

TATA INSTITUTE FOR GENETICS AND SOCIETY









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OVERVIEW

The Tata Institute for Genetics and Society (TIGS), founded in 2017, is a non-profit research institute that aspires to develop solutions to challenges in human health and agriculture. TIGS is a unique initiative of the Tata Trusts to support, in a major way, applications of cutting-edge science and technology in genetics and genomics to solve societal problems of the country.



Research programs at TIGS are focused on the following broad areas:

1. Infectious Diseases: The Infectious Diseases program studies vectors, pathogens, and their relationship to humans and the environment. The program includes understanding how vectors, such as mosquitoes, interact with their environment and adapt, which would help devise strategies to control them; employing environmental surveillance to understand the prevalence of disease-causing pathogens; and developing strategies to reverse the threat of antibiotic resistance.

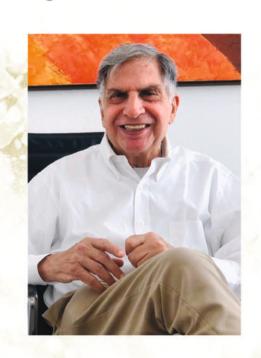


TIGS has also been working towards establishing technology platforms that facilitate cutting-edge research and training in the country. The institute houses a state-of-the-art, world-class insectary that supports research on mosquito biology, disease transmission, parasite interactions, population dynamics, etc. We are also building platforms for protein therapeutics, mRNA and cell-based therapeutics, and diagnostics development.

TIGS' research efforts are synergized by valuable scientific associations that it has established with institutes and researchers across the country. These associations bring together exceptional talent and know-how, thus accelerating and amplifying its resolve in tackling some of the big challenges in human health and agriculture. The institute is also deeply invested in engaging with society and disseminating scientific knowledge among communities through socially conscious community engagement programs and science communication. It is equally important to create platforms for regulatory and policy aspects to ensure that the benefits of advanced and safe technologies are not ignored. Through these efforts, TIGS endeavours to fulfil its vision of synergising visionary philanthropy and outstanding science to serve humanity.



"Recent advancements in genetics and genomics have the potential to solve some of the most complex challenges in agriculture and healthcare and create significant societal value. The Tata Institute for Genetics and Society was established with this vision and I am pleased to note that the institute continues to focus on research in the areas of crop improvement, food security, point of care diagnostics and modern therapeutics"







DIRECTOR'S MESSAGE

With each passing year, we are seeing incredible advancements being made in science and technology. Cures and effective treatments for debilitating genetic diseases, mitigation strategies for infectious diseases, and the means to ensure food and nutritional security for a burgeoning global population are now within our reach. TIGS was established on the idea of translating the progress we have seen in fundamental research to technologies that can be used to solve problems and improve people's everyday lives. The Tata Trusts, with its incredible legacy of being a pioneer in supporting social and economic development in India through multiple philanthropic ventures, recognised the significance of this undertaking and generously contributed to establishing TIGS as a significant institution that serves as a conduit between path-breaking scientific and technological research and the needs of vulnerable and disadvantaged populations in India.

Advances in genomics have not only given us access to the genetic blueprint of any species on the planet but have also made it possible for us to access genomic details at population scale. This, when put in the perspective of phenotypic correlations, will pave the way for precision and personalised medicine. This is not too far from becoming routine practice. Furthermore, genome editing technologies allow us to change the genetic code with ultimate precision, which enables cell and gene therapy on the one hand and improvement of crop and livestock on the other.

TIGS is a novel innovative concept that channels philanthropic resources to nurture a much needed connect between science and societal needs. We identify problems and use the latest science and technological means to provide solutions to these problems. To achieve this in the shortest possible time and be effective, our in-house team collaborates with and involves committed scientists from a variety of organisations across the country.



The progress we are making in fundamental and applied research needs the support of a robust policy framework that facilitates the translation of beneficial technologies into societal impact. It is important to work with policy makers and regulators to advocate for the use of safe and efficient technologies that have shown promise in improving health and nutrition. We must ensure that India is not left behind in harnessing the benefits of scientific knowledge. It is also pertinent to create awareness among the public and various stakeholders for broad acceptance of safe technologies that are key to creating a healthy ecosystem for society and environment.

Rakesh K Mishra

Director, TIGS



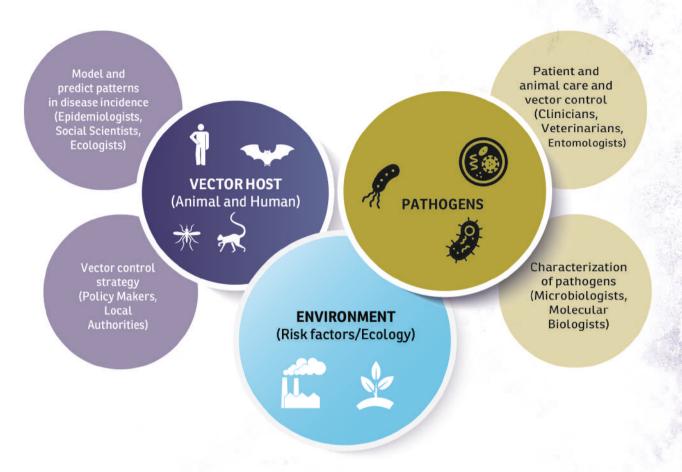
1. RESEARCH PROGRAMS

From its inception, TIGS has made conscious efforts to develop interdisciplinary research and coalitions of science-based groups with humanitarian values. In this milieu, our scientists work on the following thematic areas.

1.1 Infectious Diseases

The emergence of virulent infectious pathogens (viral, parasitic, or bacterial), antimicrobial resistance (AMR), and lack of adequate surveillance are serious evolving threats to human and animal health.

We integrate human health with disease ecology using a transdisciplinary strategy — a One Health approach, which recognizes that the health of people is closely connected to the health of animals and our shared environment. Animal species provide a shared reservoir for pathogen exchange and spread, and many emerging infectious diseases (EIDs) are driven by varied and dynamic human-animal interactions. Using a collaborative, multisectoral, and transdisciplinary approach, we aim to work with various stakeholders to mitigate the risks of emerging zoonotic and infectious diseases.



Infectious diseases have at least three components embedded in the broader context of the environment and ecology of disease. These components include animal health, behaviour, and environmental change/disruptions.

1.1.1 Disease Ecology

The field of disease ecology encompasses the ecological study of host-parasite interactions within the context of their environment and evolution, and this is fundamental to the One Health strategy. Here we strive to understand the mechanism and scale of pathogen impacts at individual, population, and community levels. We take an interdisciplinary approach drawing on genetics, molecular ecology, epidemiology, and modelling to understand how biological, social, and physical aspects of environment can influence disease transmission, intensity, and distribution. We aim to gather information that can help design effective vector control strategies, map disease ecology at the local scale for vector-borne diseases such as dengue, malaria, chikungunya, and zoonoses such as scrub typhus in India.



1.1.2 Environmental Surveillance

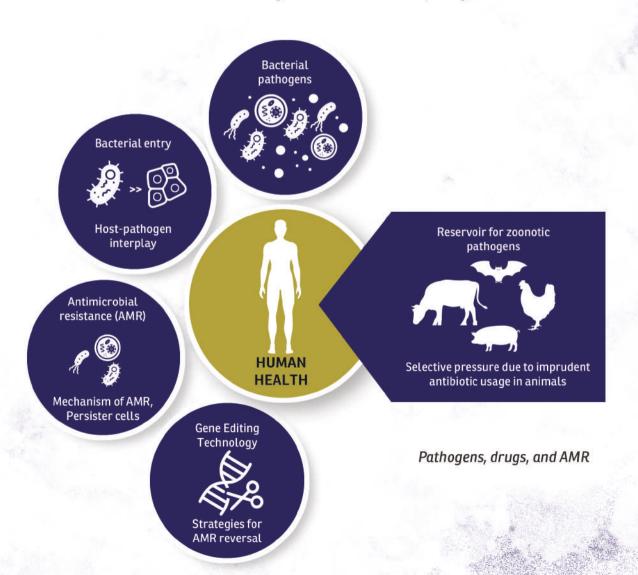
Environmental surveillance offers a powerful tool for monitoring disease in a population by detecting pathogens, shed by infected individuals or in host and vector species. Vector-pathogen interactions are key to understanding the transmission and epidemiology of vector-borne diseases. We aim to track the rise and fall in pathogen prevalence and diversity using sewage wastewater-based epidemiology (WBE), soil samples, and human infection data. The COVID-19 pandemic has brought WBE to the forefront of monitoring strategy. It is a particularly effective and promising opportunity for a populous country like India where lack of health surveillance has been a major problem; wastewater testing can provide an unbiased snapshot of community health.

We aim to identify circulating pathogens by metagenomic approaches to get a granular map of the pathogen landscape in India. For example, by tracking SARS-CoV-2 using wastewater-based epidemiology we aim to track the progression of the COVID-19 pandemic and to understand its relationship with community testing. This will also be applied to other viral pathogens, e.g., hepatitis A virus, rotavirus, poliovirus, etc. Similarly, AMR is a complex problem with multiple and interconnected drivers, which may include changing dynamics in travel, trade, climate change, and populations. Most studies on antibiotic resistance have concentrated their efforts on human pathogens and in human-linked environments (hospitals, human hosts). However, the full understanding of the origin, evolution, spread, and maintenance of antibiotic resistance requires an integrative approach in which all ecosystems that may contribute to such evolution are studied, modelling a One Health approach. Our final objective is to set up environmental surveillance across sewage networks and build models that link spill over and its spatial and temporal monitoring through such surveillance.



1.1.3 Antimicrobial Resistance

Bacterial pathogens such as *Pseudomonas aeruginosa*, *Salmonella*, *Shigella*, and pathogenic *Escherichia coli* (EPEC and EHEC) cause life-threatening diseases, particularly in young children and immuno-compromised individuals. This, combined with the wide spread of AMR, has made bacterial infections a major public health crisis all over the world. We are investigating health linkages between humans, animals, and their shared environments. With AMR among bacterial pathogens reaching an all-time high, it has been characterised as a 'silent tsunami' by the World Health Organization (WHO). A careful examination of our approach towards countering the multifaceted complex problem of multidrug resistant pathogens is needed as the rise of antibiotic failure poses a severe threat to global health. There is growing concern that this failure is not solely driven by stable antibiotic resistance but also by a subpopulation of transiently non-growing, antibiotic tolerant bacteria, called 'persisters', that are thought to seed relapsing infections. At TIGS, we are developing a strategy to isolate and characterize these persister forming bacteria. It will pave the way to specifically target persister cells without the use of any further antibiotics. Eventually, we aim to turn our research into innovative strategies to counter bacterial pathogenesis and AMR.

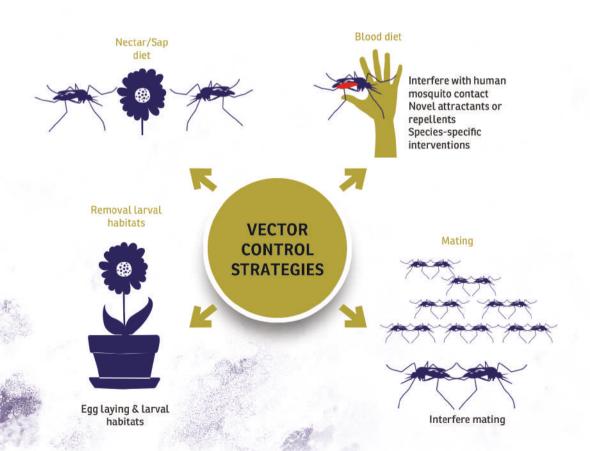


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1.1.4 Vector Control

Many infectious diseases are transmitted via an obligatory insect vector host for the successful completion of the pathogen's life cycle. Managing such vector-borne diseases effectively involves dealing with a triad of players — the human host, the pathogen, as well as the vector. Mosquitoes are one such vector. We seek to use evidence-based understanding of the behaviour, biology, and ecology of mosquitoes to develop better, more specific, and ecologically responsible means of controlling mosquito vectors. This is a challenging problem and requires a tiered approach.

The first tier is environmental engineering – we seek to understand what features in our environment support and sustain or deter mosquito populations at the larval and adult stages. In a second approach, we seek to improve methods that reduce mosquito-human encounters. For this, we use our knowledge of the chemical ecology of mosquitoes as well as tap into traditionally used deterrents to identify novel compounds that either attract or repel mosquitoes. In our third tier, we seek to use specific molecular knowledge of mosquito species to intervene in its behaviour, particularly the host seeking and mating behaviours. We aim to apply both modern and traditional knowledge in this context to develop specific and ecologically responsible interventions.



1.2 Rare Genetic Disorders

Genetic disorders are far from rare in India, owing to the high population density in the country, which translates to a higher disease burden. Due to the prevailing cultural/social practice of consanguineous marriages that contribute significantly to the accumulation of founder mutations in the population, the numbers predicted for India could be a gross underestimation.

Rare Genetic Disorders (RGD): The definition of RGD differs in different regions. For example, in the European Union, it is defined as 1 in 2,000 and in the United States, as fewer than 1 in 200,000. In India it remains to be settled. The National Policy for Rare Diseases (NPRD) emphasized the need for systematic epidemiological studies to estimate the incidence and prevalence of genetic diseases in India.

5000-8000 rare genetic diseases have been identified globally, 450 of which have been reported in India. Difficulties involved in reaching out to widely dispersed carriers or patients and absence of point-of-care diagnosis adds to the complexity in tackling these disorders at an early stage.

Number of people affected by rare diseases		
Region	Population (in million)	Population afflicted with rare diseases (in million)
USA	330	25 – 30
EU	447	30
India	1380	72 – 96

We take multiple approaches to reduce the rare genetic disease burden. One approach is to develop diagnosis that can be used for screening at population scale. In parallel, we also aim for indigenization and development of low-cost / affordable interventions, which are currently out of reach for average individuals.





1.2.1 Carrier Screening

Carrier screening is genetic testing on a target ethnic population or families of patients, who do not show any overt physical attributes associated with the genetic disorder, which helps in identifying asymptomatic carriers of the genetic disease.

TIGS aims to facilitate carrier screening of rare genetic disorders like β -thalassemia and spinal muscular atrophy (SMA). In collaboration with specialized institutes, non-governmental organizations (NGOs), and industries, genetic counselling can be offered to at-risk couples and individuals. This will be crucial to decrease the incidence of children born with defects.



1.2.2 Diagnosis

Diagnosis of rare genetic diseases is another challenge faced by our country. Accurate and early diagnosis is critical for saving lives, especially in the case of rare genetic diseases. Poor (absent or inaccurate) diagnosis remains a healthcare challenge. Major hurdles in this area include a) high-cost and b) non-availability in rural settings because of technology and skilled labour-intensive diagnostic assays.

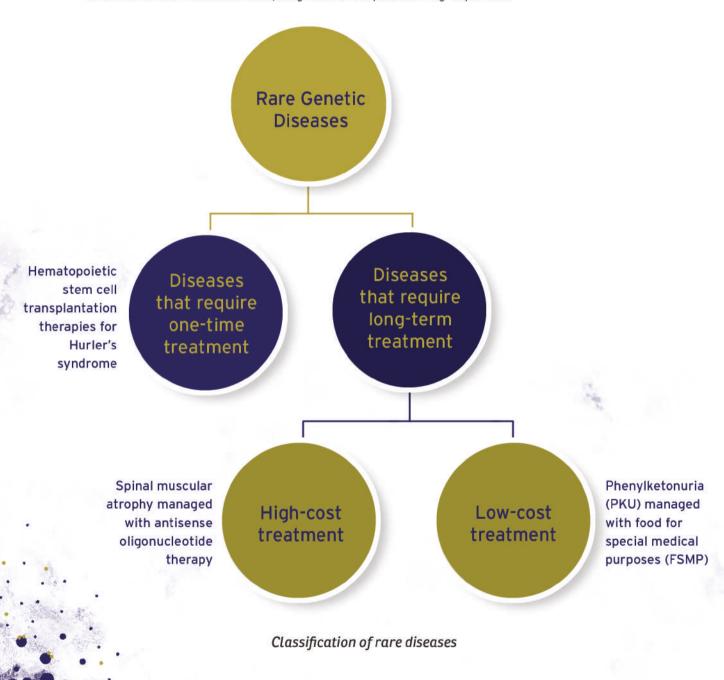
To address the existing diagnostic gap, we aim to develop a platform for novel point-of-care, largely DNA based, diagnostic solutions using the latest cutting-edge technologies that are rapid, robust, affordable, and accessible. For example, genetic diseases caused by single or multiple mutations can be detected by CRISPR-based diagnostic assays. Currently available tests for many RGDs are too expensive and resource-intensive to implement for large-scale testing. Our aim is to ensure that such tests are accessible and affordable enough for population-scale implementation



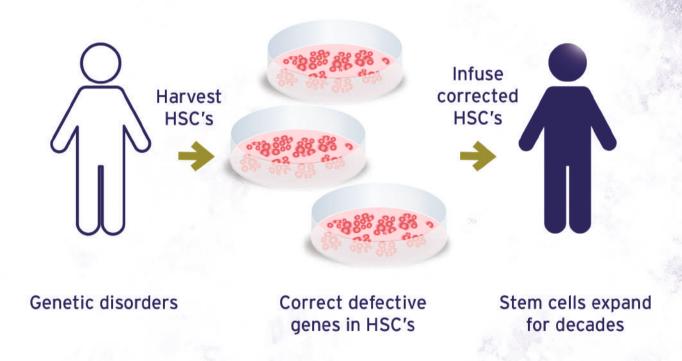


1.2.3 Treatment

There are no approved treatment regimens available for ~95% of RGDs. They are the 'orphan diseases', as pharma companies rarely venture into this area due to poor profitability. Further, when treatments are made available, they tend to be prohibitively expensive.



TIGS aims for indigenous cost-effective production of molecular therapeutics, such as enzymes and mRNA for lysosomal storage diseases (LSDs). Point-of-care production of enzymes that are defective in LSDs like Fabry, Pompe, and Gaucher can significantly reduce the cost of treatment, with indigenous production, increasing accessibility to the patient population. With new advancements in mRNA therapeutics, treating LSDs will have many advantages including reduced dosing intervals and improved efficacy as compared to the standard of care. At TIGS, we also aim to use genome editing approach to correct defective genes in autologous patient hematopoietic stem cells (HSCs) for LSDs and hemoglobinopathies. HSCs residing in bone marrow are multipotent with self-renewal capacity and an ability to differentiate to different types of blood cells. Bone marrow transplantation has been extensively used in treating genetic disorders like hemoglobinopathies. Though the gene editing approach to treat hemoglobinopathies has the potential to work in the Indian context, the treatment cost of about Rs.50 lakhs, makes this life-saving treatment less accessible. We aim to engineer inexpensive processes to enable affordable access in a clinical set up.





1.3 Crop Improvement

In the face of climate change and an increasing global population, food security and nutrition have become some of the biggest challenges of the day. We need to innovate and implement different approaches to improve nutritional quality of food grains, reduce crop losses due to diseases and pests, and develop varieties that can tolerate the changing environment. The bright side is that promising tools are available for crop improvement, such as conventional plant breeding, mutation breeding, and genome editing technologies, which can be harnessed to achieve sustainability in agriculture.



Rice is one of the most important staple food crops, and India is the second largest consumer of rice. Worldwide, more than 2 billion people are affected by malnutrition, and this is linked to dependence on cereal grains that lack substantial amounts of nutrients. Mutation breeding offers an excellent opportunity to identify crop lines that show improved grain nutrient values.

Rice is susceptible to many diseases and pests. It also requires huge quantities of freshwater, accounting for more than half the freshwater used in agriculture. Biotic stress tolerant varieties that can be cultivated under non-puddled conditions (direct seeding and aerobic cultivation) are highly desirable.

Mutation breeding and genome editing approaches could enable us to create random and targeted mutations, respectively, in native genes for creating better and desirable agronomic traits. Therefore, the successful development of rice lines with improved grain nutrient values and with important biotic and abiotic resistant traits through mutation breeding and genome editing approaches are the future pathways in agricultural sciences.

At TIGS, we work with plant breeders to identify rice varieties that can be improved through genome editing. For example, we edit sties in the genome of selected cultivars, which make them resistant to diseases and pests and tolerant to herbicides. We also work with collaborators to identify rice mutant lines with improved nutrient values and low glycemic index values by screening ethyl methanesulfonate (EMS) or gamma irradiated rice populations. Such modified cultivars will not only contain the desired qualities that traditional breeding offers but will also be less susceptible to diseases, pests, and herbicides and have improved nutrient values.

Our aim is to develop rice cultivars with disease and herbicide tolerance traits using genome editing technology and develop cultivars with improved nutrient values using the mutation breeding approach. These lines would have enhanced yield under aerobic and irrigated conditions, thus increasing productivity and improving grain nutrient values. Lines improved for individual traits and/or stacked lines can serve as excellent donor material for transferring disease and herbicide tolerance and improved grain nutrient values to any other elite rice cultivars by breeders. While we are currently working on rice, these approaches can be extended to address some of the issues associated with disease and pest incidence and nutritional quality of other crops such as pulses and millets.

2. FACILITIES AND TECHNOLOGY PLATFORMS

While we collaborate extensively to find solutions to problems, we also recognise the significance and need for key facilities and technology platforms inhouse to facilitate these activities. The following are the major and often unique world-class facilities and technology platforms that we maintain at TIGS centres.

2.1 Insectary

Mosquito-borne diseases such as malaria, dengue, Chikungunya, Japanese encephalitis (JE), lymphatic filariasis, and Zika have a significant impact on public health causing morbidity and mortality.

The development of strategies to control mosquito vectors requires thorough understanding of their biology, ecology, behaviour, and vector bionomics. We have developed a state-of-the-art Insect Bio-safety Level 2 (IBSL-2) and IBSL-3 containment facility at TIGS to support contemporary research on insecticides, repellents, attractants, vector development and physiology, disease transmission, host-parasite/pathogen interactions, life histories studies, population dynamics, behavioural genetics, ecological interactions, and related subjects.

The facility has walk-in controlled environment rooms that mimic the dawn-dusk cycle; interlocking doors, insect traps, and negative pressure to retain any stray mosquitoes; high efficiency particulate air (HEPA) filtered inlet air with 70% air re-circulation; separate autoclave and decontamination rooms for the safe-disposal of bio-hazard waste; separate building management system with 24x7 CCTV surveillance, environmental chamber for controlled small-scale experiments; parasite culture facility; and microinjection workstations with laser needle pullers and beveller for bio-manipulation of mosquitoes and other insect pests. The Insectary is managed by a team of skilled vector biologists who have extensive experience and are engaged in national and international collaborations.

2.2 Therapeutic Platforms

Therapeutic platforms for protein, RNA, and cell-based therapeutics can facilitate proof-of-concept studies for the development of innovative treatment strategies. The specificity of biotherapeutic platforms makes it popular for the treatment of some diseases refractory to small molecule therapy. TIGS has developed these platforms that include instrumentation and knowledge expertise, aiming to accelerate early research for quick transition to the development of a treatment modality.

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2.2.1 Protein Therapeutics Platform

Therapeutic proteins of interest will be expressed in periplasm, cytoplasm, or secreted into the supernatant of the cell-culture based on the nature of the protein, in bacterial, yeast, insect, and mammalian systems. This is followed by multi-step purification of recombinantly expressed proteins with affinity chromatography, cation/anion exchange chromatography and size exclusion chromatography employing fast protein liquid chromatography fplc. The process will be optimized for high level expression and purification of homogenous proteins, for end applications. Purified proteins can be characterized with biophysical and biochemical techniques like circular dichroism (CD), differential scanning fluorimetry (DSF), differential scanning calorimetry (DSC), and functional assays. The end-to-end capabilities include expression construct generation, expression, purification, and characterization, including optimization of the process of protein production, which can be translated for good manufacturing practice (GMP) scale manufacturing.

2.2.2 mRNA Therapeutics Platform

Messenger RNAs (mRNAs) are a fast-emerging class of biotherapeutics. mRNA therapies offer a new opportunity for targeted treatment of challenging diseases and flexible manufacturing, as demonstrated by the rapid development of mRNA vaccines against COVID-19. They are non-infectious, non-integrating, and cell-free, offering both rapid and readily scalable production with high productivity. Our team at TIGS will be working on improving the purification of synthesized mRNA and developing alternative lipid formulations for improved encapsulation and stability, using specialized devices for encapsulation and high throughput assessment of lipid formulations.



2.2.3 Cell-Based Therapeutics Platform

Induced pluripotent stem cells (iPSCs) developed from patients have enabled the investigation of disease mechanisms in the lab without dependence on animal models, which do not always mimic human disease conditions. As the cells differentiated from patient iPSCs also show the disease phenotype, they have proved valuable in drug screening and testing. However, obtaining patient samples can be marred with ethical concerns, sample accessibility, and the mutation from a specific patient may not represent the most prevalent disease variant. Using genome editing, it is now possible to disrupt a gene function by introducing the mutation of interest and to correct a disease associated mutation. Therefore, to study a specific genetic disorder, the mutation of interest can be introduced in the target gene in a pluripotent stem cell derived from a normal donor. Once generated, the cell line can be differentiated to lineages to study disease pathogenesis or drug screening.

We aim to generate pluripotent stem cell models to study lysosomal disorders. Using the CRISPR-Cas gene editing tool, mutations that are widely prevalent in India will be introduced in pluripotent stem cells derived from normal donors. The cell lines carrying the disease associated mutation will then be differentiated to lineages affected by this disorder to study the disease pathogenesis. The disease models can also be used for testing biotherapeutics and drug screening.



2.3 Diagnostics Development Platform

Setting up an effective public health system to prevent, detect early, and respond to adverse health events requires good surveillance in conjunction with sensitive, economical, and readily available diagnostic options.

The availability (or lack thereof) of diagnostic healthcare in rural India is a pressing issue. In rural India, there is a dearth of good, well-functioning licensed laboratory services. Translational research towards the development of new and improved diagnostics is the need of the hour.

FRUGAL SCIENCE Developing low-cost

point-of-care diagnostics solutions

BIOMARKER IDENTIFICATION

Identifying disease biomarkers with OMICS and AI-ML based approaches

LATEST **TECHNOLOGY**

CRISPR **Aptamers Antibodies** Microarray Lateral Flow Strips Microfluidics RDT kits

Involving stake holders from the beginning (clinicians and industry partners)

DIAGNOSTIC PLATFORM

Commercialization of technology reaching the end-user (patents) TIGS is developing platforms for novel, low-cost, point-of-care diagnostic solutions that are rapid, robust, affordable, and accessible to the remotest parts of the country. We are currently focused on developing CRISPR-based diagnostic solutions for malaria and tuberculosis, as they remain major infectious diseases in our country, and rare diseases. India accounts for 27% of global tuberculosis cases, one fourth of which are drug resistant, and 3% of global malaria cases. There are several disadvantages to the current rapid diagnostic test-based detection of malaria, and drug-resistant tuberculosis detection takes several weeks. Similarly, for rare diseases, diagnosis using sequencing or multiplex ligation-dependent probe amplification (MLPA) after the observation of symptoms is quite expensive and requires infrastructure and expertise.

The following are the activities under the diagnostic platform:

- Development of diagnostic platforms for assays like lateral flow, microarray, fluorescence, microfluidics, etc.
- Development of innovative devices, point-of-care devices that are high-end tech-based but affordable and expandable.
- Development of miniaturized diagnostic or handheld devices for point-of-care diagnosis as well as surveillance programs.
- Development of rapid diagnostic kits for various infectious and rare diseases.
- Biomarker identification using OMIC-based and artificial intelligence and machine learning-based approaches for diagnostics.

3. COMMUNITY ENGAGEMENT AND HUMANITARIAN TECHNOLOGY

TIGS is driven by a goal to integrate scientific advancements with a holistically developed community engagement program to engage with local communities in India with the fundamental aim of achieving health equity and nutrition security. We are committed to building socially conscious and ethically bound research programs to develop humanitarian technologies that will systematically benefit; strengthen and serve the Indian society; and bring forth beneficial impact in the lives of the resource poor and vulnerable communities.

In this pursuit, TIGS aims at proactive community engagement that will entail amplifying, addressing and allaying community concerns through consistent and clear science communication and practices of societal interface. Further, TIGS is committed to dissemination of scientific knowledge to differently literate communities using innovative tools, thereby attaining social inclusion to processes of scientific advancements. This process requires building trust with communities; networking with humanitarian groups; developing global coalitions and networks to create communication channels to share resources; and enabling efficient technology transfer to stakeholders.

It is evident from global scientific research practices that community engagement is a very relevant process and reinforces positive impact when there is a need to address complex societal challenges such as: 1) affordable and efficient health care technologies and epidemiological surveillance in the realm of Infectious Diseases, 2) cost efficient precision diagnostics and therapeutic treatments for Rare Genetic Diseases, and 3) developing nutrient rich local food crop varieties that can be a solution to impending threats of droughts and famines.

TIGS has also established several training programs to engage and mentor students in the life sciences. These programs are designed to develop valuable skills necessary in academic research and subsequently build scientific temper.

TIGS aspires to be a pioneering research institute in India to deepen the relationship between scientists and recipient communities of their research by serving as a catalyst to bring forth pathbreaking developments in technologies. This pursuit will predominantly consist of using indigenous materials and developing sustainable humanitarian technologies that could be easily accessible and affordable to local communities and gain fruition in terms of contributing to achieving health equity and nutrition security in India. Subsequently, to be at par with global excellence in the field of genomics and its allied technologies, the vision of TIGS as a socially conscious scientific research institute is an asset to India. Such dynamic and socially serving scientific research can contribute towards modelling and scaling technological solutions to address issues faced by developing countries.







