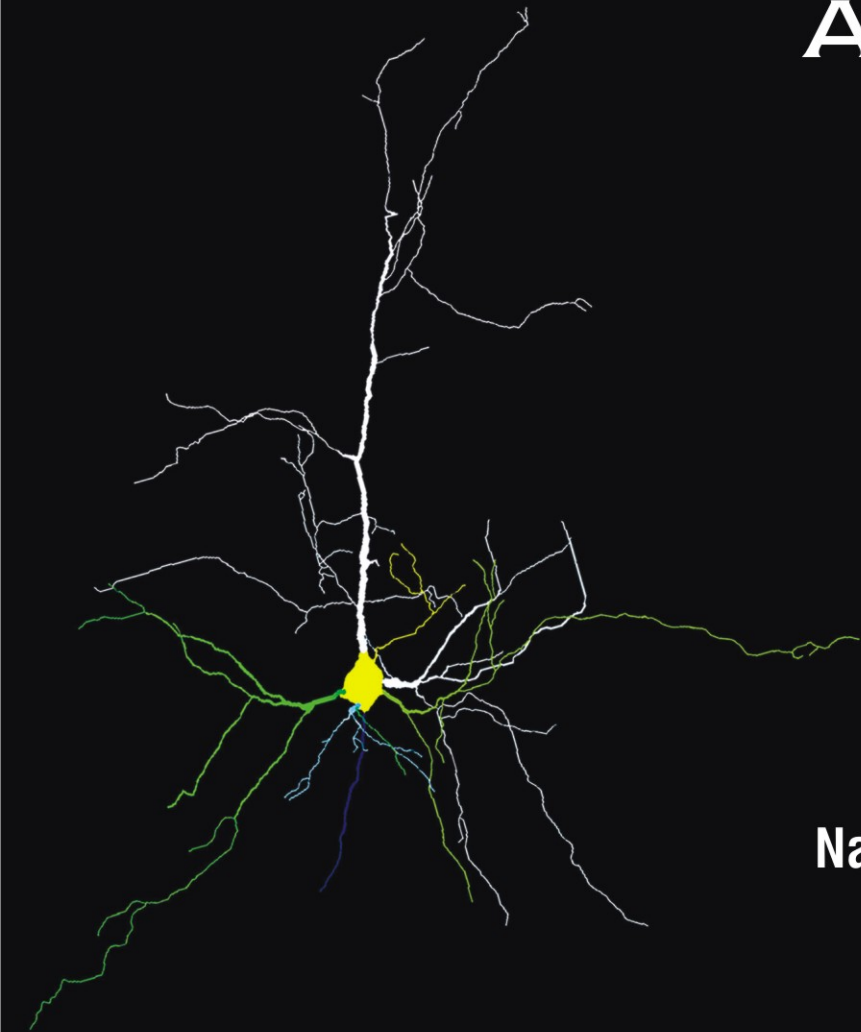




Annual Report 2012-13



National Brain Research Centre
Manesar, Haryana (India)

Compiled and edited by
V. Rema and Kedar Singh

Cover neuron from
Rat Barrel Cortex. credit V. Rema



Annual Report 2012-13

National Brain Research Centre
Manesar, Haryana (India)

Contents

Mandate	v
From the Director's Desk	vii
Research Reports	01
Molecular & Cellular Neuroscience Division.....	03
• Prof. Subrata Sinha	05
• Dr. Nihar Ranjan Jana	09
• Dr. Pankaj Seth.....	13
• Dr. Ellora Sen	16
• Dr. Shiv K Sharma	19
• Dr. Anirban Basu	21
• Dr. Ranjit Kumar Giri	26
• Dr. Sourav Banerjee.....	30
• Dr. Sayali Ranade	32
Systems & Cognitive Neuroscience Division	35
• Prof. Neeraj Jain.....	37
• Dr. Soumya Iyengar.....	40
• Dr. Narender K. Dhingra	45
• Dr. Yoganarasimha Doreswamy.....	47

Computational Neuroscience & Neuroimaging Division	51
• Dr. Nandini Chatterjee Singh.....	53
• Prof. Prasun Kumar Roy	57
• Dr. Pravat Kumar Mandal	64
Publications & Patents	67
Presentations.....	71
Distinctions, Honours & Awards.....	77
Externally Funded Research Projects.....	81
Core Facilities.....	87
• Distributed Information Centre (DIC).....	89
• Animal Facility.....	90
• Library.....	92
DBT's Electronic Library Consortium (DeLCON).....	93
National Neuroimaging Facility.....	97
Translational Research : Clinical Unit.....	101
Meeting and Workshop.....	105
International Collaborations & Networking.....	109
• International Collaborations	111
• Networking.....	111
Invited Lectures	113
Academic Programmes	117
• Ph.D. in Neuroscience	119
• Integrated Ph.D. in Neuroscience	119
• Summer Training & Short Term Programmes.....	119
General & Academic Administration - A Profile	121
Institutional Governance Structure & People at NBRC.....	125
Annual Financial Statements	137

Mandate & Objectives

MANDATE

- Pursue basic research to understand brain function in health and disease.
- Generate trained human resources with the capability to carry out inter-disciplinary research in neuroscience.
- Promote neuroscience in India through networking among institutions across the country.

OBJECTIVES

- To undertake, aid, promote, guide and coordinate research of high caliber in basic and clinical neuroscience related to diseases and disorders of the nervous system.
- To develop NBRC as the national apex centre for neuroscience research and promote neuroscience research at different centres in the country and to provide consulting services to other institutions, agencies and industries.
- To promote, encourage and augment effective linkages, alliances and affiliations between the Centre and National and International Scientific and Research Institutions, bodies, agencies/laboratories and other organizations working in the field of brain and neurosciences research.
- To establish one or more satellite centers to serve

different regions of the country for efficient achievement of the objectives of the Center.

- To collect, assimilate, publish and disseminate data and information on relevant aspects of neuroscience to the scientific community.
- To establish, operate and maintain state-of-the-art facilities as well as databases for carrying research and development activities and make such facilities and databases available to scientists and researchers from all over the country and abroad.
- To provide for instructions and training in such other branches of learning as the Centre may deem fit.
- To provide facilities for the advancement of research and development to facilitate learning and dissemination of knowledge.
- To undertake extramural studies, extension programmes and field outreach activities to contribute to the development of society.
- To promote, develop, collaborate or otherwise assist in providing services of research, training, consulting or guidance related to neurosciences activities comprising biological, psychological, sociological and clinical aspects; and
- To do all such other acts and things as may be necessary or desirable to further the objectives of the Centre.

From the Director's Desk

The National Brain Research is one of the very few centres that has the entire spectrum of neuroscience research under one roof. Though, for purposes of convenience it could be said to have research groups in molecular and cellular neuroscience, systems neuroscience, neuro-imaging and computational and clinical neuroscience, the frontiers of each research area extend far beyond the limitations set out by these functional boundaries. Our endeavour in NBRC is to ask fundamental scientific questions that enhance the horizons of our understanding and to then translate new knowledge to public good. As we struggle in our effort to transform the incremental to the revolutionary, our effort has been to strive for excellence. India struggles with the social and demographic battles of both a developing and a developed society – neither does the past let go so easily, eg. in terms of neonatal hypoxia and brain infections, nor are we free of the attendant problems of a longer life span in terms of degenerative diseases and dementias. As the only research institute in the country dedicated to the brain, we have a unique responsibility of towards increasing our basic understanding of neuroscience, as well as finding ways of ameliorating disorders of the brain.

At NBRC, the neuro AIDS laboratory is focusing its research efforts to decipher intricacies of neuron-glia interactions following exposure to HIV-1 Tat using a human fetal brain derived neural stem cell culture system. Live cell imaging techniques are being used to evaluate the role of HIV-1 Tat on alterations of intracellular calcium in glial cells, particularly astrocytes, and its relation to neuron damage. The laboratory is also actively engaged in understanding cellular and molecular pathways possibly involved in HIV-1 and drugs of abuse induced co-morbidity.

Research from another group which works on the Japanese Encephalitis Virus (JEV) has provided important insights into JEV-induced neuropathology. They have demonstrated that JEV infection is more robust in undifferentiated Neural Stem Progenitor Cells (NSPCs) compared to differentiated ones. Further, JEV infected NSPCs show hampered differentiation and arrested migration in adherent neurosphere cultures. Interestingly, they have also shown that neuronal differentiation appears to be more severely affected by JEV compared to astrocyte differentiation and that transcription factors involved in both neuronal and astrocyte differentiations are significantly decreased following JEV infection.

One of the research groups at NBRC which has been working on the pathogenesis of neurodegenerative diseases has created brain Ube3a-deficient Huntington's disease (HD) transgenic mice that manifest severe disease pathology and early death compared to HD mice. This group has also identified neuronatin as a novel substrate of the ubiquitin ligase malin in Lafora disease and has demonstrated that neuronatin mediated aberrant calcium signalling plays a crucial role in the pathogenesis of Lafora disease.

Another research group has developed a novel in vitro model of Alzheimer's disease (AD) using CNS stem cell cultures which manifests beta amyloidopathies similar to animal models of AD except plaque formation. This group has further reported that a novel anti-cancer drug, 8-Methoxypyrimido [4,5-f]thieno[2,3-b] Quinoline-4(3H)-One (MPTQ) can inhibit the growth of neuroblastoma cells. For the first time, they have also demonstrated the molecular mechanisms associated with MPTQ-mediated cell death in neuroblastomas.

Ongoing research on brain tumours (glioblastoma multiforme) at NBRC has identified β -defensin 3 as a negatively regulator of HLA-G expression in glioma cells. As HLA-G constitutes a way for gliomas to escape from immune-surveillance, this finding may be of direct clinical relevance in the modulation of immune escape mechanisms in glioma. By demonstrating how (i) JNK-NF κ B axis regulates resistance to TNF α induced apoptosis (ii) Ras/NF κ B axis sensitizes glioma cells to Sonic-hedgehog inhibitor induced death, this research group has analyzed pathways that lead to glioma progression and also suggested ways for combating the same. This research group has also been granted a European patent on the bicyclic triterpenoid Iripallidal which may have therapeutic potential as a novel anti-glioma and anti-neoplastic therapy in vitro in 2013.

Research on the molecular basis of learning and memory had earlier shown that acetylation level of alpha tubulin in the hippocampus is enhanced in an activity-dependent manner. They have recently begun investigating the molecular mechanisms of alpha tubulin acetylation and have found that increasing acetylation levels enhances glutamate receptors on the cell membrane. Since glutamate receptor trafficking plays important roles in synaptic plasticity related to memory, these results suggest that acetylation regulates this process and thus contributes to synaptic plasticity and memory.

One of the laboratories at NBRC is interested in understanding mechanisms of brain reorganization following spinal cord injuries. This research group has found that large-scale brain reorganization is not mediated by cortical mechanisms. Their findings suggest that changes in the cortex following spinal cord injuries are likely mediated by reorganization at the medullary level, which is also a site for large-scale plasticity.

The research group that is interested in neuroethology has been studying how brain structure and function relates to behaviour in crows which are known to perform certain cognitive tasks on par with non-human primates. They have used histology and immunohistochemistry to study the dopaminergic system in these birds, which is known to be involved in cognition. They have shown for the first time that the hyperpallium, a part of the avian cortex contains a dense plexus of TH-positive fibers. These findings suggest that this brain region may be important for the remarkable cognitive abilities of corvids.

Research on speech and language at NBRC has demonstrated that children with autism across the spectrum show strong neural activity for sung speech as compared

to normal speech. This suggests that music processing pathways may be preserved in autism. Given that verbal communication or speech is often impaired in children with autism, these findings suggest that musical speech may prove to be beneficial in improving verbal communication in autism.

A number of cutting-edge techniques for imaging the human brain have been developed recently at NBRC which are of special importance for those suffering from brain diseases. The group specializing in Neurospectroscopy has established novel non-invasive imaging techniques to correlate brain oxidative stress and brain pH (combined) in patients diagnosed with mild cognitive impairment and Alzheimer's disease.

MRI-based Elastometric relaxation mapping has been used by another research group to track the ageing process in the brain, especially in Alzheimer's disease, who found that temporal elasticity relaxation coefficient of the parenchyma is an effective temporal rate index that can act as a brain ageing biomarker. This group has also explored the feasibility of using a preclinical rodent model for MRI and immunohistochemical studies, to enable the determination of the process kinetics of endogenous neurogenesis and synaptogenesis in cerebral stroke. In this model, diffusion imaging and allometric analysis have been used to delineate the time duration required for neuroblasts to move from the subventricular zone to the stroke penumbra zone, which can then be used to plan pharmacological interventions for neurogenesis and synaptogenesis, so that optimal neural recovery occurs.

NBRC is pleased to welcome a new faculty member, Dr. Arpan Bannerjee, who joined us this year. He plans to use a diverse set of techniques which include building theoretical models of the brain and behaviour, developing signal processing algorithms to study brain network mechanisms and using functional brain imaging techniques (Electroencephalography and Magnetoencephalography) to understand the neurodynamics of decision making, the neural basis of speech processing, multisensory processing and developing neuro-markers for brain disorders.

In addition to research, NBRC is an educational centre and continues its activities as a Deemed University. As of March 31st, 2013, NBRC has awarded the degree of Doctor of Philosophy in Neuroscience to 36 students. NBRC also provides hands-on training to a number of summer trainees (selected by the Indian Academy of Science, Bangalore, Indian National Science Academy, New Delhi and National Academy of Sciences, Allahabad),

to encourage them to pursue Neuroscience as a career. NBRC celebrated its 9th Foundation Day on 16 December, 2012 by inviting students from five schools in Gurgaon / Manesar to attend a lecture on Neuroscience, a scientific poster presentation, demonstrations and quiz on its campus conducted by NBRC students. A major highlight of NBRC's Foundation Day celebrations was a public lecture entitled "Stem Cells and Disorders of the Brain: What have we learned?" by the distinguished neuroscientist Professor Mahendra S. Rao (Director, Centre for Regenerative Medicine National Institute of Health, Bethesda, USA) who specializes in the use of human embryonic stem cells (hESCs) and other somatic stem cells in regenerative therapies. Besides academics and research, NBRC also encourages extra-curricular activities. NBRC's month-long annual festival Tantrika is unique in that it combines scientific events as well as sports, arts and crafts and is organized almost entirely by students of NBRC. This year's highlights included a talk entitled "Tum Vahaan, Mein Yahaan, Naseeb Apne Apne: The effect of Position on Cell Fate" by the noted neuroscientist Dr. Shubha Tole (TIFR, Mumbai) and a scientific poster presentation for NBRC students. For the first time, students took the initiative to organize a Blood Donation Camp with the Red Cross Society of India on campus during Tantrika.

As a part of its community outreach programmes, NBRC also celebrated the National Science Day (to celebrate the Nobel Laureate CV Raman's birthday, 28 February, 2012)

with talks on neuroscience presented by Prof. NR Jana (Amity University, Manesar) and postdoctoral fellows, Dr. Chaitra Rao (Government Senior Secondary School, Pachgaon) and Dr. Nabonita Sengupta (Kendriya Vidyalaya, NSG, Manesar).

To promote awareness about neuroscience and networking between different institutions involved in the discipline across India, NBRC sponsored the Brain Awareness Week in different institutions across the country. Under the aegis of the Brain Awareness Week, talks, poster sessions and demonstrations were organized at the Regional Science City, Lucknow, Banaras Hindu University, AIIMS, Bhubaneswar, Jawaharlal Nehru University, New Delhi, CDRI, Lucknow and IIT, Allahabad to educate the general public about the brain and various disease processes that can affect it. The dual purpose served by the Brain Awareness Week is to educate students (at school and college levels) about the brain and to motivate them to pursue neuroscience as a career option.

The phrase "Molecules to behaviour" has been used so many times that it has become a cliché. However, like all clichés it succinctly expresses a kernel of truth that is central to the dreams of all neuroscience researchers. We hope that in the coming year the incipient scientific dreams of all scientists and students at NBRC come one step closer to fruition and we would take one step forward in this uncharted journey towards unraveling the complexities of our last frontier.

Prof. Subrata Sinha



Research Reports

Molecular & Cellular Neuroscience Division
Systems & Cognitive Neuroscience Division
Computational Neuroscience & Neuroimaging Division



Molecular & Cellular Neuroscience Division

Prof. Subrata Sinha
Dr. Nihar Ranjan Jana
Dr. Pankaj Seth
Dr. Ellora Sen
Dr. Shiv Kumar Sharma
Dr. Anirban Basu
Dr. Ranjit Kumar Giri
Dr. Sourav Banerjee
Dr. Sayali Ranade

THERAPY OF GLIOMA: ROLE OF HYPOXIA AND ABERRANT GENE EXPRESSION

Principal Investigator
Subrata Sinha

Work continues on the response of glioma to therapy, and how hypoxia affects this response. Glioma are among the most hypoxic of all tumours and hypoxia-necrosis cycle is a hallmark of Glioblastoma multiforme (GBM), the most malignant of glial tumours. Hypoxia and inflammation are closely linked. Cytokines mediating inflammation may promote tumour growth by either facilitating a conducive host microenvironment for the tumour, as well as by acting as autocrine growth factors. There are several mechanisms leading to the dysregulation of the inflammatory microenvironment in tumours. In collaboration with Dr. Kunzang Chosdol, Department of Biochemistry, AIIMS, we have identified a novel link between inflammation and tumorigenesis.

Our initial work on identifying differences between tumour and corresponding normal DNA by profiling differences in their DNA fingerprinting patterns had identified a region in the chromosomal region 4q34 – 35, as being altered in a significant proportion of glial tumours. Analysis of LOH profiles indicated that it harboured a tumour suppressor gene (TSG), the most likely being the human homologue of the Drosophila TSG FAT 1 (Chosdol et al 2009). However, in an apparent contradiction, this gene was highly expressed in glial tumour cell lines derived from high grade tumours but not in those derived from low grade ones. Knock down of this gene by siRNA resulted in reduced cell migration and invasion in the high grade glioma cells, though it did not affect proliferation. Microarray analysis of the knockdown indicated an inverse relationship with the TSG, PDCD4 (Programmed Cell Death 4), which was increased by this knock down. PDCD4 inhibited AP1 activation by

reducing c-Jun expression and phosphorylation. This attenuation was relieved by increased FAT1 expression in the high grade glioma cell lines. The results were confirmed by simultaneously knocking down FAT1 and PDCD4. The molecules that were increased due to high Fat1 expression included MMP3, VEGF, PLA2, the pro-inflammatory regulator COX-2 and cytokines IL1 β and IL-6.

These results were validated in 35 primary human WHO grade IV Glioblastoma multiforme samples. There was a marked variation in FAT1 expression within the same histological grade. There was a significant negative correlation between the expression of FAT1 and PDCD4 ($p=0.0145$) and a positive correlation with COX 2 ($p=0.048$). For IL6 there was a similar positive trend, though it was not statistically significant. The results, which validate the in-vitro findings, indicate that there may be a possible explanation for the manifestation of heterogeneity of the inflammatory response within Glioblastoma multiforme. There have been several attempts to sub-classify this histological grade in an attempt to associate molecular pathways with tumour behaviour and prognosis. FAT1 and inflammation could be amongst the parameters that may be taken into account for this purpose.

This novel pathway for inflammation is being studied in the context of its role in the activation of inflammatory responses in hypoxia. Work is in progress on how hypoxia affects the expression of FAT1 and its differential role in hypoxia and normoxia. The association of FAT1 expression with the markers of the hypoxic response in primary human tumours would also be studied.

Publication

1. Dikshit B, Irshad K, Madan E, Aggarwal N, Sarkar C, Chandra PS, Gupta DK, Chattopadhyay P, **Sinha S**, Chosdol K. FAT1 acts as an upstream regulator of oncogenic and inflammatory pathways, via PDCD4, in glioma cells. *Oncogene* advance online publication, 17 September 2012; doi: 10.1038/onc.2012.393 (joint corresponding author).

Patent

Use of the FAT1 gene and its products, including RNA, protein and the derivatives of the same, as suitable molecule/s for either inflammation or cancer and the

associated phenotype and the processes linking the same and also as a biomarker for the above processes (PCT/IB2013/050086, filed on 4 Jan 2013). (Jointly by DBT, AIIMS and NBRC).

Collaborators

1. Dr Kunzang Chosdol (Biochemistry), Dr Parthaprasad Chattopadhyay (Biochemistry), Dr Chitra Sarkar (Pathology), Dr. P S Chandra (Neurosurgery) and Dr Deepak Gupta (Neurosurgery), AIIMS
2. Dr Tapasya Srivastava, University of Delhi, South Campus
3. Dr Ellora Sen, NBRC

RECOMBINANT ANTIBODIES AS THERAPEUTIC AGENTS: TARGETING TUMOURS THROUGH PLACENTAL ALKALINE PHOSPHATASE

Principal Investigator
Subrata Sinha

Alkaline phosphatase (AP) has 4 major isozymes: (1) Tissue non specific (TNAP) (2) Intestinal (IAP) (3) Placental (PAP) (4) Placental like or germ cell alkaline phosphatase (PLAP/GCAP). Of these the PAP and PAP/GCAP isozymes have been shown to be expressed ectopically in a number of tumours, hence would come under the category of Onco-placental antigens. While all the AP isozymes have considerable homology, PAP and PLAP/GCAP are very highly homologous and are immunologically indistinguishable. While both PAP and PLAP/GCAP are highly expressed in germ cell tumours, these are also expressed in a variety of cancers, including cervix, breast etc.

Germ cell tumours comprise of 2 to 10% of childhood brain tumours. In addition, PAP is expressed on tumours metastatic to the brain, depending on tumour type.

The work aims to develop a tumour specific targeting modality using a combination of: (1) Recombinant isozyme specific antibodies of human origin that can specifically target PAP or PLAP/GCAP but not the other constitutively expressed isozymes. (2) using PLAP/GCAP promoters for (a) specific prodrug activation within tumour cells for expression of exogenous prodrug drug metabolizing genes or (b) for expression of TGS inducing dsRNA. This approach would utilise a particulate delivery system (till now the Sendai virosome system) for targeted delivery.

Earlier we had been successful specific particulate delivery vehicle (Sendai immunovirosome), that is able to bind specifically to PLAP expressing cells. This was because of an engineered recombinant scFv fragment, oriented on the virosome surface based its surface by the fusion with

a fragment a transmembrane Sendai virus F protein. The virosome could deliver a drug payload (Doxorubicin), that resulted in enhanced death of the PAP expressing cells. We have now been able to show that the combination of recombinant antibody based targeting with the Sendai virosome delivery system is able to specially deliver the payload to the cytoplasm of cells expressing PAP. Antibody based targeted delivery is often directed to the endosomal compartment, resulting in degradation of the payload as well as increased immunogenicity of any protein component of the same. However, it has been earlier shown by our collaborators that the F protein on the Sendai virosome is able to mediate membrane fusion which results in cytoplasmic delivery of most of the components being carried. We have demonstrated that the Sendai immunovirosome generated in this study is specifically able to target PAP expressing cells and also results in about 75% cytoplasmic delivery. This would translate into increased efficacy as well as lower immunogenicity.

Use of PLAP/GCAP promoter for specific gene expression within tumour cells: This is intended to bring about a dual level of specificity as the promoter is only active in cell lines that express PLAP. The PLAP/GCAP promoter was coupled with an NF kappaB enhancer. The promoter/promoter-enhancer activities were assayed by various reporter systems in a battery of cell lines along with their appropriate controls. The utility of these constructs for gene dependent enzyme prodrug therapy (GDEPT) was studied upon and preliminary results revealed the activation of the inactive form of drug 5-fluorocytosine to its active form 5-fluorouracil by the enzyme cytosine deaminase, when its expression was governed by PLAP promoter/enhancer

systems. This resulted in significant enhancement of cell killing.

Work is also ongoing in developing recombinant antibody based approaches for generating neutralizing antibodies to HIV. Both viruses have central nervous system effects. Hepatitis encephalopathy is seen in a large proportion of ICU admissions in most hospitals. HIV encephalopathy is also a problem especially for long term survivors on anti HIV drugs. Our work has been to generate recombinant antibody libraries from EBV transformed B cell lines, which secreted specific neutralizing antibodies to the HIV Clade C which is the commonest Clade in India and is comparatively less studied than Clade B viruses. This is also a new strategy for generating scFv antibodies from pre-selected EBV transformed lines, which results in a directed library which has a higher proportion of the desired antibodies than a conventional library from peripheral lymphocytes of patients.

Publications

1. Kumar R, Andrabi R, Tiwari A, Sankaran S.P, Wig N, Dutta D, Sankhyan A, Khan L, **Sinha S**, Luthra K. A novel strategy for efficient production of anti-V3 human scFvs against HIV-1 clade C, BMC Biotechnology Online Publication, 15 November 2012; doi:10.1186/1472-6750-12-87 (joint corresponding author)
2. Andrabi, R, Kumar R, Bala M, Nair A, Biswas A, Wig N, Kumar P, Pal R, **Sinha S**, Luthra K. Production and characterization of human anti-V3 monoclonal antibodies from the cells of HIV-1 infected Indian donors. **Virology Journal** 2012, 9:196

Collaborators

1. Dr. Parthaprasad Chattopadhyay, Dr. Kunzang Chosdol and Dr. Kalpana Luthra, (Biochemistry), AIIMS
2. Prof. Debi P Sarkar, Dept. of Biochemistry, University of Delhi, South Campus

UNDERSTANDING THE FUNCTION OF THE AUTISM AND AUTISM SPECTRUM DISORDERS ASSOCIATED UBIQUITIN LIGASE, UBE3A/E6-AP

Principal Investigator

Nihar Ranjan Jana

Post Doctoral Fellows

Supriya Bhavnani, Ruchi Gaur

Research Fellows

Swetha K. Godavarthi, Megha Maheswari,
Imran Jamal

Project Assistants

Rajarshi Mukherjee, Anirudha Das

Technical Assistants

Ankit Sharma, Mahendra Singh

E6-AP protein encoded by UBE3A gene was first identified as a cellular protein linked in ubiquitin-mediated proteolysis of tumor suppressor p53 in assistance with E6 oncoprotein of the human papilloma virus. Subsequently, it is characterized as a HECT (homologous to E6-AP C terminus) domain family of E3 ubiquitin ligase, an important enzyme involved in targeting protein for ubiquitination. Ube3a also acts as a transcriptional co-activator of steroid hormone receptors. Ube3a shows neuron specific imprinting and dysfunction of maternally inherited Ube3a causes Angelman syndrome (AS). AS is a neurodevelopmental disorder characterized by severe mental retardation, speech impairment, vulnerability to seizures, ataxia and unique behavioural features such as improper laughter and autistic features. Copy number variation of the UBE3A gene (duplication) also reported in autism. Ube3a maternal deficient mice exhibit many features of AS, including cognitive and motor dysfunction. These mice also display defects in hippocampal LTP, altered function of hippocampal CAMK-II α and abnormal dendritic spine morphology. Studies in these mice also provided further hint that Ube3a is necessary for development of synapse, experience-dependent cortical plasticity and maturation of neocortex.

Past several years we are engaged in exploring the physiological function of Ube3a and how its defect could lead to AS. We are particularly interested in (1) identification and functional characterization of novel substrates of Ube3a, (2) molecular mechanism of cognitive impairment in AS mice model, and (3) role of Ube3a in the progression of Huntington's disease.

Recently, we have demonstrated that deranged glucocor-

ticoid receptor signalling in hippocampus could lead to chronic stress and increased anxiety-like behaviour in AS mice (Ube3a-maternal deficient mice). Chronic stress also could be associated with learning and memory impairment in these mice. We have now tested the role of fluoxetine (a selective serotonin reuptake inhibitor) on resetting of HPA axis and recovery of anxiety-like behaviour in AS mice. Chronic treatment of fluoxetine partially rescued the expression of GR in the hippocampus along with GR target proteins like BDNF, SGK and FKBP5 and also restored HPA axis as seen by normalization of blood corticosterone level in AS mice. The anxiety-like behaviour also partially recovered upon fluoxetine treatment as evident from the open field and light-dark box tests. Presently, we are testing the role of enriched environment in the recovery of learning and memory deficits in AS mice.

Earlier we have demonstrated that Ube3a function as a cellular protein quality control ubiquitin ligase. We have also demonstrated that the partial loss of function of Ube3a might be associated with abnormal synaptic function in HD transgenic mice brain. In order to obtain further insight of the role of Ube3a in HD pathogenesis, we created brain Ube3a deficient HD transgenic mice. Male HD mice were crossed with Ube3a-maternal deficient (m-/p+) female to obtain brain Ube3a-deficient HD mice. It is important to note that paternally expressed Ube3a is imprinted in brain and Ube3a-maternal deficient mice exhibits loss of Ube3a expression in brain. Interestingly, we observed that the disease progression (onset and severity) was much faster in Ube3a-deficient HD mice in comparison with only HD mice. Ube3a-deficient HD mice also dies much earlier compared to HD mice (Fig.1). Ube3a-deficient HD

mice manifest motor abnormalities as early as 5 weeks old, when HD mice behaves like wild type mice. However, by 7-8 weeks, Ube3a-deficient HD mice shows severe motor problems and during this age HD mice begin to exhibits motor problems. These mice also showed frequent seizure that often leads to death. Total brain weight and the straital volume were significantly reduced in these mice at 7-8 weeks of age compared to age-matched HD mice. No apoptotic cell death was detected in the straitum and other brain regions and there was no sign of inflammation. Immunohistochemical staining revealed increased mutant huntingtin aggregate load in Ube3a-deficient HD mice brain compared to HD mice at 7-8 weeks age. Currently, we are investigating the probable cause of early neuronal dysfunction in Ube3a-deficient HD mice.

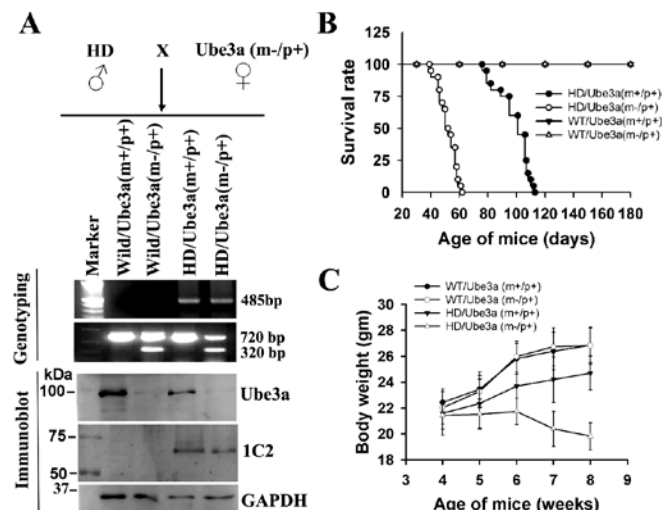


Figure 1. Ube3a-deficient HD transgenic mice exhibits shorter life-span. A) Cross breeding, genotyping of mice and immunoblot analysis. B) Life-span of wild-type, Ube3a-maternal deficient, HD and Ube3a-maternal deficient HD mice. C) Ube3a-deficient HD mice exhibits drastic decrease in body weight.

Publications

1. S. Bhutani, A. Das, M. Maheshwari, S.C. Lakhota and **N.R. Jana (2012)**. Dysregulation of core components of SCF complex in polyglutamine disorders. *Cell Death and Disease*, 3, e428.

2. D. Chhangani, **N.R. Jana** and A. Mishra (2013). Misfolded Proteins Recognition Strategies of E3 Ubiquitin Ligases and Neurodegenerative Diseases. *Molecular Neurobiology*, 47, 302-312.
3. A. Mishra, M. Maheshwari, D. Chhangani, N. Fujimori, F. Endo, A. P. Joshi, **N. R. Jana** and K. Yamanaka (2013). E6-AP association promotes SOD1 aggregates degradation and suppresses toxicity. *Neurobiology of Aging*, 4, 1310, e11-23.
4. M. Maheshwari, A. Samanta, S. K. Godavarthi, R. Mukherjee, and **N.R. Jana (2012)**. Dysfunction of the Ubiquitin Ligase Ube3a May Be Associated with Synaptic Pathophysiology in a Mouse Model of Huntington Disease. *Journal of Biological Chemistry*, 287, 29949-29957.

Presentations

1. A.Das, S. Bhutani, M. Maheshwari, S. C. Lakhota and N. R. Jana. Dysregulation of core components of SCF complex in polyglutamine disorders. Annual Meeting of Society for Biological Chemists (SBCI), Kolkata, 2012.
2. N. R. Jana. Involvement of Ube3a in cellular protein quality control: Implication in protein misfolding neurodegenerative disorders. NEUROCON, Kolkata, 2013.
3. N. R. Jana. Role of ubiquitin ligase Ube3a in the pathogenesis of Huntington's disease. Annual Meeting of the Society for Neurochemistry, India (SNCI), 2013. New Delhi.

Funding

1. Study the defect in neurogenesis and initial synapse formation in mouse model of Angelman mental retardation syndrome. Council of Scientific and Industrial Research. Govt. of India., Grant No: 37(1408)/10/EMR-II dt. 25-06-2010
2. Role of E6-AP in the progression of Huntington's disease. Department of Biotechnology, Govt. of India (National Bioscience Award for Career Development). Grant No: BT/HRD/34/18/2008 dt. 16-04-2010.

Collaborators

- I. Dr. Nobuyuki Nukina, RIKEN Brain Science Institute, Japan.
- II. Dr. Nikhil Jana, Indian Association for the Cultivation of Sciences, Kolkata.

UNDERSTANDING THE PHYSIOLOGICAL FUNCTION OF MALIN, A UBIQUITIN LIGASE MUTATED IN LAFORA'S PROGRESSIVE MYOCLONUS EPILEPSY

Principal Investigator

Nihar Ranjan Jana

Post Doctoral Fellows

Supriya Bhavnani, Ruchi Gaur

Research Fellows

Swetha K. Godavarthi, Megha Maheswari,
Imran Jamal

Project Assistants

Rajarshi Mukherjee, Anirudha Das

Technical Assistants

Ankit Sharma, Mahendra Singh

Lafora disease (LD) is an inherited (autosomal recessive) progressive myoclonus epilepsy, usually evident during teenage and patient dies within first decade of disease onset. The disease is clinically characterized by progressive increase in myoclonic and visual seizures, dementia, psychoses, muscles wasting leading the patient into a vegetative state and ultimately death. Cytopathological features of LD include intracellular accumulation of insoluble polyglucosan bodies (known as Lafora bodies) and widespread neurodegeneration. Lafora bodies are not only observed in brain but also in other non-neuronal tissues like liver, heart, skeletal muscle, skin etc.

LD is caused by mutations in the EPM2A or EPM2B (NHLRC1) genes encoding laforin (a protein phosphatase) and malin (a E3 ubiquitin ligase) respectively. Patients with mutations in either laforin or malin are clinically and pathologically indistinguishable, signifying that both proteins work together in some common signalling cascades and deficiency in those pathways could lead to disease appearance. Emerging proof indicates that both laforin and malin could play a significant role in regulating glycogen metabolism and autophagy. Knockout mice for both laforin and malin also display progressive accumulation of Lafora bodies in various tissues including brain, defects in autophagic degradation pathway and extensive neurodegeneration. But how Lafora bodies induce neurodegeneration is poorly understood at present and the possible mechanism of dysfunction of protein degradation pathways in LD is also not clear. Since malin is an E3 ubiquitin ligase and its mutation causes to LD, it

is hypothesized that the altered clearance of substrates of malin might lead to disease pathogenesis. Therefore, identification of substrates of malin could open a new opportunity in understanding the pathogenesis of LD. In the proposed project, we are trying to identify and exemplify the novel substrates of malin. In addition, we are also exploring the role of intracellular protein degradation pathways in LD pathogenesis.

Earlier we have shown malin interacts with neuronatin and promotes its proteasome-mediated degradation. Malin also negatively regulates neuronatin-stimulated glycogen synthesis. Now we demonstrate that the level of neuronatin is significantly up-regulated in the skin biopsy sample of LD patients having mutations in both malin and laforin. Neuronatin is highly expressed in human fetal brain with gradual decrease in expression in developing and adult brain. However, in adult brain, neuronatin is predominantly expressed in parvalbumin-positive GABAergic interneurons and localized in their processes. The level of neuronatin is increased and accumulated as insoluble aggregates in the cortical area of LD brain biopsy samples and there is also a dramatic loss of parvalbumin-positive GABAergic interneurons (Fig.2). Ectopic expression of neuronatin in cultured neuronal cells result in increased intracellular Ca²⁺, endoplasmic reticulum stress, proteasomal dysfunction and cell death that can be partially rescued by malin. These findings suggest that the neuronatin-induced aberrant Ca²⁺ signaling and endoplasmic reticulum stress might underlie LD pathogenesis.

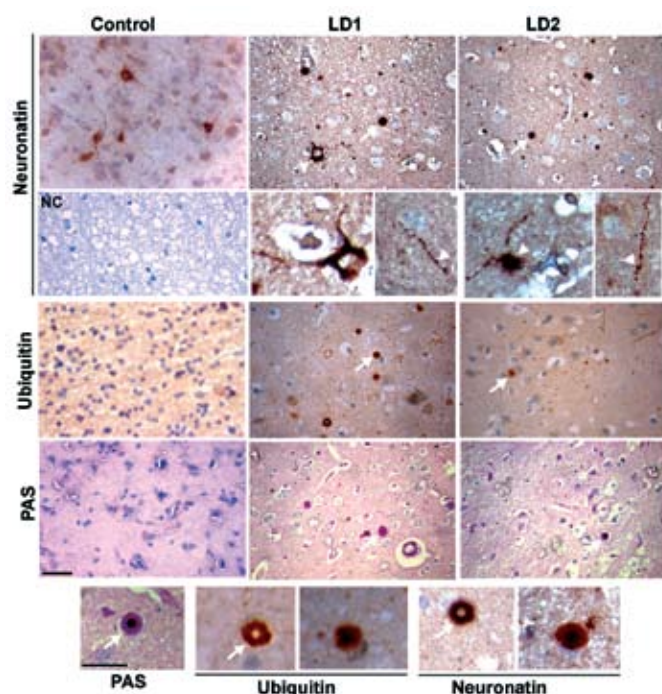


Figure 2. Immunohistochemical staining of neuronatin and ubiquitin in control (15 years old) and two different LD brain biopsy samples (LD1 and LD2 of 17 and 23 years old respectively). Lower panel of neuronatin staining shows higher magnification images. Arrow indicates neuronatin or ubiquitin-positive inclusions. Arrowhead pointed the cell or neurites exhibiting high level of neuronatin in LD brain. PAS staining was conducted to confirm the presence of Lafora bodies (indicated by arrow) in LD brain samples. In negative control (NC), LD brain section was processed without neuronatin antibody. Scale bars; 40 μ m in smaller magnification images and 20 μ m in higher magnification images. Bottom panel shows higher magnification images of localization of neuronatin or ubiquitin into Lafora bodies.

Publications

1. J. Sharma, D. Mukherjee, S. N. Rao, S. Iyengar, S. K. Shankar, P. Satishchandra and **N. R. Jana (2013)**. Neuronatin mediated aberrant calcium signaling and endoplasmic reticulum stress underlie neuropathology in Lafora disease. **Journal of Biological Chemistry**, 288, 9482-9490.

Presentations

1. N. R. Jana. Understanding the physiological function of malin and pathogenesis of Lafora disease. Annual Meeting of Society for Biological Chemists (SBCI), Kolkata, 2012.
2. D. Mukherjee, J. Sharma, S.N Rao, S. K. Shankar, P. Satishchandra and N. R. Jana. Neuronatin mediated altered calcium signalling and ER stress cause neuropathology in Lafora disease. Annual Meeting of Society for Biological Chemists (SBCI), Kolkata, 2012.
3. N. R. Jana, J. Sharma, D. Mukherjee, S. N. Rao, S. K. Shankar and P. Satishchandra. Neuronatin mediated aberrant calcium signaling underlie neuropathology in Lafora disease. Annual meeting of the Society for Neuroscience (SFN), New Orleans, 2012.

Funding

1. Understanding the physiological function of malin, a ubiquitin ligase mutated in Lafora's Progressive Myoclonus Epilepsy. Department of Biotechnology. Govt. of India. Grant No: BT/PR13590/Med/30/286/2009 dt. 17-09-2010.

Collaborators

1. Drs. S. K. Shankar and P. Satishchandra, National Institute of Mental Health and Neurosciences, Bangalore.

CELLULAR AND MOLECULAR MECHANISMS OF HIV-1 NEUROPATHOGENESIS

Principal Investigator

Pankaj Seth

Research Fellows

Shaily Malik, Manju Tewari, Mahar Fatima and Chitra Singal

Project Assistants

Aparna Pandey, Ankita Srivastava, Monika Sharma and Rabia Khatoon

Technical Assistant

Durgalal Meena and Naushad Alam

Human Immunodeficiency Virus-1 (HIV-1) virus traffics and resides in human brain as latent infection for several years in HIV-1 patients. While advent of combinatorial anti-retroviral therapy (cART) has successfully limited viral replication in circulating blood cells, it has failed to do so in brain tissue of HIV/AIDS patients. The poor penetration of cART drugs into central nervous system (CNS) is the leading cause of their inability in clearing the virus from brain, making brain as “HIV-1 sanctuary”. The HIV-1 in brain reservoirs has potential to repopulate the host circulation. Low viral load in circulating blood cells is reported following successful cART in majority of AIDS patients. Interestingly even though cARTs have failed to clear the virus from brain, a significant improvement in the neurocognitive functions has been reported. This is perhaps because continuous pouring of virus from blood into brain is prevented in patients undergoing cART. Although prevalence of frank dementia in HIV/AIDS patients has decreased following cART, a milder form of HIV-1 associated neurocognitive disorder (HAND) is prevalent in around 50% of HIV/AIDS patients undergoing cART as HIV-1 and HIV-1 transactivator of transcription (Tat) protein continues to affect normal brain functions. This suggests that neurocognitive deficits would continue to be cause of morbidity in HIV/AIDS patients until eradication of virus occurs from the host. Efforts to design novel approaches to address this problem of morbidity in HIV/AIDS patients is mandatory to reduce the burden of compromised cognition in AIDS survivors.

Cognitive abilities and optimal neuronal functions are supported by astrocytes in several ways. Astrocytes being the most abundant type of brain cells contribute significantly to normal brain physiology. Recent literature

suggests that neuron-glia interactions are of paramount importance for optimal neuronal functions. Perturbations in neuron-glia interactions have been implicated in several neurodegenerative disorders such as Alzheimer’s disease, Parkinson’s disease and HIV-1 associated dementia.

Our laboratory is investing efforts to decipher intricacies of the neuron-glia interactions using a human fetal brain derived cell culture system. We are currently investigating whether HIV-1 Tat protein affects neuron-glia interactions, and if it does, how? We are employing live cell imaging techniques to evaluate the role of HIV-1 Tat on alterations of intracellular calcium in glial cells, particularly astrocytes, and its relation to neuron damage. Our data suggest that HIV-1 Tat modulates intracellular calcium ion concentration which is mediated via purinergic receptors on glial cells. We observed that HIV-1 Tat resulted in a significant increase in mRNA and protein levels of a particular purinergic receptor on primary cultures of human astrocytes. Ongoing experiments are suggestive of the fact that HIV-1 Tat mediated neuronal damage is indeed mediated by astrocytes, as agonists and antagonists of purinergic receptors directly influence neuronal damage as assayed by apoptotic assays in our settings. We have confirmed the functionality of the over-expressed purinergic receptors using live cell imaging tools and time lapse microscopy. We performed calcium imaging studies by employing non ratiometric fluorescent dyes and high resolution time lapse microscopy. Calcium imaging studies indicate robust increase in intracellular calcium levels in human astrocyte cultures following exposure to HIV-1 Tat protein (Figure-1). Further, we observed that HIV-1 Tat treatments to neuron-glia coculture resulted in significant decrease

in the expression of glutamate receptors on astrocytes. Interestingly, we also observed a subsequent increase of glutamate concentrations in supernatant of these co-cultures that account for the increase in neuronal death following exposure to HIV-1 Tat protein. Further experiments to investigate astrocyte mediated neuronal damage are currently pursued in detail using a well characterized human astrocyte-neuron co-culture system. We have several interesting leads in this direction and believe our findings will provide novel insights into role of astrocytes in HIV-1 induced neuronal damage.

Clinical and basic science studies reveal augmented neurological complications in drug abusing HIV/AIDS patients due to enhanced neuronal damage. Literature in the area of neuroAIDS suggests that human neural stem cells are susceptible to HIV-1 infection and harbor the virus for long durations. Furthermore, several clinical and experimental studies have established the link between HIV-1 and opiate induced disturbances in their growth dynamics. The molecular mechanisms underlying the alterations in neural stem cell properties with concurrent HIV-1 infection and illicit drug use are poorly understood. Our laboratory has recently contributed in this area and demonstrated that the neurotoxic protein HIV-1 Tat alters the proliferative ability of human fetal brain derived neural stem cells. We demonstrated enhanced neurotoxicity due to comorbidity of HIV-1 Tat and opiates in human neurons. These findings provide scientific basis for poor prognosis of neurological

disorders in HIV/AIDS and drug abusing patients.

In addition to this, we continue to pursue our quest into HIV-1 and drug abuse co-morbidity with our experiments focused to investigate effect of opiates and HIV-1 Tat on properties of human neural stem cells. We have convincing data to believe that HIV-1 Tat and morphine adversely affect proliferation of human neural stem cells under acute and chronic exposure of these agents. Importantly, the co-morbidity of HIV-1 Tat and opiates does not affect the viability of human neural stem cells. We utilized well characterized human fetal brain derived neural stem cell model and observed that co-exposure of HIV-1 Tat and opiate significantly reduced the number of Ki67 positive cells as well as exhibited reduced proliferation by other proliferation assays. Detailed experiments were designed to dissect out cellular and molecular mechanisms that may underlie this phenomenon. Our data from flow cytometry suggests that HIV-1 Tat and morphine stall human neural stem cells in the G1/S phase of cell cycle and fail to progress into the S-phase. Furthermore mRNA and protein studies reveal that Tat and morphine down-regulate Cyclin D1 and several cell cycle regulatory proteins affecting cell cycle progression and proliferation of human neural stem cells. In addition to this, HIV-1 Tat and morphine attenuated SOX-2 transcription factor that culminates into directly affecting proliferation of human neural stem cells. These findings have far reaching clinical implications in understanding comorbidity of drugs of abuse and HIV/AIDS.

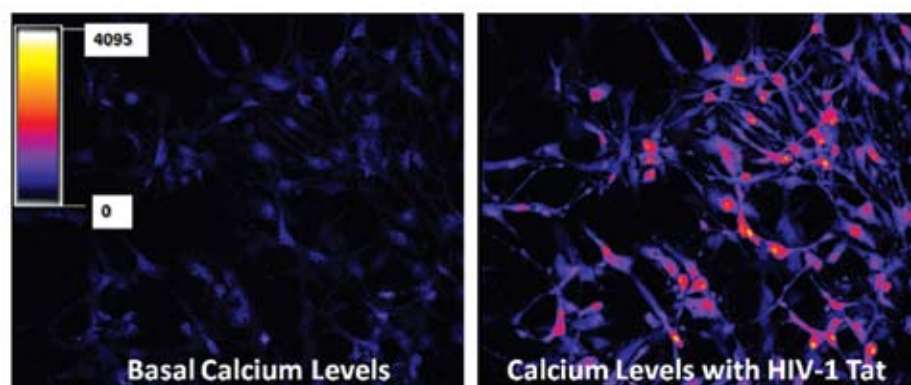


Figure: HIV-1 Tat increases in intracellular calcium levels in human neuron-glia coculture. Human neuron-glia co-cultures were treated with vehicle or HIV-1 Tat protein at 100 ng/ml concentration and calcium imaging was performed using non-ratiometric dye fluo-3 as calcium indicator. Fluorescence imaging of intracellular Ca^{2+} was performed with epifluorescence imaging system (NIKON eclipse) upon exciting cells at 488nm with laser. Images were acquired with a CCD camera from random fields containing 80-100 cells. Initially basal level of fluorescence was recorded and then cells were treated with HIV-1 protein Tat (100 ng/ml). The change in fluorescence intensity of Fluo-3 was used as a measure of increased intracellular calcium and depicted in the figure. Notice a robust increase in the calcium concentration following HIV-1 Tat treatment as most cells fluoresce due to activation of calcium indicator fluo-3. Scale represents intensity of Calcium fluorescence.

Presentations

1. Pankaj Seth (Invited Speaker): Neural Stem Cells - a Tool for Basic Research. At Amity University, Haryana, India, April, 2012.
2. Pankaj Seth, Pretty Garg and Manju Pant Tewari. Role of Neuron Glia Crosstalk in HIV-1 Neuropathogenesis. 11th International Symposium on Neurovirology and 2012 Conference on HIV in the Nervous System. New York, USA, May, 2012.
3. Pankaj Seth (Invited Seminar in Calendar of Events of National Institutes of Health (NIH)): Neuron - Glia interactions during HIV Neuropathogenesis. National Institutes of Health (NIH), Bethesda, USA, May, 2012.
4. Pankaj Seth (Invited Session Speaker): Neural Stem Cells - a window into neurodegenerative diseases. At Rajiv Gandhi Institute of Technology, Amethi, During National Seminar on "Stem Cell an emerging Healthcare Frontier" during August, 2012.
5. Pankaj Seth (Invited Session Speaker and Co-Chair): HIV-1 Induced Neuronal damage: Who is to be blamed? At XXX Annual meeting of Indian academy of neurosciences, Guru Nanak Dev University, Amritsar, India, Oct, 2012.
6. Pankaj Seth (Guest Speaker): Neural Stem Cells – an in vitro model to understand brain disorders. At Seminar Series on Stem Cell Application in health care at Amity University, Haryana, India October, 2012.
7. Pankaj Seth (Invited Resource Person): Are we doing enough to cure HIV/AIDS in India? Seminar on HIV/AIDS and Drug Abuse, Ukul District, Manipur, India, November, 2012.
8. Pankaj Seth, Shaily Malik and Rinki Saha (Invited Speaker and Co-Chairperson): In vitro neural stem cell system - An opportunity to "peep" inside the degenerating human brain? At NeuroCon 2013 meeting at Indian Institute of Chemical Biology, Kolkata, India, January 2013.

9. Pankaj Seth, Manju Tewari, Ankita Srivastava (Invited Lecture and Chairperson): Glia Mediated Neuronal Injury in HIV-1 Neuropathogenesis: "the other side of the coin" At 27th Annual Meeting of Society of Neurochemistry, All India Institute of Medical Sciences, India, February, 2013.

Presentations by Students –

10. Shaily Malik, Rinki Saha and Pankaj Seth. "Modulation of human neural precursor cell proliferation and differentiation by HIV-1 transactivating protein, Tat and drugs of abuse". 18th Annual Scientific Conference of Society on Neuroimmune Pharmacology, Hawaii, USA. April 2012.
11. Manju Tewari. Role of Glial cells in HIV-1 neuropathogenesis. At NeuroCon 2013 meeting at Indian Institute of Chemical Biology, Kolkata, India, January 2013.

Funding

This work is supported by NBRC Core, DBT, Indo-US R21 ICMR and NIH-RO1 funds.

Collaborators

1. S. Sharma, NBRC, India.
2. N. Thapar and A. Singh, Civil Hospital, Gurgaon, India.
3. U. Ranga, JNCSCAR, Bangalore, India.
4. Pardo, Johns Hopkins University, Baltimore, USA.
5. A. Nath, National Institute of Health, Bethesda, USA.
6. S. Buch, University of Nebraska Medical College, Nebraska, USA.

Award

Shaily Malik Integrated-PhD student in Laboratory - IBRO International Travel Grant (January-June 2012) for presenting her work at Society of Neuroimmune Pharmacology (SNIP), Hawaii, USA, April 2012.

INFLAMMATION REGULATED ABERRANT TRANSCRIPTIONAL CIRCUITRIES AND SIGNALING CASCADES IN GLIOBLASTOMA MULTIFORME

Principal Investigator

Ellora Sen

Research Fellows

Deobrat Dixit, Sadashib Ghosh, Ruchi Ghildiyal, Piyushi Gupta, Fahim Ahmad

Post Doctoral Fellow

Dr. Sanchari Sinha, Dr. Arpita Chatterjee

Project Assistant

Nikhil P Anto, Ashwat Nagarajan

Technical Assistant

Shanker Dutt Joshi

Lab Attendant

Rajesh Kumar Kumawat

Glioblastoma multiformes (GBM) represents one of the most malignant brain tumors characterized by intense proliferation and poor prognosis. Gliomas are also characterized by their effective immune escape mechanisms that evade immuno-surveillance. As inflammation is an indispensable participant in tumor progression, the focus of our group is to understand the importance of inflammatory mediators in the transcriptional regulation of genes associated with evasion of immune response, survival and resistance to apoptosis in GBM. The highly resistant nature of GBM to chemotherapy has also prompted us to identify new treatment strategies that target aberrant signaling pathways. Dissecting the role of inflammation in the regulation of aberrant signalling and transcriptional circuitries associated with glioma progression is an active area of research in the lab.

Understanding regulation of genes associated with immune evasion

β -defensin-3 negatively regulates TLR4-HMGB1 axis mediated HLA-G expression in IL-1 β treated glioma cells.

The non-classical HLA class-I antigen HLA-G contributes to immune escape mechanisms in GBM. As we have previously shown that IL-1 β -HIF-1 α axis connects inflammatory and oncogenic pathways in GBM, we investigated the role of IL-1 β induced inflammation in regulating HLA-G expression. IL-1 β increased HLA-G and Toll like receptor 4 (TLR4) expression in a HIF-1 α dependent manner. Inhibition of TLR4 signaling abrogated IL-1 β induced HLA-G. IL-1 β increased the expression of HMGB1- a late mediator of systemic inflammation, and its interaction with

TLR4. Inhibition of HMGB1 inhibited TLR4 and vice versa suggesting the existence of HMGB1-TLR4 axis in glioma cells. Interestingly, HMGB1 inhibition prevented IL-1 β induced HLA-G expression. Human β -defensin-3 (hBD-3) - primarily associated with adaptive and innate immune responses, is elevated in GBM tumors. Importantly, hBD3 prevented IL-1 β induced HLA-G, TLR4, HMGB1 expression and release of pro-inflammatory mediators. Our studies indicate that hBD3 abrogates IL-1 β induced HLA-G expression by negatively affecting key molecules associated with its regulation.

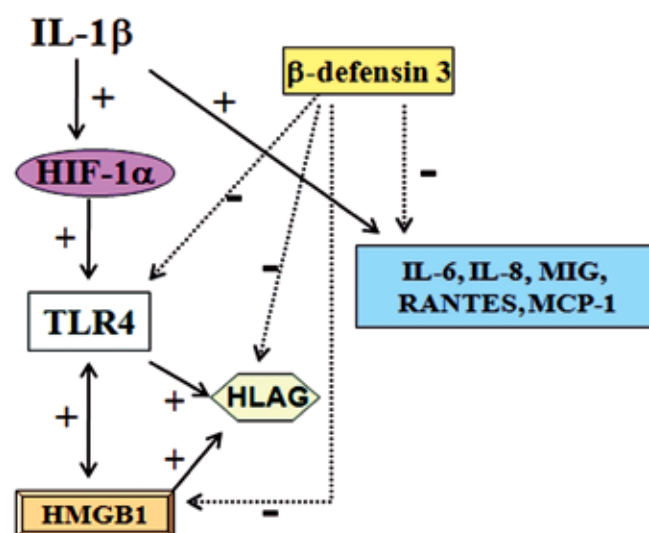


Figure 1. Proposed model indicating hBD3 mediated regulation of HLA-G through a TLR4-HMGB1 axis in IL-1 β treated cells.

2. Understand mechanisms that confer resistance to apoptosis in GBM and identify new treatment strategies that can manipulate the aberrant signaling pathways to induce death.

(i) Targeting JNK-NF κ B axis sensitizes glioma cells to TNF α induced apoptosis

As we have previously reported that certain anti-cancer chemotherapeutics can sensitize glioma cells to TNF α induced apoptosis by abrogating NF κ B activation, we investigated the potential of Oncrasin in sensitizing glioma cells to TNF α induced apoptosis. Oncrasin reduced glioma cell viability, inhibited TNF α mediated NF κ B activation, and sensitized cells to TNF α induced apoptosis. Oncrasin increased JNK phosphorylation and pharmacological inhibition of JNK rescued Oncrasin-induced apoptosis. JNK inhibition prevented Oncrasin induced decrease in TNF α induced NF κ B activity, and inhibition of NF κ B increased JNK phosphorylation in TNF α treated cells. Oncrasin inhibited anchorage independent growth of glioma cells in a JNK dependent manner. By elucidating the existence of JNK-NF κ B cross-talk that regulates resistance to TNF α induced apoptosis, this study has highlighted the importance of JNK in regulating viability of glioma cells.

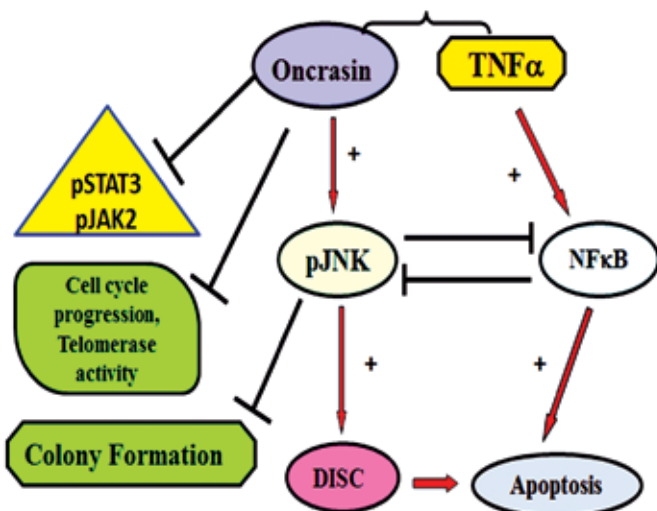


Figure 2. Schematic depicting Oncrasin mediated sensitization of glioma cells to TNF α induced apoptosis through regulation of JNK-NF κ B axis.

(ii) Inhibition of Ras /NF κ B axis sensitizes glioblastoma cells to Shh inhibitor induced apoptosis.

Shh pathway effector Gli1 is overexpressed in gliomas and is induced by both canonical Shh signaling and non-

canonical pathways including NF κ B. Although Shh inhibitor SANT1 alone failed to induce cell death, it sensitized glioma cells to Ras/NF κ B inhibitor Guggulsterone via Caspase 9 activation. While SANT1 decreased Gli1 activity, Guggulsterone inhibited Ras and NF κ B activity. Functional inactivation of Ras/NF κ B axis sensitized glioma cells to SANT1. Guggulsterone induced ERK contributed to Caspase-9 activation. SANT-1 reduced proliferation of glioma stem-like spheres. Since SANT-1 and Guggulsterone differentially targets stem-like and non-stem glioma cells respectively, this combination warrants investigation as an effective anti-glioma therapy.

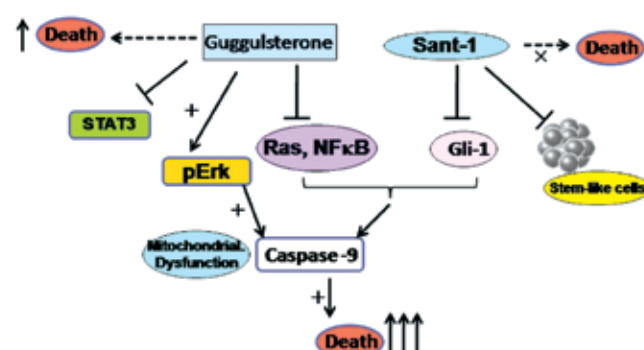


Figure 3. Proposed model demonstrating Guggulsterone mediated sensitization of the glioma cells to Gli-1 inhibitor induced apoptosis.

Publications

- Dixit D, Ghildiyal R, Anto NP, Ghosh S, Sharma V and **Sen E (2013)**. Guggulsterone sensitizes glioblastoma cells to Sonic hedgehog inhibitor SANT-1 induced apoptosis in a Ras /NF κ B dependent manner. **Cancer Letters**.
- Gupta P, Ghosh S, Nagarajan A, Mehta VS, **Sen E (2013)**. β -defensin-3 negatively regulates TLR4-HMGB1 axis mediated HLA-G expression in IL-1 β treated glioma cells. **Cellular Signaling**. 7;25(3):682-689.
- Gupta P, Dixit D and **Sen E (2013)**. Oncrasin targets the JNK-NF κ B axis to sensitize glioma cells to TNF α induced apoptosis. **Carcinogenesis** 34(2): 388-396.
- Ghildiyal R, Dixit D, **Sen E. (2012)**. EGFR inhibitor BIBU induces apoptosis and defective autophagy in glioma cells. **Molecular Carcinogenesis**.
- Tewari R, Choudhury SR, Mehta VS, **Sen E. (2012)** TNF α regulates the localization of CD40 in lipid rafts of glioma cells. **Mol Biol Rep**;39 (9):8695-9.

Patents

- Granted European patent: European Pat. 2.367 784 B1–

"Bicyclic triterpenoid Iripallidal as a novel anti-glioma and anti-neoplastic therapy in vitro". Patent granted on 02.01.2013, International publication number (WO 2010/073258).

Presentations

International

- I. Ellora Sen. Inflammation mediated oxidative stress in cancer. 4th International Congress on Cell Membrane and Oxidative Stress, Suleyman Demirel University, Isparta, Turkey. June 2012. Invited lecture and Session Chair

National

1. Ellora Sen. HLA gene regulation in glioma: Role of Inflammation. Indian Association of Cancer Research, New Delhi, February, 2013.
2. Deobrat Dixit. Guggulsterone sensitizes glioblastoma cells to Sonic hedgehog inhibitor SANT-1 induced apoptosis. Emerging Trends and Challenges in Basic and Translational Research in Biochemistry, Department of Zoology, Banaras Hindu University, Varanasi, February 2013
3. Ellora Sen. TNF α regulates resistance to apoptosis in glioblastomas. 3rd International Cancer Research Symposium, Kolkata, December 2012.
4. Ellora Sen. Inflammation and resistance to apoptosis in gliomas: The rehabilitation of thoughts. Carcinogenesis, New Delhi, November 2012.
5. Deobrat Dixit. Inhibition of G9a in glioma cells inhibits hypoxia signalling and induces cell death through apoptosis and autophagy. Carcinogenesis, New Delhi, November 2012.
6. Fahim Ahmad. Identification of signalling circuitries regulating telomerase activity in glioma. Carcinogenesis, New Delhi, November 2012.

New Delhi, November 2012.

7. Piyushi Gupta. β -defensin-3 negatively regulates TLR4-HMGB1 axis mediated HLA-G expression in IL-1 α treated glioma cells. Carcinogenesis, New Delhi, November 2012.
8. Sadashib Ghosh and Ellora Sen. TNF α induced HIF-1 α - β catenin axis regulates MHC class I gene activation. Carcinogenesis, New Delhi, November 2012.
9. Ghildiyal R. Inhibition of EGF Receptor by BIBU induces apoptosis and defective autophagy in glioma cells. Carcinogenesis, New Delhi, November 2012.
10. Deobrat Dixit. Inhibition of Ras /NF κ B axis sensitizes glioblastoma cells to Shh inhibitor induced apoptosis. Indian Academy of Neuroscience, Amritsar, October 2012
11. Ellora Sen. Hypoxia-Inflammation nexus: A potential anti-glioma target? Indian Society of Neuro-Oncology (ISNOCON), NIMHANS, Bangalore, April, 2012.

Funding

1. Understanding signaling circuitries involved in transcriptional regulation of genes associated with survival and immune response in an inflammatory environment: Implications in glioblastoma progression. Funded by Department of Biotechnology, Govt. of India. BT/PR12924/MED/30/235/2009

Collaborator

Dr. VS Mehta, Paras Hospital

Awards

1. Shakuntala Amir Chand Award, 2009, Indian Council of Medical Research (ICMR), awarded 2013
2. Elected member of Guha Research Conference (GRC), 2012

MOLECULAR CHANGES RELEVANT TO SYNAPTIC PLASTICITY AND MEMORY FORMATION

Principal Investigator

Shiv K Sharma

Research Fellows

Chinmoyee Maharana, Shilpa Mishra,
Kaushik Sharma, Kiran Pandey, Kautuk
Kamboj, Apurva Agrawal

Project Assistants

Bandhan Mukherjee, Neha Sharma,
Rashmi Ray

Lab Attendant

Narayan

Activity-dependent molecular and synaptic changes are known to play crucial roles in memory formation. However, the detailed processes involved in these changes are not clearly understood. We are examining activity-dependent molecular changes with a focus on the underlying signaling mechanisms.

Activity-Dependent Alpha Tubulin Acetylation

In our previous study, we showed that treatment of hippocampal slices with KCl increases alpha tubulin acetylation. KCl treatment of neuronal cells produces molecular changes that are important for plasticity and memory formation. More importantly, KCl induces long-term potentiation (LTP), which is considered a cellular mechanism of memory formation. These and related

observations make KCl a good stimulus to study molecular processes relevant for synaptic plasticity and memory. Calcium influx through NMDA receptors is critical for the development of LTP. We found that stimulation of NMDA receptors also results in enhanced alpha tubulin acetylation. We extended this study and examined the molecular mechanisms that regulate activity-dependent alpha tubulin acetylation in the hippocampus. Our results show that blocking the activity of a serine/threonine kinase using pharmacological inhibitors blocks KCl-induced alpha tubulin acetylation, suggesting a critical role of a kinase in the regulation of this molecular event. Further, we found that the kinase activity is also required for the NMDA receptor-mediated increase in alpha tubulin acetylation. Thus, a particular kinase is critical for activity-dependent acetylation of alpha tubulin in the hippocampus.

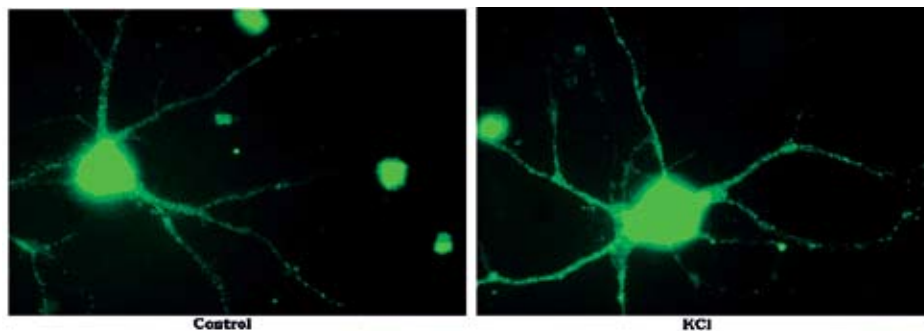


Figure KCl increases surface glutamate receptor levels. Primary hippocampal neurons were untreated (control) or treated with KCl (KCl). Surface glutamate receptors were labeled with specific antibody and detected using secondary antibody linked to a dye.

Since the level of acetylation of a protein is controlled by the relative activities of acetylase and deacetylase enzymes, we next asked whether activity-mimicking stimulus regulates deacetylase activity. We found that KCl treatment reduces the activity of a deacetylase in the hippocampus. Furthermore, KCl-induced reduction in deacetylase activity requires the activity of the particular serine/threonine kinase. Collectively, these results show that KCl activates a kinase, which in turn inhibits the activity of a specific deacetylase leading to increased acetylation of alpha tubulin in the hippocampus.

It is well known that glutamate receptors play crucial roles in LTP and memory. We are examining the mechanisms involved in glutamate receptor trafficking. Our results suggest that KCl enhances glutamate receptor expression on the membrane surface (Fig 1). We are now examining the processes involved in enhanced expression of glutamate receptors on the membrane.

Mechanisms of cAMP-Induced Activation of Extracellular Signal Regulated Kinase

In our previous study, we showed that KCl treatment of hippocampal slices induces sustained activation of extracellular signal-regulated kinase (ERK). We also investigated the mechanisms involved in keeping ERK activated long after the stimulus has been withdrawn. We are now examining whether other agents having important roles in synaptic plasticity and memory induce sustained ERK activation. Our results show that increasing the cAMP level induces sustained ERK activation in the hippocampal slices. We are examining the mechanisms

downstream of cAMP that help in sustained ERK activation. We find that blocking the translational and transcriptional events differentially affect cAMP-induced immediate and sustained ERK activation. Given the significance of cAMP signaling pathway in LTP and memory formation, our results indicate that cAMP-induced sustained ERK activation may play important roles in these processes.

Publications

1. Maharana C, Sharma KP, Sharma SK (2013) Feedback mechanism in depolarization-induced sustained activation of extracellular signal-regulated kinase in the hippocampus. *Sci Rep.* 3:1103.

Presentations

- 1 S.K. Sharma and C. Maharana. Mechanisms of pattern-dependent activation of extracellular signal-regulated kinase in the hippocampus. Society for Neuroscience meeting, Oct. 13-17, 2012, New Orleans, USA.
- 2 Kiran Pandey and Shiv K. Sharma. HDAC inhibition facilitates surface recruitment of AMPA receptors in the hippocampus. XXX Annual Meeting of Indian Academy of Neurosciences, 27-30 October, 2012, Guru Nanak Dev University, Amritsar.

Funding

This work is supported by NBRC Core.

Degree awarded (Ph.D.)

Chinmoyee Maharana

MOLECULAR APPROACHES TO UNDERSTAND THE PATHOPHYSIOLOGY AND PHARMACOLOGY OF INFECTION AND INFLAMMATORY DISORDERS OF CENTRAL NERVOUS SYSTEM

Principal Investigator
Anirban Basu

Research Fellow

Deepak Kumar Kaushik, Arshed Nazmi, Iqbal
Mohamed Ariff, Sourish Ghosh

Research Associate

Dr Nabonita Sengupta, Dr Menka Chanu
Thonujam

Project Assistant

Dwaipayan Adhya, Kiran Kundu, Sriparna
Mukherjee

Technical Assistant

Kanhaiya Lal Kumawat

Lab Attendant

Manish Dogra

Immune responses in the central nervous system (CNS) are very common, despite its perception as a site of immune privilege. These responses can be mediated by resident microglia (brain macrophages), which are innate immune cells without direct counterparts in the periphery. While peripheral immune access to the CNS is restricted and tightly regulated, the CNS is capable of dynamic immune responses to a variety of insults. Infections, trauma, stroke, toxins and other stimuli are capable of producing an immediate and short lived activation of the innate immune system within the CNS. This acute neuroimmune or neuroinflammatory response includes activation of the resident immune cells (microglia) resulting in a phagocytic phenotype and the release of inflammatory mediators such as cytokines, chemokines, and other inflammatory mediators. The sustained release of inflammatory mediators works to perpetuate the inflammatory cycle, activating additional microglia, promoting their proliferation, and resulting in further release of inflammatory factors, and help in recruiting leukocytes from the periphery. Neurodegenerative CNS disorders, including multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), tauopathies, and age-related macular degeneration (ARMD), are associated with chronic neuroinflammation and elevated levels of several cytokines. The recognition of microglia as the brain's intrinsic immune system, and the understanding that chronic activation of this system leads to pathologic sequelae, has led to the modern concept of neuroinflammation.

Our research question evolves around the understanding the molecular basis of host-pathogen interaction in viral infection of the brain and the signaling events associated with neuro-inflammation. In last few years our research have been primarily focused on neuropathology of host pathogen interaction in Japanese encephalitis Virus (JEV), causative agent of most common Viral encephalitis in Asia-Pacific region. The impact of emerging and reemerging viral induced encephalitis is being felt globally. In India, although many encephalitis outbreaks have been associated with JEV several outbreaks have remained undiagnosed. The association of Chandipura virus with the recent outbreak of acute encephalitis in Andhra Pradesh implicates that this virus should be considered as an emerging pathogen of substantial public health importance. As a new initiative we have started a project to understand the host-pathogen interaction in Chandipura Virus infection.

Japanese encephalitis virus (JEV) predominantly infects neurons and causes damage to the central nervous system (CNS). Neural stem/progenitor cells (NSPCs) constitute multi-potent stem cell population in postnatal/adult brain, with capacity to differentiate into neurons, astrocytes or oligodendrocytes. NSPCs are known to play a pivotal role in CNS repair mechanisms during various neurological disorders. Previous studies from our laboratory have shown that JEV infection of NSPCs depletes the stem-cell pool, which may result in impaired repair functions leading to motor and cognitive deficits in survivors. In the present study, we evaluated the effect of JEV infection on

differentiation potential of NSPCs isolated from BALB/c mouse pups (Post natal day 7). Results clearly indicated that, JEV infection was more robust in undifferentiated NSPCs as compared to differentiated ones. Further, JEV infected NSPCs showed hampered differentiation and arrested migration in adherent neurosphere cultures. Interestingly, the neuronal differentiation appeared to be more severely affected by JEV as compared to astrocyte differentiation. The transcription factors involved in both neuronal and astrocyte differentiations were significantly decreased upon JEV infection. Overall, results presented in this study comprehensively provide first evidence for JEV induced alteration of neuronal and astrocyte differentiation (Figure 1 and 2)

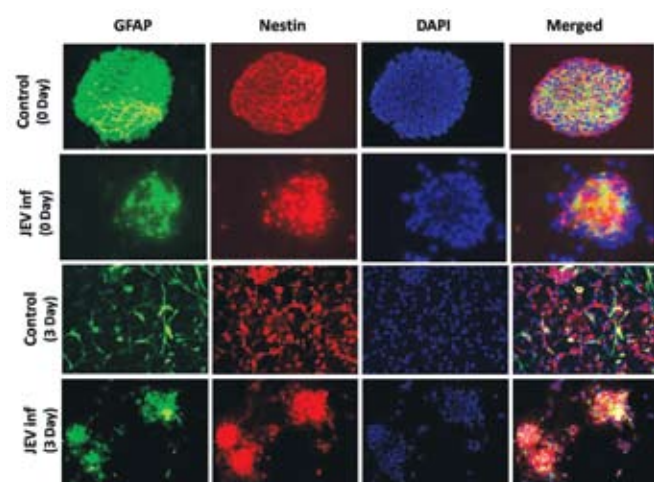


Figure 1 Effect of JEV infection on expression of GFAP and nestin in undifferentiated (Day 0) and, differentiated (day 3) neurosphere. Undifferentiated (Day 0) and differentiated neurospheres (day 3) were stained for astrocyte marker GFAP (FITC, green) and NSPC marker nestin (Alexa 594, red) along with DAPI (blue).

JEV is a common cause of encephalitis in humans. But, humans are dead-end hosts producing negligible viremia. The virus reaches the brain and causes massive inflammation. We have tried to understand the virus-host interaction using the murine monocyte/macrophage cells, an antigen presenting cell involved in eliciting an innate immune response. We have found several interesting phenomena occurring in JEV-infected macrophage cells which diverge from established observations. JEV remains inside macrophages and appears to have little negative effect on viability. Expression studies of major histocompatibility complexes (MHC) and co-stimulatory molecules show inhibition of antigen presentation. There is

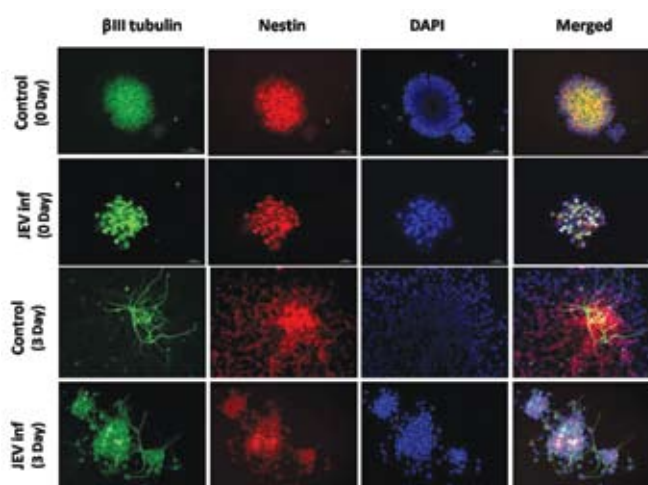


Figure 2 Effect of JEV infection on expression of β -III tubulin and nestin in undifferentiated (Day 0) and, differentiated (day 3) neurosphere. Undifferentiated and differentiated neurospheres were stained for newly generated neuronal marker β -III tubulin (FITC, green) and NSPC marker nestin (Alexa 594, red).

enhanced immune suppression creating an anti-viral milieu. Expression of pro-inflammatory cytokines and chemokines is suppressed along with increased expression of anti-inflammatory molecules. Histone deacetylases (HDACs) have known inflammatory properties. The significance of the HDACs can be assumed from the predictome map (Figure 3) that shows the possible protein-protein interactions between the four HDACs that are currently under investigation with other proteins, both in humans and in mouse, the model of our investigation. This map has been based on a database of predicted functional associations among proteins in many different organisms with the help of the VisANT Project, a web-based data exploration tool. We have shown, through modulation of HDACs JEV seems to play a crucial anti-inflammatory and anti-viral role in host macrophages. HDAC3 expression is down-regulated on JEV-infection of macrophages which also corresponds with the inhibition of NF κ B activity. This clearly demonstrates that in macrophages, JEV promotes a negative regulation of inflammatory responses through the inhibition of HDACs.

Besides studying fundamental aspects of JE neuropathology we are always keen to do translational research to develop newer generation of therapy for JE. Recently in collaboration with Dr Guruprasad R. Medigeshi from Vaccine and Infectious Diseases Research Centre, Translational Health Science Technology Institute (THSTI), Gurgaon we have

showed that Bispidine-Amino Acid conjugates act as a novel scaffold for the design of antivirals that block JEV replication. We have demonstrated that the amino-acid conjugates of 3,7 diazabicyclo[3.3.1]nonane can serve as a molecular scaffold for development of potent antivirals against encephalitic viruses. Our findings will provide a novel platform to develop effective inhibitors of JEV and perhaps other RNA viruses causing encephalitis.

Based upon our previous findings a Phase III clinical trial in JE patients has started at Department of Pediatrics, CSM Medical University (King George Medical College), Lucknow. Prof. Rashmi Kumar, Head of the Department of Pediatrics is supervising this trial. This trial has been registered to Clinical Trial Registry of India. Unimark Remedies Ltd a

Mumbai based pharmaceutical company is manufacturing the PFOS (Powder for oral Solution) formulation of the Minocycline and placebo for this trial. NBRC has been appointed CliniRx, a CRO to monitor the trial. As of today's date out of 332 adults screened 97 has been enrolled and 577 children screened 177 has been enrolled for this trial. Simultaneously follow up study is going on with the patients who have left the hospital after the administration of drug or placebo.

Alongside with biology of JE, our laboratory is also deeply engaged in basic research to understand the transcriptional regulation of microglial activation. Microglia are the resident macrophages of the Central Nervous System (CNS), which secrete several pro- and anti-inflammatory cyto-chemokines in response to pathogenic stimuli. One key player that is believed to drive this neuroinflammatory process is interleukin (IL)-1 β , a pro-inflammatory cytokine that is up-regulated in Alzheimer's disease (AD), Parkinson's disease, multiple sclerosis, and other neurodegenerative disorders. Once secreted, IL-1 β binds to IL-1 receptor present on microglia and initiates the production of inflammatory cytokines in microglia. However, the detailed information regarding the molecular mechanisms of IL-1 β triggered inflammatory pathways in microglia is lacking. We have focused our study on the role of Krüppel-like factor 4 (Klf4) in mediating the regulation of pro-inflammatory gene expression upon IL-1 β stimulation in microglia. We have demonstrated that stimulation of microglia with IL-1 β robustly induces Klf4 via PI3K/Akt pathway which positively regulates the production of endogenous IL-1 β as well as other pro-inflammatory markers, cyclooxygenase-2 (Cox-2), monocyte chemoattractant protein-1 (MCP-1) and interleukin-6 (IL-6). In addition, we have reported that Klf4 negatively regulates the expression of iNOS, thereby playing a key role in regulating the immunomodulatory activities of microglia. Our findings strongly suggest that Klf4 is one of the key players of inflammation and therefore is one of the key targets of therapeutic intervention in neurodegenerative diseases which has distinct pathology of inflammation.

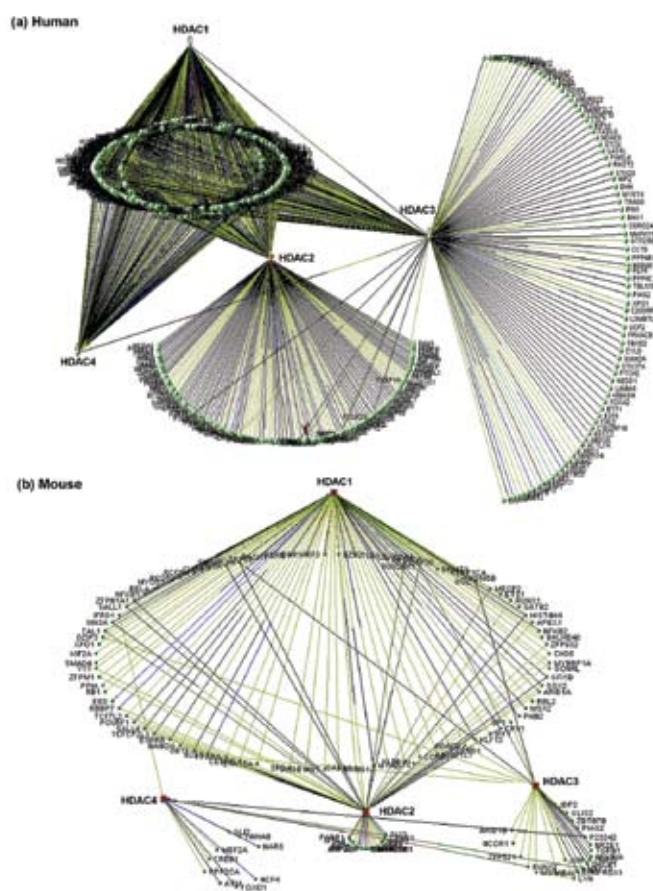


Figure 3 A predictome of interactions between HDAC1, 2, 3 and 4 with other proteins, both in human and in mice. Given the complex and varied array of proteins with which these HDACs can interact, a multitude of pathways and processes could be affected by the suppression of these enzymes by JEV.

Publications

1. I M Ariff, M C Thounajam, S Das, and **A Basu (2013)** Japanese Encephalitis virus infection alters both neuronal and astrocytic differentiation of Neural Stem/progenitor Cells. **J Neuroimmuno Pharmacology** (in press)
2. V Haridas, K S Rajgokul, S Sadanandan, T Agrawal, V Sharvani, M V S Gopalkrishna, M B Bijesh, K L Kumawat, **A Basu**, G R Medigeshi **(2013)** Bispidine-

amino acid conjugates act as a novel scaffold for the design of antivirals that block Japanese encephalitis virus replication. **PLoS Neglected Tropical Diseases** 7(1): e2005

3. A Majhi, A Mahanti, K Kundu, K Dutta, **A Basu**, and B Bishayi (2013) Increased resistance of immobilized-stressed mice to infection: correlation with behavioral alterations. **Brain, Behaviour, and Immunity** 28:115-27

Review

1. M C Thounajam, D K Kaushik, and **A Basu** (2013) MicroRNAs in the Brain: It's regulatory role in Neuroinflammation. **Molecular Neurobiology** 47:1034-1044
2. D K Kaushik, and **A Basu** (2013) A friend in need may not be a friend indeed: role of microglia in neurodegenerative diseases. **CNS & Neurological Disorders-Drug Targets** (in press)
3. N Sengupta, and **A Basu** (2013) Japanese Encephalitis Virus Infection: Effect on brain development and repair. **Current Science** (in press).

Book Chapter

K Dutta, A. Nazmi and A Basu (2013) Japanese encephalitis virus and human CNS infection. In *Neuroviral Infections*, ed S.K. Singh, D. Ruzek, CRC Pr 1 LLC. [ISBN-10: 1439868522]

Presentation

- 1) A Basu (2013) The transcriptional regulation of microglial function: the tightrope walk of CNS innate immune response. Society for Neurochemistry Meeting 2013, AIIMS, New Delhi, 21-23rd February. (Invited speaker)
- 2) A Basu (2013) Host pathogen interaction in Japanese Encephalitis Virus infection: from bench to bedside. South Asian University, New Delhi, 8th February, 2013. (Invited speaker)
- 3) A Basu (2013) An introduction to Psychoneuroimmunology Preconference workshop (Neurocon 2013), IPGIMER, Kolkata, 17th January, 2013. (Invited speaker)
- 4) A Basu (2013) Neuronal Innate Immune Response in Japanese Encephalitis Virus infection. 3rd Molecular Virology Forum meeting, National Institute of Virology, Pune, 10-11th January 2013. (Invited speaker)
- 5) A Basu (2012) Krüppel Like Factor 4 in neuro-

inflammation: a new therapeutic target? BioWorld 2012, Kusuma School of Biological Sciences, Indian Institute of Technology Delhi, New Delhi, 10th-12th December, 2012. (Invited speaker)

- 6) D K Kaushik, M C Thounajam, and A Basu (2012) Kruppel Like Factor 4 regulates microglial activation in response to Interleukin-1 β . XXX Annual Meeting of Indian Academy of Neurosciences, 27th-30th October, 2012, Amritsar.
- 7) A Nazmi, I A Mohammed, K Dutta, K Kundu, and A Basu (2012) Neural Stem/Progenitor Cells induces conversion of encephalitogenic T-cells into CD4⁺-CD25⁺ FOXP3⁺ Regulatory T-cells. XXX Annual Meeting of Indian Academy of Neurosciences, 27th-30th October, 2012, Amritsar
- 8) A Nazmi, K Dutta, K Kundu, and A Basu (2012) TLR7 regulates expression of suppressor of cytokine signaling (SOCS) in CNS post Japanese Encephalitis Virus infection. XXX Annual Meeting of Indian Academy of Neurosciences, 27th-30th October, 2012, Amritsar
- 9) A Basu (2012) Basic and Translational Studies at the Host-Pathogen Interface. UGC refresher courses for college and university faculty members, Center for Biotechnology, JNU, 20th July, 2012
- 10) A Basu (2012) Therapeutic targeting of Krüppel like factor 4 abrogates inflammation and oxidative stress in brain. 4th International Congress on Cell Membrane and Oxidative stress. 26th-29th June. Suleyman Demirel University, Isparta, Turkey. (Invited speaker)
- 11) A Basu (2012) Antiviral and Neuroprotective Role of Octaguanidinium Dendrimer-Conjugated Morpholino Oligomers in Japanese Encephalitis. 9th International Symposium on Polymer Therapeutics: From Laboratory to clinical practice 28th -30th May, 2012, Valencia, Spain. (Invited speaker)

Funding

- 1) Host -Directed Drug Targeting: Implication of Suppressors of cytokine signaling (SOCS) in the pathogenesis of Japanese Encephalitis [Funded by Department of Biotechnology (awarded along with the National Bio Science Award for Career Development)]
- 2) To study the role of Neuronal innate immune response in Japanese encephalitis virus infection [Funded by CSIR (27(0238)/10/EMR-II)]
- 3) To elucidate the role of inflammasome and other

molecular events leading to Hypoxia induced neuro inflammation [Funded by Life science Research Board, DRDO (No LSRB-213/EPB/2010)]

Collaborations

"Innate Immune responses in flaviviruses" with Dr Guruprasad Medighesi, VIDRC, THSTI, Gurgaon.

Award

F1000 Faculty Member of the Year Award' for the Faculty of Neurological Disorders-2012*

*The awards recognize Faculty Members who have made the most significant contribution to the F1000 service over the past year, as judged by their editorial team.

NEUROSPHERE CULTURES ARE USEFUL TOOLS TO MODEL ALZHEIMER'S DISEASE IN VITRO

Principal Investigator

Ranjit Kumar Giri

Research Fellow

Pankaj S. Ghate

Technical Assistant

Rajiv Kumar Mishra

Lab. Attendant

Lalit Bidla

Alzheimer's disease (AD) is a progressive and irreversible neurodegenerative disease of elderly people. It is the most common cause of dementia worldwide. Genetic linkage studies of early onset familial Alzheimer's disease (FAD) had identified amyloid precursor protein (APP), Presenilin 1 (PSEN1) and Presenilin 2 (PSEN2) as three causative genes. Mutations in these genes increase the production and aggregation of more fibrillogenic beta amyloid peptides, the hallmark pathology of Alzheimer's disease. Very little is known about the role of beta amyloid peptides toward neurotoxicity. In order to study the mechanisms in AD associated neurodegeneration in humans, transgenic animals expressing human FAD genes were developed. Though these transgenic mice show beta amyloid deposits, astrogliosis, impaired learning abilities and mild cognitive impairments, the role of beta amyloid peptides towards neurotoxicity remained puzzled. Moreover, the effect of beta amyloid on various mature brain cells is also not known. Therefore, an alternative model that retains the capacity to generate major cell types of adult brain and generates human beta amyloid peptides endogenously is warranted.

Earlier reports have demonstrated the presence of neural stem cells in adult and embryonic brain of animals and humans. These CNS stem cells can differentiate towards major cell types of an adult brain except microglia in vitro and in vivo. It is not clear why these cells fail to replenish the neuronal cell loss seen in AD, especially in hippocampus where CNS stem cells are enriched. Thus, we hypothesize that beta amyloid peptides might be affecting the normal functioning of CNS stem cells. So, to recapitulate most of the pathological features of AD, such as, endogenous

beta amyloid production and to study its effect on major cell types of an adult brain, my lab is working towards developing an alternative in vitro model employing CNS stem cells. Since, beta amyloid peptide is the central and key molecule in the development of AD, endogenous production and multimerization of human beta amyloid peptides are warranted in developing AD model in vitro.

My lab has developed 4 separate neurosphere lines. Two of these were positive for huAPPswe and huPS1ΔE9 gene (Tg +ve) and two are negative (Tg -ve) which served as wild type controls. Our results demonstrated that, Tg +ve lines express huAPPswe and huPS1ΔE9 transgenes at mRNA level (by RT-PCR) which are not present in Tg -ve neurosphere lines.

Western blot analysis of neurosphere lysates and immunofluorocytochemistry (IFCC) analysis indicated the expression of human APP protein and its fragments only in Tg +ve neurosphere lines but not in transgenic negative lines. Presence of beta amyloid peptides in neurosphere lysates was minimal in transgenic positive neurosphere lysates. However, western blot analysis of human beta amyloid peptides from culture supernatants of both Tg -ve and Tg +ve neurosphere cultures demonstrated the presence of human beta amyloid peptides in all Tg +ve neurosphere lines but not at all in Tg -ve lines. These beta amyloid peptides are seen both as monomers and oligomers. Moreover, resolution of beta amyloid peptides in Tris-Bicine Urea gel followed by western blot analysis clearly demonstrated the presence of human beta amyloid 40 and beta amyloid 42 peptides in Tg +ve (NS1 and NS3) but not in Tg -ve NS lines. Furthermore, beta amyloid 42 to

beta amyloid 40 ratio is higher in the present model than any other in vitro model of AD.

Intracellular beta amyloid load is another pathological feature of various cells in AD brain. Immunofluorescent staining of adherent cells from neurosphere cultures demonstrated Tg +ve neurosphere lines have significant increased immunosignal towards 6E10 antibody than Tg -ve neurosphere lines without epitope retrieval. Upon epitope retrieval, Tg +ve cells showed significant increased immunosignal over non-epitope retrieval counterparts, whereas Tg -ve cells showed little increased signal than non-epitope retrieval cells. Increased immunosignal in Tg+ve neurosphere cultures might be due to the presence of beta amyloid peptides in beta-sheet isoforms or in oligomeric form that required epitope retrieval prior to its interaction with 6E10 antibody. Taken together, the results strongly indicate the expression, protein misfolding

and accumulation of human beta amyloid peptides in Tg +ve neurosphere cultures in parallel with transgenic mice brain. Collectively, it indicates the genesis of a newer in vitro model for AD that has the potential to address other pathological effect of beta amyloid peptides on various adult brain cells like neurons, astrocytes, oligodendrocytes and CNS stem cells.

Presentation

1. Ranjit K. Giri. Utilization of Neurosphere Culture in the Development of a Novel in vitro model of Alzheimer's Disease, McLaughlin Research Institute, Great Falls, Montana, USA, 2012.

Funding

This work is supported by Ramalingaswami Fellowship from DBT (102/IFD/SAN/758/2007-08) and NBRC core fund to PI.

CURCUMIN INDUCES APOPTOSIS THROUGH INTRINSIC APOPTOTIC PATHWAY IN MOUSE NEURO 2A NEUROBLASTOMA CELLS

Principal Investigator

Ranjit Kumar Giri

Research Fellow

Himakshi Sidhar

Lab Attendant

Lalit Bidla

Neuroblastoma is the tumor of sympathetic nervous system. It develops from uncommitted neural crest cells. It accounts for 8-10% of childhood cancers. These tumors can either spontaneously regress in stage I and II or exhibit resistance to current cancer therapy in stage III and IV patients. In addition, side effects of current chemotherapy or radiotherapy are major area of concern. Therefore, alternative and safer therapy for neuroblastoma is warranted.

Dietary phytochemicals with anti-cancer properties might serve as a superior alternative. These small molecules are non-toxic and might have an enduring effect on human health. Curcumin is the main active component of a common Indian spice, turmeric (*Curcuma longa*). Turmeric is used as traditional medicine in Indian ayurveda because of its anti-oxidant and anti-inflammatory properties. Moreover, curcumin preferably induces apoptosis in highly proliferating cancer cells but not in normal cells. Cytotoxic effect of curcumin has been addressed on various cancer cell lines including cervical, ovarian cancers etc. Curcumin mediates apoptosis through both caspase-dependent and -independent pathways. Literature survey strongly suggests that curcumin has a wide range of molecular targets and activates/upregulates pro-apoptotic genes like p53, JNK, Akt, Rb and many more. It also downregulates oncogenes and anti-apoptotic genes like c-Myc, Ras, MAPKs, PI3K,

CDKs, etc. However, very little is known about the effect of curcumin on neuroblastoma cells. To understand the molecular mechanisms underlying curcumin mediated neuro 2a cell death, we first established cytotoxicity of curcumin on neuro 2a cells. Our results from LIVE-DEAD, MTT assay demonstrated the toxic effect of curcumin on neuro 2a cells (Figure 1). DNA fragmentation and TUNEL positive cells were significantly higher in curcumin treated neuro 2a cells which suggest the possible activation of apoptotic pathways (Figure 2). Our results also showed increased activation of caspase-9 and caspase-3 in curcumin treated neuro 2a cells. However, caspase-8, a molecular marker for the activation of extrinsic apoptotic pathways was not activated in curcumin treated neuro 2a cells (data not shown). Thus, curcumin kills neuro 2a neuroblastoma cells by employing intrinsic apoptotic pathway.

List of genes related to apoptosis are growing. Expression of some of these genes is associated with sensitizing the cancer cells to currently used cancer drugs. Curcumin may activate those genes as well. To study these, our future goals are,

- 1) The effect of curcumin on the induction of newer pro-apoptotic genes in neuro 2a cells.
- 2) The molecular mechanism underlying curcumin-mediated induction of these genes in neuro 2a cells.

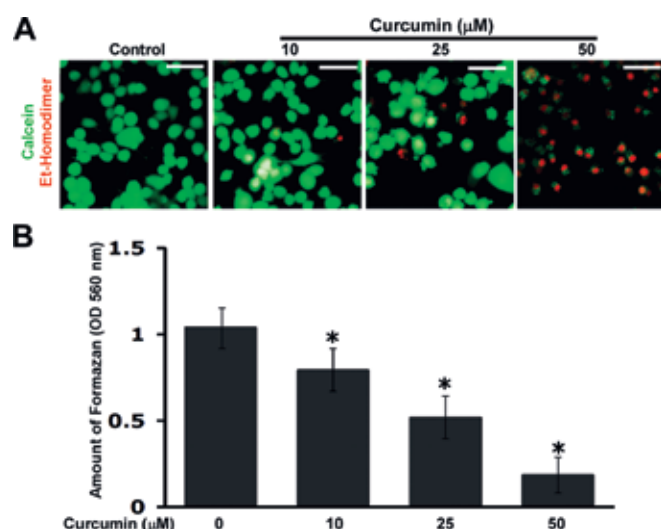


Figure 01 Curcumin activates cell death in mouse neuro 2a neuroblastoma cells. Neuro 2a cells were treated with 10, 25, 50 μM curcumin or with equal amount of DMSO (control) for 24 hrs. A) LIVE DEAD assays were performed. Fluorescent images were captured from three random fields employing similar image acquisition settings. Live (green) and dead (red) cells were counted. Results strongly indicate that, curcumin causes neuro 2a cell death in a dose dependent manner. B) MTT assays on curcumin treated neuro 2a cells were performed. Amount of formazan was measured by absorbance at 560 nm with a reference wavelength at 620 nm. Our results indicate the curcumin-mediated neuro 2a cell death is dose dependent. Data represents mean $\pm$ standard deviation of at least three independent experiments (* $p < 0.001$).

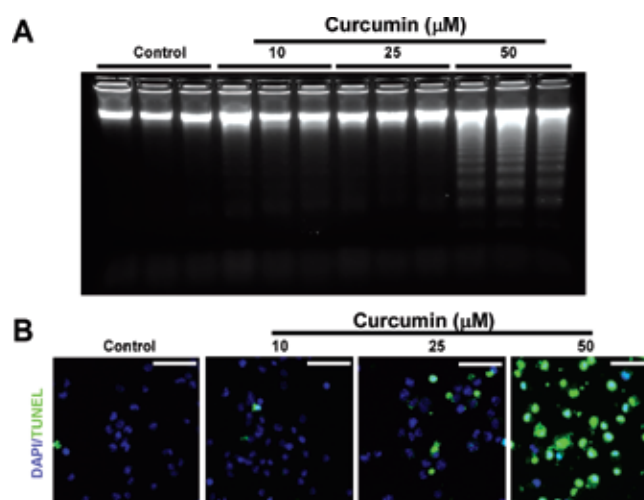


Figure 02 Curcumin-mediated cell death is associated with apoptotic pathways. Neuro 2a cells were treated with 10, 25, 50 μM curcumin or with equal amount of DMSO (control) for 24 hrs. A) Agarose gel electrophoresis of genomic DNA isolated from control and curcumin treated neuro 2a cells were performed. Results indicate, curcumin induces genomic DNA fragmentation in a dose dependent manner. B) TUNEL assays were also performed in curcumin treated or untreated cells. DAPI (blue) and TUNEL labeled (green) cells were imaged from three random fields with same image acquisition settings. The increase in number of TUNEL positive cells in curcumin treated cells than corresponding controls indicate that curcumin induces cell death by activating apoptotic pathways.

Funding

This work is funded by NBRC Core and partially by Ramalingaswami fellowship (w2/IFD/SAN/758/2007-08) and a grant from DBT (No BT/PR10721/Med/30/ 105/2008) to PI.

NON-CODING RNA – MEDIATED REGULATORY MECHANISMS INVOLVED IN DEVELOPMENT AND FUNCTION OF NEURONAL CONNECTIVITY

Principal Investigator

Sourav Banerjee

Research Fellows

Pushpa Kumari, Mandrita Barua

Project Assistant

Sarbani Samaddar, Prajwal Thakre

Technical Assistant

D. Narendar, Musadiq Hussain

All brain functions ranging from simple reflexes to complex behaviors are regulated by vast neuronal network. The communication gateway of neuronal connectivity, known as synapse, is established during development and in adult brain with spatio-temporal precision. Synapses are dynamic and modification of synaptic connections (or synaptic plasticity) occurs in an experience dependent manner. Thus, identifying the processes that regulate synaptic development and function will be essential to understand how synapses are formed and how they modulate function of neuronal networks.

Among various regulators that modulate neuronal development and plasticity, much interest is currently focused on post-transcriptional control by non-coding RNAs. Of particular interest is long non-coding RNAs or linc RNAs (>200 nucleotide long transcript that does not encode proteins) that were initially thought to be spurious transcriptional noise. However, emerging reports suggest that expressions of such lincRNAs are spatio-temporally regulated during development and also in adult animal. LincRNAs are expressed ubiquitously and also exhibit cell type specific expression pattern in various neuroanatomical region. More recently, lincRNAs have emerged as a key gene regulatory switch that can modulate gene expression system through various transcriptional, post-transcriptional and translational controls. Taken together, these observations raise the possibility that lincRNAs may be involved in development of precise neuronal circuitry.

To address the role of lincRNAs in development and function of neuronal connectivity, we are screening a list of lincRNAs; those that are differentially regulated during

activity dependent control of synapse formation. To assess the differential expression of lincRNAs upon synaptic activation, neurons from mouse brain in primary culture was stimulated by membrane depolarization and then the expression pattern of these non-coding transcripts were assessed by quantitative real time PCR method. To our surprise, we observed that two novel lincRNAs have been differentially expressed in response to neuronal activation. This poses some interesting questions: Are these lincRNAs critical for synapse formation? If so, what type of synapse (excitatory or inhibitory) development is modulated by these lincRNAs? What are the molecular mechanisms of activity dependent synapse development –mediated by lincRNAs? Which synaptogenic transcripts are regulated by these lincRNAs? Is the regulatory control of synaptogenic programme by lincRNAs occurring in a calcium responsive manner? We are currently using wide range of biochemical, cell biological and biophysical approaches to address these questions.

Apart from lincRNAs, we are investigating the role of miRNA (miRNAs), ~21-23 nucleotide long non-coding transcripts, in modulation of synaptic function. miRNAs regulate gene expression reversibly by binding to the 3' untranslated region (UTR) of target mRNAs resulting in translational repression or transcript degradation. Importantly, spatio-temporal regulation of dendritic protein synthesis has emerged as a key modulator of synaptic plasticity. Thus, the reversibility of miRNA-mediated regulation of their targets makes them perfect candidates for activity-dependent control of synaptic plasticity. Emerging reports have shown that miRNAs guide a multi-protein complex, known as the RNA-induced silencing complex (RISC), to specific sites on

mRNAs targeted for gene silencing. Interestingly, a miRNA can target multiple mRNAs and also a single mRNA can be regulated by multiple miRNAs at the synapse. This poses some intriguing questions: How is specific miRNA-target interaction at the synapse is modulated in response to neuronal activity? How does miRNA-mediated transcript-specific control of protein synthesis modulate synaptic plasticity?

To elucidate novel biochemical mechanisms that are critical for miRNA-mediated control of synaptic function, our laboratory is focusing on two important aspects: (1) Molecular mechanisms underlying the transcript specificity of miRNA-mediated control of protein synthesis at the synapse. (2) Significance of transcript-specific translational control in fine-tuning of synaptic plasticity. Towards these key questions, a recent study identified a set of RNA

Binding Proteins (RBPs) that can remodel ribonucleoprotein complex. RBPs can bind to target mRNAs through specific cis-element located in non-coding region of the transcript. Among several neuronally expressed RBPs, Cytoplasmic Polyadenylation Element Binding protein (CPEB) has already been implicated in the synaptic plasticity mechanism. CPEB binds to the Cytoplasmic Polyadenylation Element (CPE) and modulates dendritic translation of specific sets of dendritic mRNAs, such as α -CaMKII and tPA and thereby modulates synaptic plasticity. Interestingly, our observations also revealed that the 3' untranslated region (3'UTRs) of α -CaMKII and tPA mRNAs are targeted by a dendritically enriched miRNA and that binding sites for this miRNA and for CPEB are juxtaposed at the 3'UTR of both mRNAs. Based on these observations, we hypothesized that CPEB can bind to set of dendritic RNAs through CPE element and can modulate RISC dependent translation from these mRNAs. We are performing genome wide screen to identify mRNAs those that are translationally regulated through CPEB-mediated control of RISC function. Furthermore, we will explore the mechanistic details of this novel mechanism of synaptic plasticity. Future directions will be to assess the implications of these novel mechanisms in modulation of emerging behavior, such as anxiety, feeding and locomotion.

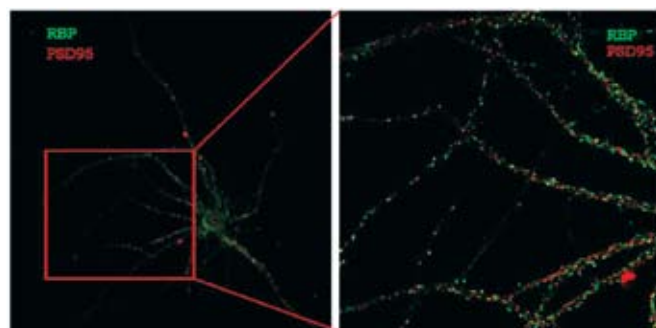


Figure:
Synaptic localization of a RNA binding protein

Presentation

1. Sourav Banerjee: Tune it up: Modulation of neuronal circuitry and synaptic mechanisms of plasticity. IISER Pune. August 2012.

Funding

Ramalingaswami Fellowship, DBT.

PERINATAL NUTRITIONAL MODIFICATIONS AND BRAIN DEVELOPMENT

Principal Investigator
Dr. Sayali C. Ranade

Environmental factors acting early in life either organize or permanently alter the developing physiological systems resulting in 'prenatal programming'. Nutrition represents one of the major important variables directly affecting growth and development of the organism. The effects of malnutrition or undernutrition on brain development have been demonstrated over the past 40 years in humans and in experimental animal models. Different types of malnutrition affect maturation of the brain and the development of cognitive function, resulting in behavioural abnormalities and disturbances in learning and memory. Since cerebellum and hippocampus are the brain structures central to learning and memory circuits, we decided to focus on studying the effect of maternal malnutrition on brain development with special attention to hippocampus and cerebellum. Three different types of malnutrition paradigms used are caloric restriction, inadequate amount of protein in the diet and condition of low iron content.

Our first major achievement this year is to show effect of protein malnourishment on cerebellar development and motor co-ordination. We showed that protein energy malnutrition suffered by the mother during the period of gestation and lactation has an adverse effect on cerebellar neurogenesis in F1 pups leading to the altered number of neurons and glia in cerebellum. Early life protein malnutrition also leads to delays of motor development.

Next we showed that maternal iron deficiency during the period of gestation and lactation affects hippocampal development in F1 pups. The hippocampus dependant spatial memory function checked in radial arm maze is specifically affected by maternal iron deficiency. We also showed association of these memory defects with components of stress pathway. This is the first report suggesting involvement of stress pathway in iron deficiency induced spatial memory dysfunction.

Our future goal is to define the optimum nutritional conditions for perinatal development. These issues are of great social importance and impact. The outcome of such studies will help us design and develop new preventive strategies and intervention therapies.

Publications

1. **Ranade Sayali**, Nawaz S, Pavan Kumar R, Rose AJ, Gressens P and Mani S (2012). Early protein malnutrition disrupts cerebellar development and impairs motor co-ordination. **Br J Nutr.** 107(8):1167-75.
2. **Ranade Sayali**, Nawaz S, Chakrabarti A, Gressens P and Mani S (2013). Spatial memory deficits in maternal iron deficiency paradigms are associated with altered glucocorticoid levels. **Hormones and behaviour.** 64(1):26-36.

A. Effect of maternal protein malnourishment on calbindin positive cells in cerebellum of pups.

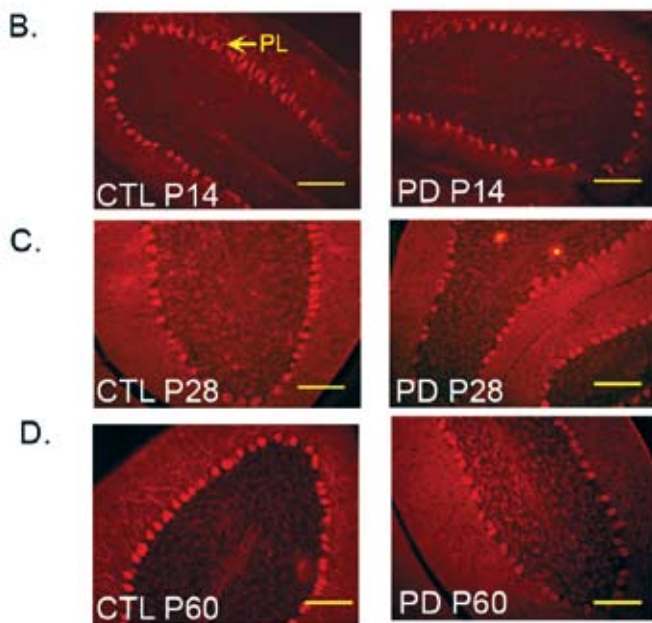
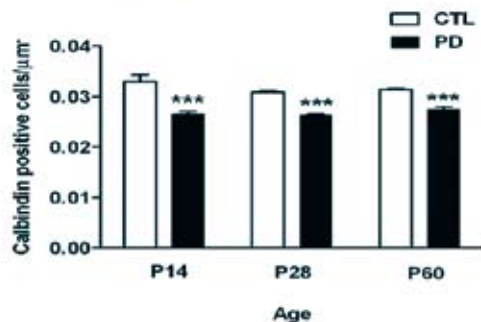


Figure 1: Maternal protein deficiency reduces number of calbindin positive Purkinje cells: Figure four shows number of calbindin positive cells in the Purkinje layer of cerebellar folds (A) The x-axis shows age and y axis shows mean number of calbindin positive cells per μm Purkinje layer. The panel B, C, D shows the calbindin positive cells at different developmental stages in both control and protein deficient groups. A significant reduction is seen in no. of calbindin positive cells in Purkinje layer of protein deficient mice at all three developmental stages (N=5 for both the groups at all ages). Bars are mean +SEM. Scale bar is 100 μm .

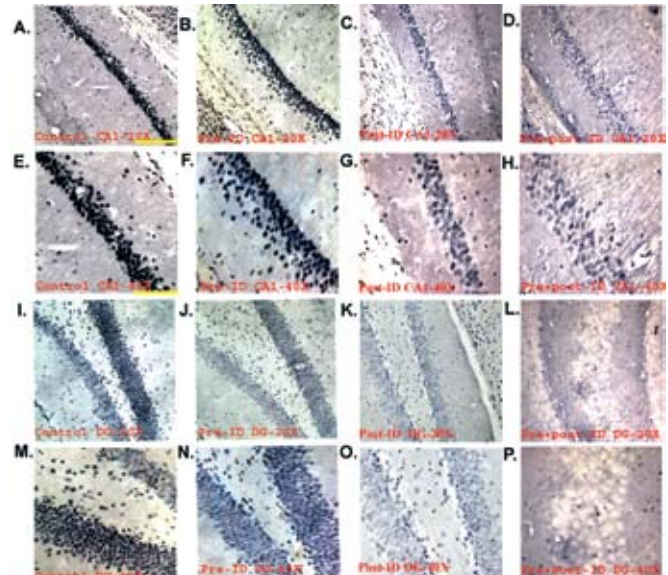


Figure 2: Effect of different paradigms of maternal iron deficiency on glucocorticoid receptor expression in DG and CA1 of hippocampus. The images showing effect of different paradigms of maternal iron deficiency on levels of glucocorticoid receptors checked in immunohistochemistry using GR M20 antibody. panels (A),(E) panels (B),(F) panels (C),(G) and panel(D),(H) are representative images of CA1 regions at different magnification in control, pre-ID, post-ID and pre+post-ID respectively. Significant reduction of staining was seen in pre+post-ID in panels (D), (H) and post-ID groups (panels C and G). Panels (I),(M) panels (J),(N) panels (K),(O) panels (L),(P) are representative images of DG region of hippocampus at different level of magnification of control, pre-ID, post-ID and pre+post-ID respectively. Note the complete disappearance of GR-M20 staining in panels (L) and (P) representing group pre+post-ID. Scale bar is 100 μm .

Funding

The Iron deficiency work is supported by WOS-A, Department of Science and technology.

The protein malnutrition work is supported by CIFPRA, Indo-French grant and ICMR.



Systems & Cognitive Neuroscience Division

Prof. Neeraj Jain
Dr. Soumya Iyengar
Dr. Narender K. Dhingra
Dr. Yoganarasimha Doreswamy

ORGANIZATION OF SOMATOSENSORY AND MOTOR SYSTEMS AND THE EFFECTS OF SPINAL CORD INJURIES

Principal Investigator
Neeraj Jain

Post Doctoral Fellows

Prem Chand, Arkadeb Dutta (Until November 2012)

Research Fellows

Leslee Lazar, Niranjana Kambi, Radhika Rajan, Hisham Mohammed, Vasav Arora, Manika Arora, Priyabrata Halder, John Thomas (Joined September 2012), Atanu Datta (Joined September 2012)

Project Assistants

G Naga Rajesh, Anshu Khandelwal

Technical Assistant

Mithlesh Singh

Laboratory Assistant

Hari Shankar

Organization of Somatosensory and Motor Systems and the Effects of Spinal Cord Injuries

Following injuries to dorsal columns of the spinal cord at cervical levels, topographically organized sensory inputs in the somatosensory cortex undergo changes such that face inputs expand and reactivate neurons in the deafferented hand region. Research work in our laboratory is focused towards understanding the extent, nature and mechanisms of such changes in the somatosensory and motor systems. We use a combination of neurophysiological, neuroanatomical and behavioural techniques in our laboratory. We perform unilateral lesions of dorsal columns leaving spinothalamic and other ascending and descending pathways intact. Behavioural effects of these lesions are restricted to an inability to form a precision grip. Our previous work at NBRC has shown that lesions of the dorsal columns in adult macaque monkeys lead to large-scale reorganization in the second somatosensory areas S2 and PV. As in area 3b, chin inputs expand into the deafferented hand region (Tandon et al., Journal of Neuroscience, 2009). This was rather unexpected because areas S2/PV continue to receive normal intact hand inputs via spinothalamic pathways after dorsal column lesions. Subsequently we showed that loss of sensory inputs also results in subtle but significant changes in movement representation in the primary motor cortex (Kambi et al., Journal of Neuroscience, 2011). Major focus of research during the last year has been on determining mechanisms of large-scale brain reorganization. The work done during the year is described below.

Mechanisms of large-scale brain reorganization.

Brain reorganization following spinal cord injury occurs at multiple sites in the brain, which include area 3b, areas S2/PV and ventroposterior nucleus of the thalamus. Since the shift in topographic boundaries is beyond any known existing normal connections, it is generally accepted that the changes must involve neuronal growth (Jain et al., PNAS 2000). It has been variously proposed that the growth could be (i) corticocortical, (ii) subcortical, occurring in the brain stem nuclei, or (iii) taking place at multiple sites. However, it is not known if in monkeys with chronic spinal cord injuries there is an expansion of the face representation into the cuneate nucleus, which normally receives inputs from the hand.

In order to answer this question we mapped area 3b and the brain stem nuclei of monkeys with long-term lesions of the dorsal columns at cervical levels. The results show that as expected, chin inputs had expanded into the deafferented hand region of area 3b (Fig. 1). Furthermore, recordings from neurons in the brain stem nuclei showed that neurons in the cuneate nucleus responded to touch on the chin showing that brain reorganization takes place even at the earliest stages of the information-processing stream. Since the lesion in the case illustrated here did not completely deafferent the cuneate fasciculus, at some recording sites responses to touch on the hand were present in both area 3b and the cuneate nucleus.

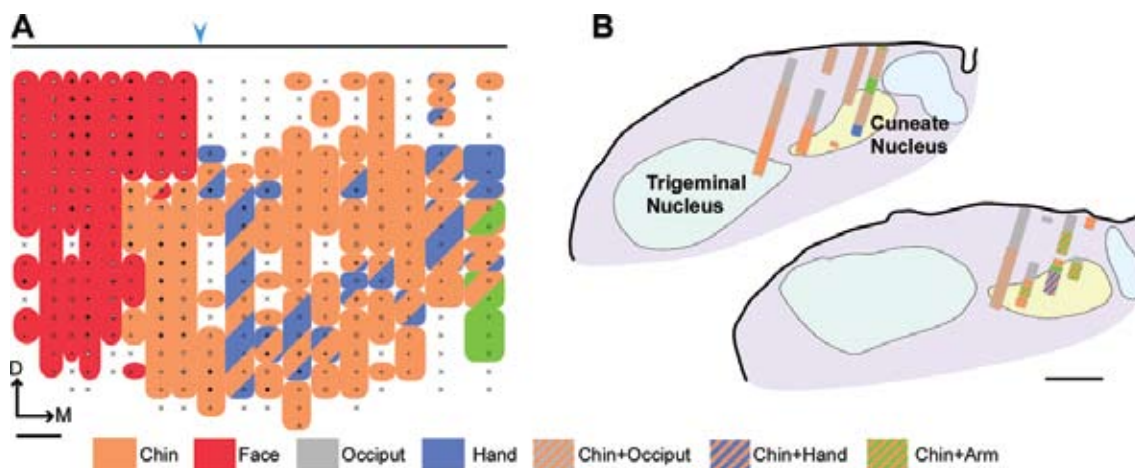


Figure 1. Reorganization of the area 3b and cuneate nucleus in a monkey with lesion of the dorsal columns of the spinal cord. (A) Details of the somatotopy showing expansion of the chin inputs (pink) into the hand region. The somatotopy is shown on the posterior bank of the central sulcus. Blue arrowhead marks location of the normal hand-face border. Chin representation to the right of the arrowhead is in the normal face area. (B) Two cross sections from the medulla showing a series of electrode penetration through the trigeminal and the cuneate nuclei. Note that neurons in the cuneate nucleus respond to touch on the chin (pink). Since the lesion was partial, neurons at few recording sites also respond to touch on the hand.

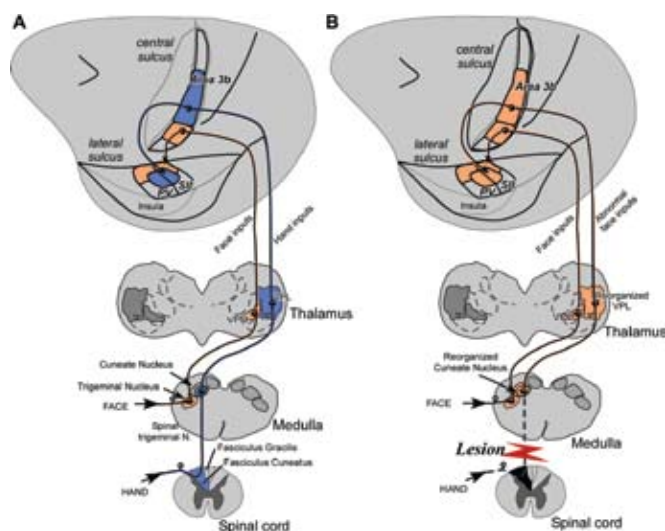


Figure 2. A schematic showing normal dorsal column-medial lemniscus somatosensory pathway and the current state of knowledge of brain reorganization. (A) Inputs from the skin enter the spinal cord and ascend in the dorsal columns to the brain stem nuclei. Inputs from the hand are located in the cuneate nucleus and those from the face in the trigeminal nucleus. Second order neurons project from cuneate nucleus to the ventroposterior (VP) nucleus of the thalamus. In the VP nucleus inputs from the hand and face terminate in its lateral (VPL) and medial (VPM) subdivisions respectively. Third order neurons primarily project to area 3b, the primary somatosensory area in the post-central gyrus. Further projections go to other somatosensory areas including those in the lateral sulcus (S2 and PV). (B) Following chronic lesions of the dorsal columns of the spinal cord at cervical levels in adult animals, chin inputs expand into the deafferented hand region in all the somatosensory regions examined – the cuneate nucleus, VPL, area 3b and areas S2 and PV.

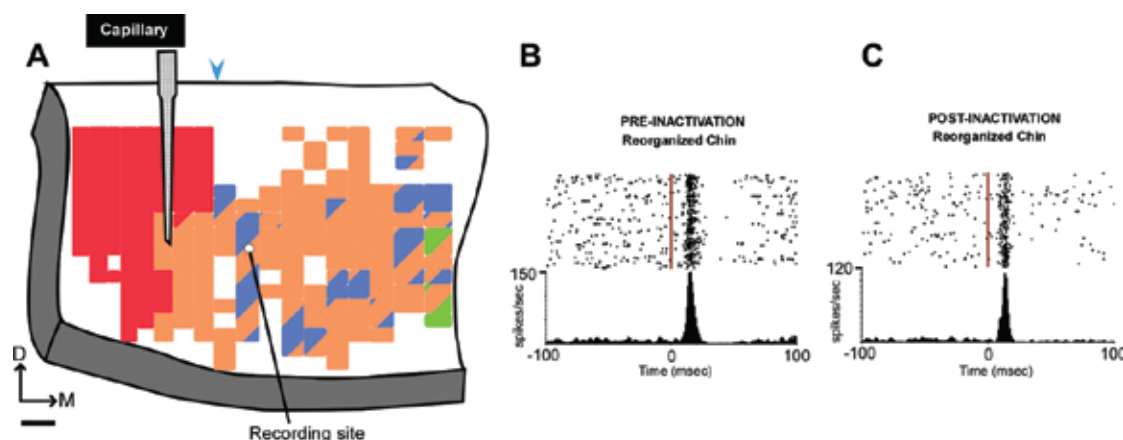


Figure 3. (A) Somatotopic map of area 3b showing expansion of chin inputs medially into the deafferented hand region in a monkey with lesion of the dorsal columns. Blue arrowhead marks location of the normal hand-face border. (B) A peristimulus time histogram and raster plot showing neuronal responses to a periodic 1 Hz stimulus of the chin at the recording site marked by a circle. This recording site is located in the reorganized part of area 3b. (C) Neuronal responses at the same site after normal chin representation in the cortex were inactivated by injecting lidocaine via a capillary tube. There was no effect on the cortical responses.

During the year we also investigated if corticocortical mechanisms contribute to large-scale brain plasticity. In monkeys with chronic lesions of the dorsal columns, we first mapped area 3b to establish that chin representation had expanded into the deafferented hand region. We then inactivated the normal chin region of area 3b using short acting sodium channel blocker lidocaine. For continuous inactivation by lidocaine we used a custom-built capillary injection system, which can simultaneously record neuronal activity. The system was designed to allow independent movement of the electrodes attached to the capillary tube. Our results showed that responses to tactile stimulation of the chin were not affected in the deafferented hand region by inactivation of the normal chin area. The expanded chin representation remained intact. Thus normal chin inputs are not essential for the observed expansion of the chin representation in the cortex. Therefore, large-scale brain reorganization is not mediated by corticocortical mechanisms. Further experiments are underway to determine mechanisms of plasticity.

Publications

1. Arkadeb Dutta, Niranjana Kambi, Partha Raghunathan, Subhash Khushu, **Neeraj Jain (2013)**. Large-scale reorganization of the somatosensory cortex of adult macaque monkeys revealed by fMRI. **Brain Structure and Function**. (In Press).
2. Shashank Tandon, Niranjana Kambi, Hisham Mohammed and **Neeraj Jain (2013)**. Complete reorganization of the motor cortex of adult rats following long-term spinal cord injuries. **European Journal of Neuroscience**. (In Press).

Funding

Department of Information Technology.
Department of Biotechnology.

Collaborators

Prof P Raghunathan, NBRC; Dr S Khushu, INMAS

COGNITION IN CORVIDS

Principal Investigator

Soumya Iyengar

Research Fellow

Shankhamala Sen

Technicians

Arvind Singh Pundir, Krishan Sharma

Lab Assistant

Ram Mehar

The main aspects of cognition include attention, learning and memory, language and perception as well as motor responses. A number of behavioural studies have demonstrated that amongst birds, corvids (including crows, rooks, jays and starlings) can perform at par with non-human primates on cognitive tasks which require causal reasoning, imagination, flexibility and foresight. Recently, studies on the organization of neural circuits, gene expression and neurotransmitters in the avian brain have demonstrated that the caudal nidopallium (NC) is the avian homologue of the prefrontal cortex, which is known to be important for cognition in mammals. However, there are almost no studies available on brain structure or function in general or of the NC in particular of corvids.

We were interested in studying the brain structure of indigenous species of corvids (house crows, *Corvus splendens*, and jungle crows, *Corvus macrorhynchos*) and comparing them with other species of birds such as zebra finches (songbirds), as a first step to understanding why crows are adept at performing complex cognitive tasks. Preliminary experiments from our lab show that the basic brain architecture of house crows was similar to that in Japanese jungle crows (Izawa and Watanabe, 2007). Different divisions of the pallium or avian cortex (hyper-pallium, mesopallium, nidopallium and entopallium) could be discerned from each other based on cytoarchitecture and the location of various fiber tracts revealed by Nissl staining. Different components of the corvid basal ganglia were similar in structure to that of songbirds and could be divided into the lateral and medial striatum (LSt and MSt) and globus pallidus (GP). Interestingly, an oval area containing densely packed

neurons could be seen within MSt on both sides and appeared to correspond to the songbird Area X. We also found an oval nucleus on either side of the midline in the posterior part of the arcopallium which appeared to be homologous to the songbird RA (a premotor cortical region, nucleus robustus arcopallium).

We have used immunohistochemical staining to demonstrate that as in other birds and mammals, the cytoplasm and elaborate dendrites of large cells in the VTA-SNC were highly positive for the enzyme tyrosine hydroxylase which is important for the breakdown of the neurotransmitter dopamine. The size of TH-positive cells in the VTA-SNC complex varied from small to large in a rostro-caudal gradient. Medium and small sized TH-positive neurons were also present in the septum (except for the medial septal nucleus, which contained a number of TH-positive fibers) and occasionally in the arcopallium near RA. All parts of the striatum (including MSt, LSt and Area X) contained a dense plexus of fibers highly immunoreactive for TH, such that the striatum could be clearly distinguished from the pallium. Within the pallium, the nidopallium had the lowest density of TH-positive fibers, followed by a slight increase in the density of these fibers in the mesopallium. The overlying hyperpallium contained the highest density of TH-positive fibers in the rostral part of the corvid brain. The NC also contained a high density of TH-positive fibers although it cannot be clearly demarcated from other pallial regions based on staining for TH. Since TH is a marker for dopaminergic input and there is a higher density of TH-positive fibers in NC and the hyperpallium, our data suggests that these regions may be important for the remarkable cognitive abilities of corvids.

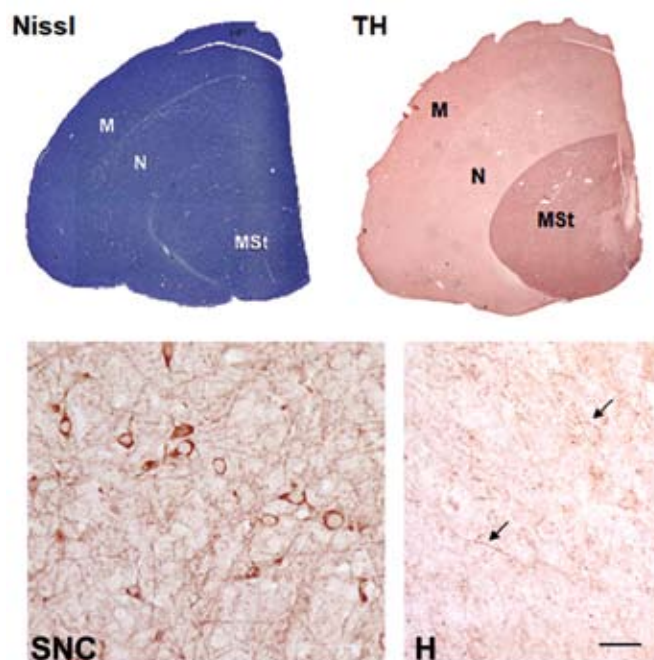


Figure 1: A coronal section of the crow brain (upper panel, right) demonstrating the presence of tyrosine hydroxylase (TH) in the meso- (M) and nidopallium (N) which are avian homologues of the cortex (pallium). This image also demonstrates high levels of TH immunoreactivity in the avian striatum (MSt, Medial striatum). A Nissl-stained coronal section is shown on the left for comparison. TH is used as a marker for the neurotransmitter dopamine which is known to be involved in cognition. High-power images (lower panel) demonstrate the presence of TH-positive neurons in the substantia nigra (SNC) and TH-positive fibers (arrows) in the hyperpallium (H), another subdivision of the pallium.

Funding

This study is supported by a grant from DST (SR/CSI/03/2010) "Neurobiology and Understanding the Circadian System Linkage of Cognitive Performance in an Avian Model

System" awarded in 2010 and NBRC Core funds.

Collaborator

Prof. Vinod Kumar, Delhi University, Delhi.

OPIOID MODULATION OF SONG IN ADULT MALE ZEBRA FINCHES

Principal Investigator

Soumya Iyengar

Research Fellows

Sandeep Kumar, Uzma Din,
Shankhamala Sen

Project Assistant

Sudha Sharma

Technicians

Arvind Singh Pundir, Krishan Sharma

Lab Assistant

Ram Mehar

Zebra finches are an excellent model system to study vocalization. Adult male zebra finches sing highly stereotyped or fixed songs in adulthood in two different contexts: to court females (female-directed song) or in isolation (undirected song). Further, zebra finches possess well-characterized neural circuits (the song control system or SCS, Fig. 2) which underlie song learning, vocalization and auditory perception, as in humans. The SCS is homologous to the basal ganglia pathway in mammals. The neural circuit connecting the song control nuclei HVC and RA (robust nucleus of the arcopallium) is important for vocalization. HVC also projects to Area X (a nucleus of the avian basal ganglia) which projects to DLM (dorsolateral nucleus of the thalamus) which in turn projects to LMAN (lateral magnocellular nucleus of the anterior nidopallium, avian pallidum or cortex). LMAN projects to both Area X and RA, forming loops within the SCS. Area X further projects to a region called the ventral pallidum (VP) which projects to the ventral tegmental area – substantia nigra complex (VTA-SNc). Earlier studies have shown that there is an increase in dopamine release by the VTA-SNc into Area X whenever male zebra finches sing to females. Further, it has also been shown that LMAN and Area X are also involved in context-dependent singing.

motor neurons in nXIIts (the hypoglossal nucleus, tracheosyringeal part) which innervates muscles of the syrinx or the vocal organ. HVC also projects to Area X (a nucleus of the avian basal ganglia) which projects to a thalamic nucleus DLM (dorsolateral nucleus of the thalamus), which in turn projects to the cortical region LMAN (lateral magnocellular nucleus of the anterior nidopallium). The circuit connecting Area X, DLM and

LMAN (red) is called the anterior forebrain pathway and is important for song learning during development. Area X and the VTA-SNc (ventral tegmental area – substantia nigra complex) are important for context-dependent singing in adult zebra finches. Area X projects to the VTA-SNc (ventral tegmental complex) via the VP (ventral pallidum). The VTA-SNc region releases high levels of the neurotransmitter dopamine (DA) into Area X when adult male birds sing to females (Modified from Gale et al., 2008).

We had earlier demonstrated that the endogenous opioid system modulates different kinds of behavior, including vocalization in adult male zebra finches. Systemic injections of low doses of naloxone led to a decrease in both female-directed and undirected songs in adult male zebra finches, whereas other behaviours were not affected. We also found changes in spectral features of song (decrease in goodness of pitch, frequency and amplitude modulation) and temporal features of song (increase in the duration of intersyllable intervals, Khurshid et al., 2010a). These results suggested that naloxone administration led to a decrease in the motivation to sing, since μ -ORs were present in the VTA-SNc (ventral tegmental area – substantia nigra complex) and other areas important for motivation and reward. Changes in the spectral and temporal features of song probably resulted from blocking μ -ORs expressed in song control areas of the brain which are important for vocalization (HVC and RA, robust nucleus of the arcopallium). In order to determine the site of action of naloxone in the brain which led to the changes in song behaviour, we decided to inject naloxone specifically into different brain regions and then study changes in the behaviour of adult male birds.

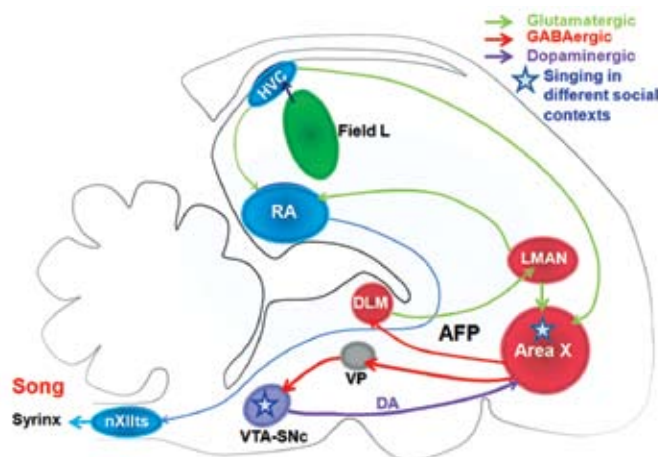


Figure 2: The Song Control System of Adult Male Zebra finches. Auditory input from Field L (the avian homologue of the auditory cortex) reaches HVC, the first of the song control nuclei, which then projects to RA. The neural circuit connecting HVC and RA (robust nucleus of the arcopallium; highlighted in blue) is important for vocalization. RA projects to motor neurons in nXlts (the hypoglossal nucleus, tracheosyringeal part) which innervates muscles of the syrinx or the vocal organ. HVC also projects to Area X (a nucleus of the avian basal ganglia) which projects to a thalamic nucleus DLM (dorsolateral nucleus of the thalamus), which in turn projects to the cortical region LMAN (lateral magnocellular nucleus of the anterior nidopallium). The circuit connecting Area X, DLM and LMAN (red) is called the anterior forebrain pathway and is important for song learning during development. Area X and the VTA-SNc (ventral tegmental area – substantia nigra complex) are important for context-dependent singing in adult zebra finches. Area X projects to the VTA-SNc (ventral tegmental complex) via the VP (ventral pallidum). The VTA-SNc region releases high levels of the neurotransmitter dopamine (DA) into Area X when adult male birds sing to females (Modified from Gale et al., 2008).

Cannulae were surgically implanted into Area X or LMAN of adult male zebra finches unilaterally. After birds recovered from surgery, a microdialysis probe was placed in the cannula and saline or artificial cerebrospinal fluid (the vehicle used to dissolve naloxone) or different doses of naloxone were infused into the brain while birds sang to females. Preliminary data demonstrated that injecting naloxone directly into Area X in awake singing birds led to an increase whereas injections into LMAN led to a decrease in the number of songs that birds sang to females compared to controls. We also found that there was a significant decrease in the mean pitch of songs sung during naloxone

infusion in LMAN, although there was no change in this measure when naloxone was injected into Area X. Further, we implanted a cannula unilaterally into an area called the ventral pallidum (VP) which receives projections from Area X and in turn, projects to the VTA-SNc complex in one bird. Infusions of naloxone in VP led to a decrease in the number of songs that the bird sang to a female, compared to control (vehicle) injections in this region. Our results suggest that blocking μ -ORs in Area X, LMAN or VP during directed song may affect the motivation to sing. It is possible that blocking μ -ORs in these brain regions leads to changes in the release of dopamine from VTA-SNc neurons which are further downstream in this pathway, which is known to be important for the production of directed song in adult male zebra finches. Additionally, blocking opioid receptors in LMAN also affects the quality of song, likely through its connections with the motor cortical region, RA.

Publications

1. Sharma J, Mukherjee D, Rao S, **Iyengar S**, Shankar SK, Satishchandra P and Jana NR (2013): Neuronatin mediated aberrant calcium signaling and endoplasmic reticulum stress underlie neuropathology in Lafora disease. **Journal of Biological Chemistry**, 288(13); 9482-9490.
2. **Iyengar S (2012):** Development of the Human Auditory System. *J. Indian Inst. Sci.* 92:4; 427-440 (Invited review), in the issue on "**Development and Disorders of the Nervous System**" edited by Dr. S. Mani.

Presentations

1. Soumya Iyengar: Organization of the Vertebrate Nervous System. Fourth DST-SERB school in Chronobiology, North-Eastern Hill University (NEHU), Shillong, June 20, 2012.
2. Soumya Iyengar: Comparative Aspects of Brain Evolution - Mammals versus Birds. Fourth DST-SERB school in Chronobiology, North-Eastern Hill University (NEHU), Shillong, June 21, 2012.
3. Soumya Iyengar: Auditory System – I. Sixth DST-SERB School in Neuroscience, National Institute of Science Education and Research (NISER), Bhubaneswar, Orissa, December 18, 2012.
4. Soumya Iyengar: Auditory System – II. Sixth DST-SERB School in Neuroscience, National Institute of Science Education and Research (NISER), Bhubaneswar, Orissa, December 18, 2012.
5. Soumya Iyengar, Arvind Singh Pundir, Bishan Radotra, Praveen Kumar, PC Dikshit, SK Shankar, Anita

Mahadevan. Development of excitatory neural circuits in the human auditory cortex. Poster presented at The 8th FENS Forum of Neuroscience, Barcelona, Spain, 14 - 18 July, 2012.

Funding

This work is supported by a DST grant (SR/SO/AS-39/2009)

“Opioid Modulation of song in Male Zebra Finches” awarded in 2010 and NBRC Core funds.

Collaborators

Prof. Neeraj Jain, NBRC.
Niranjan Kambi (Prof. Jain’s lab).
Vasav Arora (Prof. Jain’s lab).

RETINAL CIRCUITRY: IN HEALTH AND IN DISEASE

Principal Investigator

Narender K. Dhingra

Research Fellows

Varsha Jain, Deepak Poria, Manvi Goel

Research Assistants

Sushma Dagar, Abhinaba Ghosh, Kaushik Deka, Bhuvaneswari Ganesan

Technical Assistant

Sumit Mahapatra

Lab Attendant

Prasannjeet

Background & Significance

Retinal degenerative diseases such as Retinitis Pigmentosa and Age-Related Macular Degeneration have high incidence rates, and are among the leading causes of blindness. These diseases have varied etiology but are characterized by degeneration and loss of photoreceptors, whereas inner retinal neurons, especially retinal ganglion cells (RGCs) are relatively preserved. Since RGCs, which transmit the retinal signal to the brain are preserved, there is an immense interest in replacing the degenerated photoreceptors with a prosthetic device or stem cells. Retinal prosthesis is an electronic device surgically implanted in eye to stimulate the retina through an array of microelectrodes. The hope is that the device would correctly encode the information in the visual scene, transmit it to the surviving RGCs, and thus produce artificial vision in blind patients. Similarly, the transplanted stem cells are expected to differentiate into photoreceptors which would functionally integrate with the host neurons. Both these approaches have shown great promise in recent years, but are yet to produce the desired clinical outcome. Our working hypothesis is that the clinical success of these treatment approaches is linked to our understanding of how the retinal circuitry develops and functions, normally as well as in retinal degeneration. The overall goal of our research is to understand how retinal circuitry functions normally, and how it responds to retinal degeneration. We believe that understanding normal retinal circuitry would also help design better treatment protocols for retinal degeneration, and conversely, understanding pathophysiology of retinal degeneration would also help unravel normal retinal function.

Retinal remodeling

We have been studying retinal changes that follow photoreceptor degeneration. The primary objective of this project is to understand the mechanism underlying oscillatory spike bursting observed in RGCs after photoreceptor loss. We have found in two animal models of retinal degeneration that synaptic activity in amacrine cells and bipolar cells is increased after photoreceptor loss. Currently we are quantifying GABA, glutamate and glycine receptors in inner retina after photoreceptor degeneration. We are testing the hypothesis that increased GABAergic signaling in amacrine cells results in increased feedback inhibition of bipolar cell terminals, which eventually leads to oscillatory glutamate release in bipolar cells and thus oscillatory burst firing in RGCs. We are also testing the hypothesis that oscillatory activity originates in On bipolar cells and is passively transferred to Off pathway via glycinergic pathway.

Role of Brn3-expressing retinal ganglion cells in vision

Brn3 family of class IV POU-domain transcription factors, including Brn3a, Brn3b and Brn3c play important roles in differentiation, axonal pathfinding and dendritic stratification of RGCs during development. The three Brn3 transcription factors are expressed in partially overlapping subsets of RGCs in adult retina, raising the possibility that they represent a combinatorial code. We showed previously that intrinsically-photosensitive RGCs (ipRGCs), which are thought to mediate non-image-forming visual functions, do not express Brn3a or Brn3c (Jain et al., 2012). However, a specific subset of ipRGCs (non-M1 cells) express Brn3b. Based on these results and previous reports, we postulated

that Brn3 transcription factors are expressed exclusively by RGCs that mediate image-forming vision. Conversely, the M1 cells that do not express Brn3 transcription factors may be involved exclusively in irradiance detection. We have further probed these ideas by studying the expression pattern of Brn3 after photoreceptor degeneration. The rationale is twofold: 1) The interplay between photoreceptors and ipRGCs in mediating non-image-forming visual functions, such as pupillary light reflex (PLR) and circadian photoentrainment is not completely clear, and 2) Although the Brn3b-positive and Brn3b-negative ipRGCs have been implicated in mediating PLR and photoentrainment respectively, it is not clear how these specific cells or their function are affected in retinal degeneration. We have found that a majority of M1 cells, which do not normally express Brn3b, start to express it in the absence of photoreceptors in rd1 mouse. To confirm that loss of photoreceptors leads to M1 cells expressing Brn3b, we have looked at two additional animal models where photoreceptor degeneration is induced chemically. We have found interesting differences in PLR between the two animal models, which we believe can be attributed to changes in the Brn3b expression in ipRGCs.

Role of Müller glial cells in rescue and recovery of photoreceptors

We have been studying the potential role of Müller glial cells in rescue and recovery of photoreceptors in retinal degeneration. We showed previously that Müller cells in rd1 mouse remain undifferentiated for several months and express rhodopsin, a mature rod photoreceptor marker, but did not express other neuronal markers of retina. These results suggested that Müller cells tended to differentiate selectively into rods that are the primary targets of the PDE6 β mutation in rd1 mouse (Goel and Dhingra, 2012). Currently, we are carrying out a series of experiments to expand on these results. For example, we are testing the hypothesis that adding specific growth factors would reinforce the differentiation of Müller cells into photoreceptors. In addition, we are growing pure Müller cells in culture and transplanting them intravitreally into rd1 mouse to see if they would differentiate into photoreceptors or would

reinforce the differentiation of the host Müller cells into photoreceptors, with or without the growth factors.

Publications

1. Goel M, **Dhingra NK (2012)** Müller glia express rhodopsin in a mouse model of inherited retinal degeneration. **Neuroscience** 225: 152-61.

Presentations

1. S Dagar, NK Dhingra. Loss of photoreceptors in rd1 mouse leads to selective upregulation of amacrine cell-specific synaptic protein mRNAs. Annual Conference of the Indian Academy of Neurosciences (Amritsar, India; October, 2012).
2. V Jain, ERavindran, RGuruswamy, NKDhingra. Expression of Melanopsin and its co-expression with Brn3b alters in Mouse model of Retinal Degeneration FASEB summer research conference on Retinal Neurobiology and Visual Processing (Steamboat Springs, CO, USA; Jul-Aug, 2012).
3. NK Dhingra, A Ghosh. Loss of Photoreceptors in rd1 Mouse is Associated with Upregulation of GABAC Receptors in Inner Retina. ARVO meeting (Fort Lauderdale, USA; May, 2012).

Funding

This work is supported by Department of Biotechnology, Govt of India, and National Brain Research Centre.

Collaborators

- I. Dr. P Seth (NBRC): Use of Human Fetal Brain Derived Neural Precursor Cells in a Retinal Degeneration Model
- II. Dr. M Ganguli (IGIB): To Study Efficiency of Cationic Peptides to Deliver Plasmid DNA into Retinal Cells in vivo
- III. Prof. SK Narayan (JNCASR): Using Photosensitive Polymer Substrates to Stimulate Retinal Neurons after Photoreceptor Degeneration.

NEURAL NETWORK MECHANISMS UNDERLYING SPATIAL LEARNING AND NAVIGATION

Principal Investigator

Yoganarasimha Doreswamy

Research Fellows

Apoorv Sharma, Guncha Bhasin,
Chetan Yadav

The hippocampus and related medial temporal lobe areas play a major role in learning and memory. The spatial component of the memory is encoded in these brain areas as a cognitive map of the external environment, resulting in efficient spatial navigation, orientation and successful interpretation of external sensory cues. The primary research focus of our laboratory is to understand how the brain constructs an internal representation of the outside world and how those representations are stored and recalled as conscious memories, thus forming a spatial relation between an organism and its environment. Through in vivo neurophysiological studies in rodents, we hope to understand the neural mechanisms underlying spatial memory and navigation, which may lead to better understanding of the memory deficits observed during aging, brain injury and neurodegenerative diseases. Place cells of the hippocampal formation and head direction cell system plays a very critical role in spatial memory and navigation, and acts as model system for deciphering the neural network mechanisms by which the brain constructs these cognitive representations from multimodal inputs. The hippocampus is critically involved in learning and memory and has been suggested to play a major role in episodic-memory, context-dependent learning, learning of spatiotemporal sequences, which requires integration of spatial and nonspatial representations. Spatially active place cells selectively fires at specific location in an environment, indicating that the hippocampus may form the locus of a “cognitive map” of the surrounding environment. Previous studies have shown that place cells are controlled by a complex interaction between self-motion cues and salient landmarks in the environment, and it has been suggested that the place cell firing may

also reflect encoding of behaviourally salient nonspatial information onto the spatial framework provided by place cells. Head direction cells present in various cortical and subcortical areas, fire selectively when the animal’s head is pointed in a particular direction in allocentric space regardless of its location and serve as internal compass for the animal. These are controlled by a complex interaction between idiothetic cues and external landmarks. Strong coupling between head direction cells and place cells



Figure 1 Multitetrode electrophysiology data recording set-up (A) and the behavioural recording room (B) for in vivo neurophysiological recordings.

have been reported, and the preferred firing locations/ directions of place cells and head direction cells remain strongly coupled to each other even when they become completely uncoupled from external landmarks. The head direction system is suggested to govern the orientation of the hippocampal spatial representation relative to the external environment. However, understanding the precise computations performed by the hippocampus has been

limited due to paucity of knowledge on representations from all of its input brain areas.

Two parallel processing streams, the lateral and medial entorhinal cortex, provide non-spatial and spatial information inputs to the hippocampus to create a conjunctive representation of the external environment. In turn, the lateral entorhinal cortex receives major input from the perirhinal cortex, which is connected with unimodal sensory areas and appears to be involved in the processing of configurations of objects, while the medial entorhinal cortex receives major input from the dorsal presubiculum and retrosplenial cortex, which contain directionally and spatially tuned neurons, and from postrhinal cortex, which is connected with visuospatial regions of the neocortex and has been linked to contextual processing. Anatomically, subicular complex area has been regarded as both an afferent and efferent area of the hippocampus. While the subicular complex neurons receives projections from the hippocampus; it connects to superficial layers of the entorhinal cortex, which are the input layers to different subfields of the hippocampus. Further, the subicular complex region, consisting of subiculum proper, presubiculum, postsubiculum and parasubiculum, receives sensory inputs from different cortical areas and connects to the entorhinal cortex and hippocampus, two major brain areas involved in processing of spatial information. The subicular complex neurons show directional and locational correlates and are modulated by theta, which may act as internal units allowing updating of position from one location to another based on the current directional heading. These neurons also encode head angular velocity and running speed, thus updating representation of head direction and location. Further, anterodorsal thalamic nuclei, containing head direction cells which encode the current heading direction, directly connects to the postsubiculum. Hence, the subicular complex area may act as an interface between different brain areas involved in spatial information processing in integration of spatial and directional information. It is critical to understand the network properties of subicular complex neurons, which give rise to the spatial tuning and other properties of place cells, to elucidate exact role of various brain regions during spatial memory and navigation.

Our laboratory uses 96-channel electrophysiology system to study spatial information processing in rodent brain in vivo, which allows recording of ongoing neural activity from large population of neurons at specific brain areas in awake freely behaving animals, through multitetrode recording technique. The microdrive (multitetrode recording device) is custom made in the laboratory, comprising of



Figure2. Representative examples of firing rate maps of a place X direction cell and a grid cell from the subicular complex area, recorded on the circular track and platform. In the colour coded rate map, red indicates >90% of the peak firing rate for that cell, blue indicates no firing and the intervening colours of the spectrum indicate successive decrements of 10% of the peak firing rate. The subsequent columns show the firing directional tuning curves and the averaged waveforms recorded on four channels of the tetrode.

18 independently movable tetrodes to target specific brain areas/layers, along with 2 reference electrodes for neurophysiological recordings. The microdrive was stereotactically implanted on the right hemisphere of the rat's brain under surgical anesthesia, targeting subicular complex neurons. Upon postsurgical recovery, the rats were subjected to behavioural training and the tetrodes lowered into the subicular complex area. Figure 1 shows the recording set-up for lowering the tetrodes while the animal rests on the pedestal and the behavioural recording room with dim light, wherein the rats are trained to run clockwise on an elevated circular track having four different textures, placed in the centre of the room surrounded by a black circular curtain. Various salient distal landmarks are either hanged or placed on the floor at the periphery of the curtain. After lowering the tetrodes to the target brain areas, the experimental recording sessions are carried out

while the rat navigated clockwise on the circular track or foraged on a circular platform. We have characterised various cell types within the subicular complex area and their representational properties. Figure 2 shows the representative firing rate maps of two neurons, a place X direction cell and a grid cell recorded from the subicular complex area. The firing directional tuning curve shows that the place X direction cells fires at a specific location in the environment, only when the rat approaches that location in a particular direction, suggesting modulation of spatial encoding by head directional information. While

the grid cell shows multiple, discrete spots representing the vertex of a triangular grid based on tessellating equilateral triangles, spanning the entire environment. Currently, the work is under progress to understand the functional properties and representational dynamics amongst different subregions of the subicular complex area during spatial navigation.

Funding

NBRC Core funds.
Department of Biotechnology, Govt. of India.



Computational Neuroscience & Neuroimaging Division

Dr. Nandini Chatterjee Singh

Prof. Prasun Kumar Roy

Dr. Pravat Kumar Mandal

SPEECH AND MUSIC NETWORKS IN CHILDREN WITH AUTISM SPECTRUM DISORDER (ASD)

Principal Investigator

Nandini Chatterjee Singh

Senior Research Fellow

Megha Sharda

Background

Recent research of the typically developing brain has suggested that music and speech rely on distinct acoustic cues for processing. The speech signal has been suggested to rely primarily on rapidly changing broadband sounds (25-30 milliseconds), whereas music patterns tend to rely on slower (200-300 milliseconds), changes in temporal information. While earlier data from our laboratory and others has shown speech processing deficits in children with autism spectrum disorder (ASD), a large subgroup of individuals with ASD show exceptional musical abilities and respond to music as treatment. In particular, the effects of music on social-communicative and brain function are understudied. Following up on earlier work we are currently investigating, the processing differences between speech and musical sounds in children with autism spectrum disorders using functional imaging and behavioural methods. The long term goals of the study are to see if music entrainment alters these brain networks in children and if so, is it possible to use these changes to develop specifically designed music therapy in ASD as a communicative intervention.

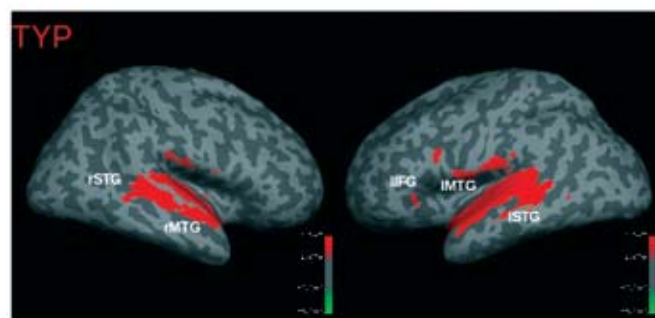
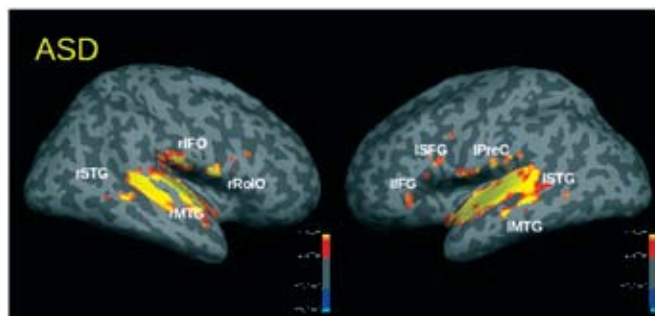
We used a sparse sampling design was developed to administer spoken and sung stimuli without the interference of scanner noise. Speech and music networks in typical adults were investigated. After successfully administering the paradigm to typical adults we have extended the experiment to children with autism. Sung stimuli elicit greater extent of the auditory-communicative network than spoken words in both ASD and typical developing children. We have collected data from approximately 20 children with ASD and 20 age-matched controls.

Conclusions

Our first finding shows that in children with autism, sung words engaged a robust bilateral temporal network (Fig. 1(a)). Interestingly, the brain networks for sung words do not significantly differ from typically developing children suggesting that these are robust stimuli that elicit the attention of children with ASD. However spoken word brain networks between ASD and TYP showed significant differences (Fig. 1(b)). Spoken words elicited an atypical right frontal activation in ASD as compared to typical children. Additionally we also found that the atypical functional activation in ASD during speech perception was concomitant with structural impairments in the dorsal language pathway. Given that sung stimuli are more salient than spoken words and show more 'normal' like patterns of activation, our results strongly advocate the exploration of more sung speech stimuli for entrainment of communicative function in children with ASD especial those with little verbal language.

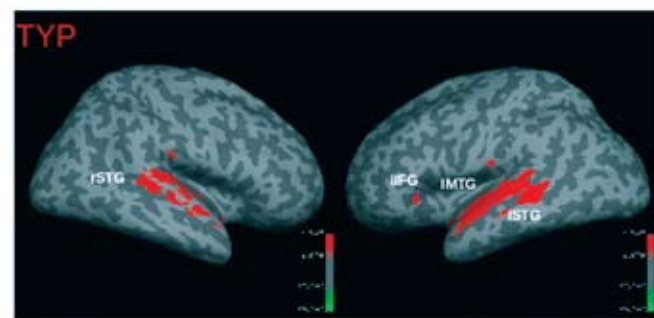
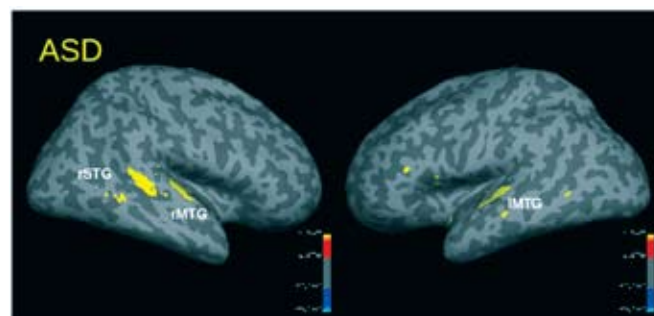
Long term goals – Recent work has demonstrated the effect of musical training on cognitive development in recent years. Basic musical competence, acquired through everyday exposure to music during development, enables listeners to tap to musical beat, memorize, recollect and reproduce familiar tunes and rhythms, and experience the emotions expressed in music, regardless of formal training. Research over the past decade has highlighted that formal musical training also has remarkable non-musical cognitive benefits. Given the robust response to sung speech compared to spoken speech we propose to investigate whether systematic music instruction in children with autism may influence the development of communication abilities in general and verbal abilities in particular.

Sung Words $p < 0.01$, FDR-corrected



Largely overlapping bilateral superior and mid temporal activation in both ASD and TYP.

Spoken Words $p < 0.01$, FDR-corrected



Right temporal activation for spoken words in ASD > TYP as compared to the left-lateralised activation in TYP > ASD

NEURAL CORRELATES OF EMOTION CONTAGION IN MUSIC

Principal Investigator

Nandini Chatterjee Singh

Junior Research Fellow

Avantika Mathur

Research Assistant

H V Suhas

Background

Communication of emotions is crucial to social relationships and survival (Ekman, 1992). Besides facial expression, the two modalities that are often regarded as effective means of emotional communication are vocal expression and music that rely on acoustic signals for their transmission of messages. Neuroimaging studies in our laboratory have shown that children with autism respond more typically to music as opposed to speech. Given that emotion processing in faces and voices is impaired in children with autism our long term objective is to investigate how emotion contagion as applied music, is processed in children with autism.

Emotional contagion is a process by which an emotion is induced by a piece of music because the listener perceives the emotional expression of the music and then mimics this expression internally wherein by means of either peripheral feedback from muscles, or a more direct activation of relevant emotional representations in the brain, leads to an induction of the same emotion.

That Indian classical music induces different emotional states is well documented and is said to evoke seven basic emotions: sadness, romance, peace, strength/courage, anger, dispassion, devotion (Bhatkande 1934). In theory, a raga depicting a particular emotion (bhava) could evoke mixed and complex emotions (rasa) in a listener. While the emotional qualities of ragas have been discussed extensively in North Indian classical music there has been little investigation to validate these theories.

As a first approach in this area we conducted an internet based study to understand emotional contagion associated

with music using North Indian classical ragas as stimuli. Based on Bhatkande's empirical classification, musical stimuli comprising of instrumental renditions of Hindustani Classical Ragas were digitally recorded. Ragas were chosen to induce both positive and plaintive emotional states. A detailed questionnaire to ascertain demographic information, details of music preference and training was administered before the survey. A website was designed to elicit and record participant responses on eight emotions (viz. Happy, Romantic/Tender, Devotional, Calm/soothed, Angry, Tensed/Restless, Longing/Yearning and Sad) on a five point scale.

Figure 2(a) shows the averaged percentage responses by participants for positive (red) and plaintive (blue) ragas played in alaap (i.e. the slow non-rhythmic introductory section of raga) while Figure 2(b) shows the effect averaged responses for the same ragas played in gat (i.e. the fast rhythmic composition).

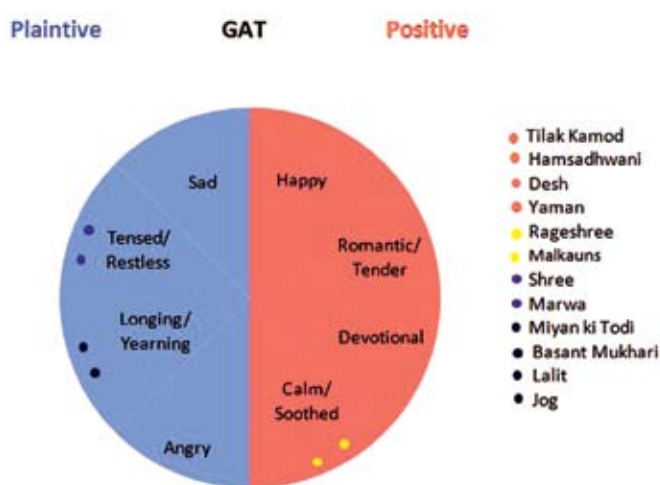
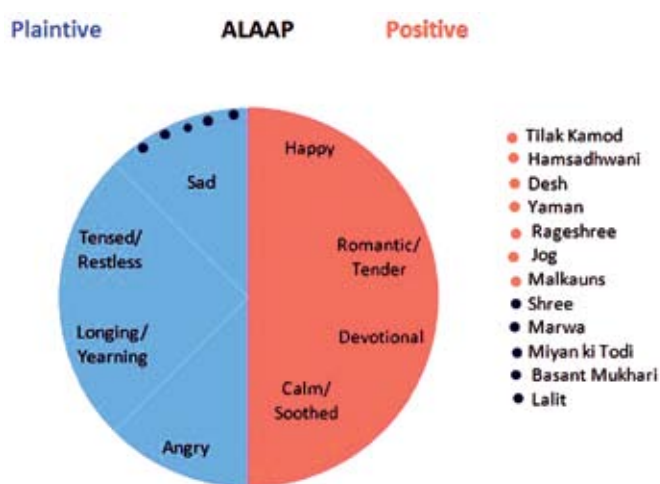
The pie chart in Fig. 2(a) represents the highest rated emotion for ragas played in alaap. The ragas that were rated 'calm/soothed (positive)' are shown by red dots and ragas rated 'sad (plaintive)' are depicted by blue dots.

Fig. 2(b) represents the highest rated emotion by participants for the same ragas played in gat. We see a shift in the rating scales. Some ragas that were rated as calm and soothing during the alaap renditions were now rated as 'happy' (Red dots). Similarly we see a discrimination among different emotional states for plaintive ragas. Our findings thereby suggest an important role for tempo in emotion perception in music.

Conclusion

Our preliminary findings indicate a strong correlation between the emotions experienced by the participants and the intended emotion by the artist for all the ragas. Current analysis is directed at understanding the role of tempo in emotion ratings. Multiple regression analysis will be used to determine prominent tonic intervals and their relative importance.

We will also use functional neuroimaging to investigate the neural correlates underlying the perception of different emotional states.



Publications

1. Katherine Sullivan, Megha Sharda, Jessica Greenson, Geraldine Dawson and **Nandini C Singh (2013)** A novel method for assessing the development of speech motor function in toddlers with autism spectrum

disorders, *Front. Integr. Neurosci.* 7:17. doi:10.3389/fnint.2013.00017.

2. Chaitra Rao, Avantika Mathur and **Nandini C Singh (2013)** 'Cost in Transliteration'–The neurocognitive he Neurocognitive Processing of Romanized Writing, **Brain and Language** 124, 205-212,.
3. Arkoprovo Paul, Megha Sharda and **Nandini Chatterjee Singh (2013)** Effect of Music Instruction on Cognitive Development: A **Review. Journal of the Indian Institute of Science**, 92, 441-445

Presentations

1. Nandini C Singh – Language and the Brain, Science Fest, Ambedkar Centre for Biomedical Research, Delhi University, March 2012.
2. Nandini C Singh – Speech and music in autism, COMDEALL workshop on autism, Bangalore, May 2012.
3. Nandini C Singh – Neuro-imaging for language function – in health and disease, Workshop on Aphasia, Indore, August 2012.
4. Nandini C Singh - 'Reading Assessments in a bilingual-biscriptal setting', Maharashtra Dyslexia Association, Mumbai, 14th February 2013.
5. Nandini C Singh – 'Number Sense' – how cognitive neuroscience can aid the teaching of mathematics in schools, Cluster Innovation Centre, Delhi University, New Delhi, 28th February 2013.
6. Nandini C Singh – 'Singing in the Brain', Frontiers of Speech and Music, Jadavpur University, Kolkata, 5th March 2013.

Funding

1. Research grant on 'Development and validation of screening tool to identify learning disability (teacher administered screening tool', Department of Science and Technology, 2013-14.
2. Research grant on 'Speech and Music Processing in Autism', from Department of Science and Technology, 2012 -2015.
3. Research grant on 'A functional imaging study of dyslexia in biscriptal Indian Children' from Department of Biotechnology (2011-2014)

Collaborator

- 1) Dr.V.S.Mehta, Director of Neuorosciences, Paras Hospital, Gurgaon, India.
- 2) Dr. Amit Sen, Children First, New Delhi.

APPLICATION OF STOCHASTIC ACTIVATION AND STABILITY ANALYSIS FOR BRAIN IMAGING AND THERAPY

Principal Investigator

Prasun K. Roy

Research Fellow

Subhadip Paul, Rekha Varrier

Project Assistant

Rajiv Ramaswamy

Perturbation-induced activation, an emerging research field in computational neuroscience, offers a promising prospect to enhance the efficiency of diagnostic or therapeutic applications in neuroscience. Stochastic activation, noise-aided resonance or fluctuation-induced transition, is a general principle of nonlinear biological systems, and occurs basically due to the statistical kinetic nature of the components that exhibits probabilistic fluctuations of parameters. However the practical application of stochastic activation effect as a novel technique in diagnostic or therapeutic radiology has not been systematically pursued, and the applicability is the aim of our project.

MRI-based Elastometric relaxation mapping of brain parenchyma with Ageing and Alzheimer's Disease:

Due to the recent looming pandemic of neurodegenerative diseases of ageing, one crucially requires non-invasive determination of the biophysical coefficients of the brain tissue parenchyma, such as elasticity, plasticity and topological connectivity. These indices can help develop new mechanistic insights and offer efficient robust structural physics-based biomarkers. Nevertheless one may note that the conventional methodology of MR-based stress-strain measurements and elastic determination of tissue parenchyma is not readily usable in the clinical domain, as one needs to administer efficient ultrasonic deformation to the brain tissue via a piezoelectric transducer through the two impervious bony diploic tables of the human skull (which produces irreversible signal weakening). There, one also needs intricate mechanostriktion-based radiofrequency signal-acquisition and processing schemes for the scanner. Thus an alternative MRI approach is required as a priority.

From MRI scans [fig. 1(a)], we have developed the MRI methodology for determining the texture characteristics and transport processes as tissue displacement and distortion, and have also estimated the temporal dynamics of biophysical mobility parameters as conductivity and perfusivity, as well as tensile elasticity and contextual connectivity. We now analyse the normal brain parenchyma in terms of the schema of a 2 phase media, namely intracellular and extracellular phase [fig. 1(b)]. For a porous substance in a fluid (the architecture of tissue parenchyma), it is known that different transport processes----properties as perfusion, conduction, permeation or deformation flow----are inter-related due to boundary conditions of the tissue geometry. We have developed a computational model of the change in elasticity and connectivity as metabolic ageing occurs, in terms of a stochastic relaxation in fluctuation of the transport parameters (like diffusivity or elasticity), under the influence of amyloid nucleation, in terms of the latter's reaction kinetics. This amyloid formation induces an extra inclusionary phase with stability [fig. 1(c)], and, as time elapses, our model predicts that the fluctuation of the transport parameters diminishes, while the absolute value of the parameters approaches a fixed stationary level [fig. 1(d)].

As ageing occurs, there is gradual decrease of basal energy metabolic rate, implying the transition from a non-equilibrium state and settling towards a stationary state [fig. 1(d)]. The elasticity and conductivity parameters have been found out using the MRI images of 48 subjects across age range of adulthood, 18-90 years [fig 1(e)]. The curves A and B show the bounds of the fluctuating level of tissue elasticity, and actually form an envelope around the mean

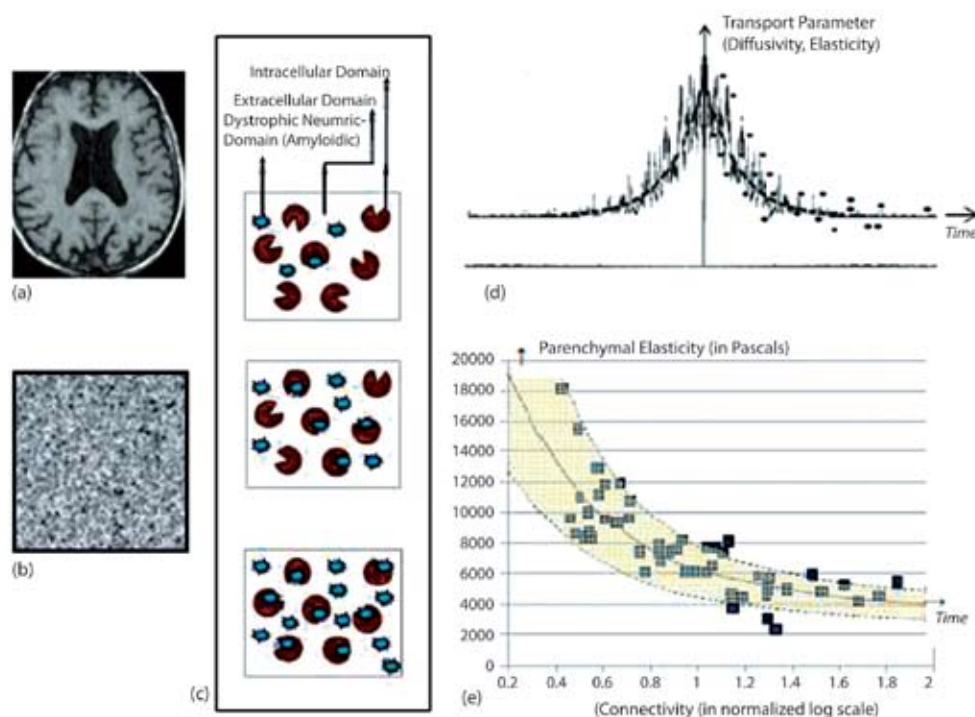


Fig. 1: (a). MRI image of brain using which the parenchymal tissue elasticity is determined from elastoporosity analysis. **(b).** Normal brain tissue as hydroporous medium consisting of two phases schematically (intracellular and extracellular phases). **(c).** Formation of the third phase of amyloid dystrophic neuritic domain under advanced ageing process (three temporally-successive stages are shown vertically from top to bottom). **(d).** Biophysics-based theoretical model of the transition of an elasoporous system from stationary state to high activation state (curve PQ), accompanied by increasing fluctuation in the transport parameter (elasticity). The reverse transition, from high activation state to stationary state (curve QR), is associated with decreasing fluctuation in elasticity. The black dots show the fluctuating descending graph at different time points. **(e).** The MRI elastoporosity analysis is used to find the tissue elasticity and topographical connectivity from the scan of each individual, the data points for 44 subjects are shown. The decreasing graph is shown in curve C, while the the evevelope curves A and B show the bounds of the fluctuations. As ageing occurs the data points (blue squares) closely correspond to the event points (dots) of the theoretical formulation in panel (d).

elasticity curve C, as time elapses. To paraphrase, as ageing process ensues, there is increasing elastoplastic relaxation, whereby the intracellular phase attenuates, decreasing the resilience and elasticity, and the contextual connectivity reduces due to the consolidation effect. As the intracellular space phase reduces, the phase can accommodate only decreasing fluctuation variance that can be lodged in the diminishing intracellular phase. The experimental data in fig. 1(e) can be satisfactorily accounted by our theoretical relaxation model ($r = 0.88$). It may be underscored that we find the temporal elasticity relaxation coefficient μ be an effective rate index, the value obtained from our study is $\mu = 127$ pascals/year. Increasing amyloid deposition, as in Alzheimer's disease, would increase the elasticity relaxation

index μ , which can thus have import as a neuroimaging marker. This is the first study of elastoporous ageing of brain parenchyma which can now be observed by ready MRI images, with incisive implications for diagnostic, screening and monitoring utility.

Enhancement of Tumour Control and Normal Tissue Protection in Radiotherapy, using Neuroimaging-based dose perturbation protocol

The major future development of neuroimaging is slated to be in the in the area of treatment planning and optimization. Based on MRI image analysis, we have utilized the stochastic activation approach to enhance the

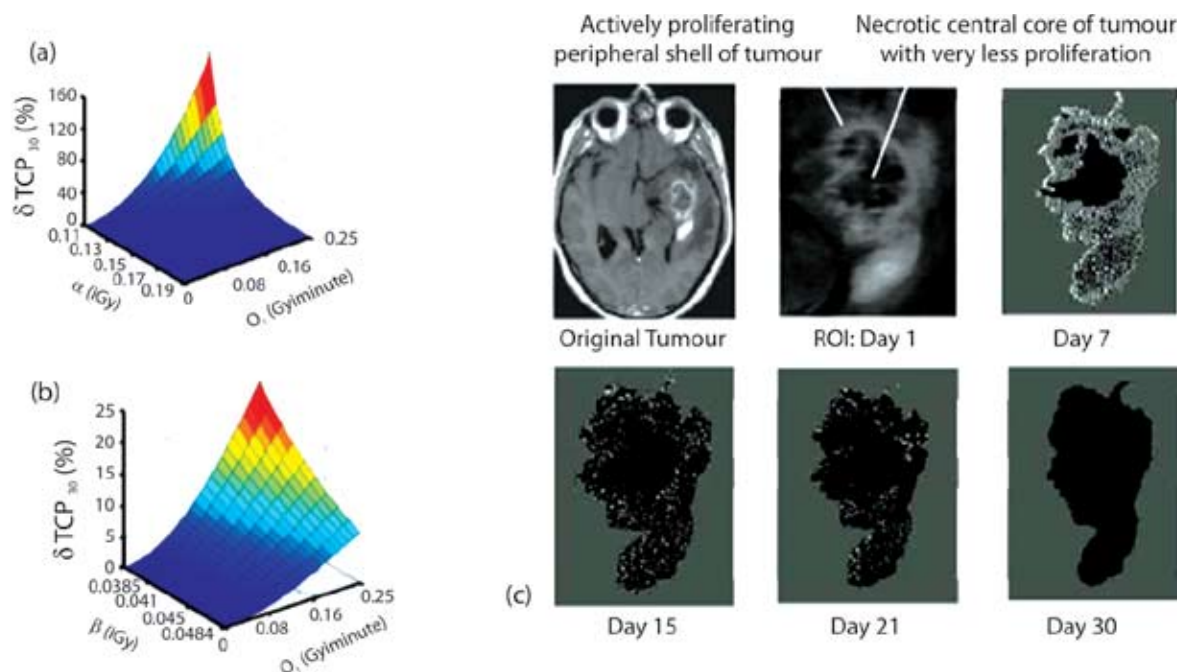


Fig. 2. (a). The 3-D surface plot of the increase of Tumour Control Probability [ΔTCP_{30} (%)] as there is increase of the stochastic fluctuation amplitude of the radiotherapy beamlet (σ_t , in Grays per minute), the response surface also depicts the TCP probability as there is change in the radiobiological parameter of single-strand interference by radiation (α , per Gray units). **(b).** Rise of Tumour Control Probability [ΔTCP_{30} (%)] vis-a-vis the increase of fluctuation of the radiation beamlet (σ_f , in Rads per minute), the third axis plots the values of the radiobiological parameter of double-strand interference by radiation (β , per Gray units). **(c).** Contrast enhanced T1 image of the tumour, the image is used to construct the MRI template to formulate the radiobiological effect of stochastic radiotherapy on the neoplastic lesion. The tumour cell density is denoted by the intensity of marker points in the third to sixth panels. The contrast MRI scan is used to segment the tumour into high active tumorigenic zone and the necrotic central zone of very low proliferation (third panel). The successive panels show planning and modelling contour of the tumour response after a month of stochastic fractionated radiotherapy. No marker point intensity in the last panel, indicating satisfactory tumour containment and maximization of the Tumour Control Probability parameter.

efficiency of tumour cell elimination vis-a-vis normal tissue protection under therapeutic radiology, with particular application to brain tumours. The major disadvantage of radiotherapy or chemotherapy is that the therapy agent damages both malignant tissue and normal tissue, leading to serious therapy-induced toxicity. We have investigated the effect of radiotherapy photon on the alteration of the DNA double-strand (linear-quadratic formulation of two-hit event), and the outcome of temporally perturbing the radiotherapy beam, done by increasing the gaussian temporal fluctuation of the beam by means of a probabilistic function generator in the pulse circuit of the linac beam. We have shown how selecting proper perturbation parameters (variance level and dose fraction interval) in

the beam flux can increase the therapeutic differential of treatment considerably, so that more malignant cells and less normal cells are eliminated. An important advantage of this approach is that the total dose administered by the beam is not increased. In clinical settings, one selects the most efficient radiotherapeutic schedule (out of different types of radiotherapy protocols) by choosing one that maximizes the tumour control probability formulation, yet minimizing the normal cell damage.

Our study shows that the increase in the level of mean-zero fluctuation of dose-rate appreciably enhances tumor control probability (TCP) in glioma, without needing dose increase [fig. 2(a-b)]. The MRI image of the gadolinium contrasted

tumour [fig.2(c)] is used to construct therapy planning and simulation template to formulate the radiobiological effect of stochastic radiotherapy on the neoplastic lesion, the tumour is segmented into two regions: the dense shell or rim of actively proliferating tumour cells, which surround the central deep core with low blood supply, harbouring the necrotic region with very less number of active tumour cells. For the radiotherapy planning and simulation, we use conformal collinear projection, so that the radiation dose is distributed spatially or temporally across multiple pencils (6-12 in number), which converge together only on the tumour tissue, leaving the surrounding normal tissue traversed by only one pencil that which gives only 8-13% of the dose to normal tissue, effectively sparing that tissue. Our study indicates the feasibility of utilizing Gaussian perturbation of the beam to increase tumor control probability and normal tissue protection without increasing the dose administered to the patient. The approach can also be applied to other antitumour modality as radiochemotherapy, where the chemotherapeutic agent is activated by pulsed radiation.

Presentation

1. Ramaswamy, R., Khanna, R., Roy, P. Effect of Ageing and Gender on modulating the Elastic Responsivity and Topological Connectivity of the Brain, Ann. Conf. on Magnetic Resonance Society of India, Indian Institute of Technology, Bombay, Feb. 2013.
2. Varrier, R., Kondra, S., Roy, P. Developmental Implications of Information Pathways in Brain using fMRI Perceptanalysis, Proc. International Symposium on Computational Neuroscience, Indian Institute of

Science, Education & Research, Pune, April. 2012.

3. Roy P, The Indian Brain Imaging Grid: Application to Diagnosis & Therapy, Canada-Israel-India Trilateral Brain Roundtable and Technology Partnering Mission, Institute of Medical Research (IMRIC), Tel- Aviv, May 2012.

Funding

Ministry of Information Technology, Govt. of India.

Core funds of NBRC.

Collaborators

- I. Dr Alan Evans, Montreal Neurological Institute, McGill University
- II. Dr. Manjari Tripathi & Dr P Sarat Chandra, All-India Institute of Medical Sciences, Delhi.
- III. Dr Ralph Martins, Edith Cowan University & CRC Mental Health Instt., University of Melbourne.
- IV. Dr T R Seshadri, University of Delhi.

Awards

- I. Paul, S. Paper on "The effect of stochastic fluctuation in radiation dose-rate on cell survival following fractionated radiation therapy" (Physics in Med. & Bio., 57: 1561-70, 2012) chosen as Target selection paper by Global Medical Discovery, Ottawa, Canada, for being of importance to drug discovery process.
- II. Paul, S. Travelling Award for participating at Society of Neuroscience Meeting, New Orleans, 2012.

SPATIOTEMPORAL PROCESSING AND INFORMATION TRANSMISSION IN BRAIN

Principal Investigator

Prasun K. Roy

Research Fellow

Suhela Kapoor

Research Engineer

VPS Rallabandi

Comprehending how flow or transport processes occur, whether that of energy, information, electrical current, drugs, cells or tissue displacement, is a fundamental problem in basic and applied neuroscience. Conventional scalar quantitative models of flow processes, have difficulty in accounting for experimentally-observed preferential flow in axial direction in layered tissues as brain or muscle. Hence, one needs a quantitative computational approach that can clarify and predict the various transport processes and their modulation across the brain, vis-à-vis tissue orientation. The recent advance of tensor neuroimaging, beyond simply scalar imaging, implies a broad general perspective towards pathophysiological processes, wherein one can study the various transport processes or flow parameters in the layered brain parenchyma, as chemical diffusion, cellular permeation, electrical conduction and information transmission. The overall objective of this program is to obtain basic insights and translational implications, regarding the physiological or pathological dynamics of the various transport or flow processes in the brain parenchyma.

MRI-enabled Preclinical & Clinical Approach to Neuroprotective Intervention in Cerebral Stroke and Vascular Dementia

Accounting for a tenth of worldwide mortality, stroke is the leading cause of brain-related deaths, while the incidence of stroke's sequelae, vascular dementia, is an important demographic problem in southern Asia, due to increasing propensity of thromboembolic disorders. Regarding therapy of cerebral stroke, there is an essential requirement of developing a quantitative approach to optimize the performance of a translational

neuroregenerative intervention. We develop a quantitative analysis of endogenous neurogenesis and neuronal migration from subventricular zone (SVZ) to the stroke penumbra zone (SPZ), and thereafter synaptogenesis and its stabilization in target penumbra tissue, that occurs normally to some extent in stroke patients, and this restoration process can be enhanced by pharmacological agents. Using a preclinical rodent model for cytological or immunohistochemical studies and MRI investigations [fig. 3(a-d)], we have developed the mathematical formulation of neural stem cell proliferation, neuroblast migration and its spatiotemporal mobility across brain parenchyma.

Utilizing the associated NFkB pathway modulation, we develop the cellular flow dynamics using the nonlinear differential equations for neural stem cell formation in the SVZ. Thereafter we formulate the neuroblast migration process that is known to be thermodynamically coupled to the CSF flow dynamics, the migration occurring across the lateral ventricular wall (MRI/CSF flow imaging), and then across the orthogonal fibre tracts (MRI-DTI image). We have thus elucidated an endogenous neural stem cell-based approach which deals with cell migration using parenchymal compartment analysis by incorporating (i) the principles of Michaelis-Menten kinetics and (ii) the chemotactic gradient-caused cell mobility, so as to formulate neuroblast renewal and its permeation. Thereafter, using allometric cytokinetic principles, we adapted the approach to the human system, and we developed a quantitative formulation for the neural progenitor cell migration using stochastic diffusion terms obtained from MRI diffusion tensor imaging [fig. 3(e)].

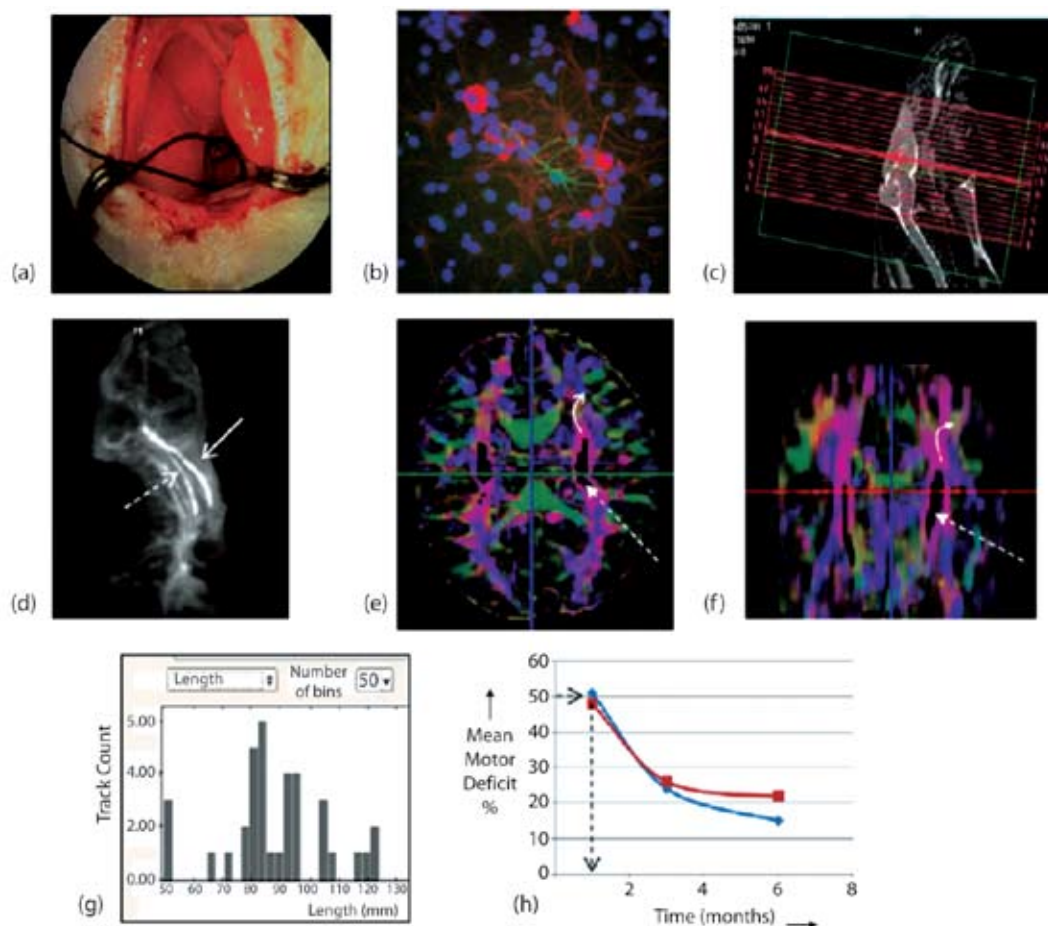


Fig. 3. (a): Development of preclinical rodent model of cerebral stroke by occluding an unilateral middle cerebral artery under the surgical preparation. (b): Obtaining neural stem cell proliferation characteristics from subventricular zone (SVZ) cultures. Staining of neuron on 3rd day by NeuN & GFAP. (c): Calibration scan for structural imaging of rodent stroke model. (d): Checking unilateral arterial occlusion of rodent stroke preparation using Magnetic Resonance Angiography (MRA) by paramagnetic Gadolinium contrast agent to delineate limitation of blood flow and constriction of a blocked arterial field (dashed arrow) when compared with the normal arterial field of the other side (continuous arrow). (e-f): MRI diffusion imaging to show oriented tracts (continuous arrows) that enable progenitor cell migration out from periventricular SVZ to peripheral cortical target region in human subject (axial and coronal views), the lateral ventricles are shown by dashed arrows. (g): MRI-based track geometry mapping, that furnishes the path length of the tracts along which the progenitor cells migrate from SVZ to peripheral cortical region. (h): Clinical corroboration of neuro-computational model that calculates the time required for progenitor cell migration and synaptogenesis (stroke recovery). Time duration of stroke recovery for lesion at temporoparietal area for subject is 39 days as predicted by the mathematical model. The predicted duration is substantiated by clinical observation of median restoration time of 5 weeks for stroke recovery of patient [arrow in panel (h), point N], the two curves (red and blue) are respectively for sensory and motor recovery.

Thereby we have estimated (i) the migration speed of the neuroblasts (ii) the path length required to be traversed by the migrating neuroblasts from SVZ to SPZ, as estimated from MRI diffusion tensor imaging of the patient [fig. 3(f-g)], (iii) the time required for the neuroblasts to move from SVZ to SPZ whence neurological recovery, synaptic

functionality and information transmission ensues. The results of the quantitative cytological and neuroimaging analysis and its prediction are corroborated by data of clinical findings from neurological patient recovering from stroke [fig. 3(h)]. Thus we now have both animal and human quantitative formulations of stroke recovery

under endogenous neurogenesis, substantiated with both mammalian and patient findings. This model can now be utilized to probe the enhancement of the performance of neurogenesis and synaptogenesis, under pharmacological action, so as to augment the scope of regenerative therapy in stroke and vascular dementia, utilizing the MRI-based architecture of brain parenchyma.

Presentation

1. Kapoor S, Subramanyam V, Roy P. Optimizing performance of endogenous neural stem cell therapy for ischaemic stroke: A Neuroimaging approach to translational medicine, International Conference on Neuroinformatics, Munich, Sept. 2012.
2. Subramanyam, VPS, Roy, P. Translational Neuroscience and imaging-guided therapy, University of Health sciences, Rohtak, April 2012.
3. Kapoor S, Subramanyam V, Roy P. Ischaemic stroke therapy using endogenous neural stem cell strategy: A validated neuroinformatics approach, NEUROCON 2012, Neurological Society of India, New Delhi, Dec. 2012.
4. Roy, P. Stereo Neuroimaging of Electrical Activation Field: Source Localization using 3-D MRI Human Brain Mapping, Indo-U.S. Workshop on Modelling Electrical Activity in Physiological Systems, Indian Institute of Science Education & Research, Mohali, May 2012.

Funding

Dept. of Biotechnology, Govt. of India.
Utrecht University Research Foundation, The Netherlands.

Collaborators

- I. Dr Peter Luijten, Dutch Centre for Translational Molecular Medicine & Utrecht University.
- II. Dr M V Padma & Dr T S Roy, All-India Institute of Medical Sciences, Delhi.
- III. Dr R. K. Padhi, Indian Institute of Science, Bangalore.
- IV. Dr Santanu Chaudhuri and Dr Raj Khanna, Indian Institute of Technology – Delhi.
- V. Dr Shinjini Bhatnagar, Translational Health Science & Technology Institute, Gurgaon.

Awards

- I. Kapoor, S. Travel Fellowship, Bernstein Workshop, Technical University of Munich, Germany.
- II. Kapoor, S. Visiting Studentship, Utrecht University Medical Centre, Netherlands.

M. Tech. thesis

B. Victor, A Systems Pathway Approach to Cerebrovascular Lesions (SRM University, Chennai).

NON-INVASIVE MAPPING OF BRAIN OXIDATIVE STRESS AND pH AS DIAGNOSTIC BIOMARKER OF ALZHEIMER'S DISEASE

Principal Investigator

Dr. Pravat Kumar Mandal, Ph.D

Researcher

Dr. Sumiti Saharan, Ph.D

Oxidative stress

Alzheimer's disease (AD) is a critical health concern, with millions of older individuals affected worldwide. As such, the last decade has witnessed AD research, focused on delineating biomolecules that reliably reflect AD pathology-induced alterations in the brain. Recent research has evidenced the role of oxidative stress (OS) in early AD pathogenesis, with increasing evidence that the mechanisms leading to development of AD pathology, and consequent neuronal death, are a result of increased OS. One of the key causes for AD-pathology related increase in OS has been shown to be decrease in levels of the antioxidant Glutathione (GSH). GSH is a major endogenous enzyme-catalyzed brain antioxidant that plays a fundamental role in regulation of the intracellular oxidative state. Various *in vivo* transgenic animal studies as well as post-mortem analyses of AD patient brains have reported depletion of GSH levels with progression of AD.

In a pioneering study, we employed MEGA-PRESS Magnetic Resonance Spectroscopy (MRS) to assess the *in vivo* distribution of GSH in brains in cognitively normal human subjects as well as patients with Mild Cognitive Impairment (MCI) and with AD. Using MEGA-PRESS MRS, we were able to detect a clear signal of GSH in the brain. Our study revealed a region-specific distribution of GSH within the brain. In addition to region-specificity, we also observed gender dependence in GSH distribution. The mean GSH content was found to be relatively higher in healthy female subjects compared to healthy male subjects, with significantly higher levels in frontal and parietal regions of female subjects. Moreover, GSH levels were found to be depleted in AD in a gender-specific manner, with significant

reduction of GSH levels in the right frontal cortex (RFC) of AD female patients and in the left frontal cortex (LFC) of AD male patients as compared to healthy young counterparts.

Recently, we also performed a comparative analysis of GSH levels in the RFC regions of female subjects over age and clinical status. Our analysis demonstrated a gradual, although non-significant, decrease of GSH levels in the RFC with aging, as reflected by comparison of GSH levels between healthy young (20-30y) and healthy old (55+y) female subjects (unpublished data, Fig. 1). The GSH levels were found to fall noticeably in MCI patients, and were further depleted in female patients with AD (Fig. 1). The GSH levels within the RFC of female AD patients were not only found to be significantly lower than healthy young female subjects, they were also significantly reduced in comparison to healthy aged controls (unpublished data). Our study highlights the importance of assessing *in vivo* GSH levels of specific brain regions such as frontal cortex, which are known to be susceptible to AD pathology. Early detection of AD will entail identifying brain alterations due to pathology at its very incipient stages. This ongoing work in our laboratory and preliminary findings suggest that GSH levels in the frontal cortex may also be able to clearly distinguish MCI subjects from healthy aged subjects.

pH

In addition to alterations in OS, our previous findings have shown AD-induced changes in brain pH, with the left hippocampus of AD subjects showing an increase towards alkalinity as compared to healthy normal as well as MCI subjects. Most brain neurochemicals, which have

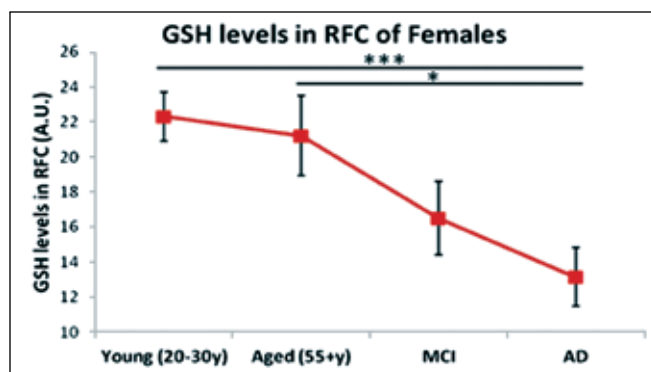


Figure 1: In vivo detection of GSH in the brain with MRS. Quantitative representation of alterations in GSH concentration in the RFC of females with aging and clinical state using MEGA-PRESS pulse sequence in 3T scanner. GSH levels in right frontal cortex were measured for (a) healthy 26y old female; (B) healthy 56y old female; (c) 50y old MCI female; and (d) 62y old probable AD female patient. GSH levels were found to gradually decrease with aging. However, there is a further sharp decline in GSH levels associated with onset of MCI, and continued depletion with progression to AD. The GSH levels in AD patients are significantly lower from healthy young as well as healthy older subjects.

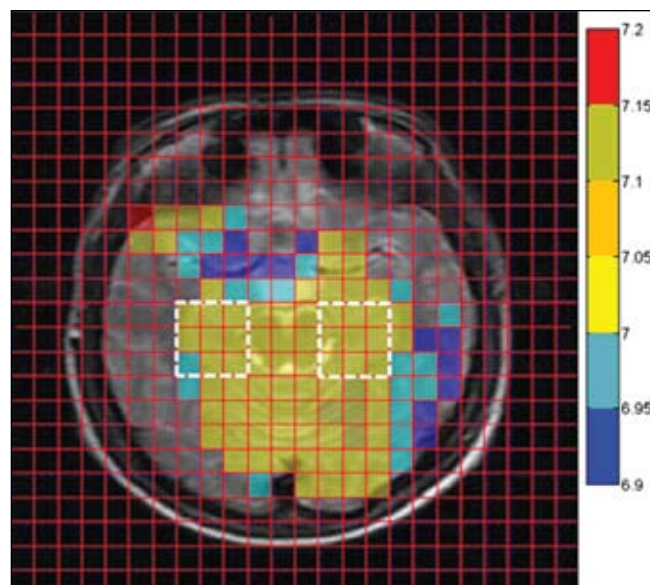


Figure 2: Preliminary multi-voxel ^{31}P MRS data showing brain pH of a healthy brain at various voxels. Data was processed using in-house MATLAB programming. Color coding represents pH values at different voxels as depicted in the color bar.

been reported to decrease with AD pathology, also decline with healthy aging. Consequently, these biomolecules may not be reliable indicators of AD pathology onset. On the other hand, brain pH has been shown to become acidic with healthy aging. This inversed of pH levels, from acidic in healthy aged individuals to alkaline in AD patients suggests that monitoring of pH levels might provide an excellent indicator of the changing healthy aged-to-AD population. Given the clinical significance of these findings, we have recently developed a novel methodology to map pH levels in the entire brain. We have standardized the methodology to measure pH in various layers of the brain using ^{31}P MRS and generated a brain pH map of healthy controls (Fig. 2). We aim to characterize the chronological changes in pH of different brain regions with healthy aging as well as in MCI and AD.

Publications

1. **Pravat K. Mandal** (2012) *Predictive biomarkers for Alzheimer's disease using state-of-the-art brain imaging techniques.* **Journal of Alzheimer's Disease**, 31, S1-3.
2. **Pravat K. Mandal***, H. Akolkar, and Manjari Tripathi (2012) *Mapping of Hippocampal pH and Neurochemicals*

from in vivo Multi-Voxel ^{31}P Study in Healthy Normal Young Male/Female, Mild Cognitive Impairment, and Alzheimer's disease. **Journal of Alzheimer's disease**, 31, S75-86.

3. **Pravat K. Mandal***, Jitesh Joshi, Sumiti Saharan (2012) *#. Visuospatial Perception: An Emerging Biomarker for Alzheimer's Disease.* **Journal of Alzheimer's Disease**, 31, S117-35.
4. **Pravat K. Mandal***, Rashima Mahajan, Ivo D. Dinov (2012) *#. Structural Brain Atlases: Design, Rationale and Applications in Normal and Pathological Cohorts.* **Journal of Alzheimer's Disease**, 31, S169-88.

#These articles were IN PRESS at the time of 2011-2012 annual progress report.

Financial Support

Agency: Department of Biotechnology, Govt. of India

Role: Principal Investigator

Collaboration

- Dr. Manjari Tripathi, MD, DM, Department of Neurology, All India Institute of Medical Sciences, New Delhi.

INTERACTIONS OF AMYLOID BETA PEPTIDE AND ANESTHETICS: DETECTION OF FLUORINATED DRUGS USING *IN VIVO* ^{19}F SPECTROSCOPY

Principal Investigator

Dr. Pravat Kumar Mandal

Researchers

Shammi More

Bharath HN

Dr. Sumiti Saharan

Magnetic Resonance Spectroscopy (MRS) has emerged as an important non-invasive technique for the *in vivo* detection of neurochemicals present in the living tissues, including the brain. There are various molecular nuclei, such as proton (^1H), phosphorus (^{31}P), carbon (^{13}C), sodium (^{23}Na) and fluorine (^{19}F), that can be detected by MRS. Due to the near absence of any endogenous ^{19}F signal from brain, ^{19}F MRS technology has found immense application in *in vivo* detection and quantification of fluorinated drugs in psychiatric disorders, such as depression. A majority of psychiatric medications, e.g. fluoxetine, fluvoxamine, trifluoroperazine, are fluoro-labelled. ^{19}F MRS studies have estimated the whole brain concentrations of fluorinated drugs in various psychiatric patients using large single voxel ^{19}F MRS. Although single voxel ^{19}F MRS enables quick estimation of fluorine levels within the whole brain; it does not address spatial heterogeneity in the distribution of fluorinated drugs. The brain is not a homogenous organ and the regional distribution of drugs within the specific brain regions of interest (ROI) depends on several factors, such as 1) differences in the cell type and density within the ROI, 2) differences in drug affinity to ROI, for e.g., phospholipid content of tissue and the lipophilicity of the drug, and 3) differences in vasculature and blood flow rate, etc. In clinical research, quantification of drug concentrations in different brain ROI is immensely important as it would not only enable assessment of the distribution pattern of the fluorinated drugs within the brain, but also allow estimation of drug concentration in different brain ROIs.

We have addressed this issue by developing a novel Matlab-based approach for the processing and quantification of the multi-voxel ^{19}F signal from various ROIs at the same time. We have successfully demonstrated the acquisition of multi-voxel ^{19}F MRSI signal from a phantom containing

hexafluorobenzene (Fig. 3). We hope to further standardize and utilize this processing and quantification approach for *in vivo* ^{19}F quantitation from various brain regions of patients on fluorinated psychiatric drugs.

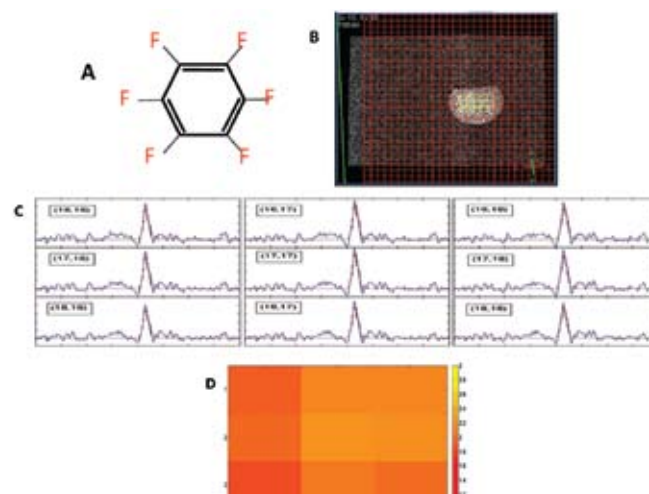


Figure 3: A) Chemical structure of hexafluorobenzene, (B) Spectroscopic imaging of the phantom containing hexafluorobenzene with chloroform. (C) Shows obtained 3x3 multi-voxel MRS signal spectra (Blue) and the fitted spectra (Red), (D) depicts the color map of the metabolite concentration (in arbitrary units) for a 3x3 multi-voxel MRS.

Financial Support

Agency: Department of Biotechnology, Govt. of India

Role: Principal Investigator

Collaboration

- Dr. Rajesh Sagar, MD (Psychiatry, AIIMS)



Publications & Patents

PUBLICATIONS

1. Dikshit B, Irshad K, Madan E, Aggarwal N, Sarkar C, Chandra PS, Gupta DK, Chattopadhyay P, **Sinha S**, Chosdol K (2012). FAT1 acts as an upstream regulator of oncogenic and inflammatory pathways, via PDCD4, in glioma cells. **Oncogene** advance online publication, 17 September 2012; doi: 10.1038/onc.2012.393 (joint corresponding author).
2. Kumar R, Andrabi R, Tiwari A, Sankaran S.P, Wig N, Dutta D, Sankhyan A, Khan L, **Sinha S**, Luthra K (2012). A novel strategy for efficient production of anti-V3 human scFvs against HIV-1 clade C, **BMC Biotechnology** Online Publication, 15 November 2012; doi:10.1186/1472-6750-12-87 (joint corresponding author)
3. Andrabi, R, Kumar R, Bala M, Nair A, Biswas A, Wig N, Kumar P, Pal R, **Sinha S**, Luthra K (2012). Production and characterization of human anti-V3 monoclonal antibodies from the cells of HIV-1 infected Indian donors. **Virology Journal**, 2012, 9:196
4. S. Bhutani, A. Das, M. Maheshwari, S.C. Lakhota and **N.R. Jana** (2012). Dysregulation of core components of SCF complex in polyglutamine disorders. **Cell Death and Disease**, 3, e428.
5. D. Chhangani, **N.R. Jana** and A. Mishra (2013). Misfolded Proteins Recognition Strategies of E3 Ubiquitin Ligases and Neurodegenerative Diseases. **Molecular Neurobiology**, 47, 302-312.
6. A. Mishra, M. Maheshwari, D. Chhangani, N. Fujimori, F. Endo, A. P. Joshi, **N. R. Jana** and K. Yamanaka (2013). E6-AP association promotes SOD1 aggregates degradation and suppresses toxicity. **Neurobiology of Aging**, 4, 1310, e11-23.
7. M. Maheshwari, A. Samanta, S. K. Godavarthi, R. Mukherjee, and **N.R. Jana** (2012). Dysfunction of the Ubiquitin Ligase Ube3a May Be Associated with Synaptic Pathophysiology in a Mouse Model of Huntington Disease. **Journal of Biological Chemistry**, 287, 29949-29957.
8. J. Sharma, D. Mukherjee, S. N. Rao, S. Iyengar, S. K. Shankar, P. Satishchandra and **N. R. Jana** (2013). Neuronatin mediated aberrant calcium signaling and endoplasmic reticulum stress underlie neuropathology in Lafora disease. **Journal of Biological Chemistry**, 288, 9482-9490.
9. Dixit D, Ghildiyal R, Anto NP, Ghosh S, Sharma V and **Sen E** (2013). Guggulsterone sensitizes glioblastoma cells to Sonic hedgehog inhibitor SANT-1 induced apoptosis in a Ras /NF κ B dependent manner. **Cancer Letters**. 33:347-358
10. Gupta P, Ghosh S, Nagarajan A, Mehta VS, **Sen E** (2013). β -defensin-3 negatively regulates TLR4-HMGB1 axis mediated HLA-G expression in IL-1 β treated glioma cells. **Cellular Signaling**. 7;25(3):682-689.
11. Gupta P, Dixit D and **Sen E** (2013). Oncrasin targets the JNK-NF κ B axis to sensitize glioma cells to TNF α induced apoptosis. **Carcinogenesis** 34(2): 388-396.
12. Ghildiyal R, Dixit D, **Sen E**. (2012). EGFR inhibitor BIBU induces apoptosis and defective autophagy in glioma cells. **Molecular Carcinogenesis**. 10.1002/Inc.21938.
13. Tewari R, Choudhury SR, Mehta VS, **Sen E**. (2012) TNF α regulates the localization of CD40 in lipid rafts of glioma cells. **Mol Biol Rep**. 39(9):8695-9.
14. Maharana C, Sharma KP, **Sharma SK** (2013) Feedback mechanism in depolarization-induced sustained activation of extracellular signal-regulated kinase in the hippocampus. **Sci Rep**. 3:1103.
15. I M Ariff, M C Thounajam, S Das, and **A Basu** (2013) Japanese Encephalitis virus infection alters both neuronal and astrocytic differentiation of Neural Stem/progenitor Cells. **J Neuroimmuno Pharmacology** (in press)
16. V Haridas, K S Rajgokul, S Sadanandan, T Agrawal, V Sharvani, M V S Gopalkrishna, M B Bijesh, K L Kumawat, **A Basu**, G R Medigeshi (2013) Bispidine-amino acid conjugates act as a novel scaffold for the design of antivirals that block Japanese encephalitis virus replication. **PLoS Neglected Tropical Diseases** 7(1): e2005
17. A Majhi, A Mahanti, K Kundu, K Dutta, **A Basu**, and B Bishayi (2013) Increased resistance of immobilized-stressed mice to infection: correlation with behavioral alterations. **Brain, Behaviour, and Immunity** 28:115-27.
18. **Ranade Sayali**, Nawaz S, Pavan Kumar R, Rose AJ, Gressens P and Mani S (2012). Early protein malnutrition disrupts cerebellar development and impairs motor coordination. **Br J Nutr**. 107(8) :1167-75.
19. **Ranade Sayali**, Nawaz S, Chakrabarti A, Gressens P and Mani S (2013). Spatial memory deficits in maternal iron deficiency paradigms are associated with altered glucocorticoid levels. **Hormones and behaviour**. 64(1):26-36.

20. Arkadeb Dutta, Niranjana Kambi, Partha Raghunathan, Subhash Khushu, **Neeraj Jain (2013)**. Large-scale reorganization of the somatosensory cortex of adult macaque monkeys revealed by fMRI. **Brain Structure and Function**. (In Press).
21. Shashank Tandon, Niranjana Kambi, Hisham Mohammed and **Neeraj Jain (2013)**. Complete reorganization of the motor cortex of adult rats following long-term spinal cord injuries. **European Journal of Neuroscience**. (In Press).
22. Goel M, **Dhingra NK (2012)** Müller glia express rhodopsin in a mouse model of inherited retinal degeneration. **Neuroscience** 225: 152-61.
23. Katherine Sullivan, Megha Sharda, Jessica Greenson, Geraldine Dawson and **Nandini C Singh (2013)** A novel method for assessing the development of speech motor function in toddlers with autism spectrum disorders, **Front. Integr. Neurosci.** 7:17. doi:10.3389/fnint.2013.00017.
24. Chaitra Rao, Avantika Mathur and **Nandini C Singh (2013)** 'Cost in Transliteration'—The neurocognitive he Neurocognitive Processing of Romanized Writing, **Brain and Language** 124, 205-212,.
25. **Pravat K. Mandal (2012.)** Predictive biomarkers for Alzheimer's disease using state-of-the-art brain imaging techniques. **Journal of Alzheimer's Disease**, 31, S1-3.
26. **Pravat K. Mandal***, H. Akolkar, and Manjari Tripathi (2012)#. Mapping of Hippocampal pH and Neurochemicals from in vivo Multi-Voxel 31P Study in Healthy Normal Young Male/Female, Mild Cognitive Impairment, and Alzheimer's disease. **Journal of Alzheimer's disease**, 31, S75-86.
27. **Pravat K. Mandal***, Jitesh Joshi, Sumiti Saharan (2012) #. Visuospatial Perception: An Emerging Biomarker for Alzheimer's Disease. **Journal of Alzheimer's Disease**, 31, S117-35.
28. **Pravat K. Mandal***, Rashima Mahajan, Ivo D. Dinov (2012) #. Structural Brain Atlases: Design, Rationale and Applications in Normal and Pathological Cohorts. **Journal of Alzheimer's Disease**, 31, S169-88.

REVIEW

1. M C Thounajam, D K Kaushik, and **A Basu (2013)** MicroRNAs in the Brain: It's regulatory role in Neuroinflammation. **Molecular Neurobiology** 47:1034–1044
2. D K Kaushik, and **A Basu (2013)** A friend in need may not be a friend indeed: role of microglia in neurodegenerative diseases. **CNS & Neurological Disorders-Drug Targets** (in press)
3. N Sengupta, and **A Basu (2013)** Japanese Encephalitis Virus Infection: Effect on brain development and repair. **Current Science** (in press).
4. **Iyengar S (2012)**: Development of the Human Auditory System. **Journal of the Indian Institute of Science** 92:4; 427-440 (Invited review), in the issue on "Development and Disorders of the Nervous System" edited by Dr. S. Mani.
5. Arkoprovo Paul, Megha Sharda and **Nandini Chatterjee Singh (2013)** Effect of Music Instruction on Cognitive Development: A Review. **Journal of the Indian Institute of Science**, 92, 441-445

BOOK CHAPTER

1. K Dutta, A. Nazmi and **A Basu (2013)** Japanese encephalitis virus and human CNS infection. In *Neuroviral Infections*, ed S.K. Singh, D. Ruzek, CRC Pr 1 LLC. [ISBN-10: 1439868522]

PATENTS

Prof. Subrata Sinha

Use of the FAT1 gene and its products, including RNA, protein and the derivatives of the same, as suitable molecule/s for either inflammation or cancer and the associated phenotype and the processes linking the same and also as a biomarker for the above processes (PCT/IB2013/050086, filed on 4 Jan 2013). (Jointly by DBT, AIIMS and NBRC).

Dr. Ellora Sen

Granted European patent: European Pat. 2.367 784 B1– "Bicyclic triterpenoid Iripallidal as a novel anti-glioma and anti-neoplastic therapy in vitro". Patent granted on 02.01.2013, International publication number (WO 2010/073258).



Presentations

PRESENTATIONS

1. A. Das, S. Bhutani, M. Maheshwari, S. C. Lakhotia and N. R. Jana. Dysregulation of core components of SCF complex in polyglutamine disorders. Annual Meeting of Society for Biological Chemists (SBCI), Kolkata, 2012.
2. N. R. Jana. Involvement of Ube3a in cellular protein quality control: Implication in protein misfolding neurodegenerative disorders. NEUROCON, Kolkata, 2013.
3. N. R. Jana. Role of ubiquitin ligase Ube3a in the pathogenesis of Huntington's disease. Annual Meeting of the Society for Neurochemistry, India (SNCI), 2013. New Delhi.
4. N. R. Jana. Understanding the physiological function of malin and pathogenesis of Lafora disease. Annual Meeting of Society for Biological Chemists (SBCI), Kolkata, 2012.
5. D. Mukherjee, J. Sharma, S.N Rao, S. K. Shankar, P. Satishchandra and N. R. Jana. Neuronatin mediated altered calcium signalling and ER stress cause neuropathology in Lafora disease. Annual Meeting of Society for Biological Chemists (SBCI), Kolkata, 2012.
6. N. R. Jana, J. Sharma, D. Mukherjee, S. N. Rao, S. K. Shankar and P. Satishchandra. Neuronatin mediated aberrant calcium signaling underlie neuropathology in Lafora disease. Annual meeting of the Society for Neuroscience (SFN), New Orleans, 2012.
7. Pankaj Seth: Neural Stem Cells - a Tool for Basic Research. At Amity University, Haryana, India, April, 2012.
8. Pankaj Seth, Pretty Garg and Manju Pant Tewari. Role of Neuron Glia Crosstalk in HIV-1 Neuropathogenesis. 11th International Symposium on Neurovirology and 2012 Conference on HIV in the Nervous System. New York, USA, May, 2012.
9. Pankaj Seth in Calendar of Events of National Institutes of Health (NIH): Neuron - Glia interactions during HIV Neuropathogenesis. National Institutes of Health (NIH), Bethesda, USA, May, 2012.
10. Pankaj Seth: Neural Stem Cells - a window into neurodegenerative diseases. At Rajiv Gandhi Institute of Technology, Amethi, During National Seminar on "Stem Cell an emerging Healthcare Frontier" during August, 2012.
11. Pankaj Seth : HIV-1 Induced Neuronal damage: Who is to be blamed? At XXX Annual meeting of Indian academy of neurosciences, Guru Nanak Dev University, Amritsar, India, Oct, 2012.
12. Pankaj Seth: Neural Stem Cells – an in vitro model to understand brain disorders. At Seminar Series on Stem Cell Application in health care at Amity University, Haryana, India October, 2012.
13. Pankaj Seth: Are we doing enough to cure HIV/AIDS in India? Seminar on HIV/AIDS and Drug Abuse, Ukul District, Manipur, India, November, 2012.
14. Pankaj Seth, Shaily Malik and Rinki Saha: In vitro neural stem cell system - An opportunity to "peep" inside the degenerating human brain? At NeuroCon 2013 meeting at Indian Institute of Chemical Biology, Kolkatta, India, January 2013.
15. Pankaj Seth, Manju Tewari, Ankita Srivastava: Glia Mediated Neuronal Injury in HIV-1 Neuropathogenesis: "the other side of the coin" At 27th Annual Meeting of Society of Neurochemistry, All India Institute of Medical Sciences, India, February, 2013.
16. Shaily Malik, Rinki Saha and Pankaj Seth. "Modulation of human neural precursor cell proliferation and differentiation by HIV-1 transactivating protein, Tat and drugs of abuse". 18th Annual Scientific Conference of Society on Neuroimmune Pharmacology, Hawaii, USA. April 2012.
17. Manju Tewari. Role of Glial cells in HIV-1 neuropathogenesis. At NeuroCon 2013 meeting at Indian Institute of Chemical Biology, Kolkatta, India, January 2013.
18. Ellora Sen. Inflammation mediated oxidative stress in cancer. 4th International Congress on Cell Membrane and Oxidative Stress, Suleyman Demirel University, Isparta, Turkey. June 2012. Invited lecture and Session Chair
19. Ellora Sen. HLA gene regulation in glioma: Role of Inflammation. Indian Association of Cancer Research, New Delhi, February, 2013.
20. Deobrat Dixit. Guggulsterone sensitizes glioblastoma cells to Sonic hedgehog inhibitor SANT-1 induced apoptosis. Emerging Trends and Challenges in Basic and Translational Research in Biochemistry, Department of Zoology, Banaras Hindu University, Varanasi, February 2013
21. Ellora Sen. TNF α regulates resistance to apoptosis in glioblastomas. 3rd International Cancer Research Symposium, Kolkata, December 2012.
22. Ellora Sen. Inflammation and resistance to apoptosis in gliomas: The rehabilitation of thoughts. Carcinogenesis, New Delhi, November 2012.

23. Deobrat Dixit. Inhibition of G9a in glioma cells inhibits hypoxia signalling and induces cell death through apoptosis and autophagy. Carcinogenesis, New Delhi, November 2012.
24. Fahim Ahmad. Identification of signalling circuitries regulating telomerase activity in glioma. Carcinogenesis, New Delhi, November 2012.
25. Piyushi Gupta. β -defensin-3 negatively regulates TLR4-HMGB1 axis mediated HLA-G expression in IL-1 β treated glioma cells. Carcinogenesis, New Delhi, November 2012.
26. Sadashib Ghosh and Ellora Sen. TNF α induced HIF-1 α - β catenin axis regulates MHC class I gene activation. Carcinogenesis, New Delhi, November 2012.
27. Ghildiyal R. Inhibition of EGF Receptor by BIBU induces apoptosis and defective autophagy in glioma cells. Carcinogenesis, New Delhi, November 2012.
28. Deobrat Dixit. Inhibition of Ras /NF κ B axis sensitizes glioblastoma cells to Shh inhibitor induced apoptosis. Indian Academy of Neuroscience, Amritsar, October 2012
29. Ellora Sen. Hypoxia-Inflammation nexus: A potential anti-glioma target? Indian Society of Neuro-Oncology (ISNOCON), NIMHANS, Bangalore, April, 2012.
30. S.K. Sharma and C. Maharana. Mechanisms of pattern-dependent activation of extracellular signal-regulated kinase in the hippocampus. Society for Neuroscience meeting, Oct. 13-17, 2012, New Orleans, USA.
31. Kiran Pandey and Shiv K. Sharma. HDAC inhibition facilitates surface recruitment of AMPA receptors in the hippocampus. XXX Annual Meeting of Indian Academy of Neurosciences, 27-30 October, 2012, Guru Nanak Dev University, Amritsar.
32. A Basu (2013) The transcriptional regulation of microglial function: the tightrope walk of CNS innate immune response. Society for Neurochemistry Meeting 2013, AIIMS, New Delhi, 21-23rd February. (Invited speaker)
33. A Basu (2013) Host pathogen interaction in Japanese Encephalitis Virus infection: from bench to bedside. South Asian University, New Delhi, 8th February, 2013. (Invited speaker)
34. A Basu (2013) An introduction to Psychoneuroimmunology Preconference workshop (Neurocon 2013), IPGMER, Kolkata, 17th January, 2013. (Invited speaker)
35. A Basu (2013) Neuronal Innate Immune Response in Japanese Encephalitis Virus infection. 3rd Molecular Virology Forum meeting, National Institute of Virology, Pune, 10-11th January 2013. (Invited speaker)
36. A Basu (2012) Krüppel Like Factor 4 in neuro-inflammation: a new therapeutic target? BioWorld 2012, Kusuma School of Biological Sciences, Indian Institute of Technology Delhi, New Delhi, 10th-12th December, 2012. (Invited speaker)
32. D K Kaushik, M C Thounajam, and A Basu (2012) Kruppel Like Factor 4 regulates microglial activation in response to Interleukin-1 β . XXX Annual Meeting of Indian Academy of Neurosciences, 27th-30th October, 2012, Amritsar.
33. A Nazmi, I A Mohammed, K Dutta, K Kundu, and A Basu: Neural Stem/Progenitor Cells induces conversion of encephalitogenic T-cells into CD4+CD25+ FOXP3+ Regulatory T-cells. XXX Annual Meeting of Indian Academy of Neurosciences, 27th-30th October, 2012, Amritsar
34. A Nazmi, K Dutta, K Kundu, and A Basu : TLR7 regulates expression of suppressor of cytokine signaling (SOCS) in CNS post Japanese Encephalitis Virus infection. XXX Annual Meeting of Indian Academy of Neurosciences, 27th-30th October, 2012, Amritsar
35. A Basu :Basic and Translational Studies at the Host-Pathogen Interface. UGC refresher courses for college and university faculty members, Center for Biotechnology, JNU, 20th July, 2012
36. A Basu: Therapeutic targeting of Krüppel like factor 4 abrogates inflammation and oxidative stress in brain. 4th International Congress on Cell Membrane and Oxidative stress. 26th-29th June. Suleyman Demirel University, Isparta, Turkey. (Invited speaker)
37. A Basu: Antiviral and Neuroprotective Role of Octaguanidinium Dendrimer-Conjugated Morpholino Oligomers in Japanese Encephalitis. 9th International Symposium on Polymer Therapeutics: From Laboratory to clinical practice 28th -30th May, 2012, Valencia, Spain. (Invited speaker)
38. Ranjit K. Giri. Utilization of Neurosphere Culture in the Development of a Novel in vitro model of Alzheimer's Disease, McLaughlin Research Institute, Great Falls, Montana, USA, 2012.
39. Sourav Banerjee: Tune it up: Modulation of neuronal circuitry and synaptic mechanisms of plasticity. IISER Pune. August 2012.

40. Soumya Iyengar: Organization of the Vertebrate Nervous System. Fourth DST-SERB school in Chronobiology, North-Eastern Hill University (NEHU), Shillong, June 20, 2012.
41. Soumya Iyengar: Comparative Aspects of Brain Evolution - Mammals versus Birds. Fourth DST-SERB school in Chronobiology, North-Eastern Hill University (NEHU), Shillong, June 21, 2012.
42. Soumya Iyengar: Auditory System – I. Sixth DST-SERB School in Neuroscience, National Institute of Science Education and Research (NISER), Bhubaneswar, Orissa, December 18, 2012.
43. Soumya Iyengar: Auditory System – II. Sixth DST-SERB School in Neuroscience, National Institute of Science Education and Research (NISER), Bhubaneswar, Orissa, December 18, 2012.
44. Soumya Iyengar, Arvind Singh Pundir, Bishan Radotra, Praveen Kumar, PC Dikshit, SK Shankar, Anita Mahadevan. Development of excitatory neural circuits in the human auditory cortex. Poster presented at The 8th FENS Forum of Neuroscience, Barcelona, Spain, 14 - 18 July, 2012.
45. S Dagar, NK Dhingra. Loss of photoreceptors in rd1 mouse leads to selective upregulation of amacrine cell-specific synaptic protein mRNAs. Annual Conference of the Indian Academy of Neurosciences (Amritsar, India; October, 2012).
46. V Jain, E Ravindran, R Guruswamy, NK Dhingra. Expression of Melanopsin and its co-expression with Brn3b alters in Mouse model of Retinal Degeneration FASEB summer research conference on Retinal Neurobiology and Visual Processing (Steamboat Springs, CO, USA; Jul-Aug, 2012).
47. NK Dhingra, A Ghosh. Loss of Photoreceptors in rd1 Mouse is Associated with Upregulation of GABAC Receptors in Inner Retina. ARVO meeting (Fort Lauderdale, USA; May, 2012).
48. Nandini C Singh – Language and the Brain, Science Fest, Ambedkar Centre for Biomedical Research, Delhi University, March 2012.
49. Nandini C Singh – Speech and music in autism, COMDEALL workshop on autism, Bangalore, May 2012.
50. Nandini C Singh – Neuro-imaging for language function – in health and disease, Workshop on Aphasia, Indore, August 2012.
51. Nandini C Singh - 'Reading Assessments in a bilingual-biscriptal setting', Maharashtra Dyslexia Association, Mumbai, 14th February 2013.
52. Nandini C Singh – 'Number Sense' – how cognitive neuroscience can aid the teaching of mathematics in schools, Cluster Innovation Centre, Delhi University, New Delhi, 28th February 2013.
53. Nandini C Singh – 'Singing in the Brain', Frontiers of Speech and Music, Jadavpur University, Kolkata, 5th March 2013.
54. Ramaswamy, R., Khanna, R., Roy, P. Effect of Ageing and Gender on modulating the Elastic Responsivity and Topological Connectivity of the Brain, Ann. Conf. on Magnetic Resonance Society of India, Indian Institute of Technology, Bombay, Feb. 2013.
55. Varrier, R., Kondra, S., Roy, P. Developmental Implications of Information Pathways in Brain using fMRI Perceptanalysis, Proc. International Symposium on Computational Neuroscience, Indian Institute of Science, Education & Research, Pune, April. 2012.
56. Roy P, The Indian Brain Imaging Grid: Application to Diagnosis & Therapy, Canada-Israel-India Trilateral Brain Roundtable and Technology Partnering Mission, Institute of Medical Research (IMRIC), Tel- Aviv, May 2012.
57. Kapoor S, Subramanyam V, Roy P. Optimizing performance of endogenous neural stem cell therapy for ischaemic stroke: A Neuroimaging approach to translational medicine, International Conference on Neuroinformatics, Munich, Sept. 2012.
58. Subramanyam, VPS, Roy, P. Translational Neuroscience and imaging-guided therapy, University of Health sciences, Rohtak, April 2012.
59. Kapoor S, Subramanyam V, Roy P. Ischaemic stroke therapy using endogenous neural stem cell strategy: A validated neuroinformatics approach, NEUROCON 2012, Neurological Society of India, New Delhi, Dec. 2012.
60. Roy, P. Stereo Neuroimaging of Electrical Activation Field: Source Localization using 3-D MRI Human Brain Mapping, Indo-U.S. Workshop on Modelling Electrical Activity in Physiological Systems, Indian Institute of Science Education & Research, Mohali, May 2012.



Distinctions, Honours and Awards

DISTINCTIONS, HONOURS AND AWARDS

Details of Ph.D. students who have obtained Degree along with Title of Thesis

Sr. No.	Name of candidate	Date of Award of Degree	Enrolment No.	Title of the thesis
1.	Dr. Chinmoyee Maharana (2004)	06/08/2012	0020	Activity-Dependent Posttranslational Modifications of Proteins: Implications for Synaptic Plasticity and Memory
2.	Dr. Parthiv Haldipur (2005)	18/09/2012	0045	The role of Sonic hedgehog signaling in the proliferation and differentiation of cerebellar granule cell progenitors
3.	Dr. Jai Prakash Sharma (2005)	05/10/2012	0047	Identification and characterization of substrates of malin, an E3 ligase mutated in Lafora progressive myoclonus epilepsy
4.	Dr. Sudheendra Rao N R (2006)	21/12/2012	0053	Protein aggregation, sequestration and ubiquitin proteasome system dysfunction in the pathogenesis of Lafora disease
5.	Dr. D. Lalitha (2005)	27/12/2012	0037	Redox signaling mechanisms and altered gene expression mediated by dopaminergic neurotoxin, MPTP : Implications in Parkinson's disease

FACULTY AWARDS

1. Dr. Anirban Basu: F1000 Faculty Member of the Year Award' for the Faculty of Neurological Disorders-2012*
**The awards recognize Faculty Members who have made the most significant contribution to the F1000 service over the past year, as judged by their editorial team.*
2. Dr. Ellora Sen: Shakuntala Amir Chand Award, 2009, Indian Council of Medical Research (ICMR), awarded 2013
3. Dr. Ellora Sen: Elected member of Guha Research Conference (GRC), 2012

STUDENTS AWARDS

1. Ms. Megha Sharda, Integrated Ph.D. 2007 student was awarded for attending International Meeting for Autism Research (IMFAR 2012), Sheraton Centre at Toronto, Canada from 17th May, 2012 to 19th May, 2012.
2. Ms. Shaily Malik, Integrated Ph.D. 2007 student was awarded for attending the 18th Annual Scientific Conference at Honolulu, HI from 24th April, 2012 to 28th April, 2012.
3. Mr. Apoorv Sharma, Ph.D. 2008 student was awarded for Conference in Technische University, Miinchen, Arisstrape 21, 80333 Miinchen, Germany from 07th September, 2012 to 08th September, 2012.
4. Ms. Suhela Kapoor, Integrated Ph.D. 2007 student was awarded for attending the Neuroinformatics 2012 Congress, Germany from 06th September, 2012 to 15th September, 2012.
5. Ms. Suhela Kapoor, Integrated Ph.D. 2007 student Visiting Studentship, Utrecht University Medical Centre, Netherlands.
6. Ms. Megha Sharda, Integrated Ph.D. 2007 student was awarded for attending the Society for Neuroscience 2012 at New Orleans, U.S.A. from 13th October, 2012 to 17th October, 2012.
7. Mr. Subhadip Paul, Ph.D. 2005 student Paper on "The effect of stochastic fluctuation in radiation dose-rate on cell survival following fractionated radiation therapy" (Physics in Med & Bio, 57: 1561-70, 2012) chosen as Target selection paper by Global Medical Discovery, Ottawa, Canada, for being of importance to drug discovery process.
8. Mr. Subhadip Paul, Ph.D. 2005 student was awarded for attending the Society for Neuroscience 2012 at New Orleans, U.S.A. from 13th October, 2012 to 17th October, 2012.
9. Ms. Megha Maheshwari, Integrated Ph.D. 2007 student was awarded for attending the Society for Neuroscience 2012 at New Orleans, U.S.A. from 13th October, 2012 to 17th October, 2012.
10. Dr. Gouri Shanker Patil, Post Doctoral Fellow received the MUKTESH AWARD for Best Paper in Speech for the scientific paper titled "The lexical iconicity in Indian Sign Language" at the 45th National Conference of Indian Speech and Hearing Association held at Chennai from 01st to 03rd February, 2013.

COURSE-WORK

Mr. Kautuk Kamboj: Ph.D. student, has been awarded first rank upon completion of course work during the year 2012 and a certificate was given to him on the 9th Foundation Day, the 16th December 2012.

Mr. John Thomas: Ph.D. student, has been awarded second rank upon completion of course work during the year 2012 and a certificate was given to him on the 9th Foundation Day, the 16th December 2012.

Ms. Utkarsha A Singh: Integrated Ph.D. student, has been awarded first rank upon completion of course work during the year 2012 and a certificate was given to her on the 9th Foundation Day, the 16th December 2012.

Ms. Pooja Parishar: Integrated Ph.D. student, has been awarded second rank upon completion of course work during the year 2012 and a certificate was given to her on the 9th Foundation Day, the 16th December 2012.

She has also been awarded for the Comprehensive Viva of Course-Work during the same year.



Externally Funded Research Projects

EXTRAMURAL FUNDING DURING 01-04- 2012 - 31.03.2013

S. No.	Name of Project	Principal Investigator	Sanctioning Agency	Date of Sanction	Sanctioned Cost	Project No.
1	DIC	NBRC INSTITUTE	D.B.T.	22.12.1999	297.16	INST/ DBT/1299/001
2	Dementia Programme	NBRC INSTITUTE	D.B.T.	14.09.2007	237.50	INST/ DBT/0907/002
3	Role of CNS Opportunistic infections in subsequent Development of HIV Dementia	PANKAJ SETH	NIH	25.05.2009	\$104,706.00	PKS/NIHRO- 1/0509/003
4	Delcon (E- Library Consortium) Project	NBRC INSTITUTE	D.B.T.	12.12.2009	11192.67	INST/ DBT/1209/004
5	Understanding Signaling Circuitries involved in glioma	ELLORA SEN	D.B.T.	18.03.2010	66.02	ELS/ DBT/0310/005
6	Study the neuroprotective role of ubiquitin ligase, E6-AP in the transgenic mice model of Huntington's disease	NIHAR RANJAN JANA	D.B.T.	21.04.2010	9.00	NRJ/ DBT/0812/006
7	Opioid modulation of motivated behaviours in male zebra finches	SOUMYA IYENGAR	D.S.T.	10.06.2010	37.20	SOA/ DST/0610/007
8	Study the defect in neurogenesis and initial synapse formation in mouse model of angelmen mental retardation syndrome	NIHAR RANJAN JANA	CSIR	25.06.2010	17.17	NRJ/ CSIR/0610/008
9	To elucidate the role of inflammasomes and other molecular events leading to Hypoxia induced Neuroinflammation	ANIRBAN BASU	DRDO	02.08.2010	21.01	ABS/ DRDO/0810/009
10	Two Photon microscope facility for advance research in basic neuroscience and unraveling the mechanism of brain disease	NEERAJ JAIN	D.B.T.	17.09.2010	934.00	NJA/ DBT/0910/010
11	Understanding the physiological function of malin, a ubiquitin ligase mutated in Lafora's progressive myoclonus epilepsy	NIHAR RANJAN JANA	D.B.T.	17.09.2010	42.11	NRJ/ DBT/0910/011
12	A Functional imaging study of dyslexia in biscriptal Indian children	NANDINI C. SINGH	D.B.T.	22.09.2010	30.65	NCS/ DST/0910/012
13	C.S.I.R. -II Study the role of Natural immune response in JEV infection	ANIRBAN BASU	C.S.I.R.	02.11.2010	18.85	ABS/ CSIR/1210/013
14	Natural Network Mechanism in subicular complex neurons during spatial, navigation and learning in awake behaving rats.	YOGANARASIMHA DORESWAMY	D.B.T.	21.01.2011	97.42	YOD/ DBT/0111/014
15	Centre for Epilepsy Project (M.E.G.)	NBRC INSTITUTE	D.B.T.	11.02.2011	3344.17	INST/ DBT/0211/015
16	Brain Mechanism of Tactile Perception	NEERAJ JAIN	D.I.T.	22/02/2011	31.65	DIT/R&D/ TDC/13(7)
17	Perception Engineering Programme	P. K. ROY	D.I.T.	22/02/2011	23.93	DIT/R&D/ TDC/13(7)

18	Role of human umbilical cord blood stem and neural stem cells in neuronal regeneration and functional restoration: A comparative study in male adults rats with acute spinal cord injuries	PANKAJ SETH	D.B.T.	28.06.2011	9.00	PKS/ DBT/0611/016
19	India Intergration with Global Imaging System via MCGill Linkage (NKN)	P. K. ROY	NICS	06.07.2011	89.89	PKR/ NIC/0711/017
20	Neurobiology and understanding circadian system linkage of cognitive performance in an avian model system	SOUMYA IYENGAR	D.S.T.	20.07.2011	25.80	SOA/ DST/0711/018
21	Host Directed Drug Targeting Implication of suppressors of cytokine signaling (SOCS)	ANIRBAN BASU	D.B.T.	29.07.2011	9.00	ABS/ DBT/0711/019
22	Collaboration for translation & Clinical Research Between Translational Health science and technology institute (glue Grant)	P. K. ROY	D.B.T.	30.08.2011	234.22	PKR/ DBT/0811/020
23	ICMR HIV Associated neurocognitive disorder (Hand)	PANKAJ SETH	ICMR	13.09.2011	22.77	PKS/ ICMR/0911/021
24	CEERI PILANI	PRAVAT K. MANDAL	BITS PILANI	14.12.2011	2.50	PKM/ BITSP/1211/022
25	Investigation of the relationship between literacy instruction and metalinguistic awareness in adults	CHAITRA RAO	D.S.T.	02.02.2012	12.48	CHR/ DST/0212/023
26	Identification of associations between genetic variants in the neural migration pathway and behavioral correlates of dyslexia linking genes and behaviour using familial and sproadic cases.	D. SUBHASHREE	D.S.T.	07.03.2012	12.48	DSU/ DST/0312/024
27	Speech and music processing in Autism Spectrum Disorder A functional neuroimaging study	NANDINI C. SINGH	D.S.T.	20.03.2012	27.12	NCS/ DST/0312/025
28	Understanding Neuron -Glia Crosstalk in HIV Research in Health and Disease	PANKAJ SETH	D.B.T.	22.03.2012	35.14	PKS/ DBT/0312/026
29	National Initiative on glial cell research in health and disease	SHIV KUMAR SHARMA	D.B.T.	27.03.2012	31.64	SKS/ DBT/0312/027
30	Pulse Sequence (invivo) and processsing scheme development for Anethetics and amyloid beta petide interactions using 19F MRS	PRAVAT K. MANDAL	D.B.T.	29.03.2012	13.73	PKM/ DBT/0312/028
31	Connectivity and role of inhibitory neurons in auditory perception DBT/ Wellcome Trust Alliance	SHORBA BANDHYOPADHYAY	Well Come Trust	30.03.2012	383.81	SHB/ WCT/0312/029
32	Using Stereo X-Ray image to develop a ready automated method for screening of Alzheimer type mild cognitive impairment from normal ageing in resource constrained setting	P. K. ROY	D.B.T.	04.05.2012	22.02	PKR/ DBT/0512/030
33	Ramalingaswamy fellowship 2011-12	SOURAV BANERJEE	D.B.T.	07.06.2012	82.00	SBN/ DBT/0612/031

34	Neuroscience education research fellowships in clinical neuroscience and Neuro-informatics & Computational neuroscience	NBRC INSTITUTE	D.B.T.	27.09.2012	100.00	INST/ DBT/0912/032
35	DST INSPIRE Fellow	SUPRIYA BHAWNANI	D.S.T.	10.01.2013	85.96	SBH/ DST/0113/033
36	Development and validation of screening tool to Identify learning disability	NANDINI C. SINGH	D.S.T.	12.02.2013	75.00	NCS/ DST/0213/034
37	Using Peptidomimetics to design small molecules from a novel P1 peptide(BIRAC)	RANJIT K. GIRI	BIRAC	04.03.2013	89.89	RKG/ BIRC/0313/035
38	Neuroplasticity and Language Anatomical Correlates of Vedic Recitation (ITPAR)	NANDINI C. SINGH	D.S.T.	13.03.2013	31.65	NCS/ DST/0313/036



Core Facilities

DISTRIBUTED INFORMATION CENTRE (DIC)

The Distributed Information Centre (DIC) manages the complete Information & communication Technology (ICT) requirements of the Institute. It manages the core computing and networking infrastructure of the institute thus aiding the academic and research activities at NBRC. The DIC staff actively provides technical and scientific support to researchers in their computational requirements. It also undertakes development of software applications for scientific as well as administrative departments thus facilitating e-Governance in the organization. We are also planning to develop an in-house program for Online Tracking System that would automate monitoring the movement and processing of all files in near future.

The IT infrastructure is constantly upgraded as per the growing needs of the Institute and technological advancement in the field. Some of the critical IT infrastructure of the Institute is listed as under:

NETWORK INFRASTRUCTURE

- The core network of the institute is running on managed switching infrastructure with a fiber optic backbone of 10Gbps with redundant paths. The network is segmented into multiple virtual LAN's to segregate unrelated traffic and ensure security. The core network is further integrated with campus wide wireless network providing secure and authenticated access to authorized users. The uptime of the entire core wired and wireless network is monitored round the clock.
- The institute is part of National Knowledge Network (NKN) of Government of India and is connected with NIC-Delhi over a high speed gigabit fiber optic connectivity, certain research projects utilizing the NKN are already operational and some other are being implemented thus directly aiding in the research activity of NBRC. The institute also has a redundant radio link for maintaining essential network services.
- The institute has secure firewall and unified threat management appliances for network safety, intrusion

detection system, gateway level antivirus, VPN facility, managing IT policy and detailed auditing and logging. The VPN facility provides NBRC users facility to access internal resources of the institute from remote locations in a secure manner.

DATACENTER AND SERVER FACILITY

- The institute has a modest datacenter facility for housing the core network and server infrastructure having precision climate control, redundant power and UPS supply, clean agent based fire detection and suppressant system.
- The institute manages an in-house hosting of all core servers for DNS services, Web servers, Email servers etc. for the official domains of the institute (i.e. www.nbrc.ac.in and www.nbrc.res.in). In addition it also provides hosting services for Indian Academy of Neurosciences (www.neuroscienceacademy.org.in) and Society of Neuro Chemistry, India (www.snci.nbrc.ac.in) as a service to neuroscience community of the country. All the public servers have nearly cent percent uptime and are efficiently maintained with detailed logging and statistics.
- The DIC also manages a pool of application servers running on Windows and Linux platforms for providing application services to students and researchers apart from dedicated application servers of different computational laboratories.

UPCOMING AND ONGOING ACTIVITIES

- The DIC has recently expanded the core network to the new Institutional Building (IB-1) apart from upgrading the wireless network.
- DIC is also planning to implement unified communication services thereby integrating data and voice networks with the planned implementation of IP-PBX facility to fulfill Government of India regulations.
- The upgradation of ageing core servers to blade servers and implementation of cross-site DR site for essential service and data is being planned.

ANIMAL FACILITY

NBRC, an autonomous institute of the Department of Biotechnology, has the mandate of carrying out frontline research to understand neurobiology of brain disorders. In order to help fulfilling this mandate, NBRC maintains a state of the art animal facility to meet the requirements of the scientists for advanced neuroscience research. The Institute recognizes that the use of laboratory animals in research is an important privilege accompanied with a great ethical responsibility to ensure humane care and use of these valuable subjects. To ensure appropriate care and use detailed programs of the best veterinary and husbandry care, and programs for the peer-reviewed evaluation of all activities prior to the use of any animal in research are in place. NBRC is committed to the highest standards of research and recognizes that laboratory animals must receive the best possible care, not only to obtain valid research data, but also to ensure the health and safety of animals, researchers and animal caretakers. The Animal Facility is registered with the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environment and Forests, Government of India, New Delhi (Registration number: 464/a/CPCSEA, dated 24/08/2001). All activities of the animal facility are carried out as per standard operating procedures (SOPs). The Animal Facility maintains records of day-to-day activities as well as breeding, maintenance and experimentation on the animals as per statutory requirements of CPCSEA.

The main responsibility of the Animal Facility is to procure and breed laboratory animals as required, and supply quality animals to in-house researchers, which are used as animal models for understanding the human brain in health and disease. Staff of the animal facility ensures humane and appropriate animal care. A high degree of hygienic conditions are maintained in the animal house by regular cleaning and sterilization of the cages, water bottles, bedding and feed. The animal rooms are also regularly disinfected. Heavy-duty steam autoclaves have been installed for these purposes. The staff is required to take shower and change to work-overalls before entering the animal rooms, and again in the evening after finishing the work. All users wear facemasks and gloves before handling animals.

All animals are housed in species appropriate cages, which are designed as per the CPCSEA guidelines.. The outdoor play area for non-human primates has six large interconnected enclosures that provide a flexible layout for optimising enrichment and social interactions. The

transgenic, knock out and mutant mice are housed under germ-free conditions in filter top cages and individually ventilated cages (IVC). Such animals are handled in laminar hoods, and the moved to fresh cages in cage-changing station under hepa-filtered air.

The animals are maintained under controlled environmental conditions as specified in CPCSEA guidelines, with temperature maintained between $22 \pm 2^{\circ}\text{C}$, relative humidity between 45-55%, 12:12 hr light-dark cycle, and 12-15 air changes per hour. The air-handling system uses 100% fresh air for each change. Qualified and trained veterinarians oversee all the animal health concerns, and provide all necessary veterinary care to ensure that healthy animals are available for research.

All animals are procured as per CPCSEA guidelines. A health surveillance program for screening incoming animals is carried out to assess animal quality. Animals procured from other places are kept in quarantine for appropriate length of time. An effective quarantine minimizes risk for introduction of infection in established colony.

The animal facility has a state-of-art surgical suite equipped with intensity controlled surgical lights, advanced surgical microscopes, gas anesthesia machines, equipment for monitoring the physiological state of the animals, including heart rate monitor, pulse oximeter and rectal thermometer. For cleaning and sterilization of the surgical instruments there is an ultrasonic instrument cleaner, glass bead sterilizer and ethylene oxide gas sterilizer. The animal facility has a necropsy room, perfusion room with a perfusion hood, deep freezer for carcass storage, and incinerator for disposal of the animal carcass.

Animal facility has been equipped with a card reader security system. The access is restricted to the animal house staff, maintenance staff and the investigators who are listed in the IAEC approved protocols. All the personnel who handle animals are required to have a current tetanus vaccination, and those who handle non-human primates (NHP) are screened for tuberculosis. Everyone handling NHP's is trained in the procedures for the first-aid in case of an injury from an animal bite or scratch.

Close circuit monitoring cameras have been installed at various locations in the facility to help in effective monitoring of the animal facility.

The Veterinary staff of animal facility conducts a training program for Integrated-Ph.D. and Ph.D. students & the Project Assistants in laboratory animal science covering

ethical guidelines that regulate scientific experiments on animals, general biology and reproduction of the laboratory animals, animal identification techniques, approved methods of blood collection, injections, anesthesia and monitoring, handling and restraint, husbandry, care, sex differentiation, humane euthanasia etc. Special emphasis is on health management, identification and management of pain in the animals.

The animal facility is currently maintaining the following species and strains of the laboratory animals.

Mice Strains

- SWISS
- BALB/c
- C57BL/6J
- CD1

Transgenic Mice

- B6C3-Tg (APP695)85DboTg(PSEN1)85Dbo (Alzheimer disease model)
- UBC-GFP (Green fluorescent protein)
- B6CBA-Tg (Hdaxon1) 62Gpb/3J (Huntington disease model)
- B6.Cg – Mapttm1 (EGFP) KltTg (MAPT) 8cPdav/ J (Alzheimer disease model)
- B6.129P2-Gsk3btm1 Dgen/J (Alzheimer disease model)

Knock Out Mice

- UBE3A null mice (Angelman syndrome model)

Mutant Mice

- CBA/J mice (Retinal degeneration model)

Rats

- Long Evans
- Sprague Dawley

Rabbits

- New Zealand white

Non-human primates

- Rhesus Monkeys (*Macaca mulatta*)
- Bonnet Monkeys (*Macaca radiata*)

Birds

- Zebra finches (*Taeniopygia guttata*)
- House crows (*Corvus splendens*)
- Jungle crows (*Corvus leuiscornis*)

All the mice strains are maintained by inbreeding and the rat strains by out-breeding. Zebra finch colonies are maintained by out-breeding. The transgenic and knockout mice are maintained under a specialized breeding program after the investigators provide the molecular genotyping of these strains based on presence or absence of the gene of interest.

LIBRARY

The NBRC Library plays a vital role in the collection, development and dissemination of scientific and technical information to meet the present and future needs of the centre and also provides facilities and support to the scientists, researchers, students, staff and NBRC's networked centers.

The NBRC library has a large collection of Journals, books and other relevant research materials on Neuroscience, Biochemistry, Genetics, Molecular Biology, Immunology & Microbiology, Pharmacology and Toxicology, Psychology, Physics, Mathematics, Computer Science and General Subjects. The NBRC Library currently subscribes to 16 journals, and also subscribes to 963 online journals through the DBT e-Library Consortium (DeLCON). It also maintains digital archives and news clips about the centre and subscribes to Newspapers and News Letters. The collection of the NBRC Library is growing day-by-day along with new developments in research and knowledge in the field of Neuroscience and related areas.

DIGITAL FACILITATION

To provide optimum service to all users, the NBRC library is currently digitizing its list of collections using the LSEASE software, to which all users will have full access. A barcode technology has also been installed for accurate and speedy circulation and the management of all library documents. The new software will also help in efficient library operations viz. administration, acquisition, circulation, serial control, cataloguing and information retrieval.

The Library has set up 22 IBM PC-Pentium-IV Computers with ISDN Internet facility to provide services for use of researchers and students in the NBRC Common room and has been providing electronic access to the subscribed journals within the campus portal.

SERVICES AVAILABLE

A total of 115 registered users including scientists, researchers, students and other staff used the NBRC library facilities in the past year. The NBRC Library also provides "Inter Library Loan" Services to NBRC's 48 networked centres all over India. Researchers at different centres send their requirement for research material or journal articles through email to NBRC Library which are then downloaded and sent to them free of cost. The library entertains an average of approximately 448 requests for articles and this number is increasing every year.

The NBRC Library regularly evaluates its information services to ensure that the Institution's requirements are met. It promotes resource sharing and cooperation activities among libraries by providing an efficient and reliable means of resource sharing, that is, the inter library loan for the maximum use of resources, by providing copies of documents which are not available to researchers at centres outside the institute.

MAIN ACTIVITIES OF NBRC LIBRARY

1. Book Acquisition
2. Periodicals Acquisition
3. Selective Dissemination Information (SDI),
4. Current Awareness Services (CAS)
5. Inter Library Loan
6. Resource Sharing
7. Circulation services
8. Reference Services, Bibliographic services
9. Indexing and Special Services
10. Collects maintains, store and retrieves information and data keeping in the view of evolving needs of its researchers
11. Help to Network Centres.



DBT's Electronic Library Consortium (DeLCON)

DeLCON CONSORTIUM

A National-level Multi-institutional Initiative for Information Resources in the Life Sciences

The 'DBT's Electronic Library Consortium (DeLCON)' is a significant initiative of the Department of Biotechnology (DBT), Govt. of India, to enhance informational resources in its research Institutions. It was launched in January, 2009 with the ten DBT member-institutions with a large number of prominent journals. It is a topical endeavour for providing access to scholarly electronic resources including full-text and bibliographic databases in all the life science subject disciplines to the DBT institutional community across the country. It facilitates access to high quality e-resources to the research institutions to enhance research, teaching and learning.

The access to all major e-resources was enabled in the beginning of 2009. It has now been extended to new 17 more institutions in 2nd phase of extension in 2010 and further 7 members have been added in the 3rd phase of extension in 2011. Last year, there emerged the enlarged DeLCON Consortium with 33 members. Besides the DBT institutions, an emphasis has been given to incorporate institutions and universities (both in the state and central govt. sectors) across the states in North Eastern India. DeLCON provides current as well as archival access to more than 963 core peer-reviewed journals and a bibliographic database (SCOPUS) in different disciplines from 21 overseas publishers and aggregators.

The faculty members, scientists, research scholars and project assistants of the institutions covered under DeLCON are the primary beneficiaries.

The DeLCON comprises currently the following 33 member institutions:

DBT Institutions

1. National Brain Research Centre (NBRC), Manesar
2. National Institute of Plant Genome Research (NIPGR) - New Delhi
3. National Institute of Immunology (NII) - New Delhi
4. National Centre for Cell Science (NCCS) - Pune
5. Institute of Life Sciences (ILS) – Bhubaneshwar
6. Institute of Bioresources and Sustainable Development (ISBD) - Imphal
7. Centre for DNA Fingerprinting and Diagnostics (CDFD) - Hyderabad

8. Rajiv Gandhi Centre for Biotechnology (RGCB) – Thiruvananthapuram
9. International Centre for Genetics and Engineering Biotechnology (ICGEB), New Delhi
10. National Agri-Food Biotechnology Institute, Mohali, Punjab
11. National Institute of Biomedical Genomics, Kalyani, Kolkata
12. Regional Centre for Biotechnology, Gurgaon
13. Transnational Health Science & Technology, Institute, Gurgaon
14. Department of Biotechnology (DBT) Head Quarters, New Delhi
15. National Institute of Animal Biotechnology, Hyderabad (NIAB).

Institutions from North Eastern region

16. Indian Institute of Technology, Guwahati, Assam
17. North Eastern Regional Institute of Science & Technology, Arunachal Pradesh
18. Dibrugarh University, Assam
19. Assam University, Silchar
20. North East Institute of Science & Technology, Assam
21. Mizoram University, Mizoram
22. D. M. College of Science, Manipur
23. Sikkim University, Gangtok
24. College of Veterinary Science, Assam Agricultural University, Guwahati
25. Gauhati University, Assam
26. Manipur University, Imphal
27. College of Veterinary Science & Animal Husbandry Central Agricultural University, Mizoram
28. Rajiv Gandhi University, Arunachal Pradesh
29. Nagaland University, Nagaland
30. North-Eastern Hill University, Shillong
31. St. Anthony's College, Meghalaya
32. Tezpur University, Tezpur, Sonitpur, Assam
33. Sikkim State Council of Science and Technology, Gangtok, Sikkim

The complete list of full-text resources (e-Journals) and bibliographic databases, subscribed under the DeLCON Consortium, is available from <http://delcon.gov.in>.



National Neuroimaging Facility

NATIONAL NEUROIMAGING FACILITY

National Neuroimaging facility, sponsored by the Department of Biotechnology, Govt. of India, came into existence in the year of 2006. The main purpose this National Facility to facilitate/support cutting edge brain imaging research. The facility is equipped with four state-of-the-art equipments such as,

1. 3T Magnetic Resonance Imaging (MRI)Scanner
2. Electroencephalography (EEG)
3. Evoked Response Potential Recording (ERP)

MAGNETIC RESONANCE IMAGING (MRI)

MRI provides much greater contrast between the different soft tissues of the body compared to computed tomography (CT), making it especially useful in neurological (brain), musculoskeletal, cardiovascular. Various imaging modalities also play important role providing crucial information which can aid to various diagnostic process. There are various imaging modalities, which are:

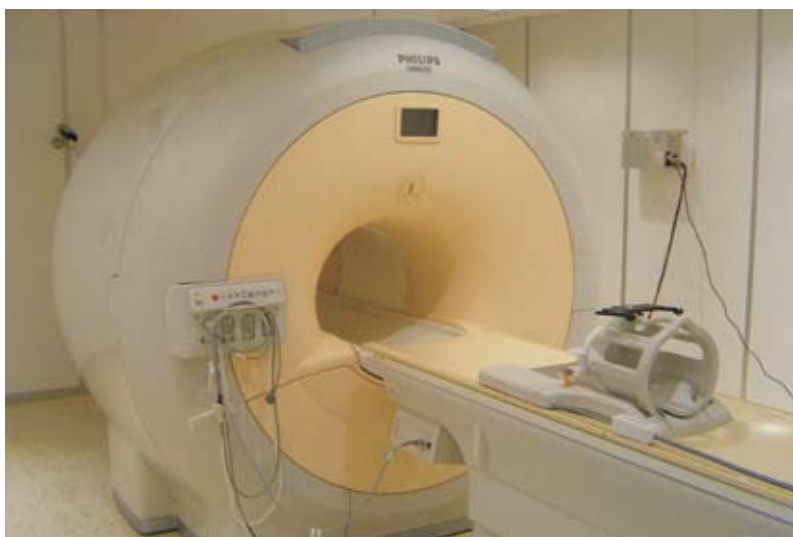
1. MR Spectroscopy (MRS) which provides non-invasive neurochemical level estimations and enables clinical correlation.
2. Functional MRI (fMRI) which, as the name suggests correlates functional (haemodynamics) activity with images of brain activation

The 3 Tesla Phillips whole body MRI scanner at our Facility is equipped with state-of-the-art hardware, software and data processing software required for each imaging modality. The facility is being used for performing structural, metabolic (multinuclear, e.g. proton and phosphorous) and functional MRI. In addition to understanding brain function and clinical research, the center also is closely interacting with leading imaging centers within the country and across the globe.

Electroencephalography (EEG) is a test that measures and records the electrical activity of the brain. Special sensors are attached to the head and hooked by wires to a computer. The computer records brain's electrical activity on the screen or on paper as wavy lines. Certain conditions, such as epilepsy, dementia, consciousness and narcolepsy (sleeping disorder) can be studied by EEG.

Evoked Response Potential Recording (ERP) is an electrical potential recorded from the nervous system of a human or other animal following presentation of a stimulus. Evoked potential amplitudes tend to be low, ranging from less than a microvolt to several microvolts

Clinical studies on patients with Alzheimer's Parkinson's and Autism as well as monitoring of aging in normal healthy brain is being performed extensively in this National Neuro imaging facility.





Translational Research: Clinical Unit

TRANSLATIONAL & CLINICAL NEUROSCIENCE UNIT

Consultant Clinical Professor: Dr. V. S. Mehta
 Consultant Clinical Assistant Professor: Dr Kapil Agarwal
 Consultant Clinical Assistant Professor: Dr Rajnish Kumar
 Clinical Neuropsychologist: Dr Preeti Singh
 Clinic Assistant: Hanuman Singh and Pawan Kumar

The unit is located at the Government General Hospital, Civil Lines, Gurgaon 122001.

INVESTIGATION FACILITIES

The following facilities are available to the patients of the unit through the hospital/clinics at concessional rates:

MRI system: Siemens Magnetom 1.5 Tesla scanner with various study protocols

CT system

Ultrasonography

Neurophysiology: EEG, Evoked response, EMG.

X-ray and Contrast imaging.

WETLAB FACILITIES

Biochemistry, Microbiology, Haematology, Pathology & Immunology.

Translational research aims to connect basic research to patient care:

"From the Bench lab to the Bedside patient". The Clinical Research Unit of NBRC covers the full spectrum of clinical neuroscience: neurology, neurosurgery, neuropsychology, neuropsychiatry, behavioral therapy, and psychometry. The unit has a morning outpatient facility, at the Government General Hospital four days a week, each of the consultant clinical faculty is available on one of the designated days. The NBRC Unit has integrated well with the Civil hospital medical team and there is an increasing number of referrals from other in-house departments and local hospitals. If a patient of the unit requires indoor treatment or observation, then, with courtesy of neuropsychiatrists and specialists of internal medicine of the General Hospital, the patient is taken care of. The out-patients facility is busy, and on some days attendance can exceed forty patients.

The follow up by the patients is about 85%. Male to female ratio is almost equal. Paediatric group patient attendance is mainly for management of epileptic seizure and disorders of the mentally challenged. There are also elderly patients

attending, and movement disorders are an important cause of attendance. Patients attending the OPD at Civil Hospital come from old Gurgaon township and the villages and towns in the surrounding districts of Haryana, while some come from neighbouring states as Rajasthan, Uttarkhand, Delhi and Uttar Pradesh.

Patients requiring advanced specialist neurology in-patient care are referred to All-India Institute of Medical Sciences (AIIMS), Institute of Postgraduate Medical Education & Research – Rohtak, Institute of Human Behaviour & Allied Sciences (IHBAS), or Vardhaman Medical College (Safdarjung Hospital), New Delhi or to other tertiary hospital as per the choice of the patient, if he so desires. As part of the major plans for renovation of Civil Hospital, the Neurology OPD rooms have been refurbished and space has been allotted for NBRC in the outpatient area, which can accommodate other members of our team.

Outpatient case records in neurology are maintained from the outset, aside from relevant entry into the patient OP case sheets, which the patients keep in their possession. A comprehensive Neurology case sheet has been formulated and formatted by Distributed Information Centre of NBRC. We are undertaking to prospectively enter all the medical data of new patients, to create computer database with relevant patient data along with any planned imaging/molecular/neurophysiological studies at the NBRC labs, thus creating a well documented "clinical window" for our research institute. In this effort to narrow the gap between Basic Neuroscience and Applied Neuroscience, an ethics committee protocol has been formulated jointly with the Government General Hospital/Government of Haryana.

The association of NBRC with Alzheimer's & Related Disorders Society of India (ARDSI) which has been going on from 2005, has been further fostered. This interaction promises to grow to the mutual benefit of both institutions concerned primarily with the common goal of the care of the elderly in its varied aspects. Besides medical and neurological health conditions, one is exposed to the psychosocial and public health problems of the ageing populace in their home environment.

Further expansion of the electrophysiological facility is underway, with procurement of 64-channel high density EEG/evoked potential response analysis, electrical dipole source mapping, Electromyography (EMG) and Neurophysiological studies as Nerve Conduction velocity system and neurometry.

For proper functioning and further clinical support, the Unit receives the fullest cooperation of the Ministry of Health - Government of Haryana, and the Deputy Commissioner - Gurgaon, as well as from the Civil Surgeon and the Principal Medical Officer of the Hospital.



Meeting & Workshops

Prof. Ramamurthi Memorial Lecture

THE LATE DR. B. RAMAMURTHI MEMORIAL LECTURE

The VIIIth late Dr. B. Ramamurthi Memorial Lecture was delivered by Prof. Vijayalakshmi Ravindranath, Chairperson, Centre for Neuroscience Indian Institute of Science (IISc), Bengaluru on 8th February 2013, at the National Brain Research Centre in Manesar. This series of lecture which were initiated in 2006 commemorates Professor Ramamurthi's immense contribution role in setting up NBRC. Prof. Subrata Sinha, Director, NBRC, discussed Prof. Ramamurthi's contributions to Neuroscience with emphasis on his role in the setting up of a centre devoted to research in Neuroscience. Prof. Ravindranath scientific oration was entitled "The changing demography and challenge for Neuroscience".





International Collaborations & Networking

INTERNATIONAL COLLABORATIONS

United States

Dr. Pankaj Seth has been awarded two grants from USA for collaborative research. The NIH-RO1 grant is in collaboration with Dr. Carlos Pardos, Johns Hopkins University, Baltimore, USA. This NIH-RO1 grant proposes to study the "Role of CNS opportunistic infections in subsequent development of HIV dementia". The NIH R21 grant is awarded in collaboration with Prof Shilpa Buch, University of Nebraska Medical Center, USA. This NIH-R21 grant proposes to study the "Molecular Mechanisms & Therapy for Cocaine Abuse in HIV Associated Neurocognitive Disorder (HAND).

Japan

Dr. Nihar Jana and Dr. Nobuyuki Nukina (RIKEN Brain Science Institute, Japan) have a grant together for studying. "Role of ubiquitin-proteasome system dysfunction in the pathogenesis of Huntington's disease." Dr. Jana also has another grant in collaboration with Dr. Amit Mishra (IIT, Jodhpur) and Dr. Koji Yamanaka (RIKEN Brain Science Institute, Japan) to study "Role of Ube3a in ALS pathogenesis."

Netherlands

Prof. Prasun Roy and Prof. Peter Luijten, Utrecht Medical Centre, are working together on developing high-field neuroimaging methodology which has been sponsored by Utrecht University Research Foundation and Philips Research

Canada

A neuroimaging project on imaging systems and networks has been initiated by Prof. Prasun Roy and Prof. Alan Evans, Montreal Neurological Institute, McGill University.

NETWORKING

A major goal of NBRC is to network the existing neuroscience groups/ institutions in the country and promote multidisciplinary research in neuroscience. This is aimed to prevent unnecessary duplication of the work and facilities already existing. It also facilitates sharing of expertise and available infrastructure for mutual benefit. Networking also helps to bring together researchers from varying backgrounds to pursue common objectives that may be beyond the capacity of an individual investigator, group or institution. This is important because major achievements in neuroscience are being made through a

multidisciplinary approach by bringing together scientists working in different disciplines into the main stream of neuroscience and brain research activity. The networking is possible by information sharing through electronic network and identifying "Collaborating" centres for mutual interaction. Currently 48 centres throughout India are networked to NBRC. The following institutions/universities are member of our network activities

List of Network Centres

1. All India Institute of Medical Sciences (AIIMS), New Delhi.
2. Banaras Hindu University (BHU), Varanasi.
3. Bangur Institute of Neurology, Kolkata.
4. Centre for Behavioural and Cognitive Sciences (CBCS), University of Allahabad, Allahabad.
5. Centre for Cellular & Molecular Biology (CCMB), Hyderabad.
6. Central Drug Research Institute (CDRI), Lucknow.
7. Centre for DNA Fingerprinting and Diagnostic, Hyderabad.
8. Central Food and Technological Research Institute (CFTRI), Mysore.
9. Cochin University of Science and Technology, Cochin.
10. Department of Biotechnology, New Delhi.
11. Delhi University, South Campus, Delhi.
12. Dr. A. L. Neurosurgical Centre, Chennai.
13. Indo American Hospital Brain and Spine Center, Kerala.
14. Institute of Cybernetics, Systems and Information Technology, Kolkata.
15. International Centre for Genetic Engineering and Biotechnology (ICGEB), New Delhi.
16. Institute of Genomics and Integrative Biology (IGIB), Delhi.
17. Institute of Human Behaviour & Allied Sciences (IHBAS), Delhi.
18. Indian Institute of Information Technology (IIIT), Allahabad.
19. Indian Institute of Technology (IIT), Mumbai.
20. Indian Institute of Technology (IIT), Delhi.
21. Indian Institute of Technology (IIT), Kanpur.
22. Indian Institute of Science (IIS), Bangalore.

23. Indian Institute of Chemical Biology (IICB), Kolkata.
24. Institute of Nuclear Medicine and Allied Sciences (INMAS), New Delhi.
25. Industrial Toxicology Research Centre (ITRC), Lucknow.
26. Indian Statistical Institute, Kolkata.
27. International School of Photomics, Cochin.
28. Jagadguru Sri Shivarathreeshwara Medical College, Mysore
29. Jawaharlal Nehru University (JNU), New Delhi.
30. Jawaharlal Nehru Centre for Advance Scientific Research (JNCASR), Bangalore.
31. Jiwaji University, Gwalior.
32. M.S. University of Baroda (Dept. of Microbiology and Biotechnology Centre), Baroda.
33. National Centre for Biological Sciences (NCBS), Bangalore.
34. National Informatics Centre (Medical Informatics and Telemedicine Division), (NIC) New Delhi.
35. National Institute of Mental Health & Neuroscience (NIMHANS), Bangalore.
36. Nizam's Institute for Medical Sciences (NIMS), Hyderabad.
37. Rajiv Gandhi Centre for Biotechnology, Trivandrum.
38. National Neuroscience Centre (NNC), Kolkata.
39. Sanjay Gandhi Post-Graduate Institute of Medical Sciences (SGPGIMS), Lucknow.
40. School of Information Technology, West Bengal University.
41. Shree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvanthapuram.
42. Sri Venkateswara Institute of Medical Sciences, Tirupati.
43. Tata Institute of Fundamental Research (TIFR), Mumbai.
44. University College of Medical Sciences (UCMS), Delhi.
45. University of Hyderabad, Hyderabad.
46. University of Calcutta, Kolkata.
47. Vidyasagar Institute of Mental Health and Neuroscience (VIMHANS), New Delhi.
48. Vision Research Foundation, Chennai



Invited Lectures

INVITED SPEAKER

Sr. No.	Name of the Speaker	Title of the Lecture	Date
1.	Dr. Supriya Ray The Smith-Kettlewell Eye Research Institute, San Francisco, California	Oculomotor Decision Making by Predictive Deselection of Antagonist Rule in Supplementary Eye Field	April 16, 2012
2.	Dr. Renu Goel Institute of Bioinformatics Bangalore	Proteomics & Signal Transduction Pathway & Computational Biology & Bioinformatics Implementation	April 26, 2012
3.	Dr. Alapakkam Sampath USC Keck School of Medicine	Optimal processing of photoreceptor signals is required to maximize behavioral sensitivity near absolute visual threshold	June 19, 2012
4.	Dr. Arvind Kumar University of Freiburg	Role of inhibition in causing and correction of Parkinson's disease related brain dynamics	June 22, 2012
5.	Dr. Ramesh Vijay Assistant Professor, Section of Sleep Medicine, Department of Pediatrics, The Knapp Center for Biomedical Discovery, The University of Chicago Medical Center, Chicago	Windows to the Brain: Domains and Determinants of Sleep Apnea Induced Morbidity	July 2, 2012
6.	Dr. Sharda Prasad Yadav NIH, USA	transcription and splicing associated protein NonO/p54nrb augments rhodopsin expression synergistically with NRL and CRX	July 2, 2012
7.	Dr. Sachin Deshmukh Mind/Brain Institute Johns Hopkins University, Baltimore	Objects, space, and memory: how the hippocampal cognitive map comes together	July 23, 2012
8.	Professor Rosalia Mendez Instituto de Biofisica Carlos Chagas, Rio de Janeiro, Brazil	Cell therapy in Neurological disorders.	September 17, 2012
9.	Dr. Utpal Das Department of Neurosciences Department of Pathology University of California San Diego USA	Neuronal Protein Trafficking and Neurodegenerative Disorders	October 3, 2012
10	Dr. Anindya Ghosh Roy University of California, San Diego	Maintenance and Repair of neural circuit	October 26, 2012
11.	Dr. Vikaas S. Sohal Assistant Professor Department of Psychiatry University of California, San Francisco, USA	Using optogenetics to study how dopamine modulates normal and pathological activity in the prefrontal cortex	November 6, 2012
12.	Dr. Nixon Abraham University of Geneva	Role of synaptic inhibition in odor discrimination	November 27, 2012
13.	Prof. Iqbal Ahmad Professor of Ophthalmology & Visual Sciences Associate Dean, Academic affairs Director, Postdoctoral Education & Research, University of Nebraska Medical Center, Omaha, USA	Treating Neuronal Degeneration - From Within And Without	November 29, 2012

14.	Dr. Dipanjan Roy from Technical University Berlin	Influence of cell type specificity, astrocytic glutamate uptake on representations in the primary visual cortex	December 3, 2012
15.	Dr. Panchanan Maiti University of California, Los Angeles	Protein misfolding and neurodegeneration caused by amyloid deposition: role of molecular chaperones	December 5, 2012
16.	Dr. Mahendra S Rao, Director Center for Regenerative Medicine, National Institutes of Health, Bethesda, USA	Using stem cells in translational medicine	December 17, 2012
17.	Dr. Kaveri Rajaraman Center for Ecological Sciences IISc, Bangalore	Listening to Bass Notes: How to Make Size Not Matter ?	December 20, 2012
18.	Prof. Vijayalakshmi Ravindranath Chairperson Centre for Neuroscience IISc, Bengaluru	The changing demography and challenge for neuroscience	February 8, 2012
19.	Dr. Debanjan Goswami, Stanford University, USA	Long-term Potentiation Requires Unique Postsynaptic SNARE Fusion Machinery	February 12, 2013
20.	Prof. Tej Pandita Department of Radiation Oncology, UT Southwestern Medical Center, Texas USA	Role of MOF in DNA Damage Response and Beyond	February 14, 2013
21.	Dr. James Chelliah Scripps Research Institute, USA	Pathogenic SYNGAP1 haploinsufficiency impairs cognitive development by disrupting the maturation of dendritic spine synapses	February 15, 2013
22.	Prof. Alan Evans Montreal Neurological Institute McGill University Montreal, Canada	Brain Networks of Anatomical Covariances	February 13, 2013
23.	Dr. Bart Krekelberg Associate professor Rutgers University	Neural Mechanisms of Perceptual Stability	February 13, 2013
24.	Dr. Amitabha Majumder Stowers Institute, USA	The role of a self-sustaining amyloidogenic protein in persistence of memory.	February 19, 2013
25.	Dr. Abrar Qurashi Mount Sinai School of Medicine, USA	Non coding RNA-mediated neurodegeneration in fragile X-associated tremor/ataxia syndrome	March 4, 2013
26.	Dr. John P John Additional Professor of Psychiatry and an Adjunct faculty of Clinical Neurosciences, and Head, Multimodal Brain Image Analysis Laboratory (MBIAL) NIMHANS	Imaging biomarkers in schizophrenia: promising leads from research at MBIAL	March 5, 2013



Academic Programmes

ACADEMIC PROGRAMMES

Deemed University Status

NBRC was awarded Deemed University status (de-novo category) in 2002 under Section 3 of UGC Act, 1956 (3 of 1956) vide notification No.F.9-52/2001-U.3 dated 20th May, 2002 issued by Ministry of Human Resources Development, Government of India. NBRC is the first Institute among the Institutes of the Department of Biotechnology to attain this status.

On completion of 5 years period from the time NBRC has been given de-novo deemed University status, a Committee (duly constituted by UGC) visited NBRC for reviewing the 'Deemed to be University' status and recommended further extension. The deemed university status has also been reviewed by an independent Committee constituted by Ministry of HRD. The Committee gave an excellent report and placed this University / Institute under "A" category.

UGC desired to re-assess and review the deemed university status and again a duly constituted Committee visited NBRC again and gave a very good report. The notification from Ministry of HRD is awaited.

COURSES OFFERED

Ph.D. in Neuroscience

NBRC has a Ph.D. Programme in Neuroscience to develop trained manpower having a broad overview of different aspects of Neuroscience.

NBRC inducts students for its Ph.D. programme from diverse backgrounds including Masters degree in any branch related to Neurosciences, Psychology or M.B.B.S., B.E., or B.Tech. NBRC recognizes that understanding brain functions requires a fusion of knowledge from multiple disciplines.

Fellowship for Junior Research Fellows is ` 16,000/- per month and for Senior Research Fellows it is ` 18,000/-

Integrated-Ph.D. in Neuroscience

NBRC has an Integrated Ph.D. Programme in Neuroscience to develop trained manpower having a broad overview of different aspects of Neuroscience.

NBRC inducts students for its Integrated Ph.D. programme

from diverse backgrounds including Bachelor's degree in any branch related to Neurosciences, M.B.B.S., B.E., B. Tech. or Psychology. NBRC recognizes that understanding brain functions requires a fusion of knowledge from multiple disciplines.

Integrated Ph.D. Students are provided a fellowship of ` 5000/- per month for the first two years. From third year onwards they are paid fellowship on par with Ph.D. students. After completion of the Integrated Ph.D. programme, the students will be given dual degree (M.Sc. and Ph.D.). NBRC is one of the first Institutes in the country to develop an integrated multidisciplinary teaching programme in Life Sciences.

NBRC offers certain benefits to its students in the form of fellowships, hostel accommodation, transportation facility, medical reimbursement to its students.

Summer Training and Short-term Programmes

NBRC conducted Summer Training Programme for the Students through three National Science Academies viz: (1) Indian Academy of Science, Bangalore (2) Indian National Science Academy, New Delhi (3) National Academy of Sciences, Allahabad. The summer training was for a period of 8 weeks. The Trainees were provided with shared accommodation in the Hostel of NBRC during their training period. Summer trainees were encouraged to attend seminars and journal clubs organized at the Institute.

The summer training projects give students an exposure to Neuroscience and encourage them to consider it as a future career option.

NBRC celebrated its 9th Foundation Day on 16th December 2012. Six schools from Gurgaon / Manesar participated in the open exhibition and quiz, held at NBRC in connection with the Foundation Day celebrations. The events included Lab visits and poster viewing by students, Lecture in the Seminar Hall (Given by senior students) and Quiz.

NBRC celebrated the National Science Day on 28th February, 2013.

On this occasion Integrated Ph.D. student, Post Doctoral Fellow and other project employee of NBRC participated in a presentation at Kendriya Vidyalaya, NSG, Manesar, Govt. Senior Secondary School, Pachgaon and Amity University, Manesar, Gurgaon.



General & Academic Administration – A Profile

GENERAL & ACADEMIC ADMINISTRATION – A PROFILE

The General Administration of the Institute consists of the following major wings:

1. General Administration, headed by the Chief Administrative Officer, who is responsible for overall Management of Establishment, Personnel & Administration Wing, Stores & Purchase Wing, Import & Project Cell, Finance & Accounts Wing, Estate Management & Engineering Maintenance Wing – Civil, Electrical & Mechanical.
2. Academic Administration is headed by the Registrar, who is responsible for the students' administration, project co-ordination, new students' admissions, course co-ordination etc. The officer is also responsible for the administration of DIC.

During the year under review, the Administration achieved excellence in execution of following activities at NBRC:

- The annual cultural festival of NBRC, 'TANTRIKA 2012' was organized within the campus which included a variety of cultural and sports events. Students, officers, and staff of NBRC participated in the event.
- Provided necessary logistics in conducting international and national conferences/seminars organized in the campus as well outside of the campus.
- Made major imports from different countries in terms of equipments and other consumables with meticulous planning and adhered to a precise schedule.
- The 9th Foundation Day of NBRC was held on 16th day of December, 2012. On this occasion, several programmes were organized within and outside the campus. The daylong celebrations included the poster presentations on ongoing research activities of NBRC. Students from various schools were invited to interact with NBRC scientists and they visited the laboratories. A quiz programme for students from local schools was also organized on this occasion. On this august occasion, Prof. Dr. Mahendra S. Rao, Director, Centre for Regenerative Medicine, National Institutes of Health (NIH), Bethesda, USA delivered the Foundation Day lecture to the students and scientific community at India International Centre, New Delhi.
- The Sadbhavana Diwas was observed in NBRC in the year 2012. The faculty, students and staff were administered a solemn pledge to work in harmony and emotional oneness of all people regardless of region, caste, religion or language.
- The process of recruiting Dr. Arpan Banerjee as Scientist was completed during 2012. Dr. Banerjee was in the

Brain Imaging and Modeling Section, National Institute on Deafness and other Communication Disorders (NIDCD), National Institutes of Health, Bethesda, MD, USA.

Implementation of Official Language

NBRC Administration has given due importance for the implementation of Hindi as the Official Language at this centre and has made full efforts to implement the use of Official Language in all the administrative jobs such as internal official meetings, interviews, debates, general applications etc. NBRC Administration received a letter of appreciation from the Ministry of Home Affairs, Regional Implementation Office, Ghaziabad towards implementation of Hindi in day to day official work during the year. The Rajbhasha Sansthan, New Delhi awarded NBRC with a shield in recognition of its efforts made towards the implementation of Hindi as the official language.

RTI Act

The provisions of RTI Act are being followed at NBRC in letter and in spirit. All RTI applications received during 2012-13 seeking information on various matters concerning NBRC were provided the requisite information within the prescribed time limit.

Women Empowerment

NBRC has a distinct feature of giving equal opportunity to women. The Committees, constituted to do various work of Administration, Academics and scientific activities, have women members in them which ensure fair participation and protection of women. There is a committee for redressal of complaints relating to any sexual harassment of women at NBRC and grievances, if any, from aggrieved girl students/ women employees of NBRC. Any lady/ woman of NBRC, among the Students/ Employees who is subjected to sexual harassment can approach any of the committee members.

Reservations and concessions in Employment & Admissions of Students

NBRC follows reservations & concessions as the per rules of Government of India in employment, and in the matter of students' admissions, the provision of exemption as provided in Gazette Notification No. 5 dated 4th January, 2007 is implemented.

Vigilance

The Institute has a Chief Vigilance Officer. As per the guidelines of DBT, one of the Officers of NBRC has been nominated as Chief Vigilance Officer of the Centre.



Institutional Governance Structure & People at NBRC

NBRC Society
Governing Council
Finance Committee
Scientific Advisory Committee
Building Committee
Academic Council
Board of Studies
Scientific Staff
Other Staff

MEMBERS OF NBRC SOCIETY

1.	Prof. P. N. Tandon, (<i>President</i>) No. 1, Jagriti Enclave, Vikas Marg, New Delhi-
2.	Dr. M.K. Bhan, <i>Secretary</i> Department of Biotechnology, New Delhi
3.	Dr. T. Ramasami, <i>Secretary</i> Department of Science & Technology, New Delhi
4.	Dr. V.M.Katoch, <i>Director-General</i> Indian Council of Medical Research, New Delhi
5.	Dr. Sandip K. Basu JC Bose, <i>Chair Professor</i> National Institute of Science Commission & Information Resources (NISCAIR) New Delhi
6.	Dr. K. Vijayaraghavan, <i>Director</i> National Centre for Biological Sciences (NCBS) Bangalore, Karnataka
7.	Prof. Samir K. Brahmachari, <i>Director General</i> CSIR Institute of Genomics & Integrative Biology Delhi
8.	Ms.Vandana Srivastava, <i>IDAS</i> JS & FA, Department of Biotechnology, New Delhi
9.	Dr. Gourie Devi, <i>Director (Retd.)</i> Flat -9, Doctors Apartments, Vasundhara Enclave, Delhi
10.	Dr. L.M. Patnaik, <i>CSA Department</i> Indian Institute of Science, Bangalore
11.	Prof. Kalluri Subba Rao, <i>Prof. & Head of Biochemistry</i> University of Hyderabad, School of Life Sciences Hyderabad, Andhra Pradesh
12.	Dr. T.S. Rao, <i>Advisor</i> Department of Biotechnology, New Delhi
13.	Prof. Subrata Sinha, <i>Director</i> National Brain Research Centre, Manesar, Haryana

MEMBERS OF THE GOVERNING COUNCIL

1.	Prof. K. VijayRaghavan, (<i>Chairperson</i>) Secretary Department of Biotechnology, New Delhi
2.	Prof. P.N. Tandon (<i>Ex-officio</i>) No. 1, Jagriti Enclave, Vikas Marg, Delhi
3.	Prof. Upinder S. Bhalla, <i>Scientist</i> National Centre for Biological Sciences (NCBS) Bangalore
4.	Prof. Dinakar M. Salunke, <i>Executive Director</i> Regional Centre for Biotechnology, Gurgaon
5.	Dr. A.K. Agarwal (<i>Ex-Officio</i>) Dean, Director, Professor & HOD, Maulana Azad Medical College, New Delhi
6.	Prof. G. Mehta, <i>FNA, FRS</i> Bhartia Chair School of Chemistry University of Hyderabad, Hyderabad
7.	Dr. Chitra Sarkar Department of Pathology, All India Institute of Medical Sciences (AIIMS), New Delhi
8.	Prof. Seyed E. Hasnain, <i>Professor</i> Kusuma School of Biological Sciences, Indian Institute of Technology (IIT Delhi), New Delhi
9.	Ms. Anuradha Mitra, <i>IDAS (Ex-officio)</i> Joint Secretary & Financial Advisor, Department of Biotechnology, New Delhi
10.	Dr. V.M. Katoch, (<i>Ex-Officio</i>) Director General, Indian Council for Medical Research, V. Ramalingaswamy Bhawan, New Delhi
11.	Dr. T. Ramasami, (<i>Ex-Officio</i>), <i>Secretary</i> Department of Science & Technology (DST), New Delhi
12.	Dr. T.S. Rao (Spl. Invitee), <i>Advisor</i> Department of Biotechnology, New Delhi
13.	Dr. Sanjeev Jain (Spl. Invitee) Professor & HOD, Department of Psychiatry, NIMHANS, Bangalore
14.	Prof. Subrata Sinha (<i>Ex-officio</i>), <i>Director</i> National Brain Research Centre, Gurgaon, Haryana

MEMBERS OF FINANCE COMMITTEE

1.	Prof.K.VijayRaghavan Chairperson (Ex-officio) Secretary, Department of Biotechnology, New Delhi
2.	Ms. Anuradha Mitra, IDAS (Ex-officio), Joint Secretary & Financial Advisor, Department of Biotechnology, New Delhi
3.	Prof. Dinakar M. Salunke, <i>Executive Director</i> Regional Centre for Biotechnology, Gurgaon, Haryana
4.	Dr. K.P. Singh (UGC Nominee) <i>Joint Secretary</i> University Grants Commission New Delhi

5.	Prof. Seyed E. Hasnain, Professor, Kusuma School of Biological Sciences, Indian Institute of Technology (IIT Delhi), Hauz Khas, Delhi, Member
6.	Prof. Subrata Sinha, Member (<i>Ex-officio</i>) Director, National Brain Research Centre, Gurgaon, Haryana
7.	Shri Rajesh Kumar Vyas, Non-Member Secretary (<i>Ex- officio</i>) Finance and Accounts Officer National Brain Research Centre Gurgaon, Haryana

MEMBERS OF SCIENTIFIC ADVISORY COMMITTEE

1.	Prof. P.N. Tandon (<i>Chairperson</i>) President, NBRC Society No. 1, Jagriti Enclave, Vikas Marg, Delhi
2.	Prof. Upinder S. Bhalla, (<i>Co-Chairperson</i>) Scientist, National Centre for Biological Sciences (NCBS), Bangalore
3.	Prof. Vijayalakshmi Ravindranath, (<i>Chairperson</i>) Centre for Neuroscience, Indian Institute of Sciences, Bangalore
4.	Prof. Amitabha Chattopadhyay <i>Scientist</i> Centre for Cellular and Molecular Biology (CCMB), Hyderabad
5.	Dr. Ayub Qadri, <i>Scientist</i> National Institute of Immunology (NII), New Delhi
6.	Prof. Dinakar M. Salunke, <i>Executive Director</i> Regional Centre for Biotechnology (RCB), Gurgaon
7.	Prof. Siddhartha Roy, <i>Director</i> Indian Institute of Chemical Biology (IICB), Kolkata
8.	Prof. Jyotsna Dhawan, <i>Scientist</i> Institute for Stem Cell Biology and Regenerative Medicine (inStem), NCBS, TIFR, Bangalore
9.	<i>Director</i> National Centre for Biological Sciences, Bangalore
10.	Prof. Rohit Manchanda Biomedical Engineering Group, School of Biosciences and Bioengineering, IITBombay, Mumbai
11.	Prof. B.N. Mallick, <i>Professor</i> Deptt. of Life Sciences, Jawaharlal Nehru University New Delhi

12.	Dr. V. Rajshekhar Department of Neurological Sciences, Christian Medical College Hospital, CMC, Vellore
13.	Dr. Sanjeev Jain Head of the Department, Department of Psychiatry, NIMHANS, Bangalore
14.	Prof. Sudipta Maiti Deptt. of Chemical Sciences, TIFR, Mumbai
15.	Prof. N.R. Jagannathan Head of the Department of NMR and MRI Facility, All India Institute of Medical Sciences (AIIMS), New Delhi
16.	Dr. Chitra Sarkar Department of Pathology, All India Institute of Medical Sciences (AIIMS), New Delhi
17.	Prof. Ajay Ray, <i>Vice-Chancellor</i> Bengal Engineering & Science University, Shibpore, Howrah International Members

International Members

18.	Prof. ARIEL RUIZ i ALTABA, Professor, Faculty of Medicine, University of Geneva, Department of Medicinal Genetics Geneva, Switzerland
19.	Prof. Baroness Susan Greenfield, Professor, Department of Pharmacology, Lincoln College, Oxford University, UK
20.	Prof. Thomas D. Albright, Professor, The Salk Institute for Biological Studies, La Jolla, California, USA
21.	Dr. Michael W. Weiner, MD, Director of the Center for Imaging of Neurodegenerative Diseases, SFVAMC, Professor of Radiology, Medicine, Psychiatry and Neurology, UCSF
22.	Dr. T.S. Rao, Member (<i>Ex-officio</i>) Adviser Department of Biotechnology (DBT), New Delhi

MEMBERS OF BUILDING COMMITTEE

1.	Dr. T.S. Rao, <i>Advisor</i> Department of Biotechnology, New Delhi
2.	Dr. Sidhartha Satpathy, <i>Professor</i> Department of Hospital Administration All India Institute of Medical Sciences (AIIMS), New Delhi
3.	Dr. Satish Gupta, <i>Deputy Director</i> National Institute of Immunology New Delhi

4.	Mr. M.K. Gupta, Engineer-In-Charge (<i>Civil</i>) Inter University Accelerator Centre, JNU (New) Campus, New Delhi
5.	Prof. Subrata Sinha, <i>Director</i> National Brain Research Centre, Manesar, Haryana

MEMBERS OF ACADEMIC COUNCIL

1.	Prof. Subrata Sinha (<i>Chairman</i>) Director, National Brain Research Centre, Manesar, Haryana
2.	Prof. Nihar Ranjan Jana National Brain Research Centre, Manesar, Haryana
3.	Prof. Basabi Bhaumik Department of Electrical Engineering, Indian Institute of Technology, New Delhi
4.	Prof. Pankaj Seth National Brain Research Centre, Manesar, Haryana
5.	Dr. V. S. Mehta Paras Hospitals, Gurgaon, Haryana
6.	Prof. P. K. Roy National Brain Research Centre, Manesar, Haryana
7.	Prof. K. Muralidhar, <i>Head, Dept. of Zoology</i> University of Delhi, Delhi
8.	Prof. Pravat K. Mandal National Brain Research Centre, Manesar, Haryana
9.	Dr. Anirban Basu National Brain Research Centre, Manesar, Haryana
10.	Dr. Ranjit K. Giri National Brain Research Centre, Manesar, Haryana

11.	Dr. Ellora Sen National Brain Research Centre, Manesar, Haryana
12.	Dr. Shiv Kumar Sharma National Brain Research Centre, Manesar, Haryana
13.	Dr. Nandini C. Singh National Brain Research Centre, Manesar, Haryana
14.	Dr. Soumya Iyengar National Brain Research Centre, Manesar, Haryana
15.	Dr. Narender K. Dhingra National Brain Research Centre, Manesar, Haryana
16.	Dr. Yoganarasimha Doreswamy National Brain Research Centre, Manesar, Haryana
17.	Prof. Neeraj Jain National Brain Research Centre, Manesar, Haryana
18.	Dr. Sourav Banerjee National Brain Research Centre, Manesar, Haryana
19.	Dr. Sharba Bandyopadhyay (Till 27-03-2013 A.N.), National Brain Research Centre, Manesar, Haryana
20.	Mr. K.V.S.Kameswara Rao
21.	National Brain Research Centre, Manesar, Haryana

MEMBERS OF BOARD OF STUDIES

1.	Prof. Subrata Sinha, <i>Director</i> National Brain Research Centre, Manesar, Haryana
2.	Prof. Pankaj Seth National Brain Research Centre, Manesar, Haryana
3.	Prof. D. N. Rao Indian Institute of Sciences, Bangalore, Karnataka
4.	Prof. P. K. Roy National Brain Research Centre, Manesar, Haryana
5.	Prof. Rohit Manchanda Indian Institute of Technology, Mumbai, Maharashtra
6.	Prof. Pravat K. Mandal National Brain Research Centre, Manesar, Haryana
7.	Dr. Anirban Basu National Brain Research Centre, Manesar, Haryana
8.	Dr. Ranjit K. Giri National Brain Research Centre, Manesar, Haryana
9.	Dr. Ellora Sen National Brain Research Centre, Manesar, Haryana
10.	Dr. Shiv Kumar Sharma National Brain Research Centre, Manesar, Haryana

11.	Dr. Nandini C. Singh National Brain Research Centre, Manesar, Haryana
12.	Dr. Soumya Iyengar National Brain Research Centre, Manesar, Haryana
13.	Dr. Narender K. Dhingra National Brain Research Centre, Manesar, Haryana
14.	Dr. Yoganarasimha Doreswamy National Brain Research Centre, Manesar, Haryana
15.	Prof. Neeraj Jain National Brain Research Centre, Manesar, Haryana
16.	Prof. Nihar Ranjan Jana National Brain Research Centre, Manesar, Haryana
17.	Dr. Sourav Banerjee National Brain Research Centre, Manesar, Haryana
18.	Dr. Sharba Bandyopadhyay (Till 27-03-2013 A.N.), National Brain Research Centre, Manesar, Haryana
19.	Mr. K.V.S.Kameswara Rao National Brain Research Centre, Manesar, Haryana

SCIENTIFIC STAFF

Scientists	
1.	Prof. Subrata Sinha (Director)
2.	Prof. Prasun Kumar Roy
3.	Prof. Neeraj Jain
4.	Dr. Nihar Ranjan Jana
5.	Dr. Pravat Kumar Mandal
6.	Dr. Pankaj Seth
7.	Dr. Narender K. Dhingra
8.	Dr. Shiv Kumar Sharma
9.	Dr. Ranjit Kumar Giri
10.	Dr. Nandini C. Singh
11.	Dr. Soumya Iyengar
12.	Dr. Anirban Basu
13.	Dr. Yoganarasimha Doreswamy
14.	Dr. Ellora Sen
15.	Dr. Sourav Banerjee
16.	Dr. Sharba Bandyopadhyay
17.	Dr. Rema Velayudhan
Consultants	
1.	Prof. Partha Raghunathan

DST-INSPIRE Faculty	
1.	Dr. Supriya Bhavnani
Research Scientist	
1.	Dr. Tora Mitra Ganguli (Till 30/04/12)
Scientist (WOS - A)	
1.	Dr. Sayali C. Ranade (DST Project) (Till 02/07/12-F.N.)
Post Doctoral Fellow (DST)	
1.	Dr. Chaitra Rao
2.	Dr. D.Subhashree
3.	Dr. Chetan Kumar Yadav
Research Associate	
1.	Dr. Shripad Arun Kondra (Till 18/05/12)
2.	Dr. Kallol Dutta (RA III DBT Project) (Till 21/06/12)
3.	Dr. Arkadeb Dutta (RA II DBT Project) (Till 29/11/12)
4.	Dr. Sanchari Sinha (Till 01/10/12)
5.	Dr. Supriya Bhavnani (Till 20/11/12)
6.	Dr. Prem Chand
7.	Dr. D.Subhashree (Till 17/09/12)
8.	Dr. Vidhata Dixit (Till 04/04/12)
9.	Dr. Amar Nath Maurya (Till 31/08/12)

10.	Dr. T. Mrudula (RA I DBT Project) (Till 31/12/12)
R & D Engineer	
1.	Mr. Rajdeep Singh Rathore (Till 23/10/12)
2.	Ms. Tejaswini Adikane (Till 30/04/12)
3.	Mr. Joshi Jitesh Narendra
4.	Ms. Shammi More
5.	Ms. Shikha Vatsa
Junior R&D Engineer	
1.	Mr. Karthik Vyawahare (Till 25/05/2012-F.N.)
2.	Mr. Simranjot Singh (Till 27/11/12)
3.	Ms. Shruti Sukumar Kothari
Psychologist	
1.	Ms. Rashi Midha (DBT Project)
JRF (PROJECT)	
1.	Mr. Rahul V. V. (Till 27/06/12)
2.	Mr. Ashwat Nagarajan (Till 23/04/12)
3.	Ms. Sushma
4.	Ms. Aparna Pandey (Till 14/03/13)
5.	Mr. Arkoprovo Paul
6.	Mr. Hemant Kumar Srivastava
7.	Ms. Rashmi Ray
8.	Ms. Monika
9.	Dr. Thounaojam Menaka Chanu
10.	Dr. Gouri Shanker Patil
11.	Dr. Neelanjana Roy
12.	Dr. Arpita Chatterjee

13.	Dr. Ruchi Gaur
Research Assistant	
1.	Mr. Sukhvir Singh Pundir (DBT Project) (Till 20/09/12)
2.	Mr. H.V. Suhas
Technical Assistant	
1.	Ms. T. A. Sumathi (Contingent Grant) (Till 20/09/12)
Programmer	
1.	Mr. Tanmay Nath (Till 31/08/12)
Statistician	
1.	Mr. Arnab Chakrabarti (Till 11/05/12)
2.	Mr. Sagnik Datta (Till 27/02/13)
Technical Officer (Project)	
1.	Mr. Ayan Sengupta
2.	Ms. T. Ammaponnu @Sumathi
3.	Mr. R. Sarvotham
4.	Ms. Kamini
Senior Research Officer (Computer Engineering)	
1.	Mr. V. P. Subramanyam Rallabandi
Computer Programmer	
1.	Mr. Mukesh Kumar Vaidya
Senior R&D Engineer (Project)	
1.	Mr. Bharath H.N.
Manager (Project)	
1.	Dr. Sumiti Saharan
Project Associate (DeLCON)	
1.	Ms. Namrata Gupta

Ph.D. STUDENTS

1.	Dr. Chinmoyee Maharana (Till 08-10-12 A.N.)
2.	Mr. Leslee Lazar
3.	Mr. Niranjana Ashok Kambi
4.	Ms. Neha Sehgal (Till 27-02-13 A.N.)
5.	Mohd. Hisham P.M.
6.	Ms. Radhika Rajan
7.	Ms. Shilpa Mishra Shukla
8.	Mr. Subhadip Paul
9.	Ms. Rupali Srivastava
10.	Mr. Kaushik Pramod Sharma
11.	Ms. Neha Bhutani
12.	Ms. K.M. Sharika
13.	Dr. Sudheendra Rao NR
14.	Mr. Rahul Chaudhary
15.	Mr. Pankaj S Ghate
16.	Mr. Deepak Kr Kaushik
17.	Mr. Deobrat Dixit
18.	Ms. Kiran
19.	Mr. Arshed Nazmi
20.	Mr. Apoorv Sharma
21.	Ms. Manju Tewari

22.	Mr. I Mohd Ariff (Till 02-08-2012)
23.	Mr. Sandeep Kumar
24.	Mr. Vaibhav Tyagi
25.	Mr. Sourish Ghosh
26.	Mr. Bharat Prajapati
27.	Ms. Mahar Fatima
28.	Mr. Atesh Koul
29.	Mr. Vasav J. Arora
30.	Mr. Brijesh Kumar Singh
31.	Mr. John Thomas
32.	Mr. Arghya Dutta Choudhury (Till 14-05-2012)
33.	Mr. Kautuk Kamboj
34.	Mr. Biswaranjan Sahoo
35.	Mr. Indrajith R. Nair
36.	Ms. Mandrita Barua
37.	Mr. Muneshwar
38.	Ms. Pushpa Kumari
39.	Ms. Shalini Swaroop
40.	Mr. Shashi Shekhar Kumar
41.	Mr. Touseef Ahmad Sheikh
42.	Mr. Tushar Arora

INTEGRATED Ph.D. STUDENTS

1	Ms. G.Swetha Kameshwari
2	Ms. Varsha Jain
3	Mr. Ajit Ray
4	Ms. Shaily Malik
5	Mr. Sadashib Ghosh
6	Ms. Megha Maheshwari
7	Mr. Deepak Poria
8	Ms. Manvi Goel
9	Mr. Pavan Kumar R.
10	Mr. Atul Gopal PA
11	Ms. Megha Sharda
12	Ms. Suhela Kapoor
13	Ms. Guncha Bhasin
14	Ms. Sarika Cherodath
15	Ms. Himakshi
16	Ms. Ruchi Ghildiyal
17	Ms. Piyushi Gupta
18	Ms. Avantika Mathur
19	Ms. Shankhamala Sen
20.	Mr. Apoorv Sharma

21.	Ms. Manju Tewari
20	Mr.Priyabrata Halder
21	Mr.Imran Jamal
22	Mr.Fahim Ahmad
23	Ms.Manika Arora
24	Ms.Uzma Din
25	Ms.Rekha S.Varrier
26	Ms.Chitra Mohinder Singh Singhal
27	Ms.Utkarsha A. Singh
28	Ms.Pooja Parishar
29	Mr.Apurva Agrawal
30	Mr.Atanu Datta
31	Mr.Naman Vatsa
32	Mr. Abhishek Kumar Verma
33	Mr. Chandan Kumar Kharga
34	Mr. Hriday Shanker Pandey
35	Ms. Reshma
36	Mr. Vikas Pareek
37	Mr. Vipendra Kumar

PROJECT ASSISTANT

1	Ms.Kanchan Bisht (Till 08-06-12)
2	Ms. Ananya Samanta (Till 31-08-12)
3	Mr.Diptendu Mukherjee
4	Mr.Dwaipayan Adhya (Till 17-08-12)
5	Ms.Anya Chakraborty (Till 30-07-12)
6	Ms.G.Revathy
7	Mr.G.Naga Rajesh (Till 28-02-13)
8	Mr. Nikhil Ahuja (Till 13-07-12)
9	Mr. Rajiv Ramaswamy
10	Ms.Panghki Medhi (Till 05-06-12)
11	Ms. Rinki Saha (Till 04-06-12)
12	Mr. Kaushik Kumar Deka (Till 07-09-12)
13	Ms. Saba Parween (Till 31-08-12)
14	Mr. Bandhan Mukherjee
15	Mr. Abhinaba Ghosh (Till 18-12-12)
16	Mr. Aniruddha Das (Till 04-01-13)
17	Mr. Rajarshi Mukherjee
18	Ms. Teesta Naskar
19	Mr. Tanveer Verma (Till 09-07-12)
20	Mr. Arkoprovo Paul (Till 31-07-12)
21	Ms. Sriya Bhattacharya
22.	Mr. Kiran Kundu

23.	Mr. Anshu Khandelwal
24	Mr. Namit Bharija (Till 28-09-12)
25	Mr. Kuldeep Tripathi
26	Mr. Nikhil Anto P.
27	Ms. Avipsa Mohanty (Till 24-04-12)
28	Ms. Snigdha Kundu (Roy) (Till 12-04-12)
29	Ms. Ankita Srivastava (Till 14-12-12)
30	Ms. Neha Sharma
31	Ms. Sarbani Samaddar
32	Ms. Keerthi Ramanujan
33	Ms. Sudha Sharma
34	Ms. Sriparna Mukherjee
35	Ms. Bhuvaneswari Ganesan
36	Mr. Hariom Sharma
37	Ms. Ananya Chakraborty
38	Ms. Neha Tewari
39	Ms. Shweta Soni
40	Ms. Rabia Khatoon
41	Mr. Prajwal Pradeep Thakre
42	Ms. Gauri Sharma
43	Ms. Jyothirmayi Vadlamudi
44	Mr. Ashwat Nagarajan (Till 11-10-12)

(OTHER STAFF) - TECHNICAL STAFF

1.	Mr. Rajbir Singh
2.	Mr. Sanjeev K. Choudhary
3.	Mr. Dev Das Lal
4.	Mr. Mahender Kumar Singh
5.	Mr. Jitender Ahlawat
6.	Mr. Arvind Singh Pundir
7.	Dr. Inderjeet Yadav
8.	Mr. Kanhaiya Lal Kumawat
9.	Mr. Kedar Singh Bajetha
10.	Mr. Shankar Dutt Joshi
11.	Mr. Sumit Kumar Sinha Mahapatra
12.	Mr. D. Narender
13.	Mr. Sanjay Kumar
14.	Mr. Mithlesh Kumar Singh

15.	Mr. Ankit Sharma
16.	Mr. Sanjeev Bhardwaj
17.	Mr. Yunis Khan
18.	Ms. Seepika
19.	Mr. S. Suresh Kumar (till 16.01.2013)
20.	Mr. Durgalal Meena
21.	Mr. Irshad Alam
22.	Mr. P. Manish
23.	Mr. Dil Bahadur Karki
24.	Mr. Rammehar
25.	Mr. Manish Kumar
26.	Mr. Hari Shankar
27.	Mr. Mahendra Singh
28.	Mr. Sanjay Kumar Singh

ADMINISTRATIVE STAFF

1.	Mr. K.V.S. Kameswara Rao
2.	Mr. N. Subramanian
3.	Mr. Rajesh Kumar Vyas
4.	Mr. Santosh Kumar Choudhary
5.	Mr. Debashish Bhattacharjee
6.	Mr. Ravinder Pal
7.	Mr. Sunil Kumar Dwivedi
8.	Ms. Pooja Gosain
9.	Mr. Sanjay Kumar Gupta
10.	Mr. Shiv Kumar
11.	Mr. Rajbir Singh
12.	Mr. Surajban
13.	Mr. Ajay Kumar Dehariaya
14.	Mr. Himanshu Mal
15.	Mr. Rakesh Kumar Yadav
16.	Mr. Surender Kumar
17.	Mr. Bhupender Pal Sharma

18.	Mr. Satish Kumar
DIC Project Staff	
1.	Ms. Reema Saxena
2.	Mr. Amit Kumar
3.	Ms. Sunita
4.	Mr. R. Ganesh Gurumoorthy
Construction Project Staff	
1.	Mr. Shailender Singh
2.	Mr. Anil Kumar Yadav
3.	Mr. Bhupender Singh
4.	Mr. Subhashji Roy
Contractual Staff	
1.	Dr. Kuldeep Sharma
2.	Dr. Aloknath Gupta
3.	Mr. Mukesh Chauhan
4.	Mr. Mukesh Kumar Pandey
5.	Ms. Shweta Mishra



National Brain Research Centre

(Deemed University)

(An Autonomous Institute of Department of Biotechnology, Ministry of Science & Technology, Govt. of India)

NH - 8, Nainwal Mode, Manesar, Haryana - 122 051 (India)

Ph: +91-124-2845200, Fax: +91-124- 2338910/28

E-mail: info@nbrc.ac.in Website: www.nbrc.ac.in