Robert.Kaminski@rl.af.mil Tue Dec 18 11:07:05 2001

This is a reminder that Quarterly Technical & Financial Status Reports are due 15 Jan for the period 1 Oct 01 - 31 Dec 01

"Quarterly Reports -

1. The recipient shall submit quarterly reports on or about the 15th of January, April, July, and October. One copy each shall be provided to the following persons as listed in Article 5, Administrative Responsibilities. The July report, Project Summary Report, shall provide a project summary and shall, in addition to the distribution shown below, be posted to a web site to be designated by DARPA.

(a) Air Force Research Laboratory (or Navy) Program Manager (electronic only; MS Office-compatible)

- (b) Grants Administration Office.
- (c) Air Force Research Laboratory (or Navy) Grants Administrator (or the AFRL Grants Officer, if no AFRL Grants Administrator is listed in Article 5)
 (d) DADRA Decement (cleature is a maked by Market and the second state is a maked by Market and the second state is a maked by Market and the second state is a maked by Market and the second state is a maked by Market and the second state is a maked by Market and the second state is a market and the second state is a
- (d) DARPA Program Manager(electronic only; MS Office-compatible)"

The report will have two major sections; the Technical Status Report and the Business Status Report (see (a) and (b), below, respectively).

(a) **Technical Status Report.** The technical status report will detail technical progress to date and report on all problems, technical issues, or major developments during the reporting period. Each of the topics described below shall be addressed:

(i) A comparison of actual accomplishments with the goals and objectives established for the period, the findings of the investigator, or both.

The three milestones from the final (i.e. post-budget cut) grant are below. "1#1: We will establish the scale-up costs of the SSR system from two bits to the theoretical upperlimit. Oligonucleotides required for reversible, irreversible, and interwoven systems will be designed. (Mr. Shendure & Dr. Church)"

The development costs have been now estimated to be higher than the costs for the single bp memory, and since the latter is more desirable for the long term (having at least 100-fold higher bit-density), we have moved it forward as a project goal.

"1#2: We will do a lab test of an alternative to Flp involving Lambda-Red homologous recombination. (Mr. Reppas)"

A new system has been developed, debugged, and proven to be a useful alternative to Flp and Int based exchange systems (commercial example is the Gateway cloning system). The advantage of our system is that the exchange oligonucleotide can be designed rather than being stuck with the natural recognition sites of specialized recombination machinery.

"1#3: We will establish a plan including all necessary existing strains and required constructs for testing a RAG recombination variant usable in mammalian whole organism cell-lineage monitoring. (Mr. Shendure)"

We established a plan for RAG, and then went on to establish an even more costeffective plan based on endogenous DNA-methylation and our polony technology.

(ii) Reasons why established goals were not met, if appropriate.

The goals were met (and significantly exceeded).

(iii) A cumulative chronological list of written publications in technical journals. Include those in press as well as manuscripts in preparation and planned for later submission. Indicate likely journals, authors, and titles.

- Badarinarayana, V, Estep, PW, Shendure, J, Edwards, J, Tavazoie, S, Lam, F and Church, GM (2001) Selection analyses of insertional mutants using subgenic-resolution arrays; Nature Biotechnology Nov;19(11):1060-5.
- Ge, H, Church, GM, Vidal, M (2001) Correlation between transcriptome and interactome data obtained from S. cerevisiae. Nature Genetics, Dec;29(4):482-6.
- Schilling, CH, Covert, MW, Famili, I, Church, GM, Edwards, JS, Palsson, BO (2002) Genomescale metabolic models of less characterized organisms: A case study for Helicobacter pylori . Submitted to J. Bact. special issue.
- Dudley, AM, Aach, J, Steffen, MA, and Church, GM (2002) Measuring absolute expression with microarrays using a calibrated reference sample and an extended signal intensity range. Submitted to Proc. Nat. Acad. Sci.
- Cheung, KJ, Badarinarayana,V, Selinger, D, Janse, D, and Church, GM (2002) Microarray analysis reveals supercoiling-dependent transcription in the Escherichia coli osmotic stress regulon. Submitted to Proc. Nat. Acad. Sci.
- Cohen, B, Pilpel, Y, Mitra, R, Church, GM (2002) Discrimination between paralogs using microarray analysis: Application to the Yap1p and Yap2p transcriptional networks. Submitted to Proc. Nat. Acad. Sci.
- Masuda, N. and Church, GM. (2002) Global Analysis of Escherichia coli Gene Expression during the Overexpression of the Response Regulator EvgA. Submitted to J. Bacteriol.
- Wright, M and Church, GM (2002) An Open-source Oligonucleotide Microarray Probe Standard for Human and Mouse. Submitted to Nature Biotechnology.
- Zhu, Z, Pilpel, Y, and Church, GM (2002) Computational Identification of Transcription Factor Binding Sites via a Transcription-factor-centric Clustering (TFCC) Algorithm. Submitted to J. Molec. Biol.

 $({\rm iv})~$ A list of professional personnel associated with the research effort. List any advanced degrees awarded, including dates, recipient, type of degree, and thesis title.

Professional Personnel

<u>George Church</u> Ph.D. Harvard University, Cambridge, MA 1984 Biochem. & Molecular Biology, B.A. Duke University, Durham, NC 1974 Zoology & Chem

John Aach 09/1980-01/1987: Boston University, Boston, MA. PhD Interdisciplinary Studies: Philosophy and Psychology 09/1972-06/1975: Princeton University, Princeton, NJ. AB Music

<u>Allegra Petti</u> B.A. Biology, cum laude, Rice University, May 1998 Research topic: Inference of transcriptional regulatory networks from microarray data using nonlinear mathematical models.

<u>Nikos Reppas</u> MBiochem. (combination of BA and MA) from Oxford University received June 1998. The MA thesis title is "X-ray Crystallographic Analysis of the Aspartate181->Alanine Substrate-Trapping Mutant of Human Protein Tyrosine Phosphatase 1B (PTP1B) Catalytic Domain".

<u>Rob Mitra</u> PHD - MIT 2000, MS - MIT 1993, BS - MIT 1993 Research Topic - High Throughput Sequencing Technology

Xiaohua Huang Ph.D. in Biophysical Chemistry (September, 1996), Stanford University B.S. in Chemistry (July, 1986), Zhongshan University, Guangzhou, China

Daniel Segre 2000 : Ph.D. in Life Sciences, Department of Molecular Genetics, The Weizmann Institute of Science, Rehovot, Israel. Advisor: Prof. Doron Lancet. Title: The primordial emergence of compositional inheritance.

(v) Papers presented at meetings, conferences, seminars, etc.

Nov 27-Dec 1, 2001 DARPA BioCOMP meeting Monterey, CA (George Church)

Dec 1, 2001 E.coli resources meeting, Chicago, IL (Doug Selinger)

Dec 17, 2001 Biomedical Informatics Grand Rounds Mon 11 AM Children's Hospital, Boston (George Church)

(vi) Consultative and advisory functions to other laboratories and agencies, especially Air Force and other DoD laboratories on research supported under the agreement. Provide factual information about the subject matter, institutions, dates, and the names of individuals involved.

George Church initiated discussion in December of a collaboration involving Tom Knight (DARPA BIOCOMP grantee at MIT EE/CS) and Eric Lander at the Whitehead Genome Center to completely sequence two nearly-minimal genomes of tactical value to both BIOCOMP projects. This should save DARPA BIOCOMP about \$600K.

(vii) New discoveries, inventions, or patent disclosures and specific applications stemming from the research effort.

A patent has been filed on Nov 14, 2001 titled "Amplification of a Nucleic Acid Strand Segments" (as a continuation of Patent # 09/143,014 filed Aug 28,1998). It was based on work funded in part by DOE, as well as impact of recent work on this DARPA BIOCOMP.

(b) Business Status Report. The business status report shall provide summarized details of the budget status of this agreement.

Provide a comparison of budgeted and actual expenditures. Any major deviations shall be explained with discussion of proposed actions to address the deviations.

We have a definite need for additional funds (closer to the original budget) if that is at all possible at this point, it will accelerate our progress in light of the new discoveries (above).

The Financial Report format is as follows:

The financial report you are expecting on Agreement No. F30602-01-2-0586 cannot be filed today due to administrative issues between Harvard Medical School and the Air Force Research Laboratory. Sponsored Programs Administration at Harvard Medical School has yet to receive a fully executed copy of the agreement from the Air Force Research Laboratory and therefore is unable to set up the award and issue an account number for Dr. Church's use.

Once a copy of the signed agreement is returned to Harvard, an account number will be established and spending will commence.

Should you have any further questions regarding this matter, please do not hesitate to contact:

Mary Beth Shertick Financial Manager Department of Genetics Harvard Medical School 617-432-7662