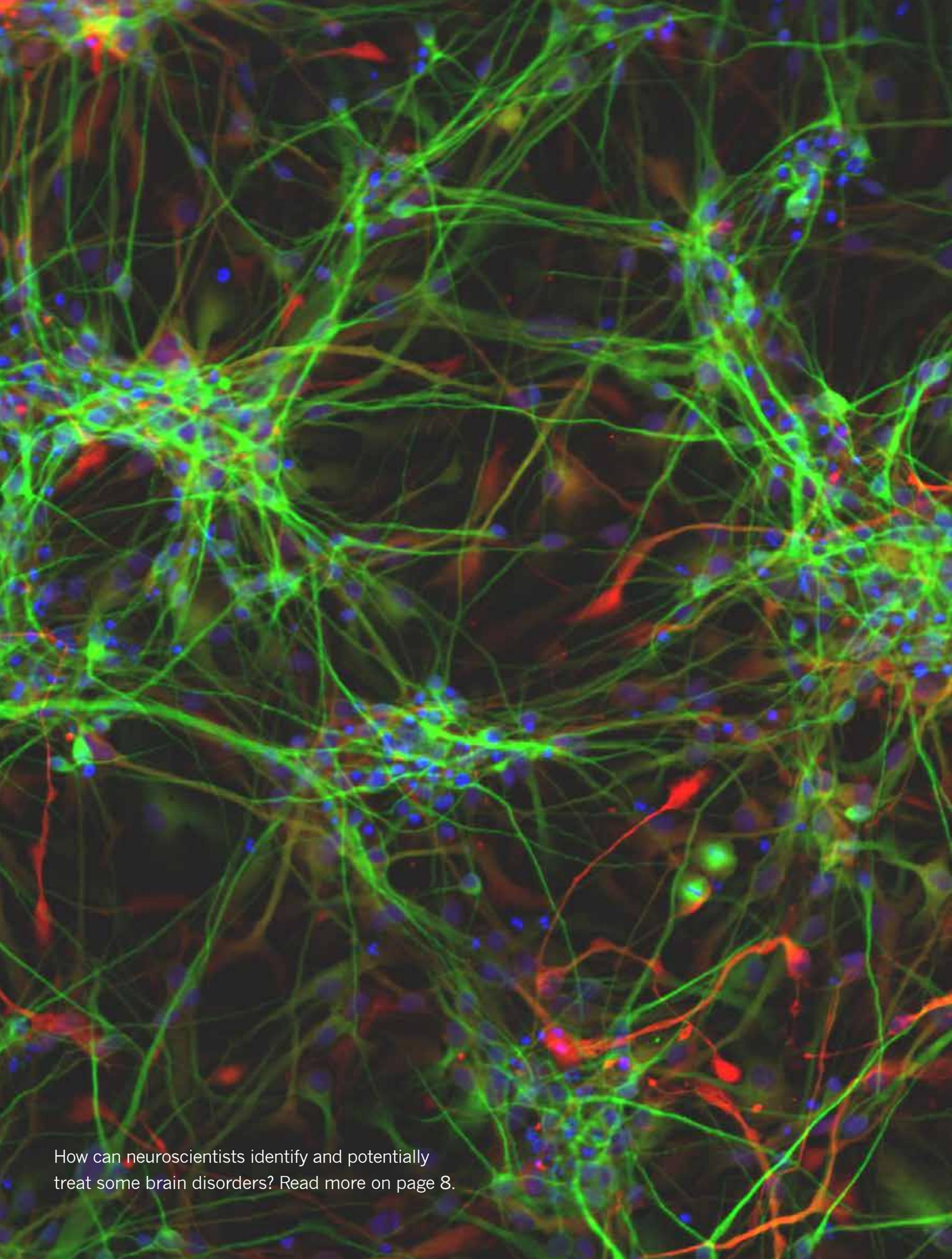


Changing the Practice of Medicine

The Novartis Institutes for BioMedical Research



How can neuroscientists identify and potentially treat some brain disorders? Read more on page 8.

Novartis Institutes for BioMedical Research

Who We Are

The Novartis Institutes for BioMedical Research (NIBR) is the global drug discovery engine for Novartis.

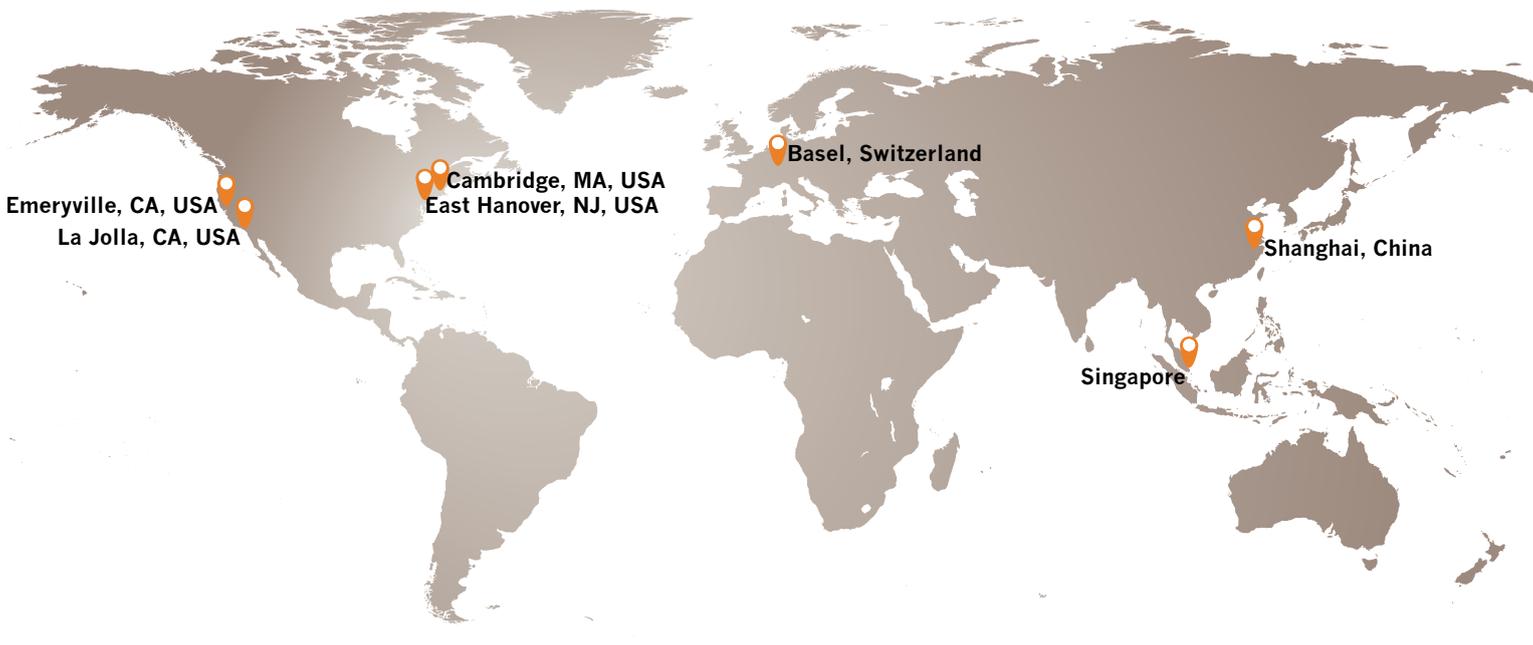
We have more than 6,000 research scientists, physicians and business professionals at seven research sites around the world who are focused on one goal – to discover new medicines that will change the practice of medicine.

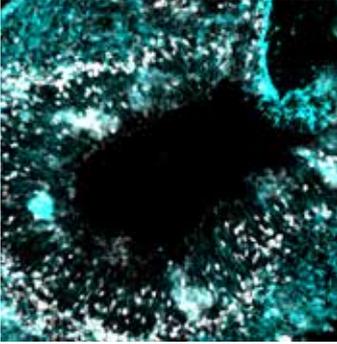
“Breakthrough medicines arise from a deep consideration of biology, a long horizon of committed research, the proximity of technology innovators, and a climate that breeds champions.”

— Jay Bradner
President, NIBR



Talented people and their ideas drive drug discovery. Talent tends to cluster in regions where there is sustained funding and infrastructure for basic research. Recognizing this, NIBR has strategically focused its geographic footprint in the leading life science clusters in the U.S., Europe and Asia. This gives us an advantage for recruiting and easy access to talent from academia and biotech for collaborations.



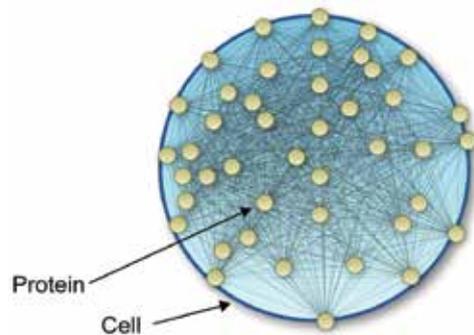


Our research strategy is driven by:

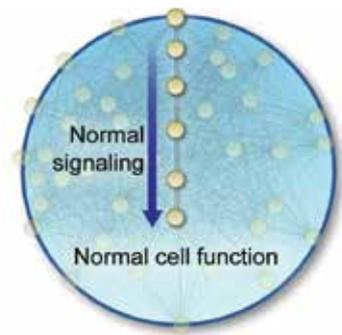
1. Unmet medical need: An unmet medical need does not mean a potential market. It means a patient or group of patients who desperately need a medicine. We start all of our projects thinking about how to get the safest medicines to the right patients as quickly as possible.

2. Scientific understanding of disease mechanism: Across all of our disease areas we work to map complex protein signaling networks inside cells known as molecular pathways. Mapping these pathways and identifying key nodes in them gives us insight into how various diseases might work.

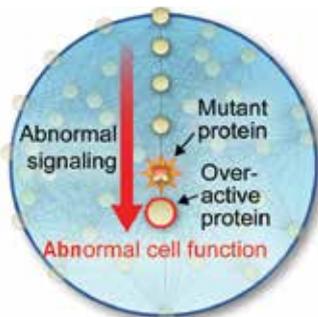
1. The interconnected proteins in molecular signaling pathways are responsible for normal cell function.



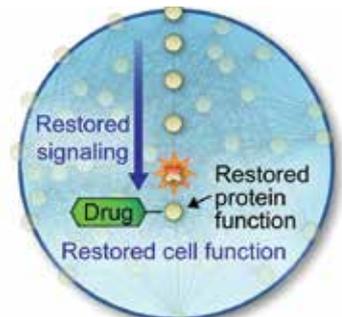
2. The proteins receive and send “molecular signals” along a “pathway.” The signals tell the cell how to function and guide it through its life cycle.



3. When anything goes awry in a pathway, it can cause disease.



4. Novartis works to develop drugs that will restore normal pathways and treat disease.



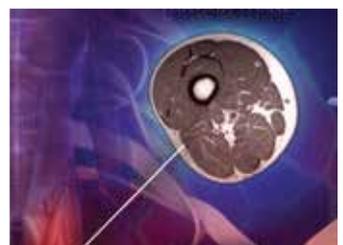
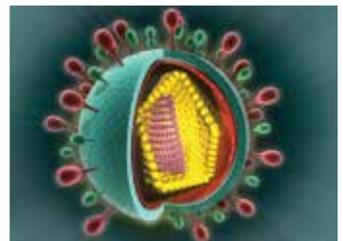
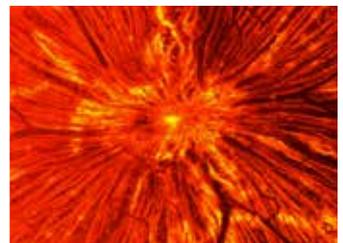
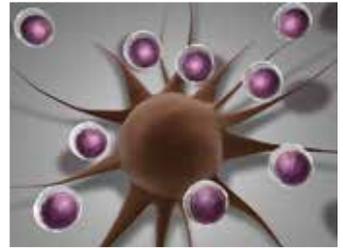
Drug Discovery

We currently have **leading edge research** to address the biggest health challenges the world is facing today.

- **Oncology.** Cancer is the second leading cause of death, according to the World Health Organization. Our oncology research team is fueling one of the most robust cancer therapy pipelines in the industry with 22 drugs on the market and 25 more under development.

We are focused on developing new mono and combination therapies to target a wide variety of cancers by using “big data” and next generation sequencing to create personalized therapies that identify and attack a patient’s specific cancer tumor.

- **Immuno-oncology.** We are also exploring how to harness the body’s immune system to fight off cancer. Our immuno-oncology portfolio includes chimeric antigen receptor (CAR-T) technology, novel checkpoint inhibitors, and STING modulators. Recent deals add IL-15, adenosine receptor and TGF- β inhibition programs.
- **Auto-immune and inflammatory disorders.** Many diseases share immune pathways. Among our disease targets are Psoriasis, Rheumatoid Arthritis, Sjogrens Syndrome, and systemic lupus erythematosus.
- **Aging and Regenerative Medicine.** Helping the growing Aging population stay strong and mobile is our goal. Focusing on regenerative medicine, we are actively seeking solutions for vision loss, hearing loss, and muscle and tendon weakness.
- **Neuroscience.** Building brain models, our Neuroscience team is exploring new medicines for psychiatric (Autism, Schizophrenia, Bipolar disorder), neurodegenerative (Alzheimer’s disease and Spinal Muscular Atrophy) and neuro-inflammatory diseases.
- **Drug-resistant bacteria.** Our Infectious Disease research team is trying to optimize known classes of antibiotics, so that physicians have additional tools to fight infections as soon as possible. Researchers are creating wholly new generations of antimicrobials, capable of penetrating the membranes of heavily armored superbugs resistant to current therapies.
- **Rare diseases.** These are often genetically well-defined. They address clear unmet medical need and can allow faster entry to the clinic. Spinal Muscular Atrophy, sporadic Inclusion Body Myositis and polymyositis are among more than 40 active preclinical and clinical rare diseases projects underway.
- **Diseases of the developing world.** We are focused on malaria, rheumatic heart disease, Human African Trypanosomiasis (HAT), Leshminiasis, and dengue.



Creating a Culture of Collaboration

Drug discovery is inherently complicated and no one company can do it all alone. It takes teamwork. Our scientists work globally in multidisciplinary teams and are actively engaged with the academic research and biotech communities outside of our walls. We have more than 100 biotech alliances and 300 academic collaborations.

Strategic Alliances

Our Strategic Alliances team serves as antenna into the biotech community to advance novel technologies and accelerate new fields. A few examples include:

Technology	Strategic Collaborator
CRISPR genome editing technology	Intellia Therapeutics and Caribou Biosciences
Cancer immunotherapy STING (stimulator on interferon genes)	Aduro Biotech
CTL019, CAR-T therapy program	University of Pennsylvania

Scientist-to-scientist relationships with academic and biotech collaborators are based on trust and shared interest rather than by funding at a distance.

Academic Relations

We have an in-kind collaboration mechanism that helps academics with their research by providing access to the latest platforms, technology and expertise they may not have, with “no strings attached.” We use simple minimal agreements that enable open sharing of data to initiate and execute projects easily. A few examples include:

In-kind Project	Academic Collaborator
Profiled compounds to advance Chagas Disease research	Stanford University
Assayed compound-target pairs to test a new targeted protein degradation method	Brandeis University
Shared unpublished data for chromatophore biology experiment	Boston Children’s Hospital
Tested kinase inhibitory activity of a natural product	ETH Zürich

Professional Development and Learning

Courage and collaboration are the hallmarks of our culture combining the boundless curiosity of academic research with the entrepreneurial spirit of a biotech company.

Our scientists are encouraged to dare greatly and have the freedom and resources to be bold, take risks and explore long-term efforts that focus on big scientific and clinical questions, address fundamental opportunities and expand directions.



Our culture of collaboration across the globe rests on our success in supporting diverse drug discovery teams, and developing skills in mentoring and coaching to improve scientific exchange.

We have exchange programs as short as a week or as long as three months for scientists to rejuvenate themselves by learning a new discipline or experiencing a new culture and work environment.

The mini-sabbatical program offers rotations for associates across our research sites interested in acquiring new skills and perspectives in their daily work. Associates return to their labs energized with fresh ideas and a more collaborative mindset.

The Developing World Sabbatical offers our scientists the chance to understand the medical needs of different cultural environments, and contribute to strengthening scientific capability. By building personal connections at local hospitals, research institutions and universities in Africa and other emerging markets, our researchers are better able to develop medicines that will help patients lead healthier lives.

Postdoctoral Program

Our postdoctoral program provides science scholars with a unique opportunity to perform both innovative and fundamental research in a pharmaceutical setting. Postdocs design and conduct their research with guidance from a principal investigator at Novartis, and an academic advisor where appropriate. Our postdocs present their work at major research conferences and aim to publish their results in leading peer-reviewed journals. We encourage applications from candidates who wish to pursue a career in academia or industry.

Gap Year Scholars Program

The Gap Year Scholars Program is a 2-year post-baccalaureate program for highly talented students from historically underserved communities. It provides research training opportunities to help students gain research experience and increase their competitiveness for top biomedical PhD and MD/PhD programs.





Developing world diseases bring additional challenges to drug discovery, such as stability under tropical conditions and access for patients living in poverty. Novartis is **committed to eradicating malaria**, which kills more than 600,000 people worldwide each year. Our researchers are driving the development of next-generation antimalarials. **Research in Singapore** and other NIBR sites is also focused on dengue fever, Human African Trypanosomiasis (HAT) — known as sleeping sickness — infectious diarrhea, typhoid fever, Leishmaniasis and Chagas disease.

Training the Next Generation of Scientists and Clinicians in Africa – Infrastructure, Education and Capability Development

NIBR is committed to advancing science and medicine capabilities in the developing world. We focus on building drug discovery, and preclinical and clinical research capacity through strategic collaborations between university and Novartis researchers with organizations in developing world countries. Not only do these collaborations help advance biomedical research, they serve as important learning platforms for Novartis that will pave the way to introduce new medicines in developing world countries.

- **Student Internship Program:** Three-month research training program for graduate-level students from emerging countries involving up to 25 Novartis host labs in Basel, Switzerland.
- **Fellows Research Program:** Three-month to one-year long research training program in Cambridge, Massachusetts for faculty from universities in South Africa, Nigeria, Kenya and Ghana.
- **Clinical Pharmacology Training and Phase I Study Sites in Africa:** Since 2012, several workshops in clinical pharmacology and early clinical phase trials have been delivered by Novartis faculty in multiple African countries, including Kenya, Ghana, Tanzania and South Africa. The South Africa study-site has tested a novel anti-malaria drug discovered by NIBR collaborator, H3D, a drug discovery center affiliated with Cape Town University. The Kenya site is used for an ACE-inhibitor PK study in Kenyan populations.

A Case Study: Treating Rheumatic Heart Disease (RHD) in Zambia

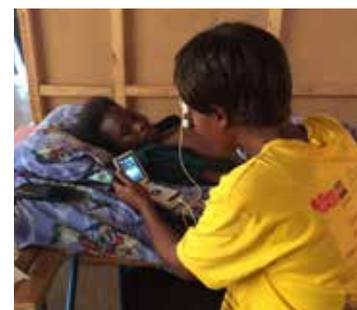
Rheumatic heart disease, which is caused by untreated streptococcal throat infection, is a common disease in developing countries. It mostly afflicts children and is frequently neglected.

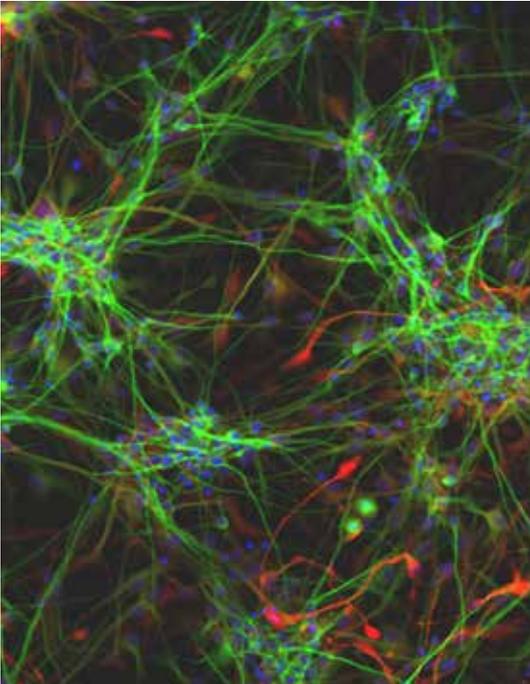
If left undiagnosed, a small percentage of the patients will develop acute rheumatic fever (ARF), an inflammatory disease affecting the connective tissue of the heart, joints, brain and skin. About half of patients with ARF will go on to develop RHD, which is characterized by progressive damage to heart valves.

In the absence of intervention, it can lead to heart failure and premature death. Since 2012, the Novartis Institutes for BioMedical Research (NIBR) and other Novartis divisions have been supporting a comprehensive program in Zambia aimed at eventually eradicating the disease in the country.

“BeatRHD Zambia” is a multifaceted initiative aimed at eliminating RHD in Zambia through research, health system strengthening, and public awareness activities. The team is led by Dr. John Musuku at University Teaching Hospital in Lusaka, and is a joint effort with the Ministry of Health; Ministry of Education; Ministry of Community Development, Mother and Child Health; University of Zambia; University of Cape Town; Novartis; and other partners. The initiative includes:

- 1) a research study to determine the prevalence of RHD in Lusaka school children,
- 2) Lusaka clinics strengthening primary and secondary prevention of RHD with Sandoz benzathine penicillin,
- 3) building awareness among the public and healthcare workers, and
- 4) policy changes to help better control and eventually eliminate RHD in Africa working with the World Health Organization (WHO) and African Union.





A Case Study: Building a Neuron Factory

Research teams at NIBR are using stem cells derived from the skin of healthy individuals to model brain diseases such as Alzheimer's, schizophrenia, and autism.

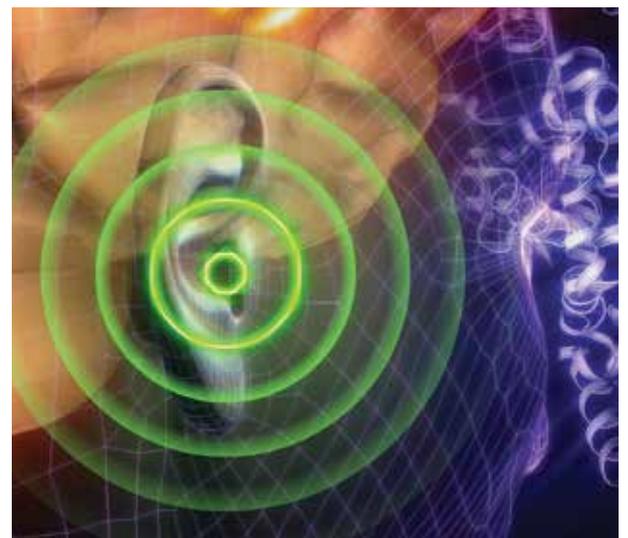
Using these stem cells, researchers will be able to create many neurons from different starting material via a standard production line. In some cases, the stem cells at the beginning of the line will be derived from people who are healthy; in others, they'll be derived from patients with neuropsychiatric and neurodevelopmental disorders. Presumably, the resulting neurons will behave differently in culture and act as a cellular proxy of disease. Some will be less healthy and die more easily, while others will lack the correct proteins to form synapses and have defects in signaling and connectivity. The researchers plan to characterize such differences in detail with a battery of tests.

The stem cell program is part of a broader effort to understand the cellular and molecular underpinnings of neuropsychiatric and neurodevelopmental diseases, which are seldom caused by a single mutation or variant of a gene. Recent studies suggest a complex model of pathogenesis, with many common variants of genes exerting subtle effects on the brain that add up to trouble. Given this complexity, it's critical to study neurons derived from many different patients, each with a unique combination of genes, to tease apart the factors that contribute to mental illness and focus drug discovery resources.

A Case Study: Using Regenerative Medicine to Treat Hearing Loss

According to the World Health Organization (WHO), approximately 360 million individuals worldwide suffer from disabling hearing loss, including many seniors. Treatment options are currently limited to surgery and devices such as hearing aids and cochlear implants. There are no approved drug therapies.

In 1999, scientists singled out a gene called *atonal* as a "master switch" for turning on the growth of inner ear hair cells, which pick up sound waves and translate them into electrical signals in the brain. Humans are born with hair cells, but the *atonal* switch flips off at birth. Any subsequent damage to hair cells is permanent.



In collaboration with a biotech company, GenVec Inc, NIBR researchers have developed an experimental gene therapy called CGF166 to restore hearing function by regenerating hair cells. It consists of a viral vector carrying the *atonal* gene. The vector has been altered with the aim of making it harmless and is injected directly into the inner ear. CGF166 is now being tested in a limited number of patients with severe-to-profound hearing loss.

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