Genomics and Discovery Research

I RATIONALE

The Committee on Genomics and Discovery Research (GDR) is a component of the Steering Committee on Strategic and Discovery Research (SDR) in TDR. The fundamental goals of GDR are to support (1) the identification and validation of new molecular targets for drugs and diagnostics using the wealth of genomic information that is now available and (2) the discovery of new lead compounds that have the potential to be developed into drugs to treat diseases in the TDR portfolio.

TDR supports discovery of novel targets and drugs for African trypanosomiasis, malaria, leishmaniasis, filarial diseases, schistosomiasis and tuberculosis. TDR has actively supported, and continues to support, the efforts of international networks to determine and exploit the genome sequences of pathogens and their vectors. These data and new technologies in genomics provide opportunities for the development of novel interventions against diseases in the TDR portfolio. "Genomics" is now a starting point for the "discovery" of new drug and diagnostic targets which can be developed as practical and affordable tools for field use. The Committee on Genomics and Discovery Research is designed to support research activities that utilize genomic data in combination with novel molecular and/or chemical technologies for the identification, characterization and validation of targets and the discovery of lead inhibitors for drug development.

The Committee has a strong commitment to support research capability strengthening within projects with the aim of forging productive collaborations between laboratories in disease-endemic countries and laboratories in well-resourced countries.

II OBJECTIVES

In drug discovery, GDR supports research to identify lead compounds that can be taken forward into lead optimization with other organizations or, in certain cases, drug candidates that can be taken forward by TDR, in partnership with other organizations, into human trials. In order to merit support, a lead compound must show good efficacy and no overt toxicity in an appropriate animal model, and have the potential to be improved by chemical means. A drug candidate must have been extensively tested and must fulfil all the essential criteria required of a drug to treat the intended disease (for example, it must be more active or better than current drugs, with an acceptable safety profile, and amenable to scale-up and production at an acceptable cost).

In diagnostics, GDR supports innovative approaches for exploiting genomic sequence information to identify potential new diagnostic targets for differentiating early and late stage African trypanosomiasis, diagnostic indicators of early infection in leprosy, and diagnostic tools for the detection of drug-resistant organisms for malaria, tuberculosis or leishmaniasis.

GDR programme of activities

- Investigator-initiated projects on novel targets, including validation and assay development to be taken forward into high throughput screening (HTS) campaigns. Those that already have genetic and/or chemical validation and some assay development will be preferred.
Projects that facilitate collaborations with academic centres and companies that have expertise in HTS, as well as the availability of large compound collections, to carry out HTS using targets and assays acquired/obtained by TDR from investigators.

Testing of compounds through a network of laboratories capable of evaluating compounds for their biological activities. GDR invites investigators to submit compounds for evaluation. (Information on submitting compounds for analysis: [http://www.who.int/tdr/grants/workplans/gdr3.htm](http://www.who.int/tdr/grants/workplans/gdr3.htm).) In addition GDR proactively solicits compounds from research groups in academia and in industry that have compounds thought to have potential as leads to new drugs for the TDR diseases.

The analysis of natural products as a source of lead compounds. Research, particularly in disease-endemic countries (DEC), is supported with the goals of identifying new lead compounds and strengthening the screening capability in DECs.

The optimization of lead compounds. GDR will also collaborate with investigators in obtaining the data necessary to prepare a strong proposal on lead optimization for co-funding with other organizations, for example, the public-private partnerships.

**Establishment of networks**

TDR has demonstrated that an effective and cost-efficient means of promoting research capacity strengthening as well as generating productive discovery research is the establishment of focused networks between investigators working in the North and South, at either research institutes or in companies.

Three new networks are planned for the 2006-2007 biennium:

1. **Network for kinetoplastids (African trypanosomiasis, Chagas disease, and leishmaniasis)** to utilize the genomes for the identification and validation of new targets and the development of assays, including whole cell assays for medium to high-throughput screening.

   The goals will be to:
   - Produce a prioritized list of targets.
   - Validate the targets (chemical and/or genetic).
   - Develop assays in liaison with HTS centres.
   - Enhance knowledge transfer to scientists in disease-endemic countries (including workshops and scientific exchanges).

2. **Network to bring together expertise from the North and South to utilize the genome of schistosomes for target identification, validation, and the development of assays for medium and high-throughput screening.**

   The goals will be to:
   - Produce a prioritized list of targets.
   - Validate the targets (chemical and/or genetic).
   - Develop assays in liaison with HTS centres.
   - Enhance knowledge transfer to scientists in disease-endemic countries (including workshops and scientific exchanges).

3. **Network to support synthetic and medicinal chemistry as part of drug discovery.**

   The goals will be to:
   - Build a collaborative network, with major participation from research groups in disease-endemic countries, to enable hit validation, hit-to-lead expansion, and lead optimization.
   - Encourage work on natural product chemistry, particularly in the disease-endemic countries.
   - Develop small libraries around leads as part of efforts to optimize leads for potency and efficacy, e.g. in vivo activity, pharmacokinetics.
Additional networks that are either ongoing or being considered for the future are:

1. Improved reporter systems for whole cell assays (for activities already in progress see [http://www.who.int/tdr/grants/workplans/transfection.htm](http://www.who.int/tdr/grants/workplans/transfection.htm)).
2. Protein expression of validated targets

Examples of possible project proposals

Most of the activities supported by GDR come from investigator-initiated proposals. These proposals should fit into the programme of activities outlined above. The examples listed below are not meant to direct potential grants but merely to illustrate possible projects:

1. The identification and validation of new drug targets and the development of assays amenable to high-throughput screening. For example:
   - Identification and validation by genetic and/or chemical means of new targets for drug discovery using genome information in conjunction with new technologies such as RNAi, inducible gene systems, genome-wide mutagenesis, genome expression analysis and bioinformatics.
   - Development of assays suitable for adaptation to high throughput screening.
   - Development of assays/reagents that improve upon existing screening techniques.
2. Taking validated drug targets forward into high throughput screening (HTS). Given that this requires large compound collections and specialized equipment and facilities, GDR supports collaborations with companies and institutions that have expertise in HTS.
3. Network of Compound Evaluation Centres. GDR supports laboratories with expertise in analysing compounds for their anti-parasitic activities and thereby identifying hit and lead compounds that can either be further developed into drugs.
4. Medicinal chemistry. GDR supports projects aimed at expanding hits into lead compounds and at optimizing lead compounds into drug candidates.
5. The identification and validation of new diagnostic targets. For example:
   - Identification and validation of targets useful in developing diagnostics for disease-staging in African trypanosomiasis.
   - Development of tests for early leprosy infection through combinations of genomic and molecular tools.
   - Development of diagnostic tools for the detection of drug-resistant organisms for malaria, tuberculosis, and leishmaniasis.

III CURRENT ACTIVITIES

The new GDR group is a result of the joining together in TDR of the Drug Discovery Research group and the Genomes to Drugs and Diagnostics group. For many years TDR has supported and coordinated a network of laboratories evaluating compounds for their biological activities. In recent years, the drug discovery efforts have expanded to include the identification of hits through high throughput screening (HTS). TDR currently collaborates with two HTS centres that are screening large compound libraries against five different molecular targets relevant to the TDR diseases. Hits from the HTS programmes are expected to be progressed to the Network of Compound Evaluation Centres for detailed biological evaluation.
Similarly, the Genomes to Drugs and Diagnostics (GDD) group at TDR has supported investigators working on applying and utilizing genome sequence information to identify and validate molecular targets focusing on the kinetoplastids (African trypanosomiasis, leishmaniasis, and Chagas) and on malaria. In addition, GDD has been providing support for projects that concern diagnostics for leprosy and the detection of drug resistance in leishmaniasis.

IV HOW THE STEERING COMMITTEE WORKS

The Steering Committee meets annually to review all ongoing activities in Genomes and Discovery Research and new proposals. The portfolio of activities includes network activities, investigator-initiated projects, and special Steering Committee initiatives. Following its annual meeting, the Steering Committee makes recommendations on funding allocations to the Director of TDR.

The GDR committee invites applications from investigators, institutions, and networks in the areas outlined under Objectives. Applications will be reviewed at the next scheduled meeting of the Steering Committee (9 -12 August 2005). With respect to investigator-initiated projects, the committee will consider new research proposals for up to US$70000 per year for a maximum duration of two years. Higher levels of funding will be considered for institutions and network activities. Applications will be reviewed and evaluated on a competitive basis.

V HOW TO APPLY

Researchers interested in collaborating in the above activities may download the application forms (Collaborative Research Grant form) from the TDR website at http://www.who.int/tdr/grants/forms.htm or request them from the TDR communications unit (tdr@who.int).

Proposals for 2005 should be submitted before 30 May 2005. All correspondence related to the Genomics and Discovery Research Committee should be sent to:

Dr Mary M. Bendig
Acting Manager
Genomics and Discovery Research
WHO/TDR
20 Avenue Appia
1211 Geneva 27, Switzerland

Tel: (41-22) 791-3960
Fax: (41-22) 791-4854
Email: bendigm@who.int