disciplines such as proteomics, genomics and bioinformatics. The names and designations of these faculty members are listed below:

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	Name	Designation
1	Dr. T. S. Keshava Prasad	Professor & Deputy Director
2	Dr. Aditi Chatterjee	Professor & Associate Director
3	Dr. Harsha Gowda	Associate Professor & Associate Director
4	Dr. Sneha M. Pinto	DST-INSPIRE Faculty & Assistant Professor
5	Dr. Yashwanth Subbannayya	Faculty Scientist
6	Dr. Pratigya Subba	Scientific Officer (AP stage -1)
7	Dr. Prashant Kumar Modi	Senior Scientific Officer
8	Dr. Sreekala K. Nair	Senior Scientific Officer

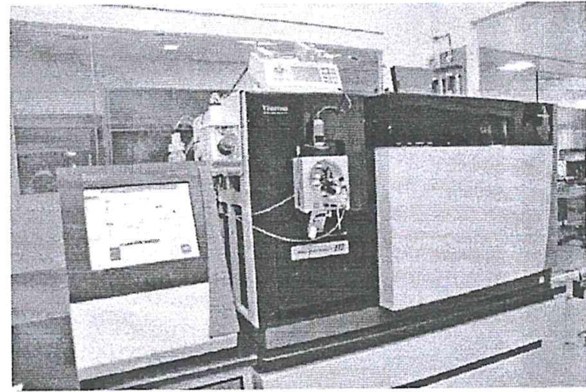
During this period, YU-IOB CSBMM team was able to attract highly qualified research scholars with fellowships from various geographical locations in India. These include, Ms Roopna Ravindran (DST INSPIRE JRF Fellow) from Gujarat, and Mr. Altaf Mohammed Najar (UGC Junior Research Fellow) from Kashmir. Mr. Saketh Kapoor, a SRF who joined our team in July has over 4 years research experience in Indian Institute of Science and Ms. Varshasnatha Mohanty who has 2 years of experience working in the quality control division of dairy industry in UK.

These students have already registered for Ph.D. program at Yenepoya University. The names and designations of the research scholars are listed below:

	Name	Designation
1	Mr. Saketh Kapoor	Senior Research Fellow
2	Mr. Ankur Tyagi	Senior Research Fellow
3	Ms. Roopna Raveendran	DST-INSPIRE Junior Research Fellow
4	Ms. Varshasnata Mohanty	Junior Research Fellow
5	Mr. Sandeep Kasaragod	Junior Research Fellow
6	Mr. Altaf Mohammed Najar	UGC Junior Research Fellow

Procurement of Equipments

The center is currently equipped with state-of-the-art mass spectrometers to carry out proteomic and metabolomic investigation to enable discovery and validation of biomarkers and therapeutic targets for human diseases. The major procured equipments in this center include Orbitrap Fusion Tribrid (Thermo Scientific) and QTRAP 6500 (SCIEX) mass spectrometers. These mass spectrometers are used for global as well as targeted proteomic, phosphoproteomic, acetylomic and glycoproteomic analyses of cancers, human pathogens, body fluids and experimental model systems. The data obtained through these high-throughput platforms is providing us insights into altered patterns of protein expression and modifications and thereby identification of



Orbitrap Fusion Tribrid mass spectrometer (Thermo Scientific)

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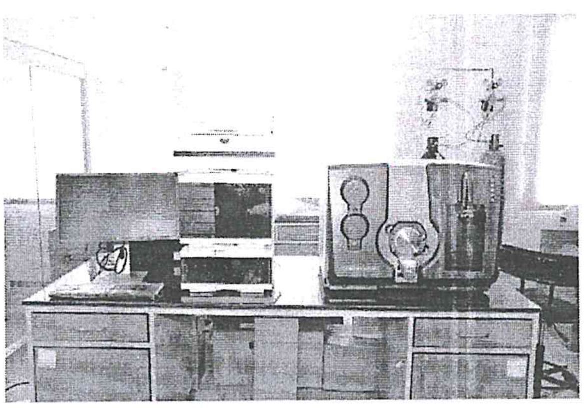
activated or altered signaling pathways. Similarly, using advanced quantitative phosphoproteomic analysis, we are focusing on identification of molecular targets of traditional medicines to allay the criticism on mode of action of these ayurvedic principles obtained from plants to make them globally acceptable. The installation of Orbitrap Fusion Tribrid (Thermo Scientific) was completed on March 2, 2016. The installation of QTRAP 6500 (SCIEX) was completed on April 28, 2016 followed by a software demonstration by the SCIEX application scientist from May 2-4, 2016.



QTRAP 6500 mass spectrometer (SCIEX)

Research Grants

The Faculty members of YU-IOB CSBMM successfully obtained extramural grants from DST worth Rs 84 lakhs and extramural grants worth Rs. 4.70 crores are under review with various funding agencies.

	Name of the Project	Investigators (Role)	Proposed share of YU in the grant amount	Funding Agency	Current status
1	Delineating the role of IL-33 in COPD	Dr. Sneha Pinto (PI)	Faculty Award INR 12,00,000 (sanctioned for Year 1) Grant amount INR 35,00,000	DST-INSPIRE	Sanctioned under progress
2	Phosphorylation-mediated induction of salt stress signaling in primary root growth of model plant	Dr. Pratigya Subba (PI) Dr. Sneha M. Pinto (Co-I)	INR 49,20,000	SERB ECRA	Project proposal approved

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	Arabidopsis thaliana				
3	Proteomic approaches to delineate molecular mechanisms of cannabis signaling	Dr. Sneha Pinto (PI)	INR 50,00,000	DST in collaboration with BOHECO	Submitted (under review)
4	Delineating Calcium/calmodulin-dependent protein kinase kinase 2 (CaMKK2)-induced signaling mechanisms using phosphoproteomic approaches	Dr. Yashwanth Subbannayya (PI) Dr. Aditi Chatterjee (Co-I) Dr. Sneha M. Pinto (Co-I)	INR 48,39,439	SERB Early Career Research Award	Not funded
5	Protein post translational modifications mediated induction of salt stress signaling in primary root growth of modern plants *Arabidopsis thaliana*	Dr. Pratigya Subba (PI) Dr. Sneha M. Pinto (Co-I)	INR 57,34,995	DBT	Submitted (under review)
6	Role of inflammatory cytokine Il-17A and p53-fibrinolytic systems in smokers with or without COPD.	Dr. Sneha M. Pinto (Co-I) In collaboration with Dr. Yashodhar Bhandary, YRC		DBT	Submitted (under review)
7	Development of molecular diagnostics for simultaneous identification of Mycobacterium tuberculosis infection and drug resistance pattern in adult and pediatric pulmonary and extra pulmonary tuberculosis	Dr. T. S Keshava Prasad (Collaborator PI) Dr. Harsha Gowda (Collaborator PI) Dr. Sneha Pinto (Co-I)	INR 41,24,000	DBT	Submitted (under review)

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8	Expression of Interest for Establishment of Biotechnology Skill Enhancement Programme-BiSEP	Dr. T. S Keshava Prasad (BiSEP course coordinator)	INR 200,00,000 for infrastructure INR 10,00,000/annum as student fee INR 10,00,000/annum as consumables	Karnataka Biotechnology & Information Technology Services (KBITS)	Submitted (under review)
9	Therapeutic potential of marine bacterial biosurfactant against *Trichophyton rubrum*, a dermatophytic fungus	Dr. T. S. Keshava Prasad (Co-I) in collaboration with Dr. Kishor Keekan, YRC	INR 18,00,000	DBT	Submitted concept note on marine natural products development under the programme area Aquaculture & Marine biotechnology
10	Identification of pathogenic effectors and host defensive molecules through multipronged OMICS (transcriptomic, proteomic and metabolomics) analyses during rice-Magnaporthe interactions	Dr. Pratigya Subba (PI) Dr. Sneha M. Pinto (Co-I) Dr. T. S. Keshava Prasad (Co-I) in collaboration with Dr. Malali Gowda, Transdisciplinary University, Bangalore	INR. 55,20,000	DBT	Submitted concept note on plant microbe interactions
11	Diagnosing survivability in early stages of bacterial sepsis based on acute phase response – designing a cost effective nanoprobe immunoassay	Dr. Sneha M. Pinto (PI)	INR 13,95,000	DST	Submitted (not approved)

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12	Assessing the predictive value of Lactate dehydrogenase isoenzymes in neonatal birth asphyxia	Dr. Yashwanth Subbannayya (Co-PI), Dr. Sneha M. Pinto (co-I) in collaboration with Dr. Sahana K S, Dept of Pediatrics, YMC	INR 48,80,000	DBT-ICMR	Submitted
13	Identification of urinary markers using high resolution mass spectrometry to predict neonatal birth asphyxia	Dr. Yashwanth Subbannayya (PI), Dr. Sneha M. Pinto (co-I) in collaboration with Dr. Sahana K S, Dept of Pediatrics, YMC	INR 55,80,000	DBT-ICMR	Submitted
14	Identification of candidate markers using predictive of preeclampsia using an integrated OMICs approach	Dr. Sneha M. Pinto (PI), Dr. Yashwanth Subbannayya (co-I) in collaboration with Dr. Sharon Rasquinha, Dept. of OBG, YMC		DBT	Submitted
15	Identification of molecular markers for predicting therapy response in oral cancer using an integrated omics-based approach	PI: Dr. M. Vijayakumar, co-ordinator: Dr. Yashwanth Subbannayya	4,47,00,000	DBT (GLUE grant)	Submitted letter of Intent (LOI) for the Glue grant
16	Novel approaches to colorectal cancer through a basic, clinical	(Co-PI: Dr. Sneha Pinto, Dr. Yashwanth	7,50,00,000 (CSBMM	DBT	Under review Letter of Intent

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	and translational partnership	Subbannayya) in collaboration with Dr. Shaida Andrabi, University of Kashmir	component: 65, 00,000)		(LOI) for the Glue grant
17	Immunomodulation by parasitic Macrophage migration Inhibitory Factor (MIF) in Type 1 and Type 2 diabetes	(Co-PI: Dr. Sneha Pinto, Dr. T. S. Keshava Prasad) in collaboration with Dr. S. L. Hoti, RMRC, Belgavi	INR 25,00,000	ICMR	Under review
18	Proteomics approach for rapid identification of clinically important bacterial species	Centers of Excellence in Science, Engineering and Medicine (CESEM)	INR 60,00,000	VGST	Under review

Publications

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Awards and recognition

- Dr. Aditi Chatterjee was awarded the "Bharat Ratna Mother Teresa Gold Medal Award" from the Global Economic Progress and Research Association for the year 2016 for her outstanding service in Health.
- Dr. Harsha Gowda was awarded the Sir C.V. Raman Young Scientist Award from Karnataka State Council for Science and Technology for the year 2013.
- Dr. Sneha Pinto and Dr. Yashwanth Subbannayya received awards for excellence in performance in the Targeted proteomics workshop held at IIT Bombay, Mumbai.
- Dr. Shyama Prasad Rao, YRC, won a "Best Poster prize" for his poster entitled "Expression pattern of protein kinases across human tissues" at NextGen Genomics, Biology, Bioinformatics and Technologies (NGBT) Conference, Hyderabad. The work was done in collaboration with Dr. Harsha Gowda and Dr. Yashwanth Subbannayya, YU-IOB CSBMM.
- Mr. Saketh Kapoor won the first prize in the event "Budding Scientist- Best Hypothesis Award" organized by Yenepoya Research Centre, Yenepoya University on the occasion of celebration of National Science day on February 24, 2016.
- Mr. Saketh Kapoor, Mr. Sandeep Kolya and Ms. Roopna Raveendran won third prize in the General Knowledge Quiz Competition organized by Yenepoya Research Centre, Yenepoya University, on the occasion of celebration of National Science day on February 25, 2016.
- Ms. Varsha Mohanty and Ms. Roopna Raveendran won the third prize in the event "Sci-Cartoon: Drawing of Scientific Cartoon" organized by Yenepoya Research Centre, Yenepoya University, on the occasion of celebration of National Science day on February 23, 2016.

Conferences/Seminar/Symposia/CME/Workshops organized

1. **Workshop on mass spectrometry-based proteomics for beginners**

The faculty members of YU-IOB Center for Systems Biology and Molecular Medicine, Yenepoya University conducted a workshop on "Mass Spectrometry-based Proteomics for Beginners" from February 09-10, 2016 at the seminar hall, Yenepoya Research Centre, Yenepoya University. The theme of the workshop was to provide basic concepts of mass spectrometry-based proteomics to the participating post-graduate students from various departments of Yenepoya University. The workshop was attended by M.D.S. and M.D. students of Yenepoya Dental College and Yenepoya Medical College respectively.

The event was coordinated by Dr. Sneha Pinto, Dr. Yashwanth Subbannayya and Dr. Pratigya Subba along with the assistance of the students of YU-IOB-CSBMM and staff of YRC. The technical aspects of the mass spectrometry instrumentation were demonstrated by Dr. Sneha Pinto at the CSBMM laboratory. The demonstrations for the proteomics experiments were conducted by Dr. Sneha Pinto and Dr. Yashwanth Subbannayya.

Participants

The following students attended the workshop

1. Dr. Sameera Begum, Department of Oral Pathology and Microbiology

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2. Dr. Umme Amarah, Department of Oral Medicine and Radiology
3. Dr. Anu Babu, Department of Oral Medicine and Radiology
4. Dr. Chandhini Begum N., Department of Oral Medicine and Radiology
5. Dr. Nimi Susan Mathew, Department of Oral Medicine and Radiology
6. Dr. Sithara Rathan, Department of Oral Medicine and Radiology
7. Dr. Tariq Ahmed, Department of Ophthalmology
8. Mr. Sandeep Kasargod, YU-IOB CSBMM
9. Mr. Saketh Kapoor, YU-IOB CSBMM
10. Ms. Varsha Mohanty, YU-IOB CSBMM
11. Ms. Roopna Raveendran, YU-IOB CSBMM
12. Ms. Faraz, Yenepoya Research Center
13. Mr. Muhammed Manzoor, Yenepoya Research Center

Outcomes of the workshop-training

Feedback forms were distributed among the participants at the end of the session. The overall feedback received was positive.

2. **Symposium on "Genomics in clinical practice: Future of precision medicine" organized by YU-IOB Center for Systems Biology and Molecular Medicine and Yenepoya Research Centre**

YU-IOB Center for Systems Biology and Molecular Medicine and Yenepoya Research Centre organized the first symposium on "**Genomics in clinical practice: Future of precision medicine**" at Yenepoya University on June 1-2, 2016. The symposium was of a scientific and technical nature highlighting the advances and applications of Next Generation Sequencing (NGS) to medicine. It covered various aspects of NGS - including oncology applications, non-invasive prenatal testing, inherited disease diagnosis, traditional medicine, microbiological applications, diagnostic and research applications. The symposium was well received by both the student and faculty participants. The resource persons included 16 individuals from various academic organizations as well as industry. The symposium was attended by 218 participants from 24 institutions around India. The inaugural session was presided over by Mr. Farhad Yenepoya, Director (Finance), Yenepoya University, Dr. C.V. Raghuveer, Registrar, Yenepoya University, Dr. M. Vijayakumar, Vice-Chancellor, Yenepoya University, Dr. Keshava Prasad, Professor and Deputy Director, YU-IOB Center for Systems Biology and Molecular Medicine.

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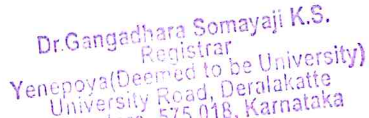
The talks at the symposium were delivered by 16 speakers from various organizations across India. The talks delivered at the symposium were as follows:

Title of the Talk	Speaker name and affiliation
Impressive advances in technology and understanding disease biology propels change from GATC to genomic medicine	Dr. B. K. Thelma University of Delhi, New Delhi
The role of genomics in evidence based medicine	Dr. Harsha Gowda Institute of Bioinformatics/ YU-IOB CSBMM
Advances in genetic testing- "what to offer and when"	Dr. S. Chikara Eurofins
Translational applications of Next Generation Sequencing in oncology	Mr. Rajendra Tari Illumina
Translating cancer genomics to medicine	Dr. Amit Dutt ACTREC, Navi Mumbai
Ion Torrent: Semiconductor based Next Generation Sequencing technology-Introduction and Applications	Dr. Sreejayan Nambiar Thermo Fisher Scientific
Pathogen signatures in the blood and the brain-an investigation using genomic tools	Dr. Chitra Pattabiraman National Centre for Biological Sciences, TIFR, Bangalore
Genomic diversity in the host-pathogen interacting genes and its association with human microbiome dysbiosis in chronic diseases	Dr. Souvik Mukherjee BMGC, NIBMG, Kolkata
Population genomic inferences indicate possibility of personalized medicine for malaria in India	Dr. Aparup Das NIMR, New Delhi
Non-invasive prenatal screening for chromosomal abnormalities	Dr. Priya Kadam MedGenome Laboratories, Bangalore
Genetic testing as tool for Beti Bachao: recipe for lawmakers	Dr. Akshay Anand PGIMER, Chandigarh
Genomics of medicinal plants and traditional	Dr. Malali Gowda Transdisciplinary University Foundation of Revitalization of



formulations	Local Health Traditions, Bangalore
Single molecule real time sequencing - beyond a single human reference genome	Dr. Stephen Rudd PacBio, Singapore
Droplet Digital PCR: Way forward for liquid biopsy	Ms. Niyati. S. Dave Bio-Rad Laboratories
A gene expression array for predicting chemotherapy response in cancer patients	Dr. Shaji George BioPharm Laboratories, New York/Bangalore
Monogenic diabetes – from bench to bedside	Dr. Radha Venkatesan Madras Diabetes Research Foundation, Chennai

Panel Discussion

The post-lunch session on Day 2 of the symposium also consisted of a panel discussion. Radha Venkatesan, Executive Scientific Officer, Madras Diabetes Research Foundation, Dr. Stephen Rudd, PacBio, Singapore, Dr. Malali Gowda, Professor, School of Conservation, Life Science and Health Science, Transdisciplinary University, Dr. Priya Kadam, Medical Officer, MedGenome Labs Private Ltd, Dr. Chitra Pattabiraman, Postdoctoral Fellow, NCBS, Dr. Shaji George, Director and Chief Scientific Officer, Mir Lifescience Pvt Ltd, Bangalore were the members of the panel and Dr. T. S. Keshava Prasad served as the moderator for the panel discussion. Several students participated in this panel discussion and asked there queries regarding genomics in clinical practice.

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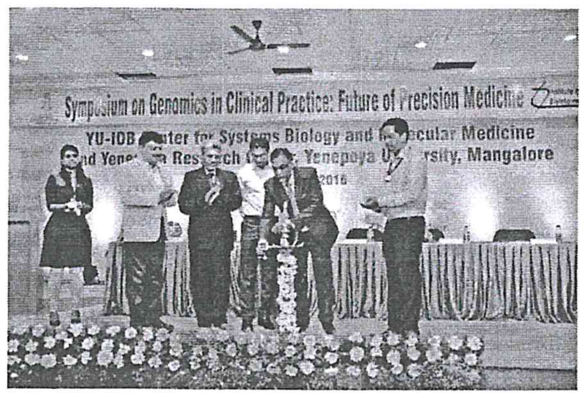

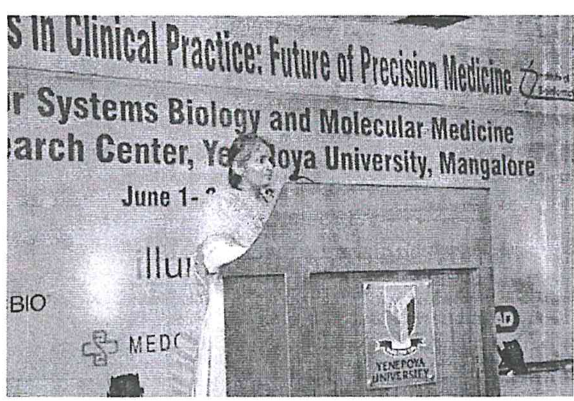

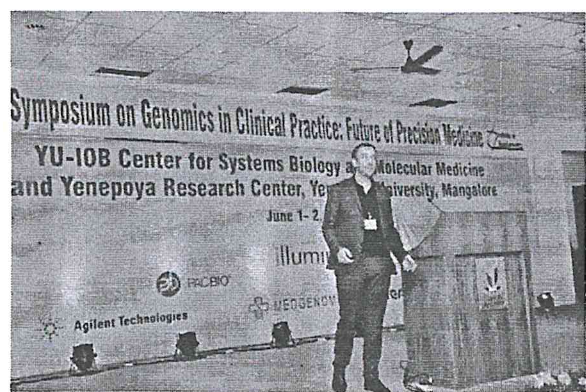

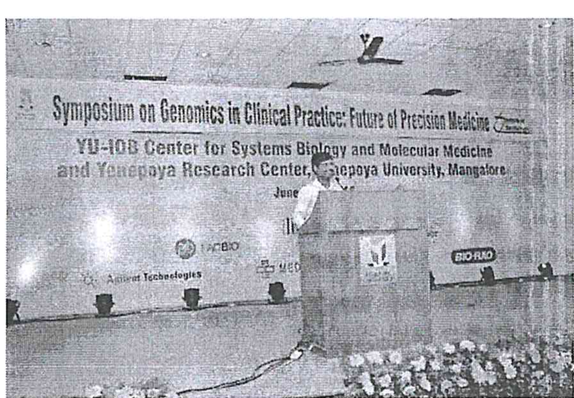

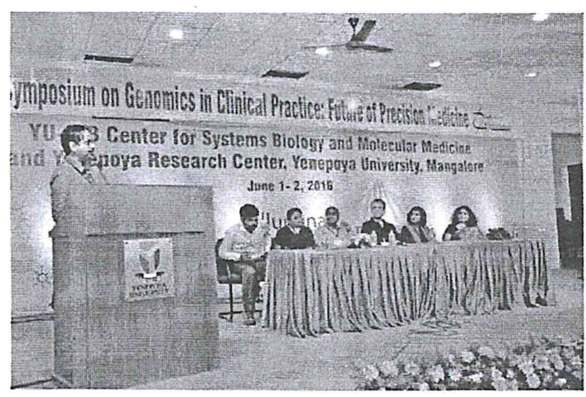

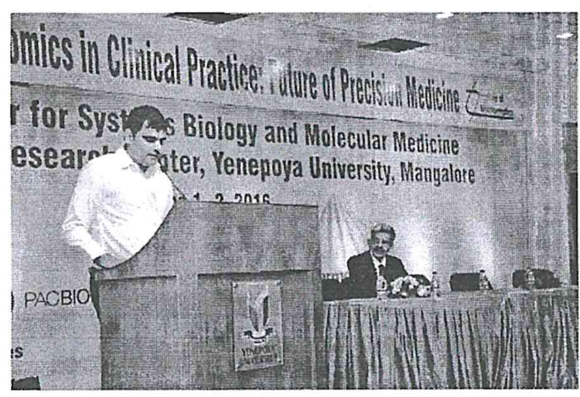

Guest lectures

1. Guest lecture on 'Taking comprehensive eye care to rural India: Focus on retinopathy of prematurity and diabetic retinopathy' was delivered by Dr. Krishna R. Murthy, Faculty scientist, Institute of Bioinformatics, Bangalore; Medical Director of Prabha Eye Clinic and Research Centre, Bangalore; Consultant Vitreoretinal Surgeon, Vittala International Institute of Ophthalmology, Bangalore; Consultant for Pediatric ROP clinic, Indira Gandhi Institute of Child Health Sciences, Bangalore on March 2, 2016.

2. Guest lecture on 'A System Biology approach to elucidate Epithelial-Mesechymal Transition (EMT) in cancer' was delivered by Dr. Shivashankar Nagaraj, Vice Chancellor's Research Fellow, Queensland University of Technology, Australia on March, 24 2016.

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Invited talks and conferences

- The following posters were presented with the YU-IOB affiliation at the 7th annual meeting of Proteomics Society, India at Vellore Institute of Technology, Vellore between December 3-6, 2015
    - Rapid processing of biological samples for proteomic analysis using pressure-cycling technology
    - Cigarette smoke induced molecular alterations in esophageal cells
    - Mapping protein coding regions in the human genome
    - Chewing tobacco and cigarette smoke-induced molecular alterations in oral cancer
    - SILAC-based proteomic analysis to delineate mechanisms underlying erlotinib resistance in head and neck squamous cell carcinoma
    - Proteomic profiling to identify tobacco-induced signaling in esophageal cells
    - Quantitative proteomics of cerebrospinal fluid from tuberculous meningitis co-infected with HIV
    - Expression dynamics of protein kinases and phosphatases across human tissues
    - Identification of differential host responses to infections in cryptococcal meningitis, toxoplasma encephalitis and tuberculous meningitis co-infected with HIV
    - Human brain proteome: molecular insights into regional heterogeneity
    - A proteome map of the human eye
    - Proteomic profiling of brain regions reveals complex biological basis for schizophrenia
    - Repertoire of differentially expressed proteins in cases of acute rabies encephalitis (<5 days) and sub-acute cases who succumbed late (>3 weeks)
    - Quantitative proteomic analysis of serum from paralytic rabies and Guillain–Barré syndrome
    - Phosphoproteomic analysis of gallbladder cancer
    - Proteogenomic analysis of Mycobacterium tuberculosis H37Ra strain
    - Identification of host response in cerebral malaria brain proteome using quantitative proteomic analysis
    - Quantitative proteomic and phosphoproteomic analysis of H37Ra and H37Rv strains of Mycobacterium tuberculosis

- Dr. Keshava Prasad chaired a session and judged posters at 7th annual meeting of Proteomics Society, India held at Vellore Institute of Technology, Vellore from December 3-6, 2015.
- Dr. Harsha.Gowda chaired a session at 7th *annual meeting of Proteomics* Society, India held at Vellore Institute of Technology, Vellore from 3-6 December 2015.
- Dr. Harsha Gowda was an instructor for the HR-LC-MS/MS workshop held at IIT Bombay, Mumbai from December 10-12, 2015.
- Dr. Harsha Gowda gave a talk on "Quantitative Proteomics using MS-based iTRAQ" at the Education Day programme of the Targeted Proteomics International Symposium, IIT Bombay, Mumbai held on December 12, *2015*.
- Dr. Harsha Gowda was an invited speaker at the Targeted Proteomics International Symposium, IIT Bombay, Mumbai held from December 13-14, 2015. He spoke on "Targeted proteomics and metabolomics approaches for validating cancer biomarkers". Dr. Harsha Gowda also chaired a session at the Targeted Proteomics International Symposium during the same time.

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- Dr. Keshava Prasad was an invited speaker at the International Conference on Frontiers of Mass Spectrometry (ICMS-2015), Mahatma Gandhi University, Kottayam, Kerala on December 14, 2015. He spoke on the "Proteogenomics analysis for accurate assembly and annotation of newly sequenced genomes".
- Dr. Keshava Prasad spoke at the Tamil Nadu Agricultural University, Coimbatore on December 15, 2015. He spoke on the "Applications of mass spectrometry for biological research" followed by collaborative discussions with the faculties of Center for Plant Molecular Biology and Department of Biotechnology
- Dr. Keshava Prasad was an invited speaker at the meeting between Ohio State University and Avinashilingam University, Coimbatore on December 16, 2015. He spoke on the "Functional proteomic approaches to identify biomarkers and therapeutic targets in cancers".
- Dr. Keshava Prasad was a Key Note Speaker at MS Ramaiah Institute of Technology, Bangalore on January 19, 2016.
- Dr. Keshava Prasad was a Key Note Speaker at Bapuji Institute of Engineering and Technology, Davanagere on January 20, 2016.
- Dr. Keshava Prasad participated in an invited meeting and delivered a lecture on "Phosphoproteomics as a novel approach to detect molecular targets of herbal medicines" at RMRC, Belgavi on February 25, 2016.
- Dr. Keshava Prasad delivered an invited lecture at Amrita University on "Proteomics and Phosphoproteomics approached to investigate human diseases". Host- Dr. Bipin Nair on February 3, 2016.
- Dr. Keshava Prasad was invited to deliver a lecture as the keynote speaker for Symbiot 2016 at Manipal Institute of Technology on April 8, 2016.
- Dr. Yashwanth Subbannayya, Dr. Pratigya Subba, Mr. Saketh Kapoor, Ms. Varshasnata Mohanty and Mr. Ankur Tyagi attended the workshop on "Stem Cell Characterisation and Sorting" from April 26-28, 2016 organized at Yenepoya Research Center, Yenepoya University

Short term research training

Several students from various academic institutions undergo short term trainings at YU-IOB CSBMM for proteomics and bioinformatics.

Sl.No	Name & designation of the student	Training
1	**Ms. Aditi Shenoy**, B.Tech.(Biotechnology), Department of Biotechnology, Manipal Institute of Technology, Manipal University	Analysis of potential bio-markers for the development of novel molecular diagnostics of Dengue and Chikungunya"
2	**Ms. Sruthi E**, M.Tech.(Computer Science and Engineering) from Canara Engineering College, Mangalore	Computational approach in proteogenomics analysis.
3	**Dr. Chandhni Begum**, pursuing post graduation from the Department of Oral Medicine and Radiology, Yenepoya Dental College, Mangalore	Proteomic technique and data analysis.
4	**Dr. Nimi Susan Mathew**, pursuing post graduation from the Department of Oral	Proteomic technique and data analysis.

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	Medicine and Radiology, Yenepoya Dental College, Mangalore.	
5	**Dr. Sitara Rathan**, pursuing post graduation from the Department of Oral Medicine and Radiology, Yenepoya Dental College, Mangalore.	Proteomic technique and data analysis.
6	**Dr. Umme Amarah**, pursuing post graduation from the Department of Oral Medicine and Radiology, Yenepoya Dental College, Mangalore.	Proteomic technique and data analysis
7	**Dr. Anu Babu**, pursuing post graduation from the Department of Oral Medicine and Radiology, Yenepoya Dental College, Mangalore.	Proteomic technique and data analysis
8	**Mr. Vinuth N. Puttamallesh**, pursuing Ph.D. (Biotechnology) at Institute of Bioinformatics, Bangalore	Attended the training session on handling QTRAP mass spectrometer and its application for Multiple Reaction Monitoring (MRM) based quantitative proteomic and metabolomic analysis.
9	**Mr Firdous Ahmad Bhat**, pursuing Ph.D. at Institute of Bioinformatics, Bangalore	Attended the training session on handling QTRAP mass spectrometer and its application for Multiple Reaction Monitoring (MRM) based quantitative proteomic and metabolomic analysis.
10	**Dr. Sreekala K. Nair**, Assistant Professor (Botany) Bharathiar University, Coimbatore	Exposure to mass spectrometry- based proteomic analysis
11	**Dr. Catherine S. Manohar**, Senior Scientist at CSIR-National Institute of Oceanography, Dona Paula, Goa.	Provided with an exposure to mass spectrometry-based phosphoproteomic analysis and signaling pathways.
12	**Mr. Gunasekaran Dhandapani**, DST-JRF in RMRC (ICMR), Port Blair.	At YU-IOB CSBMM, he analyzed proteomic data from collaborative projects between YU-IOB CSBMM and RMRC proteomic data analysis and manuscript writing.
13	**Ms. Pragya Barua**, pursuing Ph.D. from National Institute of Plant Genome Research.	At YU-IOB she is being trained in labelling-based differential proteomic analysis using mass spectrometry.
14	**Mr. Nilesh Vikram Lande**, pursuing Ph.D. from National Institute of Plant Genome Research.	At YU-IOB he is being trained in mass spectrometry-based proteomic analysis of chloroplast.
15	**Dr. Sandhya Sanand** obtained her Ph.D. degree from NDRI, Karnal. She is currently working as a Scientist at ICAR-National Research Centre on Plant Biotechnology, New Delhi.	At YU-IOB CSBMM, she is being trained in mass spectrometry-based proteomics and data analysis.

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Progress of existing projects:

Progress of *Mycobacterium tuberculosis* genome sequencing project

Scientists at IOB and YU-IOB CSBMM in collaboration with JALMA and PGIMER, Chandigarh are carrying out whole genome sequencing of Indian clinical isolates of *M. tuberculosis* as an effort to investigate a panel of mutations associated with drug resistance. This will provide candidates for the early detection of MDR and XDR *M. tuberculosis*, which will help TB control programs in India.
We have obtained DNA samples from 206 clinical isolates of *M. tuberculosis* from JALMA, Agra. These include 198 samples of pulmonary TB and the remaining extra pulmonary TB. From Genome sequencing is being outsourced to MedGenom. In all, we have already received the sequencing data for 107 samples. Out of these, alignment and analysis of data has been completed for 100 clinical isolates. We have identified mutations associated with drug resistance in ~30% of the clinical isolates that have been labeled as drug sensitive isolates. In addition, we also identified mixed infection in some of the clinical samples. The phylogenetic analysis performed using whole genome sequencing data have identified distribution among 4 lineages - East-African Indian (87%), Indo-Oceanic (21%), Euro-American (16%) and Beijing (6%). Strain-to-strain variability in MTB can have important phenotypic consequences. Phylogeographical strain variation might affect the development of new diagnostics, drugs, and vaccines. Data on genotypic diversity of MTB is important to understand its epidemiology, clinical phenotypes, and drug resistance. Further, we have received sequencing data of 90 pulmonary M Tb samples from MedGenom. Currently initial QC check is being performed on the received sequences. We have received sequencing data for 85 of the 90 pulmonary samples and data analysis is currently on-going. Also we have standardized the protocol for drug susceptibility testing (DST) profiling for the clinical strains sequenced thus far and have subcultured close to 200 clinical isolates for initiating DST profiling in these samples

Progress of *M. tuberculosis* proteomics and phosphoproteomics analysis project

Protein phosphorylation is an important post-translational modification in *Mycobacterium tuberculosis*. The two laboratory strains H37Rv and H37Ra of *Mycobacterium tuberculosis* show different pathogenic phenotypes. Alterations in the protein expression and phosphorylation status among the two strains could be an important factor for the virulence attenuation in H37Ra strain. To this end, we carried out tandem mass tag based quantitative proteomic and phosphoproteomic analysis of the two strains at log and stationary phase. We identified 2,793 proteins and 522 phosphorylation sites. Comparative proteomic analysis revealed upto 20 fold overexpression of several proteins associated with virulence. Data analysis and manuscript writing was carried out by faculty of YU-IOB CSBMM. The manuscript has been finalized for submission to *Journal of Proteome Research.*

Progress of "MyKINOME- a compendium of protein kinases and phosphatases in *Mycobacterium tuberculosis*." Project

Mycobacterium tuberculosis (MTB) expresses various serine/threonine and tyrosine protein kinases that play essential roles in the fundamental biological processes. However the biological

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functions of these systems are largely unknown. Various studies have reported the roles of these signaling molecules in the pathophysiology of tuberculosis. The MTB genome contains 11 serine/threonine protein kinases (STPKs) namely; *pknA* to *pknL* and here we present the current knowledge on their substrates. We catalogued substrates of known Ser/Thr kinases using a manual literature-based curation strategy and compiled a list of 255 substrates with 701 threonine and 144 serine phosphorylation sites. Majority of the proteins are substrates for multiple kinases. This compendium will foster the development of information networks which will provide novel insights into MTB pathogenesis. The data is being reviewed and the manuscript is being prepared by faculties and students of YU-IOB CSBMM.

Progress of Head and Neck cancer project

Using a cell line model chronically treated with chewing tobacco, Stearoy-CoA desaturase (SCD) was identified as a potential therapeutic target in head and neck squamous cell carcinoma, especially in patients who are users of tobacco. This data was recently published in the journal "*Cancer Biology and Therapy*". Currently, using the cell secretome of the same model, we identified Sparc/osteonectin, cwcv and kazal-like domains proteoglycan (testican) 1 (SPOCK1) and Prosaposin (PSAP) which is being validated using ELISA based validation on saliva samples from oral cancer patients to serve as potential early detection biomarkers in oral cancer patients, especially in tobacco users. We have performed phosphotyrosine analysis of HNSCC cell lines and dual-specificity tyrosine- (Y) - phosphorylation regulated kinase 1A (DYRK1A) was identified to be hyperphosphorylated in all HNSCC cell lines. We have evaluated the therapeutic potential of targeting DYRK1A using *in vitro* and mouse models. The study is currently submitted to *BMC Cancer* and is under review. p-Ser/Thr analysis of all HNSCC cell lines was also carried out and the data revealed significant enrichment of molecules involved in RNA splicing. We validated the role of serine arginine rich protein kinase 2 (SRPK2) in HNSCC cells. The manuscript is accepted for publication in *Cancer Biology and Therapy*.
Using the untreated normal oral keratinocytes, OKF6/TERT1 and the derivative cell line chronically treated with chewing tobacco, we carried out mass spectrometry-based secretome analysis to identify the proteins that secreted at higher or lower abundance in response to chewing tobacco. A total of 2,873 proteins were identified among which 360 and 184 proteins were shed at higher and lower abundance, respectively by the tobacco treated cells compared to untreated OKF6/TERT1 cells. Among the proteins that are abundantly secreted, immunohistochemistry-based validation further revealed the overexpression of Prosaposin (PSAP) and Testican-1 (TIC1) in HNSCC tissues compared to normal tissues, thus, showing the probable role of PSAP and TIC1 in inducing transformation of normal oral keratinocytes in response to chewing tobacco. Further, ELISA-based validation of TIC1 and PSAP in saliva from oral cancer patients and healthy individuals will be carried out.

Mechanisms of erlotinib resistance in head and neck squamous cell carcinoma

Epidermal growth factor receptor (EGFR) plays an important role in the pathogenesis of HNSCC. Overexpression of EGFR is observed in about 90% of HNSCC cases and has been implicated in more aggressive phenotypes. Tyrosine kinase inhibitors (TKIs) such as erlotinib and gefitinib among several other drugs are currently under Phase III investigations as treatment options. However, most of these TKIs have shown a modest activity in recurrent or advanced

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HNSCC in clinical trials. One of the major reasons for acquired resistance over relatively short periods being development of intrinsic mechanisms by these tumors to circumvent blockade of EGFR signaling. Elucidating the molecular mechanism of resistance to EGFR-targeted therapies is therefore essential to identifying potential therapeutic targets. Drug resistant cell lines (SCC-R) were generated via a process of slowly escalating exposure of UM-SCC1 cells to erlotinib. SCC-S is used to designate the parental UM-SCC1 cells exposed to DMSO.SILAC-based global quantitative proteomic analysis was carried out to gain insights into the mechanism of erlotinib resistance in these cell lines. SCC-S cells were grown in heavy SILAC media whereas SCC-R cells were grown in light SILAC media. The lysates were mixed in equal amounts and subjected to in-solution tryptic digestion and fractionated. The fractions were analyzed on high resolution Fourier transform Orbitrap Fusion Tribrid mass spectrometer.
SILAC-based quantitative proteomics experiment led to identification of 5,427 proteins of which 509 proteins were overexpressed and 504 proteins were down regulated by more than 2 fold in SCC-R cells with respect to SCC-S cells. We observed overexpression of several signaling molecules downstream of EGFR such as, breast cancer androgen receptor 1(BCAR1) and paxillin (PXN). In addition, we also observed overexpression of AXL which have been previously implicated in mediating erlotinib resistance in HNSCC. Furthermore, we identified 6.4 fold overexpression of Cub-domain containing protein 1(CDCP1), a transmembrane protein involved in cell adhesion and cell matrix association and a known interactor of integrin β1 in SCC-R cells implicating its role in erlotinib resistance. Additionally, we also observed 12 fold overexpression of vimentin in SCC-R cells and loss of E-cadherin and dysregulation of proteins involved in actin-cytoskeleton remodeling indicating epithelial to mesenchymal transition (EMT).

Progress of Lung cancer project

Epidemiological data clearly establishes cigarette smoking as one of the major cause for lung cancer worldwide. Though certain targeted therapies such as anti-EGFR are in clinical practice, they have shown limited success in the smokers suffering from lung cancer. This demands discovery of alternative drug targets through systematic investigation of altered signaling mechanisms. To study dysregulated signaling pathways due to chronic cigarette smoke exposure, we carried out SILAC-based phosphoproteomic analysis of lung cell line H358 chronically exposed to cigarette smoke. We identified 1,812 phosphosites, of which 278 phosphosites were hyperphosphorylated (≥ 3-fold) in lung cells chronically exposed to cigarette smoke. Our data revealed hyperphosphorylation of Ser560 which is conserved in the kinase domain of group II PAKs (PAK4/5/6). Activation of PAK6 is associated with various processes in cancer including metastasis. We further assessed the role of PAK6 in non-small cell lung cancer cells. Inhibition of PAK6, leads to reduction in cell proliferation and invasive ability of lung cancer cells. Further, in vivo studies have shown that PAK6 inhibitor could significantly reduce tumor burden in mouse tumor xenograft model. Our study indicates that PAK6 is a promising novel therapeutic target for NSCLC especially in smokers. We are currently working on addressing the reviewer's comments and have initiated mice tumorigenicity experiments to evaluate the effect of PAK6 inhibitor on H358 smoke treated cells (**Manuscript under revision, Oncotarget, 2016**).

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Phosphotyrosine profiling of lung cancer cells chronically exposed to cigarette smoke

Tyrosine phosphorylation accounts for a minority of total phosphorylation; however it is critical for activation of signaling pathways and plays a disproportionately large role in diseases, especially cancer. We have compared phosphotyrosine profile of H358 cells (bronchioalveolar carcinoma cells) chronically treated with cigarette smoke condensate with the parental H358 cells. We have employed SILAC based quantitative approaches where H358 cells were metabolically labelled with heavy isotopes of amino acids (K6R6). The H2358 cells chronically exposed to cigarette smoke were maintained in media containing natural isotopes of amino acids. Protein lysates obtained from untreated and treated cells were normalized, pooled, fractionated by in-gel and SCX and subjected to LC-MS/MS analysis using LTQ-Orbitrap Velos. The protein mixture was then digested by trypsin, desalted with C18 reversed phase column and enrichment of phosphotyrosine containing peptides were carried out using anti-phosphotyrosine antibodies. The fractions are then analyzed on LTQ-Orbitrap Velos mass spectrometer. Data was searched using Mascot and Sequest and after application of 1% FDR, phosphosites passing 75% PhosphoRS probability score were considered. With these criteria, 322 phosphosites were identified (278 pY, 24 pT and 20 pS) of which 123 were hyperphosphorylated and 49 hypophosphorylated.

Progress of ESCC proteomics projects

We have performed phosphoproteomic and proteomic analysis of non-neoplastic esophageal cell line model chronically treated with chewing tobacco. Phosphoproteomic analysis of Het1A-parental and tobacco treated cells resulted in the identification of 2029 phosphopeptides corresponding to 1142 proteins. Among them 263 and 264 proteins were found to be hyper- and hypo-phosphorylated respectively in response to chewing tobacco in Het1A cells. Currently, data is being analyzed for significantly altered molecular pathways which will be further validated using cell line and mouse models. In addition, we have performed temporal proteomic analysis of esophageal cells treated with chewing tobacco. We will now analyze the data to identify molecules which display progressive expression trends with increasing treatment period. We have currently harvested the temporal treated cells for metabolomics analysis.

We have also performed several phenotypic assays including proliferation and invasion assays to determine the effect of chewing tobacco on esophageal (Het1A) cells. The results show that tobacco treated Het1A cells have increased proliferation and invasive properties. Using western blot, we have screened for levels of apoptotic and anti-apoptotic molecules such as BCl2, BCL-XL and BAX in chewing tobacco treated esophageal cells. Our data reveals that chewing tobacco treated Het1A cells have elevated anti-apoptotic molecules contributing to enhanced survival of the cells. Further, we assayed for EMT markers and our data showed increased expression of mesenchymal markers such as N-Cadherin and vimentin whereas E-cadherin was downregulated in Het-1A-Tobacco cells. We also find significant upregulation of MAPK signaling (ERK and JNK pathways), however AKT signaling remained unaffected in Het1A-Tobacco cells. Next we evaluated the effect of JNK inhibitor on ESCC cell proliferation and invasion. We performed colony formation assay and our results indicate significant reduction in ESCC cell proliferation upon treatment with JNK inhibitor. We also performed invasion assay using ESCC cell lines in the presence of JNK inhibitor (10 μM) and we observed reduced

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invasive properties in ESCC cell lines treated with JNK inhibitor compared to the corresponding vehicle treated control.

Progress of gallbladder cancer projects

We have performed total proteomic analysis of GBC cell lines. We identified 3,653 proteins, of which, more than 1,000 proteins were found to be differentially regulated. Of these, macrophage migration inhibitory factor (MIF) was identified to be overexpressed in the invasive GBC cell lines when compared to the non-invasive GBC cell line, TGBC24TKB. Immunohistochemical studies revealed that MIF was found to be overexpressed in GBC tissues. The therapeutic potential of targeting MIF in GBC was evaluated through *in vitro* assays using siRNA-mediated silencing as well as pharmacological MIF inhibitors. MIF was found to have a potential as a therapeutic target for GBC. This study has been published in *BMC Cancer* (November 2015). We have in addition done pSer/Thr enrichment from GBC cell lines, following TMT labelling. The labelled fractions were run on M/S. We identified 2,418 phosphopeptides corresponding to 2,665 proteins. In this study, we have identified Thr 246 of AKT1S1 to be hyperphosphorylated greater than 2-fold in all the four gallbladder cancer cell lines used in the experiment. This molecule is a substrate of AKT and PIM1. We have observed significant decrease in cell survival following treatment with PIM inhibitor in GBC cell lines. At present, we are checking the effect of PIM inhibitor on downstream signaling through Western blot.

Progress of bladder cancer proteomics project

Prior to harvesting the bladder cancer cell lines for proteomic studies, we analyzed classical indicators of epithelial or mesenchymal cell status in seven human bladder cancer cell lines and two non-neoplastic bladder cell lines. As epithelial marker we measured E-cadherin and as mesenchymal markers we measured N-cadherin and vimentin by Western blot. E-cadherin was expressed strongly in non-neoplastic bladder cell lines and bladder cancer cell lines derived from female patients (RT-112 and SW-780). All the bladder cancer cell lines derived from male patients did not express E-cadherin but was positive for N-cadherin expression. As expected non-neoplastic cell lines SV-HUC1 and TERT-NHUC did not show any expression of N-cadherin reconfirming their epithelial origin. We performed TMT- based quantitative proteomic data analysis on the panel of bladder cancer cells. The LC-MS/MS data was acquired in triplicates with MS3 quantitation. We identified a total of 5,527 proteins across 7 cancer cell lines among which 3,982 has triplicate quantitative values. Presently, analyzing the differentially regulated proteins in comparison with the two normal bladder cell lines.

Data acquisition for the human brain proteome map project

We are currently acquiring data on different regions of the human brain. These samples were received from Dr. Keshava Prasad's team at NIMHANS, Bangalore. We have carried out a part of the sample preparation here and completed acquisition of 3 human brain regions on Thermo Orbitrap Fusion Tribrid mass spectrometer namely- caudate nucleus, striate cortex and Thalamus. We have identified 5306, 6094 and 5081 proteins respectively in each of these regions. We also received in-gel digested fractions of orbito prefrontal cortex (OPFC), globus pallidus (GP) regions and bRPLC fractions of dorsolateral prefrontal cortex (DPFC) samples and

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identified 6229, 5119 and 5943 proteins respectively in each of these regions. This is by far the largest number of proteins identified to date.

Proteogenomic analysis of *Mycobacterium tuberculosis* H37Ra

Dr. Keshava Prasad has an ongoing collaboration with Dr. Sheetal Gandotra, IGIB, New Delhi. In continuation of their collaboration, we received protein pellet for H37Ra from Dr. Sheetal Gandotra. *Mycobacterium tuberculosis* H37Ra is an avirulent strain closely related to the virulent type strain H37Rv. The genome sequencing of H37Ra strain of *Mycobacterium tuberculosis* was completed in 2008. However, annotation of its genome remains challenging because of high GC content and dissimilarity to other model prokaryotes. To this end, we plan to carry out an in-depth proteomic analysis of *M. tuberculosis* H37Ra strain using high resolution Fourier transform mass spectrometry.
Currently, we have estimated the protein amount in the samples provided and also ran a SDS-PAGE gel. One mg of protein lysate was taken for in-solution trypsin digestion and the peptides were further fractionated using bRPLC. Equal amount was taken for in-gel digestion. The peptides from each fraction were analyzed using reversed phase nano scale liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) on Orbitrap Fusion Tribrid mass spectrometer (Thermo Scientific, Bremen, Germany) interfaced with Easy-nLC nano flow liquid chromatography system (Thermo Scientific, Odense, Denmark). After LC-MS/MS we have identified a total of 3,076 *Mycobacterium tuberculosis* H37Ra proteins by bRPLC and in-gel method (76.4%). The search is performed in PD 2.0 against H37Ra protein database using only SEQUEST.

Proteomic investigation of clinically relevant microorganisms

Scientists at YU-IOB CSBMM in collaboration with Dr. Prakash P.Y, Assistant Professor, Mycology lab, KMC, Manipal, carried out experiments on the proteomic analysis of *Rhodotorula mucilaginosa,* an emerging opportunistic pathogen. The fungi were cultured and processing of cell proteome and secretome was carried out. We have now analyzed the samples on the mass spectrometer. We are currently analyzing the data.
Fungal cultures of three bio-medically important fungi *Aspergillus flavus*, *Aspergillus niger* and *Rhizopus oryzae* were cultured by Dr. Prakash PY at Department of Microbiology, Manipal Institute of Technology, Manipal. The cultures were centrifuged to obtain the pellets of the fungi. The samples were then transported to YU-IOB CSBMM and are currently stored at -80°C.

Proteomic analysis of *Elizabethkingia meningoseptica*

Scientists at YU-IOB CSBMM in collaboration with NIMHANS, Bangalore carried out experiments on the proteomic analysis of an emerging opportunist pathogen, *Elizabethkingia meningoseptica.* This fungi is known to cause meningitis in newborn babies and meningitis or bloodstream and respiratory infections in people with weakened immune systems. We carried out bRPLC fractionation of this fungus here at YU-IOB CSBMM and identified 1634 proteins.

ATTESTED

Dr.Gangadhara Somayaji K.S.
Registrar
Yenepoya(Deemed to be University)
University Road, Deralakatte
Mangalore- 575 018

Proteomic analysis of *Mycobacterium fortuitum*

We acquired data on *Mycobacterium fortuitum* which were received from Dr. Ravi Kumar, NIMHANS, Bangalore. We have carried out a part of the sample preparation here and completed the data acquisition on Thermo Orbitrap Fusion Tribrid mass spectrometer. We identified 594 proteins from the bRPLC fractions of *Mycobacterium fortuitum*.

Proteomic analysis of urine samples from *Plasmodium vivax* infected malaria patients

We acquired data on three urine samples from *Plasmodium vivax* infected malaria patients. These samples were received from National Institute of Malaria Research (NIMR), Goa. We carried out sample preparation here and completed acquisition of 3 urine samples on Thermo Orbitrap Fusion Tribrid mass spectrometer labeled- Goa_37, Goa_55 and Goa_08. We identified 321, 864 and 1045 proteins respectively in each of these samples of which 2, 21 and 56 were *Plasmodium vivax* proteins. These data of these samples were already acquired in NIMHANS, Bangalore and were carried out here to do the reproducibility check.

Chickpea nuclear phosphoproteomics

In order to gain a better understanding of the signaling mechanisms under dehydration stress in plants, we plan to generate differential nuclear phosphoproteome of chickpea (*Cicer arietinum* L.) cv. JG-62. Nuclei enriched fractions were isolated from three-weeks old seedlings subjected to water-deficit stress (Control, 72 h, 144 h). The nuclear pellets were received from Dr. Niranjan Chakraborty, National Institute of Plant Genome Research, New Delhi by Dr. Keshava Prasad and Dr. Pratigya Subba.
Nuclear proteins were extracted using 4% SDS solution and ~2 mg of the proteins were precipitated using acetone. The proteins were then digested using trypsin followed by TMT labeling. These processes were carried out by Mr. Kiran Kumar at the Institute of Bioinformatics, Bengaluru. At YU-IOB-CSBMM, the TMT labeled peptides were pooled and fractionated into 12 bRPLC fractions. Mass spectrometric analysis led to the identification of 5010 protein groups. Quantitative proteomic analysis is currently being carried out.

Optimization of metabolomics analysis using QTRAP 6500 mass spectrometer

After the installation of QTRAP 6500, the data for a mixture of TCA cycle metabolite standards were acquired. Parameters like Declustering Potential (DP), Entrance Potential (EP) and Collision Energy (CE) were optimized using various scan modes viz., Q1MS, EPI, Q1MI and MRM. Some of the expected m/z values were observed after which the data for each metabolite was acquired individually using Q1MI scan mode. Expected m/z values for some of the metabolites without any adducts were observed. The six point calibration curve of the TCA metabolite standard mix was generated using MRM scan type. A three-point calibration curve for all the metabolite was observed and the lower limit of detection was found to be 200 nmol.

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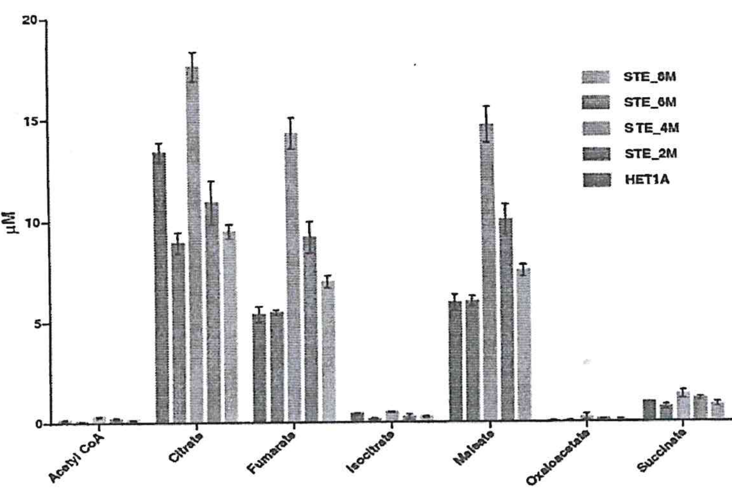
Metabolomic analysis of smokeless tobacco extract treated HET1A and STE cell lines

The data for metabolite extract samples derived from HET1A and cell lines treated with smokeless tobacco (STE cell lines; time-points 2, 4, 6, 8 months after treatment) were acquired using the MRM scan mode. The transitions for most of the metabolites present in the metabolite extracts were observed and the data was also used to generate a metabolic profile graph. In addition, a spike-in experiment was also conducted wherein 100 nmol Acetyl CoA was spiked into one of the STE sample (6 months after treatment) to test if it can be observed in the complex matrix. Data for these metabolite extracts derived from HET1A and STE cell lines has been acquired using EMS (Enhanced MS) type scan mode and will be analyzed using the MarkerView software.



National facility for proteometabolomic characterization of Ayurvedic and traditional medicinal plants

With an aim to characterize metabolites and proteins involved in the production of secondary metabolites, YU_IOB investigators are planning to prepare a dossier and submit it to Ministry of AYUSH. We expect to receive huge support from the ministry for such an endeavor. We seek PACBIO genome sequencer and three different types of mass spectrometers which will be used to carry out screening of global genomic, proteomic and metabolomics profile of Ayurvedic plants and formulations. We intend to provide this data freely to the international community by developing public databases. For this, we have already procured Triphala preparations and extracted metabolites and we have acquired the data in the mass spectrometer and generated untargeted metabolomics profile. Now, we are in the process of preparing the dossier and project proposal.

Visitors at YU-IOB CSBMM

Several eminent scientists visited YU-IOB CSBMM in past year. They interacted with the faculty members and research students at YU-IOB CSBMM.

1. Dr. Malali Gowda, Professor, School of Conservation, Life Science and Health Science, Transdisciplinary University, Bangalore visited YU-IOB CSBMM laboratory on June 2, 2016.
2. Dr. Shaji George, Director and Chief Scientific Officer, Mir Lifescience Pvt Ltd, Bangalore, Dr. Priya Kadam, Medical Officer, MedGenome Labs Pvt Ltd, Bangalore and Dr. Stephen Rudd, Pacific Biosciences, Singapore visited YU-IOB CSBMM laboratory on June 2, 2016.

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3. Dr. Akshay Anand, Additional Professor, PGIMER, Chandigarh visited YU-IOB CSBMM laboratory on June 2, 2016.
4. Dr. B. K. Thelma, Professor, Department of Genetics, University of Delhi, New Delhi visited YU-IOB CSBMM laboratory on June 1, 2016
5. Dr. Anurag Bhargava, Dept of Medicine, YMC, Yenepoya University visited YU-IOB CSBMM laboratory on June 1, 2016.
6. Dr. Chitra Pattabiraman, Postdoctoral Fellow, NCBS, Bangalore visited YU-IOB CSBMM laboratory on June 1, 2016.
7. Dr. Veena Shetty, Associate Professor, Department of Mocrobiology, K S Hegde Medical Academy, Mangalore visited YU-IOB CSBMM laboratory on May 25, 2016.
8. Dr. Rajendra B. Surpam, Professor and Head, Department of Mocrobiology, Government Medical College and Hospital, Nagpur, visited YU-IOB CSBMM laboratory on May 23, 2016.
9. Mr. Syed Sajjad Ahmed, Inspiring authority, Maulana Azad Education Foundation, Ministry of Minority Affairs, Government of India, New Delhi, visited YU-IOB CSBMM laboratory on May 10, 2016.
10. Dr. Rajashekhar, Professor, Department of Bioscience, Mangalore University, visited YU-IOB CSBMM laboratory on May 5, 2016.
11. Dr. Ajeet Mohanty, Scientist, National Institute of Malaria Research, Goa, visited YU-IOB CSBMM laboratory on May 5, 2016.
12. Honorable Chancellor Dr. S. Kumar, Registrar Dr. A. V. Moideen Kutty, Director of Academics Dr. Mohan Kumar and Executive Engineer Mr. Hanumantha Rao from Sri Devaraj Urs Academy of Higher Education and Research, Kolar, visited YU-IOB CSBMM laboratory on May 2, 2016.
13. Dr. Shivashankar Nagaraj, Vice Chancellor's Research Fellow, Queensland University of Technology, Australia visited YU-IOB CSBMM laboratory and delivered a talk on 'A System Biology approach to elucidate Epithelial-Mesechymal Transition (EMT) in cancer' on March 24, 2016.
14. Dr. Krishna R. Murthy, Faculty scientist, Institute of Bioinformatics, Bangalore; Medical Director of Prabha Eye Clinic and Research Centre, Bangalore; Consultant Vitreoretinal Surgeon, Vittala International Institute of Ophthalmology, Bangalore; Consultant for Pediatric ROP clinic, Indira Gandhi Institute of Child Health Sciences, Bangalore visited YU-IOB CSBMM laboratory and delivered a talk on 'Taking comprehensive eye care to rural India: Focus on retinopathy of prematurity and diabetic retinopathy' on March 2, 2016.
15. Dr. A. S. Kiran Kumar, Chairman, Indian Space Research Organization (ISRO), visited YU-IOB CSBMM laboratory on February 28, 2016.
16. Honorable Chancellor Mr. Yenepoya Abdulla Kunhi visited YU-IOB CSBMM Laboratory along with other dignitaries of Yenepoya University on February 2, 2016

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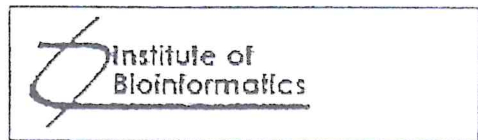

(Recognized under Sec 3(A) of UGC Act 1956)

MEMORANDUM OF UNDERSTANDING

Between

YENEPOYA UNIVERSITY
Mangalore -575018
India

And

INSTITUTE OF BIOINFORMATICS
Unit-1, Discoverer-7th Floor
International Tech Park
Whitefield,
Bangalore-560066
India

Collaborative Research and Academic Programme

This memorandum of understanding (MOU) sets down the mutually agreed broad framework for joint research and academic activities in various fields of interest between Yenepoya University (YU) and Institute of Bioinformatics (IOB). It also incorporates the modalities of collaboration.

1. Preamble:

1.1 Yenepoya University is a deemed to be university, mainly engaged in health care delivery and research in health sciences. It has developed a strong basis for patient care, training programmes and research activities. YU is also the first unaided Deemed University in the district of Dakshina Kannada, Karnataka. Yenepoya University has four constituent colleges; Yenepoya Dental College, Yenepoya Medical College, Yenepoya Nursing College and Yenepoya Physiotherapy College. Yenepoya University has a well-established hospital, Yenepoya Medical College Hospital with 1250 beds with an additional state-of-the-art infrastructure. It offers secondary and tertiary health care (super specialty) and treatment free of cost or at highly subsidized rates to all the needy. It has Intensive care Units, Modern Operation theaters, 24 h Radiology with CT, MRI, Color Doppler, Echo Cardiograph, Endoscopy Units, Blood Bank, 24x7 Central Clinical Lab, Pharmacy, Dialysis Unit, Physiotherapy, Nutrition and Dietetics services, Casualty and Emergency services and thousands of poor patients from Karnataka and neighboring states avail the benefits of health care offered by us. Approximately 75-80 % of the patients visiting the hospital are from Minority and Backward Communities. The food (costing Rs. 65/person/day), bed charges and drugs (more than 150 prescriptions) are provided free of cost to all. Most of the Govt. health care plans and schemes available for the poor, backward and general public are implemented by the hospital. Mortuary services, cold storage and medico legal autopsies are also part of the service provided by the hospital. The Hospital works in association with at least twenty service organizations including orphanages, old age homes, palliative care centers, HIV/AIDS care and support centers, Endosulphan Rehabilitation centers etc. to extend timely free health care service and support. Quality of education is maintained by trained and experienced teaching faculty under the leadership of the Deans of the respective faculty. Best and highly qualified (>90%) faculty with MCh. DM, MD/MS, MDS, Ph.D and MSc. degrees are recruited for teaching and research. Several faculty members enjoy wide national and international recognitions for their exemplary and extraordinary service in their respective areas of specialization.

1.2 The Institute of Bioinformatics (http://www.ibioinformatics.org) is a non-profit researc[h] institute that was established by Dr. Akhilesh Pandey, who is the Director and Scientific Advise[r] of IOB and also an Professor at Johns Hopkins University, Baltimore, USA. The institut[e] currently has a research staff of 50 scientists including 9 Ph.D level faculty scientists. **IOB ha[s] been recognized as a Scientific and Industrial Research Organization (SIRO) by DSI[R] (Department of Scientific and Industrial Research) since 2004.** Institute of Bioinformatic[s] is recognized as full time research center to carry out Ph.D. studies by Manipal Universit[y] Pondicherry University, Amrita University, KIIT University and Kuvempu University. Currentl[y] 30 students are carrying out their doctoral work at IOB. Because of the close collaboration of IO[B] with Johns Hopkins University, 5 Ph.D. students are carrying out research work in Dr. Akhiles[h] Pandey's Laboratory at McKusick-Nathans Institute of Genetic Medicine at Johns Hopki[ns] University, Baltomore, USA. In the last five years, IOB has established state-of-the-art hig[h] resolution tandem mass spectrometry facility for proteomic and metabolomic investigations a[nd] an associated wet lab and animal cell culture facility to carry out molecular biology and genomi[c] oriented research. IOB has also collaborated over 50 National and International research institute[s] particularly on clinical research in the area of human diseases including cancers, infections a[nd] neurological disorders. In a short span of twelve years, the scientists from IOB have been a pa[rt]

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of more than 210 publications in the journals of international repute including *Nature, Nature Biotechnology, Nature Genetics, Nature Methods, Nature Protocols, PNAS* and *Genome Research*. IOB investigators in collaboration with Johns Hopkins University, Baltimore, USA and National Institute of Mental Health and Neuroscience (NIMHANS), Bangalore, have led a landmark investigation on proteomic profiling of 30 human organs/tissues and published a draft map of human proteome for the first time in the world. It was featured on the cover of *Nature*.

1.3 The Institute of Bioinformatics has already established itself as a leading center for genomics, proteomics and bioinformatics research. In addition, Scientists at IOB are poised to strengthen further the genomics, proteomics and proteomics-related bioinformatics in India through establishment of collaborative research.

Thus, the activities of YU and IOB are complementary in several ways and it is felt that initiating collaborative research and academic programs would be of considerable mutual benefit. The samples provided by YU for collaborative research studies will strictly be handled by IOB and will not be allowed to leave India under any circumstances. The collaboration will be only for research purposes and will be shared between IOB and YU and joint manuscripts will be written up for submission to international journals. It is also expected that collaborations will result in transfer of such technologies used in the project to YU.

2. Purpose

YU and IOB would like to initiate cooperative and collaborative activities, which would address scientific, technological and educational problems of relevance to the country. The instrument of this MOU, elements of which, facilitates this as follows:

Article-1

Consistent with the goals and purpose of the collaboration, YU and IOB have proposed the following areas of joint research and academic activities:

Investigating clinical genomics/proteomics/metabolomics of different diseased conditions using global genomic, proteomic and metabolic profiling will be one of the core areas for collaborative research. Applications of bioinformatics in data analysis and database management will be another preferred subject for collaboration.

Additional areas to be identified from time to time in future.

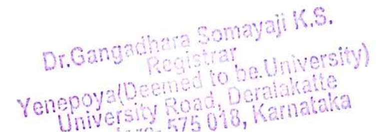
Article-2

The faculty of YU and IOB will hold regular scientific meetings on problems of mutual interest. The faculty and research scholars of YU and IOB will have access to the appropriate facilities of both the institutes, subject to their respective rules and regulations.

Article-3

Provision is hereby made for the:

1. Exchange of faculty, research scholars and students between YU and IOB
2. Joint organization of symposia, seminars and workshops and lectures
3. Mutual sharing of research material, and data and scientific knowledge on



collaborative projects, ensuring the material is not transported outside India.

4. Offer joint academic programmes (Ph.D, MSc., Diploma, Certificate and Short term Certificate courses)

Article-4

Intellectual property:

1. Important research findings arising out of the activities covered under this MOU may be published in national and international journals, and presented at national and international scientific meetings reflecting collaboration.
2. Knowledge developed, which can result in commercial exploitation, shall be covered by patents filed jointly by YU and Institute of Bioinformatics involved in the collaborative research work.
3. YU and IOB can make use of, for their internal purposes, all the information and data generated during collaborative research programs. However, neither of them shall reveal intellectual property belonging to the other institute, to any third party without the prior written concurrence of the scientists involved from the other institute.
4.The benefits of all IPR developed from the collaborative projects between YU and IOB shall be shared equally between these two institutions.

Article-5

Non–exclusivity of the MOU:

Notwithstanding anything contained in the provisions, excepting Articles of the MOU, both institutes have the unrestricted right to seek additional funding for and to co-operate with any agency or institute, ensuring that it is outside the purview of the collaboration agreed upon.

Article-6

Changes and Modifications:

Any article of the MOU may be modified or changed by mutual agreement of the parties hereto in writing. The modifications and changes shall be effective from the date on which they are made unless otherwise agreed to.

Article-7

All disagreements, difference of opinion, disputes regarding the interpretation of the provision of this MOU shall be resolved by mutual consultation of the heads of the institute or their authorized representatives.

Article-8

The tenure of the MOU shall be three years from the date of signing this MOU. The MOU can be extended for a further period of three years by mutual consent.

1. YU and IOB will together establish **IOB-YU Center for Systems Biology and Molecular Medicine** at Yenepoya University.

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2. All the parties decided initially to work closely on the research projects in the areas entitled, clinical genomics, proteomics and metabolomics of different diseased conditions. This study will be an attempt to enhance the knowledge in the field of OMICs with particular reference to cancers and infectious diseases.
3. All participating researchers will be co-authors in research articles that emanate from the proposed work.

Project Investigators and Research Staff involved in the project from both the Institutes-

YU investigators-

Faculty /Investigators and Principal Coordinators of the Constituent Centers/Departments/ Colleges from YU will be involved in the research activities.

IOB Investigators-

The Director and Faculty Scientists of the Institute of Bioinformatics, Bangalore, India, who are carrying out research in genomics, proteomics and bioinformatics, will be involved in the collaborative research projects.

In witness whereof the undersigned, duly authorized thereto, have signed this at Mangalore on the ………………., 2014

Signing Date: 20/11/2014

Dr. P. Chandramohan, MD. MCh.
Vice-Chancellor
Yenepoya University
Deralakatte, Mangalore-575018

Dr. Keshava Prasad, Ph.D
Director I/C
Institute of Bioinformatics
International Technology Park, Bangalore
Whitefield, Bangalore-560066

Prof. (Dr.) C. V. Raghuveeer, MD
Registrar, Yenepoya University
Deralakatte, Mangalore-575018

Dr. Akhilesh Pandey, MD, Ph.D
International Technology Park, Bangalore
Whitefield, Bangalore-560066

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UNIVERSITY

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Mangalore - 575018
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Fax: 0824-2203943

No.YU/REG/Cir/Nov 2014

Date: 26.11.2014

CIRCULAR

Sub: MoU entered into between Yenepoya University & Institute of Bioinformatics.

In order to generate knowledge in the area of genomics & proteomics relevant to human diseases & advanced molecular diagnostics in the clinical community, Yenepoya University signed a MoU on 20th of November, 2014 with the Institute of Bioinformatics (http://www.ibioinformatics.org), started by Dr. Akilesh Pandey, Prof of Pathology at Johns Hopkins, USA. IOB is carrying out research in the area of genomics & proteomics in India. Through this MoU, the University intends to start a Centre for Systems Biology & Molecular Medicine (CSBMM), with intentions i) to establish a state of the art high-resolution mass spectrometry-based proteomics facility ii) to provide exposure & hands-on training in proteomics, genomics, transcriptomics and bioinformatics to students, young researchers, clinicians and scientists at YU & iii) to enable exchange of students & faculties between YU & IOB.

In continuation of this association, a 2-day workshop has been planned on 8th & 9th December 2014 at YU to generate ideas for Research Projects & prepare at least 2 concept proposal from each department (one departmental project & one inter-departmental project) in the area of prevalent diseases based on availability of samples in the constituent colleges. A senior Professor will be the Principal Investigator & the other faculty members contributing to the project will be Co-Investigator. The intellectual property & publications generated out of this research shall be shared equally between the investigators & IOB.

Principals of constituent colleges are requested to nominate 2 team members from each department before 5th December 2014, to attend the meeting with short proposals or relevant ideas envisaging genomics, proteomics & metabolomics approach to management of human diseases. The ideas will be developed & fine-tuned to a full research proposal after discussion. A short confirmation message and a write up on the topic should be mailed by the prospective investigator to registrar@yenepoya.org with a copy marked to dydirectoryrc@yenepoya.edu.in latest by 5th December, 2014.

Registrar

To:
The Principals of all the constituent colleges – also with a request to circulate among all HODs.

Cc to:
All the Statutory Officers, Dy.Director, YRC
The Notice Boards of all the colleges & Library.

Office of the NAAC Co-ordinator
No....254
Received on...26/11/14
Despatched on..........

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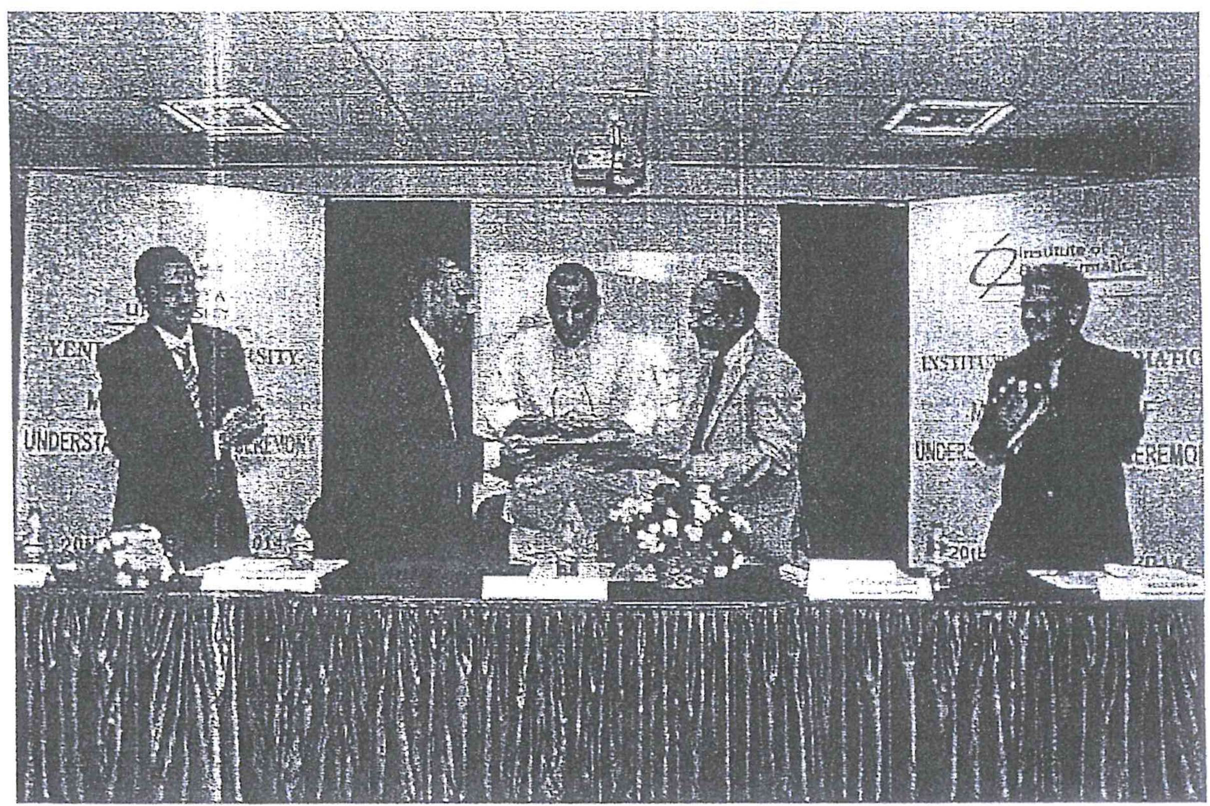
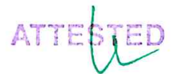
Yenepoya University, Mangalore and Institute of Bioinformatics, Bangalore signed a Memorandum of Understanding to establish a joint YU-IOB Center for Systems Biology and Molecular Medicine at Yenepoya University.

Yenepoya University is a deemed to be University engaged in health care delivery and research in health sciences. It has developed a strong basis for patient care, training programmes and research activities. In order to generate knowledge in the area of genomics and proteomics relevant to human diseases and advanced molecular diagnostics in the clinical community, Yenepoya University signed a memorandum of understanding on 20th of November, 2014 with the Institute of Bioinformatics (http://www.ibioinformatics.org), Bangalore, a premier institute carrying out pioneering research in the area of genomics and proteomics in India that was established by Dr. Akhilesh Pandey, who is also a Professor at Johns Hopkins University, Baltimore, USA. The major goals of this new center will be: i) to establish a state of the art high-resolution mass spectrometry-based proteomics facility at YU; ii) to provide exposure and hands-on training in proteomics, genomics, transcriptomics and bioinformatics to students, young researchers, clinicians and scientists at YU; and, iii) to enable exchange of student and faculties between YU and IOB. Mr. Yenepoya Abdulla Kunhi, Chancellor, Yenepoya University, presided over the function.





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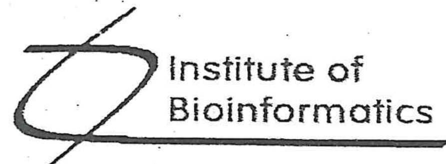

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Whitefield Road, Bangalore-560 066. India
Phone : + 91 80 28416140
Fax : + 91 80 28416132
Web : www.ibioinformatics.org

To,
Dr. Arun Bhagwath,
Deputy Director,
Yenepoya University, Mangalore

March 31, 2016

Subject: Student exchange and deputation to YU-IOB Center for Systems Biology and Molecular Medicine- Mr. Vivek Todur

Dear Dr. Bhagwath,

Mr. Vivek Todur is currently working as research student at Institute of Bioinformatics, Bangalore. He has several years of experience in NextGen sequencing data analysis. Prior to joining IOB, he was working with MedGenome Labs Pvt. Ltd., Bangalore. He will train our students in NextGen sequencing data analysis and set up genomics data analysis pipelines. In addition, he will also be trained in proteomic and integrated data analysis pipelines.Therefore, I have asked him to work with Dr. Pinto and Dr. Subbannayya at CSBMM from April 4, 2016 to May 7, 2016. Please permit IOB-CSBMM to reimburse him travel bills and other logistics against invoices. I request you to also provide him free hostel accommodation.

Sincerely,

Keshava Prasad, Ph.D.
Faculty Scientist,
Institute of Bioinformatics,
Bangalore

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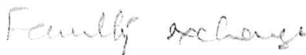

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To whom it may concern

Dr. Prashant Kumar Modi, Assistant Professor, Centre for Systems Biology and Molecular Medicine, Yenepoya Research Centre, Yenepoya University, had visited our institute. He has used our HPLC facility for his research work. He has worked in our institute for two days from 17.11.2017 to 18.11.2017.

Institute of Bioinformatics Bangalore I.T.P.L.

Santosh S. Shiri
Accounts and Admin Incharge

ATTESTED

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Registrar
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YENEPOYA
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Ph: 0824-2204667/68/69/71
Fax: 0824-2203943

Ref: No. YU/REG/ACA/010/JRF/2017 29.08.2017

Mr. Ankur Tyagi
Senior Research Fellow
Yenepoya Research Centre

Through Dy. Director, YRC

Sub: Request for on duty leave - Reg

Ref: Your Letter dated 26.08.2017

*****

Permission is granted to you to visit Institute of Bioinformatics, Bangalore for sample processing for your Ph.D work. On Duty Leave on 01.09.2017 (one day) is sanctioned for the above purpose.

(Dr. G. Shreekumar Menon)
Registrar

Copy to:

1. Dy. Director, YRC
2. Academic Section

ATTESTED

Dr. Gangadhara Somayaji K S
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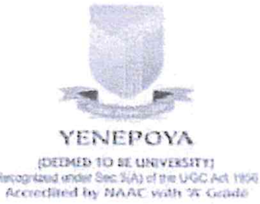
Mangalore 575 018, Karnataka.



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Fax: 0824 - 2203943

Ref: No. YU/REG/ACA/YRC/003/2019 14.03.2019

Dy. Director
Yenepoya Research Centre

Sub: Permission for reimbursement of travel and arrangement for accommodation for the Research Scientist from IOB, Bangalore

Ref: Letter dated 08.03.2019 from Dr. T S Keshava Prasad, Professor, YRC

****

Permission is granted to invite Mr. Ajay Balakrishnan, Research Scientist from Institute of Bioinformatics, Bangalore on 25.03.2019 to demonstrate and train in the new methodology for the isolation of CTCs in our lab and provide hands on training to our facilities and research students.

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1. Finance Officer - with a request to reimburse his travelling expenses
2. PRO - to make accommodation arrangements
3. Academic Section

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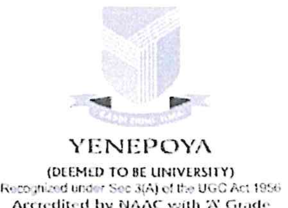

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Mr. Chinmaya Narayana K
Junior Research Fellow
Yenepoya Research Centre

Sub: Request for on duty leave from 27th August to 30th August 2019

Ref: Your letter dated 21.08.2019

****

Permission is granted to you to visit Institute of Bioinformatics (IOB), Bangalore from 27th to 30th August 2019. There shall be no financial implication to the University.

The period of absence from 27th to 30th August 2019 shall be treated as on duty.

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mj
24/8.

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Journal of Cell Communication and Signaling
https://doi.org/10.1007/s12079-020-00590-3

NUTS AND BOLTS

An assembly of galanin–galanin receptor signaling network

Lathika Gopalakrishnan[1,2,3] · Oishi Chatterjee[1,3,4] · Chinmayi Raj[5] · Deepshika Pullimamidi[5] · Jayshree Advani[1,8] · Anita Mahadevan[6,7] · T. S. Keshava Prasad[3]

Received: 6 October 2020 / Accepted: 8 October 2020
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Abstract

The galanin receptor family of proteins is present throughout the central nervous system and endocrine system. It comprises of three subtypes—GalR1, GalR2, and GalR3; all of which are G-protein-coupled receptors. Galanin predominantly acts as an inhibitory, hyper-polarizing neuromodulator, which has several physiological as well as pathological functions. Galanin has a role in mediating food intake, memory, sexual behavior, nociception and is also associated with diseases such as Alzheimer's disease, epilepsy, diabetes mellitus, and chronic pain. However, the understanding of signaling mechanisms of the galanin family of neuropeptides is limited and an organized pathway map is not yet available. Therefore, a detailed literature mining of the publicly available articles pertaining to the galanin receptor was followed by manual curation of the reactions and their integration into a map. This resulted in the cataloging of molecular reactions involving 64 molecules into five categories such as molecular association, activation/inhibition, catalysis, transport, and gene regulation. For enabling easy access of biomedical researchers, the galanin–galanin receptor signaling pathway data was uploaded to WikiPathways (https://www.wikipathways.org/index.php/Pathway:WP4970), a freely available database of biological pathways.

Keywords Galaninergic neuromodulatory system · NetPath · Post-translational modifications · Protein–protein interactions · Neuromodulation

Abbreviations

GAL	Galanin
GalR	Galanin receptor
GALP	Galanin-like peptide
CNS	Central nervous system
GPCR	G-protein coupled receptor
CREB	cAMP response element-binding protein
PKA	Protein kinase A
MAPK	Mitogen activated protein kinase

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12079-020-00590-3) contains supplementary material, which is available to authorized users.

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Article

Extracellular Proteome Analysis Shows the Abundance of Histidine Kinase Sensor Protein, DNA Helicase, Putative Lipoprotein Containing Peptidase M75 Domain and Peptidase C39 Domain Protein in *Leptospira interrogans* Grown in EMJH Medium

Abhijit Sarma [1], Dhandapani Gunasekaran [1,2], Devasahayam Arokia Balaya Rex [3], Thoduvayil Sikha [1,4], Homen Phukan [1], Kumar Mangalaparthi Kiran [5,6], Sneha M. Pinto [3,5], Thottethodi Subrahmanya Keshava Prasad [3,5,6] and Madathiparambil G. Madanan [1,*]

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Abstract: Leptospirosis is a re-emerging form of zoonosis that is caused by the spirochete pathogen *Leptospira*. Extracellular proteins play critical roles in the pathogenicity and survival of this pathogen in the host and environment. Extraction and analysis of extracellular proteins is a difficult task due to the abundance of enrichments like serum and bovine serum albumin in the culture medium, as is distinguishing them from the cellular proteins that may reach the analyte during extraction. In this study, extracellular proteins were separated as secretory proteins from the culture supernatant and surface proteins were separated during the washing of the cell pellet. The proteins identified were sorted based on the proportion of the cellular fractions and the extracellular fractions. The results showed the identification of 56 extracellular proteins, out of which 19 were exclusively extracellular. For those proteins, the difference in quantity with respect to their presence within the cell was found to be up to 1770-fold. Further, bioinformatics analysis elucidated characteristics and functions of the identified proteins. Orthologs of extracellular proteins in various *Leptospira* species were found to be closely related among different pathogenic forms. In addition to the identification of extracellular proteins, this study put forward a method for the extraction and identification of extracellular proteins.

Keywords: *Leptospira*; protein; extracellular; surface; secretory; pathogenic; proteomics

1. Introduction

Leptospirosis, the zoonotic disease once confined to posing a risk during agricultural activities, has been re-emerging due to increasing urbanization and slum areas that have increased the reservoir rodent population [1]. The increase in outbreaks during floods has been due to water getting contaminated with the urine from rats and several other domestic and wild animals that spread out during the floods. Humans exposed to such

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> OMICS. 2021 Sep;25(9):605-616. doi: 10.1089/omi.2021.0057. Epub 2021 Aug 24.

How to Achieve Therapeutic Response in Erlotinib-Resistant Head and Neck Squamous Cell Carcinoma? New Insights from Stable Isotope Labeling with Amino Acids in Cell Culture-Based Quantitative Tyrosine Phosphoproteomics

Ankit P Jain [1 2], Aneesha Radhakrishnan [1], Sneha Pinto [1 3], Krishna Patel [1 4], Manish Kumar [1 5], Vishalakshi Nanjappa [1], Remya Raja [1 5], Thottethodi Subrahmanya Keshava Prasad [1 3 6], Premendu P Mathur [2 7], David Sidransky [8], Aditi Chatterjee [1 5 3], Harsha Gowda [1 5 3]

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PMID: 34432535 PMCID: PMC8591087 (available on 2022-09-01) DOI: 10.1089/omi.2021.0057

Abstract

Resistance to cancer chemotherapy is a major global health burden. Epidermal growth factor receptor (*EGFR*) is a proven therapeutic target for multiple cancers of epithelial origin. Despite its overexpression in >90% of head and neck squamous cell carcinoma (HNSCC) patients, tyrosine kinase inhibitors such as erlotinib have shown a modest response in clinical trials. Cellular heterogeneity is thought to play an important role in HNSCC therapeutic resistance. Genomic alterations alone cannot explain all resistance mechanisms at play in a heterogeneous system. It is thus important to understand the biochemical mechanisms associated with drug resistance to determine potential strategies to achieve clinical response. We investigated tyrosine kinase signaling networks in erlotinib-resistant cells using quantitative tyrosine phosphoproteomics approach. We observed altered phosphorylation of proteins involved in cell adhesion and motility in erlotinib-resistant cells. Bioinformatics analysis revealed enrichment of pathways related to regulation of the actin

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> OMICS. 2021 Nov;25(11):693-710. doi: 10.1089/omi.2021.0158. Epub 2021 Oct 29.

The Normal Human Adult Hypothalamus Proteomic Landscape: Rise of Neuroproteomics in Biological Psychiatry and Systems Biology

Oishi Chatterjee [1 2 3], Lathika Gopalakrishnan [1 3 4], Praseeda Mol [1 2], Jayshree Advani [1], Bipin Nair [2], Susarla Krishna Shankar [5 6], Anita Mahadevan [5 6], Thottethodi Subrahmanya Keshava Prasad [3]

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PMID: 34714154 DOI: 10.1089/omi.2021.0158

Abstract

The human hypothalamus is central to the regulation of neuroendocrine and neurovegetative systems, as well as modulation of chronobiology and behavioral aspects in human health and disease. Surprisingly, a deep proteomic analysis of the normal human hypothalamic proteome has been missing for such an important organ so far. In this study, we delineated the human hypothalamus proteome using a high-resolution mass spectrometry approach which resulted in the identification of 5349 proteins, while a multiple post-translational modification (PTM) search identified 191 additional proteins, which were missed in the first search. A proteogenomic analysis resulted in the discovery of multiple novel protein-coding regions as we identified proteins from noncoding regions (pseudogenes) and proteins translated from short open reading frames that can be missed using the traditional pipeline of prediction of protein-coding genes as a part of genome annotation. We also identified several PTMs of hypothalamic proteins that may be required for normal hypothalamic functions. Moreover, we observed an enrichment of proteins pertaining to autophagy and adult neurogenesis in the proteome data. We believe that the hypothalamic proteome reported herein would help to decipher the molecular basis for the diverse range of physiological functions attributed to it, as well as its role in neurological and psychiatric diseases. Extensive proteomic profiling of the hypothalamic nuclei would further elaborate on the role and functional characterization of several

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Accepted Article

Identification of host-response in cerebral malaria patients using quantitative proteomic analysis

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> J Cell Commun Signal. 2021 Nov 1. doi: 10.1007/s12079-021-00653-z. Online ahead of print.

Opioid receptors signaling network

Lathika Gopalakrishnan [1 2 3], Oishi Chatterjee [1 3 4], Namitha Ravishankar [1], Sneha Suresh [1], Rajesh Raju [5], Anita Mahadevan [6 7], T S Keshava Prasad [8]

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PMID: 34724150 DOI: 10.1007/s12079-021-00653-z

Abstract

Opioid receptors belong to the class A G-protein-coupled receptors and are activated by alkaloid opiates such as morphine, and endogenous ligands such as endorphins and enkephalins. Opioid receptors are widely distributed in the human body and are involved in numerous physiological processes through three major classical opioid receptor subtypes; the mu, delta and kappa along with a lesser characterized subtype, opioid receptor-like (ORL1). Opioids are the most potent analgesics and have been extensively used as a therapeutic drug for the treatment of pain and related disorders. Chronic administration of clinically used opioids is associated with adverse effects such as drug tolerance, addiction and constipation. Several investigations attempted to identify the molecular signaling networks associated with endogenous as well as synthetic opiates, however, there is a paucity of a cumulative depiction of these signaling events. Here, we report a systemic collection of downstream molecules pertaining to four subtypes of opioid receptors (MOR, KOR, DOR and ORL1) in the form of a signaling pathway map. We manually curated reactions induced by the activation of opioid receptors from the literature into five categories- molecular association, activation/inhibition, catalysis, transport, and gene regulation. This led to a dataset of 180 molecules, which is collectively represented in the opioid receptor signaling network following NetPath criteria. We believe that the public availability of an opioid receptor signaling pathway map can accelerate biomedical research in this area because of its high therapeutic significance. The opioid receptors signaling pathway map is

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Research Article

What Makes Cornea Immunologically Unique and Privileged? Mechanistic Clues from a High-Resolution Proteomic Landscape of the Human Cornea

Yashwanth Subbannayya,[1] Sneha M. Pinto,[1] Varshasnata Mohanty,[1] Shobha Dagamajalu,[1]
Thottethodi Subrahmanya Keshava Prasad,[1] and Krishna R. Murthy[2–5]

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Abstract

Success rates of corneal transplantation are particularly high owing to its unique, innate immune privilege derived from a phenomenon known as Anterior Chamber-Associated Immune Deviation (ACAID). Of note, cornea is a transparent, avascular structure that acts as a barrier along with sclera to protect the eye and contributes to optical power. Molecular and systems biology mechanisms underlying ACAID and the immunologically unique and privileged status of cornea are not well known. We report here a global unbiased proteomic profiling of the human cornea and the identification of 4824 proteins, the largest catalog of human corneal proteins identified to date. Moreover, signaling pathway analysis revealed enrichment of spliceosome, phagosome, lysosome, and focal adhesion pathways, thereby demonstrating the protective functions of corneal proteins. We observed an enrichment of neutrophil-mediated immune response processes in the cornea as well as proteins belonging to the complement and ER-Phagosome pathways that are suggestive of active immune and inflammatory surveillance response. This study provides a key expression map of the corneal proteome repertoire that should enable future translational medicine studies on the pathological conditions of the cornea and the mechanisms by which cornea immunology are governed. Molecular mechanisms of corneal immune privilege have broad relevance to understand and anticipate graft rejection in the field of organ transplantation.

Keywords: proteomics, visual health, immunology, tandem mass spectrometry, corneal proteome, biomarkers, keratoplasty

Introduction

The cornea is the transparent anterior tissue of the eye overlying the iris, pupil, and the anterior chamber of the eye. It is avascular and contributes to ~70% of the refractive power of the eye (Sridhar, 2018). The cornea is one of the most common tissues to be transplanted across individuals. The success of the corneal transplantation has been attributed, in part, to its inherent immune privilege conferred by a phenomenon known as anterior chamber-associated immune deviation (ACAID) (Niederkorn, 2013). As part of ACAID, cellular responses such as delayed-type hypersensitivity, cytotoxic T cell response are dampened whereas antibody-mediated responses remain intact (Hori, 2008).

In a recent study, it was estimated that 184,576 corneal transplants were performed in 116 countries over the world (Gain et al., 2016). The same study also reported that corneal transplants were inaccessible to about 53% of the world population, and that there was a considerable shortage of transplantable corneas, with a ratio of one available for every 70 required. Although corneal transplants have been a major success in restoring vision, there have been several reports of

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Digging Deeper for the Eye Proteome in Vitreous Substructures: A High-Resolution Proteome Map of the Normal Human Vitreous Base

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Kalpana Babu Murthy,[2,3] Thottethodi Subrahmanya Keshava Prasad,[1] and Krishna R. Murthy[2–5]

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Abstract

Mapping the normal eye proteome in healthy persons is essential to unravel the molecular basis of diseases impacting visual health. The vitreous occupies a large portion of the human eye between the lens and the retina and plays a significant role in vitreoretinal diseases as well as maintaining clarity in the visual field, providing nutrition to the lens, and protecting the eye from mechanical shocks. It comprises four distinct anatomical regions, namely the vitreous core, vitreous cortex, vitreous base, and anterior hyaloid. Among these, the vitreous is attached to other substructures in the eye by the vitreous base, which is its strongest point of attachment. Alterations in vitreous substructures have been reported in several vitreoretinal disorders, including vitreomacular traction, vitreoretinopathies, and age-related macular degeneration. There has been limited knowledge on proteomics variations at a resolution of vitreous substructures, including the functionally and pathophysiologically significant vitreous base. We report here new findings on the proteome map of the vitreous base in normal healthy tissue. We employed a global, unbiased proteomic profiling approach resulting in the identification of 6511 proteins. Of these, 302 proteins were involved in metabolic processes essential for energy utilization. Moreover, we identified several structural and nutrient transport proteins. Notably, the identified proteome repertoire indicates that the vitreous base might possess additional physiological functions and may not be a passive structure. This study constitutes the most extensive catalog of vitreous base proteins to our knowledge and offers novel insights as a baseline for future studies on the pathobiology of various eye diseases. These data also invite us to consider a potentially more active functional role for the vitreous base in eye physiology and visual health.

Keywords: eye proteome, visual health, omics technology, ophthalmology, LC-MS/MS, protein network

Introduction

The vitreous is one of the largest structures in the eye and lies adjacent to the retina posteriorly and the lens and ciliary body anteriorly. The human vitreous comprises four distinct anatomical regions, namely the vitreous core, vitreous cortex, vitreous base, and anterior hyaloid. The vitreous core is surrounded by the cortical vitreous, which comprises the anterior hyaloid membrane and the vitreous base. It is the largest compartment and houses the vitreous humor. The anterior hyaloid membrane is made up of condensation of protein fibers and is attached to the posterior lens. The vitreous base consists of dense collagen fibers, which are implanted in an area that extends 2 mm anteriorly to adjoining pars plana region of the ciliary body and 3 mm posteriorly to peripheral retina posterior to the *ora serrata*. The fibers also extend radially in toward the vitreous gel. The vitreous base is the strongest point of attachment of the vitreous.

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OPEN

Cigarette smoke and chewing tobacco alter expression of different sets of miRNAs in oral keratinocytes

Received: 2 October 2017
Accepted: 23 March 2018
Published online: 04 May 2018

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Carcinogenic effect of tobacco in oral cancer is through chewing and/or smoking. Significant differences exist in development of oral cancer between tobacco users and non-users. However, molecular alterations induced by different forms of tobacco are yet to be fully elucidated. We developed cellular models of chronic exposure to chewing tobacco and cigarette smoke using immortalized oral keratinocytes. Chronic exposure to tobacco resulted in increased cell scattering and invasiveness in immortalized oral keratinocytes. miRNA sequencing using Illumina HiSeq 2500 resulted in the identification of 10 significantly dysregulated miRNAs (4 fold; $p \leq 0.05$) in chewing tobacco treated cells and 6 in cigarette smoke exposed cells. We integrated this data with global proteomic data and identified 36 protein targets that showed inverse expression pattern in chewing tobacco treated cells and 16 protein targets that showed inverse expression in smoke exposed cells. In addition, we identified 6 novel miRNAs in chewing tobacco treated cells and 18 novel miRNAs in smoke exposed cells. Integrative analysis of dysregulated miRNAs and their targets indicates that signaling mechanisms leading to oncogenic transformation are distinct between both forms of tobacco. Our study demonstrates alterations in miRNA expression in oral cells in response to two frequently used forms of tobacco.

Oral squamous cell carcinoma (OSCC) is one of the most common cancers worldwide and remains the most common malignancy of the head and neck cancers. Tobacco use, alcohol consumption and human papilloma virus (HPV) 16/18 have been identified as the main risk factors for the initiation and progression of OSCC[1]. Tobacco is mainly consumed worldwide in the form of manufactured cigarettes. Tobacco is also consumed in the form of smokeless tobacco, especially chewing tobacco in South-East Asian countries[2]. Despite being one of the most common cancers in India, molecular alterations in oral cancer development in tobacco chewers and smokers is not well understood.

MicroRNAs have been established as key regulators of oncogenic potential in cells. Alterations at the genetic and epigenetic levels in the complex enzymatic machinery involved in miRNA biogenesis can result in aberrant miRNA expression[3]. Post-transcriptional regulation of gene expression by miRNAs has an influence on multiple pathways, including those involved in cellular transformation and proliferation[4]. miRNAs function as either oncogenes or tumor suppressors, playing crucial roles in tumorigenesis, tumor invasion and metastasis[5]. In recent

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NUTS AND BOLTS

A network map of IL-33 signaling pathway

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Abstract
Interleukin-33 (IL-33) is a member of the IL-1 family of cytokines that play a central role in the regulation of immune responses. Its release from epithelial and endothelial cells is mediated by pro-inflammatory cytokines, cell damage and by recognition of pathogen-associated molecular patterns (PAMPs). The activity of IL-33 is mediated by binding to the IL-33 receptor complex (IL-33R) and activation of NF-κB signaling via the classical MyD88/IRAK/TRAF6 module. IL-33 also induces the phosphorylation and activation of ERK1/2, JNK, p38 and PI3K/AKT signaling modules resulting in the production and release of pro-inflammatory cytokines. Aberrant signaling by IL-33 has been implicated in the pathogenesis of several acute and chronic inflammatory diseases, including asthma, atopic dermatitis, rheumatoid arthritis and ulcerative colitis among others. Considering the biomedical importance of IL-33, we developed a pathway resource of signaling events mediated by IL-33/IL-33R in this study. Using data mined from the published literature, we describe an integrated pathway reaction map of IL-33/IL-33R consisting of 681 proteins and 765 reactions. These include information pertaining to 19 physical interaction events, 740 enzyme catalysis events, 6 protein translocation events, 4 activation/inhibition events, 9 transcriptional regulators and 2492 gene regulation events. The pathway map is publicly available through NetPath (http://www.netpath.org/), a resource of human signaling pathways developed previously by our group. This resource will provide a platform to the scientific community in facilitating identification of novel therapeutic targets for diseases associated with dysregulated IL-33 signaling. Database URL: http://www.netpath.org/pathways?path_id=NetPath_120.

Keywords Immune response · Inflammation · NetSlim · Pro-inflammatory cytokine · Post-translational modifications · Protein-protein interactions

Abbreviations

IL-1	Interleukin-1
IL-33	Interleukin-33
PAMPs	Pathogen-associated molecular patterns

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Proteomic approach and expression analysis revealed the differential expression of predicted leptospiral proteases capable of ECM degradation

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Abstract

Leptospira, the causative agent of leptospirosis is known to have many proteases with potential to degrade extracellular matrix. However, a multipronged approach to identify, classify, characterize and elucidate their role has not been attempted. Our proteomic approach using high-resolution LC-MS/MS analysis of Triton X-114 fractions of Leptospira interrogans resulted in the identification of 104

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Research Article

Intracranial Aneurysm Biomarker Candidates Identified by a Proteome-Wide Study

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Abstract

The scientific basis of intracranial aneurysm (IA) formation, its rupture and further development of cerebral vasospasm is incompletely understood. Aberrant protein expression may drive structural alterations of vasculature found in IA. Deciphering the molecular mechanisms underlying these events will lead to identification of early detection biomarkers and in turn, improved treatment outcomes. To unravel differential protein expression in three clinical subgroups of IA patients: (1) unruptured aneurysm, (2) ruptured aneurysm without vasospasm, (3) ruptured aneurysm who developed vasospasm, we performed untargeted quantitative proteomic analysis of aneurysm tissue and serum samples from three subgroups of IA patients and control subjects. Candidate molecules were then validated in a larger cohort of patients using enzyme-linked immunosorbent assay. A total of 937 and 294 proteins were identified from aneurysm tissue and serum samples, respectively. Several proteins that are known to maintain structural integrity of vasculature were found to be dysregulated in the context of aneurysm. *ORM1*, a glycoprotein, was significantly upregulated in both tissue and serum samples of unruptured aneurysm patients. We employed a larger cohort of subjects ($n=26$) and validated *ORM1* as a potential biomarker for screening of unruptured aneurysms. Samples from ruptured aneurysms with vasospasm showed significant upregulation of *MMP9*, a protease, compared with ruptured aneurysms without vasospasm. We validated *MMP9* as a potential biomarker for vasospasm in a larger cohort ($n=52$). This study reports the first global proteomic analysis of the entire clinical spectrum of IA. Furthermore, this study suggests *ORM1* and *MMP9* as potential biomarkers for unruptured aneurysm and cerebral vasospasm, respectively.

Keywords: cerebral vasospasm, intracranial aneurysm, mass spectrometry, proteomics, subarachnoid hemorrhage, biomarker

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ORIGINAL RESEARCH
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Mutational Landscape of Esophageal Squamous Cell Carcinoma in an Indian Cohort

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Esophageal squamous cell carcinoma (ESCC) is the most common histological subtype of esophageal cancer in India. Cigarette smoking and chewing tobacco are known risk factors associated with ESCC. However, genomic alterations associated with ESCC in India are not well-characterized. In this study, we carried out exome sequencing to characterize the mutational landscape of ESCC tumors from subjects with a varied history of tobacco usage. Whole exome sequence analysis of ESCC from an Indian cohort revealed several genes that were mutated or had copy number changes. ESCC from tobacco chewers had a higher frequency of C:G > A:T transversions and 2-fold enrichment for mutation signature 4 compared to smokers and non-users of tobacco. Genes, such as *TP53*, *CSMD3*, *SYNE1*, *PIK3CA*, and *NOTCH1* were found to be frequently mutated in Indian cohort. Mutually exclusive mutation patterns were observed in *PIK3CA–NOTCH1*, *DNAH5–ZFHX4*, *MUC16–FAT1*, and *ZFHX4–NOTCH1* gene pairs. Recurrent amplifications were observed in 3q22-3q29, 11q13.3-q13.4, 7q22.1-q31.1, and 8q24 regions. Approximately 53% of tumors had genomic alterations in *PIK3CA* making this pathway a promising candidate for targeted therapy. In conclusion, we observe enrichment of mutation signature 4 in ESCC tumors from patients with a history of tobacco chewing. This is likely due to direct exposure of esophagus to tobacco carcinogens when it is chewed and swallowed. Genomic alterations were frequently observed in PIK3CA-AKT pathway members independent of the history of tobacco usage. PIK3CA pathway can be potentially targeted in ESCC which currently has no effective targeted therapeutic options.

Keywords: tobacco, mutation signatures, squamous cell carcinoma, esophageal cancer, whole exome sequencing

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Triton X-114 Fractionated Subcellular Proteome of Leptospira interrogans Shows Selective Enrichment of Pathogenic and Outer Membrane Proteins in the Detergent Fraction

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Abstract

The Triton X-114-based solubilization and temperature-dependent phase separation of proteins is used for subcellular fractionation where, aqueous, detergent, and pellet fractions represents cytoplasmic, outer membrane (OM), and inner membrane proteins, respectively. Mass spectrometry-based proteomic analysis of Triton X-114 fractions of proteomic analysis of Leptospira interrogans identified 2957 unique proteins distributed across the fractions. The results are compared with bioinformatics predictions on their subcellular localization and pathogenic nature. Analysis of the distribution of proteins across the Triton X-114 fractions with the predicted characteristics is performed based on "number" of unique type of proteins, and "quantity" which represents the amount of unique protein. The highest number of predicted outer membrane proteins (OMPs) and

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ORIGINAL ARTICLE

Phosphoproteomic analysis identifies CLK1 as a novel therapeutic target in gastric cancer

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Abstract

Background Phosphorylation is an important regulatory mechanism of protein activity in cells. Studies in various cancers have reported perturbations in kinases resulting in aberrant phosphorylation of oncoproteins and tumor suppressor proteins.
Methods In this study, we carried out quantitative phosphoproteomic analysis of gastric cancer tissues and corresponding xenograft samples. Using these data, we employed bioinformatics analysis to identify aberrant signaling pathways. We further performed molecular inhibition and silencing of the upstream regulatory kinase in gastric cancer cell lines and validated its effect on cellular phenotype. Through an ex vivo technology utilizing patient tumor and blood sample, we sought to understand the therapeutic potential of the kinase by recreating the tumor microenvironment.
Results Using mass spectrometry-based high-throughput analysis, we identified 1,344 phosphosites and 848 phosphoproteins, including differential phosphorylation of 177 proteins (fold change cut-off $\geq$ 1.5). Our data showed that a subset of differentially phosphorylated proteins belonged to splicing machinery. Pathway analysis highlighted Cdc2-like kinase (CLK1) as upstream kinase. Inhibition of CLK1 using TG003 and CLK1 siRNA resulted in a decreased cell viability, proliferation, invasion and migration as well as modulation in the phosphorylation of SRSF2. Ex vivo experiments which utilizes patient's own tumor and blood to recreate the tumor microenvironment validated the use of CLK1 as a potential target for gastric cancer treatment.
Conclusions Our data indicates that CLK1 plays a crucial role in the regulation of splicing process in gastric cancer and that CLK1 can act as a novel therapeutic target in gastric cancer.

Keywords Phosphoserine/threonine · Spliceosome complex · Targeted therapy · Biomarker · PDX in vivo models

List of abbreviations

CLK	Cdc2-like kinase
PDX	Patient-derived xenografts
IHC	Immunohistochemistry
TMT	Tandem Mass Tag
bRPLC	Basic pH reverse phase chromatography
HCD	Higher energy collision dissociation
IPA	Ingenuity pathway analysis
FBS	Fetal bovine serum

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Introduction

Gastric cancer is the fifth most common type of cancer in terms of incidence and third leading cause of cancer related deaths globally [1]. Surgical resection is the predominant curative treatment in addition to traditional radiotherapy and chemotherapy as adjuvant or neoadjuvant therapy [2]. Drugs such as 5-fluorouracil (5-FU) and leucovorin have been frequently used in neoadjuvant chemotherapy in gastric cancer [3, 4]. In addition, viable clinical therapies for gastric cancer

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MAP2K1 is a potential therapeutic target in erlotinib resistant head and neck squamous cell carcinoma

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Epidermal growth factor receptor (EGFR) targeted therapies have shown limited efficacy in head and neck squamous cell carcinoma (HNSCC) patients despite its overexpression. Identifying molecular mechanisms associated with acquired resistance to EGFR-TKIs such as erlotinib remains an unmet need and a therapeutic challenge. In this study, we employed an integrated multi-omics approach to delineate mechanisms associated with acquired resistance to erlotinib by carrying out whole exome sequencing, quantitative proteomic and phosphoproteomic profiling. We observed amplification of several genes including *AXL* kinase and transcription factor *YAP1* resulting in protein overexpression. We also observed expression of constitutively active mutant MAP2K1 (p.K57E) in erlotinib resistant SCC-R cells. An integrated analysis of genomic, proteomic and phosphoproteomic data revealed alterations in MAPK pathway and its downstream targets in SCC-R cells. We demonstrate that erlotinib-resistant cells are sensitive to MAPK pathway inhibition. This study revealed multiple genetic, proteomic and phosphoproteomic alterations associated with erlotinib resistant SCC-R cells. Our data indicates that therapeutic targeting of MAPK pathway is an effective strategy for treating erlotinib-resistant HNSCC tumors.

Head and neck squamous cell carcinoma (HNSCC) is one of the leading cause of cancer-related deaths with a dismal 5-year survival rate[1]. Epidermal growth factor receptor (EGFR) is overexpressed in most epithelial malignancies including HNSCC[2]. Molecular target-based therapies against EGFR activity using small molecule EGFR-tyrosine kinase inhibitors (TKI) such as erlotinib or monoclonal antibodies against EGFR (Cetuximab) are under evaluation as potential therapeutic options. However, clinical trials with erlotinib have shown modest response rates of less than 15% in most cases and up to 25% in select cases of HNSCC[3,4]. Also, EGFR-TKIs have shown minimal improvement in overall or progression-free survival of patients. Median overall survival response to erlotinib in EGFR overexpressing HNSCC patients was reported to be 6 months[5]. This dismal performance of erlotinib in clinical trials is attributed to development of drug resistance. Though T790M gatekeeper mutations in EGFR and KRAS mutations define resistance in a majority of non-small cell lung carcinoma (NSCLC) and colorectal cancer patients respectively, these mutations contribute minimally to resistance in HNSCC patients[6]. Activation of related tyrosine kinases, "bypass" signaling mechanisms and mutations in downstream effectors are known as mediators of acquired resistance in HNSCC and other cancers[7,8]. However, full spectrum of molecular

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Human muscle pathology is associated with altered phosphoprotein profile of mitochondrial proteins in the skeletal muscle

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Abstract

Analysis of human muscle diseases highlights the role of mitochondrial dysfunction in the skeletal muscle. Our previous work revealed that diverse upstream events correlated with altered mitochondrial proteome in human muscle biopsies. However, several proteins showed relatively unchanged expression suggesting that post-translational modifications, mainly protein phosphorylation could influence their activity and regulate mitochondrial processes. We conducted mitochondrial phosphoprotein profiling, by proteomics approach, of healthy human skeletal muscle (n = 10) and three muscle diseases (n = 10 each): Dysferlinopathy, Polymyositis and Distal Myopathy with Rimmed Vacuoles. Healthy human muscle mitochondrial proteins displayed 253 phosphorylation sites (phosphosites), which contributed to metabolic and redox processes and mitochondrial organization etc. Electron transport chain complexes accounted for 84 phosphosites. Muscle pathologies displayed 33 hyperphosphorylated and 14 hypophorphorylated sites with only 5 common proteins, indicating varied phosphorylation profile across muscle pathologies. Molecular modelling

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Article

Chronic Exposure to Chewing Tobacco Induces Metabolic Reprogramming and Cancer Stem Cell-Like Properties in Esophageal Epithelial Cells

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Abstract: Tobacco in its smoke and smokeless form are major risk factors for esophageal squamous cell carcinoma (ESCC). However, molecular alterations associated with smokeless tobacco exposure are poorly understood. In the Indian subcontinent, tobacco is predominantly consumed in chewing form. An understanding of molecular alterations associated with chewing tobacco exposure is vital for identifying molecular markers and potential targets. We developed an in vitro cellular model by exposing non-transformed esophageal epithelial cells to chewing tobacco over an eight-month period. Chronic exposure to chewing tobacco led to increase in cell proliferation, invasive ability and anchorage independent growth, indicating cell transformation. Molecular alterations associated with chewing tobacco exposure were characterized by carrying out exome sequencing and quantitative proteomic profiling of parental cells and chewing tobacco exposed cells. Quantitative proteomic analysis revealed increased expression of cancer stem cell markers in tobacco treated cells. In addition, tobacco exposed cells showed the Oxidative Phosphorylation (OXPHOS) phenotype with decreased expression of enzymes associated with glycolytic pathway and increased expression of a large number of mitochondrial proteins involved in electron transport chain as well as enzymes of the tricarboxylic acid (TCA) cycle. Electron micrographs revealed increase in number and size of mitochondria. Based on these observations, we propose

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Research Article

Global Proteome Profiling Reveals Drug-Resistant Traits in *Elizabethkingia meningoseptica*: An Opportunistic Nosocomial Pathogen

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Abstract

Elizabethkingia meningoseptica is Gram-negative, rod-shaped opportunistic bacterial pathogen increasingly reported in hospital-acquired outbreaks. This bacterium is well known to thrive in the hospital environment. One of the leading causes of meningitis in pediatric and immune-compromised patients, *E. meningoseptica* has been noted as a "pathogen of interest" in the context of nosocomial diseases associated with device-related infections in particular. This pathogen's multidrug-resistant phenotype and attendant lack of adequate molecular mechanistic data limit the current approaches for its effective management in hospitals and public health settings. This study provides the global proteome of *E. meningoseptica*. The reference strain *E. meningoseptica* ATCC 13253 was used for proteomic analysis using high-resolution Fourier transform mass spectrometry. The study provided translational evidence for 2506 proteins of *E. meningoseptica*. We identified multiple metallo-β-lactamases, transcriptional regulators, and efflux transporter proteins associated with multidrug resistance. A protein Car D, which is an enzyme of the carbapenem synthesis pathway, was also discovered in *E. meningoseptica*. Further, the proteomics data were harnessed for refining the genome annotation. We discovered 39 novel protein-coding genes and corrected four existing translations using proteogenomic workflow. Novel translations reported in this study enhance the molecular data on this organism, thus improving current databases. We believe that the in-depth proteomic data presented in this study offer a platform for accelerated research on this pathogen. The identification of multiple proteins, particularly those involved in drug resistance, offers new future opportunities to design novel and specific antibiotics against infections caused by *E. meningoseptica*.

Keywords: proteomics, drug resistance, microbial proteomics, *E. meningoseptica*, infectious diseases, nosocomial pathogens

Introduction

ELIZABETHKINGIA MENINGOSEPTICA is a Gram-negative, rod-shaped bacterium, found in the environment both in community and hospital settings (Kim et al., 2005). It is a leading cause of meningitis in pediatric and immune-compromised patients (Ceyhan and Celik, 2011) and has been identified as a "pathogen of interest" in the context of nosocomial infections associated with various device-related infections (Hoque et al., 2001). Infections caused by *E. meningoseptica* are further complicated by its innate resistance to multiple antibiotics, including colistin (Jean et al., 2014).

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RESEARCH ARTICLE

Quantitative mass spectrometric analysis to unravel glycoproteomic signature of follicular fluid in women with polycystic ovary syndrome

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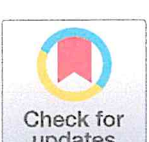

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Abstract

Polycystic ovary syndrome (PCOS) is a complex endocrinopathy affecting women of reproductive age, and whose etiology is not well understood yet. In these women, the follicular growth is arrested at preantral stage leading to cyst formation, consequently resulting in anovulatory infertility in these women. As the follicular fluid provides the conducive microenvironment for the growth of oocytes, molecular profiling of the fluid may provide unique information about pathophysiology associated with follicular development in PCOS. Post-translational addition of oligosaccharide residues is one of the many modifications of secreted proteins influencing their functions. These glycoproteins play a significant role in disease pathology. Despite glycoproteins having such essential functions, very limited information is available on their profiling in human reproductive system, and glycoproteomic profile of follicular fluid of women with PCOS is yet unexplored. In the present study, we performed a comparative glycoproteomic analysis of follicular fluid between women with PCOS and controls undergoing in vitro fertilization, by enrichment of glycoproteins using three different lectins viz. concanavalin A, wheat germ agglutinin and Jacalin. Peptides generated by trypsin digestion were labeled with isobaric tags for relative and absolute quantification reagents and analyzed by liquid chromatography tandem mass spectrometry. We identified 10 differentially expressed glycoproteins, in the follicular fluid of women with PCOS compared to controls. Two important differentially expressed proteins- SERPINA1 and ITIH4, were consistently upregulated and downregulated respectively, upon validation by immunoblotting in follicular fluid and real-time polymerase chain reaction in granulosa cells. These proteins play a role in angiogenesis and extracellular matrix stabilization, vital for follicle maturation. In conclusion, a comparative glycoproteomic profiling of follicular fluid from women with PCOS and controls revealed an altered

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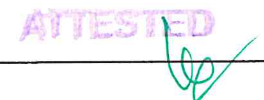
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Whole Genome Sequencing of *Mycobacterium tuberculosis* Isolates From Extrapulmonary Sites

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Abstract

Tuberculosis (TB) remains one of the leading causes of morbidity and mortality worldwide. Extrapulmonary tuberculosis (EPTB) constitutes around 15–20% of TB cases in immunocompetent individuals. Extrapulmonary sites that are affected by TB include bones, lymph nodes, meningitis, pleura, and genitourinary tract. Whole genome sequencing has emerged as a powerful tool to map genetic diversity among *Mycobacterium tuberculosis* (MTB) isolates and identify the genomic signatures associated with drug resistance, pathogenesis, and disease transmission. Several pulmonary isolates of MTB have been sequenced over the years. However, availability of whole genome sequences of MTB isolates from extrapulmonary sites is limited. Some studies suggest that genetic variations in MTB might contribute to disease presentation in extrapulmonary sites. This can be addressed if whole genome sequence data from large number of extrapulmonary isolates becomes available. In this study, we have performed whole genome sequencing of five MTB clinical isolates derived from EPTB sites using next-generation sequencing platform. We identified 1434 nonsynonymous single nucleotide variations (SNVs), 143 insertions and 105 deletions. This includes 279 SNVs that were not reported before in publicly available datasets. We found several mutations that are known to confer resistance to drugs. All the five isolates belonged to East-African-Indian lineage (lineage 3). We identified 9 putative prophage DNA integrations and 14 predicted clustered regularly interspaced short palindromic repeats (CRISPR) in MTB genome. Our analysis indicates that more work is needed to map the genetic diversity of MTB. Whole genome sequencing in conjunction with comprehensive drug susceptibility testing can reveal clinically relevant mutations associated with drug resistance.

Keywords: coding DNA sequence, lineage, lymphadenitis, nonsynonymous, octal code

Introduction

Diagnosis and treatment of tuberculosis (TB) are regarded as major public health concern. According to World Health Organization (WHO) report, an estimated 10.4 million people developed TB and 1.4 million died from the disease in 2016. Emergence of drug resistance TB has further complicated management and control of the disease. Globally, 3.9% of new and 21% of previously treated TB cases were estimated to have multidrug-resistant TB (MDR-TB; WHO, 2016 TB report). Tuberculosis bacilli can infect any organ system in the body with pulmonary TB being its most

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Whole Genome Sequencing of *Mycobacterium tuberculosis* Clinical Isolates From India Reveals Genetic Heterogeneity and Region-Specific Variations That Might Affect Drug Susceptibility

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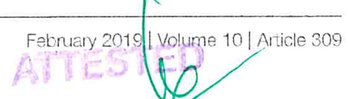
Whole genome sequencing (WGS) of *Mycobacterium tuberculosis* has been constructive in understanding its evolution, genetic diversity and the mechanisms involved in drug resistance. A large number of sequencing efforts from across the globe have revealed genetic diversity among clinical isolates and the genetic determinants for their resistance to anti-tubercular drugs. Considering the high TB burden in India, the availability of WGS studies is limited. Here we present, WGS results of 200 clinical isolates of *M. tuberculosis* from North India which are categorized as sensitive to first-line drugs, mono-resistant, multi-drug resistant and pre-extensively drug resistant isolates. WGS revealed that 20% of the isolates were co-infected with *M. tuberculosis* and non-tuberculous mycobacteria species. We identified 12,802 novel genetic variations in *M. tuberculosis* isolates including 343 novel SNVs in 38 genes which are known to be associated with drug resistance and are not currently used in the diagnostic kits for detection of drug resistant TB. We also identified *M. tuberculosis* lineage 3 to be



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Proteomics of Asrij Perturbation in *Drosophila* Lymph Glands for Identification of New Regulators of Hematopoiesis

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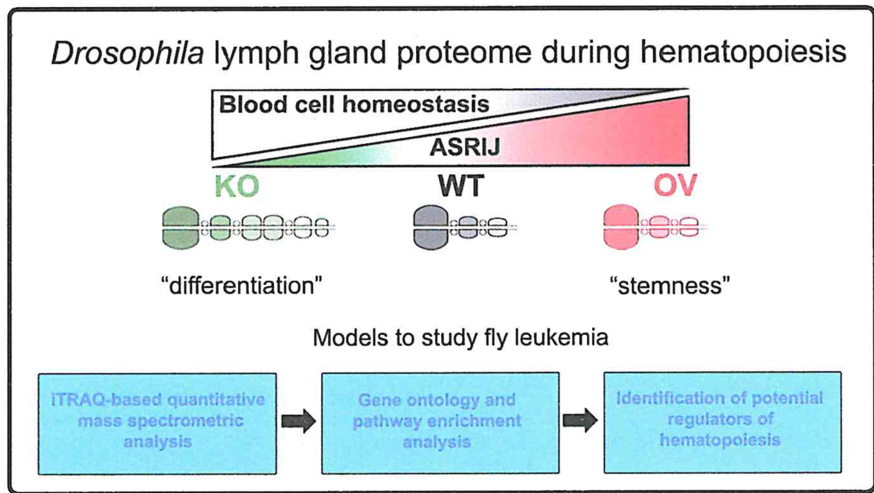
In Brief

Identification of molecules and processes that regulate hematopoiesis using *Drosophila* lymph gland (LG) as a model, is important for widening its scope and applicability as a tool to understand mechanisms regulating blood cell homeostasis. Using Asrij modulation, we compared the LG proteome under conditions that maintain precursors or promote differentiation *in vivo* and identified conserved as well as additional regulators of *Drosophila* hematopoiesis. The LG proteome provides an invaluable resource for studying insect as well as vertebrate blood cell development.

Graphical Abstract



Highlights

- First report on the quantitative proteomic profiling of *Drosophila* lymph glands.
- Comparative proteomic analysis under conditions of perturbed blood cell homeostasis.
- Resource for identifying new regulators of insect and vertebrate hematopoiesis.

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RESEARCH ARTICLE

PIM1 kinase promotes gallbladder cancer cell proliferation via inhibition of proline-rich Akt substrate of 40 kDa (PRAS40)

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Abstract
Gallbladder cancer (GBC) is a rare malignancy, associated with poor disease prognosis with a 5-year survival of only 20%. This has been attributed to late presentation of the disease, lack of early diagnostic markers and limited efficacy of therapeutic interventions. Elucidation of molecular events in GBC can contribute to better management of the disease by aiding in the identification of therapeutic targets. To identify aberrantly activated signaling events in GBC, tandem mass tag-based quantitative phosphoproteomic analysis of five GBC cell lines was carried out. Proline-rich Akt substrate 40 kDa (PRAS40) was one of the proteins found to be hyperphosphorylated in all the invasive GBC cell lines. Tissue microarray-based immunohistochemical labeling of phospho-PRAS40 (T246) revealed moderate to strong staining in 77% of the primary gallbladder adenocarcinoma cases. Regulation of PRAS40 activity by inhibiting its upstream kinase PIM1 resulted in a significant decrease in cell proliferation, colony forming and invasive ability of GBC cells. Our results support the role of PRAS40 phosphorylation in GBC cell survival and aggressiveness. This study also elucidates phospho-PRAS40 as a clinical marker in GBC and the role of PIM1 as a therapeutic target in GBC.

Keywords Cell survival · Gastrointestinal cancer · mTOR signaling · Phosphoproteomics · SGI-1776 · Targeted therapy

Abbreviations

GBC	Gallbladder cancer
PRAS40	Proline-rich Akt substrate 40 kDa
TEABC	Triethyl ammonium bicarbonate
TMT	Tandem mass tag
IHC	Immunohistochemistry
TMA	Tissue microarray
bRPLC	Basic reverse phase liquid chromatography
PI3K	Phosphatidylinositol 3 kinase

Tejaswini Subbannayya and Pamela Leal-Rojas contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12079-018-00503-5) contains supplementary material, which is available to authorized users.

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Introduction

Gallbladder cancer (GBC) represents the most prevalent form of biliary tract tumors. Although uncommon, this malignancy is aggressive and rapidly metastatic (Misra et al. 2006). Early detection is rare and incidental, with surgical resection being the only potential curative approach (Lazcano-Ponce et al. 2001). Five year survival rate is 32% for lesions confined to gallbladder mucosa and 1 year survival rate is 10% for advanced stages (Lazcano-Ponce et al. 2001). GBC patients present with poor prognosis since the disease is difficult to diagnose and treat. Majority of the GBC cases are diagnosed at advanced stages, where resection cannot be an option of treatment. In addition, the response to traditional methods of chemotherapy along with radiotherapy is limited (Bizama

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Research Article

Rise of Clinical Microbial Proteogenomics: A Multiomics Approach to Nontuberculous Mycobacterium—The Case of *Mycobacterium abscessus* UC22

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Abstract

Nontuberculous mycobacterial (NTM) species present a major challenge for global health with serious clinical manifestations ranging from pulmonary to skin infections. Multiomics research and its applications toward clinical microbial proteogenomics offer veritable potentials in this context. For example, the *Mycobacterium abscessus*, a highly pathogenic NTM, causes bronchopulmonary infection and chronic pulmonary disease. The rough variant of the *M. abscessus* UC22 strain is extremely virulent and causes lung upper lobe fibrocavitary disease. Although several whole-genome next-generation sequencing studies have characterized the genes in the smooth variant of *M. abscessus*, a reference genome sequence for the rough variant was generated only recently and calls for further clinical applications. We carried out whole-genome sequencing and proteomic analysis for a clinical isolate of *M. abscessus* UC22 strain obtained from a pulmonary tuberculosis patient. We identified 5506 single-nucleotide variations (SNVs), 63 insertions, and 76 deletions compared with the reference genome. Using a high-resolution LC-MS/MS-based approach (liquid chromatography tandem mass spectrometry), we obtained protein coding evidence for 3601 proteins, representing 71% of the total predicted genes in this genome. Application of proteogenomic approach further revealed seven novel protein-coding genes and enabled refinement of six computationally derived gene models. We also identified 30 variant peptides corresponding to 16 SNVs known to be associated with drug resistance. These new observations offer promise for clinical applications of microbial proteogenomics and next-generation sequencing, and provide a resource for future global health applications for NTM species.

Keywords: acquired resistance, next-generation sequencing, global health, proteogenomics, multiomics, nontuberculous mycobacterial species

Introduction

Nontuberculous mycobacterial (NTM) species are responsible for a wide range of disease manifestations ranging from pulmonary to skin infections (Katoch, 2004). Among the NTMs, *Mycobacterium abscessus*, a rapidly growing mycobacterium, is known to be responsible for a wide spectrum of soft tissue diseases and disseminated infections in immunocompromised patients (Griffith et al., 2007; Moore and Frerichs, 1953). Several hospital-based

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Mapping the protein phosphorylation sites in human mitochondrial complex I (NADH: Ubiquinone oxidoreductase): A bioinformatics study with implications for brain aging and neurodegeneration

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Abstract

In eukaryotes, mitochondrial complex I (NADH: ubiquinone oxidoreductase; CI) is central to oxidative phosphorylation (OXPHOS). Mammalian CI is a 45 subunit complex that forms supercomplexes with other OXPHOS complexes. Since CI defects are associated with aging and neurodegeneration, it is pertinent to understand its structure-function relationship. Although genetic mutations could lower CI activity causing mitochondrial dysfunction in several pathologies, post-translational modifications (PTMs) have emerged as a key mechanism contributing to altered CI activity. Among non-oxidative PTMs, protein phosphorylation is the most intricate regulatory mechanism controlling CI structure and function during normal physiology, aging and neurodegeneration. To comprehend this, we carried out a comprehensive bioinformatics analysis of protein phosphorylation of human CI subunits using software-based prediction of phosphorylation (phospho) sites and associated kinases. Phosphorylation was higher among core subunits and active domains of the complex. Among the subunits, NDUFS1 displayed significantly higher number as well as percent phospho sites compared

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Proteomics and Visual Health Research: Proteome of the Human Sclera Using High-Resolution Mass Spectrometry

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Abstract

Eye disorders and resulting visual loss are major public health problems affecting millions of people worldwide. In this context, the sclera is an opaque, thick outer coat covering more than 80% of the eye, and essential in maintaining the shape of the eye and protecting the intraocular contents against infection and the external environment. Despite efforts undertaken to decipher the scleral proteome, the functional and structural picture of the sclera still remain elusive. Recently, proteomics has arisen as a powerful tool that enables identification of proteins playing a critical role in health and disease. Therefore, we carried out an in-depth proteomic analysis of the human scleral tissue using a high-resolution Orbitrap Fusion Tribrid mass spectrometer. We identified 4493 proteins using SequestHT and Mascot as search algorithms in Proteome Discoverer 2.1. Importantly, the proteins, including radixin, synaptopodin, paladin, netrin 1, and kelch-like family member 41, were identified for the first time in human sclera. Gene ontology analysis unveiled that the majority of proteins were localized to the cytoplasm and involved in cell communication and metabolism. In sum, this study offers the largest catalog of proteins identified in sclera with the aim of facilitating their contribution to diagnostics and therapeutics innovation in visual health and autoimmune disorders. This study also provides a valuable baseline for future investigations so as to map the dynamic changes that occur in sclera in various pathological conditions.

Keywords: eye proteome, proteomics, omics technology, visual health, tandem mass spectrometry, ophthalmology

Introduction

The sclera is an opaque, thick outer coat covering more than 80% of the eye, and essential in maintaining the shape of the eye and protecting the intraocular contents against infection and the external environment. Despite efforts undertaken to decipher the scleral proteome, the functional and structural picture of the sclera still remain elusive.

The human sclera comprises episclera, scleral stroma, and lamina fascia (Coudrillier et al., 2015; Yoshida et al., 2014). It primarily consists of type I and III types of collagen, along with a lower amount of collagens IV, V, VI, VIII, XII, and XIII (Shelton and Rada, 2009). The extracellular matrix also consists of elastin, proteoglycans, and noncollagenous glycoproteins (Frost and Norton, 2007; Liu et al., 2017; Marshall, 1995; Rada et al., 2006). The extracellular matrix of sclera is synthesized by the fibroblasts that are located in between the irregularly arranged lamellae (Rada et al., 2006). The scleral thickness is not uniform throughout and its rigid structure prevents the fluctuation of intraocular pressure,

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Testican 1 (SPOCK1) and protein tyrosine phosphatase, receptor type S (PTPRS) show significant increase in saliva of tobacco users with oral cancer

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Abstract

Objectives: To identify potential candidate proteins which are secretory in nature and present at a higher abundance in oral cancer patients with tobacco habits.

Methods: Conditioned media of tobacco-treated and -untreated non-neoplastic oral keratinocytes were analyzed using iTRAQ-based mass spectrometry. Hypersecreted proteins; SPARC (osteonectin), cwcv and kazal like domains proteoglycan 1 (SPOCK1);

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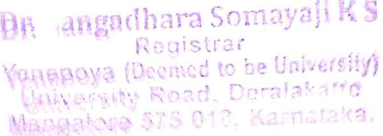
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Research Articles

Proteomic Analysis of the Human Anterior Pituitary Gland

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Abstract

The pituitary function is regulated by a complex system involving the hypothalamus and biological networks within the pituitary. Although the hormones secreted from the pituitary have been well studied, comprehensive analyses of the pituitary proteome are limited. Pituitary proteomics is a field of postgenomic research that is crucial to understand human health and pituitary diseases. In this context, we report here a systematic proteomic

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Data Article

Data on whole genome sequencing of extrapulmonary tuberculosis clinical isolates from India

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ABSTRACT

This article describes the whole genome sequencing data from 5 extrapulmonary tuberculosis clinical isolates. The whole genome sequencing was carried out on Illumina MiSeq platform to identify single nucleotide variations (SNVs) associated with drug resistance. A total of 214 SNVs in the coding and promoter regions were identified in the whole genome sequencing analysis. Among the

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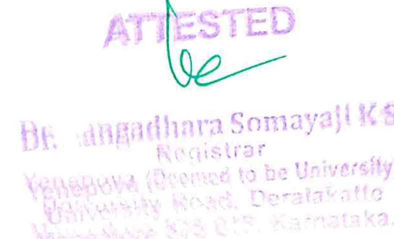

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Data Article

Proteome data of *Anopheles stephensi* ovary using high-resolution mass spectrometry

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A B S T R A C T

This article contains data on the proteins expressed in the ovaries of *Anopheles stephensi*, a major vector of malaria in India. Data acquisition was performed using a high-resolution Orbitrap-Velos mass spectrometer. The acquired MS/MS data was searched against *An. stephensi* protein database comprising of 11,789 sequences. Overall, 4407 proteins were identified, functional analysis was performed for the identified proteins and a protein-protein interaction map predicted. The data provided here is also related to a published article - "Integrating transcriptomics and proteomics data for accurate assembly and annotation of genomes" (Prasad et al., 2017) [1].

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Human Optic Nerve: An Enhanced Proteomic Expression Profile

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Abstract

Ophthalmology and visual health are new frontiers for postgenomic research and technologies such as proteomics. In this context, the optic nerve and retina extend as the outgrowth of the brain, wherein the latter receives the optical input and the former relays the information for processing. While efforts to understand the optic nerve proteome have been made earlier, there exists a lacuna in its biochemical composition and molecular functions. We report, in this study, a high-resolution mass spectrometry-based approach using an Orbitrap Fusion Tribrid mass spectrometer to elucidate the human optic nerve proteomic profile. Raw spectra were searched against NCBI Human RefSeq 75 database using SEQUEST HT and MASCOT algorithms. We identified nearly 35,000 peptides in human optic nerve samples, corresponding to 5682 proteins, of which 3222 proteins are being reported for the first time. Label-free quantification using spectral abundance pointed out to neuronal structural proteins such as myelin basic protein, glial fibrillary acidic protein, and proteolipid protein 1 as the most abundant proteins. We also identified several neurotransmitter receptors and postsynaptic density synaptosomal scaffold proteins. Pathway analysis revealed that a majority of the proteins are structural proteins and have catalytic and binding activity. This study is one of the largest proteomic profiles of the human optic nerve and offers the research community an initial baseline optic nerve proteome for further studies. This will also help understand the protein dynamics of the human optic nerve under normal conditions.

Keywords: ophthalmology, proteomics, neurology, omics, systems biology

Introduction

Visual health and diseases have gained new tool with the advent of postgenomic technologies such as proteomics. Chief among the ocular tissues that is of interest to systems biology and proteomics is the optic nerve, the second cranial nerve, which courses from the posterior segment of the eye to the brain. The optic nerve plays a vital role in the transduction of visual signals and as a biomechanical structure. It is essentially the axonic extensions of the retinal ganglions that relay visual information to the central nervous system (Rizzo, 2005).

The point of contact of the optic nerve to the retina is called the optic disc or optic nerve head, which is devoid of photoreceptor cells and does not take part in the visual perception, thereby known as the blind spot (Selhorst and Chen, 2009). An insult to the optic nerve, in most cases, results in loss of vision or other significant ocular pathology (Athappilly et al., 2008; Dutton, 2004; Kiyota et al., 2017).

High-throughput mass spectrometry (MS)-based proteomics has empowered our understanding of human disease mechanisms, potential drug targets, and biomarkers. The Human Eye Proteome Project was initiated in 2012, during the 11th Human Proteome Organization World Congress (Semba et al., 2013). Many studies have focused on the proteome profiling of the ocular tissues and a few notable ones include proteomic profiling of tears (Zhou et al., 2012); aqueous humor (Murthy et al., 2015); iris (Murthy et al., 2016); ciliary body (Goel et al., 2013); lens (Wilmarth et al., 2006); vitreous humor (Murthy et al., 2014); choroid-retinal pigment epithelium (Dammalli et al., 2017); retina (Kim et al., 2014); and a retrobulbar segment of the optic nerve (Zhang et al., 2016).

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NUTS AND BOLTS

A network map of thrombopoietin signaling

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Abbreviations

THPO	Thrombopoietin
MPL	MPL proto-oncogene, thrombopoietin receptor
JAK2	Janus kinase 2
STAT	Signal transducer and activator of transcription protein
MAPK	Mitogen-activated protein kinase
PIK3	Phosphatidylinositol-4,5-bisphosphate 3-kinase
MPN	Myeloproliferative neoplasms
RT-PCR	Real-time polymerase chain reaction
BioPAX	Biological Pathway Exchange
SBML	Systems Biology Markup Language
PSI-MI	Proteomics Standards Initiative for Molecular Interaction`
PTM	Post-translational modification

Introduction

Thrombopoietin (THPO) is a 332 amino acid-long protein, which is highly glycosylated and has a molecular mass of approximately 70 kDa (Wolber and Jelkmann 2002). Production of THPO predominantly occurs in the liver while other organs including kidney, lung, spleen, bone marrow and brain also secrete the hormone in small amounts (Nomura et al. 1997). The gene encoding THPO protein is located on chromosome 3q26.33-q27 in humans (Suzukawa et al. 1995). THPO is a cytokine that has been reported to play an important role in proliferation and differentiation of megakaryocyte progenitors (Bacon et al. 1995; Kaushansky et al. 1995). It acts in early and late stages of megakaryocyte lineage to promote the proliferation of megakaryocyte progenitors and increases the ploidy of these cells (de Sauvage et al. 1996). Pro-platelet processes are formed from polyploid megakaryocytes, which later fragment into platelets (Kaushansky 2005). It has been shown that THPO and MPL knockout mice have reduced number of platelets and megakaryocytes indicating the importance of THPO signaling in maintaining the high number of platelets in blood (Murone et al. 1998). It also stimulates the growth of other blood cells including granulocytes, erythrocytes and monocytes (Wolber et al. 1999; Kaushansky et al. 1996).

Receptor for THPO is MPL (THPOR), which belongs to the type I hematopoietic cytokine receptor family (Vigon et al. 1992). The MPL gene is located on chromosome 1p34 (Le Coniat et al. 1989). MPL is predominantly expressed on the surface of megakaryocyte progenitors, platelets and hematopoietic stem cells (HSCs), where it plays a major role in maturation of megakaryocytes, regulation of platelet production, maintenance and self -renewal of HSCs (de Sauvage et al. 1996, Debili et al. 1995, Qian et al. 2007).

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Dysregulation of splicing proteins in head and neck squamous cell carcinoma

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ABSRTRACT

Signaling plays an important role in regulating all cellular pathways. Altered signaling is one of the hallmarks of cancers. Phosphoproteomics enables interrogation of kinase mediated signaling pathways in biological systems. In cancers, this approach can be utilized to identify aberrantly activated pathways that potentially drive proliferation and tumorigenesis. To identify signaling alterations in head and neck squamous cell carcinoma (HNSCC), we carried out proteomic and phosphoproteomic

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Dissecting Candida Pathobiology: Post-Translational Modifications on the *Candida tropicalis* Proteome

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Abstract

Candida tropicalis belongs to the non-albicans group of Candida, and causes epidermal, mucosal, or systemic candidiasis in immunocompromised individuals. Although the prevalence of candidiasis has increased worldwide and non-albicans Candida (NAC) are becoming more significant, there are very few studies that focus on the NAC biology. Proteins and their post-translational modifications (PTMs) are an integral aspect in the pathobiology of such medically important fungi. Previously, we had reported the largest proteomic catalog of *C. tropicalis*. Notably, PTMs can be identified from proteomics data without *a priori* enrichment for a particular PTM, thus allowing broad-scale omics analyses. In this study, we developed the "PTM-Pro," a graphical user interface-based tool for identification and summary of high-confidence PTM sites based on statistical threshold of users' choice. We mined available proteomic data of *C. tropicalis*, and using PTM-Pro identified nearly 600 high-confidence PTM sites. The PTMs identified include phosphorylation of serine, threonine, and tyrosine; acetylation, crotonylation, methylation, and succinylation of lysine. These PTMs reside on biologically significant molecules, including histones, enzymes, and transcription factors. To our knowledge, this is the first report of PTMs in *C. tropicalis* and lays a foundation for future investigations of *C. tropicalis* PTMs. In addition, the PTM-Pro offers a graphical user interface tool for research on PTM sites in the field of proteomics.

Keywords: candidiasis, mass spectrometry, proteomics, bioinformatics, infectious diseases

Introduction

Candida tropicalis is a member of the non-albicans Candida (NAC) species and is a leading cause of candidiasis in immunocompromised individuals. Epidemiologically, it is more commonly encountered in Asia-Pacific than the rest of the world (Papon et al., 2013). Most published literature addressing fundamental processes of candidiasis are focused on *C. albicans* and not on NAC. Recent studies have demonstrated marked differences in morphology (Thompson et al., 2011), stress adaptation (Li et al., 2010), ploidy, and sexual behavior (Bennett, 2010) of different Candida species. Therefore, it is important to understand the fundamental biology of *C. tropicalis*.

One of the mechanisms by which proteins are regulated dynamically and spatiotemporally is post-translational modifications (PTMs). PTMs help in the precise orchestration of complex biological processes. Databases such as UniMod have documented >200 types of PTMs (Creasy and Cottrell, 2004). Studies have established that PTMs play a major role in cell–cell interactions, host defense, development and differentiation of medically important fungi (Leach

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Data Article

Data from quantitative proteomic analysis of lung adenocarcinoma and squamous cell carcinoma primary tissues using high resolution mass spectrometry

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A B S T R A C T

Lung cancer is the leading cause of preventable death globally and is broadly classified into adenocarcinoma and squamous cell carcinoma. In this study, we carried out mass spectrometry based quantitative proteomic analysis of lung adenocarcinoma and squamous cell carcinoma primary tissue by employing the isobaric tags for relative and absolute quantitation (iTRAQ) approach. Proteomic data analyzed using SEQUEST algorithm resulted in identification of 25,998 peptides corresponding to 4342 proteins of which 610 proteins were differentially expressed (≥ 2-fold) between adenocarcinoma and squamous cell carcinoma. These differentially expressed proteins were further classified by gene ontology for their localization and biological processes. Pathway analysis of differentially expressed proteins revealed distinct alterations in networks and pathways in both adenocarcinoma and squamous cell

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Article

Phosphoproteomics of Retinoblastoma: A Pilot Study Identifies Aberrant Kinases

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Abstract: Retinoblastoma is a malignant tumour of the retina which most often occurs in children. Earlier studies on retinoblastoma have concentrated on the identification of key players in the disease and have not provided information on activated/inhibited signalling pathways. The dysregulation of protein phosphorylation in cancer provides clues about the affected signalling cascades in cancer. Phosphoproteomics is an ideal tool for the study of phosphorylation changes in proteins. Hence, global phosphoproteomics of retinoblastoma (RB) was carried out to identify signalling events associated with this cancer. Over 350 proteins showed differential phosphorylation in RB compared to control retina. Our study identified stress response proteins to be hyperphosphorylated in RB which included H2A histone family member X (H2AFX) and sirtuin 1. In particular, Ser140 of H2AFX also known as gamma-H2AX was found to be hyperphosphorylated in retinoblastoma, which indicated the activation of DNA damage response pathways. We also observed the activation of anti-apoptosis in retinoblastoma compared to control. These observations showed the activation of survival pathways in retinoblastoma. The identification of hyperphosphorylated protein kinases including Bromodomain containing 4 (BRD4), Lysine deficient protein kinase 1 (WNK1), and Cyclin-dependent kinase 1 (CDK1) in RB opens new avenues for the treatment of RB. These kinases can be considered as probable therapeutic targets for RB, as small-molecule inhibitors for some of these kinases are already in clinical trials for the treatment other cancers.

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Integrated Multi-Omic Analysis of *Mycobacterium tuberculosis* H37Ra Redefines Virulence Attributes

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H37Ra is a virulence attenuated strain of *Mycobacterium tuberculosis* widely employed as a model to investigate virulence mechanisms. Comparative high-throughput studies have earlier correlated its avirulence to the presence of specific mutations or absence of certain proteins. However, a recent sequencing study of H37Ra, has disproved several genomic differences earlier reported to be associated with virulence. This warrants further investigations on the H37Ra proteome as well. In this study, we carried out an integrated analysis of the genome, transcriptome, and proteome of H37Ra. In addition to confirming single nucleotide variations (SNVs) and insertion-deletions that were reported earlier, our study provides novel insights into the mutation spectrum in the promoter regions of 7 genes. We also provide transcriptional and proteomic evidence for 3,900 genes representing ~80% of the total predicted gene count including 408 proteins that have not been identified previously. We identified 9 genes whose coding potential was hitherto reported to be absent in H37Ra. These include 2 putative virulence factors belonging to ESAT-6 like family of proteins. Furthermore, proteogenomic analysis enabled us to identify 63 novel proteins coding genes and correct 25 existing gene models in H37Ra genome. A majority of these were found to be conserved in the virulent strain H37Rv as well as in other mycobacterial species suggesting that the differences in the virulent and avirulent strains of *M. tuberculosis* are not entirely dependent on the expression of certain proteins or their absence but may possibly be ascertained to functional changes.

Keywords: next-generation sequencing, orbitrap, genome annotation, virulence attenuation, multiomics

INTRODUCTION

Among the *M. tuberculosis* strains, H37Ra, derived from *M. tuberculosis* H37 clinical isolate has been widely used as a reference strain to study virulence attenuation mechanisms (Zheng et al., 2008). Owing to its avirulent properties, it was used initially to develop tuberculosis vaccines in various animal models (Collins, 2000). Despite multiple efforts, the mechanisms of virulence attenuation are still not completely understood (Philips and Ernst, 2012). Identification of the factors involved in these processes is therefore crucial to understand the mechanisms of immune evasion and host persistence.

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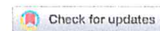

RESEARCH PAPER

Molecular alterations associated with chronic exposure to cigarette smoke and chewing tobacco in normal oral keratinocytes

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ABSTRACT

Tobacco usage is a known risk factor associated with development of oral cancer. It is mainly consumed in two different forms (smoking and chewing) that vary in their composition and methods of intake. Despite being the leading cause of oral cancer, molecular alterations induced by tobacco are poorly understood. We therefore sought to investigate the adverse effects of cigarette smoke/chewing tobacco exposure in oral keratinocytes (OKF6/TERT1). OKF6/TERT1 cells acquired oncogenic phenotype after treating with cigarette smoke/chewing tobacco for a period of 8 months. We employed whole exome sequencing (WES) and quantitative proteomics to investigate the molecular alterations in oral keratinocytes chronically exposed to smoke/ chewing tobacco. Exome sequencing revealed distinct mutational spectrum and copy number alterations in smoke/ chewing tobacco treated cells. We also observed differences in proteomic alterations. Proteins downstream of MAPK1 and EGFR were dysregulated in smoke and chewing tobacco exposed cells, respectively. This study can serve as a reference for fundamental damages on oral cells as a consequence of exposure to different forms of tobacco.

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KEYWORDS
Orbitrap Fusion; high-throughput; carcinogenesis; smoking; chronic exposure

Introduction

Tobacco is mainly consumed in two different forms *viz.* smoking and chewing, besides intake in the form of snuff. Cigarette smoking is prevalent in the West and epidemiological studies link cigarette smoking as a cause for development of oral cancer.[1,2] The habit of chewing tobacco is mostly prevalent in the South East Asian countries such as India, Pakistan, China, Korea and Sri Lanka[3] and in the African countries such as Sudan[4] where smokeless tobacco-associated oral cancer cases are high. Case control studies undertaken on the Indian population have identified tobacco chewing as a major risk factor for multiple oral premalignant lesions compared to smoking.[5,6] Significant differences exist in the etiology, prognosis and therapeutic response of oral cancer patients who are tobacco users compared to non-users.[7-9] The pathogenesis of cancer between chewers and smokers may vary significantly since the two forms of tobacco differ in their mode of intake and in their composition.

A number of *in vitro* and *in vivo* studies employ the use of research grade cigarettes to study quantitative and qualitative comparison of results across laboratories.[10] In addition, these cigarettes resemble cigarette brands available commercially. Upon burning of a cigarette, the smoke that is inhaled by a smoker is termed as mainstream smoke (MSS). Composition of MSS from a research grade cigarette smoked using standardized machine smoking protocols has been previously documented by Roemer et al.[10] Studies have identified a number of compounds including nicotine, aldehydes, aromatic amines, polycyclic aromatic hydrocarbons (such as Benzo[a]pyrene, Benz[a]anthracene), phenols, volatile N-nitrosamines and tobacco-specific N-nitrosamines. IARC categorizes at least 70 out of 5,300 identified components of cigarette smoke as carcinogenic.[11] Chewing tobacco is generally available as loose leaves, plugs or twists. The composition of tobacco leaves change as the leaves are cured, processed and stored. Smokeless tobacco is known to contain more than 3,000 chemical compounds including alkaloids (such as nicotine, nornicotine), aliphatic and aromatic hydrocarbons, aldehydes, ketones and amines.[12] Of these, 28 compounds have been classified as carcinogens by the IARC.[13]

Molecular studies have implicated cigarette smoke and its components in sustained inflammation and suppression of immune response.[14] We have previously documented the adverse effects of chronic exposure to cigarette smoke

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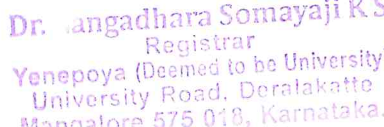
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ORIGINAL RESEARCH
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Mutational Landscape of Esophageal Squamous Cell Carcinoma in an Indian Cohort

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Esophageal squamous cell carcinoma (ESCC) is the most common histological subtype of esophageal cancer in India. Cigarette smoking and chewing tobacco are known risk factors associated with ESCC. However, genomic alterations associated with ESCC in India are not well-characterized. In this study, we carried out exome sequencing to characterize the mutational landscape of ESCC tumors from subjects with a varied history of tobacco usage. Whole exome sequence analysis of ESCC from an Indian cohort revealed several genes that were mutated or had copy number changes. ESCC from tobacco chewers had a higher frequency of C:G > A:T transversions and 2-fold enrichment for mutation signature 4 compared to smokers and non-users of tobacco. Genes, such as *TP53*, *CSMD3*, *SYNE1*, *PIK3CA*, and *NOTCH1* were found to be frequently mutated in Indian cohort. Mutually exclusive mutation patterns were observed in *PIK3CA–NOTCH1*, *DNAH5–ZFHX4*, *MUC16–FAT1*, and *ZFHX4–NOTCH1* gene pairs. Recurrent amplifications were observed in 3q22-3q29, 11q13.3-q13.4, 7q22.1-q31.1, and 8q24 regions. Approximately 53% of tumors had genomic alterations in *PIK3CA* making this pathway a promising candidate for targeted therapy. In conclusion, we observe enrichment of mutation signature 4 in ESCC tumors from patients with a history of tobacco chewing. This is likely due to direct exposure of esophagus to tobacco carcinogens when it is chewed and swallowed. Genomic alterations were frequently observed in PIK3CA-AKT pathway members independent of the history of tobacco usage. PIK3CA pathway can be potentially targeted in ESCC which currently has no effective targeted therapeutic options.

Keywords: tobacco, mutation signatures, squamous cell carcinoma, esophageal cancer, whole exome sequencing

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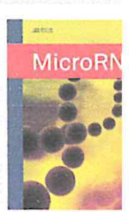
RESEARCH ARTICLE

miRNA and Proteomic Dysregulation in Non-Small Cell Lung Cancer in Response to Cigarette Smoke



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Abstract: ***Background***: Dysregulation of miRNAs is associated with the development of non-small cell lung cancer (NSCLC). It is imperative to study the dysregulation of miRNAs by cigarette smoke which will affect their targets, either leading to the overexpression of oncoproteins or downregulation of tumor suppressor proteins.

Objective and Methods: In this study, we carried out miRNA sequencing and SILAC-based proteomic analysis of H358 cells chronically exposed to cigarette smoke condensate. Using bioinformatics analysis, we mapped the dysregulated miRNAs to differentially expressed target proteins identified in our data. Gene ontology-based enrichment and pathway analysis was performed using the deregulated targets to study the role of cigarette smoke-mediated miRNA dysregulation in NSCLC cell line.

Results: miRNA sequencing resulted in the identification of 208 miRNAs, of which 6 miRNAs were found to be significantly dysregulated (2 fold, Log Base 2; p-value ≤ 0.05) in H358-Smoke cells. Proteomic analysis of the smoke exposed cells compared to the untreated parental cells resulted in the quantification of 2,610 proteins, of which 690 proteins were found to be differentially expressed (fold change ≥ 2). Gene ontology based analysis of target proteins revealed enrichment of proteins driving metabolism and a decrease in expression of proteins associated with immune response in the cells exposed to cigarette smoke. Pathway study using Ingenuity Pathway Analysis (IPA) revealed activation of NRF2-mediated oxidative stress response and actin-cytoskeleton signaling, and repression of protein kinase A signaling in H358-Smoke cells. We also identified 5 novel miRNAs in H358-Smoke cells using unassigned reads of small RNA-Seq dataset.

Conclusion: In summary, this study indicates that chronic exposure to cigarette smoke leads to widespread dysregulation of miRNAs and their targets, resulting in signaling aberrations in NSCLC cell line. The miRNAs and their targets identified in the study need to be further investigated to explore their role as potential therapeutic targets and/or molecular markers in NSCLC especially in smokers.

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Keywords: Bioinformatics analysis, cigarette smoke, mass spectrometry, metabolic labeling, miRNA sequencing, proteomic alterations.

1. INTRODUCTION

Lung cancer accounts for the highest incidence of all cancer cases in the world and 90% of these cases are attributed to cigarette smoking [1]. However, the mechanism by which cigarette smoking induces cellular transformation, leading to the development of non-small cell lung cancer (NSCLC) is not well established. Studying the molecular basis of lung cancer due to cigarette smoking will help in better understanding of the disease and further aid in diagnosis and treatment. miRNA profiling of solid tumors and cell lines of various cancers have shown a marked alteration in their expression levels compared to non-cancerous tissues

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Multi-Omics Driven Assembly and Annotation of the Sandalwood (*Santalum album*) Genome[1]

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Indian sandalwood (*Santalum album*) is an important tropical evergreen tree known for its fragrant heartwood-derived essential oil and its valuable carving wood. Here, we applied an integrated genomic, transcriptomic, and proteomic approach to assemble and annotate the Indian sandalwood genome. Our genome sequencing resulted in the establishment of a draft map of the smallest genome for any woody tree species to date (221 Mb). The genome annotation predicted 38,119 protein-coding genes and 27.42% repetitive DNA elements. In-depth proteome analysis revealed the identities of 72,325 unique peptides, which confirmed 10,076 of the predicted genes. The addition of transcriptomic and proteogenomic approaches resulted in the identification of 53 novel proteins and 34 gene-correction events that were missed by genomic approaches. Proteogenomic analysis also helped in reassigning 1,348 potential noncoding RNAs as bona fide protein-coding messenger RNAs. Gene expression patterns at the RNA and protein levels indicated that peptide sequencing was useful in capturing proteins encoded by nuclear and organellar genomes alike. Mass spectrometry-based proteomic evidence provided an unbiased approach toward the identification of proteins encoded by organellar genomes. Such proteins are often missed in transcriptome data sets due to the enrichment of only messenger RNAs that contain poly(A) tails. Overall, the use of integrated omic approaches enhanced the quality of the assembly and annotation of this nonmodel plant genome. The availability of genomic, transcriptomic, and proteomic data will enhance genomics-assisted breeding, germplasm characterization, and conservation of sandalwood trees.

The genus *Santalum* belongs to the family Santalaceae and consists of 15 extant species. It is a slow-growing, hemiparasitic tree distributed throughout tropical and temperate regions of India, Indonesia, Australia, and the Pacific Islands (Harbaugh and Baldwin, 2007). Commercially, the most valuable species is Indian sandalwood (*Santalum album*), which yields a unique essential oil used in perfumes, cosmetics, medicines, and incense sticks. The heartwood of this tree is treasured for its fragrance and is well known as one of the finest natural materials available for carving. Sandalwood is intertwined with Indian culture, and globally, it is the second most valuable and expensive tree after African blackwood (*Dalbergia melanoxylon*). Sandalwood is known to have cardiotonic, diuretic, diaphoretic, expectorant, aphrodisiac, hemostatic, anodyne, and antipyretic properties (Nambiar, 1993). Unfortunately, its population is declining from overharvesting and illegal trading, caused in part by its high commercial value. This alarming genetic erosion emphasizes the need for proper in situ conservation. Although efforts have been made for ex situ conservation, the planning and implementation of such programs have been limited due to the lack of genetic diversity existing in sandalwood populations (Rao et al., 2007; Kole, 2011).

Currently, large-scale transcriptomic data sets are available for sandalwood (Diaz-Chavez et al., 2013; Srivastava et al., 2015; Zhang et al., 2015, 2017; Celedon et al., 2016) and *Santalum spicatum* (Moniodis et al., 2015). Most of these genomic resources have been utilized to identify genes involved in sandalwood oil biosynthesis, cold stress response, and the hemiparasitic nature of its roots. However, a whole-genome sequence has not yet been reported for sandalwood. Our objective was to generate a draft genome assembly and annotate protein-coding genes of sandalwood based on genomic, transcriptomic, and proteomic data. We believe that this work will have a substantial impact in the near future with respect to sandalwood germplasm conservation, genetic diversity assessment, and cloning genes involved in natural essential oil production.

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Toward Postgenomics Ophthalmology: A Proteomic Map of the Human Choroid–Retinal Pigment Epithelium Tissue

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Abstract

Ophthalmology and visual health research have received relatively limited attention from the personalized medicine community, but this trend is rapidly changing. Postgenomics technologies such as proteomics are being utilized to establish a baseline biological variation map of the human eye and related tissues. In this context, the choroid is the vascular layer situated between the outer sclera and the inner retina. The choroidal circulation serves the photoreceptors and retinal pigment epithelium (RPE). The RPE is a layer of cuboidal epithelial cells adjacent to the neurosensory retina and maintains the outer limit of the blood–retina barrier. Abnormal changes in choroid–RPE layers have been associated with age-related macular degeneration. We report here the proteome of the healthy human choroid–RPE complex, using reverse phase liquid chromatography and mass spectrometry-based proteomics. A total of 5309 nonredundant proteins were identified. Functional analysis of the identified proteins further pointed to molecular targets related to protein metabolism, regulation of nucleic acid metabolism, transport, cell growth, and/or maintenance and immune response. The top canonical pathways in which the choroid proteins participated were integrin signaling, mitochondrial dysfunction, regulation of eIF4 and p70S6K signaling, and clathrin-mediated endocytosis signaling. This study illustrates the largest number of proteins identified in human choroid–RPE complex to date and might serve as a valuable resource for future investigations and biomarker discovery in support of postgenomics ophthalmology and precision medicine.

Keywords: personalized medicine, proteomics, omics technology, innovation systems

Introduction

Ophthalmology and visual health research have received relatively limited attention from the personalized medicine community, but this trend is rapidly changing. Postgenomics technologies such as proteomics are being utilized to establish a baseline biological variation map of the human eye and related tissues. In this context, the choroid is the posteriormost part of the vascular coat of the eyeball, known as the uvea, which also includes the iris and the ciliary body. Choroid extends from the head of the optic nerve posteriorly up to the ora serrata, where it is continuous with the ciliary body anteriorly. It generally comprises blood vessels and supplies blood to the outer retina (Nickla and Wallman, 2010). Choroidal cells include vascular and lymphatic endothelia, melanocytes, smooth muscle cells, mast cells, fibroblasts, autonomic

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Integrating transcriptomic and proteomic data for accurate assembly and annotation of genomes

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Complementing genome sequence with deep transcriptome and proteome data could enable more accurate assembly and annotation of newly sequenced genomes. Here, we provide a proof-of-concept of an integrated approach for analysis of the genome and proteome of *Anopheles stephensi*, which is one of the most important vectors of the malaria parasite. To achieve broad coverage of genes, we carried out transcriptome sequencing and deep proteome profiling of multiple anatomically distinct sites. Based on transcriptomic data alone, we identified and corrected 535 events of incomplete genome assembly involving 1196 scaffolds and 868 protein-coding gene models. This proteogenomic approach enabled us to add 365 genes that were missed during genome annotation and identify 917 gene correction events through discovery of 151 novel exons, 297 protein extensions, 231 exon extensions, 192 novel protein start sites, 19 novel translational frames, 28 events of joining of exons, and 76 events of joining of adjacent genes as a single gene. Incorporation of proteomic evidence allowed us to change the designation

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Quantitative proteomic and phosphoproteomic analysis of H37Ra and H37Rv strains of *Mycobacterium tuberculosis*

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Proteogenomics of *Candida tropicalis*—An Opportunistic Pathogen with Importance for Global Health

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Research Article

Mosquito-Borne Diseases and Omics: Tissue-Restricted Expression and Alternative Splicing Revealed by Transcriptome Profiling of *Anopheles stephensi*

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Abstract

Malaria is one of the most debilitating mosquito-borne diseases with high global health burdens. While much of the research on malaria and mosquito-borne diseases is focused on Africa, Southeast Asia accounts for a sizable portion of the global burden of malaria. Moreover, about 50% of the Asian malaria incidence and deaths have been from India. A promising development in this context is that the completion of genome sequence of *Anopheles stephensi*, a major malaria vector in Asia, offers new opportunities for global health innovation, including the progress in deciphering the vectorial ability of this mosquito species at a molecular level. Moving forward, tissue-based expression profiling would be the next obvious step in understanding gene functions of *An. stephensi*. We report in this article, to the best of our knowledge, the first in-depth study on tissue-based transcriptomic profile of four important organs (midgut, Malpighian tubules, fat body, and ovary) of adult female *An. stephensi* mosquitoes. In all, we identified over 20,000 transcripts corresponding to more than 12,000 gene loci from these four tissues. We present and discuss the tissue-based expression profiles of majority of annotated transcripts in *An. stephensi* genome, and the dynamics of their alternative splicing in these tissues, in this study. The domain-based Gene Ontology analysis of the differentially expressed transcripts in each of the mosquito tissue indicated enrichment of transcripts with proteolytic activity in midgut; transporter activity in Malpighian tubules; cell cycle, DNA replication, and repair activities in ovaries; and oxidoreductase activities in fat body. Tissue-based study of transcript expression and gene functions markedly enhances our understanding of this important malaria vector, and in turn, offers rationales for further studies on vectorial ability and identification of novel molecular targets to intercept malaria transmission.

Keywords: *Anopheles stephensi*, global health innovation, malaria transmission, mosquito-borne diseases, transcriptomics

Introduction

Malaria poses a significant challenge in the tropical and subtropical regions as a life-threatening mosquito-borne disease. According to World Health Organization (WHO) World Malaria Report in 2016, there were ∼212 million malaria cases in the year 2015, which resulted in an estimated death of about 429,000 individuals globally. Most of these cases (90%) are from the African region. Southeast Asia accounts for about 7% incidence. About 50%

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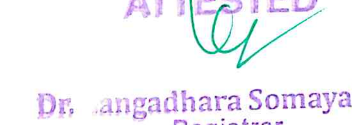

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RESEARCH ARTICLE

Quantitative mass spectrometric analysis to unravel glycoproteomic signature of follicular fluid in women with polycystic ovary syndrome

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Abstract

Polycystic ovary syndrome (PCOS) is a complex endocrinopathy affecting women of reproductive age, and whose etiology is not well understood yet. In these women, the follicular growth is arrested at preantral stage leading to cyst formation, consequently resulting in anovulatory infertility in these women. As the follicular fluid provides the conducive microenvironment for the growth of oocytes, molecular profiling of the fluid may provide unique information about pathophysiology associated with follicular development in PCOS. Post-translational addition of oligosaccharide residues is one of the many modifications of secreted proteins influencing their functions. These glycoproteins play a significant role in disease pathology. Despite glycoproteins having such essential functions, very limited information is available on their profiling in human reproductive system, and glycoproteomic profile of follicular fluid of women with PCOS is yet unexplored. In the present study, we performed a comparative glycoproteomic analysis of follicular fluid between women with PCOS and controls undergoing in vitro fertilization, by enrichment of glycoproteins using three different lectins viz. concanavalin A, wheat germ agglutinin and Jacalin. Peptides generated by trypsin digestion were labeled with isobaric tags for relative and absolute quantification reagents and analyzed by liquid chromatography tandem mass spectrometry. We identified 10 differentially expressed glycoproteins, in the follicular fluid of women with PCOS compared to controls. Two important differentially expressed proteins- SERPINA1 and ITIH4, were consistently upregulated and downregulated respectively, upon validation by immunoblotting in follicular fluid and real-time polymerase chain reaction in granulosa cells. These proteins play a role in angiogenesis and extracellular matrix stabilization, vital for follicle maturation. In conclusion, a comparative glycoproteomic profiling of follicular fluid from women with PCOS and controls revealed an altered

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Proteomics of Asrij Perturbation in *Drosophila* Lymph Glands for Identification of New Regulators of Hematopoiesis

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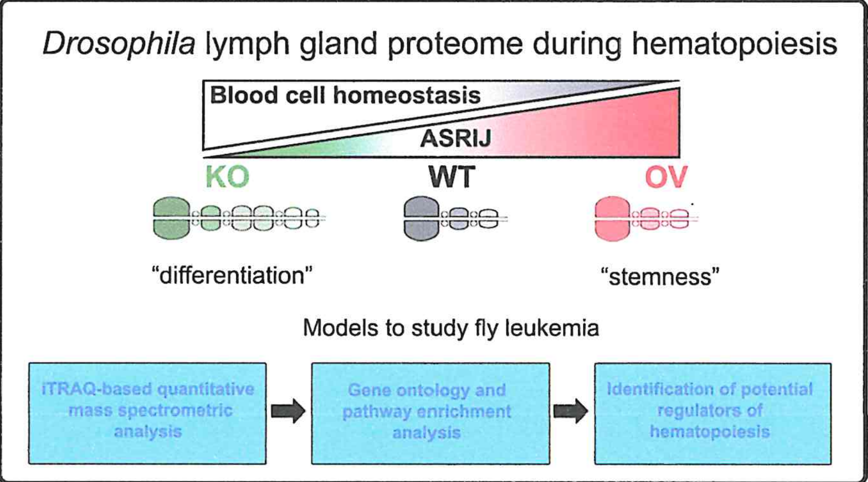
Graphical Abstract



In Brief

Identification of molecules and processes that regulate hematopoiesis using *Drosophila* lymph gland (LG) as a model, is important for widening its scope and applicability as a tool to understand mechanisms regulating blood cell homeostasis. Using Asrij modulation, we compared the LG proteome under conditions that maintain precursors or promote differentiation *in vivo* and identified conserved as well as additional regulators of *Drosophila* hematopoiesis. The LG proteome provides an invaluable resource for studying insect as well as vertebrate blood cell development.

Highlights

- First report on the quantitative proteomic profiling of *Drosophila* lymph glands.
- Comparative proteomic analysis under conditions of perturbed blood cell homeostasis.
- Resource for identifying new regulators of insect and vertebrate hematopoiesis.

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