Signed details of the excellence in research work for which the Sun Pharma Research Fellowship is claimed, including references & illustrations (Max. 2.5 MB). The candidate should duly sign on the details *

This application is focused on my research work and my contribution in the area of molecular genetics of diabetes mellitus. My work pertains to both Polygenic and monogenic diabetes. While the former deals with the genetic susceptibility to diabetes, the latter deals with different single genes that are causally responsible for the disease.

1) Genomics of type 2 diabetes

At the turn of this century, in 1999 December I started the molecular genetics lab in MDRF which was one of the first diabetes research Institutions to have electronic medical record in the world. I was instrumental in collecting patients' samples for genetic research with their consent. As an architect of the genetics laboratory, I set up a workflow in genetics lab starting from sample collection, storage, consent form drafting, approvals and pedigree analysis. I was one of the team members in the collection of big South Indian pedigree (n=30), with about 30% diabetes in them for genetic study and analysis. The protocols in genetics were standardized by me which is now being performed by my PhD students and technicians. In my lab, the genetic perspective are central and we use the molecular biology tools which are necessary for answering the question at hand. The main aim in my lab is to understand the genetic susceptibility of polygenic T2D and disease pathophysiology. The overall aim is to develop paradigm for the genetics of T2D and to assess how genomic information can be used in modern clinical medicine in the era of personalized medicine. I am heading various efforts in genotyping from single SNP study, gene-gene interactions between multiple genes, replication of GWAS findings and GWAS studies in Indian population. This has given a lot of insights into the genetic architecture of T2D in Asian Indian who have higher predilection of disease and who have specific phenotypes which have been correlated with specific genotypes. I have been one of the key scientists in the Genome Asia100k pilot project that addresses the lack of reference genome datasets in Asian populations enabling scientists to work on these results.

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Humans. Am J Hum Genet.105(6):1254-1261. doi: 10.1016/j.ajhg.2019.11.005.

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10. Jeffrey D Wall, J Fah Sathirapongsasuti, Ravi Gupta, Asif Rasheed, **Radha Venkatesan,** Saurabh Belsare, Ramesh Menon, Sameer Phalke,[…..], Somasekar Seshagiri, Sekar Kathiresan, Arkasubhra Ghosh, V Mohan, Danish Saleheen, Eric W Stawiski, Andrew S Peterson (2023). South Asian medical cohorts reveal strong founder effects and high rates of homozygosity Nature Communications 14:3377.

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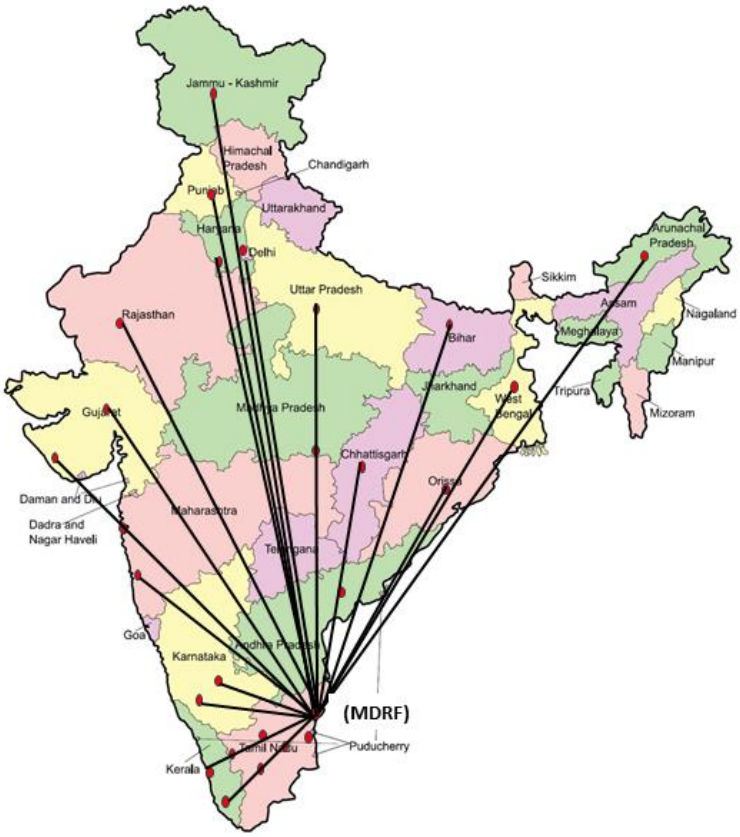
RESEARCH WORK FOR WHICH THE SUN PHARMA RESEARCH FELLOWSHIP IS CLAIMED

The following section details my main work for which this award is claimed. *My major effort has been in understanding the genetic etiology of monogenic diabetes and CHI towards precision medicine. One approach to precision medicine is correctly defining and diagnosing subtypes of diabetes to improve clinical care. In order to accomplish that I have not only identified what the variants are but also classified them as either pathogenic(P),likely pathogenic (LP), likely benign (LB), benign (B), or variants of uncertain significance (VUS). This has been done using multi-pronged approach-bioinformatics, functional experiments and structural biology understanding in a few cases. This approach clearly gives the idea*

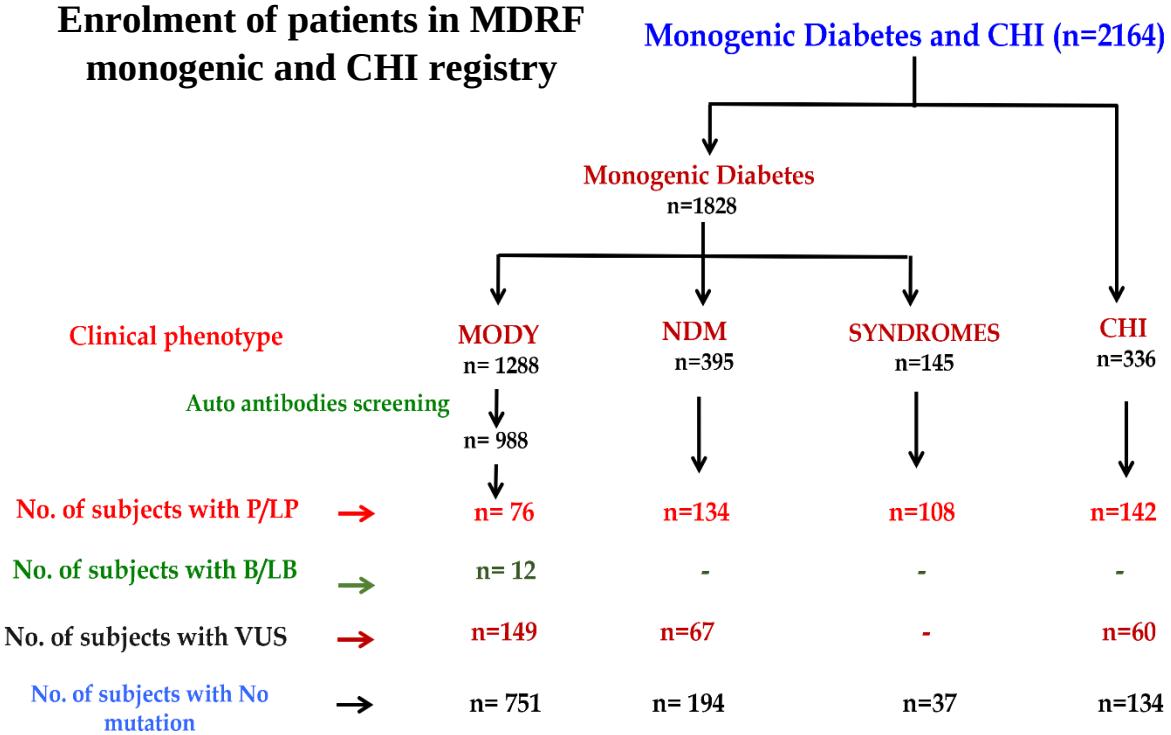
of whether the identified gene variant, both novel and known, are pathogenic or not. This was possible because I established a functional genomics lab at MDRF where I performed cell based molecular assays to understand the mechanisms of how these gene variants function and how they impact the protein function in the human body. This propelled me to the forefront of efforts to understand how and which are the variants that have impact in health and disease, in diabetes in particular. ***The consequences of my findings led to dramatic, practical outcomes in the clinic. It has helped hundreds of children with Neonatal diabetes (age at onset of diabetes with 12 months of life and auto antibody negative and not type 1 diabetes) in India to be shifted from insulin injections to oral Sulphonylureas for life.*** *Likewise, in the case of Congenital hyperinsulinemia hypoglycaemia, where children have very low sugar that impairs the brain, my findings have helped children to be given diazoxide or octreotide instead of going for a pancreatectomy. Moving beyond this is my long term follow up of patients after switching over the treatment to investigate how the treatment strategies have worked. This has helped me in classifying clinically actionable variants that require specific treatments. In patients where novel variants have been identified I am performing functional genomics studies to classify them for the pathogenicity status and deliver precision treatments on such children. Furthermore,* ***I embarked on the idea that it would be very helpful if prospectively we know what the function of the gene variants would be.*** *I have therefore started to re-create such variants in the lab and find their pathogenicity status beforehand so that, in the near and far future anywhere in the globe,* ***this will serve as "look up tables" for the future.*** *This work has already been established in the lab and I am continuing to study them.*

My work has been recognized in the global scene and I have been invited to the expert panel of Scientists who annotate and curate the variants and upload them into reference data base such as Clin Var. *The following section gives the details under specific monogenic disease, the papers I have published and the illustrations of what I have accomplished.* ***My work has truly been transformative and translational towards precision medicine in clinical setting.***

Map showing states of India from where samples are referred to MDRF for genetic analysis



Enrolment of patients in MDRF monogenic and CHI registry



2) Genomics of Maturity Onset Diabetes in the Young (MODY) in India

I was the first to work on the molecular basis of MODY subtypes in Indian population. My work has led to a number of known mutations and few novel mutations in genes such as *HNF1A, HNF4A, GCK, HNF1B, ABBCC8* and *KCNJ11* genes pertaining to MODY.Of particular interest is the Arg263His to mutations which was described in the MODY family for the first time in the world showing the segregation with disease phenotype in the family and also correlating in the expression and its structural biology basis.

I perform MODY genetic testing in our laboratory, a Pan India effort and interpret the variant pathogenicity in them. This study has taught the relationships of some these genes in type 2 diabetes also. We have prospectively recreated mutations in monogenic MODY genes and have come up with an atlas of clinically actionalable common MODY gene variations which has the potential to serve as ready reference for clinicians and scientists to deliver on Precision Diabetes. This has been *one of the kind work* in the world scenario (Reference 20)

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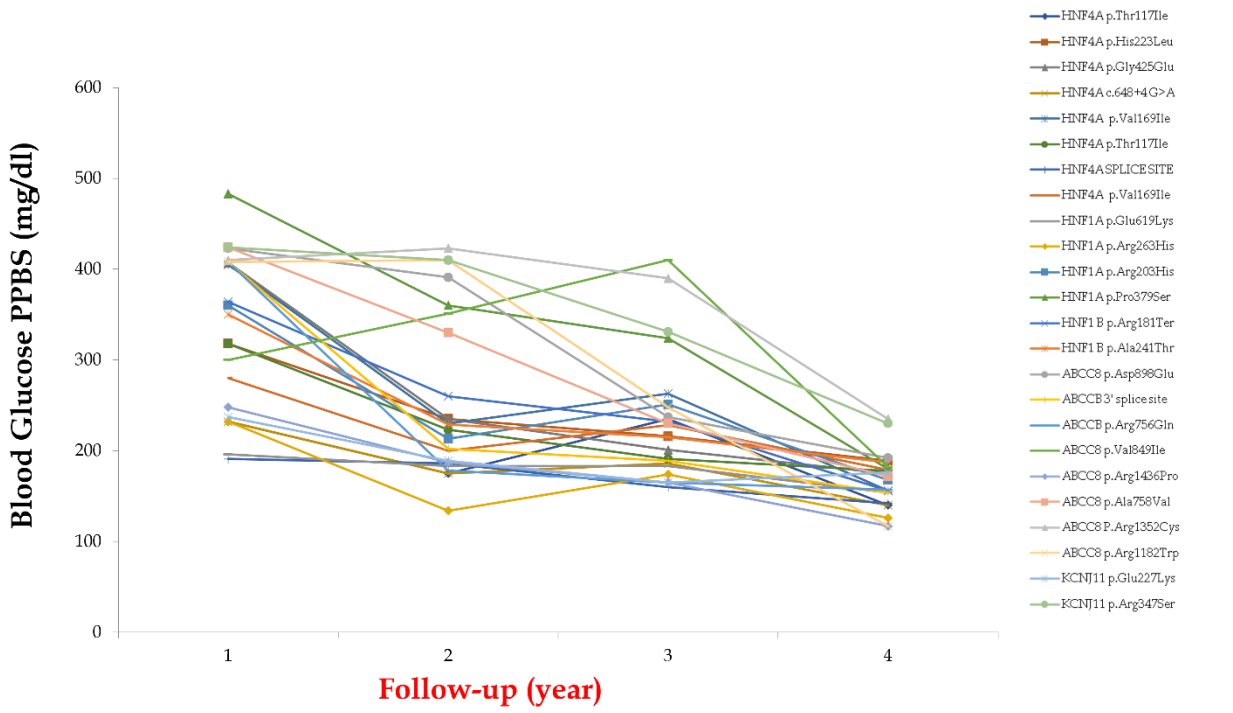
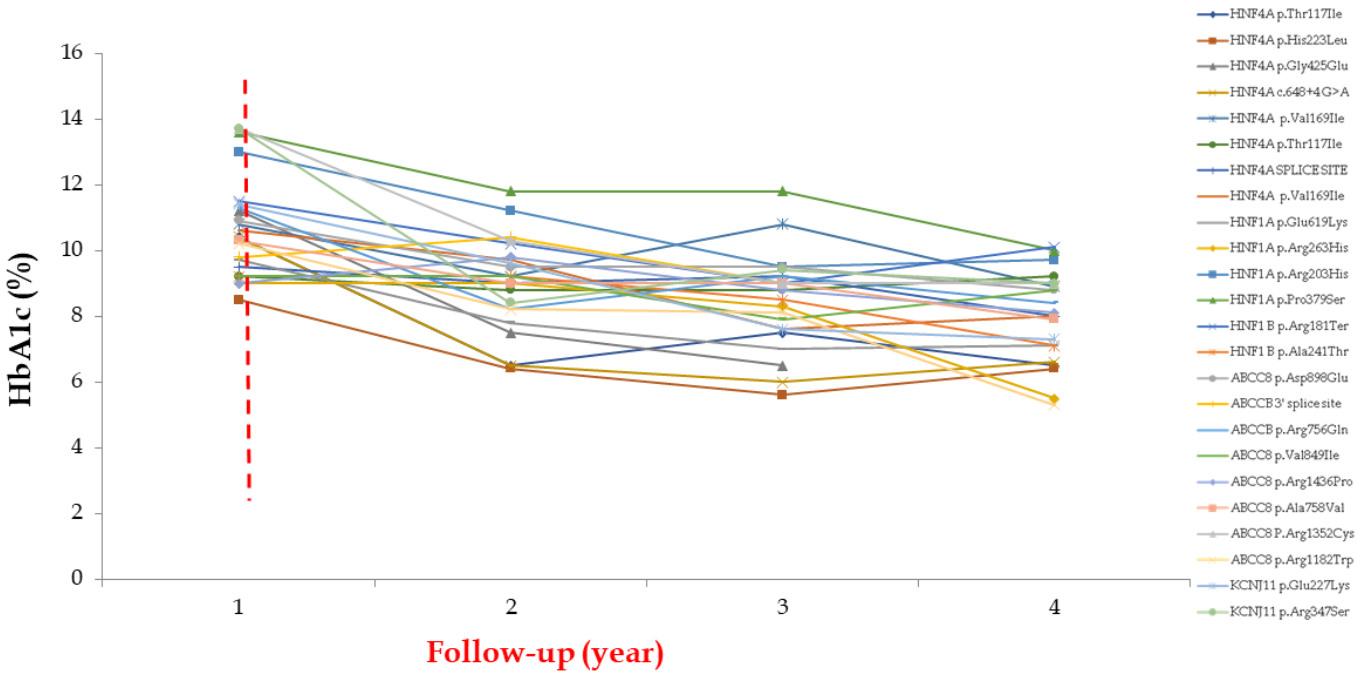
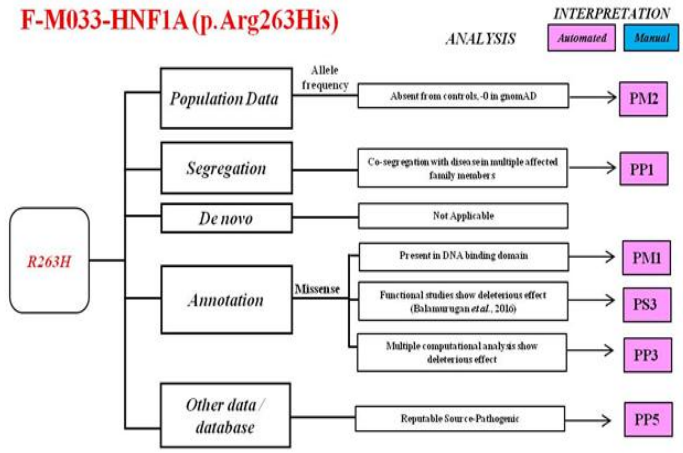
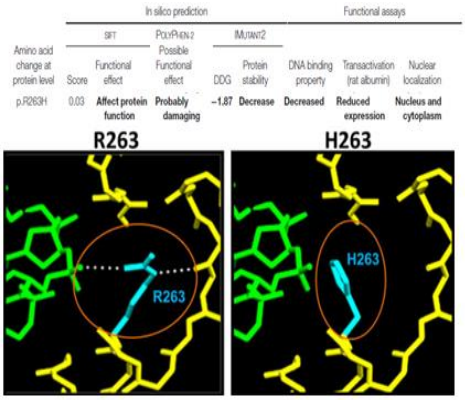
MODY Patients with Mutations and their glucose and HbA1c trajectories

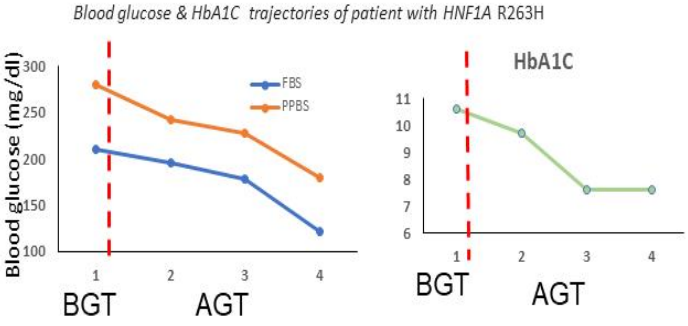


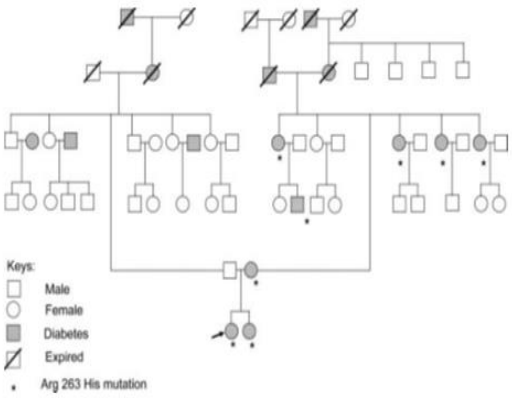


Delivering on Precision diabetes to patient with *HNF1A* – MODY (R263H pathogenic variant) using bioinformatics, genetic segregation study, functional genomics study and long term follow-up study for glucose and HbA1c trajectories









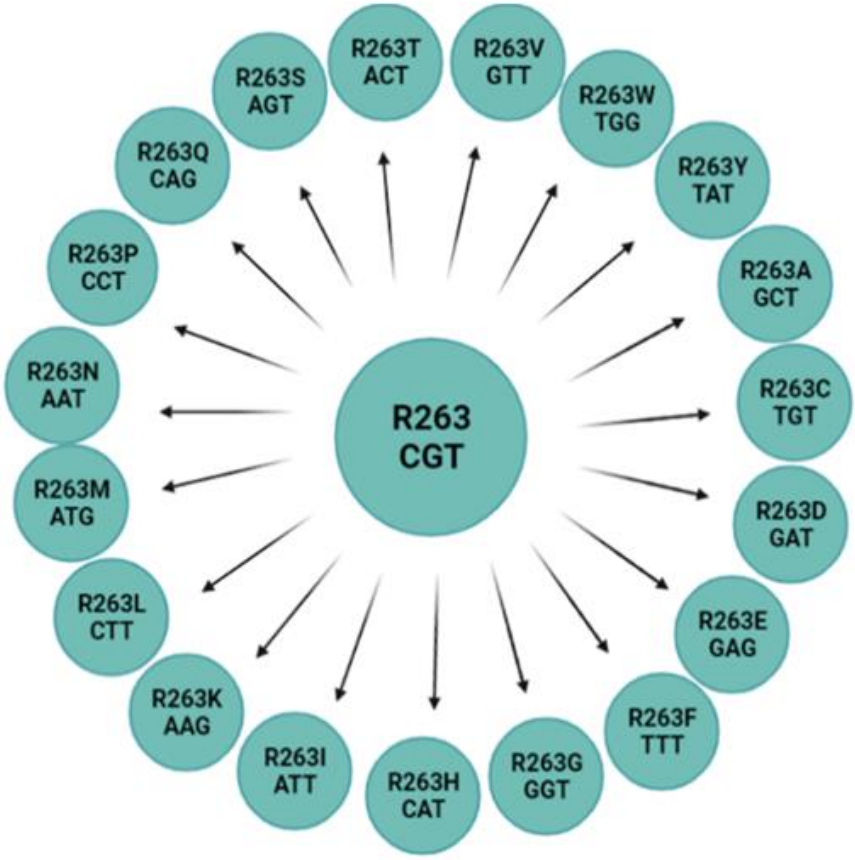
Reinterpretation of *HNF1A* variants after functional studies

S.No	Protein Change	c.DNA Change	Variant Interpretation _ACMG guidelines 2015		Functional Assay							Clinical Work up				Reinterpretation Based on functional Assay	
									GSIS			Before Genetic Testing		After Genetic Testing			
			Evidences	Classification	Transactivation Assay	Protein Expression (% WT)	Localisation (% WT)	DNA Binding Activity (% WT)	Basal Insulin	Stimulated Insulin	Insulin levels on adding 100µM GBC	FBS/PPBS/HbA1C	Treatment	FBS/PPBS/HbA1C	Treatment	Evidences	Classification
1	K120N	c.360G>C	PM1,PM2	VUS	Reduced (46)	Normal (76)	Normal (81)	Normal (92)	5	4	15	103/194/6.3	Insulin	188/315/7.1	Insulin + Glimepiride	PS3	LP
2	Q125H	c.375 G>C	PM1,PM2	VUS	Reduced (53)	Normal (67)	Normal (77)	Normal (104)	9	4	32	134/248/6.9	Insulin	121/147/5.8	Insulin + Glimepiride	PS3,PP6	LP
3	N127Del	c.377_379delACA	PM1,PM2	VUS	Reduced (26)	Reduced (66)	Reduced (57)	Reduced (21)	7	5	19	277/414/9.7	Insulin	124/261/7.3	Gliclazide	PS3	P
4	V134I	c.400G>A	PM1,PM2,PP3	VUS	Reduced (38)	Normal (75)	Normal (71)	Reduced (39)	8	1	21	194/390/9.8	Insulin	147/250/6.8	Glycomet	PS3	LP
5	R200W	c.598C>T	PM1,PM2,PP5	VUS	Reduced (25)	Normal (71)	Normal (67)	Reduced (32)	5	2	19	161/280/8.3	Metformin	90/231/6.5	SU	PS3	LP
6	R272H	c.815G>A	PM1,PM2,PP3, PP5	LP	Reduced (26)	Normal (91)	Normal (84)	Reduced (31)	7	4	19	322/379/14.6	Insulin	82/96/13.5	SU	PS3	P
7	G292Fs*25	c.872-873dupC	PVS1	LP	Reduced (18)	Reduced (58)	Normal (98)	Reduced (22)	9	4	31	127/225/8.7	Insulin+ Metformin	102/146/6.5	Glipizide	PS3	P
8	G292Fs*25	c.872-873dupC	PVS1	LP	Reduced (18)	Reduced (58)	Normal (98)	Reduced (22)	9	4	31	204/197/10.8	Glycomet	164/183/8.1	Gliclazide	PS3	P
9	A301T	c.901G>A	PM1,PM2	VUS	Normal (105)	Normal (95)	Normal (75)	Normal (105)	8	45	48	114/155/7.3	Metformin	89/167/5.9	SU	BS3,BS5	B
10	T354M	c.1061C>T	PM1,PM2,PP3	VUS	Reduced (62)	Normal (97)	Normal (71)	Normal (119)	5	2	11	159/243/6.9	SU	140/200/6.9	SU	PS3	LP
11	P379S	c.1135C>T	PM1,PM2,PM5,PP3	LP	Reduced (42)	Normal (80)	Reduced (65)	Normal (125)	15	5	37	305/521/15.4	Glycomet	299/268/11.5	Insulin	PS3	LP
12	P379S	c.1135C>T	PM1,PM2,PM5,PP4	LP	Reduced (42)	Normal (80)	Reduced (65)	Normal (125)	15	5	37	228/349/7.6	Insulin	171/134/7	Insulin	PS3	LP
13	P379S	c.1135C>T	PM1,PM2,PM5,PP4	LP	Reduced (42)	Normal (80)	Reduced (65)	Normal (125)	15	5	37	219/280/15.8	Glipizide+ Metformin	248/347/11.4	Gliclazide	PS3	LP
14	L611P	c.1832T>C	PM1,PM2,PP3	VUS	Reduced (44)	Normal (76)	Normal (71)	Normal (113)	5	7	25	161/185/6.9	Metformin	113/149/6.3	Glibenclamide+Metformin	PS3	LP
15	E619K	c.1855G>A	PM1,PM2,PP3	VUS	Normal (97)	Normal (81)	Normal (86)	Normal (97)	6	16	11	134/191/9.5	Insulin+ Metformin	132/165/8.2	Insulin+ Gliclazide	BS3,BS5	B

"Look up" table with variant pathogenicity and clinical actionability of *HNF1A* variants identified in MODY patients based on molecular characterization

S.No	Nucleotide change at nucleotide level	Amino acid change at protein level	Variant Change	Variant Interpretation	Clinical Actionability
1	c.377_379delACA	p.Asn127del	N127Del	*Pathogenic*	*Actionable*
2	c.598C>T	p.Arg200Trp	R200W	*Pathogenic*	*Actionable*
3	c.788G>A	p.Arg263His	R263H	*Pathogenic*	*Actionable*
4	c.815G>A	p.Arg272His	R272H	*Pathogenic*	*Actionable*
5	c.872-873dupC	p.Gly292fs*25	G292Fs*25	*Pathogenic*	*Actionable*
6	c.360G>C	p.Lys120Asn	K120N	*Likely Pathogenic*	*Actionable*
7	c.375G>C	p.Gln125His	Q125H	*Likely Pathogenic*	*Actionable*
8	c.400G>A	p.Val134Ile	V134I	*Likely Pathogenic*	*Actionable*
9	c.1061C>T	p.Thr354Met	T354M	*Likely Pathogenic*	*Actionable*
10	c.1135C>T	p.Pro379Ser	P379S	*Likely Pathogenic*	*Actionable*
11	c.1832T>C	p.Leu611Pro	L611P	*Likely Pathogenic*	*Actionable*
12	c.901G>A	p.Ala301Thr	A301T	*Likely Benign*	_
13	c.1100C>T	p.Ala367Val	A367V	*Variant of Uncertain Significance*	*Unresolved*
14	c.1804G>A	p.Asp602Asn	D602N	*Variant of Uncertain Significance*	*Unresolved*
15	c.1855G>A	p.Glu619Lys	E619K	*Variant of Uncertain Significance*	*Unresolved*

Schematic Representation of prospective re-creation of site specific saturation mutagenesis in *HNF1A* gene accomplished in the lab for future "look-up" tables



3) Genetics of Neonatal Diabetes in India

One of the focus areas of my research is on Neonatal diabetes genetics. I spearhead the genetic screening service for neonatal diabetes and syndromes in Indian. We have recently published a large series of NDM patients with KATP channel mutations and have helped many of them shift from insulin injection to oral Sulfonylurea therapy. We have also shown the genotype-phenotype correlation in them. Some of these highly mutable sites and some lying in important domains are now being prospectively recreated using saturation mutagenesis for the first time ever and now being characterized as an attempt to create a partial look-up-table for future references. I also follow up the patients on a regular basis to understand the disease course as glucose trajectories. Neonatal Diabetes is a true poster child of precision medicine.

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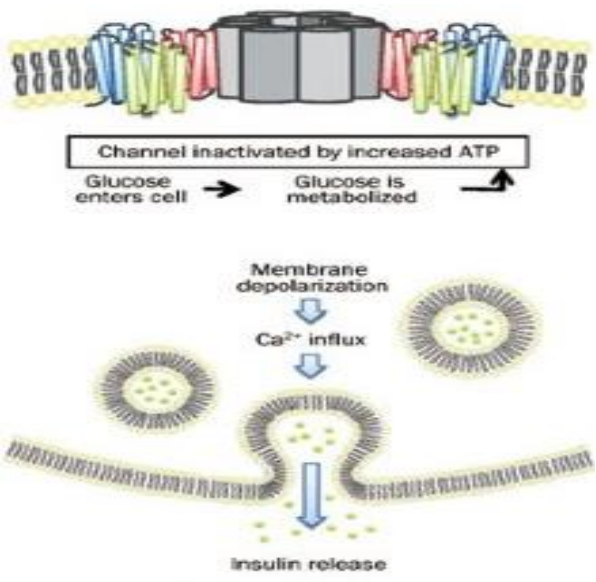
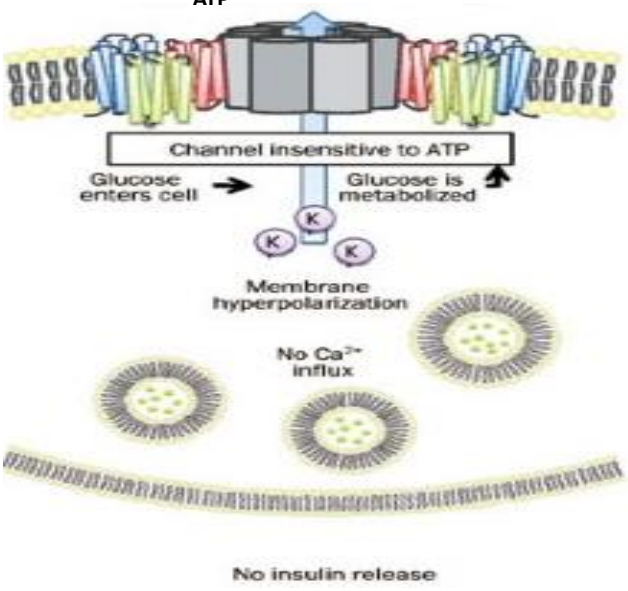
Role of K_{ATP} channels in insulin release from pancreatic β-cells

(*From Previous knowledge*)

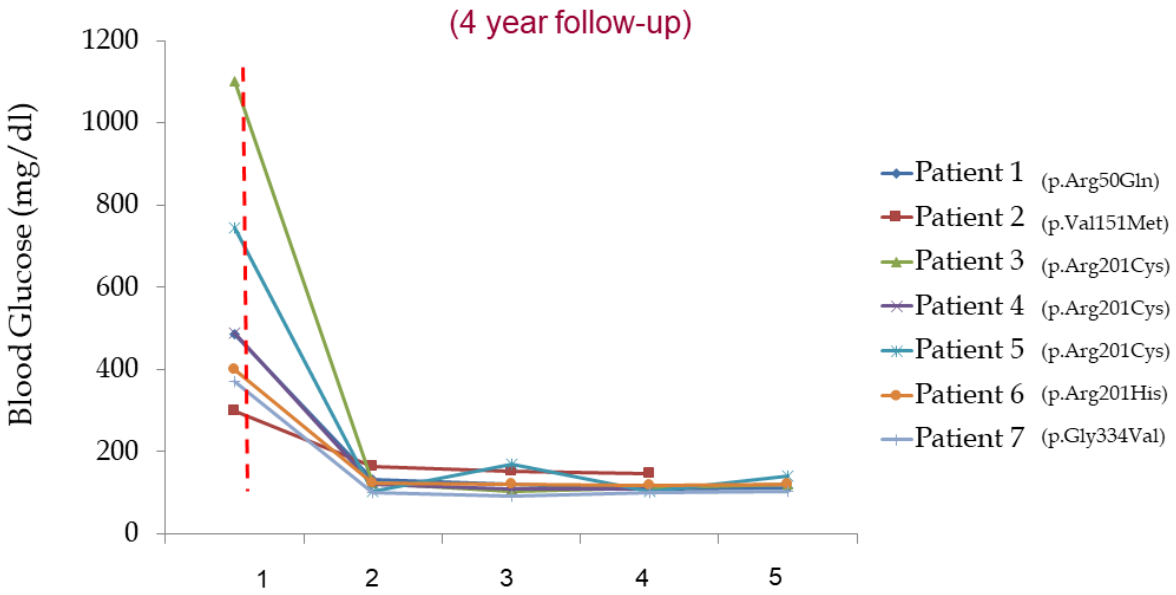
Activation / Gain of Function Mutation in K_{ATP} channel Genes





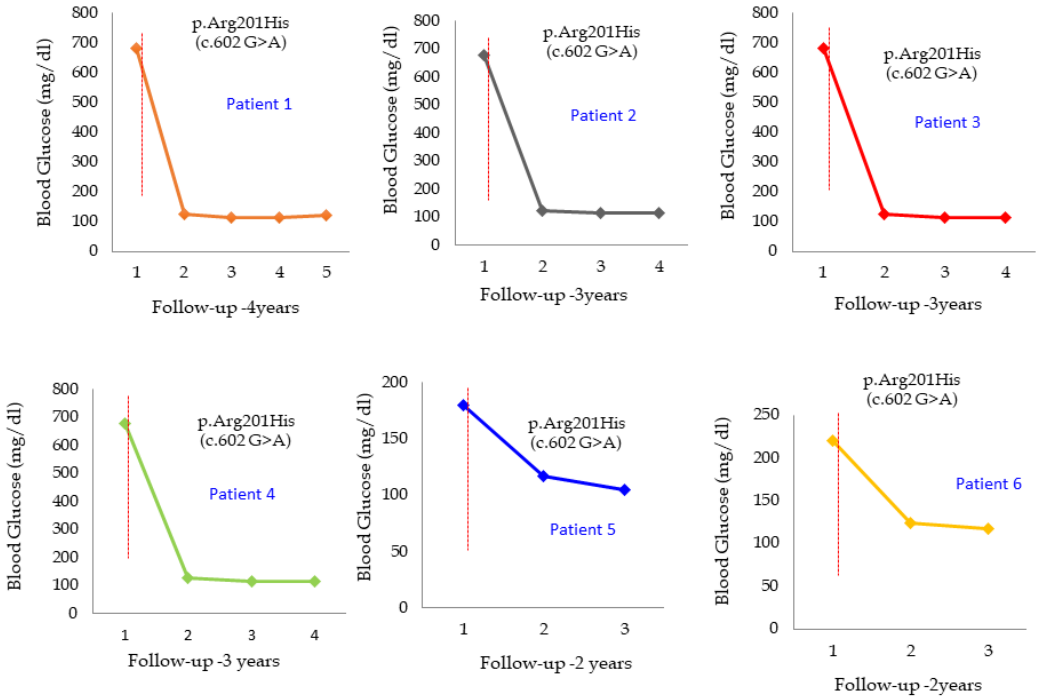
Normal Condition ***Neonatal Diabetes***

Blood glucose trajectories of NDM patients with *KCNJ11* variants after change in treatment - insulin to OHA



Dotted lines indicates change of treatment

Six different NDM patients with *KCNJ11* Gene variant (p.Arg201His) showing similar response to SU therapy



Dotted lines indicates change of treatment

4) Genetics of Congenital Hyperinsulinism in India

I was instrumental in starting the genetic screening of congenital hyperinsulinism in the country. I serve as the single point of contact for the neonatologist and pediatricians to refer the patients for genetic analysis. I have reached out to many clinicians who treat this condition and this has resulted in building more than 300 CHI patient cohort. I have also established functional genomics analysis of CHI patients, particularly with KATP channel mutations. We are currently investigating KATP mutations in the context of both NDM and CHI. Separating casual mutations from those due to coincidence is one of the important areas of my study. My lab is focused on fundamentals of human genetics particularly as it relates to the understanding of both polygenic and monogenic diabetes. It thus extends from lab to clinic by delivering on translational precision medicine.

30. **Radha V**, Bodhini D, Narayani N, Mohan V. Association study of the ABCC8 gene variants with type 2 diabetes in south Indians. IJHG, 2014: 20(1):37-42.

31. Jahnavi S, Poovazhagi V, Mohan V, **Radha V**. Neonatal Diabetes and Hyperinsulinemia: The Indian experience. Journal of Neonatology 2013: 27(2):15-23.

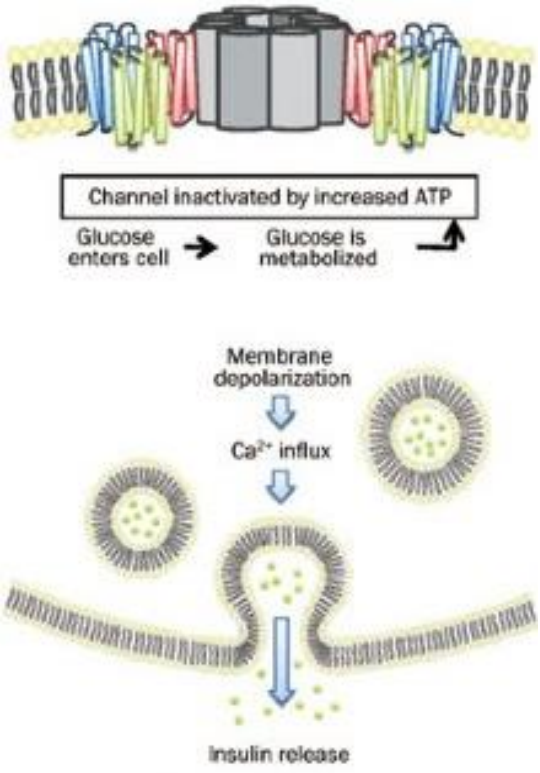
32. Varadarajan P, Ananthanarayanan K, Mirna K, Suresh J, **Venkatesan Radha**, Mohan V. Clinical Profile and Outcome of Persistent Hyperinsulinemic Hypoglycemia of Infancy. Pediatric Oncall, 2013: 50(8):759-63.

33. Jahnavi S, Poovazhagi V, Kanthimathi S, Balamurugan K, Bodhini D, Jaivinder Y, Vandana J, Khadgawat R, Jevalikar G, Mahuya S, Bhavatharini A, Dass AK, Kaur T, Mohan V, **Radha V.** Novel ABCC8 (SUR1) gene mutations in Asian Indian children with Congenital hyperinsulinemic hypoglycemia. Annals of Human Genetics, 2014: 78: 311–319.

34. Roy K, Satapathy AK, Houhton JAL, Flanagan SE, **Radha V**, Mohan V, Sharma R, Jain V.Congenital Hyperinsulinemic Hypoglycemia and Hyperammonemia due to Pathogenic Variants in GLUD1.Indian J Pediatr. 2019 May 22. doi: 10.1007/s12098-019-02980-x.

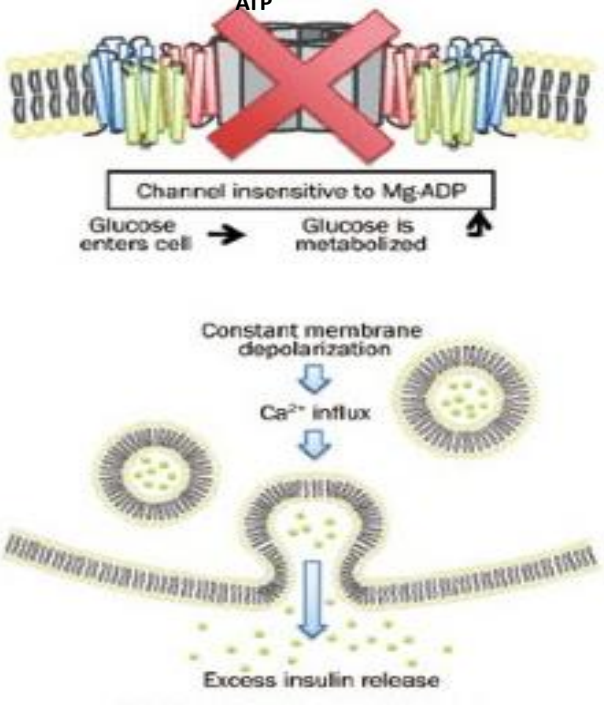
Role of K_{ATP} channels in insulin release from pancreatic β-cells

(*From Previous knowledge*)



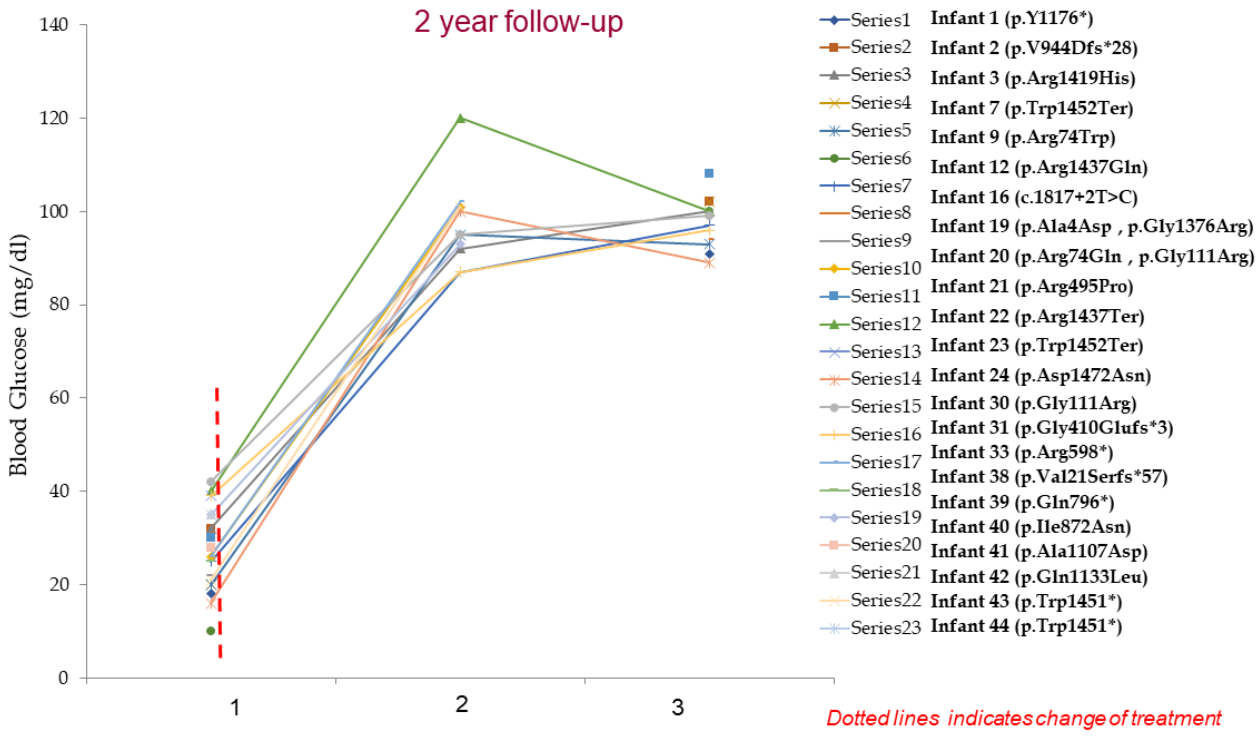
Normal Condition

Inactivation / Loss of Function Mutation in K_{ATP} channel Genes

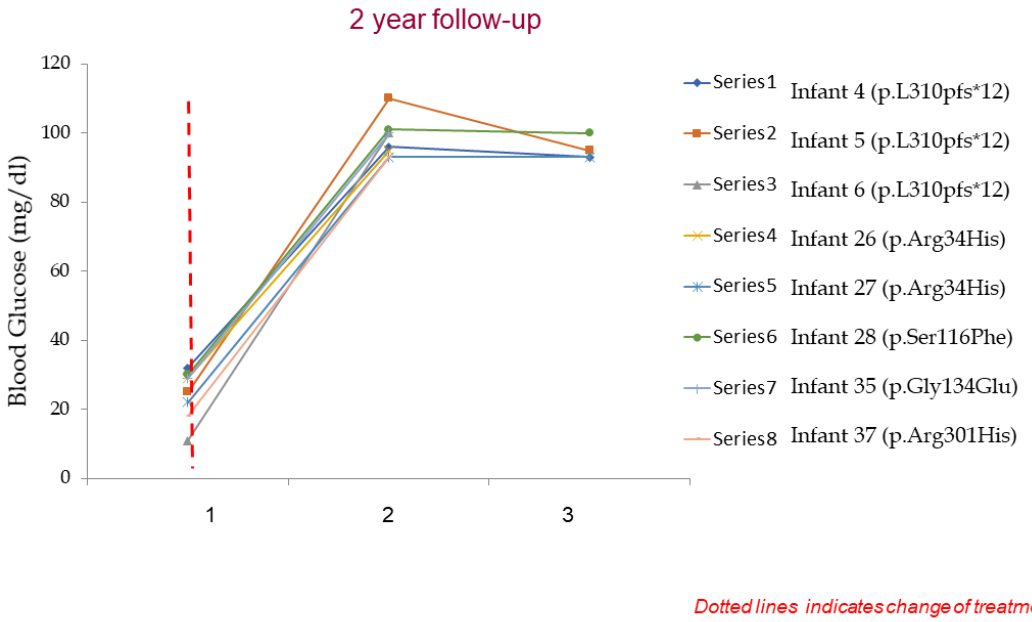


Congenital Hyperinsulinism

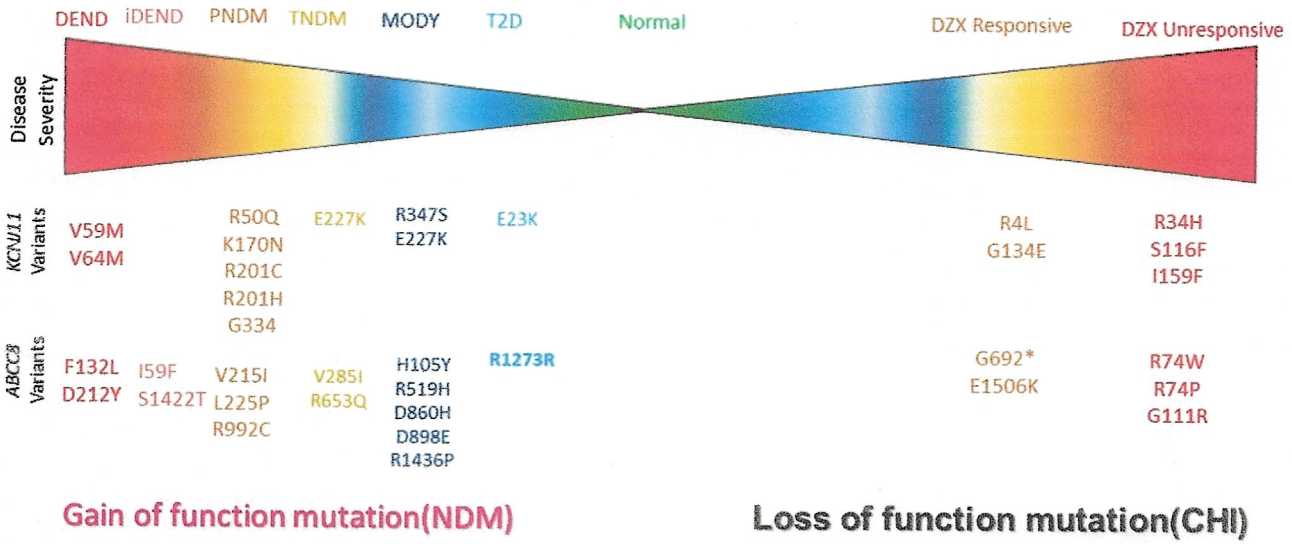
Blood glucose trajectories of CHI Patients with *ABCC8* Gene variants (Diffuse) after change in treatment



Blood glucose trajectories of CHI Patients with *KCNJ11* Gene variants (Diffuse) after change in treatment



KATP mutation spectrum & clinical presentations from my studies- a continuum of causality



In a nutshell, my contribution to the field of genetics and genomics of monogenic diabetes and their clinical implications has turned to be a reference point in the country. There has since been a leap from Bench to bedside.

Radha Venkatesan

Signature of the Applicant

30th Aug 2024

(Dr. Radha Venkatesan)

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