

## Concept Papers for two new DNA Sequencing Technology Development Programs

The following document presents two concept papers that were discussed at the May 19, 2003, meeting of the National Advisory Council for Human Genome Research. The papers describe future plans for the National Human Genome Research Institute and its Sequencing Technology Development Program. The concepts were approved by the Council. NHGRI staff will incorporate comments made by council members as these concepts are converted into formal Requests for Application. No attempt has been made to revise the concept papers based on Council comments. It is anticipated that the RFAs will be issued in the fall of 2003.

NHGRI is presenting two concept papers for program announcements for DNA Sequencing Technology Development (attached). While the two concepts have several features in common, there are also some differences, so we propose two separate, parallel announcements. In the list of features presented in each concept paper, **items that differ between the two concepts/ announcements are highlighted with bold text.**

In addition to general comments on those concept papers, NHGRI requests Council members' comments on the following proposals:

- 15-20% of the funds allotted to sequencing technology development will not be included in the initial awards, but will be held by NHGRI for use in making supplements that will be awarded based on needs identified by grantees and staff after milestone evaluations. It is staff's experience that grantees pursuing technology development projects frequently encounter unanticipated technical challenges, and this device will provide the Institute with additional flexibility to respond to such challenges. The milestones evaluation/ advisory processes that will be implemented should provide the information necessary to make supplemental awards, or to reduce awards if necessary.
- Anticipated cost-sharing by companies participating in this program will be expected to be in the range of 20 – 50%, depending on the individual situation. It will take different forms (e.g., the company may split the budget down the middle, purchase equipment, pay indirect costs, etc.).
- The number of receipt dates is limited because it is important for the Institute to be able to directly compare grant applications in assembling a balanced portfolio. For the effective development of useful sequencing technology, staff believes that this need outweighs the usual desire to allow investigators to submit ideas when they are ready, and to submit revised applications more quickly.
- Through these programs, NHGRI wishes to advance the state of knowledge leading to the development of advanced DNA analysis technologies, while simultaneously stimulating the development of practical devices and methods. Therefore, NHGRI proposes the following language regarding requirements for dissemination of the results of this research: e.g., applicants must describe their plan for providing access to the technology developed under partial support of this grant. For example, the technology might be made available as a fee-for-service, through sale of instruments and/or reagents, through collaboration, or through publication and posting of results, plans and methods.
- Successful applications will incorporate knowledge of process and scale issues involved in handling of samples and data of the magnitude required for genomic DNA sequencing. One obvious way to incorporate such knowledge is through collaboration with a large-scale sequencing center. However, other approaches will also be acceptable, in order to avoid limiting the creativity of applicants and placing undue burdens on a relatively small number of experienced production sequencing centers.

## Program Announcement Concept:

### Near-Term Technology Development for Genome Sequencing

Purpose: The purpose of this program announcement is to solicit grant applications to develop novel technologies for sequencing DNA. Current technologies (as of summer 2003) are able to produce, for approximately \$50M, a high-quality draft sequence of a complex genome such as human or mouse (7.7-fold coverage, 6.5-fold coverage in Q20 bases, assembled into 225,000 sequence contigs that are connected by at least two read-pair links into supercontigs [total of 7,418 supercontigs at least 2 kb long], with N50 length for contigs equal to 24.8 kb and for supercontigs equal to 16.9 Mb. *Nature* **420**:520, 2002). Development of technologies that can reduce sequencing cost for a comparable product by two to three orders of magnitude – to approximately \$100,000 – will be supported under this program. Technologies/strategies are required to sequence and assemble genomes that have never been sequenced before, e.g., *de novo* sequencing, as well as to re-sequence genomes from additional individuals to study genetic variation. It is anticipated that initial implementations of the technologies supported under this program will begin producing substantial amounts of sequence data by 2008.

#### Features:

- Two receipt dates in the first year, one receipt date in each of years 2 and 3.
- Open to foreign and domestic, for-profit and non-profit organizations, public and private, such as universities, colleges, companies, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Companies applying for funds, or as partners with universities, will be expected to provide substantial cost-sharing as a demonstration of their commitment to the development path.
- Applicants must explicitly state if the goal of their project is *de novo* or re-sequencing.
- Applicants will propose specific milestones to guide their own R&D path, and will be evaluated **semiannually** against progress toward those milestones.
- The most obvious measure of success is demonstration of sequencing a substantial amount of DNA (at least 0.5 – 1 gigabase) at the target cost and quality; other measures may be proposed by the applicant.
- Applicants may request a full-scale project if sufficient preliminary data are available to support such an application. Applicants requiring support to demonstrate feasibility may propose a pilot/exploratory phase followed by a full scale research project, within a single grant application. The description of the exploratory phase must include specific milestones to demonstrate feasibility; progress toward these will receive administrative review to determine eligibility for scale-up.
- Grantees will participate actively and openly in one grantee meeting per year. Substantial information sharing will be required and is a condition of the award, because information sharing is required to advance the field; failure to openly share information will be grounds for discontinuation of funding. It is understood that some information developed

under the grants will be proprietary and cannot be shared without damaging the commercialization potential of the technology.

- Grantees will include funds in their budgets for travel of up to three members of their team to the grantee meetings. At the time of award, NHGRI will negotiate with the grantees, to include funds in their budgets to host the grantee meetings on a rotating basis, and the grantees will be expected to administer those funds and play a central role in organizing and hosting the meetings at their sites.
- Grantees will also include funds in their budget requests to bring advisors chosen by NHGRI to their site twice a year for progress evaluation.
- NHGRI will use information from reports, site visits, etc. to evaluate each grantee's progress; this information will be used to determine if funding levels should be increased or decreased in each funding cycle (each budget period within the project period).
- **anticipated cost per grant: not more than \$2.5M/yr.**
- **anticipated duration of grants: up to 3 years.**
- **funds required: up to \$8M in 2004 (4-6 awards), additional \$5M in 2005, additional \$3M in 2006 (if necessary, depending on how other projects are doing and if there are more good ideas). (All of these levels are pending discussion of other priorities.)**

## Program Announcement Concept:

### Technology Development for the \$1000 Genome

Purpose: The purpose of this program announcement is to solicit grant applications to develop novel technologies for sequencing DNA. Current technologies (summer 2003) are able to produce, for approximately \$50M, a high-quality draft sequence of a complex genome such as human or mouse (7.7-fold coverage, 6.5-fold coverage in Q20 bases, assembled into 225,000 sequence contigs that are connected by at least two read-pair links into supercontigs [total of 7,418 supercontigs at least 2 kb long], with N50 length for contigs equal to 24.8 kb and for supercontigs equal to 16.9 Mb. Nature 420:520, 2002). Development of technologies that can reduce sequencing cost by four to five orders of magnitude – to approximately \$1,000 – will be supported under this program. Technologies/strategies are required to sequence and assemble genomes that have never been sequenced before, e.g., *de novo* sequencing, as well as to re-sequence genomes from additional individuals to study genetic variation. It is anticipated that technologies supported under this program will begin producing genomic sequence data by 2013.

New sensing and detection modalities will need to be developed to achieve these goals; it is therefore anticipated that these research programs will require fundamental and engineering research conducted by interdisciplinary teams of investigators. The research conducted in response to this program announcement will entail substantial risk, balanced by outstanding scientific and management plans designed to achieve the very high payoff goals of the solicitation.

#### Features:

- Two receipt dates in the first year, one receipt date in each of years 2 and 3. **The program announcement may be reissued after 3 years.**
- Open to foreign and domestic, for-profit and non-profit organizations, public and private, such as universities, colleges, companies, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Companies applying for funds, or as partners with universities, will be expected to provide substantial cost-sharing as a demonstration of their commitment to the development path.
- Applicants must explicitly state if the goal of their project is *de novo* or re-sequencing.
- **It is anticipated that this program will require ten years to achieve its goals. For projects that receive five years of funding, an administrative site visit during the third year will recommend the level of funding for the fourth and fifth years, with the possibility of phase-out if progress is deemed insufficient. Also, as a result of this site visit, the P.I. will receive advice about the NHGRI's interest in accepting a competing renewal application to extend the initial award.**
- Applicants will propose specific technical and research milestones to guide their own R&D path, and will be evaluated **annually** against progress toward those milestones. **These projects will require a substantial amount of research, not just engineering, and milestones will be evaluated accordingly.**

- Applicants may request a full-scale project if sufficient preliminary data are available to support such an application. Applicants requiring support to demonstrate feasibility may propose a pilot/exploratory phase followed by a full scale research project, within a single grant application. The description of the exploratory phase must include specific milestones to demonstrate feasibility; progress toward these will receive administrative review to determine eligibility for scale-up.
- Grantees will participate actively and openly in one grantee meeting per year. Substantial information sharing will be required and is a condition of the award, because information sharing is required to advance the field; failure to openly share information will be grounds for discontinuation of funding. It is understood that some information developed under the grants will be proprietary and cannot be shared without damaging the commercialization potential of the technology. **Other investigators in the field may be invited to participate in these grantee workshops.**
- Grantees will include funds in their budgets for travel of up to three members of their team to the grantees' meetings. At the time of award, NHGRI will negotiate with the grantees, to include funds in their budgets to host the grantees' meetings on a rotating basis, and the grantees will be expected to administer those funds and play a central role in organizing and hosting the meetings at their sites.
- Grantees will also include funds in their budget requests, to bring advisors chosen by NHGRI to their site annually for progress evaluation.
- NHGRI will use information from reports, site visits, etc. to evaluate each grantee's progress; this information will be used to determine if funding levels should be increased or decreased in each funding cycle (each budget period within the project period).
- **anticipated cost per grant: not more than \$2.5M/yr.**
- **anticipated duration of grants: up to 5 years.**
- **funds available: \$6M in 2004 (3 – 5 awards), additional \$5M in 2005, additional \$5M in 2006. (All of these levels are pending discussion of other priorities.)**