

Briefing document for partnership opportunity

A NATIONAL RESEARCH AND DEVELOPMENT PLATFORM FOR NOVEL DRUG DEVELOPMENT FROM INDIGENOUS MEDICINAL PLANTS (Innovation Fund Project: TM1002FP)

BACKGROUND

The Novel Drug Development Platform (NDDP) project brings together a multi-disciplinary research and development team in a consortium which has the combined technical skills, research facilities and strategic capability required to develop novel drugs from medicinal plants. The platform further provides for the establishment of new agro-processing businesses in rural communities for supply of plant material required for new drugs. The consortium is made up of 10 organisations, including science councils, higher education institutions and a parastatal.

SIGNIFICANCE OF HEALTH PROBLEM THAT IS BEING ADDRESSED

Tuberculosis, malaria and diabetes are important and (in the developing world) neglected diseases, representing a huge burden to developing nations. Estimates by the WHO for the year 2000 indicated 8.7 m cases of tuberculosis worldwide, with 80% diagnosed in two high-burden countries. 1.9 m deaths occurred as a result of tuberculosis, 98% of them in the developing world. Malaria poses a serious threat to the population in the tropical and sub-tropical regions of Africa, South-East Asia and parts of Latin America. According to the WHO, malaria claims 3 000 lives each day, more than 90 per cent of them in Africa. Infants and children are at particular risk of dying from the fatal complications of malaria. Diabetes affects many millions of people in the developing world, and the incidence can be expected to rise with increasing urbanisation of rural people.

There are continuing indications that the global pharmaceutical industry is suffering from declining productivity (fewer new medicines are introduced despite increased spending on research) (*Scrip Reports, 2001: Natural Product Pharmaceuticals: A diverse approach to drug discovery*). Yet there is increasing need for innovation in selecting therapeutic targets and finding lead compounds. The vast majority of current drug discovery carried out by the pharmaceutical industry relies on molecular approaches, involving defined molecular targets. And molecular approaches in turn are dominated by high-throughput screening. Pharmaceutical companies with the best and most diverse chemical collections will ultimately dominate the industry (*Strohl, 2000: Drug Discovery Today*). Broadly speaking, chemically diverse collections can only come from two sources of large numbers of compounds: combinatorial chemistry and natural products. Although combinatorial chemistry can provide large numbers of compounds for high-throughput screening such compounds tend to have limited structural diversity. By contrast, natural products provide a wealth of small molecules with drug-like properties and with incredible structural diversity (*Scrip Reports, ibid*).

The most common therapeutic areas for natural product-based drugs are cancer, followed by metabolic diseases (diabetes mellitus and obesity), anti-infective agents (antibacterial, anti-fungal and antiviral) and neuropharmacological agents (including analgesics) (*Pharmaprojects, 2001*). There is a vast resource of biodiversity that has not yet been tested for useful pharmacological activity. Even with higher plants, which probably represent the most thoroughly examined source, it is estimated that less than 10% of the world's species have been tested for biological activity (*Verpoorte R, 1998: Drug Discovery Today, 3, 232-238*). Of the 20 best selling non-protein drugs in 1999, nine were derived from or developed as a result of leads generated by natural products (*Scrip, ibid*).

SCIENTIFIC RATIONALE

The special feature of this project is that it is done on indigenous plants by researchers in the developing world, working in close collaboration as part of a carefully coordinated plan. The project contains all the necessary elements required in drug discovery to take the process through from plant to drug. The consortium incorporates microbiology, chemistry, pharmacology, botany, traditional medicinal practices and drug development science so as to make a considerable and special contribution to the search for novel drugs in the developing world. Many of the plants that are presently being investigated by the consortium are indigenous to the participating countries, providing opportunities for discovery that are not available elsewhere. At least 5 000 African, Asian and Latin American terrestrial plants are believed to have medicinal significance. Moreover, the diverse marine plant flora in South Africa warrant further investigation of their potential scientific medicinal application; they might expand enormously the search for novel therapeutic compounds.

ANTICIPATED SCIENTIFIC AND TECHNICAL ADVANCES/OUTPUTS/OUTCOMES

The following outcomes are envisaged over the coming 3-5 years:

- Development of effective and safe novel drugs for malaria, tuberculosis and diabetes, and immune modulators.
- Benefits from transfer of technology.
- Creation of agricultural processing opportunities in rural communities.
- Patents on novel plant-derived compounds.
- Placing South Africa in the forefront of discovery and development of plant-derived medicines.
- Establishment of a competent and experienced multidisciplinary team for drug development.
- A research platform for cost-effective screening of new drug entities of medicinal plant origin.
- Validated fractionation methods available to the research community in South Africa and to the rest of the continent.
- A comprehensive and valuable data base and herbarium for medicinal plants (approximately 30 000 items).
- A channel for benefits to the source communities, to enable full sharing of such benefits.

IMPACT OF SCIENTIFIC AND TECHNICAL ADVANCES ON THE DEVELOPMENT OF NEW MEANS TO TREAT DISEASE IN SOUTH AFRICA, THE AFRICAN CONTINENT AND ELSEWHERE IN THE DEVELOPING WORLD

- Specialists from a number of clinical and scientific disciplines are collaborating to develop and apply selection criteria aimed at identifying plants with the highest potential for activity and safety for the diseases concerned.
- A dedicated and comprehensive electronic database has been developed to facilitate this approach.
- Candidate plants are being processed and extracted under GLP conditions and screened for *in vitro* activity.
- Promising candidate compounds identified after bioassay are selected for further work, and extracted in sufficient quantities and purity for further investigation and development.
- Once the chemical structure(s) of the active compounds has (have) been determined, candidate molecules are analysed retro-synthetically in order to identify readily available and/or accessible starting materials.
- A clinical trial platform is being established to bring the evidence to the point of proof of concept.
- Pharmaceutical and manufacturing development will be conducted in collaboration with pharmaceutical chemists and with the pharmaceutical industry, as necessary (industrial collaboration will be preferred with partners in the developing world).

POTENTIAL ECONOMIC, ENVIRONMENTAL AND OTHER BENEFITS

The use and conservation of traditional medicinal plants are activities that address not only health care but also nature conservation, biodiversity, economic assistance, trade and legal issues. Besides serving medical and cultural functions, medicinal plants have an economic role.

The sustainable cultivation and purchase of plant material will offer opportunities for development. Such endeavours will help raise rural employment in South Africa (and elsewhere in Africa) through agricultural and agroprocessing opportunities, boost domestic commerce and contribute to the social and financial advancement of many.

PROGRESS AND ACHIEVEMENTS OVER THE PAST 15 MONTHS (FEB 2004 – APRIL 2005)

The consortium has succeeded in putting together a research base consisting of 10 institutions, 17 academic departments and research units, and an estimated 135 scientists including 40 postgraduate students. There is a determined and strong focus on corrective action.

The project has several strengths. These include the country's natural heritage, the access to plant extracts made possible by the CSIR collection of more than 14 000 items, and the two comprehensive databases provided by the South African Biodiversity Institute (SANBI) and the University of Cape Town/Medical Research Council. The inter-institutional collaboration and participative decision taking, and information sharing, that have been achieved in the programme are unusual anywhere in the academic and research world. The project leadership has attempted to set up exemplary standards of peer review, internal scientific audit and quality assurance of laboratory conduct and data and it is resolved to move to good laboratory practice (GLP) and certification of those participating laboratories where that is not already established. The efficiency of the financial management of the programme and the controls on spending and accounting are exemplary. The consortium is determined that the highest respect should be shown for the intellectual property of others, and that any benefits issuing from the successful outcome of its work would be equitably shared. There is careful adherence to the principles of the recent Biodiversity Bill of the South African Parliament (2004). Regular meetings are held of the steering and management committees, and there are frequent bilateral meetings and site visits. Reviews of results are held frequently between the project management and the scientists of the participating laboratories so as to assure the scientific integrity and high morale of the programme.

The following are considered to be realistic outcomes of the programme, anticipated by 31st January 2007 when the current funding cycle is due to terminate: (i) discovery of between 3-5 active compounds, and an understanding of their mechanisms of action and chemical characterisation, for the diseases and conditions concerned; (ii) arrangements in place for royalty earnings that would be equitably shared; (iii) progress towards agricultural processing and potential job creation; and (iv) an established and highly efficient model for interdisciplinary, inter-institutional, national and international collaboration in this specialised aspect of novel drug discovery.

With the exception of the component of the programme that deals with tonics, which has its own logic, the selection of diseases addressed in this project is based on three broad considerations: (i) the diseases are prevalent and contribute significantly to the burden of disease on the African continent generally, and in South Africa in particular, and they represent a considerable public health problem; (ii) activity is validated *in vitro* using test systems that allow for reliable screening of activity and for iterative bioactivity testing after repeated fractionation; and (iii) demonstrated *in vitro* activity is followed up by *in vivo* testing using validated models of disease in small animals. Active compounds are not further pursued if there is associated cytotoxicity (all active compounds are tested in parallel for efficacy and cytotoxicity, and the safety margin determined), or if further scientific study of the plants concerned might constitute an ecological risk.

The most advance so far has been in the field of malaria. That is because the malaria research programme was best developed at the inception of the project in January 2004. We have discovered several promising leads for the treatment and prevention of drug-sensitive and drug-resistant malaria, respectively, as revealed by *in vitro* testing. The main focus of the malaria programme in 2005 will be to determine whether the promising *in vitro* data translate to confirmatory *in vivo* results. That will depend in part on bioavailability of the novel compound or extract, and it may be necessary to produce different formulations to determine the optimum pharmacokinetics. Special expertise is required for the purpose, and the consortium is seeking a partner within South Africa to assist with formulation issues. It may be necessary to look beyond the country, and tentative discussions in that regard have been held with the Universiti Sains Malaysia.

Promising progress has been made in discovering novel plant-derived mosquito repellent and larvicidal activity. Biofractionation of the most active compounds is currently being pursued. It is necessary to confirm that the results are reproducible in another laboratory and arrangements have been made for this to happen at the Central Drug Research Institute of India (CDRI) in the latter part of 2005. (In general, the consortium is committed to ensuring that positive results are corroborated in another independent laboratory, as part of the drug discovery process.)

The start of the tuberculosis discovery programme has been slower, due to logistical reasons in 2004 with the laboratory concerned that have been unavoidable. That was anticipated and planned for. They are now overcome, and it is expected that from now on there will be rapid and substantial progress in both *in vitro* and *in vivo* testing of anti-tuberculosis activity, including drug-resistant *Mycobacterium tuberculosis*. The immune modulation component of the programme, too, is in its early stages but progress has been made.

For testing novel drugs active against diabetes mellitus there are financial constraints that limit the number of *in vitro* and *in vivo* tests. Selection of candidate plants has accordingly been limited. Nevertheless, a small number of promising leads have been identified and these will be pursued during 2005 by *in vivo* confirmation.

The same bioavailability concerns apply for testing of antidiabetic activity *in vivo* as have been referred to above for malaria, and the consortium will be seeking a similar solution. A small but functional clinical testing facility has been established at the University of Limpopo, and this is due to be ready for human testing during 2005.

The consortium is committed to international collaboration. That would make possible a broadening of the pool of expertise and facilities available for conduct of the work. It would further contribute to an approach to drug discovery that promotes self-sufficiency in developing countries, and appropriate use of natural resources and traditional heritage in healing and in the prevention of disease. There would be less reliance on the pharmaceutical industry with which (if deemed necessary and desirable) negotiations might be conducted at a later stage, when that would be favourable to the public sector and to research and development in countries such as our own. The project leader and project manager have travelled to and set up collaborative arrangements with several sister institutions in India and Malaysia, respectively. It is intended to do the same with Brasil in 2005 or 2006. Arrangements have been made, in conjunction with the World Health Organization, for the consortium to collaborate with seven countries in sub-saharan Africa, subject to additional resources being found.

A VISION FOR THE PROGRAMME

Short-term (2006 -2007)

An additional 18 million rand would be used to promote Africa-wide collaboration in drug development research from medicinal plants, an advanced data base on indigenous medicinal plants that would have considerable research and industrial application and value, and upgrading of the participating laboratories and clinical facilities to international standards of GLP (this applies to those participating laboratories that have not already achieved such standards and accreditation).

The future of this programme, after January 2007, looks promising. There will be a generally respected drug discovery platform, agricultural processing with the potential for community involvement in a number of places in the country and elsewhere in participating countries, a successful model of enlightened research management and scientific leadership, participation of the World Health Organization and the Geneva-based Drugs for Neglected Diseases Initiative (DNDi) and integration with their respective drug discovery programmes, and a data base for medicinal plants and related aspects of drug discovery from medicinal plants. These arrangements will be unmatched in the developing world, and the platform will be generally accessible to the research community. Other diseases, including cancer and HIV/AIDS, will be added to the research portfolio.

Medium –term (2008– 2012)

The consortium aims to have established by 2009 a research-based infrastructure for the discovery and development of novel medicines from plants that will be without peer for its efficiency, excellence and vision.

WHAT IS ON OFFER?

- i. A national research and technology platform for medicinal plant research.
- ii. Special opportunities available in South Africa for such work.
- iii. Potential leads (minimum 1; maximum 3-5) in each of the following fields: antimalarials, anti-tuberculosis agents, antidiabetic agents, immune modulators.
- iv. Agricultural development, training, research capacity, national drug development capacity.
- v. Clinical trials study sites.
- vi. Links to international drug discovery and development activities. Research institutions from the following countries have expressed a keen interest in collaborating: India, Sudan, Nigeria, Botswana, Cameroon, Kenya, Tanzania and Malaysia. Other countries presently being considered are Cuba, China, Turkey, Thailand and Brazil.

FURTHER INFORMATION

Prof Peter Folb
Medical Research Council
PO Box 19070
Tygerberg
7505

Tel: +27 21 938 0844
Fax: +27 21 938 0460
Email: pfolb@mrc.ac.za

Dr Niresh Bhagwandin
Medical Research Council
PO Box 19070
Tygerberg
7505

+27 21 938 0207
+27 21 938 0460
niresh.bhagwandin@mrc.ac.za

June 2005 - briefing document for partnership opportunity final.doc