

## **BUDGET JUSTIFICATION**

### **Einstein Medical School, Leavittown, New York**

All costs are stated in year 1 dollars. Fringe benefit costs at Darwin will be 36.75% of salary in year 1 with a projected increase of 1% each successive year. The indirect cost rate is 59.78% in year 1, 59.9% in years 2 through 4. All costs are projected to increase at a rate of 3% per year except where noted.

#### **Personnel**

**Jane Smith, Ph.D.** Professor, Department of Epidemiology, Einstein Medical School, will serve as an epidemiologist and principal investigator for the study at 10% effort each year. Dr. Smith is an epidemiologist with specific expertise in the conduct of complex, interdisciplinary investigations. She has been principal investigator on 13 NIH grants over the past 10 years and co-investigator on numerous others. Dr. Smith is the Principal Investigator on the case-control study of prostate cancer that will contribute the New York portion of the population for the proposed research plan. For this study, she will provide scientific leadership and guidance for the study, and maintain regular contact with all study investigators and ensure the efficient and timely conduct of the research activities. She will actively participate in the design of the study methods and procedures for all aspects of the study and will prepare manuscripts particularly focusing on the case-control component.

**Samantha James, Ph.D.** Assistant Professor, Department of Epidemiology, Einstein Medical School, will serve as a molecular epidemiology co-investigator for the project at a 20% annual effort. Dr. James will participate in design of the study, statistical analysis and manuscript preparation. Dr. James is a molecular epidemiologist, with training in toxicology and epidemiology. She has conducted studies related to DNA repair gene expression and polymorphisms and has provided oversight for the pathology component for the New York Study. She will collaborate on the design of the study methods, including histologic and molecular components with Drs. Bond, Evans, Samuels, and Lawson. She will work closely with Dr. Juras on refining the study follow-up methods and materials. She will directly supervise Ms. Martinez on follow-up of the New York cases and Ms. Conroy on record review. She will assist in coordination between the collaborating centers on the data collection and management issues and provide guidance and direction to Mr. Zoloft. She will participate in the preparation of manuscripts, particularly for the prognostic component.

**August Evans, M.D.** Professor of Pathology, Einstein Medical Center, will serve as a urologic pathologist on the project at 5% effort. Dr. Evans conducts the histopathology re-review and p53 IHC evaluation for Dr. Smith's prostate cancer epidemiology study and participated in a collaborative project with Dr. Lawson to assess the concordance in pathological and p53 IHC readings between New York and Singapore. Dr. Evans will collaborate with the Dr. Lawson to in providing pathology and immunohistochemistry expertise to the project.

**James Bond, M.D.** Professor of Surgery (Urology), Einstein Medical Center, will serve as a clinical urologist on the study on an as needed basis. Dr. Bond currently is a collaborator on the New York Pancreatic Cancer Study with Drs. Smith, James, and Evans.

**Sticky Wicket, Ph.D.** Associate Professor, Department of Biostatistics, Einstein Medical School, will serve as a biostatistician for the project at 5% effort each year. Dr. Wicket is Director of the Biostatistics at the Norris Cotton Cancer Center and has particular expertise in statistical analysis of clinical and behavioral follow-up data of cancer patients. He will provide statistical guidance and support to the investigators on the prognostic component and case-control components of the project.

**Oscar Zoloff, M.S.** Research Associate, Department of Biostatistics, Einstein Medical School, will assist with programming and data analysis at 20% effort each year. Mr. Zoloff will be responsible for generating and maintaining computerized tracking databases to enable efficient collection and linkage of follow-up data obtained from subjects, medical records and vital records, as well as tracking and sharing data collected in the participating laboratories. He will generate specific reports for each portion of the study that will facilitate monitoring progress of activities and sharing data between the three collaborating institutions. He will be responsible for creating the analytic files and under the guidance of the study investigators, the statistical analysis.

**Ann Martinez** Research Assistant, Department of Biostatistics, Einstein Medical School, will be responsible for coordination and follow-up activities, specimen retrieval and shipment, and research assistant support at an annual 50% effort. Ms. Martinez will contact surviving cases or next-of-kin by telephone to inform them of the study, to obtain consent and to administer a brief follow-up questionnaire. She will be responsible for all mailings to subjects, including the annual newsletter and medical record release forms, and will telephone subjects to request unreturned release forms. She will maintain current patient contact information and will be responsible for working with nationwide locator databases to determine current address information and vital status of subjects we are unable to contact. She also will be responsible for retrieving and abstracting death certificate information, for medical record review and abstraction to verify updated prognostic and treatment information into a computerized database system, and conducting quality control activities. She will produce periodic (e.g., monthly and annual) status reports for the project. Ms. Martinez also will serve as the liaison with the pathology department and the laboratory storing the tissue and blood samples and coordinate retrieval and shipment of the specimens to Hoboken and ISIS. She will be responsible for updating study protocols and will participate in regular staff meetings.

## **Travel**

Investigators from the three study locations will meet annually at a scientific conference to review progress, discuss data and set priorities. Annual travel expenses for three Einstein co-investigators are estimated to be \$1,100 per person, or \$3,300 in year 1. This estimate covers the following costs: airfare (\$600) and lodging and meals (\$170 per day for 3 days, \$510).

**Other Expenses**

**Conference Calls:** Four conference calls per year will be needed with study investigators at the three locations (Einstein, Hoboken, Singapore). From historical precedent each call is estimated to cost \$480, for a year 1 total of \$1,920.

**Patient Contact Calls:** Study staff will contact patients about release forms and to administer the follow-up questionnaire. These calls are estimated to last approximately 30 minutes per subject at a cost of \$0.10 per minute for 400 subjects per year (approximately 850 subjects x 2 years x 10% reminder calls overall). The year 1 cost is estimated at \$1275.

**Medical Release Form Postage:** Medical record release forms will be sent to and from each subject at a cost of \$0.37 per letter with 2 letters per subject, approximately 850 subjects in all for a total of \$629 in year 1.

**Shipment of Samples:** Patient blood work will be shipped each year between study locations at a cost of \$100 in year 1. There will be four shipments each year at an estimated cost of \$25.

**Computer Network/Software/Hardware:** Fees are requested in all years of the study to cover the expected computer network costs. This includes hardware/software needs as well as the cost of maintaining network connections. These fees are estimated at \$3,069 per full-time employee. The total cost for year one is \$3,376.

**IRB Review.** The Institutional Review Board at Einstein charges for review of research protocols. The one-time charge is estimated at \$1,500 and is included in year 1.

## **SUBCONTRACTS**

### **Hoboken School of Public Health, Hoboken, New Jersey**

All costs are stated in year 1 dollars. Fringe benefit costs at Hoboken will be 23.7% for Dr. Samuels, 38.4% for all other staff. The indirect cost rate is 64% in all years. All costs are projected to increase at a rate of 3% per year except where noted.

#### **Personnel**

**Saul Samuels, M.D.** Professor, Department of Cancer Cell Biology, Hoboken School of Public Health, will serve as Principal Investigator for this subcontract and will oversee the administrative and scientific aspects of this subcontract. He will participate on this project at a 15% effort each year. Dr. Samuels is a leader in the field of molecular and genetic epidemiology. For several years, he has had a very productive collaboration with Dr. Smith and has extensive experience applying molecular biomarkers of susceptibility, exposure and effect in the New York prostate cancer epidemiology study. His responsibilities for the proposed project include input into the study design, data collection, quality control, laboratory supervision and handling of the budget. Specifically, Dr. Samuels will oversee the mutational analyses of p53 on the New York and Singapore cases, and p53 polymorphism of the New York cases and controls. Dr. Samuels will be responsible for the coordination with Dr. Smith at Einstein and the Singapore collaborators, and work closely with Dr. Matson and others in the scientific and technical aspects of the analyses of the molecular markers. He will work with Dr. Smith to organize the data transfer and sample transfer and handling of the Hoboken laboratory data. He will communicate on a weekly basis by meeting with Dr. Smith and the Einstein/Singapore team to coordinate all aspects of study and to monitor study progress. In addition, Dr. Samuels will oversee, direct and participate in all manuscript preparation.

**Mona Longo** will serve as a laboratory technician at 50% annual effort. Ms. Longo will be primarily responsible for conducting mutation and genotype analyses. She has considerable expertise in this, having worked on other projects performing this type of experimental procedure. She will train the technician and provide expertise in specimen handling, tracking and storage, as well as data entry and retrieval.

**To be named, Technician** will serve on the project at 50% effort and will be responsible for direct specimen handling and preparation as well as assisting in molecular analyses. Specifically, this will include specimen tracking and storage. He/She will receive, log and archive specimens, maintaining an up to date computerized record of samples, receipt dates and current amounts during the preceding period. He/She will extract DNA and will be responsible for ordering supplies, conducting and monitoring the mutation and genotyping procedures and coordinating DNA banking. He/She will be required to have extensive experience in the laboratory and be an expert at applying these methods.

## Supplies

**Laboratory Supplies:** The estimated cost for sample preparation and storage includes miscellaneous tubes, pipettes, disposable clothing and DNA extraction kits and chemicals needed for PCR amplification and for mutation analysis. Molecular analysis costs will include primers, dNTPs, and miscellaneous PCR supplies. Barrier clothing and disposable eye protection will be needed. We will also require additional PCR supplies, including Taq, buffers, pipette tips, reaction tubes, and acryamide gels. The breakdown of costs per year is:

	Cost per Sample	Per Year		Yr1	Yr2	Yr3	Yr4
		Tumor Samples	Blood Samples				
DNA Extraction	\$7.50	423		\$3,173	\$3,268	\$3,366	\$3,467
Mutation Analysis	17.50	423		7,403	7,625	7,853	8,089
Genotyping	5.00		580	2,898	2,984	3,074	3,166
				\$13,473	\$13,877	\$14,293	\$14,722

## Other Expenses

**Shipment of Samples:** Patient blood work will be shipped each year between study locations at a cost of \$100 in year 1. There will be four shipments each year at an estimated cost of \$25.

## **SUBCONTRACTS**

### **Impressive Singapore Institute of Science (ISIS), Singapore**

All costs are stated in year 1 U.S. dollars. Fringe benefit costs at ISIS will be 33%. The indirect cost rate is 8% in all years. All costs are projected to increase at a rate of 3% per year except where noted.

#### **Personnel**

**Max Matson, M.D. Ph.D.**, Coordinator of the Unit of Cellular and Molecular Biology, ISIS, will serve as Principal Investigator of this subcontract at a an annual effort of 15% with no salary support requested. He will be responsible for the overall coordination of the work in Singapore and for interacting with Dr. Smith regarding the joint project. Dr. Matson has extensive experience in molecular studies of cancer and is co-P.I. of the Singapore Prostate Cancer Study where he has taken responsibility for the supervision of all laboratory work related to sample collection and for the molecular genetics studies of the project. Together with the study pathologists, methods have been standardized for the immunohistochemical detection of p53 and the genetic analysis of p53 alterations. Together with Dr. Samuels, Dr. Matson will lead the laboratory studies of this project. He will specifically be responsible for coordinating the molecular analyses using DNA from cases included in the Singapore study, setting up immunohistochemical assays for p53 targets, and coordinating the work with the pathologists responsible for the immunohistochemical evaluation. He will take leadership in the preparation of manuscripts regarding the molecular characterization of prostate tumors and - specifically - the status of the p53 pathway.

**Nina Juras, M.D. Ph.D.**, Scientist at the Unit of Environmental and Endocrinology Research, ISIS, will serve as a co-investigator on the project at a 35% annual effort. Dr. Juras has extensive experience in the area of molecular and clinical epidemiology of cancer, in particular for bladder tumors. She was co-P.I. of the Singapore Prostate Cancer Study and coordinated the work of epidemiologists, pathologists, clinicians, nurses, molecular biologists, and statisticians, and continues as PI for a prostate cancer network. For the proposed study, Dr. Juras will assist in the coordination of the follow-up and laboratory activities in Singapore. She will be responsible for supervising the active and passive follow-up of cases in the Singapore Prostate Cancer Study and will keep a close interaction with the staff responsible for the laboratory assays to be performed in Singapore and in the US. She will provide scientific leadership in proposing models of the natural history of bladder cancer and the application of standard as well as novel strategies for the survival analyses. In collaboration with Drs. Smith, Evans, Lawson, Matson, and James, she will take leadership in the preparation of manuscripts related to the identification of prognostic factors associated with bladder cancer progression and survival.

**Magdelana Koch, M.D. Ph.D.**, a Scientist at the Unit of Environmental and Endocrinology Research, ISIS, will serve as a co-investigator on the project at an annual 10% effort, but with no salary requested. Dr. Koch has internationally recognized experience in the area of occupational and environmental epidemiology, with a special emphasis in cancer. She is co-P.I. of the Singapore Prostate Cancer Study. Within this project, she has played a key role in the interaction with the collaborating US investigators at the National Cancer Institute and has taken scientific leadership in the etiological studies. Dr. Koch will be predominantly involved in the study of the relationship between molecular alterations in the p53 pathway and environmental risk factors for bladder cancer. She will participate in the overall conduct of the study and will take leadership in the etiological aspects of the project.

**John Lawson, M.D. Ph.D.**, Attending Pathologist at Hospital ISIS, will serve as the pathologist for the project at an annual 15% effort. Dr. Lawson is responsible for the pathological evaluation of urological tumors. He has international recognition in the area of ultrastructural pathology. He is responsible for the coordination of retrieval of blocks from all participating centers in Singapore and for the pathological evaluation of cases in the Singapore Prostate Cancer Study and for supervising the immunohistochemical evaluation of p53 overexpression. Together with Dr. Evans, Dr. Lawson has conducted a pilot study aimed at determining the concordance of pathological evaluation of a subset of tumors from the Singapore and the New York cases. With Dr. Matson, Dr. Lawson will be responsible for the overall supervision of the proposed immunohistochemical analysis of p53 and p53 pathway genes and with Dr. Evans he will be responsible for pathology oversight for the project.

**Antonia Stoker** is a Technician who has been involved in the immunohistochemical studies of p53 overexpression in the samples from the Singapore study, will serve as the technician on this project at an annual 50% effort. She has been responsible for registration of tissue blocks received from the participating hospitals, preparation of sections, immunohistochemical assays, registration of immunohistochemical evaluation and coordination of laboratory work. She also has experience with tissue microarray preparation. She will be responsible for obtaining sections, performing immunohistochemical assays, quality controls, and computerized registration of results of immunohistochemical assays for p53 and p53 pathway genes.

**Gina Carr, R.N., and Angela Ford, R.N.** will serve as a Research Assistants at 50% effort each, each year of the study. Ms. Carr and Ms. Ford have each conducted chart reviews, telephone interviews, and have participated in administering questionnaires and materials required for biological sample collection for subjects the Singapore Prostate Cancer Study. They will maintain current patient contact information, perform annual mailings to patients and will be responsible for working with nationwide locator databases to determine current address information and vital status of subjects we are unable to contact. They will be responsible for bi-annual contact with surviving cases to administer a brief follow-up questionnaire. Additionally, they will request and abstract death certificate information, conduct medical record reviews to document prognostic and treatment information into a computerized database system, and perform quality control activities. They will produce periodic (e.g., monthly and annual) status reports for the project and participate in regular staff meetings.

**Victor Vargas, B.S.**, will serve as a program/analyst for the project at 20% effort. He has a degree in Statistics and has participated in the survival analyses under the supervision of Dr. Juras. Under Dr. Juras's supervision, he established the databases for the pilot follow-up study. He and will refine and maintain databases containing information on pathological characteristics of tumors, active and passive follow-up, and molecular and immunohistochemical studies to be shared between institutions for the joint project.

### Consultants

**Simon Pope, Ph.D., Anthony Cope, Ph.D., and Stella Ness, MPH** will serve as unpaid consultants to the project. The three are investigators on the NCI Intramural component of the Singapore Prostate Cancer Study and have agreed to provide the results of the *p53* polymorphism and haplotype analysis being carried out at the NCI Core Genotyping Facility on the study samples. In addition, they will ensure that the genotyping results are comparable to the analysis that will be carried out on the New York samples at Hoboken.

### Supplies

**Automatic Pipettes:** Two sets of automatic pipettes are needed for the study. These items will be purchased in year 1 only at a total cost of \$1,200.

**There are seven different items that will be analyzed over a three-year period. Itemized, they are:**

1. Supplies needed for the immunohistochemical staining with the VENTANA automated immunostainer (for 100 slides):

Special slides	\$70.00
Washing Buffer (approx 125 mL)	85.00
DAB Solution (approx 35 mL)	35.00
Anti-mouse envision antibodies (25 mL)	300.00
Peroxidase blocking reagent (25 mL)	2.00
Hematoxyen (25 mL)	4.00
Staining racks (50 units)	20.00
Absorbing pads (10 units)	55.00
<u>Primary antibody (500 uL @ 1:50 dilution) 100 tests per vial</u>	<u>350.00</u>
Total Cost for 100 slides (cases)	\$921.00
<b>Cost per slide (case)</b>	<b>\$9.21</b>

850 cases for New York immunostained with antibodies DO7 and 1801 + control slides + 10% replica validation + 10% repeats for an approximate total of 2,000 cases. 2,000 cases at \$9.21/case equates to \$18,420.

Other analysis costs will be:

2. Additional cost of general laboratory materials (i.e., PBS, cover slips) is estimated at \$3,580.
3. 13 antibodies at \$350 per antibody vial equates to \$4,550.
4. Testing of antibodies, optimization of conditions for all antibodies. There will be 40 slides per antibody, 13 antibodies, for a total of 520 slides at a cost of \$5.71 per slide. This amounts to \$2,969.
5. Testing TMA from Singapore. 2,500 cases at 200 tumors per array amounts to 12.5 arrays with 1 repeat. A total of 25 arrays will then be needed at \$5.71 per array for a total cost of \$143.
6. Validation using individual tumor tissue sections. 13 antibodies at 50 cases per antibody amounts to 650 slides. 650 slides at \$9.20 per slide, including primary antibody, equates to \$5,980.
7. Additional cost of general laboratory reagents and materials, office supplies, computer diskettes, etc. is estimated at \$1,980.

Cumulatively, these seven items amount to an estimated cost of \$37,622.

Averaged over three years, the analysis costs will be: \$12,541 per year (years 1-3 only).

### **Travel**

An annual trip to the United States is budgeted for each of the two leading Singapore investigators each year is requested. The cost is estimated at \$1,500 per person, or \$3,000 in year 1. This estimate covers the following costs: airfare (\$990) and lodging and meals (\$170 per day for 3 days, \$510).

### **Other Expenses**

**Block Shipping:** To retrieve samples from hospitals and return blocks to hospitals, shipping costs are requested. There will be 20 shipments per year at an estimated year 1 cost of \$15. The year 1 total is \$300.

**Molecular Analyses Shipping:** 3 shipments per year will be sent to the United States at \$100 per shipment. The year 1 cost will be \$300.