SUMMARY OF NEW AWARDS

BIOENGINEERING RESEARCH PARTNERSHIPS (BRP)

FY 2003

The following text provides a summary of new Bioengineering Research Partnerships (BRP) grants awarded during Fiscal Year 2003 by the BECON member institutes and centers in response to program announcements PA-01-024, PAR-02-010 and PAR-03-032. The objective of the BRP program is to support basic bioengineering research addressing important biological or medical problems with the work being done by a multidisciplinary research team which applies an integrative, systems approach to develop knowledge or methods to focus on the project objectives.

Funded grants are listed below in alphabetical order by the principal investigator's (PI's) last name. Other information provided for each grant includes PI affiliation, project title, grant number, funding organization, and a brief summary of the project.

1. **Principal Investigator:** Chiocca, E. A **Affiliation:** Massachusetts General Hospital
   Project Title: Interdisciplinary Tumor Complexity Modeling
   Grant Number: 1 R01 CA085139-01A2 **Funding Organization:** NCI
   Abstract:

"Interdisciplinary Tumor Complexity Modeling" (2nd RESUBMISSION). In spite of aggressive l therapies, the outcome for patients suffering from highly malignant brain tumors remains uniformly fatal. Responsible for this grim outcome are rapid tumor growth, clonal heterogeneity, acquired treatment resistance and extensive tumor invasion, rendering cytoreductive therapy ineffective. We believe that malignant tumors behave as complex dynamic, adaptive and self-organizing biosystems rather than as unorganized cell masses. If this is true, such malignant tumors also have to be investigated and ultimately targeted as complex: systems. Our work is therefore motivated by the following three hypotheses: (1) malignant brain tumors behave as complex dynamic biosystems; (2) these tumors systems invade according to the principle of "least resistance, most permission and highest attraction "; (3) their spatio-temporal behavior can be studied, simulated and predicted using an interdisciplinary approach combining in vitro and in vivo experiments, human imaging data and computational modeling. To investigate these hypotheses, our specific aims are as follows. Specific AIM 1: We will develop a novel 3D in vitro assay system, suitable of displaying several key-features of multicellular tumor spheroids (MTS) in parallel over a prolonged period of time. The experimental studies using these devices include the microstructural analysis of the extracellular matrix gel-medium as well as the structural, genetics and functional analysis of the spatio-temporal expansion of the micro-tumor system (i.e., on site proliferation and invasive cell network). We will also study tumor growth, invasion and physiology (blood flow and blood volume) in vivo, using MR-imaging of an orthotopic xenogeneic brain tumor model in athymic rats. Studies follow, which investigate invasive tumor cell dynamics in vivo with and without specifically implanted "attractor" sites. Both, in vitro and in vivo results will generate dynamic, multiscaled multi-modality data sets, which will then be incorporated into the computational models. Specific AIM 2: We will develop a set of related, innovative computational models to simulate brain tumor proliferation, genetic and epigenetic heterogeneity, angiogenesis and most importantly, tissue invasion. Discrete and continuum approaches include a variety of techniques such as cellular automata, Kinetic Monte Carlo (KMC) simulations, agent based modeling, gene-regulatory net modeling, fractal analysis and coupled reaction-diffusion equations. Once developed, the computational models will drive the experiments and vice versa. Finally, the merged models will be used to predict the course of brain tumor expansion using real human imaging data (retrospective study) and will be further developed into powerful virtual reality platforms for treatment planning and surgical training tools (feasibility study). Based on our convincing preliminary studies paradigm-shifting insights into brain tumor growth, heterogeneity, invasion and angiogenesis can be expected. The presented work is highly innovative and profoundly interdisciplinary as it combines many

seemingly disparate disciplines such as cancer research, statistical physics and mechanics, materials science, biomedical engineering and -imaging, computational visualization, mathematical biology, computational and complex systems science. This Bioengineering Research Partnership investigates groundbreaking tumor biology concepts. This work can therefore very well build the basis for the development of novel diagnostic tools, innovative patient specific treatment planning devices and thus, may ultimately lead to more successful therapeutic strategies, capable of changing the grim outcome of the many patients suffering from this devastating disease.-

2. **Principal Investigator:** **Clarke, Robert** **Affiliation:** Georgetown University
Project Title: Molecular Analysis of Human Breast Cancer
Grant Number: 1 R01 CA096483-01A1 **Funding Organization:** NCI
Abstract:

Many women with small, node-negative breast cancers are essentially overtreated. For example, most Stage I breast cancers are treated with both local and systemic therapies but approximately 80% are effectively cured with local interventions alone. Separating these patients from the approximately 20% who recur, irrespective of their treatment, remains problematic. Consequently, the development of novel methods that can more accurately predict for a nonrecurrent vs. recurrent phenotype is a major priority. We address this issue in our response to PAR-02-010, for which we have established an imaginative and integrated Bioengineering Research Partnership comprising three research teams (Bioengineering & Biostatistics; Clinical & Pathology; Microarray & Molecular Analysis) from two local sister universities (Georgetown University and The Catholic University of America) and the University of Edinburgh (Scotland). We will apply expression microarray and tissue array technologies and powerful new data analysis algorithms to define the gene expression profiles of 600 invasive breast tumors (Stages I-III). Our multidisciplinary teams will use these molecular profiles and established prognostic factors to build artificial intelligence-based classifiers and multivariate models that accurately predict those patients with nonmetastatic disease (especially Stage I) who will not recur. In the long terms, the genes in this classifier and the classifier's algorithms will be used to build custom diagnostic arrays and software for routine clinical use. HYPOTHESES: We hypothesize that differences in the gene expression profiles of tumors determine outcome (recurrence) in patients with nonmetastatic disease. We also hypothesize that computational bioinformatics can discover these differences and use this knowledge to build classifiers that predict each patient's prognosis (especially in Stage I disease). AIM 1: We will perform gene expression analysis on breast needle biopsies of 600 invasive, nonmetastatic breast tumors. AIM 2: We will build an integrated data processing and management system for data acquisition and retrieval, to support the data analysis algorithms to be optimized and applied in Aim 3. AIM 3: We will optimize and apply novel pattern recognition and information visualization technologies, recognizing the high dimensional nature of the data, to discover and validate gene subsets that separate recurrent from nonrecurrent tumors. We will integrate advanced artificial intelligence algorithms and biostatistical models to build predictive classifiers that can more accurately define cancer phenotypes and predict clinical outcomes. AIM 4: We will use tissue arrays (multiple cores from archival tissues arrayed on glass slides) to validate and optimize the performance of these classifiers in a retrospective prognostic study of human breast tumors.-

3. **Principal Investigator:** **Del Nido, Pedro J** **Affiliation:** Children's Hospital (Boston)
Project Title: Image-guided Intracardiac Beating Heart Surgery
Grant Number: 1 R01 HL073647-01 **Funding Organization:** NHLBI
Abstract:

Modem cardiac surgical practice involves the routine use of cardiopulmonary bypass (CPB) for performing both coronary artery bypass graft (CABG) procedures on the heart surface as well as procedures inside the heart, classified broadly as intracardiac surgery. However, recent studies indicate that CPB carries important risks that can lead to reduced neuropsychiatric function and stroke in adults,