BIO-DATA

1. Name and full correspondence address :
Kolluru Venkata Atchuta Ramaiah,
UGC-BSR Faculty (January 1, 2020 onwards)

Professor,(July 27, 1998-Dec31, 2019)
Department of Biochemistry, School of Life Sciences, University of Hyderabad, Hyderabad 500046, Telangana

2. Email(s) and contact number(s), kvarsl@uohyd.ernet.in, ramaiah.kolluru@gmail.com
040-23134520, 91-9490703241

3. **Institution :** University of Hyderabad

4. **Date of Birth :** 15 December 1954

5. Gender (M/F/T) : Male

6. **Category Gen/SC/ST/OBC** : General

7. **Whether differently abled (Yes/No)** : No

8. **Academic qualifications (Undergraduate onwards**)

	Degree	year	Subject	University/ Institution	% Marks
	B.Sc	1973	Chem Botany Zoology	Andhra University, waltair	66%
	M.Sc	1976	Botany	Institute of Advanced Studies/ Meerut Univ	69.8% I class I
	M.Phil	1978	Environmental Biology	Jawaharlal Nehru University, New Delhi	A grade
	Ph.D	1981	Environmental Biology	Jawaharlal Nehru University, New-Delhi	

9. **Ph.D thesis title, Guide's Name, Institute/Organization/University, Year of Award**.

A Comparative Analysis of Membranes of Normal and Crowngall Tissues Under Some Environmental Stresses , School of Environmental Sciences, JNU, New-Delhi-67, Year-1981. Supervisor: Professor Anjali Mookerjee

10. **Work experience (in chronological order).**

	Position held	Name of the inst	From	To	Pay scale
1	Postdoctoral Fellow	University of Lincoln Nebraska, School of Life Sciences , USA	1982 Apr	January 1984	14,500/- US$
2	Post Doctoral fellow	University of Lincoln, Lincoln, Nebraska, Dept Chemistry USA	Feb 1, 1984	June 30, 1986	160000/- US$
3	Post Doctoral fellow	Harvard University-MIT Health Sciences and Technology Cambdridge , USA	Sept 1986	October 1987	21100 US$
4	Lecturer	School of Life Sciences University of Hyderabad, Hyderabad-AP, India	Nov3. 1987	Feb, 19, 1991	Rs2650 Basic in the pay Scale of 2200-4000
5	Reader	School of Life Sciences, Dept Biochemistry , Univ Hyderabad	Feb 20, 1991	26, July 1998	Rs3750-125-4950-150-5700
6	Professor	School of Life Sciences, Dept Biochemistry, Univ Hyderabad	27 Jul 1998	Dec 31, 2019	Rs144,200- 218200/-
7	UGC-BSR Faculty	School of Life Sciences, Dept Biochemistry, Univ Hyderabad	January 1, 2020	December 31, 2022	Rs 50, 000/-- PM. Fellowship

11. Professional Recognition/ Award/ Prize/ Certificate, Fellowship received by the applicant.

S	Name of award	Awarding Agency	Year
1	Career Fellowship Award in Biotechnology from Developing Nations Visiting Scientist at MIT, Cambridge, USA	Rockefeller Foundation , USA	1988-91 summer months May1-jul30, 1989, 90, 91 years
2	Career Fellowship Award in Biotechnology , Visiting Scientist at MIT, Cambridge, USA	Rockefeller Foundation , USA	1992-94 , Summer months, May 1-Jul30.
3	Visiting Scientist < National Institutes of Child Health and Development (NICHD), National Institutes of Health (NIH), Bethesda, Maryland	National Institutes of Health (NIH), Bethesda, Maryland, USA	Oct1- Dec 30, 1996
4	Visiting Scientist , Hebrew University, Jerusalem	Dept Science and Technology , Indo-Israel Res Project	18-05-1998 to -04-06-1998; 14-5-1998 to 28-05-1999
5.	FNASc	The National Academy of Sciences, India	2003
6	APAS	Andhra Pradesh Akademi of Sciences	2005
7	Andhra Pradesh State Council of Science and Technology	AP Scientist Award in Biology	2007
8	Prof M Shadakshara Swamy Endowment Lecture Award	Society of Biological Chemists (India)	2010 Meeting held at IISc, Bangalore

Research Projects: Funded by Nat'l & Int Nat'l Agencies

S. No	Completed Projects	Sanctioned by and Ref No	Years and released amt
1	Biotechnology, Career Fellowship Awards Structure and Function of heme-regulated	Rockefeller Foundation, USA, Dated Feb 27, 1989, RF 88061,	i) US$ 34,400, to work at MIT, Cambridge 1989,90 and 91 (Summer

	inhibitor (HRI)protein of anemic rabbit redblood cells	Allocation No,76, Dec 9, 1991 RF91055/allocation no153;	months May, June, July) ii) US$ 39, 200/- to work at MIT, Cambridge 1992,93, 94 (Summer months May, June, July)
2.	" Regulation of Eukaryotic Initiation Factor 2 Activity in Wheat Germ Lysate"	DST, New Delhi SP/SO/D70-89	1991-95, Rs 15,00, 020/-
3	" Expression of Wild Type and Mutant Human Eukaryotic Initiation Factor2 alpha Subunit in *Spodoptera frugiperda* Insect Cells to Characterise the Importance of eIF2 Phosphorylation in the Regulation of Protein Synthesis".	DBT, New-Delhi, BT/R&D/15/17/95	April1996-August 2000; Rs. 27,50, 000/-
4	"Improving Crop Yield Through High Translation Efficiency: The Interaction of Plant eIF2 with mRNA" January 1, 1998-March, 2000. Rs. 21, 34, 825/- ;	DST, International Division INT/ISRAEL/BT-95	January 1, 1998-March, 2000. Rs. 21, 34, 825/-
5	"Protein Synthesis, Phosphorylation of eukaryotic initiation factor 2 alpha (eIF2α) and apoptosis in uninfected and baculovirus-infected insect cells of *Spodoptera frugiperda*" (Total Sanctioned amount) Rs/- 13,00, 000.;	CSIR-New Delhi, 37(1120)/02/EMR-II dt 8th August 2002	2002-to August 2006 ; Rs/- 13,00, 000
6	Stress-induced apoptosis: Mechanisms and importance of phosphorylation of the alpha-subunit of eukaryotic translational initiation factor 2 (eIF2 α) Rs	DST- New-Delhi BR/SO/BB-372006	2007Feb/Mar-2010 Rs 42, 00, 000
7	Regulation of phosphorylation of eIF2 alpha mediated cell death or survival in *Sf9* cells: Coincident signaling pathways, chemical chaperones, specific caspase(s), proteases, and role of altered gene products Rs. 50, 95, 000/- But used 39, 00, 000	DST-New Delhi Ref. No.: *SR/SO/BB -83//2010 dt 16th Feb 2012*l:	Rs. 50, 95, 000/- But released/used 39, 00, 000
8	Raman Spectroscopy to Determine Stress-induced Unfolded Protein Accumulation in the Endoplasmic Reticulum (ER), a Sub cellular Compartment in *Sf9* and *He La* Cells	UPE Univ Hyd UH//UGC/UPE-Phase-2/Interface studies/ res project /r-50	2014 Rs,3.00 Lakhs
9	Cellular Homeostasis: Importance of Interorganellar Communication Rs 3.5 Lakhs	UH/-2/28/2015; UPE, Univ Hyderabad	2015 Rs 3.5 lakhs, Total Rs/- 35 lakhs/10 investigators
10	" Cross talk between mitochondria and PERK-eIF2u-ATF4 arm of unfolded protein response (UPR): Importance of Chemical Chaperones"	DST, New-Delhi *EMR/2016/005215* (SERB) Dt 20 March, 2018	2018 March- Rs. 47,46, 800/- On going
11	UGC BSR Faculty Fellowship	January 1, 2020- 31 DecDecember 2022	Rs 5.00 lakhs/)/ Yr Contingency

12. Publications (*(List of papers published in SCI Journals, in year wise descending order).*

As on Jun 30, 2020, Citations are 1212 ; h index-17 and I10idex-22, citations for last 5 years -368. Many of the citations have come into high end journals such Genes and development, EMBO.J, Nucleic Acid Res, Sci Advances, Sci.Signaling, PNAS, e-Life, JBC, J.Virol, RNA, Molecular Cell , Ageing research reviews, Aging Cell, Nature Communications etc., in Text Books (Biochemistry (2 Volume set) The Chemical Reactions of Living Cells, By Dr. David E. Metzler, **Biochemistry**, 2nd Edition Volume 2, 2003,Academic Press, NY, ISBN 978-0-12-492541-0, Page 1733, Ref no 324. . Two Volume set ; **Hand Book of the Biology of Ageing Ed by Edward J. Masoro, Steven N. Austad - 2010 – 313 page number, Academic press, NY. Translational Control of Gene Expression**, 2000, *(Cold Spring Harbor Monograph Series 39)* Edited By Nahum Sonenberg, John W.B. Hershey, and Michael B. Mathews. CSHL Press.etc.,

/ Monographs and international theses

S. No	Authors	Title	Name of Journal	Vol	Pages	Year
1	Uppala J K, Gani A R, **Ramaiah K V**	Chemical chaperone, TUDCA unlike PBA, mitigates protein aggregation efficiently and resists ER and non-ER stress induced HepG2 cell death.	**Scientific Reports** /DOI:10.1038/ s41598-017-03940-1,	7, 3831	**1-13**	2017
2	Medchalami S, and Ramaiah KV	Insulin treatment promotes tyrosine phosphorylation of PKR and inhibits poly IC induced PKR threonine phosphorylation	**Arch. Biochem. Biophys.**	585	**98-108.**	2015
3	Gani R A, Uppala K J, and Ramaiah K V	Tauroursodeoxycholic acid prevents stress induced aggregation of proteins in vitro and promotes PERK activation in HepG2 cells	**Arch. Biochem. Biophys.**	568	8-15	2015
4.	Rasheedi S, et al.,	Functional characterization of PeIF5B as eIF5B homologue from *Pisum sativum*,	**Biochimie**	118	36-43	2015
5.	Yadiah M et al.,	Arrested cell proliferation through cysteine protease activity of eukaryotic ribosomal protein S4.	**FASEB.J**	27	803-810	2013
6.	Iyer A et al.,	Phosphorylation of eIF2 alpha in *Sf9* cells: A stress, survival and suicidal signal,	**Apoptosis**	15	679-692	2010
7	Pendyala P and Ramaiah K V	PKC activation contributes to caspase-mediated eIF2alphą phosphorylation	**Biochemica Biophysica Acta- Gen Subj**	1800	518-525	2010
8	Kamindla R, et al.,	Intersubunit and interprotein interactions of alpha and beta-subunits of human eIF2: Effect of phosphorylation	**Biochem. Biophys. Res Commun.,**	374	336-340	2008
9	Hussain S G and Ramaiah K V	Endoplasmic Reticulum: Stress Signaling and Apoptosis (Review)	**Current Sci**	23	1684-1696	2007
10	Hussain SG and Ramaiah K V	Reduced eIF2 alpha phosphorylation and increased proapoptotic proteins in aging.	**Biochem. Biophys. Res Commun.,**	355	365-370	2007
11	Suragani R N V S,et al	Expression and Purification of the Subunits of Human Translational Initiation Factor 2 (eIF2): Phosphorylation of eIF2α and β.	**Protein Expression and Purification,,**	47	225-233	2006
12	Suragani R N V S,et al	Interaction of Recombinant Human eIF2 Subunits with eIF2B and eIF2α Kinases	**Biochem. Biophys. Res**	338	1766-1772	2005

			Commun.,			
13	Aparna G et al.,	Stress-induced apoptosis in *Spodoptera frugiperda (Sf9)* cells: Baculovirus p35 mitigates eIF2α phosphorylation,	**Biochemistry**	42	15352 - 15360	2003
14	Hasnain SE et al.	Host-pathogen interactions during apoptosis (Review),	**J. Biosci**	**28,**	**349-358.**	2003
15	Burela L, et al.,	Translation and phosphorylation of wheat germ (WG) lysate: Phosphorylation of WG initiation factor 2 (eIF2) by casein kinase 2 and in N-ethylmaleimide-treated lysates	**Arch. Biochem. Biophys.**	400	85-96	2002

6.	Sudhakar A et al.,	Phosphorylation of Serine 51 in Initiation Factor 2alpha (eIF2α) promotes complex formation between eIF2α(P).eIF2B and causes inhibition in the guanine nucleotide exchange activity of eIF2B,	**Biochemistry**	39	12929 - 12938	2000
17	Rao CP et al.,	Transition metal sachharide chemistry and biology synthesis, characterization, solution stability and putative bio-relevant studies of iron-sachharide complexes	**Inorganica Chimica Acta**	297	373-382	2000
18	Sudhakar A et al.,	Serine 48 in initiation factor2 alpha (eIF2α) is required for high affinity interaction between eIF2α(P) and eIF2B,	**Biochemistry ,**	38	**15398 - 15405** .	1999
19.	Krishnamoorthy T,	Reducing agents mitigate protein synthesis inhibition mediated by vanadate and vanadyl compounds in reticulocyte lysates,	**Arch. Biochem. Biophys.**	349	122-128	1998
20	Pavitt et al.,	eIF2 independently binds two distinct eIF2B subcomplexes that catalyse and regulate guanine nucleotide exchange	**Genes and Development**	12	514-526	1998
21	Vattem MK, Narahari J and Ramaiah K V	Wheat germ initiation factor 2 decreases the inhibition of protein synthesis and eIF2B activity of reticulocyte lysates mediated by eIF2 alpha phosphorylation,	**Arch. Biochem. Biophys.**	346	28-36	1997
22	Ramaiah K V et al.,	The effects of Pyrroloquinoline Quinone on heme-regulated eIF2α kinase and eIF2B activities in eukaryotic protein synthesis	**Blood Cells Molecules & Diseases.**	23	177-187	1997
23	Sepuri V Naresh Babu and Ramaiah K V	Type1 phosphatase inhibitors reduce the restoration of guanine nucleotide exchange activity of eIF2B in inhibited reticulocute lysates rescued by hemin,	**Arch. Biochem. Biophys.**	327	201-208	1996
24	Narahar J et al.	Phosphorylation of wheat germ initiation factor 2 by N-Ethylmaleimide-treated wheat germ lysates and by purified Casein Kinase II does not affect the guanine nucleotide exchange on eIF2	**Arch. Biochem. Biophys.**	324	1-8	1995
25	Ramaiah KV et al.,	Expression of mutant eukaryotic initiation factor 2α subunit (eIF2α) reduces inhibition of guanine nucleotide exchange activity of eIF2B mediated by eIF2αphosphorylation,	**Mol Cell Biol**	14	**4546-4553**	1994
26	Chefalo PJ et al.,	Inhibition of protein synthesis in insect cells by baculovirus-expressed eIF2α kinase,	**J.Biol. Chem.,**	269	25788 - 25794	1994
27	Ramaiah K V et	Recycling and phosphorylation of eukaryotic	**Proc. Natl.**	89	12063	1992

	al.,	initiation factor 2 on 60S subunits of 80S initiation complexes and polysomes	**Acad. Sci, USA**		- 12067	
29	Chakrabarti D,et al.,	Mechanism of protein synthesis inhibition by vaccinia viral core and reversal of inhibition by peptide chain initiation factors	**J Biosci.,**	11	503-511	1987
30	Davies E, et al.,	Wounding inhibits protein synthesis yet stimulates polysome formation in excised aged pea epicotyls	**Plant Cell Physiol.,**	27	1377-1386	1986
31	Ramaiah K V and Davies E	Wounding of aged pea epicotyls enhances the reinitiating ability of isolated ribosomes,	**Plant Cell Physiol.,**	26	1223-1231	1985
32	Ramaiah KV & Anjali.Mookerjee	A comparitve study of membrane related phenomena in normal and crown gall tissues of red beet (*Beta. Vulgaris.L*),	**Experientia**	38	1324-1325	1982
33	Ramaiah KV & Anjali Mookerjee	Modifying effects of divalent ions on the sulfhydryl content of normal and tumorous beet root tissue under thermal and gamma-irradiation stress	**Experientia,**	37	132-133	1981
34	Ramaiah KV & Anjali Mookerjee	Temperature induced permeability changes in beetroot membranes effect of divalent cations and sugars	**Ind. J. Exptl. Biol.,**	19	561-563	1981
35	Ramaiah KV & Anjali Mookerjee	Stabilizing effect of divalent metallic cations on membranes against thermal and gamma-radiation damages	**Ind. J. Exptl. Biol.,**	16	857-861	1978

Administrative Responsibilities:

1) Dean, School of Life Sciences, March1, 2018---Feb 2019
2) EC member as a Senior Most Professor at the University of Hyderaba
3) **Director, Academic Staff College, Human Resource Development Center**, Feb 2017-April, 2018
4) **Vice Chairman of the Campus School, University of Hyderabad**, Hyderabad. Dec 2007-2009;
5) **Head, Dept Biochemistry Dec 2008**-2011
6) **School Coordinator of Integrated Masters' Programme** (I. M.Sc Systems Biology, 2006-) and
7) **Chairman, Sabbatical committee, 2016-2018**
8) Panel Advisory Committee (PAC) member Seri- Biobiotechnology. DBT, Govt of India, New-Delhi,2008-11,
9) Peer Reviewer for DST/ DBT /CSIR, and Indo-French research projects,
10) External Academic Council Member of Pondicherry Central University, 2008-10
11) Executive Council Member of the University of Hyderabad as seniormost Professor June2019-December2019

Ph.D's Awarded under the <u>main</u> supervision of Dr. K V A Ramaiah, Dept Biochemistry, School of Life Sciences, University of Hyderabad

No	Name of the Student	Thesis Title	After Ph.d
1	Sepuri Naresh Babu (1996)	Regulation of protein synthesis in rabbit reticulocyte lysates mediated by initiation factor 2 alpha (eIF2α) phosphorylation	Worked as a postdoc at UPenn for abt 10 yrs and joined Dept Biochem, Univ Hyd, now Professor at HCU
2	Narahari Janaki (1996)	Regulation of initiation factor 2 activity and phosphorylation in translating wheat germ lysates.	After working as a Postdoc at Dept. of Microbiology and Immunology, m/c 790, University

			of Illinois at Chicago, she is now working for Thermo Scientific, Pierce Protein Research Products Rockford, IL U.S.A., 61105
3	Vattem M Krishna (1996)	Regulation of the guanine nucleotide exchange activity associated with wheat germ initiation factor 2 (eIF2): Effect of phophorylation of wheat germ and reticulocyte eIF2.	Post Doc at University of Indianapolis; Now working for Thermo Scientific, Pierce Protein Research Products Rockford, IL U.S.A., 61105
4	Thanuja Krishna Moorthy (1997)	Regulation of the function of eukaryotic initiation factor 2(eIF2): Effect of Vanadium compounds, Cloning and characterisation of the baculovirus-expressed human eIF2α subunit.	Post Doc Fellow at NIH, NICHD, Maryland USA, 1997- 2001; 2001-2008, Research scientist at Wistar Institute /National Cancer Institute, Philadelphia. Start Up at BioNest-University of Hyderabad
5	Akulapalli Sudhakar/ Yakkanti (2000)	Studies on the interaction between eukaryotic initiation factor 2 (eIF2) and eIF2B proteins: Experiments with baculovirus-expressed recombinant mutants of human eIF2	Post Doc at Harvard University, Asst Professor at Boys Town National Hospital, Omaha, NE, USA and now, Sr. Vice President of "USG United Scientific Group, LLC" by USG-Editors Association on July 1st 2016.
6	Burela Lakshmi-narayana, 2002	Translational regulation in wheat germ lysate mediated by eIF2α phosphorylation	(Post Doc at NIH, NICHD, Maryland, USA 2003-2006; At present working with Dr. Ronald Gartenhaus of School of Medicine, University of Maryland, Baltimore campus, MD; Now, Research Scientist, Revelations Biotech Pvt Ltd., Hyderabad
7	**Gunda Aparna, (2004)**	Apoptosis in uninfected and baculovirus-infected *Sf9* cells: Phosphorylation of the alpha subunit of eukaryotic initiation factor 2 (eIF2α).	(Postdoctoral Fellow at National Center for Biological Sciences Bangalore) Senior scientist at OncoStem Diagnostics Pvt Ltd
8	**Suragani N V Rajasekhar, (2005)**	Recombinant human translational initiation factor 2: Expression of subunits, purification and characterization.	Post Doctoral Fellow, MIT, Cambridge, Mass. USA). Now, Director, Preclinical and Translational Biology, Acceloron Pharma, Greater Boston Area
9	**Syed G Hussain (2008)**	Age-related changes in translational regulation and endoplasmic reticulum (ER) stress response.	Post doc at the Dept of Medicine,University of California, San Diego, SCRB 409, MC0711, La Jolla, CA 92093, USA. Now Scientist D at Institute of Life Sciences, Bhubaneswar
10	**Rajesh Kamindla** (2008)	'Intersubunit and interprotein Interactions of bacterially expressed subunits and the importance of eIF2 α phosphorylation in apoptosis"	Post doc in Lady Davis Institute, Mcgill University, Canada, Now woring for a start up in Hyderabad
11	**Pushpanjali Pendyala** (2010)	Apoptosis in the ovarian cells of *Spodoptera frugiperda*: Caspase-mediated PKC activation and	As a DBT post doc in CCMB, worked at the Institute of Genetics at Hyderabad. Now

		eIF2α phosphorylation,	
12	**Aarti Iyer (2011)**	Phosphorylation of eIF2α in the ovarian cells of Spodoptera frugiperda : Mechanisms affecting cell death,	Left For Canada with the husband
13	**Shobha Kruparani** (2014)	Eukaryotic initiation factor2 (eIF2): Conformational studiesc of beta subunit, intersubunit interactions and Met-tRNAi binding.	Working as a Prinicipal Scientist at CCMB, Hyderabad, in Dr Sankarnarayana's laboratory
14	**Amina Rafath Gani (2015)**	Stress induced protein aggregation and cellular homeostasis" importance of TUDCA (Tauroursodeoxycholic acid) Dec, 2015	Left for USA with the husband
15	**Medchalami Swetha (2015)**	Cross talk between tyrosine kinase activation and eIF2α kinase activation.	Working as a DST SERB Post Doc fellow at CCMB, Hyderabad
16	**Jagadeesh Uppala (2017)**	Chemical Chaperones, TUDCA and PBA on stress induced protein and cellular homeostasis	Working as a post doc at the Department of Biological Sciences in the college of Letters and Science, University of Wisconsin – Milwaukee

Some of the Papers presented in National and International Conferences

1. Reddy R . Koncha, Naresh B. Sepuri, Ramaiah K V. Kolluru (2018) CCCP induced mitochondrial dysfunction affects cytosolic translational initiation, ER stress induced UPR and cellular homeostasis," **Translational Control" Coldspring Harbor Laboratory**, Newyork, Sept4-8, 2018., Abst # 146.

2. Ramagopal R. Koncha, Naresh B. Sepuri, Ramaiah V. Kolluru (2019) **Mitochondrial dysfunction affects translational initiation pathways and cellular homoestasis, Invited Lecture at RNA meeting held at Rajivgandhi Institute of Biotechnology, Tiruvanthapuram, May02-05, 2019.**

3. K V A Ramaiah (2017) Ageing: Importance of Regulation of Protein Synthesis and Unfolded Protein Response, **National Conference on Physiology of Ageing, ,SVS Medical College, Mahabubnagar, August 30-31**

4. U.K. Jagadeesh and Ramaiah K V (2017) TUDCA mitigates stress induced protein aggregation and HepG2 cell death efficiently than PBA, **Gordon Research Conference (GRC),** 'Translational Machinery in Health and Disease' March 19-24, Galveston, Texas, USA. Doctoral Student UKJ has presented it and his travel and Registration were supported by DST, New-Delhi.

5. Swetha M and Ramaiah K V (2016) Insulin treatment promotes tyrosine phosphorylation of PKR and inhibits Poly IC- induced PKR threonine phosphorylation in HepG2 cells**. "Translational Control Meeting" Sept 4-8, Cold Spring Harbor Laboratory (CSHL).** Page #136

6. . Swetha M and Ramaiah K V (2012) Signaling pathways that stimulate tyrosine kinase activation or active tyrosine kinases regulate eIF2 alpha phosphorylation, **"Translational Control Meeting" Sept 4-8, Cold Spring Harbor Laboratory (CSHL)**. Page #190.

7. **Ramaiah K V** , Aarti. I, and Rajesh. K (2010) "BiP, a chaperone of the endoplasmic reticulum, interferes in the eukaryotic initiation factor 2-alpha phosphorylation- mediated cell death" ,

"Translational Control Meeting" Sept 13-17, Cold Spring Harbor Laboratory (CSHL). .N.Y, USA.Page #225

8. Aarti Iyer, Kamindla Rajesh and Kolluru VA Ramaiah(2010) Stress-induced cell survival and Death: Importance of phosphorylation of ERK and eIF2α in Sf9 cells. "**Translational Control Meeting" Sept 13-17, Cold Spring Harbor Laboratory (CSHL). .N.Y, USA , Page # 146**

9. Aarti I, P. Pendyala and Ramaiah K.V (2008) Phosphorylation of the α-subunit of eukaryotic initiation factor 2:A stress survival and suicida signal. Presented in **'Translational Control' Meeting" Sept 3-7, 2008, t Coldspring Harbor Laboratory (CSHL), NY , USA.** page #172

10. Rajesh K Aarti I, RNVS Surgani and Ramaiah K V, (2008) Intersubunit and interprotein interactions: Recombinant betasubunit of human eIF2. Presented **in 'Translational Control' Meeting" Sept 3-7, 2008, Coldspring Harbor Laboratory (CSHL), NY , USA**. page #181,

11. **Ramaiah, K. V** (2011) Phosphorylation of eIF2alpha as a major determinant in cellular function, In **'From Innovations in Nucleic acid Research to Regulation of Biological Processes (FINAR2RBP), In Honor of Prof Uttam Lal Raj Bhandary**, Dec17-19, **Indian Institute of Science (**IISc), Bangalore. Part of the organizing committee as well.

12. **Ramaiah, K. V**, (2010) Phosphorylation of eIF2alpha--mediated signalling pathways in cell survival and suicide. International Conference and Exhibition on **Bioeqvivalence and Bioavaialbility summit 2010 held in Taj Krishna, Hyderabad** on 3rd March 2010. **6.**

13. **Ramaiah, K. V** (2008) Recombinant human eukaryotic translational inititation factor 2 (eIF2): expression, phosphorylation and intersubunit interactions**. 2nd International conference on 'Trends in Cellular and Molecular Biology' held by the School of Life Sciences, Jawaharlal Nehru University, New- Delhi, India** on Jan 5-7, 2008.

14. **Ramaiah K . V** (2014) Importance of phosphorylation of eukaryotic translational initiation factor 2 alpha (eIF2 alpha) in infection, metabolic health and disease**. Key Note lecture Intl Conference on Cellular and Molecular Mechanisms of Disease Processes. 13-16th April, 2014, University of Kashmir**.

15. **Ramaiah, K. V** (2008) eIF2α Phosphorylation: A stress, survival and death signal. Harvard University-MIT Health Sciences and Technology **Invited talk: (HST-MIT) Cambridge, USA. Special Seminar on Monday 8th September, 2008 Building # E-25, Room # 406.**

16. **Ramaiah K V** (2016) Chaired a session and spoke on "Translational Regulation" in **VIII RNA meet** held at Center for Cellular and Molecular Biology (CCMB), Hyderabad during 8-10 January

17. **Ramaiah K. V (2015**) Translational Regulation: Importance of Phosphorylation of eIF2α in Ageing and Insulin Signaling. **Bioquest** Meeting held at School of Life Sciences, University of Hyderabad, 23-24th September 2015.

18. **Ramaiah K V (2012**) Chaired Session: on **Mi RNAs and Control of Translation** and spoke on the same subject in **VI RNA meet held at Indian Institute of Sciences, Bangalore,** on March 30 and 31, 2012.

19. **Ramaiah. K. V (2010)** Chaired session on "**RNA Biology"** and spoke on the same theme in **79th (SBCI) meeting held at the Indian Institute of Science Campus, Bangalore** from December 13-15.

20. **Ramaiah, K. V (2010) "**Phosphorylation of eIF2alpha couples translational regulation to cellular homeostasis" Professor **M. Shadaksharaswamy endowment lecture in the 79th annual meeting of the Society of Biological Chemists (India) (SBCI) held at the Indian Institute of Science, Bangalore, Dec 13-15, 2010.**

21. **Ramaiah, K. V (2010)** Signalling activities associated with caspase-mediated eIF2α Phosphorylation: CHOP-GADD-34 and PKC pathways **V RNA Group Meet,** Pune University, January 18-19, 2010

22. Ramaiah, K. V (2013) Protein synthesis in cells and cell free systems, Invited lecture at **Neozion National symposium at Chaitanya Bharathi Institute of Technology (CBIT), Gandipet, Hyderabad** on 13 March 2013. Invited Chief Guest.

23. **Ramaiah, K. V** (2008) Phosphorylation of the α-subunit of Eukaryotic Initiation Factor 2 (eIF2): A Stress, Survival and Suicidal Signal **4th RNA Group Meet** held in JNU, School of Life Sciences, on 28th and 29th March, 2008.

24. Ramaiah, K. V (2009) Molecular Biology to Systems Biology at **Joginapally B.R. Engineering College. Feb 20, 2009. Invited Guest.**

25. Ramaiah, K. V (2008) Protein Synthesis, control and post translational modifications on 27th September 2008 at **Gulbarga University,** Organized by Indian Science Academies

26. . **Ramaiah, K. V** (2008) Eukaryotic Intiation Factor 2 (eIF2): Role and Regulation in Translation and Stress Signaling. In Guha Research Conference (GRC), held at Gangtok, Sikkim.

Research: A Self Appraisal (1987-2020 Jun)

Research: Our laboratory is working on the regulation of protein biosynthesis in eukaryotes particularly mediated by phosphorylation of the small or alpha-subunit (α) of heterotrimeric eukaryotic initiation factor2 (eIF2) that occurs by diverse stress activated eIF2α kinases some of which are well characterized. These are heme-regulated inhibitor (HRI), general control nonderepressible kinase (GCN2), double stranded RNA dependent kinase (PKR) and endoplasmic reticulum resident eIF2α kinase called (PERK) which are activated in response to heme-deficiency, amino acid starvation or nutrient depletion, virus infection, and unfolded proteins respectively. Phosphorylation of 20-30% of eIF2α inhibits general mRNA translation/ protein synthesis and evokes integrated stress response (ISR) characterized by the expression of gene-specific mRNAs such as transcriptional factors ATF4 & CHOP, and GADD34, a cofactor of eIF2α phosphatase etc., While HRI, PKR and GCN2 are cytosolic kinases, PERK, a transmembrane protein of the endoplasmic reticulum (ER) and one of the three stress sensors which are activated as part of unfolded protein response (UPR), an adaptive signaling pathway that is evoked in response to accumulation of unfolded proteins in the lumen of ER. Unfolded proteins can accumulate whenever protein synthesis goes beyond the capacity of protein folding or due to improper degradation or post translational modification or release of ER calcium. Our studies are focused on the mechanism of inhibition of protein synthesis mediated by eIF2α phosphorylation, its importance in virus infection, insulin signaling, organellar functions and communication between organells and in maintaining protein and cellular homeostasis

Our earlier research is focused in studying the mechanism of inhibition of protein synthesis and changes in intersubunit and interprotein interactions mediated by ser^{51} phosphorylation in eIF2α. Our findings suggest that phosphorylation of ser^{51} or its variant aspartic $acid^{51}$ (S^{51D}) but not the variants in which ser^{51} or ser^{48} residues are replaced by alanine (S^{51A}/S^{48A}) in eIF2α, impairs the catalytic activity of eIF2B, a heteropentameric guanine nucleotide exchange factor that recycles non functional eIF2.GDP, that is released at the end of initiation step in protein synthesis, to functional eIF2.GTP to enable the latter to join initiator tRNA and to deliver the same to 40S ribosomal subunits in the initiation step in protein biosynthesis Based on these results, we hypothesized and eventually demonstrated that 25-30% phosphorylation of eIF2α (P) that is sufficient to inhibit protein synthesis completely, sequesters limiting

eIF2B into a tight 15S complex: eIF2α(P).eIF2B, in which eIF2B becomes non functional. The 15S complex formation and the inhibition in eIF2B activity requires phosphorylation of ser^{51} and maintenance of adjacent ser^{48} (Ramaiah et al., 1994; Sudhakar et al, 1999, 2000). These observations explaining the mechanism of inhibition of protein synthesis in response to eIF2α phosphorylation is seminal and are well cited. Our findings also suggest that the substrate for eIF2α phosphatase is eIF2α(P).eIF2B that migrates as a 15Scomplex but not free eIF2α. Accordingly we devised our studies and characterized the lysate phosphatase as a type1 phosphatase that restored eIF2B activity from the 15S complex, formed in shut off heme-deficient lysates that is supplemented with hemin (Babu and Ramaiah, 1996). Also our studies have shown that phosphorylation of eIF2α occurs more efficiently when it is ribosome bound and it translocates from 48S initiation complexes to 60S subunits of 80S initiation complexes, particularly when the GDP/GTP exchange activity of eIF2B becomes non functional due to eIF2α phosphorylaion (Ramaiah et al., 1992). Analysis of the five subunits of yeast eIF2B reveals that it has a catalytic complex (that exchanges GTP for GDP bound to eIF2) comprising of the gamma and epsilon subunits which binds equally well to phosphorylated and unphosphorylated complex where as the alpha, beta and delta subunits that form the regulatory complex binds to the phosphorylated form more tightly than unphosphorylated eIF2α (Pavitt et al., 1998).

Subsequently while analyzing the interaction among the recombinant baculovirus expressed human subunits of eIF2, we noticed that three subunits of human eIF2 interact with each other forming αβ, αγ, and βγ complexes, unlike the archeal and yeast eIF2 subunits where it is shown that alpha and beta subunits do not interact with each other and gamma subunit is viewed as central interacting with alpha subunit on either side. Also unlike yeast eIF2a, phosphorylated human eIF2α does not interact well with eIF2B in the absence of β-subunit of eIF2. Based on these results, we hypothesized that β- subunit human eIF2 is central in the various functions of eIF2 as its interaction with eIF2B is critical to inhibit the guanine nucleotide exchange activity of eIF2B activity when eIF2α is phosphorylated, and eIF2β also interacts with various other proteins, mRNA and aids the gamma subunit of eIF2 in all its functions like GDP/GTP binding, GTPase activity or GTP hydrolysis and Met-tRNAi binding etc. Although not understood, the human beta subunit is phosphorylated by a variety of kinases like PKA, PKC, DNA-PK and casein kinase etc., and the phosphorylated, than unphosphorylated, forms eIF2α-and β-subunits are resistant to caspase action (Suragani et al., 2005; 2006 and Kamindla Rajesh et al., 2008).

While expressing the various subunits of baculovirus and variants of eIF2α in insect cells, using baculovirus expression system, we observed that stress induced eIF2a phosphorylation and cell death is mitigated readily in insect cells infected by wild type baculovirus but not by mutant viruses deleted of their genes: p35 that inhibits caspase activity and pk2 that suppresses eIF2that suppresses eIF2α kinase activation (Aparna et al., 2003; Iyer et al., 2010). These studies while suggesting eIF2α phosphorylation, a stress, survival and suicidal signal may be a cause and consequence of caspase activation (Iyer et al., 2010; Pushpanjali et al., 2010). Subsequently our studies on chronological ageing have shown that unlike the young and suckling rats, aged rats are unable to phosphorylate their eIF2 efficiently in spite of increased levels of eIF2α kinases like PKR and PERK and their inability to phosphorylate eIF2α is correlated with the increased expression of proapoptotic proteins like CHOP and GADD-34, a cofactor of eIF2α phosphatase and decreased expression of BiP, an ER chaperone suggesting that eIF2alpha phosphorylation mediated translational attenuation is a survival signal. Ageing decreases the ability to mount unfolded protein response (UPR) characterized by activation of ER-resident PERK eIF2α kinase which may be the cause for several metabolic neurological disorders (Hussain and Ramaiah 2007a and b). Further our studies have pointed that eIF2alpha phosphorylation declines with ageing but it does not raise protein synthesis since ageing also declines the mTOR pathway and thereby reduces phosphorylation of eIF4E, 4EBP and S6. The observation suggesting a decline in UPR in ageing is upheld by various other researchers as well. In a recent study, we observed that PKR, a ser-thr eIF2α kinase that is activated by double stranded RNA (or polyIC) or virus infection, interacts with Insulin receptor beta (IRβ) during insulin sensitive (within 5-15 minutes of insulin treatment) conditions and is phosphorylated on its tyrosine residues, suggesting that it may serve as a substrate for the tyrosine kinase activity associated with IRβ. However the interaction between IRβ and PKR is lost in insulin resistance conditions and PKR is phosphorylated on its serine residues. Coiniciding these changes phosphorylation of eIF2α declines during insulin sensitive conditions where as it is enhanced during insulin resistance conditions.correlating the levels of insulin induced protein synthsis (Swetha and Ramaiah, 2015). Hence it is likely that tyrosine phosphorylated PKR plays a role in the regulation of insulin induced protein synthesis and in maintaining insulin sensitivity, whereas, suppression of polyIC-

mediated threonine phosphorylation of PKR by insulin compromises its ability to fight against virus infection in host cells

Subsequently, we started working on the importance of chemical chaperones like TUDCA (tauroursodeoxycholic acid), a hydrophilic bile salt and 4- PBA (Phenyl butyric Acid) to determine whether these agents can regulate protein aggregation, can mitigate the accumulation of unfolded proteins and there by the unfolded protein response mediated by eIF2α phosphorylation. TUDCA mitigates stress induced protein aggregation in vitro efficiently than PBA and also unlike PBA, TUDCA enhances trypsin mediated BSA digestion invitro. TUDCA relieves efficiently than PBA chronic ER and non ER stress induced eIF2alphaphosphorylation mediated cell death (Gani et al., 2015; Uppala et al., 2018)

Our studies to identify regulation of protein synthesis mediated by eIF2α phosphorylation in plants using wheat germ lysates however indicates that phosphorylation of wheat germ eIF2 can occur by mammalian eIF2a kinases in vitro but that does not inhibit the GDP/GTP exchange activity of eIF2 and protein synthesis suggesting probably the GDP/GTP exchange on wheat germ eIF2 may be carried out by mass exchange reaction rather than requiring a catalytic protein like eIF2B. (Krishna et al.,1997; Janaki et al 1995). In addition we used cell free translational systems to study the protein synthesis in the presence of novel redox compounds like vanadate and vanadyl complexes (Krishnamoorthi et al., 1998) and pyrroloquinolone quinine (PQQ) (Ramaiah et al., 1997) .

Recently while evaluating the importance of cytosolic or ER stress induced eIF2α phosphorylation that inhibits general protein synthesis on the functioning and integrity of mitochondria to determine the cross talk between organelles like ER, cytosol and mitochondria, it has been observed that mitochondrial dysfunction by CCCP (carbonyl cyanide m-chlorophenyl hydrazone), an inhibitor of oxidative phosphorylation, evokes integrated stress response (ISR) that is characterized by increased heme-regulated kinase (HRI) activation, eIF2α phosphorylation, expression of ATF4 and CHOP genes in HepG2 cells. CCCP promotes autophagy leading to noncaspase mediated cell death. CCCP also enhances phosphorylation of AMPK, cellular energy sensor, phosphorylation of AKT kinase, a regulator implicated in cell survival, and suppresses phosphorylation of eIF4E-BP that controls initiation of protein synthesis and is regulated by mammalian target of rapamycin (mTOR) pathway. NAC, an antioxidant, and ISRIB, an inhibitor of ISR pathway mitigate CCCP induced expression of ATF4 and CHOP, activation of AKT and autophagy. In contrast, NAC, but not ISRIB reverses CCCP induced activation of AMPK. Also CCCP induced phosphorylation of eIF2α and suppression of eIF4E-BP phosphorylation are reversed by NAC, where as phosphorylation of eIF2α occurs albeit slowly, and eIF4EBP phosphorylation is partly restored by ISRIB in CCCP treated cells. These findings therefore suggest that CCCP induced ISR pathway is a consequence of oxidative stress generated by dysfunctional mitochondria in CCCP treated cells; CCCP induced autophagy appears to be due to expression of ATF4 rather than AMPK activation and phosphorylation of eIF4E-BP and AKT may be linked to the expression of ATF4 that occurs during activation of ISR pathway (Presented in Coldspring Harbor meeting on Translational Control, 2018, and RNA meeting held at Tiruvanthapuram, 2019)

Teaching: I am involved in teaching various courses such as Molecular Biology to 2- Yr M.Sc students, Molecules and information Processing in Biological Systems for 5-yr Integrated Masters Programme in Systems Biology ; Protein Phosphorylation and Signal Transduction, as an optional course to who ever opts in the various Departments of Life Sciences; Also taught Recombinant DNA technology, Nucleotide Meabolism and portions of enzymology to the students of Biochemistry, M.Tech in Medical Biotechnology,and to other students of other Depts in Life Sciences as well.