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Malagasy Institute for Applied Research

ANTANANARIVO, MADAGASCAR

IMRA



EXCELLENCE IN SCIENCE

Profiles of Research Institutions in Developing Countries

PUBLISHED WITH THE SUPPORT OF
the David and Lucile Packard Foundation

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Foreword

Founded in 1983 and officially launched in 1985 in Trieste, Italy, by the secretary general of the United Nations, TWAS, the academy of sciences for the developing world, is dedicated to the promotion of scientific excellence and research capacity in developing countries.

With an initial membership of 42 'Founding Fellows', TWAS now counts 880 eminent scientists in 90 countries among its members. More than 85 percent of these scientists live and work in developing countries. This membership not only gives the Academy insight into the state of science in developing countries, but also provides a unique network of individuals and institutions through which the Academy can coordinate its activities.

Among these activities are annual TWAS Prizes designed to honour scientists in the South for their outstanding work in the fields of agriculture, biology, chemistry, earth sciences, engineering sciences, mathematics, medical sciences and physics. TWAS Prizes help bring the achievements of scientists working in the South to the attention of their national governments, providing them with a rare opportunity for recognition in their home countries. TWAS also offers research grants to individual scientists working in developing countries, as well as to research groups based in the world's least developed countries (LDCs) and other science – and technology – lagging countries. In

addition, in collaboration with the governments of Brazil, China, India and Pakistan, TWAS oversees the world's largest South-South fellowship programme. Under this scheme, young scientists from one developing country visit participating institutions in another developing country – particularly those mentioned above – to further their research, often by having access to equipment and materials not available at their home institution.

Institutions of scientific exellence in the developing world are included in a unique resource book, *Profiles of Institutions for Scientific Exchange and Training in the South*, produced jointly by TWAS and the Commission of Science and Technology for Sustainable Development in the South (COMSATS), based in Islamabad, Pakistan. The fourth edition of this book, published in 2007, lists 485 such institutions located in 65 different countries in the South and outlines their main scientific achievements, facilities and future plans.

Despite the perception that science in the South is lagging behind science being carried out in laboratories in the North, these 485 institutions provide evidence that top-quality research can be carried out in developing countries. And with a growing consensus that indigenous capacity in science and technology drives sustainable economic development, there is a need for more countries in the South to build their own scientific infrastructure – in terms of both human and institutional resources.

The purpose of this series of TWAS publications, which has been generously funded by the Packard Foundation, is to provide details about individual 'centres of excellence', including how they developed, how their research programmes are organized, their achievements, their strengths and weaknesses, and – most important – how they can

act as a model that other governments and organizations can follow when considering building scientific capacity. In this way, we hope the series will form a 'blueprint for a centre of excellence' that can be used by policy makers and those involved in the administration of national science policies.

The choice of which institutions to include in the series was difficult. However, it was felt that if the selected institutions all focused on a similar research area, then comparisons between institutions and countries would be simplified, making it easier to draw valid conclusions once several institutions have been studied. We have therefore taken advantage of the existence of a network of institutions created thanks to a programme originally operated by the Third World Network of Scientific Organizations (TWNSO), a TWAS-affiliated organization also based in Trieste and recently transformed into the Consortium on Science, Technology and Conservation for the South (COSTIS), which focuses on indigenous and medicinal plants and the conservation and sustainable use of biodiversity. Despite the common theme, the institutions profiled in this series cover a wide range of activities, from the scientific validation of traditional medicines to the use of modern biotechnology. Taken together, however, these institutions are representative of a cross-section of countries in the South. They have also been instrumental in taking indigenous resources – in terms of local biodiversity – and transforming them into profitable commercial products available on local and international markets. In this way, these institutions are excellent examples of how capacity in science and technology can lead to innovation and socio-economic development.

Contents

Introduction and History

Many cultures throughout the world rely on indigenous and medicinal plants for their primary healthcare needs. Indeed some 25 percent of modern medicines are derived from plants or plant extracts first used by traditional medical practitioners. Among the commercial pharmaceutical products based on medicinal plants are two anti-leukaemia drugs extracted from the Madagascar periwinkle *(Catharanthus roseus)* and the anti-diabetic drug, Madeglucyl, produced from the commonly found java plum, *Eugenia jambolana* (or *Syzygium cumini*, which was originally a native plant of India).

For more than 40 years, the Malagasy Institute for Applied Research (IMRA) has been investigating Madagascar's traditional medicines and food plants, such as the java plum, which, despite being nutritionally and medically valuable, are often overlooked and underused by local people.

Albert Rakoto Ratsimamanga, former research director at the *Centre National de Recherche Scientifique* (CNRS) and a pioneer of scientific research in Madagascar, founded IMRA in 1957. At its inception, IMRA was a non-governmental organization. But in 1993 it was granted 'foundation' status following a government decree. This status has helped to stabilize the institute's funding.

Today, IMRA is among Madagascar's leading research institutions. It is by far the best-equipped centre in Madagascar dedicated to biodiversity conservation and the discovery of drugs from natural products. In addition, the institute maintains a strong network of collaborations with like-minded institutes in both the developing and developed world.

MALAGASY INSTITUTE FOR APPLIED RESEARCH (IMRA)

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Currently under the guidance of Suzanne Urverg Ratsimamanga, IMRA has developed pharmaceutical products from endemic indigenous plants that are used to treat asthma, cardiovascular problems, diabetes, gastrointestinal ulcers, leprosy, malaria, nephrolithiasis (kidney stones) and wounds.

While Madagascar did not benefit from the development and commercialization of the two highly profitable anti-leukaemia drugs from *C. roseus,* royalties generated by such products as the highly successful diabetic drug Madeglucyl developed by IMRA have been ploughed back into IMRA's research budget and the local economy.

In addition, as a collaborative centre of the World Health Organization (WHO), IMRA has contributed to national economic development by educating researchers and students, training and assisting the local population, and conserving and protecting biodiversity. IMRA employs a permanent staff of about 150 and provides temporary and seasonal employment for some 15,000 people, mostly from rural areas. It also has its own medical clinic that offers free medical examinations to patients.

"For more than 40 years, the Malagasy Institute for Applied Research (IMRA) has been investigating Madagascar's traditional medicines and food plants."

ALBERT RAKOTO RATSIMAMANGA (1907-2001), founder and former president of IMRA

• *In 1929, Albert Rakoto Ratsimamanga obtained his undergraduate degree from the* Ecole de Médicine de Befelatanana, *Antananarivo, Madagascar. He then moved to Paris, where he worked as a researcher at* the Institut de Médicine Exotique, Institut Pasteur, *and the* Ecole des Hautes Etudes Internationales. *He also found time to earn two doctorates at the* Université de Paris – *one in science in 1938 and another in medicine in 1939.*

Soon after, Ratsimamanga became research director at the Centre National de la Recherche Scientifique *(CNRS), and director of the* Ecole Pratique des Hautes Etudes *at the Faculty of Medicine in Paris until his retirement in 1975. There, he studied hormone physiology and medicinal plants, mainly from Madagascar where his research focused on the presence of hormones in food, their role in body development and the existence of hepatic detoxification substances.*

Ratsimamanga skillfully translated his research findings into medical practice. His successes included the development of Cortine, an adreno-cortical extract for treating post-surgical shock; Madecassol, a cutaneous wound-healing agent isolated from Centella asiatica*; and Patelen, for treating hepatitis and allergic reactions.*

In 1958, Ratsimamanga founded the Malagasy Institute for Applied Research (IMRA) with the royalties earned from the commercialization of his discoveries.

Under Ratsimamanga's leadership, IMRA soon developed into the best-equipped centre in Madagascar for research into biodiversity conservation and drug discovery from natural products.

During the course of his career, Ratsimamanga published more than 250 scientific articles and 10 books, and was awarded five patents. He was one of the founders of TWAS, the academy of sciences for the developing world, and the African Academy of Sciences (AAS), and was vice-president of the executive council of the United Nations Educational, Scientific and Cultural Organization (UNESCO). He also served as a consultant to the United Nations Food and Agricultural Organization (FAO), the World Health Organization (WHO) and the Organization of African Unity (OAU).

In 2001, shortly before his death, Ratsimamanga was awarded the title 'International Man of the Year' by the International Biographical Centre, Cambridge, UK, in recognition of his services to science and humanity.

Then and now

In 1957, Albert Rakoto Ratsimamanga invested royalties from his scientific discoveries to establish the Malagasy Institute for Applied Research (IMRA), a centre of scientific research and training built on six hectares of land located near the capital city of Antananarivo. In addition to IMRA's headquarters, Ratsimamanga created 14 'annex stations' focusing on the collection of plants and reforestation, and relying on the local, rural population for its development and maintenance. In all of these initiatives, he successfully combined basic medicinal plant research with the conservation and protection of biodiversity.

Ratsimamanga's ultimate goal was to create an institute that focused on understanding the mechanisms by which local medicinal plants and medical practices could serve as the basis for inexpensive, yet effective, treatments for diseases afflicting the poorest and least fortunate people of Madagascar. At the same time, he hoped such efforts could provide livelihoods for the local population and help preserve Madagascar's unique natural flora and fauna.

> *IMRA employs a permanent staff of about 150 and provides temporary and seasonal employment for some 15,000 people, mostly from rural areas.*

The institute's short-term objectives have focused on promoting medicinal plant compounds and indigenous foods to advance public health and spur sustainable economic development. In the field of nutrition, for example, IMRA has produced foods to combat calcium and protein deficiencies and to counter malnutrition, especially among new-borns and young children.

As IMRA has grown, cutting-edge research and the commercial production of pharmaceutical products have remained tightly linked. To date, the institute has developed and formulated about 40 plant-based drugs to improve nutrition and combat a wide range of diseases in Madagascar. These include Cortine Naturelle, an adreno-corticol drug; Madecassol, a wound-healing agent based on extracts from the plant *Centella asiatica*; Madeglucyl, to treat diabetes; Madetoxyl, an antitoxin agent with potent activity to counteract hepatitis and alcoholic and drug intoxication; Madetussyl to suppress coughing; malagashanine to combat chloroquine-resistant malaria; Masy calcium to counteract protein and calcium deficiencies; Ody Vato, a phytomedicine to treat kidney stones; and TMM to fight leprosy.

In addition, over the past half century, IMRA has developed numerous therapeutic preparations used to treat such ailments as arterial hypertension and asthma. The development of the safe anti-diabetic medicine, Madeglucyl, from *E. jambolana,* which is now widely used both nationally and internationally, represents the institute's most outstanding success story and helped to make IMRA a globally recognized research centre.

Today, the institute enjoys a well-deserved reputation for excellence in research and collaborates with many groups, including the science and health ministries, research centres and universities not only in Madagascar but also in other African nations, Europe and the United States. It has also forged partnerships with such major pharmaceutical companies as Sanofi-Aventis and Hoffman LaRoche Switzerland. IMRA's portfolio of partnerships and scientific successes has attracted many talented Malagasy researchers to the institute, several of whom had previously settled in Europe only to return home. Thus its efforts have helped reverse the brain drain that afflicts many African nations.

Drug Development Pathway

"IMRA is an excellent example of how scientific research can be integrated with healthcare, conservation and commercial production", says Philippe Rasoanaivo, IMRA's director of scientific research.

To achieve these goals, IMRA maintains well-equipped departments and laboratories for analyzing and standardizing plant-based drugs and essential oils to combat, for example, cancer, diabetes and malaria. Its multidisciplinary fields of investigation include biodiversity, drug discovery from plants, marine animals and microorganisms, and phytopharmaceutical formulation. One of IMRA's main achievements has been a computerized compilation of the ethnomedical uses of more than 6,500 plants growing in Madagascar, which is regularly updated thanks to continual ethnobotanical fieldwork. In addition, the institute maintains a free healthcare centre with a medical analysis laboratory and four field stations for the cultivation of endemic medicinal and endangered plants.

THE IMRA CHARTER

- *Study Madagascar's endemic flora to provide scientific knowledge and safeguard threatened species.*
- *Develop drugs from Malagasy medicinal plants to aid the poor, rural population.*
- *Contribute to the improvement of traditional foods and research new sources of nutrition.*
- *Protect and manage the biodiversity of Madagascar, specifically medicinal and aromatic plants, and pursue research projects concerning agronomy and agroforestry.*
- *Promote technical and practical training to assist and advance the above activities and welcome to the institute national and international researchers, trainees and PhD students.*

According to Rasoanaivo, natural products offer a range of structurally diverse molecules that can be exploited as novel lead compounds for drug development either as an impetus for chemical synthesis or as biochemical tools for better understanding biological processes. In this regard, Madagascar offers excellent opportunities for the discovery of useful drugs or the formulation of relevant phytomedicines. However, because the science of natural products is multifaceted, successful drug discovery based on natural products requires multidisciplinary partnerships in which complementary expertise is a key feature.

"Patents and widely cited publications are testimony to the productivity of research investments", explains Philippe Rasoanaivo. "However, such investments do not help poor countries unless the research is turned into tangible products or improved practices and policies. At IMRA, we have taken drug discovery research projects to the market place while, at the same time, strengthening our research capacity and training activities. Personally, I have tried to find a balance between business-oriented activities based on both national needs and global diseases, whose treatments could provide potential blockbuster profits for developed countries", he continues.

MALARIA IN MADAGASCAR

• *Malaria can be treated using different anti-malarial drugs possessing different mechanisms of action. Unfortunately, over the years and partly due to the incorrect use of these drugs, malaria parasites (*Plasmodium *species) have developed resistance to some compounds, rendering certain treatments ineffective. Chloroquine, for example, was the most widely used anti-malarial until resistance emerged in the 1960s in both Colombia and Thailand. Since then, chloroquine resistance has spread to most areas where malaria is endemic. Although such resistance is now widespread in much of sub-Saharan Africa, where malaria kills nearly one million people each year, its frequency remains low in Madagascar. Even so, in the Malagasy highlands, some two hours from the capital of Antananarivo, the damp climate leaves stagnant pools of water everywhere, which provide breeding grounds for the mosquito,* Anopheles gambiae, *whose females transmit malaria when they take a blood meal. Malaria remains the biggest killer of children in Madagascar – and many other African countries.*

A huge effort is underway by the United Nations Children's Fund (UNICEF) and other UN and international organizations to fight malaria by providing insecticide-treated bed nets that ward off mosquitoes. Vast distances and poor infrastructure in Madagascar, however, mean that many people rarely visit health facilities. Health workers and volunteers have tried to overcome this problem by visiting village markets and using entertaining theatrical shows to get the message across to children and parents. These health workers also warn anyone experiencing malaria-like symptoms to seek immediate medical care. Against this background, Philippe Rasoanaivo and his research team's discoveries of a phytomedicine to treat chronic malaria and the alkaloid tazopsine to treat the hepatic stage of the malaria parasite attain all the more significance.

SNAPSHOTS

For example, the investigation of the African holly (*Ilex mitis*), under a research grant awarded to Rasoanaivo in 1978 by theInternational Foundation of Science (IFS), led to the local marketing of a wound-healing drug trade-named Fanaferol.

Following the sudden resurgence of malaria in Madagascar in the mid-1980s, people returned to the large-scale use of herbal remedies. A shortage of conventional drugs forced many Madagascans to rely on medicines from more than 200 plants to fight malaria. This in turn triggered scientific interest in Madagascar whose long isolation from neighbouring countries had created a unique mix of plants and animals.

About this time, Rasoanaivo was awarded a second IFS grant for phytochemical studies of alkaloid-bearing plants, mainly species belonging to the *Strychnos* genus. Among the alkaloid compounds previously extracted from such *Strychnos* plants are strychnine, a poison that can be used medically to stimulate the nervous system, and curare, used by natives of South America to coat the tips of arrows.

During his research, Rasoanaivo discovered that rural people in Madagascar were treating malaria with chloroquine (see box, 'Malaria in Madagascar,' page 18) – a drug that has been widely used as a prophylactic treatment against malaria and to which many strains of the malaria parasite have become resistant – together with a decoction (a boiled-water induced extract) made from various plants. This ethnobotanical finding was a key factor in the discovery of alkaloids with unique structures that markedly enhance the action of chloroquine.

PHILIPPE RASOANAIVO, director of scientific research and director of the Phytochemistry Laboratory

• *After obtaining his BSc in chemistry from the University of Madagascar in 1970, Rasoanaivo completed his PhD at the French* Centre National de Recherche Scientifique *(CNRS)* Institut de Chimie des Substances Naturelles *in 1975. Since the start of his PhD programme in 1970, when he studied the Malagasy periwinkle (*Catharanthus longifolius*), Rasoanaivo has continued researching Madagascar's natural products.*

In 1976, he returned to Madagascar, and was appointed lecturer at the Faculty of Sciences of the University of Antananarivo. Two years later, he was selected head of the department of chemistry at the Centre National de Recherches Pharmaceutiques. *Following his Fulbright post-doctoral studies at the University of Illinois at Chicago in 1989-1990, his priorities changed when malaria re-emerged in Madagascar in the 1980s and quickly became the most devastating tropical disease in the country. He moved on to IMRA to set up and implement a research programme on malaria, in addition to serving as a full professor at the* Ecole Supérieure Polytechnique*, University of Antananarivo. This pioneering programme has put Madagascar on the world map of malaria research and placed him in the rank of experts in plant-based malaria chemotherapy.*

Rasoanaivo has authored nearly 100 articles in peer reviewed journals and more than 70 book chapters and entries in published conference proceedings. He has been awarded nine patents and has supervised more than 30 dissertations and doctoral theses in science or medicine.

He is a former World Health Organization (WHO) expert in traditional medicine and has served as a WHO temporary advisor in traditional medicine. He also founded the Natural Products Research Network for Eastern and Central Africa (NAPRECA) branch in Madagascar. Rasoanaivo played an instrumental role, with colleagues from Uganda and Ghana, in the adoption of the Decade (2001-2010) of Traditional Medicine in Africa during the Organization of African Union (OAU) Summit in Lusaka in 2001, and he was the recipient of the Research Prize 2000, the highest research award in Madagascar. One year later, he received the International Foundation for Science (IFS) Sven Brohult Award in recognition of excellence in research and creation of a better scientific environment in developing countries. In 2003 Rasoanaivo was awarded the prestigious French honour Chevalier des Palmes Académiques Françaises *for his outstanding academic achievement. The President of the Republic appointed him* Grand Croix de 2ème Classe *in 2006, the highest Malagasy honour. In 2006 he was elected a member of TWAS and received the Academy's first CNR RAO Prize for Scientific Research.*

In total, three grant-funded research projects on herbal anti-malarial compounds have resulted in two patents: the first has been applied in the local use of a standardized chemosensitizing phytomedicine from *Strychnos myrtoides* to treat chronic malaria. The second is related to the discovery of a new alkaloid, tazopsine, from *Strychnopsis thouarsii*, that is selectively active against the hepatic stage of the malaria parasite.

Tazopsine is the first naturally occurring compound that is active in the liver stage of malaria parasites. It is important because there are few alternative drugs that tackle this stage of the parasite's life cycle which precedes the fever-causing blood-infecting stage. The discovery of this new class of molecules could lead to the development of a true causal prophylactic drug. The treatment targets the early stages of malaria infection when liver stage parasites are much less numerous than blood-stage parasites. This makes it more difficult for the parasite to develop drug resistance that hampers conventional malaria treatment programmes.

Additional investigations are now underway to bring derivatives of these compounds into drug development and clinical trials. Tests on chimpanzees and rhesus monkeys are planned in collaboration with colleagues in Gabon and Thailand.

Collaboration has been key for translating Madagascar's unique biodiversity into revenue-generating applications that not only provide economic benefits to the keepers of traditional knowledge but also afford training benefits to young scientists. Rasoanaivo cites, for example, IMRA's malaria programme, which has been done in collaboration with Italian colleagues at the *Istituto Superiore di Sanità* in Rome and the *Università degli Studi di Roma "La Sapienza"* and with French colleagues at the *Muséum National d'Histoire Naturelle* and *Hôpital Pitié-Salpêtrière,* in Paris, and the *Université de Montpellier II* and the *Université des Sciences et Technologies de Lille*.

"Collaboration has been key for translating Madagascar's unique biodiversity into revenue-generating applications."

At IMRA, three main departments function in an integrated manner:

The Department of Research, which has three areas of activity: discovery of biomolecules in the areas of diabetes, cancer, cardiovascular, inflammatory and respiratory diseases; biotechnology research, including *in vitro* micropropagation and investigation of endophyt fungi and mychorrizas; and analyses. IMRA has fully equipped laboratories to carry out all these activities.

The Department of Production and Export, which produces nearly 40 plant-based drugs, nutraceuticals and cosmetics for local use at affordable prices, and exports *Centella asiatica, Drosera ramentacea* (the insect-eating sundew plant used to produce a cough linctus) and other medicinal plants as well as essential oils for commercial purposes. The latter activity is an important source of income for the institute.

The Department of Clinics, which carries out some 30 medical consultations daily. Patients may be treated either with phytomedicines, conventional drugs or a combination of the two. The centre offers free healthcare and medical tests.

"Twenty-five percent of modern medicines are derived from plants or plant extracts first used by traditional medical practitioners."

DAVID RAMANITRAHASIMBOLA, head of the pharmacology unit in the 'Laboratoire des substances marines et aquatiques' in IMRA's Department of Research

• *As head of the pharmacology unit within IMRA's Department of Research, David Ramanitrahasimbola works closely with president, Suzanne Urverg Ratsimamanga, and research director, Philippe Rasoanaivo. Together they have analyzed the bioactive compounds of Madagascar's medicinal plants, studying such endemic species as* Adansonnia fony, Budlejia madagascariensis, Phymatodes scolopendria *and* Ravenala madagascariensis *for their potential to treat arterial hypertension, asthma and inflammatory diseases.*

A researcher in pharmacology at IMRA since 1995, Ramanitrahasimbola focuses primarily on experimental malarialogy and cardiovascular and respiratory systems. He has authored or co-authored some 20 peer-reviewed papers and three book chapters on such topics as malagashanine (extracted from the chemosensitizing medicinal plant Strychnos myrtoides*) and its ability to inhibit the chloroquino-resistance of* Plasmodium *malaria and the bronchodilator activity of* Phymatodes scolopendria*, a plant widely used in Madagascar to treat asthma. As a result of his collaborative research on the anti-asthmatic* Phymatodes scolopendria *(that has been supported by a Swedish nongovernmental organization and the IFS, IMRA will soon manufacture a phytomedicine from this plant.*

Ramanitrahasimbola is currently investigating the mechanism of action and toxicity of the molecule responsible for the anti-hypertensive activity of the plant Ravenala madagascariensis.

He completed all his education in Madagascar. He obtained his BSc in biology and earth sciences from the University of Antananarivo and was awarded his PhD in pharmacology from the same institution. In addition to his current job responsibilities at IMRA, Ramanitrahasimbola lectures at the IMAGE-APPLI institute in Madagascar and supervises students pursuing master's degrees in pharmacology.

In 2005, he was awarded the title 'best young scientist' presenter at the 11th Natural Products Research Network for Eastern and Central Africa (NAPRECA) symposium and was recently selected a TWAS Young Affiliate.

Department of Research

In terms of drug discovery and development, the process starts with the Ethnobotany Section that is in charge of collecting and identifying plants. Plants are then extracted with appropriate solvents and submitted to a panel for biological screening. Different laboratories collaborate closely to put products through biological screening procedures that lead to the purification and identification of the agents responsible for the biological activity and a preliminary understanding of the compound's mechanism of action.

Two phytochemistry laboratories focus on extraction, fractionation and purification of a range of plant-derived molecules. Bioactive compounds are sent to Europe for spectral data recording and the results are sent back to IMRA through internet facilities for data processing. Three pharmacology laboratories, headed by Suzanne Ratsimamanga and Adolphe Randriantsoa, focus on various tests, including *in vitro* tests, conducted on cellular, parasitic and microbial cultures; isolated organs tests; assessments of blood pressure and the respiratory system *in vivo;* and anti-diabetic tests *in vivo*.

Since 1996, IMRA has maintained a dedicated facility to breed rats, mice, rabbits and guinea pigs for testing purposes – specifically for the acute and chronic toxicology tests required if scientists are to proceed from *in vitro* to *in vivo* stages of the drug development pathway.

Department of Production and Export

In addition to medicinal cosmetics, essential oils and food additives, the Department of Production and Export manufactures about 40 plant-based drugs to meet the local population's current health needs. These drugs are the result of careful research and are distinguished by their efficacy, absence of toxicity and low price, which makes them affordable to the Malagasy people. For example, the highly successful anti-diabetic drug, Madeglucyl, is provided free of charge to more than 6,000 diabetic patients in the country as part of an ongoing clinical trial.

As a result of such extensive trials, some of the drugs produced by IMRA, such as Madeglucyl, have merited development by major pharmaceutical companies.

"The Department of Production and Export manufactures about 40 plant-based drugs to meet the local population's current health needs."

The Department of Production and Export comprises several units that include:

- an extractor equipped with two reactors, several macerators and one concentrator; three alembics for essential oils distillation;
- a manufacturing and packaging unit;
- a quality control centre, linked with the research department for analytical chemistry and biological control of plant-based drugs manufactured by the Department of Production; and
- a collection, drying and sorting unit that prepares plants for export. For example, the plant *Centella asiatica* for the preparation of Madecassol; *Drosera ramentacea* for the preparation of a cough medicine; and *Melaleuca viridiflora, Cinnamomum camphora* and *Ravensara aromatica* for essential oils.



Drugs produced by IMRA are distributed throughout Madagascar to treat a variety of diseases, such as asthma, respiratory infections and ear, nose and throat ailments; hepatic and digestive diseases, including hepatitis, gastroduodenal ulcers and gastritis, bacterial and parasitic dysentery, diarrhoea and intestinal worms; heart failure and hypertension; dermatological diseases such as leprosy, ulcers, burns and excema; diabetes; malaria; rheumatism; and urogenital diseases. In addition, IMRA produces a range of cosmetic drugs and foods to treat infant malnutrition and calcium deficiency, and to aid weaning.

Department of Clinics

The Department of Clinics operates a health centre that provides free medical examinations and inexpensive biomedical tests. Operated by Kiban Cheuck, director of the Biomedical Department, the clinic is frequented by the neighbouring population and by many Malagasy who live farther away. Medical examinations are conducted free of charge, a policy that has been in place since 1957. Doctors frequently examine 30 to 40 patients a day.

"Since the creation of IMRA, such services have been free", explains Cheuck. "IMRA is a centre for the poor. Yet others who are not poor still come both for the quality care and services that we provide. The benefit of our organization is that a patient can do everything in one day. You can't find this even in the United States or in other developed countries. Our medical services are done quickly, well and inexpensively".

Cheuck adds that only consultations are free and that patients must pay something for tests and some medications.

At the clinic, phytomedicines (or plant-based medicines) are preferred over modern drugs. "We use phytomedicines first and modern medicines second", confirms Cheuck. "If I don't know the plant that can treat the sickness, then I treat the patient with a generic drug. The only limit is our limit to our knowledge of plants".

Protecting Madagascar's Biodiversity

IMRA's annex stations

Madagascar is considered one of the world's 25 'biodiversity hotspots' along with the other Indian Ocean islands that split off from the African continent some 160 million years ago. This long period of isolation helped create an island with thousands of examples of endemic species – species that are found nowhere else on Earth. Indeed some 98 percent of Madagascar's land mammals, 91 percent of its reptiles and 80 percent of its flowering plants (including the representatives of eight entire plant families) are endemic. Madagascar's flagship species, the lemurs, are 100 percent endemic and include 33 different species.

IMRA'S ANNEX STATIONS AND THEIR ACTIVITIES

Mangoro	6 hectares	Centre for the collection and distillation of aromatic plants. Maintains a 1,700 litre still.
Moramanga	3 hectares	Important regional collection and drying centre for medicinal plants, particularly *Centella asiatica.* Maintains a still for the production of essential oils.
Ampasimpotsy	3 hectares	Varied cultures.
Ampanatoamaizina	50 hectares	Local population responsible for reforestation. Entire village involved in the production of essential oil from *Melaleuca viridiflora.* Industrial plant cultures.
Ambohimena	13 hectares	Reforestation and cultivation of *Eucalyptus citriodora, globulus* and *robusta.*
Andranovaky	93 hectares	Protection of endangered plants. Research station for improvement of food cultures. Cultivation of medicinal plants, such as *Eucalyptus citriodora, Artemisia annua* (an anti-malarial plant), *Spilanthes acnella* and *Cinnamomum camphora.*
Ambatolampy	43 hectares	Reforestation and cultivation of *Eucalyptus robusta* and *E. raculata, Pinus khana* and P. *dalula*.
Anjozorobe	100 hectares	Reforestation and important cultivation of *Quinquina*.
Avarabohitra (Pilot station)	6 hectares	Important regional centre of collection of all medicinal plants used in manufacture of IMRA's drugs, and for such exported plants as *Centella asiatica* and *Drosera ramentacea*.
Marozevo	2 hectares	Fruit trees cultivated and *Eucalyptus citriodora.*
Anosibe'An'Ala and Analabe		Two important collection stations for medicinal plants, especially *Centella asiatica*.
Ivato	3 hectares	Cultivation of *Eucalyptus robusta*.
Nosy Be		Cultivation of various medicinal plants.
Mahabo	4 hectares	Culture of medicinal and endangered plants.

The protection and preservation of Madagascar's unique fauna and flora have always been primary objectives of IMRA. In addition to IMRA's headquarters near the capital city, where most of the scientific research, quality control and drug production are carried out, the institute's founding director, Ratsimamanga, created 14 annex stations that focus on the sustainable collection of medicinal and aromatic plants and the replanting of denuded areas of forest.

Directed by an agronomist and a forestry engineer, the annex stations are closely linked with the rural population. Their mandate is to:

- supervise gathering, drying and preparation of medicinal and aromatic plants collected or cultivated by rural population;
- provide advice and assistance to rural population on cultivating medicinal and food plants; and
- protect the environment and work with local population on reforestation.

At several of the annex stations, entire villages participate in such IMRA activities as the gathering of plants and production of essential oils. At the Ampanatoamaizina station, for example, the entire village of some 170 people is involved in planting the aromatic tree, *Melaleuca viridiflora,* that provides an antiseptic essential oil. The village operates two stills set up by IMRA. Local residents have been trained to use the stills and produce the essential oil that is then sold to IMRA.

In this way, an isolated rural village that previously had few resources has been able to generate an income without damaging the surrounding forest (IMRA provides courses for local people, giving instructions on the sustainable collection of plant products). By involving local people in such activities, IMRA has increased the income of several thousand rural families by 50 percent, in addition to cultivating and protecting many endemic plant species.

The Ampanatoamaizina station itself is located near the country's east coast and sits amid a 500-hectare forest concession that was given to IMRA by the state on the understanding that IMRA would ensure its reforestation and the sustainable cultivation of native medicinal and aromatic plants. In total, IMRA's annex stations cover 250 hectares (plus another 500 hectares at the Ampanatoamaizina site). More than 3,000 people are involved in the collection of plants, creating more than 100 collection points. An additional 2,000 people are employed seasonally to collect the seeds of *Eugenia jambolana,* the plant used in the production of the anti-diabetic drug, Madeglucyl.

"Madagascar is considered one of the world's 25 'biodiversity hotspots'. The protection and preservation of its unique fauna and flora have always been primary objectives of IMRA."

Ethnobotanical Unit: the herbarium and botanical garden

The Ethnobotanical Unit, directed by Madagascar's most eminent specialist in systematic botany, Armand Rakotozafy, is dedicated to the collection of Madagascar's endemic plants, particularly those that are endangered. Rakotozafy has an encyclopedic knowledge of most of the plant species that exist in Madagascar, information that is vital to the safeguarding of Madagascar's biodiversity.

Each year the Ethnobotanical Unit organizes eight to fifteen field expeditions to collect endemic plants, both those that have medicinal properties and those that are endangered. The goal is to cultivate them in the botanical garden or at one of the annex stations. In 2006, IMRA scientists collected 400 samples of plants for research purposes, for cataloging in the herbarium, and for the production of pharmaceuticals. Traditional healers often accompany these field expeditions to share their empirical knowledge of Madagascar's medicinal plants. In addition, soil samples are collected for research being carried out in collaboration with other laboratories to examine rare actinomycetes and hyphomycetes – soil-dwelling microorganisms – that produce bioactive metabolite compounds.

> *About 50 percent of traditional healers' knowledge that has been checked by IMRA scientists has been validated by rigorous research.*

Back at the laboratory, the collected plants are examined and the information, including their vernacular names, ethnobotanical uses and scientific identification, is entered into a database. Of Madagascar's 12,000 plant species, some 6,500 have already been identified and logged into the database – a database that is rapidly becoming a valuable resource not only for the conservation of the island's biodiversity, but also for helping scientists seek out potentially useful plant compounds to enter into the drug discovery pathway.

IMRA's botanical garden covers three hectares. In addition to the forest and fruit trees, some 100 plants from all parts of Madagascar are cultivated, each one clearly labelled with its scientific and vernacular names. In the 80 percent of cases where the cultivated plants have medicinal properties, the labels also highlight their therapeutic uses. There is also a rock garden where many endangered plants, including examples of the families Didieraceae and Orchidaceae, are cultivated. In addition, there are *Pachypodium* species (family Apocynaceae), 20 of the 25 known species of which are endemic to Madagascar, and many other medicinal and aromatic plants that are intrinsic to Malagasy culture. Rakotozafy is also responsible for the botanical garden, assisted by an agronomist and seven gardeners, who care for the garden and tree nursery. Rakotozafy is also currently developing a seed collection, or genebank, to provide additional safeguards for the protection of Madagascar's rare plants.

MADAGASCAR'S TRADITIONAL HEALERS

• *According to IMRA's president, Suzanne Urverg Ratsimamanga, about 50 percent of traditional healers' knowledge that has been checked by IMRA scientists has been validated by rigorous research.*

"Traditional healers are clever people", says Ratsimamanga. "They make up for their lack of formal education by being good observers. The methods used by traditional healers are important to IMRA. They provide us with precious information", she adds.

Indeed, IMRA's founder, Albert Rakoto Ratsimamanga, worked hard to overcome the distrust held by traditional healers for outsiders. Healers believed that traditional knowledge should stay within the family. From 1975 to 1980, he used radio announcements to request the help of the nation's healers. Now there is an association of about 5,000 traditional healers, l'Association Nationale des Tradipraticiens Malagasy, *which has been recognized officially by the Malagasy Ministry of Health since 2002. It was established to protect traditional healers' rights and their extensive knowledge of Madagascar's medicinal plants and healing properties.*

All traditional healers use plants in their treatment of sickness and disease. Tazopsine, for example, a compound derived from tree bark that is being analyzed by IMRA for its potential to treat the early stages of malaria, is the sole ingredient in a traditional tea prescribed by healers to treat the disease.

> *"Albert Rakoto Ratsimamanga worked hard to overcome the distrust held by traditional healers for outsiders."*

The Ministry of Health recognizes four types of traditional healers: accoucheuses, *who are midwives;* herboristes, *who are plant vendors;* medico-drogistes, *who are healers that use remedies from animals or mineral products; and* traditherapeutes, *who are traditional practitioners working on various diseases as well as burns and fractures.*

In 1996, the Ministry of Health gave traditional healers the provisional right to treat people and in 1997 the Ministry promoted traditional medicine as a legitimate practice. Cultivating the relationship begun by Rakoto Ratsimamanga, IMRA continues to work with the best of Madagascar's traditional healers. The institute sends researchers into the field to speak with village chiefs to find out which healers are the most effective and knowledgeable.

In addition, IMRA takes care of the intellectual property rights related to traditional knowledge and the equitable sharing of benefits.

Measures of Success

By seeking the right reseachers and acquiring the right equipment, IMRA has become Madagascar's pre-eminent 'centre of excellence' for the conservation of biodiversity and the discovery of drugs from natural products. The institute also maintains a strong network of collaborations with institutions in the North and South that help provide additional expertise and access to cutting-edge scientific equipment.

Despite the excellent reputation that IMRA has developed for itself since its inception, measures of scientific success can be difficult to quantify. There are, however, certain research and development 'outputs' that can be assessed.

For example, since 1957, IMRA scientists have published about 300 papers in international journals. The institute has also had major scientific successes with the discovery

of such drugs as the anti-diabetic Madeglucyl; malagashanine for the reversion of malarial treatment chemoresistance; the highly effective wound-healing agent, Madecassol; an antitoxin agent with potent activity in hepatitis, alcoholic and drug intoxication called Madetoxyl; the adreno-cortical drug Cortine Naturelle; tazopsine, which is active in the hepatic stage of the malaria parasite; and pervilleines, resistance modulators in cancer isolated from the endemic plant Erythroxylum pervillei and which are in the pre-clinical stage of drug development in the United States. In addition, IMRA produces some 40 herbal medicines, or phytodrugs, that are used to treat common ailments and are affordable for the local Malagasy population.

Suzanne Urverg Ratsimamanga provides her definition of IMRA's success: "First, success for IMRA is defined by our ability to promote and safeguard Madagascar's endemic flora. Second", continues Ratsimamanga, "is our excellent relationship with traditional healers who have told us, for example, that 'this plant is for malaria' and who have opened up so many new research avenues. We have an extraordinary relationship with them because we have always respected them".

Indeed, founder and former president of IMRA, Albert Rakoto Ratsimamanga and his successor (and wife) Suzanne Urverg Ratsimamanga worked hard to give traditional healers more status. "They used to be considered charlatans and unreliable", explains Urverg Ratsimamanga. "Now, in Madagascar, they have recognition and a better image". In addition, traditional healers have been educated by IMRA staff on unsafe practices concerning, for example, such issues as toxicities and poisonous plants, and they have been taught to be more productive.

"The third measure of our success has been the development of IMRA and its scientific research", adds Urveg Ratsimamanga.

> *"IMRA has become Madagascar's pre-eminent 'centre of excellence' for the conservation of biodiversity and the discovery of drugs from natural products."*

Sweet smell of success: the java plum

For more than 40 years, IMRA has been investigating the traditional medicines and food plants of Madagascar that, despite being nutritionally and medically valuable, are often overlooked and underused by local people. The discovery of an anti-diabetic drug from the local java plum tree, *Eugenia jambolana* (or *rotra* as it is known in Madagascar), by Albert Rakoto Ratsimamanga and Suzanne Urverg Ratsimamanga, has become one of IMRA's most interesting and successful research projects.

In 1965, the two began to work with local traditional healers. Their curiosity was aroused when they came across a simple way of diagnosing diabetes: healers were asking their patients to urinate close to an anthill and then observing how the ants reacted. Ants usually avoid urine, but the urine of people suffering from diabetes contains a great deal of sugar that attracts the insects. Patients with sweet-tasting urine (at least to the ants) were thus diagnosed as diabetic and prescribed *E. jambolana* by the healers. Once the scientists discovered this, they began to conduct laboratory work on the potential medicinal properties of this plant.

From 1967 until 1985, the Ratsimamangas studied and experimented with *E. jambolana* at both IMRA and the National Centre of Scientific Research (CNRS) in Paris, France.

Trials on laboratory rats conducted over several generations showed that Madeglucyl did indeed alleviate the symptoms of diabetes. Additional experiments and tests showed that the drug is not toxic, does not cause cancer or lead to the malformation of embryos and has no other detrimental side effects.

In 1984, the Ratsimamangas patented their discovery of the antidiabetic properties of *E. jambolana* in France. Additional tests have since established that a formulation, now sold under the trade name Madeglucyl, is stable and consistently effective as a treatment for diabetes.

In 1996, a second license was issued and granted the product international recognition. Following this, in December 1997, Madeglucyl was registered as a licensed medicine in Madagascar. At present, some 6,000 diabetic Malagasy patients receive Madeglucyl, most of them free of charge, as part of the ongoing clinical trial process. More recently, diabetic patients in Germany and the United States have become involved in the ongoing trials.

The main features of Madeglucyl include:

- it improves the ability of the body's tissues to absorb glucose, thus enhancing the effectiveness of insulin;
- it reduces the daily insulin required by type I insulin-dependent patients by nearly 40 percent;
- when used on patients with type II diabetes, it returns glycaemia rates to normal levels within three to six months in 75 percent of cases. It has proven particularly effective for obese patients, whose glycaemia rates start to decline after 15 days and return to normal within three months (again in 75 percent of cases); and
- in some cases, it has improved the functioning of the kidneys and relieved some of the eye problems that can be caused by diabetes.

In addition to providing an effective anti-diabetic drug and the royalties that such success brings, the java plum has been made into jams, jellies and health drinks that provide a valuable source of nutrition. Although Malagasy traditional healers have been successfully using *E. jambolana* to relieve the symptoms of diabetes, its full potential had never been exploited, mainly because there was a general lack of knowledge and interest in collecting, using, and preserving java plums. Until IMRA launched its project to evaluate the potential of *E. jambolana* in 1970, much of this valuable resource had been ignored and wasted.

SUZANNE URVERG RATSIMAMANGA, President of IMRA

• *Suzanne Urverg Ratsimamanga obtained her BSc in Paris in 1953, followed two years later by her Diploma in Industrial Hygiene and Medicine. She received her MSc in biochemistry in 1963 before obtaining her* Docteur ès-Sciences d'Etat *in Paris and a doctorate in biology from the London College of Applied Science, UK, in 1969.*

In addition to her current role as president of the Malagasy Institute for Applied Research (IMRA), she also directs the Tropical Nutrition Laboratory at the French University, Paris, and heads the department of biochemistry at the University of Madagascar, Antananarivo, Madagascar.

Her research interests include traditional medicine, medicinal plants (particularly those with anti-malarial properties) and tropical nutrition. She has studied the relationship between corticosteroids and ovarian hormones, and has explored a new approach for the treatment of leprosy. For more than 40 years, she collaborated closely with IMRA's founder and her husband, Albert Rakota Ratsimamanga, first in the laboratory of the National Centre of Scientific Research (CNRS), Paris, then as director of the French University's Tropical Nutrition Laboratory and later at IMRA. Her research was fundamental to the discovery of the anti-diabetic drug, Madeglucyl, that was patented in France in 1984.

In 2001, following the death of Albert Rakoto Ratsimamanga, Suzanne Urverg Ratsimamanga became president of IMRA.

Urverg Ratsimamanga also serves as a consultant on traditional medicine for the World Health Organization (WHO), a member of the governing council for the African Academy of Sciences (AAS) and, since 1989, a Fellow of TWAS.

> *"IMRA is searching for partners in the food industry so that java plum jams and jellies can be produced and marketed on a commercial scale."*

Now, through IMRA's efforts, java plums are preserved to produce a range of tasty and healthy foods that are rich in sugars, mineral salts, vitamins C and PP (which fortifies the beneficial effects of vitamin C), anthocyans, flavonoids and other beneficial compounds.

IMRA is searching for partners in the food industry so that java plum jams and jellies can be produced and marketed on a commercial scale. Nutritionists are also looking for other ways of using this fruit and have had particularly interesting and well-received results from a java plum wine. The plums, both fresh and dried, also may have potential in the expanding exotic fruits market of developed countries.

IMRA's work with *E. jambolana* has also helped to protect the environment and slow the pace of deforestation.

In the past, java plum trees were often felled for timber or fuel or to clear land for crop cultivation. Since the plums' medical uses have been discovered and become well known, such destructive practices have declined. At the same time, rural people have generated extra income from seed collection (in Madeglucyl production, the seeds are the most important part of the tree and must be collected and processed when they are at the correct stage of ripeness).

It took IMRA several years to devise an efficient seed collecting system. The problem proved complicated because the plant products that the institute needs perish very quickly. The answer was to train local people in the best ways to collect and dry the seeds. The work is relatively easy and the pay is good, especially for people with few alternative sources of income. By 1998, annual harvests of 20 tons were being gathered during relatively brief collection seasons (the fruits mature during the rainy season, which runs from February to April).

In recent decades, many medicinal plants from the developing world have been exploited by pharmaceutical companies from the developed world without the benefits being shared with the native country. *Catharanthus roseus* is a classic example. The plant grows in Madagascar but is harvested and marketed as an important anti-cancer agent by a multinational pharmaceutical company.

IMRA's *E. jambolana* project has helped to redress this imbalance. As a result, the country of origin of the plant resource now enjoys the economic and health benefits from this effort. Indeed, since the development of the anti-leukaemia drugs from *C. roseus*, many countries have signed up to an international protocol, the 1992 Convention on Biological Diversity, which gives countries sovereign rights over their biological resources. The agreement aims to prevent so-called 'bio-piracy', whereby a company

from another country exploits a biological resource without giving anything back to the host country.

Kiban Cheuk, IMRA's medical director, defines the institute's success as "The production of things that are useful to the Malagasy population". He notes that if such efforts help others, all the better.

IMRA is currently establishing partnerships with private companies in France and other European countries to build a production unit where pharmaceuticals can be manufactured according to international manufacturing standards and practices. This unit will initially produce enough Madeglucyl to meet the demand in Madagascar. In the future, IMRA hopes to expand distribution to other African markets. However, for now, Madeglucyl is produced for local markets only.

The success of the *E. jambolana* project could easily be applied to other countries, especially those bordering the Indian Ocean where the plant grows naturally and extensively. The process of producing Madeglucyl from seeds is protected by international license. But commercial agreements could be signed with both public and private sector agencies in other developing and developed countries to allow this safe and affordable diabetes treatment to be made available to patients worldwide. IMRA and INDENA have signed an accord to jointly market Madeglucyl on an international scale. IMRA is particularly interested in working with national health authorities in African countries to establish commercial links for the sharing of Madeglucyl.

Measuring success in terms of training

Another measure of scientific output is the number of students that receive advanced training. IMRA researchers, including four professors from the University of Antananarivo, assist students in the preparation of their doctorate theses in science, medicine and dental medicine, and engineering. IMRA's Philippe Rasoanaivo, for example, has supervised more than 30 dissertations and doctoral theses in science and medicine. Medical and chemical engineering technicians are also trained at IMRA. Foreign researchers from Africa and neighbouring islands are welcome to pursue all or part of the work for their thesis at IMRA. Post-doctoral scientists from abroad are also encouraged to spend time in IMRA's laboratories.

In the past, IMRA has organized summer schools to teach the modern techniques of *in vivo* and *in vitro* testing, as well as the screening of activities and valorization of medicinal plants and other natural resources. In September 1994, researchers from Ethiopia, Kenya, South Africa and Uganda took advantage of this training and, with several Malagasy researchers, worked closely with French and Canadian specialists.

Researchers at IMRA have also been appointed by the Faculty of Medicine at the University of Antananarivo to teach biochemistry to medical students. Each year, 300 students, in groups of 25, receive high-level theoretical and practical training. Among the trainees are those intending to specialize in biochemistry.

In addition to academic training, IMRA has implemented training programmes for the rural population in the sustainable cultivation, harvest and ultimate sale of medicinal plants and plant products.

For example, IMRA buys such medicinal plants as *Centella asiatica* – used as a wound-healing drug and also to increase mental concentration and combat ageing – from several local communities. "Large amounts of *Centella asiatica* are needed for export and for the production of drugs", explains Suzanne Urveg Ratsimamanga, adding that: "IMRA pays community workers by the kilogramme to collect the plants. We guarantee the villagers that we will pay them well for their services. No one is exploited."

For many Malagasy people, their cash incomes have increased by about 50 percent. For example, after a brief training period, local people found that the task of java plum seed collecting and drying (necessary in IMRA's production of the anti-diabetic drug Madeglucyl) provided relatively easy work and good pay in an area where there are few alternative sources of cash income.

Product pipeline

Competing with multinational drug companies – albeit on a much smaller scale – requires not only a successful portfolio of products, but also a strong 'product pipeline'. In many ways, the strength of a research institution such as IMRA should be measured less by its current products and more by what it is currently developing and has the potential to produce in both the near-future and the long-term. Using such a measure of success, IMRA stands alongside the best institutions in the developing world and competes favorably with many institutions in developed countries.

Based on the results of an integrated approach to screening medicinal plants used traditionally to treat infectious and parasitic diseases, in July 2004, the French institute CNRS signed a protocol with the University of Antananarivo to pursue a bioprospecting programme with the active participation of IMRA. The project, run by IMRA's Philippe Rasoanaivo in Madagascar, is progressing well and results are expected soon. Researchers anticipate new compounds to be discovered from this activity, while relevant data with strong ethnobotanical support are exploited locally.

IMRA's latest area of interest is the search for drugs to treat such chronic degenerative diseases as diabetes and cognitive impairment, focusing on the role of methylglyoxal. This work is being done in collaboration with Uppsala University in Sweden. Patents have recently been granted on the bioactive constituents of two promising medicinal plants, and data are still being treated confidentially.

IMRA's European colleagues are currently developing the anti-malarial drugs malagashanine and tazopsine by synthesizing several derivatives for drug optimization. In addition, new tropane alkaloids endowed with resistance modulating activities in multiple drug resistant (MDR) cancer, extracted from the stem bark of *Erythroxylum pervillei,* a tree endemic to southern Madagascar, are now in the early pre-clinical stage of drug development under the Rapid Access to Invention for Development (RAID) programme overseen by the US National Institutes of Health (NIH). IMRA will receive royalties under a memorandum of agreement between IMRA and NIH once a drug is on the market. The process, however, is likely to be lengthy.

Research and Commercial Partnerships

IMRA maintains a strong network of collaborations with local, African and Northern institutes. As scientific research director, Philippe Rasoanaivo, points out: "The science of natural products is multifaceted. As a result, successful drug discovery, based on natural products, requires multidisciplinary partnerships marked by complementary expertise".

Rasoanaivo cites as an example IMRA's collaboration with Italian and French institutions to find an effective drug for use in the treatment of malaria in Madagascar. The research programme focused on the search for naturally occurring compounds that could reverse chloroquine resistance. The collaborative effort resulted in the discovery of several chemosensitizing alkaloids. One, malagashanine (isolated from the Malagasy plant, *Strychnos myrtoides*), has been targeted as a candidate for further development.

IMRA has also signed a memorandum of agreement with the University of Illinois, USA, for pre-clinical development of tropane alkaloid polyesters as chemosensitizers in multiple drug resistant (MDR) cancer.

In 1999, following the creation of the Research Initiative for Traditional Anti-malarial Methods (RITAM) in Tanzania, IMRA collaborated with the *Hôpital Pitié-Salpêtrière*, Paris, to screen plant extracts against the hepatic stage of malaria. This resulted in the isolation of a new morphinan alkaloid named tazopsine, for which a derivative N-cyclopentyl-tazopsine is now under further pre-clinical investigation. Based on the results and the research methods used, in July 2004, the French institute CNRS signed a protocol with the University of Antananarivo for a bioprospecting programme, appointing Rasoanaivo head of the project in Madagascar.

IMRA not only collaborates with research institutes, but also encourages commercial partnerships.

> *"Pharmaceutical companies based in Europe, North America and elsewhere ask us to collaborate with them because they are interested in drug discovery."*

"Pharmaceutical companies based in Europe, North America and elsewhere ask us to collaborate with them because they are interested in drug discovery", explains Suzanne Urverg Ratsimamanga. "They are also interested in endemic plants. They often discover new molecules in IMRA's collection of plants".

Concerning funding, Rasoanaivo says: "Stable and sufficient funding is necessary to start a successful research program, as are funding activities generated by the marketing of biodiversity (the export of plants). We are moving towards self-sufficiency and self-sustainability by implementing successfully funded research projects with extensive training components. And we are bringing such research into development through income-generated programmes."

Sanofi-Aventis, for example, patented the chemical structure of the anti-diabetic drug, Madeglucyl, and LaRoche-Navarron (now Hoffman LaRoche Swiss) patented the adreno-corticol drug, Cortine Naturelle (now Cortine).

Among IMRA's current international partners are: Aventis, *Corporation Francaise*, Hoffman LaRoche, *Université de Bruxelles a Louvains* (on standardization and essential oils projects), *Université Libre de Bruxelles* (on biodiversity projects), the US National Institutes of Health (NIH) and the World Health Organization (WHO).

IMRA also collaborates closely with universities in Madagascar in training students and on research projects. In addition, IMRA provides a consultancy service to Madagascar's Ministry of Health, offering advice on how to establish and implement new drug registration procedures.

Strengths and Weaknesses

Such long-established and on-going collaborations with both research institutes and the commercial pharmaceutical sector indicate that IMRA is doing many things correctly.

According to Suzanne Urverg Ratsimamanga, the institute's greatest strength "is that it is well-known, strong, totally involved, committed, proud and that its researchers are well trained".

Factors that contribute to IMRA's continuing success are highlighted on the next page. Among these strengths are IMRA's success in drug discovery based on natural products, the institute's support for traditional medicines, its protection of biodiversity and the free healthcare it provides for the Malagasy people, which helps build trust with the local residents, including traditional healers.

However, as a research organization in a developing country there is still plenty of room for improvement. Ratsimamanga admits that IMRA's major weaknesses are a lack of marketing capacity, especially as the institute does not distribute its products widely outside Madagascar. "We are scientists, not sales people", she explains.

IMRA'S STRENGTHS AND WEAKNESSES

Strengths

- As a private, non-profit institute, IMRA is scientifically autonomous. This reduces bureaucracy.
- Its location in a biodiversity hotspot ensures almost unlimited raw materials for drug discovery from natural products. IMRA is also seen as protecting this biodiversity.
- Scientists can tap into the traditional knowledge base and reinforce traditional medicine practices.
- Well-trained researchers – most have received training in the US or Europe. Extra training is provided if required.
- Strong collaborations with foreign institutions and collaboration with industry, which allows royalties to feed back into the research and development budget.

Weaknesses

- A lack of or inadequate materials. Sometimes orders are not met due to IMRA's limited budget or high prices for imported material and equipment, which slows research.
- Limited access to on-line literature.
- Lack of marketing capacity. Product presentation and marketing need to be improved.
- Product distribution is limited primarily to Madagascar.

> *"Collaborations with both research institutes and the commercial pharmaceutical sector indicate that IMRA is doing many things correctly."*

Conclusions

IMRA – a truly unique institute in the developing world – operates independently of any government or charitable funding. The goal of founder Albert Rakoto Ratsimamanga was to create an institute that focused on understanding the ways by which local medicinal plants and medical practices could serve as the basis for inexpensive, yet effective, treatments for the poorest and least fortunate people of Madagascar, while preserving Madagascar's natural flora and fauna. Current president Suzanne Urverg Ratsimamanga stays true to the vision of her late husband while continuing to develop IMRA into a globally recognized 'centre of excellence'. The institute has been fortunate to have her leadership following the passing of Albert Rakoto Ratsimamanga in 2001.

Thanks to IMRA's current partnerships – especially those that result in royalties from commercial companies – allied to Madagascar's rich, endemic flora, the continued success of the institute is virtually guaranteed. However, increasing IMRA's financial income to maintain its operations will be a challenge and increasing access to materials, equipment and scientific literature in what is one of the world's 50 least developed countries (LDCs) remains a major obstacle. In addition, given that the leadership of the institute has remained 'in the family', so to speak, since its inception in 1957, IMRA's preparation of future leaders and key personnel will also be critical to its future success. The employment of eminent scientists such as Philippe Rasoanaivo and Armand Rakotozafy, the institute's ability to attract indigenous talent back from contracts abroad, and its effective training programme, however, suggest that IMRA's future is in good hands – for the benefit of science in general and the health of the local Malagasy people in particular.

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TWAS

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TWAS

TWAS, the academy of sciences for the developing world, is an autonomous international organization that promotes scientific capacity and excellence in the South. Founded in 1983 by a group of eminent scientists under the leadership of the late Nobel Laureate Abdus Salam, TWAS was officially launched in Trieste, Italy, in 1985, by the secretary-general of the United Nations.

TWAS has 880 members from 90 countries, over 85 percent of whom live and work in developing countries. A Council of 13 members is responsible for supervising the Academy affairs. TWAS is assisted in the administration and coordination of programmes by a small secretariat, headed by the executive director. The secretariat is located on the premises of the Abdus Salam International Centre for Theoretical Physics (ICTP) in Trieste, Italy. UNESCO is responsible for the administration of TWAS funds and staff. A major portion of TWAS funding is provided by the Ministry of Foreign Affairs of the government of Italy.

The main objectives of TWAS are to:

- recognize, support and promote excellence in scientific research in the South;
- provide promising scientists in the South with research facilities necessary for the advancement of their work;
- facilitate contacts between individual scientists and institutions in the South;
- encourage South-North cooperation between individuals and centres of scholarship.

To achieve these objectives, TWAS is involved in various activities and collaborates with a number of organizations, especially UNESCO, ICTP and the International Council for Science (ICSU).

For additional information, see www.twas.org.

THE DAVID AND LUCILE PACKARD FOUNDATION

The David and Lucile Packard Foundation was created in 1964 by David Packard (1912–1996), co-founder of the Hewlett-Packard Company, and his wife, Lucile Salter Packard (1914–1987). Throughout their lives in business and philanthropy, the Packards sought to use private funds for public good.

Guided by the founders' values, the David and Lucile Packard Foundation supports both people and organizations with the aim of enabling the creative pursuit of science; conserving and restoring the Earth's natural systems; improving the lives of children; and advancing reproductive health.

For additional information, see www.packard.org.

EXCELLENCE IN SCIENCE

This series of booklets – published by TWAS, the academy of sciences for the developing world – highlights successful scientific institutions in the South and explains how their research has both been sustained over a number of years and is helping their host nations achieve sustainable economic development.

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