TIGS
Tata Institute for Genetics and Society

ORDI
Organization for Rare Diseases India

RARE GENETIC DISEASES RESEARCH SUMMIT (REDRESS - 2022)

24th and 25th November, Bengaluru

Meeting Proceedings

RARE GENETIC DISEASES RESEARCH SUMMIT, REDRESS-2022

Meeting proceedings

Contents:

Background:

Rare genetic disorders (RGDs) are far from rare in India, owing to the high population density in the country, which translates to a very high disease burden. Nearly 8000 rare genetic diseases have been identified globally, 450 of which have been reported in India. Mostly affecting children, they carry a huge socio-economic, emotional and physical burden on affected families. Difficulties involved in reaching out to widely dispersed carriers or patients and absence of point-of-care diagnostics adds to the complexity in tackling these disorders at an early stage. Where available, the cost of diagnostic and medical tests is beyond the reach of most people in our country.

In the past year, the National Policy for Rare Diseases 2021 has been released by the Indian government with provisions to promote research and development for diagnosis and treatment of rare diseases. In this context, the Tata Institute for Genetics and Society (TIGS) and Organization for Rare Diseases India (ORDI) organised the 1st National Rare Genetic Diseases Research Summit (REDRESS-2022) on the 24th and 25th of November 2022 in Bengaluru.

Rationale:

REDRESS-2022 is envisaged as a platform to bring together a comprehensive group of RGD stakeholders in India, with the aim of indigenization and acceleration of diagnostics, therapeutics, and management of RGDs. Interactive sessions were organized at the first summit to discuss unmet needs, along with panel discussions on nurturing the ecosystem for basic and translational research in RGDs, diagnostics and drug development, enabling clinical trials in India, and providing access to RGD medications. Finally, the summit covered India's journey in the field so far with speakers presenting their research findings as well as posters describing their work. Several potential collaborations and partnerships were discussed, involving multiple stakeholders. Such partnerships are the need of the hour to fast forward solutions and alleviate the suffering of a substantial proportion of the population of our country. Most importantly, several focus areas emerged from the two days of interactions, which are presented here as action points that can expedite this goal.

Summary of the key discussions and talks:

Dr Rakesh Mishra, Director, TIGS introduced the scale of the problem in India and the scope and urgency for interventions for patients suffering from RGDs.

Mr. Prasanna Shirol, Co-Founder, ORDI welcomed the delegates to the 1st edition of the RGD summit. He emphasized that RGD patients live in hope but face a huge gap - 95% of the diseases do not have FDA approved drugs.

There are over 8000 RGDs, and most affect children. There is an urgent need to bring together stakeholders who can make a difference, and this summit is the first attempt at such a platform. Bengaluru being home to one of the biggest advocacy platforms for RGDs, it is apt for TIGS and ORDI to come together with specialists from all over the country contributing their work and expertise to forge a path ahead for these patients.

Part 1: Keynote address

Prof. Madhulika Kabra, Division of Genetics, Dept of Pediatrics, AIIMS, New Delhi

Prof. Kabra began her talk by explaining how RGDs mimic common paediatric ailments, so they often get missed out in clinical diagnosis; 80% are genetic in origin and thus early diagnosis is key to their management. Public awareness and awareness amongst clinicians has improved tremendously in the last decade, yet only <5% patients with RGDs currently have treatment options. Often the cost of the treatment, when available, is prohibitively high. Prevention is thus all important in bringing down the burden of RGDs. Also, supportive care needs to be offered by doctors, especially when patients don't know enough to seek them.

Some states in India have RGD services but not all have them in the public sector. They may also be scattered – diagnostics, counselling, treatment, paediatric care – making it very difficult for patients to avail these separate modules; comprehensive centres are needed across the country to bring them under one platform. Education and training in this area has improved, with a formal and comprehensive curriculum in the medical community, yet these measures are insufficient.

The Rare Policy of India, declared by the Government of India in March 2021, focusses on an integrated and comprehensive preventive strategy to tackle the problems of RGDs. Some of its key inclusions are:

- Upto 50 lakh INR support for any of the four groups of disorders, which now allows a provision for RGDs recompensation.
- Centres of excellence set up at multiple places, with low cost diagnostics, drug repurposing and therapeutics funded and promoted.
- Because India does not have enough data, there is an urgent need for epidemiological studies – prevalence data, registries, carrier frequency determination, Indian population-specific variation databases and identification of the spectrum of variations in monogenic disorders.

Prof. Kabra emphasized that hospitals have prevalence data on frequency and types of disorders, so they need to be the primary source of information. The ICMR's National Initiative for RGDs includes registries that are hospital based and encompasses some disorders from all groups (Group 1 to 6; appendix 1). Screening programs are crucial for determining extent of carriers for a particular disorder; screening of parents, both high and medium risk, showed that even cystic fibrosis (CF) has a much higher prevalence in India than estimated. Newborn screening is also essential for providing prevalence information and holistic screening programs such as NEEV - which includes checking for hearing and seeing defects, cardiac anomalies, birth defects, etc - are a step in this direction. We thus need Indian databases, collating NGS data coming in from many labs in the country. Projects like the Genome India Initiative should directly feed into such databases. Several opportunities were mentioned in this context for funding and research intiatives:

- ICMR Task Force on Rare Diseases
- ICMR Task Force on Gene Therapy Research
- DBT "Genome India" and "Human Microbiome" initiatives
- ICMR National Consortium on Research & Development of Therapeutics in Rare diseases
- Therapeutic strategies for prevalent Rare/Orphan disorders under the new initiative of Therapeutic Chemicals (DST)

- Mission Program on Paediatric Rare Genetic Disorders (DBT)
- Virtual Centre for Molecular Medicine with focus on Rare Genetic Disorders (ICMR)

Prof. Kabra concluded by appealing to the stakeholders to come together for a way forward for translational research in RGDs. She cited the examples of stalwarts such as Prof. IC Verma and Prof. SS Agarwal who have already shown the path ahead as clinician mentors for RGDs in the country.

Part 2: Invited talks

Session 1: India's Journey in Rare Genetic Disease Research

1. *Dr. Parag Tamhankar, Medgenome Labs, Bangalore and Centre for Medical Genetics, Mumbai*

Dr. Tamhankar emphasized that the cause of most genetic diseases is generally a chromosomal aberration or a defective gene (monogenic or polygenic), but there could be multifactorial causes as well. He gave examples of several case studies and syndromes that have been described by Indian doctors, often in collaboration with national and international research partners (listed in appendix 2).

Many of these diseases are known internationally, but they have Indian population-specific mutations that are not known in Caucasian data. Similarly, there are specific genes that have been mapped only in India, such as for Primary microcephaly type 7, and the Handigodu syndrome of Shimoga and Chikmaglur districts of Karnataka. There is thus enormous scope for research and identification of disorders in the Indian context.

Dr. Tamhankar also talked about various mutations in the HEXA gene for Tay-Sachs syndrome (DOI: https://doi.org/10.1371/journal.pone.0039122.t002) and how genetic testing can help in its differentiation from Sandhoff disease, which has similar symptoms. Enzyme assays for HeX A enzyme are also useful to identify carrier status.

He described the work being done on Progeria syndromes; their team has currently identified 6 patients across India while they target to identify 60 patients going ahead. He talked about founder mutations in genodermatoses in India. The c.2808G>A variation has been suggested as a possible founder mutation (DOI: 10.1159/000339896). It would be worthwhile to be able

to identify such founder mutations and map them onto a chip for such diseases, making screening much easier and cost-effective. Finally, he emphasized on the importance of testing for prenatal diagnosis and pre-implantation diagnosis.

2. Dr. B R Lakshmi, MDCRC, Coimbatore

Dr. Lakshmi gave an overview of the MDCRC and shared the journey of setting up a molecular diagnostic and counseling facility at Coimbatore for Duchenne Muscular Dystrophy (DMD). This was the first institute to set up MLPA for molecular diagnosis of DMD, with the result that even children with DMD in rural Tamil Nadu have been identified by MDCRC. They have a provision of diagnostics, counseling, care, rehabilitation, family support, and outreach activities. Her talk showed the way how an NGO can lead from the front in providing state of the art diagnostics to Indian children.

3. Prof. Girish Katta, KMC Manipal

Prof. Katta emphasized how there is a huge potential for rare gene discovery in India (DOI: 10.1002/ajmg.a.61866). With a population of 1.4 billion people and 4500 anthropologically defined groups, bottlenecks and founder effects can be captured relatively easily. Apart from this, we have a high degree of endogamy (upto 45%) which can precipitate many otherwise rare disorders. He emphasized that technology has now reached a point where a new disease and its cause can be discovered simultaneously. An average of 300 new Mendelian diseases/genes are discovered annually.

As an example, he discussed his work of finding a novel subtype of mucopolysaccharidosis caused by arylsulfatase K deficiency (doi:10.1136/jmedgenet-2021-108061), a very rare disease but for which multiple patients existed in a small defined area. This is the right time for India to harness this population potential, not only in terms of its patient pool, but also in manpower and intellectual capabilities, to focus on RGDs and their alleviation in the Indian context.

4. Prof. Seema Kapoor, Maulana Azad Medical College, New Delhi

Prof. Kapoor emphasized how newborn screening (NBS) is the only way to ensure the early diagnosis of genetic disorders, and can help remedy treatable diseases by allowing immediate therapy. From a single drop of blood, technology exists today to detect up to 30 conditions even with just mass spectrometry. This ability to screen for many targets at a time is most suitable for small molecule disorders, which can be followed up with confirmatory diagnosis through nucleic acid-based detection. Genomics in NBS can step up the screening program several fold by bringing in many other RGDs into the testing ambit, for example screening for SMA. This has been recently introduced in the US (since 2018), where SMA is the most common cause of floppy infant, based on the DNA method. SMA can be handled well if detected within 6 weeks of birth, making it an ideal disease for NBS. It is prevalent in India as well, with a high carrier frequency, and patients will benefit hugely from early diagnosis.

Prof. Kapoor spoke about the importance of diagnosis for Inborn errors of metabolism which are likely to affect 1 in 1000 newborns (incidence data for 20,335 newborns screened at 20 hospitals from Delhi state - the incidence of IEM including G6PD is 1 in 170 (unpublished data). Their study confirmed the disease by mutation analysis of the diseased cohort. She emphasized that NBS must be expanded to include diseases like lysosomal storage disorders such as Gaucher's disease (can be diagnosed by MS/MS and enzymatic assays), Fabry disease (newborn diagnosis can identify most conditions of those patients who will remain asymptomatic till later in their life) and for SMA. Estimates indicate that 2 lakh plus births are expected to be detected if a full scale NBS effort is launched in the country and there are multiple things that invested stakeholders can do to ensure and enable it.

India should adopt a Digital Health Policy – One Unique Health Card for tracing the family history of disorders. The Digital Health Mission should hopefully help make electronic health records (EHRs) common, but it is not yet in place. The ICMR registry is another attempt to collect all hospital-based data from the country, but all these efforts need to be stepped up to support our country's RGD population.

5. Dr. Rita Christopher, NIMHANS, Bangalore

Dr. Christopher discussed her work in establishing the workflow at NIMHANS for the diagnosis of Inborn errors of metabolism (IEMs) through TLC, biochemical tests, enzymatic assays, and HPLC for analysis of amino acids. This was followed by establishing tandem Mass Spec for diagnostics over the last 25 years. Mass spectrometry has truly scaled its ability to diagnose many disorders in a single attempt using dried blood spots. In 1993, there was no diagnostics for IEMs available, but it was an urgent need since such patients can present as acute metabolic emergencies; if treated immediately they can recover completely, but if damage accumulates then the changes become irreversible.

The tandem mass spec diagnostics effort (2007) was a first of its kind initiative in a government institution and required much background set-up in terms of establishing reference ranges for the Indian population as well as age specific ranges. A lot of their lab's research work tested the effect of different storage conditions of the blood spots used for diagnostics and generated data for the successful detection of enzymes involved in lysosomal storage disorders (LSDs).

With this set-up, NIMHANS was in a position to move beyond IEMs, selecting 5 LSDs since these are treatable (Gaucher, Pompe, Fabry, Nieman-Pick, Krabbe disease) as well as peroxisomal disorders screening from just 3.5 ml blood. Various lysosomal disorders, peroxisomal disorders, X-linked adrenoleukodystrophy, carnitine transport defects, organic acidurias, fatty acid oxidation disorders, and disorders of amino acid metabolism can be diagnosed by mass spectroscopy.

6. Prof. Shefali Gulati, AIIMS, New Delhi

Prof. Gulati presented her views on India's journey in RGDs with a focus on neurodevelopment and neuromuscular disorders. She emphasized the fact that India has recorded around 450 rare disorders, and at least 23.7 million children in the age group of 2-9 are estimated to be affected. However, due to the lack of epidemiological data, we are still far from having a clear definition of rare diseases.

With the 2021 Rare Disease policy, some support is now being provided by the government. However patient registries are the need of the hour – currently, registries are being maintained for a few thrust areas like Autism, ADHD, CP, and Intellectual disability. Some centres of excellence have been established across India, focussed on RGDs and providing counselling and treatment options to patients and their caregivers. Prevention is the best remedy for reducing the RGD burden, and can be implemented via counselling and prenatal diagnosis taking a cue from the preimplantation testing available for Thalassemia.

Prof. Gulati also discussed the need and utility of digital technology. Artificial intelligence (AI) and virtual reality (VR) can play a major role in the rehabilitation of patients (Appendix 3). Apart from the work at AIIMS, Prof Gulati showcased the example of the GUARDIAN program led by IGIB involving over 250 clinicians. She concluded with a discussion on newer therapies and trials being conducted in India such as antisense oligonucleotides for DMD, and stem cell therapies.

Session 2: Rare Genetic Disease treatments: Past, Present and Future

1. Dr. Sunil Bhat, Mazumdar Shaw Medical Centre and Narayana Medical Centre, Bangalore.

Dr. Bhat provided an overview of bone marrow transplantation and hematopoietic stem cell (HSCs) transplants and its importance not only in lymphomas but also RGDs such as blood disorders (hemoglobinopathies and thalassemia), storage disorders (LSDs and mucopolysachharidosis) and immunodeficiencies. He discussed how allogenic hematopoietic transplant therapy is advertised as the only option for many hematopoietic disorders (80-90% cure rate), as well as in storage disorders where >80% recovery of the defective enzymes can be achieved post transplantation. This highlights the importance of maintaining donor registries; Indian patients find it very difficult to find unrelated matched donors (India has less than 5 lakh donor entries). Immunologically naïve cord blood cells can overcome these problems, as they do not induce as much rejection in patients as other mature cell types, but have not yet been brought into general therapeutic use due to the low volume obtained from the neonatal donor circulation.

Dr. Bhat illustrated his points via a case study of a child (the only living child in the family) who suffered for nearly 7 years (the average time to diagnose RGDs in India) due to the absence of an accurate diagnosis. Once diagnosed, a paternal bone marrow transplant could completely cure the child. He concluded with a mention of the Thalassemia Bal Seva Yojana and the S-Varna Arogya Suraksha Trust that provide transplant options along with financial aid.

2. Dr. Arvind Ramanathan, inStem, Bangalore

Dr. Arvind spoke about fatty acid oxidation disorders and the platform developed by DBT-NCBS-inStem-TIGS for rapid biomarker discovery, to develop diagnostics for detection of metabolite levels and to create a system for small molecule drug screening using fly models (testing FDA approved drugs and neutraceuticals).

The collaboration is working on developing an induced pluripotent stem cell (iPSC)-based model for VLCADD (very long-chain acyl-CoA dehydrogenase deficiency). Acyl carnitine is needed to metabolize long chain fatty acids; however, the enzyme is non-functional in VLCADD due to which carnitines accumulate in the cells. This can be used as a diagnostic and early detection system, because the disease leads to muscle damage and is triggered by exercise and starvation. CRISPR technology can be used to make changes in the stem cells that mimic the disease and then derive skeletal muscle cells to serve as a 'disease-in-a-dish' model for VLCADD. He also stressed on the need to develop 3D skeletal muscle organoids from engineered iPSCS as well as from patient samples. This can help generate a state-of-the-art personalized muscle model system to study the effects of environmental factors and nutritional management for such patients.

3. Dr Arkasubhra Ghosh, Narayana Nethralaya Foundation, Bangalore

Dr. Ghosh spoke about the work at the basic research arm of the Narayana Nethralaya Foundation. He explained the advantages of adenoviral vector technology for gene therapy; the AAV genome has its replicating genes removed and is made into a vector that can become a plasmid in the cell to continuously produce a corrected protein. In this manner, augmentation can be done where a normal gene is inserted to complement a non-functional gene, or an abnormal gene is traded for a normal one. Gene regulation changes can also be corrected.

However, there is a high cost associated with such therapies, in the range of 1-3 million dollars and there are no trials currently for gene therapy in India.

Their team has developed the dual viral vector technology where they can cut a large gene into two parts and insert into two AAV vectors which is then reassembled in the cell. He cited the example of how this can be useful for genes such as Dystrophin (a large gene about 2.6 megabases in length). Their focus is on eye tissue and retinal gene therapy. He mentioned the caveat that lab scale production is not sufficient for human application, so there is an urgent need to make this scalable.

4. Dr. Gurudatta V Baraka, Centre for Human Genetics, Bangalore

Dr. Baraka spoke about the Epidermolysis Bullosa Research Partnership (EBRP) program covering Epidermolysis Bullosa, a disorder that can present with varied clinical manifestations, including early skin blistering. It is a polygenic disorder, and very hard to diagnose accurately. A couple of case studies were presented to highlight the journey of the patients suffering from this disease. Future directions to develop a cure would require the development of preclinical disease models and gene therapy testing.

Session 3: Rare genetic disease model systems

1. Prof. Raghu Padinjat, NCBS, Bangalore

Prof. Padinjat spoke about mental disorders and how over 900 million people in India are estimated to have some sort of mental illness. He explained the aetiology of neurodevelopmental disorders and their pre-, peri-, or post-natal manifestation. As an example, he mentioned diseases caused due to abnormalities in the nervous system development such as enhancement of astrocytes due to neural precursor cell enhancement whose mechanisms are not yet elucidated but point towards a plasma membrane trafficking disorder due to many possible mutations in OCRL gene. His talk demonstrated how developing an induced pluripotent stem cell (iPSC) model from patient biopsies is useful to recapitulate the disease phenotype. Disease-in-dish models can be employed to understand molecular events related to disorders such as Lowe syndrome, especially where mouse models cannot help understand neurodevelopmental symptoms.

Lowe Syndrome (LS) was discussed in some detail in this context, a very rare X-linked recessive disorder (1:100000). Patients suffer from many neurodegenerative symptoms (that are usually not well managed) and have eye issues (requiring surgery), as well as kidney dysregulation (managed via electrolytes administration). There is a lot of phenotypic variability in LS, with mild to severe combinations of kidney, brain and eye defects. He described a case study from Bengaluru, where the affected cousins had different symptoms while all suffering from the same disorder, making diagnosis very difficult. Only one of the affected children showed severe neurodevelopmental defects due to additional mutations.

His talk also highlighted the use of next generation sequencing (NGS) based technologies such as mRNA-seq to reveal differences in gene expression profiles from iPSC models and whole genome sequencing for variant identification from patients. He concluded by reiterating that every LS patient therefore needs personalized care. This work provides a great example of how clinicians and patient groups can come together to work directly with patients.

2. Dr. Bhavana Muralidharan, InStem, Bangalore

Dr. Muralidharan discussed her team's work studying the chromatin regulation of human neural stem cells (NSCs) via LSD1/KDM1A (lysine specific histone demethylase) that activates chromatin to regulate gene transcription. Deregulation is responsible for many disorders including CPRF disorder with craniofacial, developmental and cognitive abnormalities associated with Kabuki-like syndrome.

NGS following chromatin immunoprecipitation (ChIP-Seq) and RNA-Seq were both performed; the data suggest up-regulation of the Notch pathway in both humans and mice, along with many other pathways, upon LSD1 inhibition. However, LSD1 appears to be differently functional in mouse and humans, probably due to differences in interacting partners, once again stressing the caveats in using animal models for neurodevelopmental disorders.

3. Prof. Upendra Nongthomba, IISc, Bangalore

Prof. Nongthomba's talk stressed on how personalized care is essential for handling RGDs. Every mutation is different and can cause different interactions in patients even within the same disease spectrum and hence customized research plans are invaluable. He emphasized the

utility of developing *Drosophila* and zebrafish models in drug discovery and recapitulating human RGD phenotypes.

He also highlighted the need for academia-industry partnerships and described his association with GenoPhe Biotech Pvt. Ltd. where they are creating models for rare diseases in zebrafish – 70 to 80% of RGD causing genes have autology in zebrafish making it a model organism for understanding disease cause, screening drug libraries as well as for toxicity screening.

4. Dr. Vasanth Thamodaran, TIGS, Bangalore

Dr. Thamodaran described his team's work on developing a human embryonic stem cell (hESC) model to study Pompe's disease, a lysosomal storage disorder (LSD) due to the accumulation of glycogen. India has the largest number of Pompe's patients among LSDs, which can be Infantile Pompe or late-onset, with cardiac and respiratory muscle defects causing mortality, also muscle loss. They have optimized CRISPR-CAS9 based gene editing in mammalian cell lines using nucleofection based delivery of RNPs; the exon 6 mutation prevalent in Indian population was used to design the guide RNA.

The stem cell model has passed chromosomal karyotyping and off-target analysis, and matches the expected morphology. The edited stem cells retain pluripotency markers and are able to differentiate into required lineages, recapitulating the disease phenotype in heart and muscle cells. This session stressed the importance of creating a platform that allows the rapid development of cell-based models for LSDs as well as other RGDs.

Session 4: Rare Genetic Disease Drug Development in India: Success Stories

A few success stories in RGD research and, more importantly, translation from bench to bedside are summarized below:

1. Dr. Rajarshi Pal, EyeStem, C-CAMP, Bangalore

A start-up focused on creating stem cell models for eye tissues incubated at C-CAMP since the last 5 years has successfully developed a patient-derived iPSC line for Oculocutaneous albinism (OCA) type 1A. Patient match via karyotyping as well as all the differentiation markers has been demonstrated. The retinal pigment epithelium cells (RPEs) are not pigmented

in culture, and have reduced melanin production so the model faithfully encapsulates the eye phenotype, affecting the approximately fifty thousand RPEs present in the human eye.

This should serve as a disease-in-a-dish model for OCA1A, the most severe form of oculocutaneous albinism, where patients have no pigmentation in skin, hair and eyes due to mutations on TYR gene. The team is now also working on retinitis pigmentosa.

2. Dr. Sheetal Mahmunkar, Preventa Clinic, and KEM Hospital, Mumbai

Dr. Mahmunkar talked about her initiatives to tackle in-born errors in metabolism like Aminoacidopathies using dietary interventions. Her team works on community awareness of such metabolic disorders, training parents to deal with infants with special dietary needs or personalized requirements. They have developed an indigenous medical food formulation which is 3 times cheaper than the imported formulations. This makes the essential formulations more accessible to Indian families.

3. Dr. Ganesh Sangle, Kashiv Biosciences, Ahmedabad

Kashiv Biosciences is working on drug redesigning and repurposing. Cerdelga, for example, is to be redesigned to lower cost for Indian patients. Dr. Sangle also talked about the development of sublingual delivery platform for eliglustat tartrate that reduced the dosage and side-effects. This drug is currently in Phase-II clinical trials.

4. Dr. Shashwati Basak, INTAS Pharmaceuticals, Ahmedabad

INTAS Pharmaceuticals is working on the X-linked disorder haemophilia. Their focus is on reducing the therapeutic cost, since RGD drugs are extremely expensive due to the comparatively fewer patient numbers for each disorder and mutation type. Dr. Basak described how they have developed drugs for DMD using morpholino attachment formula and received SERB-TETRA grant for the same.

5. Prof. Surajit Sinha, Indian Association for the Cultivation of Science, Kolkata

Prof. Sinha described the success with developing morpholino ASO-based exon skipping strategy. Though designed for DMD treatment, many other morpholinos can now be made for many other diseases, using their set protocol. The strategy relies on designing a small DNA or RNA structure (morpholino) that can bind to the problematic region in the genome and correct

the mutation effects via exon skipping (though the protein will be partially truncated, this can create a treatment for each of the mutated exons in Dystrophin gene).

Part 3: Panel Discussions

The panels discussed multiple questions on their respective session themes, with audience queries and interactions. The key points that emerged from each of the three sessions are listed:

Discussion 1: Nurturing the Ecosystem for Basic and Translational Research of Rare Genetic Diseases in India

Chair: **Dr. Madhulika Kabra**
Panellists:

Prof. Subba Rao V M, JSS Medical College, JSS Academy of Higher Education and Research, Mysore

Dr. Vijay Chandru, Karnataka State Vision Group on Science and Technology and Lancet Citizens Commission for Reimagining India's Health Systems

Dr. Devendra Singh, The Wellcome Trust/DBT India Alliance

Dr. Ravi Manjithaya, JNCASR, Bangalore

Dr. Meera Purushottam, ADBS-NIMHANS, Bangalore

Dr. Sonali Rawal, World Health Organization and formerly at Niti Aayog

a) Improving research in medical colleges

- Creating in-house diagnostic team of researchers can fasten the diagnostics process and also enhance research in medical institutions.
- Developing an interdisciplinary team of clinicians and basic researchers.
- Academia-industry trust building - rather than duplicating the scarce resources, summits like REDRESS can map out the different expertise and add them together.
- Understanding the importance of diagnostics in a medical set up and nurturing research teams towards this goal

  - example of setting up research initiative in JSS medical college to improve diagnostics.

  - example of NIMHANS where the team started with an ICMR grant to look at triplet repeat expansion disorders, SMA and DMD. And then developed the diagnostics into a service mode at the hospital. This is needed because many physicians in small areas have not seen the whole

spectrum of patients with the disease, which can have varying degrees of severity and needs many patient numbers to catch the RGD spectrum and diagnose correctly. Furthermore, experienced and senior neurologists in clinics do not have time to handhold the patient beyond the diagnosis.

b) Incentivizing students to take up disease-oriented research

- Acknowledging the slow but gradual shift in funding agencies goals
- Basic research to Technology to Product is not a linear path but needs a Knowledge + Utility model, the so-called Pasteur model.
- Initiation of NGS based clinical genomics program in 2013 - the first cases were indeed focussed on investigating RGDs.
- High throughput compound screening can enable drug discovery to treat RGDs, and the potential use of small molecular drugs that modulate autophagy for therapeutic purposes, with special mention of ATAXIA and Griscelli syndrome type 1.
- Need to attract students towards translational research.
- Undertaking both basic and translational research together.
- Importance of frequent interactions between the clinical, student and the science community.

  - Example cited of Wellcome Trust's goal to promote science and research ecosystem and stakeholder engagement and their willingness to support RGD research. There are various 5-year fellowship programs provided with an aim to transform Indian science; DBT-Wellcome has basic and clinical grants at various career stages for
    - Capacity building
    - Engaging the right stakeholders
    - Fund health research with focus on RGDs
    - Emphasis on basic research of monogenic disorders

c) Obstacles in translating lab research to therapy

- Disconnect between metrics of publications and product development needs to be bridged in order to reach marketable therapeutics.

- Lack of awareness on RGDs makes it difficult to get funding; links between academia and industry are required for better funding.
- Need for a specific policy for research and development of therapies for RGDs like Orphan drug policy in USA, to fast-track therapeutics to enter clinics. DCGI already has an orphan drug component in its recent guidelines, defined as a target population of upto 5 lakhs.
- Encouragement by the government needed for global clinical trial registrations in the country.
- International collaborations must be encouraged by funding agencies.

d) Research perspective in hospitals

- Urgent need for large genomic databases for basic research, correlative analysis, and model system studies.
- Initiatives from clinicians
  – example of Huntington's Disease (HD); banking DNA samples of neurodegerative disorder patients needed along with setting up HD support centres to raise awareness. And initiatives from the government to stock HD generic medication for free and create awareness in government hospitals

e) Developing an ecosystem for RGDs between academia and the industry

- No compromise in taking orphan drugs to the clinic, in the context of developing trust between academia and industry.
- Identify where companies, clinicians and academicians can complement each other and contribute diverse skills.
- Work towards bringing down the cost of some of the expensive therapies like gene therapy.
  - example of gene therapy-based treatment for hemophilia cited, with an estimated cost of 3.5 million USD.
- Absence of measures for compassionate treatment possibilities in India

The session ended with a discussion on how toxicity studies in relevant animal models are important with an example of failed trials of stem cell therapy in many cases. A cautionary note to create awareness against malpractices in experimental usage of the therapy was added.

Discussion 2: Accelerating rare genetic disease diagnostics and drug development in India

Chair: **Prof. Vijay Chandru**, Karnataka State Vision Group on Science and Technology and Lancet Citizens Commission for Reimagining India's Health Systems.

Panellists:

Dr. Neelanjana Janardhan, Centre for Cellular and Molecular Platforms (C-CAMP), Bangalore

Dr. Aparna Sharma, BIRAC, Dept of Biotechnology, Govt of India.

Dr. Narayanan Venkatasubramanian, Peptris Technologies, Bangalore

Dr. Ashraf Mannan, Strand Life Sciences, Bangalore

Dr. Subhendu Bhowmik, NIPER, Kolkata

Dr. Vishwanath Pingali, Indian Institute of Management, Ahmedabad

Dr Chandru initiated the discussions and asked the panellists their opinions on diverse questions pertaining to the session theme

a) Accelerating RGD diagnostics and drug development

- Discussion about a start-up supported by C-CAMP on oligonucleotide-based therapy for Duchenne Muscular Dystrophy (DMD).
- RGDs should not be neglected for funding - schemes funded by BIRAC were specifically discussed (Appendix 4).
- Encouragement from DBT through inStem and CMC Vellore for various programs in stem cell therapy was also cited.
- Support already provided for indigenization of certain therapeutics, such as those for haemophilia B, was discussed.

b) Drug discovery in industry

- Discussion on Peptris, a drug discovery biotech company to identify small molecules interacting with proteins. They have created large and complex pipelines to accelerate drug discovery through data science - identifying potentially relevant molecules, screening, and preclinical drug testing (small molecule repurposing as well as de novo development).
- Discussion on Strand Life Sciences, especially in the context of diagnostics. Genomics has entered a tipping point with 100 USD genome sequencing now a technical possibility. Genomics will soon lead diagnostics, once the cost to test samples falls below 1000 INR.
- Instead of sequencing in different areas, companies need to pool the samples so that sequencing capacity is used to full potential. Extensive phenotypic correlation with phenomic and genomic data capture in relevant and reliable databases is helpful for diagnosis, developing future diagnostics and as information for industry and academia.
- Understanding the importance of phytopharmaceuticals; India can lead in drug development via isolating the active components in natural compounds.
- Importance of bringing together medicinal chemistry, organic synthesis, developing de novo synthesis methods, and process development.
- By reducing the currently high cost of available therapeutics, India could be poised to even export them to the global RGD market. However, the current job market in India is geared towards generic drugs and their export.

c) Economic perspectives

- Discussion on the financial aspects of RGD drug development, with the following points put forth for consideration –

1) India as a manufacturing hub for the production of drugs for RGDs,

2) innovation potential in the short run and in the long run,

3) value of procurement from the point of view of the government, and

4) directions in which entrepreneurship is heading.

- Costs for therapy can be reduced by doing bulk productions in India (consolidating manufacturing into one geographical area makes it economical).
- Innovations need not be only in direct drug discovery but can also involve process optimization, supply chain innovation, and repurposing.
- Discussion on the importance of orphan drug policies in India. Orphan drug policies need to be innovative, and crowdfunding cannot be the answer in the long term.
- Supporting innovation and indigenization is necessary and this requires clear procurement policies from the government.
- Patenting laws should be loosened for RGDs.

The session ended with a comparison of drug development scenario in other diseases like cancer to understand if the key issues include insufficient technology or neglect or a lack of funds. While the lack of technology remains a problem, this is fuelled by the comparatively low demand, and the supply of ingredients. As there are very few people suffering from individual RGDs, the availability is low and the costs are high. Further, while in oncology the models and reagents are available, each RGD patient is unique, and personalized resources are not currently available.

Discussion 3: Innovating Rare Genetic Disease clinical trials for India and access to Rare Genetic Disease medications

Chair: **Prof. Alok Bhattacharya**, Ashoka University

Panellists:

Dr. Aparna Sharma, BIRAC

Dr. Rakesh Mishra, TIGS

Dr. Surinder Kher, Aster Hospitals, Bangalore

Dr. Ramesh Jagannath, Indian Society for Clinical Research

Dr. Ashwin Dalal, CDFD Hyderabad, CoE Rare Diseases

Dr. Abhay Joshi, TAKEDA India

Prof Bhattacharya started the session by listing out the questions that need to be addressed in the field.

a) Drug trials for RGDs – funding, regulations and procedures

- Funding guidelines were elaborated - BIRAC funding for translational research looks for indigenous technologies, even to build requisite reagents as this reduces cost, as well as animal models and *in vitro* models for RGDs (Appendix 4). Drug trials need a program which has no funding cap and requires equal contribution from industry and BIRAC. At the last stage, BIRAC certainly has few projects for clinical trials. BIRAC also discusses all the regulatory approvals that will be needed before giving the fund, and the companies can discuss the regulatory approvals with IRAC as well.
- Importance of drug trials in determining affordability of the treatment
- Commitment towards a solution is already there in India, the problem remains challenging due to less numbers of patients, as well as the costs involved. The first step is to create the right intentions and connections and then to discuss incentives and facilities that can be given to industries for putting efforts in drug development for RGDs.
- The lack of family history databases; these data are necessary for evaluating efficacy and developing biomarker readouts. The currently approved global drugs for RGDs are based on surrogate biomarkers and not the main disease phenotypes. Disease data is missing even in hospitals - such as numbers and profiles of the patients, evidence-based patient journey records, family histories - which are critical for designing and evaluating clinical trials based on real world evidence of symptoms and side effects. This lack of patient data and natural history of each patient leads to reduced incentives for drug trials in India.
- Natural history repositories, though essential for industry partnership, require significant investment for a company to manage on its own. Industry typically relies on a few specialty hospitals and centres for such data; however, the lack of nationally available databases causes apprehension in foreign companies and drug investors, with uncertainty about sample size and pre-data availability.
- The real solution begins with accurate and thorough data collection at hospitals, with data ownership not restricted to the hospital alone. Often digital systems in hospitals are limited

to billing information and patient numbers; many electronic health records (EHRs) are restricted, and the patient journey is not stored or shared.

- Data ownership rules need to be clarified; currently it is individual doctors who may have collected data of their patients, that is owned by the doctor but that cannot be used by others. Systems need to be developed to transfer encrypted patient data ownership details along with the data itself such that patient data collected at hospitals is accessible to academic institutions, and for research as well as clinical trials by industry.
- The Digital Health Mission will be a much-needed solution, and the government needs to fund the generation of RGD patient databases, with targeted and rapid fund release.
- The limited patient population leads to exorbitant drug costs. It takes about a billion dollars to develop a drug, but with such a small market size, companies cannot take up such drugs profitably. Currently the only source of funds for the costly therapies appears to be crowdfunding, which is not a long-term or cover-all solution.
- If these issues can be overcome, Indian regulators are forthright in making regulations as easy as possible in the context of RGD drug development. They have reduced the processing times, while ensuring safety regulations that are very important for patients and the end-users.

b) Taking research in India forward from the lab to the market

- Disconnect between the researchers and the next stakeholders, be it industry or clinicians. The success metrics and assessment systems for scientists in academia are very different and their funding and career progress reflects this. The diverse viewpoints and pitfalls are often unclear to those outside their field of expertise, and it is thus important for academics to understand the system and work towards what would be a suitable real-life solution.
- The stakes are much larger when developing a product for the market than a conceptual stage in the lab since companies can suffer severe losses or even shut down on the basis of an ill-timed research investment or the failure of a project. Even if we reach potential solutions at the laboratory level they can only be translated into a treatment with proper guidelines in place.

- Publication-based focus of academia contributes to the lack of translation of lab research. Most of the panellists agreed that good ideas are often buried in academia due to the strong focus on publications. A change in funding approaches will help accelerate this transition. Already, granting agencies have now begun looking for an application or a translational component. Similar changes, with decreased emphasis on journal impact factor and publication metrics, could be considered during the academic hiring process.
- Incubators have provided a good framework for young academics and students to go into startups or set up their own companies, and this improves the overall connect. Though the trend is changing towards mutual partnerships from both sides, these are relatively new concepts in India and will take some time to be established.
- Urgent need for IP training and awareness in academia. Grant initiatives like BIG for start-up companies after doctoral training have been a right step in this direction.

- The Indian Society for Clinical Research (ISCR) was cited as an example, that has about 40 pharmaceutical companies, many CROs, doctors and patient societies as members. Founded in 2006, the ISCR as an organization has built a connect with the Indian drug regulator, the DGCI, and have member companies that can conduct clinical trials. Many of them are interested in conducting indigenous clinical trials for RGDs, provided some of the issues discussed are straightened out.

- In several cases drugs that have been approved do not become available in the market.
- Many hospitals are either not equipped or do not handle sufficient patient volumes for RGDs to emulate the standard models. Patient numbers, a mostly paediatric population and gaps in natural history remain the biggest hurdles.

c) Role of patient advocacy groups (PAGs)

- Heterogeneity among RGD patients with respect to symptoms, onset and disease progression. Patient advocacy groups can understand the need for natural disease data and family history and help fill these gaps.
- There are significant operational challenges of patient retention as well; patient advocacy groups could work with hospitals and pharmaceutical and drug companies from the

initiation of the trials to increase patient retention and long term follow-up. Partnerships developed with patient groups as early in as possible in such studies may give the best benefits.

- Patient advocacy also becomes a platform to bring about change in policy, for example the change in RGD policy by the government in allowing 50 lakh INR per patient across the country.
- The Indian government has established ten centers of excellence (COEs) for RGDs, and patient support organizations should approach these COEs for help, and publicize them. RGD patients have to be brought into the CoE, so support and advocacy groups can fill in this gap and develop channels to connect patients to the CoEs.
- Lobbying for the modification of the patent laws and use of compulsory licensing for exorbitantly costly drugs. Without epidemiological data, efficient utilization of current benefits, and strong patient advocacy, budget allocation for RGDs or policy changes become an even more difficult task for government agencies.

Part 4: Discussions with Patient Advocacy Groups

Events such as REDRESS-2022 help in sensitization of patient advocacy groups, scientists and clinicians to the problems that need to be tackled together. It would be useful to develop a framework for patient groups and companies to work with Indian scientists, regulators and policy makers, as is happening in a few other countries.

The REDRESS discussions would not have been complete without the inclusion of the end users - the patients and their caregivers. Patient advocacy groups (PAG) leaders were invited to share their experiences, achievements, pain points and expectations. The key points are summarized below:

1. Mr Prasanna Shirol, Founder & Executive Director, ORDI

The objectives of the ORDI include working with various PAGs across the country towards the following:

- To promote Rare Diseases as human rights priority through public awareness.

- To contribute towards development of Public Policy and take part in implementation, such as Rare Disease Policy and Orphan Drug Policy.
- To collaborate with advocacy organizations from India, and people living with rare diseases and to work jointly to connect them with national & international forums such as NORD, EURORDIS, RDI, Global gene, UDN, etc.
- To accelerate diagnosis and treatment options for patients with rare diseases through public-private partnerships, and by advocating mandatory newborn screening.
- To facilitate & encourage Clinical Trials, Research & Orphan drug development activities.

2. Mr. Samir Sethi, Chairman, Advocacy Group

- Registry: A structured and user-friendly registry at all levels of medical intervention is the first step needed to build better support for patients.
- Definition of Rare Disease: A clear definition of rare disease should be included in the Rare Disease Policy. This would remove ambiguity on the beneficiary of the Rare Disease Policy.
- Nidan Kendra/Rare Disease Clinics should be started at every District Hospital for clinical diagnoses and counselling with a well-defined treatment/management path for the patient.
- Centre of Excellence: As per the policy CoE should be opened in every state capital
- Financial Support: Rs.50 Lakhs financial support to be given to patients with rare disease should be to cover the treatment, management and rehabilitation of patients from all 3 groups as mentioned in the Rare Disease Policy.
- Orphan Drug Act: The act with clear guidelines is urgently needed in the country to encourage larger investments in R&D and protection of IPR.
- CSR Support: A specified part of the CSR disbursement from the Corporates should be earmarked towards Rare Diseases causes.
- Tax Exemptions: Cost incurred towards R&D of therapies and medicines for Rare Diseases should be given tax exemptions so as to encourage larger investments towards R&D.
- Course Curriculum: Basic knowledge and information about Rare diseases should be included as part of the course curriculum at MBBS and in more details at the post graduate levels.

3. Ms. Satvinder Kaur and Ms. Sukhvinder Kaur, ALS Care & Support Foundation

Set-up in 2015, the forum is a 24 x 7 assistance community which has touched the lives of 550+ patients and their caregivers. The foundation guides fellow PALS/CALS in every aspect of the disease based on their own experiences and extensive research, including nutrition, PEG management, using BiPAP, home ICU management, creating awareness, advocacy and much more. The speakers highlighted the following action points that would make a difference to ALS patients in India:

- DRUG DEVELOPMENT FROM INDIA: Indian Pharma companies can be incentivized to come forward to manufacture drugs which the ALS community depend upon through imports - Rilutor, Ibudilast, Edavorane (IV & oral form), RELYVRIO (called AMX0035 previously)
- R&D LABS: Re-use of Research & Development labs in India to expedite ALS Research e.g. DRDO
- ALS RESEARCH & DRUG DISCOVERY: Collaboration with ICMR, research teams, clinicians, labs & pharma, policy makers and technology to initiate the path of drug/molecule discovery from India.
- FUNDING: Allocation of substantial and dedicated funds for ALS research and to initiate clinical trials in India. For example, a recently announced US Government Act for ALS provides $100,000,000 funding per year for the ALS community.
- WORLDWIDE TRIALS ACCESS: Legal and easy access to worldwide clinical trials by patients of India.
- IMPORT DUTY WAIVERS: Custom free import of drugs under trials, associated supplements and equipment.
- Inclusion of ALS in Rare Disease policy
- Awareness on ALS and building a National registry of ALS patients

4. Kirtida Oza Co-Founder and Director, Sjögren's India

There is woefully inadequate Indian data regarding Sjögren's syndrome. Therefore the aetiology, the mechanism, the manifestations and the impact of the disease on the life of the

patients remain underexplored. Sjögren's India undertook a small citizen research study on the patients' perspective, with the following key findings

- Patients and the medical community look at quality of life (QoL) parameters differently. While doctors tend to focus on organ threatening or life threatening problems, patients look at how their life gets impacted on a daily basis.
- Doctors only focus on the physiological impact of the disease, while patients need an understanding of the impact on their overall life including education, careers, relationships and daily living.
- Collaborative research frameworks: Patient involvement in medical and laboratory research findings would bring in the patients' perspective into clinical and translational research. This would enrich medical understanding and also ensure a better acceptance of the findings within the patient community.
- Citizen Research: Patients have a wealth of experience with the disease and this knowledge needs to be valued and formalized through providing opportunities for patients and caregivers to understand and engage in the scientific research process. An example was shared on how Oxford University has now made such opportunities available.
- Science writing, communication and outreach: The scientific and academic community in India can benefit by provide opportunities for patients to engage in scientific writing and communication. For example, the British Medical Journal has made a provision for a Patient Editor with the recognition that while scientific research is the key to finding targeted treatments and disease cures, the involvement of patients in the process will facilitate a better overall understanding and a better acceptance of the outcomes.

5. Mr. Vikas Bhatia, founder, MERD India

- Awareness is the key to success with RGDs, especially for inborn errors of metabolism (IEMs), where prevention is most important along with strong advocacy for early intervention.
- New-born screening should be included in the Rare Policy to become a part of the protocol in every childcare centre, started with high-risk pregnancies and eventually including all new-borns, e.g., congenital hypothyroidism, visual, auditory and pulse oximetry screening.

- Availability of treatment in CoEs, eg, medicines, special diets, enzyme replacement therapy on a regular basis. The genetics disease department in every state and government hospital can be linked directly with Centre for Excellence under the Rare Disease Policy. Options for clinical trials for new treatments should be under experts in the CoEs.
- Implementation of insurance for RGDs in new pregnancies.

6. Ms. Shikha Metharamani, Indian Prader Willi Syndrome Association

- Availability of Free Growth hormone, subsidised rates on essential medicines & medical tests for PWS patients.
- Government aid and special insurance schemes under govt funded schemes, including financial support for expensive counselling sessions and therapies along with funding to IPWSA to help the needy families with supporting instruments like BiPAP, oxygen cylinder.
- Funding for creating special schools and adult homes, specifically meant for PWS kids that need special attention, dietary needs and controlled environment.
- The PWS fraternity needs well-funded multidisciplinary clinics to monitor the health condition of the patients.

7. Mr. Rahul Vipparthi, Managing Trustee, Tuberous Sclerosis Complex Alliance India

- Awareness on Tuberous Sclerosis Complex (TSC) and its impact on patients and families.
- Bringing together patients, healthcare providers, and researchers to collaborate and find solutions for managing the disease and ultimately a cure.
- Active lobbying for setting up TSC clinics, and a center of excellence.
- Initiatives for setting up a Natural History Database of TSC patients. The data collected should be available for researchers to study as well as for the medical and patient communities.
- Collaboration with global TSC patient groups, acting as a bridge between the global researchers (US, Europe) and India to promote research for TSC cures.
- Policy changes that improve access to medicines, care and treatments for TSC patients.

8. Ms Vaishali Pai, Founder-Director, Tamahar Trust

- Holistic developmental interventions inchildren suffering from developmental delays due to brain damage (like Autism, Cerebral Palsy, Down's Syndrome, and other RGDs).
- Education of families to look beyond life-saving treatments and at quality of life of patients (children as well as adults) and the need to engage in post-medical rehabilitation, including special schooling, aids and appliances, plans towards independence, etc.
- Engagement with the Government to address the issue of UDID, and other benefits to RGD families, and raising awareness among families for the need to utilise these services.
- Advocacy by the families for the need to increase the support services (post-medical, surgical or pharmaceutical treatment). There is very poor infrastructure for rehabilitative services and lack of human resources, leading to poor quality of such interventions.
- There are very few professionals addressing rehabilitation issues and most of them are centered in cities and catering to wealthy families; there is an urgent need to create intermediate support in Tier 2 and 3 cities, and in rural areas. As a signatory to the SDGs, India needs a bottom-up approach in service provision.
- Psychological and counseling support to families and awareness about mental health has to be created at multiple levels.

Directions for future

This summit would be utilized as a springboard for taking ahead RGD research in the country. With patient target numbers unknown, and given the rarity and patient-specificity of RGDs, the key question we need to address is how to develop and market diagnostics and therapeutics in the country; even if there are solutions developed how they can be translated into viable trials and treatment given market dynamics and profitability required for industry sustainability.

In this context, the summit highlighted the following key objectives:

1. To build Centres of Excellence or CoEs as platforms for researchers working on RGDs in the Indian context to come together not only for cross-disciplinary collaboration and sharing of ideas but also to enable data sharing, and product development and indigenisation.

2. Epidemiological data for most RGDs in India is not available, and numbers of patients are usually extrapolated from the prevalence data from other countries, mostly Caucasian populations. The Digital Health Mission will be crucial at a national level to address current uncertainties in sample size and pre-data availability. Data registries, electronic health records, digital tools for easy and integrated recording of pedigree, family history and symptomatic patient-centric history, as well as evidence-based patient journey records will need to be the basis.

3. Personalized medicine can be made into a reality for RGDs since these are specific disorders that affect a small number of individuals. Developing the means to utilize the genome data that will be available at an increasing scale and designing screens for prevention is crucial.

4. Develop rapid and portable diagnostics, especially point-of-care and cost-efficient tools that can be used in low resource settings. Enable handholding for translation by industry and start-up partners into the healthcare market.

5. mRNA therapeutics as a rising intervention should be utilized. Disease-in-a-dish models for RGD therapeutics are also an unmet need. Investment into developing disease-specific models as well as disease-agnostic platforms for therapeutics and drug screening is a practical and translatable approach to addressing the country's RGD burden.

6. To publicise the rare disease research work going on in India or on Indian populations, and to put out the work being done so that it is available for the patients to know about. Continuous interaction with patient groups is critical, and often ignored by the research community, to develop smaller and feasible patient-centric solutions to improve their quality of life.

TIGS aims to pave the way for creating a rare disease research ecosystem in India that addresses ummet needs and advances the documentation, understanding and management strategies for rare genetic diseases. To enable cross-disciplinary collaborations, an attempt was made at REDRESS-2022 to create a robust research ecosystem with the ORDI, encompassing science, healthcare, innovation, entrepreneurship, and policy. This urgently needs to be taken ahead to develop patient-scientists-clinicians-industry and government-supported partnerships to fast forward solutions and alleviate the suffering of a substantial proportion of our population.

Acknowledgements:

Organizers: Organization for Rare Diseases, India (ORDI) and TIGS, Bengaluru

ORDI is a national umbrella organization representing the collective voice of all patients with rare diseases in India, setup as a section 25 non-profit company. It's mission is to be a strong united voice for all rare diseases in India, to reduce inequalities and ensure that people living with rare diseases have access to the same resources as any other population. Its vision is to ensure a better life for patients and families afflicted by rare diseases.

Scientific Committee:

- Dr. Alok Bhattacharya, Head, Scientific Advisory Committee, Organization For Rare Diseases India
- Dr. Rakesh Mishra, Director, Tata Institute for Genetics and Society
- Mr. Prasanna Shirol, Co-Founder & Executive Director
  Organization for Rare Diseases India.
- Dr. Sudheendra Rao, Scientific Advisor, Organization For Rare Diseases India
- Dr. Saveetha Meganathan, Senior Scientist, Lead Community Engagement Program,Tata Institute for Genetics and Society
- Dr. Deepti Chugh, PDF Neuroscience, IIT-Kanpur, Volunteer for Organization For Rare Diseases India

Organizing Committee:

- Dr. Sudheendra Rao, Scientific Advisor, Organization For Rare Diseases India
- Dr. Saveetha Meganathan, Senior Scientist, Lead Community Engagement Program,Tata Institute for Genetics and Society
- Dr. Deepti Chugh, PDF Neuroscience, IIT-Kanpur, Volunteer for Organization For Rare Diseases India
- Samir Sethi - President, Indian Rett Syndrome Foundation and Chairman, Advocacy Committee,Organization for Rare Diseases India
- Swamy C J Head - Operations, Organization for Rare Diseases India
- Dr. Pankaj Gupta, Senior Program Manager, Tata Institute for Genetics and Society
- Sham Bharadwaj – Communications Coordinator, Tata Institute for Genetics and Society
- Medappa P K – Assistant Manager – IT, Tata Institute for Genetics and Society

Minuting and compilation: Dr Surabhi Srivastava, TIGS.

Minuting support & review: Dr. Bhagyashree Kaduskar, Dr. Harvinder Khera, Dr. Jay Prakash Shukla, Dr. Shivranjani C Moharir, and Dr. Vasanth Thamodaran (TIGS).

PAG minutes: ORDI team

Critical review: Dr Surabhi Srivastava, Dr. Saveetha Meganathan, and Dr. Rakesh Mishra (TIGS).

Participants at REDRESS 2022

Appendix 1: List of disorders covered under the 6 groups in the ICMR's National Initiative for RGDs

Group 1	Storage Disorders	Gaucher's disease, MPS disorders, Pompe's disease, Fabry's disease, GSDs (I & II)
Group 2	Small Molecule IEMs	PKU, HCU, Tyrosinemia, Citrullinemia, OTC, MSUD, MMA, GAI, Galactosemia
Group 3	Hematological Disorders	Hemophilias, Thalassemias, Sickle cell disease,
Group 4	Skeletal Dysplasias	Osteogenesis Imperfecta, Achondroplasia
Group 5	Primary Immune Deficiencies	SCID, Pan Hypogammaglobulinemia
Group 6	Neuromuscular Disorders	DMD, SMA, LGMD

Appendix 2: Examples of disorders causing developmental abnormalities that affectthe Indian population

S. No.	Name of disease	Symptoms
1	Shula Verma Naumoff Syndrome	Autosomal recessive disorder characterized by short rib thoracic dysplasia with or without polydactyly, with mutation in DYNC2H1 gene
2	Faundes Banka Syndrome	Autosomal dominant disorder characterized by developmental delay, microcephaly with mutation in EIF5A gene
3	Shukla Vernon Syndrome	Developmental delay and behavioral abnormalities including autism spectrum disorder and ADHD with mutation in BCORl1 gene
4	Shah Waardenburg Syndrome	Pigmentary abnormalities of hair, skin and eyes, congenital sensorineural hearing loss with mutations in EDNRB, EDN3 or SOX10 gene
5	Shashi Pena Syndrome	Autosomal dominant disorder characterized by delayed psychomotor development, variable intellectual disability with mutation in ASXL2 gene
6	Chopra Amiel Gordon Syndrome	Autosomal dominant characterized by development delay, speech delay nonspecific brain abnormalities with mutation in ANKRD17
7	Hardikar Syndrome	X linked dominant syndrome characterized by obstructive liver and kidney disease, intestinal malrotation, genitourinary abnormalities, pigmental retinopathy with mutation in MED12 gene

Appendix 3: Digital Health Initiatives at AIIMS, New Delhi

- AI-based web application as a remedial intervention program for dyslexic children.
- Tools for autism diagnosis (http://pedneuroaiims.org/inclen-tool.html). The webpage provides information useful to doctors, patients, caretakers, and parents in English and Hindi.
- PedNeuroAiims Diagnostics App for Epilepsy, Autism, Attention-deficit/hyperactivity disorder (ADHD), and Neuromotor impairment (NMI).
- Apps such as Exon Map explorer to help DMD.
- Child neurology helpline and tele-neurology via toll-free number services.

Appendix 4: Funding schemes from BIRAC (for research as well as drug trials)

- BIRAC is a DBT Section 8 company that supports translational research in industries and some specific programs for academic institutes as well. It provides support from ideation till commercialization through a series of schemes like BIG, SBIRI, BIPP, and PACE, as well as calls on digital health for RGDs.
- BIRAC also encourages projects in the field of drug development including small molecules, repurposing, *in vivo* and *in vitro* models, preclinical models, biosimilars, gene therapy, cell therapy, stem cell therapy, and CRISPR-based therapy. Projects such as for antisense therapy for Gaucher's, Neiman's disease and DMD are already being funded by BIRAC, although gene therapy projects for RGDs have not yet been funded.
- Currently BIRAC is focussed on indigenous drug development, creation of biomaterials - such as constructs and delivery vectors - refining technology processes, disease model development and drug testing. This is to support a low-cost pipeline where each component would otherwise add to the cost, and increase reliance on imported drugs. In the case of repurposed drugs, phase 3 trials can directly be initiated (as long as the route of administration remains the same). BIRAC has programs that support late stage validation by industry, such as some examples under the Biotechnology Industry Partnership Programme (BIPP).