

Indoleamine 2,3-dioxygenase controls conversion of Foxp3⁺ Tregs to TH17-like cells in tumor-draining lymph nodes

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The immunoregulatory enzyme indoleamine 2,3-dioxygenase (IDO) is expressed by a subset of murine plasmacytoid DCs (pDCs) in tumor-draining lymph nodes (TDLNs), where it can potentially activate Foxp3⁺ regulatory T cells (Tregs). We now show that IDO functions as a molecular switch in TDLNs, maintaining Tregs in their normal suppressive phenotype when IDO was active, but allowing inflammation-induced conversion of Tregs to a polyfunctional T-helper phenotype similar to proinflammatory T-helper-17 (TH17) cells when IDO was blocked. In vitro, conversion of Tregs to the TH17-like phenotype was driven by antigen-activated effector T cells and required interleukin-6 (IL-6) produced by activated pDCs. IDO regulated this conversion by dominantly suppressing production of IL-6 in pDCs, in a GCN2-kinase dependent fashion. In vivo, using a model of established B16 melanoma, the combination of an IDO-inhibitor drug plus antitumor vaccine caused up-regulation of IL-6 in pDCs and in situ conversion of a majority of Tregs to the TH17 phenotype, with marked enhancement of CD8⁺ T-cell activation and antitumor efficacy. Thus, Tregs in TDLNs can be actively reprogrammed in situ into T-helper cells, without the need for physical depletion, and IDO serves as a key regulator of this critical conversion. Pharmacologic IDO inhibitor 1-methyl-D-tryptophan (1MT) is now in Phase I clinical trials and Phase II trials are planned. The synergy between 1MT and vaccines in the mouse model, with the mechanistic explanation of converting Tregs into TH17 cells, gives a strong molecular rationale for testing 1MT+vaccines in Phase II clinical trials.

What Can Brown Do For You? The Many Roles of the Ubiquitin-Proteasome System (UPS) and Monoubiquitination in Regulating Mammalian Transcription

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Major histocompatibility class II (MHC II) molecules are glycoproteins that present extracellular antigens to CD4⁺ T cells and are essential for initiation of adaptive immune response. MHC II molecules are critical for tumor recognition as multiple highly metastatic tumors down regulate the expression of MHC II to evade activation of the anti-tumor inflammatory response. Because MHC II is regulated solely at the level of transcription, it is important to understand MHC II gene expression in order to aid in the development of novel anti-tumor therapies. MHC II expression requires recruitment of a master regulator, the class II transactivator (CIITA), to the MHC II promoter. We have previously linked CIITA to the UPS by demonstrating that monoubiquitination of CIITA dramatically increases its transactivity whereas polyubiquitination leads to CIITA degradation. The 26S proteasome, the master regulator of protein degradation, has also been shown to have non-proteolytic roles in transcription. We have shown that 19S ATPase subunits of the 26S proteasome regulate MHC II transcription and are necessary for stable promoter binding of CIITA. Here, we identify an ATPase binding domain in the N-terminus of CIITA that is crucial for CIITA stability and MHC II expression. Furthermore, we have identified phosphorylation and ubiquitination sites in CIITA that are critical for CIITA transactivity and MHC II expression. An understanding of the proteolytic and non-proteolytic role of the UPS in MHC II transcription will provide novel strategies for manipulating the expression of MHC II genes and thus aid in the development of novel anti-tumor therapies.

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Genome-wide DNA Methylation Maps in Follicular Lymphoma Cells.

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We developed a large-scale bisulfite sequencing approach for analyzing genome-wide DNA methylation patterns by combining bisulfite treatment of genomic DNA with single-molecule-based parallel sequencing. The methylated DNA fragments from lymphoma cells were isolated and enriched using Methylated CpG Islands Recovery Assay (MIRA) which is based on the high affinity of the MBD2b and MBD3L1 proteins complex for methylated DNA. The methylation-enriched genomic DNA was treated with bisulfite and amplified by PCR with primers designed to amplify DNA molecules carrying bisulfite-modified adapter sequences at both ends. The PCR amplicons were sequenced using the Roche-454 GS FLX sequencer. We generated 516K mappable bisulfite sequencing reads (approximately 100Mb data) with an average read length of 143bp (range 20bp to 444bp). Among the 516K bisulfite sequences approximately 436K reads (85%) were uniquely mapped to the human genome. The total number of bases covered on the genome was 18.6 million including 5.4 million cytosines and 739,260 CpGs. We identified 11,972 methylated regions of interests with an average methylation index above 20%. These methylation hot-spots were associated with 4,033 CpG islands (CGIs) that include CGIs associated with several large gene clusters such as HOX and Protocadherin gene clusters. The genome-wide DNA methylation patterns were correlated with transcriptome data from Illumina Beads arrays and ChIP-on-Chip analyses of genome-wide histone modifications such as tri-methyl-H3K27, and tri-methyl-H3K4. These integrated approaches have led to the discovery of novel targets for aberrant DNA methylation in the lymphoma epigenome and provided a comprehensive analysis of the DNA methylation sequence composition and distribution.

To metastasize or not to metastasize – roles for epigenetics in tumor metastasis

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Epigenetic regulation is an essential mechanism by which cells regulate accessibility to chromatin DNA, hence allowing critical processes such as DNA repair or gene transcription to occur. The contribution of dysregulated epigenetic states to specific human cancers remains unknown. In order to achieve metastatic ability, tumor cells alter gene expression to escape from host immunosurveillance. Major histocompatibility class II (MHC-II) molecules are glycoproteins which present tumor derived antigens to CD4⁺ T cells and activate anti-tumor immune responses in order to limit tumor growth. MHC-II molecules are regulated at the level of transcription by a master regulator, the Class II Transactivator, CIITA, whose association with the MHC-II promoter is necessary to initiate MHC-II transcription. Thus, MHC-II are crucial for initiation, regulation and maintaining the anti tumor immune response. To further understand the role played by epigenetics in regulating CIITA and MHC-II expression in metastatic tumor cells, we have investigated histone modifications to CIITA and MHC-II promoters which result in opposing gene expression patterns in three variants of the metastatic breast cancer line MDA-MB435. The MHC-II was down-regulated in highly metastatic variant that shows elevated levels of H3K27 trimethylation indicating closed chromatin structure. Epigenetic changes are now thought to play important roles in the cancer progression. Development of compounds targeting enzymes that regulate histone modifications can be a future of cancer treatment.

EPLIN is a putative invasion suppressor in prostate cancer

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Acquisition of migratory and invasive capabilities by cancer cells is the first step in metastasis, resembling epithelial-to-mesenchymal transition (EMT). It remains elusive whether EMT plays an important role in prostate cancer (PCa) progression. We have established the ARCaP experimental model closely mimicking PCa EMT and clinical bone metastasis. Here, unbiased comparative proteomics analyses were performed in low- and highly-invasive ARCaP cells to identify important proteins involved in PCa EMT. Intriguingly, Epithelial Protein Lost In Neoplasm (EPLIN), a key protein in the stabilization of the cadherin-catenin adhesion complex and actin cytoskeleton, was found to be dramatically reduced upon EMT. EPLIN depletion in PCa cells resulted in significant remodeling of the actin cytoskeleton, transition to a mesenchymal morphology, and enhanced capabilities of *in vitro* migration and invasion. Microarray analyses identified a subset of EPLIN-regulated genes involved in EMT and tumor invasion. Importantly, differential expression of EPLIN was found to be associated with clinical PCa progression and metastasis. Mechanistic studies revealed that prostatic tumor microenvironment, presumably mediated by epidermal growth factor (EGF), induced progressive downregulation of EPLIN, promoted EMT, activated β -catenin signaling, facilitated actin cytoskeleton reorganization, and enhanced migration and invasion. Downregulation of EPLIN was further associated with EMT and clinical progression of human head and neck cancer towards lymph node metastasis. These findings indicate a novel role of EPLIN as an invasion suppressor in certain epithelial cancers.

Hoxc9 is a key mediator for retinoic acid-induced cell cycle arrest and differentiation of human neuroblastoma cells

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Retinoic acid, a derivative of vitamin A, has a key role in vertebrate morphogenesis, cellular differentiation, and tissue homeostasis. In the nervous system, it is involved in the induction of neural differentiation and patterning. It has long been observed that retinoic acid can cause arrest of cell proliferation and differentiation of human neuroblastoma cell lines. As a result, retinoic acid has been in clinical trials as a differentiation therapy for high-risk neuroblastoma, a common childhood malignant tumor of the sympathetic nervous system. The molecular mechanism underlying retinoic acid-induced differentiation of neuroblastoma cells remains poorly understood. Here we report that retinoid acid-induced differentiation of neuroblastoma cells is associated with downregulation of mitotic cyclins. Microarray gene expression profiling identifies the homeobox gene Hoxc9 as one of the genes that are upregulated during the differentiation process. Similar to retinoic acid treatment, ectopic expression of Hoxc9 causes growth arrest, terminal differentiation and senescence of neuroblastoma cells by repressing the expression of mitotic cyclins. Moreover, Hoxc9 knockdown in neuroblastoma cells compromises the ability of retinoic acid to downregulate mitotic cyclins and to induce differentiation. These findings reveal a cellular function of Hoxc9 in the control of mitotic cyclin levels and cell cycle progression, and suggest a molecular mechanism for the action of retinoic acid in neural differentiation.

Axon guidance molecule Slit3 is a novel angiogenic factor

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Slits are large, secreted repulsive axon guidance molecules. Recent genetic studies revealed that the Slit3 is dispensable for neural development, but required for non-neuron-related developmental processes, such as the genesis of organs of diaphragm and kidney. Here we report that Slit3 potently promotes angiogenesis, a process essential for proper organogenesis during embryonic development. We observed that Slit3 is expressed and secreted by both endothelial cells and vascular smooth muscle cells in vasculature, and that the Slit cognate receptors Robo1 and Robo4 are universally expressed by endothelial cells, suggesting that Slit3 may act in paracrine and autocrine manners to regulate endothelial cells. Cellular function studies revealed that Slit3 stimulates endothelial cell proliferation, promotes endothelial cell motility and chemotaxis via interaction with Robo4, and accelerates endothelial cell vascular network formation *in vitro* with a specific activity comparable to vascular endothelial growth factor. Furthermore, Slit3 stimulates neovessel sprouting *ex vivo* and new blood vessel growth *in vivo*, and *Slit3* knockout mice exhibit disrupted vascular development in diaphragm. Taken together, our studies demonstrate that the repulsive axon guidance molecule Slit3 is a novel and potent angiogenic factor, and suggest that Slit3 functions to promote angiogenesis in coordinating organogenesis during embryonic development.

Leptin regulation of VEGF in breast cancer cells.

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We have previously reported that *in vitro* and *in vivo* leptin signaling mediates proliferation of mouse 4T1 and human MCF-7 and MDA-MB231 breast cancer (BC) cells and levels of VEGF and VEGFR2. Specific antagonists of leptin signaling, PEG-LPrAs, were successfully produced and tested in mouse models for BC in our laboratories. Here we present data on how leptin signaling regulates VEGF gene in mouse BC cells (4T1, EMT6 and MMT). BC cells were firstly characterized for expression of VEGFR2 and leptin and estrogen receptor and transiently transfected with VEGF-promoter Luc-reporters [full-length & transcription factor (TF)-binding deletions]. Leptin dose-response, hypoxia and TF and kinase inhibitor effects on reporter activity, signaling pathways, TF and VEGF levels (protein and mRNA) were investigated. Our data suggest that leptin signaling can regulate the transcriptional activity of VEGF gene in breast cancer cells by activating gene transcription at several sites of the VEGF promoter. Leptin-induced PI-3K/AKT1 and NF κ B and HIF-1 α are relevant for the regulation of VEGF in BC. However, leptin activation of NF κ B for VEGF expression has different impact in BC cells. Leptin activation of MAPK/ERK 1/2 and AP1/SP1 was linked to the expression of VEGF. These results delineate the mechanisms for leptin regulation of VEGF and reinforce that the disruption of leptin signaling could impact BC growth by angiogenesis. This further supports the potential use of PEG-LPrA2 for leptin-signaling inhibition for prevention/treatment of BC that could be important for post-menopausal and obese women that show the higher levels of leptin and greatest risk for BC.

Enigma of BRCAness and ER-negative/positive Breast Cancers

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BRCA1 dysfunction is associated with Triple Negative Breast cancers (TNBC). We have identified a consensus SUMO modification site in the amino-terminal region of BRCA1 /1a /1b proteins and mutation in this potential SUMO acceptor site (K 109 to R) impaired their ability to bind and repress ligand dependent ER α transcriptional activity in breast cancer cells. We have found SUMO E2-conjugating enzyme Ubc9 to bind BRCA1 proteins. BRCA1 Mutant #1 (K109 to R) was impaired in its ability to both bind, as well as modulate Ubc9 mediated SUMO-dependent/independent E2-induced ER α transcriptional activity in breast cancer cells. Similarly, BRCA1 cancer -predisposing mutation (61Cys-Gly) abrogated the ability to both bind Ubc9 as well as inhibit ER α activity suggesting physiological significance. Addition of BRCA1 but not mutant #1 to E2-induced ER α in the presence of SUMO-1 and Ubc9 resulted in the degradation of ER α suggesting BRCA1 to be a putative SUMO-1 and Ubc9-dependent E3 Ubiquitin ligase for ER α . This is the first report demonstrating the participation of Ubc9 in BRCA1 E3 Ubiquitin ligase mediated degradation of ER α . These results suggest a novel function for BRCA1 in regulating the dynamic cycles of SUMO and Ubiquitin modifications required for ER α turn over and deregulation of this molecular switch due to lack of BRCA1 results in ER α -negative/positive breast cancers. This study will help in designing novel BRCA1 function-based targeted treatment for TNBC.

Probing the Microrheology of Mesenchymal Stem Cell-Based Therapeutics

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Breast cancer is a leading cause of cancer morbidity and mortality in women, afflicting 1 in 8 women world-wide and resulting in >40,000 deaths per year in the United States. Despite advances in breast cancer screening and treatment, approximately 30% of the patients presenting with early stage disease develop recurrent, advanced, or metastatic disease [1]. Current therapies, including surgery, chemotherapy, and radiotherapy, focus on treating or restraining the primary tumor and are ineffective in treating metastatic disease. The development of mesenchymal stem cell (MSC) vectors for gene delivery may offer a new method of specifically targeting breast cancer cells in tumors and their metastases and delivering prolonged levels of therapeutic proteins in the local region of the cancer cells. The development of cell-based therapeutics requires the availability of cells that can be expanded *ex vivo*, are amenable to genetic manipulation, and circulate sufficiently to allow exposure to the blood vessels and accumulation in tumors. MSCs, derived from bone marrow (BM) stroma, are multipotent progenitor cells that can self-renew and differentiate even upon *ex vivo* culture and expansion [2]. MSCs spontaneously migrate from the BM and infiltrate wounded tissues and tumors [3,4]; however, the majority of MSCs reinfused after *ex vivo* manipulation become trapped in the lungs [5]. The identification of soluble growth factors that stimulate their migration in the wound bed or tumor may be a key element in the development of MSC-based therapeutics that can overcome current transport limitations [6]. Soluble growth factors stimulate the proliferation and differentiation of MSCs *in vitro*; however, little is known about their effects on the migratory behavior of MSCs. Using multiple particle tracking microrheology we have quantified the effects of tumor secreted soluble factors on the viscoelasticity of MSCs. We have also used an *in vitro* migration assay to investigate the effect of tumor-secreted soluble factors on MSC migration. Our results indicate that treatment with tumor-secreted soluble factors increases MSC elasticity, reduces MSC viscosity, and increases MSC migration. Quantitative studies of MSC microrheology will be used to optimize the migration of MSC-based therapeutics to tumors.

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Heparan sulfate is required for cell fate commitment of embryonic stem cells

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Embryonic stem cells (ESCs) are able to self-renew infinitely and are pluripotent, *i.e.* they can differentiate into all adult cell types. The regulatory network that maintains self-renewal has been under intense investigation and is increasingly defined, however the molecular mechanisms that control the transition from self-renewal to differentiation are only poorly understood. Heparan sulfate (HS) is a linear, heavily sulfated polysaccharide that is found abundantly on the cell surface of ESCs. The HS- biosynthetic enzyme EXT1 is part of a co-polymerase complex and initiates the extension of the HS chain. In this study we investigated the role of HS by creating conditional *EXT1* knockout ESCs. Ablation of *EXT1* resulted in complete loss of HS and enabled us to study the role of HS in ESC self-renewal and cell fate commitment. *EXT1*^{-/-} ESCs could be stably maintained in long-term feeder-free culture conditions demonstrating that HS is not required for the maintenance of self-renewal. Upon reduction or complete withdrawal of LIF, an experimental condition that induces spontaneous differentiation of mouse ESCs, *EXT1*^{-/-} ESCs remained undifferentiated and failed to commit into developmental lineages. *EXT1*^{-/-} ESCs retained characteristics of pluripotent, self-renewing ESCs including high alkaline phosphatase activity, compact colony morphology and expression of pluripotency genes such as *NANOG* and *OCT-4*, revealing that HS is required for the exit of self-renewal and commitment to differentiation. Moreover, we directly show that the aberrant lineage commitment of *EXT1*^{-/-} ESCs underlies defects in FGF signaling and consequently impaired ERK1/2 activation. Heparin, a HS analogue, was able to restore ERK1/2 activity and rescued cell fate commitment. Altogether our findings identify and define HS as a novel factor involved in the initial cell fate decision of ESCs, promoting the transition from self-renewal to cell fate commitment.

Gene expression profiling analyses indicate that human ovarian surface epithelia are multipotent and capable of serving as the somatic stem cell origin of epithelial ovarian cancer.

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Background:

Accumulating evidence suggests that somatic stem cells undergo mutagenic transformation into cancer initiating cells. The serous subtype of ovarian adenocarcinoma in humans has been hypothesized to arise from at least two possible classes of progenitor cells: the ovarian surface epithelia (OSE) and/or an as yet undefined class of progenitor cells residing in the distal end of the fallopian tube. We present data that reveals OSE are somatic stem cells capable of serving as the precursor cells of ovarian cancer.

Methods:

Comparative gene expression profiling analyses were carried out on OSE removed from the surface of healthy ovaries and ovarian cancer epithelial cells (CEPI) isolated by laser capture micro-dissection (LCM). Differentially expressed genes were analyzed using gene ontology, molecular pathway, and gene set enrichment analysis algorithms. The results of the gene expression analyses were selectively confirmed using immunohistochemistry.

Results:

Consistent with multipotent capacity, genes in pathways previously associated with adult stem cell maintenance are highly expressed in ovarian surface epithelia and are not expressed or expressed at very low levels in serous ovarian adenocarcinoma. Among the over 2000 genes that are significantly differentially expressed between OSE and CEPI, a number of pathways and novel pathway interactions are defined that may contribute to ovarian adenocarcinoma development.

Conclusions:

Our results demonstrate that human ovarian surface epithelia are multipotent and capable of serving as the origin of ovarian adenocarcinoma. While our findings do not rule out the possibility that ovarian cancers may also arise from other sources, they are *inconsistent* with claims that ovarian surface epithelia cannot serve as the origin of ovarian cancer initiating cells.

Study of Machine-based Nucleus Discrimination with Nuclear Feature Quantification and Analysis Techniques for large-scale Microscopy Imaging of Diffuse Glioma

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Quantitative study of histologic features present in human tissue samples using computer image analysis techniques has recently captured intensive interests. Having emerged as a key tool not only for diagnosing diseases, but also for understanding the underlying pathological mechanisms, imaging and related machine-based image analysis methodologies have played an essential role in facilitating these goals. Motivated by the idea of alleviating the interpreters' bias and improving the diagnostic reproducibility, we explore the possibility of generating a quantitative feature set associated with the nucleus of glioma cells from digital whole-slide images of diffuse gliomas using image analysis tools. More importantly, the efficacy of derived features for characterizing and distinguishing nuclei of histologically distinct gliomas was carefully evaluated. The complete study procedure includes several sequential phases: 1) image segmentation on individual nuclei, 2) micro-anatomic feature extraction for segmented nuclei characterization, and 3) regression analysis for validating feature discriminating power. Gold standard information on virtual microscopy image data was provided by a certified surgical neuropathologist, who manually delineated boundaries of each nucleus of interest, and then graded each nucleus with an integer, predefined within a range of 1-10, representing the degree of belongingness to a specific pathological category (oligodendroglioma vs. astrocytoma). A total of 220 nuclei were randomly selected from 11 distinct regions of interest. In terms of the overall accuracy of the machine-generated nucleus segmentation, the mean ratio of the overlapped region area to the union region area recognized by human and machines reached 72.45%. The most discriminating features for describing nuclei of distinct classes were determined to be: area, eccentricity, average magnitude of gradient, and sum of Canny-edge pixels. When the best set of nuclear features was used, the mean of the Mean Absolute Grade Errors and the mean of Standard Deviation of Absolute Grade Errors associated with 100 repeated experiments having different testing (20%) and training (80%) data partitions were 1.32 and 1.23, respectively. As a result, we conclude that the system developed is promising for automating the generation of quantitative micro-anatomic features from images of glioma samples for nuclear classification.

Kinetic Model Characterization of Protease Activity in Tumor Microenvironments

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Macrophages are involved in proteolytic tissue remodeling during inflammation, and tissue associated macrophages (TAMs) are hypothesized to play roles in tumor growth and extracellular matrix breakdown leading to metastasis. The papain family of cysteine proteases, the cathepsins, is an understudied class of powerful collagenases and elastases implicated in extracellular matrix degradation that are secreted by macrophages and cancer cells and shown to be active in the slightly acidic tumor microenvironment. Due to the tight regulatory mechanisms of cathepsin activity and their instability outside of those defined spaces, detection of the active enzyme is difficult to precisely quantify, and therefore challenging to target therapeutically. Engineers use models to test hypotheses that are difficult to determine experimentally. Using valid assumptions that consider these complex interactions we have developed a system of ordinary differential equations to calculate the concentration of mature, active cathepsins in a biological space. The system of reactions considers four enzymes (cathepsins B, K, L, and S, the most studied cathepsins with reaction rates available), three substrates (collagen IV, collagen I, and elastin) and one inhibitor (cystatin C) and comprise more than 30 differential equations with over 50 specified rate constants. Along with the mathematical model development, we have been developing new ways to quantify proteolytic activity to provide further inputs. This predictive model will be a useful tool in identifying the time scale and culprits of proteolytic breakdown leading to metastasis and angiogenesis in malignant tumors.

RNA-driven DNA modifications from bacteria to human cells

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As recently demonstrated in the yeast *Saccharomyces cerevisiae* model system, RNA can be used as template for DNA synthesis by cellular DNA polymerases at the chromosomal level during the process of double-strand break (DSB) repair (Storici et al., *Nature*, 2007, 447: 338). Now we have found that the phenomenon of RNA-mediated DNA repair and modifications is not limited to yeast cells, but can also occur in mammalian cells, as well as in bacterial cells. Here we show that RNA-containing oligodeoxynucleotides can serve as templates to repair a DSB in chromosomal DNA of human cells and can introduce base modifications into the genomic DNA. We utilized RNA-containing oligodeoxynucleotides designed to repair a chromosomal break generated within a copy of the green fluorescent protein (GFP) gene randomly integrated into the human genome of HEK-293 cells. In order to test the capacity of RNA to modify DNA in bacterial cells, we examined the frequency of gene modification at the *lacZ* gene in *Escherichia coli* following transformation with RNA-containing oligodeoxynucleotides. Interestingly, the RNA-containing oligodeoxynucleotides could be used to correct a deletion mutation in the *lacZ* gene in the *E. coli* genome without any break induction, with a frequency only 5 fold less than that obtained using corresponding DNA-only molecules. These results demonstrate that RNA bases, as well as RNA molecules, can have a direct and active role in DNA modification and remodeling from bacteria to mammalian cells.

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Needs Assessment to Facilitate Pediatric Cancer Survivorship Care through SurvivorLink

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Background: Cancer survivorship has become a national public health priority, especially for childhood cancer survivors where the overall cure rates are 80%. Survivor care aims to educate and empower survivors to seek lifelong individualized surveillance and treatment for late effects, but is compromised by lack of knowledge about survivor issues among both healthcare providers (HCP) and patients/families.

Methods: This project aims to address these challenges by building SurvivorLink, an IT system designed to 1) facilitate communication between HCPs and survivor/families through an electronic web based survivor healthcare plan and 2) provide educational materials to improve awareness and best practices in survivor care.

Results: The first phase of SurvivorLink targeted HCPs. To date, we have met with the cancer survivor teams in Augusta, Savannah, Macon and Columbus, and completed interviews with 11 Georgia-based HCPs, to discuss current challenges in survivor care. All HCPs reported moderate to very low familiarity with late effects management in pediatric cancer survivors. Overall, HCPs expressed a high level of interest in SurvivorLink, and requested survivor healthcare issues be presented as quick facts that focused on patient specific information. A soft launch is underway for the HCP portal of SurvivorLink, with a full launch in September to include CME modules. The HCP portal will be displayed, and utilization metrics will be reported.

Conclusions/Implications: The development of SurvivorLink will improve provider and patient/family awareness, facilitate communication, and improve compliance with surveillance recommendations for late effects monitoring. These principles can be easily translated to adult cancer survivor care.

Validation of the Pedigree Assessment Tool (PAT) in Families with BRCA1 and BRCA2 Mutations

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BACKGROUND: The lifetime risk of breast cancer (BC) in patients with hereditary breast cancer syndromes is as high as 80%. The Pedigree Assessment Tool (PAT) is a scoring system to aid in identifying these patients. This validation study compares the PAT to *BRCA* gene mutation probability models in predicting suitability for genetic referral.

METHODS: Retrospective review identified subjects undergoing genetic counseling and *BRCA* testing from 2001-2008 at two institutions. PAT score and *BRCA* mutation probabilities were calculated using Myriad II and Penn II models. Comparisons were made between models in ability to discriminate patients appropriate for genetic evaluation based on accuracy in predicting a positive test result.

RESULTS: Records evaluated represent 520 families. *BRCA* testing revealed 146 mutation positive families and 374 negative. C-statistic analysis compared the discriminating ability of the models to correctly assign families as mutation (+) and (-). Both the PAT and Penn II model outperformed the Myriad II model. Using a threshold PAT score ≥ 8 and mutation probability $\geq 10\%$ to assign families as mutation (+) versus (-), sensitivity, specificity, positive predictive and negative predictive values were calculated for each model. The PAT was more sensitive than the Myriad II model and more specific than the Penn II model.

CONCLUSION: In overall performance, the PAT is at least comparable to the Myriad II and Penn II models in screening women appropriate for genetic referral. Simplicity and identification of families with non-*BRCA* hereditary breast cancer syndromes suggest that the PAT is better suited for BC risk screening.

Table 1. Comparison of PAT, Myriad and Penn Mutation Prediction Models

	c-statistic	Sensitivity*	Specificity*	Positive predictive value (PV+)	Negative predictive value (PV-)
PAT	0.690 \pm 0.004	0.952 \pm 0.038	0.190 \pm 0.042	0.303 \pm 0.046	0.914 \pm 0.066
Myriad	0.664 \pm 0.005	0.839 \pm 0.065	0.381 \pm 0.052	0.333 \pm 0.052	0.865 \pm 0.055
Penn	0.706 \pm 0.004	0.911 \pm 0.050	0.145 \pm 0.038	0.289 \pm 0.045	0.824 \pm 0.099
p-value PAT v. Myriad	0.213	0.037	< 0.0001	0.384	0.293
p-value PAT v. Penn	0.436	0.293	0.119	0.695	0.129

*Probability threshold: PAT ≥ 8 , Myriad and Penn $\geq 10\%$. χ^2 test used to determine p-value. Statistical significant $p \leq 0.05$

Vimentin –a novel antimetastatic target for Breast cancer metastasis

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Cancer metastasis is the major cause of death in nearly all tumor types; however, most treatments target the primary tumor and not the highly invasive metastatic cells. We propose to prevent cancer metastasis by precisely targeting the cancer invasion machinery in patients at a high risk for metastatic disease. To do this we disrupt a novel target- the vimentin cytoskeleton. Here we show that *Withania somnifera* root extracts (WRE) and one of its primary constituents, the small molecule Withaferin A (WFA), targets vimentin to inhibit cancer cell motility and migration, while having negligible effects on viability. We employ cutting-edge live cell confocal imaging studies in combination with traditional molecular biology techniques to dissect the precise mechanism of how WRE and WFA inhibit cancer cell migration and invasion. Our results show WFA has weak anti-proliferative activity at low concentrations but potently inhibits breast and lung cancer migration and invasion in a dose-dependent manner. We determine that the vimentin-binding A ring of WFA is critical for its anti-invasive efficacy using A-ring modified WFA analogs. In a murine metastatic breast cancer model, WFA administration three-times per week potently inhibits metastatic lung nodules at doses that show little anti-proliferative activity, suggesting that WFA can inhibit tumor invasion without affecting proliferation. Ultimately, we envision WFA can be used as a vimentin-targeting chemopreventative in high-risk metastatic patients and has the potential to be used with traditional cytotoxics.

The use of magnetic nanoparticles for the targeted removal of ovarian cancer cells

Kenneth Scarberry* and John McDonald School of Biology, Georgia Institute of Technology

Ovarian Cancer is the 5th leading cause of cancer deaths in women. While primary tumors are often successfully removed by surgery, there is currently no effective method to prevent metastasis of ovarian cancer cells that slough off primary tumors and spread to other organs within the abdominal cavity. In an effort to reduce ovarian cancer metastasis, we have developed a minimally invasive procedure whereby ovarian cancer cells present in the abdominal cavity of patients can be captured ex-vivo by magnetic nanoparticles specifically targeted to the cancer cells. We report the results of a series of studies suggesting that the procedure may be of significant clinical benefit in reducing ovarian cancer metastasis.

Rapid Mass Spectrometric Metabolic Profiling of Blood Sera Detects Ovarian Cancer with High Accuracy

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Ovarian cancer is the most lethal of gynecological cancers and the 5th leading cause of all cancer-related deaths among women. While the 5-year survival rate for women diagnosed with the disease early in its progression is greater than 90 %, the survival rate for patients diagnosed at later stages is only ~20%. Most ovarian cancers are not diagnosed early because the disease is essentially asymptomatic at early stages. In addition, there is currently no sufficiently accurate screening test due to the extremely high levels of sensitivity and specificity required to reliably predict low prevalence diseases like ovarian cancer³. We report here the application of a new mass spectrometric procedure for the measurement of relative metabolite levels in sera combined with a customized functional Support Vector Machine (SVM)-based classification algorithm for diagnostic applications. As an initial test of the diagnostic power of our method, we examined sera from 94 women. The assay was able to distinguish between the cancer and control groups with an unprecedented 99-100% accuracy (100% sensitivity; 99-100% specificity) demonstrating its potential as a clinically significant diagnostic test.

Understanding the biology of therapeutic approaches in multiple myeloma.

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We have been studying the mechanism of action of several classes of agents that are in use for the treatment of multiple myeloma. We have determined the biology of a myeloma cell or its response provided important clues for determining the mechanism of action as well as cellular sensitivity.

Myeloma is a malignancy that retains much of the normal phenotype of a plasma cell. We reasoned that this could explain the sensitivity of these cells to proteasome inhibitors and have determined that ER stress is induced by these agents.

We determined that in the case of arsenic trioxide (ATO), the depletion of glutathione was important to sensitize cells and consistent with this, the primary cellular response to ATO is an anti-oxidant response. In contrast, the organic arsenical Darinarpsin does not induce a significant anti-oxidant response and is not sensitized to GSH depletion.

Finally we have determined that the sensitivity of myeloma cells to a Bcl-2 inhibitor is not correlated with the expression of Mcl-1 as observed in other tumors since Mcl-1 is widely expressed in myeloma. We found that analyzing the function not the expression of the Bcl-2 family is necessary to determine sensitivity.

Multi-scale Integrative Investigation of Brain Tumor

Joel Saltz, Carlos Moreno, Tahsin Kurc, Ashish Sharma, Jun Kong, Sharath Cholleti, Tony Pan, Erwin van Meir, Daniel Brat, Emory University

Tom Mikkelsen, Henry Ford Hospital
Daniel Rubin, Stanford University
Adam Flanders, Thomas Jefferson University

In this talk, we describe a newly initiated project, funded by the NCI cancer Biomedical Informatics Grid (caBIG) program as a collaboration of four institutions, to carry out novel integrative in silico experiments to study brain tumors. Our effort is designed to leverage complementary molecular, pathology and radiology brain tumor data obtained in The Cancer Genome Atlas (TCGA), Rembrandt, and Vasari studies. These studies involve collection and generation of Radiology, full-slide digital Pathology, high throughput genetic, genomic and epigenetic analyses for patient populations accrued at a large number of clinical sites. Our research focuses on the following aims: 1) Determine the influence of tumor micro-environment on gene expression profiling and genetic classification using TCGA data; 2) Determine genetic and gene expression correlates of high resolution nuclear morphometry in the diffuse gliomas and their relation to MR features using Rembrandt and TCGA datasets; 3) Examine the gene expression profile of low grade gliomas that progress to GBM for predictive clustering, prognostic significance and correlates with pathologic and radiologic features; and 4) Identify correlates of MRI enhancement patterns in astrocytic neoplasms with underlying vascular changes and gene expression profiles. To accomplish these aims, we will develop and employ workflows consisting of novel image analysis algorithms and bioinformatics analyses to correlate imaging characteristics defined by feature sets with pathologic grade, vascular morphology and underlying gene expression profiles. Advanced information technologies developed by caBIG and by our group will be employed to manage, explore, and share among researchers semantically complex datasets representing analysis results.

Grid Computing for Integrative and Translational Cancer Research

Tahsin Kurc, Ashish Sharma, Tony Pan, Joel Saltz
Center for Comprehensive Informatics, Emory University
Shannon Hastings, Stephen Langella, Scott Oster, David Ervin, Justin Permar
Department of Biomedical Informatics, Ohio State University

In this talk, we present two examples of Grid middleware systems that are designed to provide support for federated access to data and analytical resources in multiinstitutional cancer studies. The first system is the caGrid infrastructure. caGrid is the core Grid architecture of the cancer Biomedical Informatics Grid (caBIG®) program. caGrid is designed to provide the core infrastructure to support federated access to data and analytical resources and applications deployed at different institutions and to enable researchers to both query, integrate, and synthesize information from distributed resources. caGrid leverages Grid computing technologies and tools to create a biomedical research Grid environment. The middleware infrastructure provides a common runtime environment and Grid-enabled tools to support the deployment, discovery, and invocation of data and analytical resources, metadata management, management of Grid-wide security, federated query across multiple data sources, and composition of resources into analysis workflows. The second example is the caBIG In vivo Imaging middleware (IVIM). This middleware is designed to support collaborative studies involving collection, analysis, and integration of biomedical imaging data. It is built on top of caGrid and provides higher-level functionality for Grid-enabled biomedical imaging. In the talk, we will describe examples of applications and tools developed using the IVIM infrastructure. These tools include a virtual PACS environment, a Grid service for managing and sharing image markups and annotations, and a software tool for management, analysis, and review of digitized microscopy images.

Integrative and Translational Cancer Research Informatics Requirements

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In this talk, we describe the core informatics requirements of large scale, collaborative integrative and translational cancer research studies. We describe these requirements using example research pattern templates. The particular approach employed by a study, the types of experiments performed, the types of data collected are determined by the specific research questions targeted by the study. However, research projects focusing on similar problems employ common processes and principles. Pattern templates provide a mechanism to classify these principles and processes into broad sets of common patterns. In our work we employ pattern templates to capture, classify, and describe requirements, best practices, and constraints on families of projects and applications. In the talk, we will describe several example pattern templates from integrative and translational research studies. We will use these examples to present the requirements imposed on software systems, tools, and applications. These requirements include interoperability of data and analysis resources, security, high-performance and federated access to databases and analysis programs. We will introduce architecture approaches undertaken by the cancer Biomedical Informatics Grid (caBIG®) program to address these requirements.

Linking Cancer Bioinformatics with Nanotechnology for Personalized Oncology

May D. Wang

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Director of Biocomputing and Bioinformatics Core in Emory-Georgia Tech NCI Center for Cancer Nanotechnology Excellence (CCNE)
GCC Distinguished Cancer Scholar

A major theme of the Emory-GT NCI Center for Cancer Nanotechnology Excellence (CCNE) is the integration of Bio-Nano-Info for personalized oncology (*Wang and coworkers, Trends in Biotech. 27, 350-358, 2009*). Specifically, our CCNE develops bioconjugated nanoparticles linked with biomolecular signatures (biomarkers) for tumor imaging, molecular profiling, targeted therapeutics in medical oncology, and early detection. The rationale is that nanometer-sized particles such as semiconductor quantum dots and iron oxide nanocrystals have optical, magnetic or structural properties that are not available from either molecules or bulk solids (Alivisatos, *Science* 271, 933-937, 1996). When linked with tumor targeting ligands such as monoclonal antibodies, peptides or small molecules, these nanoparticles can be used to target tumor antigens (biomarkers) as well as tumor vasculatures with high affinity and specificity (Nie and coworkers, *Annu. Rev. Biomed. Eng.* 9, 257-288, 2007). These developments have raised exciting opportunities for personalized oncology, when genetic and protein biomarkers are used to diagnose and treat cancer based on the molecular profiles of individual patients.

My bioinformatics team first built a high-speed biocomputing and data storage infrastructure for CCN, and then has been focusing on identifying clinical valid biomarkers, and processing bionanotechnology results generated by multiple CCNE project teams. In addition, we have been working with two major national initiatives: (1) to interface with the NCI's cancer Biomedical Informatics Grid (**caBIG**); and (2) to work with two large consortiums led by US-FDA, with the goal of regulating biomarker discoveries. During the past few years, my team has developed multiple bioinformatics tools: (A) biomarker data quality control, analysis, and knowledge archive systems such as caCORRECT, omniBiomarker, and ArrayWiki; (B) multiplex in vitro diagnostic data quality control and quantification systems such as Q-IHC, 3D-CellViz, omniVisGrid, PASuite, MTDynamics; (C) therapeutics PK/PD effect modeling and visualization systems such as nanoDRIVE, and VirtualOncology.

In this talk, I will focus on a couple of tools that have been submitted to NCI caBIG for review. Two of the tools for cancer biomarker data quality control and analysis, called "caCORRECT" and "omniBiomarker", have completed many steps of quality check and compatibility reviews by caBIG, and have received caBIG silver-level certification in July 2009. Two other tools, Q-IHC and omniVisGrid, which focus on multiplex nanoparticle imaging quantification and a grid-based bionanotechnology data and information visualization service, have been submitted to NCI caBIG to go through review process now. The NCI certification would make the tools available to more users from other comprehensive cancer centers and various cancer groups in US and around the world.

Optimally splitting cases for training and testing high dimensional classifiers

Kevin K. Dobbin, College of Public Health, University of Georgia

Richard M. Simon, Biometric Research Branch, National Cancer Institute

We consider the problem of designing a study to develop a predictive classifier from high dimensional data. A common study design is to split the sample into a training set and an independent validation set, where the former is used to develop the classifier and the latter to evaluate its performance. In this paper we address the question of what proportion of the samples should be devoted to the training set. How does this proportion impact the mean squared error (MSE) of the prediction accuracy estimate? This question is investigated using both a model-based and a data-based approach, and by applying these approaches to a number of synthetic and real microarray datasets. We find that the MSE can be decomposed into three intuitive component parts. Our findings support the conclusion that in most settings 40% to 80% of the samples should be devoted to the training set. The optimal proportion depends on the overall number of samples available, number of differentially expressed genes, and the standardized fold change for informative genes. Over a wide range of settings, it was found that 2/3-to-1/3 training-to-validation allocation performs as well as or better than 1/2-to-1/2 allocation. A resampling approach that can be applied to any dataset, using any predictor development method, to determine the best split is presented.

Multimodality Molecular Imaging for Cancer Research

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During the past decade, significant advances in small animal imaging technologies have been made in such areas as high-field magnetic resonance imaging (microMRI), dedicated animal positron emission tomography (microPET), high-resolution computed tomography (microCT), and *in vivo* fluorescence imaging. As a result, there is a tremendous need to synthesize the information obtained from multiple imaging modalities and sources. Our imaging and analysis technologies can (1) provide efficient methods and procedures for mapping the properties of tissues in space and time, (2) integrate multiple information streams acquired from different imaging technologies into a single coherent picture, and (3) validate and interpret *in vivo* imaging data for biologic, physiologic, and pathologic interpretation. The imaging research will exploit our current knowledge of the genetic and molecular bases of various diseases and therefore have substantial positive implications for cancer prevention, detection, diagnosis, and therapy. In this project, we utilized microMRI, microPET, and fluorescence imaging to study photodynamic therapy in mouse prostate cancer models. Our results show that multispectral *in vivo* fluorescence imaging can monitor the distribution of photosensitizing drug in mouse body, that microPET with radio-labeled choline can detect the tumor response from one hour to 48 hours after therapy, and that diffusion-weighted MR imaging can detect residual tumors within one week after treatment. The imaging technologies can be translated to evaluate and optimize the therapy for each individual patient.

hESCs Cell Surface Markers on Carcinomas

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Tracking the phenotypic changes that occur during human embryonic stem cell (hESC) differentiation is vital to their use in regenerative medicine. These changes include differences in the level of expression of cell surface molecules which can be used as markers. Detection of hESC markers with mAbs is the most common tool used to confirm their pluripotent progenitor status. Among the limited number of markers that are used to demonstrate the undifferentiated, pluripotent status of human stem cell populations are the cell surface glycoproteins TRA-1-60, TRA-1-81 and the glycolipids SSEA-4 and SSEA-3. Other cell surface glycoconjugates are used to define differentiated lineages such as CD34 which is used to identify and isolate haematopoietic progenitor cells. CD133 and PSA-NCAM (polysialylated neural cell adhesion molecule) are used delineate neural stem cells.

In a collaborative project with Novocell we have generated a number of anti-hESC mAbs that were raised to the human embryonic stem cell line BG-01(NIH registry). These mAbs, Hesca-1 and Hesca-2, stain novel cell surface antigens on undifferentiated progenitor cells and are commercially available (Millipore). Our whole-cell immunization strategy results in an enrichment of antibodies to cell surface antigens. Thus, the identity of the antibody targets is not known beforehand and must be determined after the fact. As part of a broader effort to identify the target antigens of these anti-hESC mAbs we have deployed various techniques including the use of a glycan microarray to screen for antibodies that recognize glycans. Using such an approach we have determined that Hesca-2, an IgM monoclonal antibody, binds with high apparent affinity (nM) to the glycan epitope [Gal Beta 1,3 GlcNAc Beta 1,3 Gal]. This glycan epitope was recognized on a number of lacto-series oligosaccharides conjugated to BSA including blood group precursor H1, lacto-*N*-tetraose (LNT), lacto-*N*-hexaose LNH, and lewis X presented as neoglycoproteins of varying ligand densities. This glycan is found on glycoproteins, glycolipids and free oligosaccharides in milk. Interestingly, this glycan is also associated with several human carcinomas including pancreatic, stomach, colorectal and ovarian. In fact, a humanized IgG mAb, RAV12, which has a similar glycan specificity, has demonstrated *in vivo* antitumor activity against gastrointestinal adenocarcinoma in a mouse xenograft model. RAV12 is also being tested in human clinical trials.

In this presentation we describe the development and characterization of the mAb Hesca-2. This characterization includes immunofluorescent staining of hESC cells (and lack of staining to mESC and differentiated feeder cells). We also detail the glycan microarray binding experiments and the determination of its apparent affinity constant for defined glycans. We also show that this mAb also cross-reacts with human ovarian cancer cell lines and is cytotoxic to them. Further, immunohistochemical analysis shows broad staining to various common tumor types on tissue microarrays from patient samples including esophageal, breast, colon and ovarian carcinomas.

Differences in smoking patterns, attitudes, and motives among two-year college and four-year university students

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Two-year college students have higher rates of smoking compared to four-year university students. However, little is known about differences in smoking patterns, attitudes, and motives among these students. We contacted 8,834 undergraduate students at a two-year college and a four-year university in 2008, with 2,700 completing the 108-item online survey (30.6% response rate). Our current analyses focused on the 2,265 undergraduate students aged 18-25. Current (past 30-day) smoking was reported by 43.5% of two-year and 31.9% of four-year college students, and daily smoking was reported by 19.9% of two-year and 8.3% of four-year college students. Among those reporting smoking in the past 30 days, two-year students were less likely to report being “social smokers” than four-year students (46.6% vs. 60.4%). Also, among current smokers, two-year students were also less likely to report being ready to quit smoking in the next 30 days (27.1% vs. 34.7%) and were less confident in their ability to quit ($M=5.98$, $SD=3.79$ vs. $M=7.03$, $SD=3.44$) despite no differences in motivation to quit smoking. Two-year students were also less likely to approve of the state smoking ban in bars (73.7% vs. 80.8%, $p<0.001$) and were less likely to have smoking restrictions in their cars (45.8% vs. 57.1%, $p<0.001$), which held true when examining smokers only. In multivariate analyses controlling for age, gender, ethnicity, and highest parental education, attending a two-year college was associated with higher rates of current smoking ($OR=1.66$, 95% $CI=1.37, 2.01$) and daily smoking ($OR=2.74$, $CI=2.09, 3.58$), and with less negative attitudes regarding smoking ($F(5, 2148) = 17.75$, $p<0.001$). Also, compared to four-year college student smokers, two-year college smokers were less likely to smoke for social reasons ($F(5, 773) = 7.79$, $p<0.001$), but more likely to smoke for affect regulation ($F(5, 773) = 3.21$, $p<0.001$), after controlling for age, gender, ethnicity, and parental education. Given these results, two- and four-year college students differ in their smoking patterns, attitudes, and motives. These distinctions should inform tobacco control messages and interventions targeting young adult smoking.

Lung Cancer Burden in Georgia by Age, Race, and Rural/Non-Rural Residence: Preliminary Analyses

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Cancer is a disease of aging and lung cancer is no exception. In 2008, 10.1% of people residing in Georgia are age 65 and over. However, the population of Georgia and the world is rapidly aging, so cancers affecting older adults will likely increase in the next several decades. Race is also associated with variance in cancer rates due to genetic predisposition, environmental factors and/or lifestyles. Residence in urban or rural areas may determine healthcare access, thereby influencing stage of diagnosis, treatment and ultimately mortality. This study examines the burden of lung cancer incidence and mortality in Georgia as related to age, race and urban/rural residence.

Two data sources were used in this study: 1998-2005 Georgia Comprehensive Cancer Registry data and Georgia Vital Statistics records. As expected, we found a dramatic increase in lung cancer incidence in people age 60-plus compared to those aged 21-59. Age-adjusted incidence rates of cancer in black men and white men were comparable, while white women were approximately 1.5 times more likely to have a lung cancer diagnosis than black women. However, blacks were more likely to be diagnosed at a later stage than whites, thereby affecting treatment options and outcome. Conversely, the age-adjusted mortality rate for whites living in rural areas was 11% higher than those living in non-rural areas, while rural/non-rural residence had negligible impact on black mortality rates. Details of these findings and implications for further research are discussed.

Physician Recommended Colorectal Cancer Screening more likely for Whites than Blacks irrespective of gender, education, insurance and income levels based on the National Health Interview Survey (NHIS) data.

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Background: Previous studies have suggested a possible relationship between ethnicity and cancer screening rates, but they did not examine race as the primary predictor of physician recommended screening. All adults over 50, irrespective of gender and ethnicity, should be screened for colorectal cancer. However, with physicians being aware that Blacks are more likely than Whites to develop and die from colorectal cancer, one might expect that they would be more likely to strongly recommend screening for the higher risk Blacks to help reduce health disparities. The purpose of this study was to determine whether this is so.

METHODS: We analyzed data from the 2005 National Health Interview Survey (NHIS). A total of 12,729 adults aged 50 to 84 were included in the analyses.

RESULTS: Among U.S. adults aged 50 to 84, Whites were more likely than Blacks to report receiving a physician recommendation to undergo colorectal cancer screening. This association persisted after adjusting for other socioeconomic and health-related factors (OR 0.61, 95% CI 0.53 - 0.71).

CONCLUSION: Since most individuals who undergo colorectal cancer screening report that physician recommendation was their primary reason for doing so, this racial disparity will likely persist unless physicians make an effort to increase their screening recommendations in the high risk Black population.

LAKE ONTARIO SPORT-CAUGHT FISH CONSUMPTION AND BREAST CANCER RISK IN THE NEW YORK STATE ANGLER COHORT STUDY (NYSACS)

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Sport fish are an important source of exposure to many persistent organic pollutants, some of which may be associated with breast cancer risk. We examined L. Ontario sport fish consumption and the incidence of breast cancer in the NYSACS, a prospective cohort of licensed anglers (n=11,431) and their spouses (n=6,645) from New York State. In 1991, cohort members completed a self-administered questionnaire inquiring about and lifetime consumption of sport-caught fish from L. Ontario. First primary incident breast cancer cases were identified through linkage with the New York State Cancer Registry, 1991-2006. Included in this analysis were women (n=6,285) who completed the baseline questionnaire. Hazard ratios (HRs) and 95% confidence intervals (95% CI) were estimated using Cox proportional hazards models adjusted for age, education, income, parity, and recent live births. Preliminary analyses suggest there may be an association between number of years of sport-fish consumption and the risk of breast cancer in the NYSACS (p for trend, 5 year lag=.02). However, the interpretation of these findings are complicated by the lack of a monotonic exposure-response gradient. Species specific analyses indicate that consuming Chinook salmon and catfish may increase breast cancer risk (HRs ~2). These results should be interpreted with caution due to the potential for exposure misclassification. Additional follow-up and analyses are ongoing to assist in clarifying these findings.

Evaluation of a new initiative in the Avon Foundation Community Education and Outreach Community Patient Navigation Program

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Background: Black women in the United States experience disproportionate breast cancer mortality. This phenomenon may be due in part to delays in diagnosis and delays in the initiation of treatment. Culturally-appropriate community education on breast health coupled with the availability of low cost mammography screening services may help improve the use of mammography screening services. The Avon Foundation/Georgia Cancer Coalition Community Patient Navigation Program delivers community education and helps individuals overcome financial barriers to mammography screening. This study presents a process and outcome evaluation of a newly implemented initiative.

Methods: As a newly implemented initiative in 2008, participants were referred to a nurse practitioner who determined eligibility for a free or low-cost mammogram. Process evaluation data were gathered via monthly tracking forms submitted by Community Patient Navigators (CPNs).

Results: For the study period August 18, 2008-July 31, 2009, a total of 335 breast health presentations and exhibits were hosted by CPNs reaching approximately 13,000 community members. Three hundred ninety-three (393) women were screened at these events; the initiative was successful in scheduling and ensuring mammography screening for 60 (15%) women who expressed interest. The program has worked towards continued improvement in compliance with follow-up mammography for clients who were screened.

Conclusions: CPNs are a useful resource for encouraging mammography screening among underserved women. The program has documented improvement in adherence to mammography referral and screening, and we are currently in the process of implementing other strategies to further grow this new initiative in our program.

Transportation barriers to mammography screening clinics in the Atlanta, Georgia metropolitan area

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Many studies have described distance as a barrier to breast cancer screening and treatment for rural areas. However, less is known about time and distance as a barrier to mammography facilities in urban areas where many women are dependent upon public transportation for access to care. Using GIS methods, we examined spatial and temporal accessibility to mammography facilities for residents living in economically disadvantaged areas in two Atlanta, Georgia metropolitan area counties.

Census 2000 data was used to characterize census tracts with economically disadvantaged female populations. Dasymetric mapping techniques were used to create weighted population centroids within the census tracts and to eliminate zones of zero population. A multimodal transportation network was built to calculate travel times and distance from each centroid to the nearest mammography facility. We compared travel times of census tracts in which women are more likely to use public transportation to tracts in more affluent areas in which women are more likely to use private transportation.

Preliminary results show transportation time may pose a barrier to mammography screening for economically disadvantaged women in Atlanta. There is a strong correlation ($r=0.912$) between poverty and no private vehicle availability. This suggests that impoverished women must rely on public transportation for access to mammography clinics. Using GIS, we will geographically describe time and distance barriers to facilities by levels of poverty as well as by race and ethnicity. These results will be useful in determining new locations for facilities to better serve low-income women who depend on public transportation.

Groundwater Uranium and Cancer Incidence in the Southeast

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Background and Objective. Uranium is a naturally occurring alpha-emitting radionuclide with carcinogenic and nephrotoxic properties. South Carolina is a rural state with significant racial health disparities, extensive groundwater use, and elevated groundwater uranium in some regions.

Methods. Counts of incident cancer (total, leukemia, prostate, breast, colorectal, kidney, bladder, 1996-2005), were aggregated among census tracts with high groundwater use. Aggregate demographic data were obtained from the 1990 census. Groundwater uranium concentrations (N=4,600) were obtained from existing federal and state databases. Ordinary kriging was used to smooth exposure data. Linear and semiparametric regression were used to model the relationship between groundwater use, groundwater concentrations, and cancer incidence together and stratified by race.

Results. A total of 134,685 total cancer cases were identified. Two percent of samples had a concentration above the MCL of 30 µg/L. Census tracts with both elevated groundwater consumption and elevated groundwater uranium concentrations had increased rates of colorectal, breast, and kidney/renal pelvic cancer, especially tracts populated primarily by African Americans (all $p < 0.05$ for low versus high exposure quartiles). A statistically significant relationship between groundwater uranium levels and increased risk of total cancers ($p < 0.05$ for highest exposure quartile) and prostate cancer ($p < 0.05$ for highest exposure quartile) was found for census tracts populated primarily by European Americans.

Conclusion. Results from this analysis suggest an association between elevated groundwater uranium concentrations and increased colorectal, female breast, and kidney/renal pelvic cancer incidence. Moreover, African-American individuals may be most affected by these exposures. An extension of this project using Georgia data is underway.

Reproductive Health in Oncologic Care

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Background: Over 692,000 women are newly diagnosed with cancer each year. Ten percent of these newly diagnosed women are of reproductive age (15 and 49 yrs). Recently, fertility preservation for young cancer survivors has obtained research and public interest. Uncertainties regarding future fertility, pregnancy, and cancer survival are challenging for the patient and cancer team. Evaluation and treatment of cancer must include an assessment of goals for fertility and family planning in order to optimize the patients' cancer treatment and her future reproductive health goals. This study will provide multifaceted data to provide better insight into this largely unexplored area of research.

Methods: The primary objective of this study is to evaluate the success of implementation of reproductive health programming. Upon eligibility and informed consent, the initial patient and follow-up assessment will include a Patient Survey and Data Form, Reproductive Health Contraceptive Assessment, and Sexual Function Satisfaction Survey. Eligibility criteria include: female patient, age 18-55, any form of cancer, and evidence of ovarian function (represented by menstruation). Exclusion: Male patients, post-menopausal patients, no longer menstruating, age <18 or >55, and hysterectomy.

Results: Available upon study completion.

Conclusion: This study should aid clinicians navigating through the issues of reproductive health in the context of cancer care. In addition, the study should identify clinical, demographic, healthcare delivery, and socioeconomic factors concerning adequacy of reproductive health management in order to develop algorithms. Reproductive health assessment, sexuality surveys, and algorithm implementation will help optimize the achievement of reproductive health objectives of women with cancer.

Cancer in Incidence and Mortality in Georgia, 2002-2006

Bayakly, Rana; Georgia Division of Public Health

Methods: Cancer incidence data (2002-2006) was analyzed using the Georgia Comprehensive Cancer Registry (GCCR) which is a statewide population-based cancer registry collecting data on all cancer cases diagnosed among Georgia residents since January 1, 1995. Cancer mortality data (2002-2006) was analyzed using the Georgia Vital Records data.

Results: It is estimated more than 14,000 cancer deaths will occur and more than 39,000 new cancer cases will be diagnosed in Georgia. The over-all age-adjusted cancer incidence rate in Georgia is 462 per 100,000 for both males and females combined. Males are more likely to be diagnosed with cancer than females (566 vs 392 per 100,000). African Americans are more likely to be diagnosed with cancer than whites (475 vs 469 per 100,000). African American males have the highest age-adjusted cancer incidence rate (639/100,000) when compared to white males (562/100,000), white females (406/100,000) and African American females (374/100,000).

The over-all age-adjusted cancer mortality rate in Georgia is 189 per 100,000 for both males and females combined. Males are more likely to die with cancer than females (244 vs 154 per 100,000). African Americans are more likely to be diagnosed with cancer than whites (217 vs 183 per 100,000). African American males have the highest age-adjusted cancer incidence rate (303/100,000) when compared to white males (233/100,000), African American females (170/100,000), and white females (150/100,000).

Breast Cancer in Incidence and Mortality in Georgia, 2002-2006

Rayakly, Rana; Berzen, Alissa; Georgia Division of Public Health

Methods: Cancer incidence data (2002-2006) were analyzed using the Georgia Comprehensive Cancer Registry which is a statewide population-based cancer registry collecting data on all cases diagnosed among Georgia residents since January 1, 1995. Cancer mortality data (2002-2006) were analyzed using the Georgia Vital Records data.

Results: Breast cancer is the leading cause of cancer diagnosed and the second leading cause of cancer death in Georgia women. While white women are more likely to be diagnosed with breast cancer, black women are more likely to die from the disease. Georgia's incidence and mortality rates for breast cancer were lower than the US: Georgia's breast cancer incidence rate was 119 per 100,000 and the mortality rate was 24 per 100,000. For the same time period, the US breast cancer incidence rate was 122 per 100,000 and the mortality rate was 25 per 100,000. Georgia women living in urban counties in Georgia have higher rate of breast cancer than those living in rural counties. Incidence rate for white women is higher than for black women, however black mortality rates are higher despite stratifying by urban status. The majority (68%) of breast cancer is diagnosed at an early stage while 30% is diagnosed at a late stage. Of the 4% diagnosed at a distant stage, black women were more likely to be diagnosed at distant stage.

Augmenting Georgia Cancer Registry Data To Support Cancer Quality-of-Care Assessment and Comparative Effectiveness Research

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This project is intended to lay the groundwork for an integrated, sustainable Georgia Cancer Data System to support quality-of-care (QOC) assessment and comparative effectiveness research (CER). Over the long term, such a data system would support a variety of cancer treatment, screening, and prevention studies in Georgia. Specifically, the project will augment the Georgia Comprehensive Cancer Registry (GCCR) with data from multiple public and private sources: Medicare, Medicaid, and several large private payers, including Kaiser Permanente of Georgia, that collectively cover all employees of the State of Georgia. First, the GCCR will be linked to each of the major payer sources to produce “bilateral” linked, de-identified data sets that, individually, can effectively support QOC and CER studies. Then a Consolidated Cancer Data Resource (alpha version) will be constructed in a way that draws jointly from *all* of these public and private data sources to support population-representative QOC and CER. In addition, a variety of other secondary data sources will be used to link each patient with the characteristics of the hospital(s) and physician(s) providing cancer care. These various linked, de-identified data bases will be applied initially to QOC assessment in breast cancer and colorectal cancer in Georgia over 2000-2005. The project is currently supported by a grant to Emory University from the U.S. Centers for Disease Control and Prevention and the Association of Schools of Public Health, with funding from the National Cancer Institute and the Georgia Cancer Coalition and administrative assistance from the Georgia Department of Community Health.

COMPARISON OF GLEASON SCORES REPORTED AT DIAGNOSIS TO THOSE ASSIGNED BY EXPERT REVIEW

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BACKGROUND: Gleason score is a primary indicator of prostate cancer prognosis, and a major factor that is considered in selecting appropriate treatment. For these reasons, and because Surveillance Epidemiology and End Results (SEER) registries began collecting Gleason score information in 2004, it is important to examine the accuracy of prostatectomy and biopsy-derived Gleason scores.

METHODS: The study population included persons diagnosed with prostate cancer from January 1, 2004 through December 31, 2005, and residing in metropolitan Atlanta or rural Georgia. The de-identified pathology slides of approximately 300 eligible cases were scanned to create digital images, which were then re-examined to assess the agreement between the Gleason scores assigned at the original diagnosis and the Gleason scores assigned by an expert urologic pathologist specializing in prostate cancer.

RESULTS: A total of 195 biopsy specimens and 99 prostatectomy specimens were retrieved, scanned and reviewed by an expert pathologist. A comparison of the original Gleason score diagnosis (dichotomized as <7 versus ≥ 7) to that assigned by an expert pathologist (gold standard) demonstrated the sensitivity and specificity of 0.75 and 0.86, respectively. The corresponding sensitivity and specificity for prostatectomy samples were both 0.77. There was little evidence that certain socioeconomic or demographic patient characteristics were associated with a discernable increase or decrease in the agreement between pathology reports and expert reviews.

IMPLICATIONS: This study demonstrates the feasibility of linking registry data to pathology images and helps determine frequency and extent of misclassification of biopsy- and prostatectomy-derived prostate cancer Gleason scores reported to SEER.