MC13-0057
A comprehensive IT platform to support GTEx operation

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Background: Designed to build upon Genome Wide Association Study (GWAS) findings, the NIH Common Fund's Genotype-Tissue Expression (GTEx) project aims to study gene expression and regulation across multiple human tissues (30+ tissue types) from approximately 1000 healthy normal donors. It is expected to provide valuable insights into gene regulation and its tissue specificity, identify correlation between genetic variations and variations in gene expression levels as expression quantitative trait loci (eQTLs), and help to understand inherited susceptibility to diseases.
Purpose/Objective: To meet the challenge of GTEx requirements for collecting and tracking high quality biospecimen samples, a custom-built software system named Comprehensive Data Resources (CDR) was developed to support sample collection work flow, clinical data entry, case management, and review and curation of study data.
Materials and Methods: CDR is built with combination of technologies from Grails, Oracle, Groovy, jQuery, Apache Solr.
Results: The CDR provides secure user access to case and sample data based on pre-defined roles and privileges. Personally Identifiable Information (PII) and Protected Health Information (PHI) are restricted to a limited data set (LDS) and to authorized users through dynamic content redaction. Intuitive graphic user interfaces for the Biopecimen Source Sites (BSS) streamline data entry workflow by strictly following SOPs for sample collection and processing. Contextual automated data checks and business rule validations confirm data integrity and SOP adherence simultaneously. Web services APIs allow the Pathology Resource Center to access digital imaging data from tissue slides housed remotely at the Comprehensive Biospecimen Resource (CBR). API's connect to CBR's LIMS systems for real-time sample inventory data. De-identified GTEx data is provided via a private API with the Broad Institute (LDACC) before the final release into dbGaP. The reporting and analytics module supports data analysis and aggregation, report generation and real-time operational data snapshots.
Conclusions: CDR is a distributed web-based system designed to support GTEx operation from pilot phase to full scale-up stage. It manages and maintains multi-dimensional data models around each donor case (average 500+ data elements/case). As an efficient case management tool capable of connecting to various remote informatics systems, CDR could be adapted to the broader biobanking community with the flexibility of building user-defined work flows in the system.

MC13-0058
Inflammation-mediated epigenetic background for switching from normal program to cancer growth

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Background: Although inflammation is closely associated with tumor growth, molecular basis of this interrelation remains unclear, especially when pathogens do not damage the DNA. However, the inflammation entails regular changes in the expression of cell microRNAs (miRNAs). Expression of miRNAs miR-155, miR-21, miR-146a, miR-125b, miR-31, miR-34c, miR-200, miR-203 and miR-205 is usually up-regulated whereas expression of miRNAs miR-7a/b, miR-34a, miR-143, miR-145, miR-320a, miR-375, miR-379 and miR-434-3p is down-regulated.
Purpose/Objective: This investigation aims to identify in what way the shifts in miRNA expression pattern contribute to the cell transformation and tumor growth.
Materials and Methods: miRNA targets within gene transcripts were predicted *in silico* using TargetScan software.
Results: miRNA miR-143 can silence *abl2*, *bcl-2*, *erbB3* and *MYST2* genes. miR-145 targets *E2F3*, *RASA1/2*, *CDK6*, *erbB3/B4*, *ESR1*, *ACTB/G1*, *KDM1B/2B* and *Elp3* genes. miR-320 suppresses *E2F1/3/7*, *RASA1*, *CDK6*, *p57*, *ESR1*, *ITGB5*, *KDM1B* and *KAT6B* genes. Down-regulation of these miRNAs causes derepression of genes encoding histone acetyltransferases, histone demethylases, key elements of proliferative and antiapoptotic signal pathways as well as genes responsible for cell motility and abnormal adhesion. Up-regulated miRNA miR-155 silences *HDAC2/4/9*, *SIRT1*, *EZH1*, *SETD7*, *CLDN1*, *CGN*, *OCLN*, *F11R* (*JAM-A*) and *TGFBR2* genes and genes coding α-actinins. miR-21 can target *DNMT3B*, *HDAC2*, *SIRT5*, *SETD6/8*, *SUV39H2*, *CLDN1*, *CGN*, *CADM1*, *VCL* and *TGFBR2* genes.
Conclusions: Inflammation is associated with miRNA expression shifts that lead to increasing of cell proliferation and survival as well as to silencing of antiproliferative and proapoptotic genes. Also, up-regulated miRNAs suppress genes encoding components of cytoskeleton and intercellular junctions. This results in alterations in cell–cell adhesion, impairs contact inhibition, facilitates cell motility and migration. Furthermore, up-regulated miRNAs silence genes encoding the histone deacetylases, histone methyltransferases and *de novo* DNA methyltransferase. This causes increasing of overall level of chromatin acetylation and expression and, therefore, makes possible the reactivation of silent oncogenes as well as transposons, which can rapidly lead to dramatic increase of DNA damage level and genome destabilization. Thus, inflammation creates epigenetic background for cell transformation as well as for tumor promotion and metastatic spread.

MC13-0059
T-cell infiltration (TCI) observed on whole liver colorectal metastases (LCM) resected after preoperative treatment is a prognostic survival factor

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Background: Colorectal cancer TCI is a strong prognostic factor for survival after primary tumor resection. Curative surgery of LCM is the only hope for cure of metastatic patients (pts). Nevertheless, 70% of them will relapse.
Purpose/Objective: TCI analysis of LCM is poorly characterized and could be a prognostic factor as in primary tumor.
Materials and Methods: Pts engaged for curative liver surgery after preoperative treatment with available FFPE blocks for all resected LCM, were included. An immunoscore (IS), defined by the TCI in the center (CT) and the invasive margin (IM) for each LCM was determined using whole-slide quantitative immunohistochemistry (markers: CD3, CD8, CD45RO). The mean value of the 3 most infiltrated fields (0.8 mm^2) for each markers was defined in the CT and IM for all LCM. The total number of high densities (Hi, above the cut-off at the median density) in CT and IM for each marker was used to stratify pts for the IS. The markers were combined 2 by 2 in CT and IM (CD3-CD8, CD3-CD45RO, CD8-CD45RO) and finally regrouped to an IS of 0–2 Hi (IS0–2: low TCI) or 3–4 Hi (IS3–4: high TCI). For pts with multiple LCM; the median value of all densities, the least and the most infiltrated LCM/pt were analyzed. Cumulative DFS/OS analyses were performed using the Kaplan-Meier estimator. OS/DFS analyses were made using univariate Cox regression and compared by log-rank tests (IS0–2 vs 3–4).
Results: 59 patients (M/F 1.1, 203 LCM, mean 3.4/pt, synchr/metachr 5.4) were included. IS3–4 in the least infiltrated metastasis is significantly associated with OS and DFS for all markers combinations.

LCM/pt	Markers	Survival	HR (IS0–2 vs 3–4; 95% CI)	Log-rank p-value	Months (IS0–2 vs 3–4)
Median of all	CD3-CD8	DFS	1.2 (0.7–2.3)	0.48	
		OS	2.4 (0.7–7.3)	0.12	
	CD3-CD45RO	DFS	1.5 (0.8–2.9)	0.16	
		OS	2.2 (0.8–5.9)	0.11	
	CD8-CD45RO	DFS	1.0 (0.6–2.0)	0.87	
		OS	1.0 (0.4–2.9)	0.17	
Least infiltrated	CD3-CD8	DFS	1.8 (1.0–3.4)	0.05	8.0 vs 14.9
		OS	8.8 (2.0–39.1)	0.0007	27.9 vs NR
	CD3-CD45RO	DFS	2.5 (1.3–4.9)	0.004	8.0 vs 17.0
		OS	4.0 (1.2–14.2)	0.01	31.8 vs NR
	CD8-CD45RO	DFS	2.0 (1.0–3.7)	0.03	8.4 vs 16.0
		OS	2.6 (0.9–7.6)	0.06	
Most infiltrated	CD3-CD8	DFS	1.0 (0.6–1.9)	0.93	
		OS	2.1 (0.7–6.6)	0.17	
	CD3-CD45RO	DFS	1.7 (0.9–3.2)	0.12	
		OS	3.7 (0.8–16.2)	0.06	
	CD8-CD45RO	DFS	1.6 (0.8–3.2)	0.16	
		OS	2.4 (0.7–8.4)	0.16	

Conclusions: The TCI score (IS0–2 vs 3–4) determined in the least infiltrated LCM/pt is a prognostic factor.

MC13-0062

Glioblastoma patients with arterio-venous normalization during anti-angiogenic therapy have prolonged survival

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Background: Vessel architectural imaging (VAI) is a new paradigm in magnetic resonance imaging (MRI) of cancer for assessment of vessel type and relative oxygen saturation (ΔSO_2) levels [1].
Purpose/Objective: We used VAI to monitor vascular remodeling in newly diagnosed glioblastoma (nGBM) patients treated with the anti-angiogenic agent cediranib and chemo-radiation.
Materials and Methods: In this IRB-approved phase I/II study of cediranib (NCT00662506), an oral pan-VEGF inhibitor [2], 40 patients with nGBM were imaged weekly for 6 weeks during therapy and then monthly thereafter. Our MRI protocol included a gradient-echo and spin-echo perfusion sequence for VAI [1]. Here, a temporal shift in the gradient-echo signal relative to that of spin-echo is used to assess *in vivo* information on vessel type (fast-inflow arterioles or slow-inflow venules) and ΔSO_2 levels. As a control group, we included 14 patients with nGBM enrolled in a parallel study at the same institution (NCT00756106). These patients underwent identical MRI and chemo-radiation, but without cediranib.

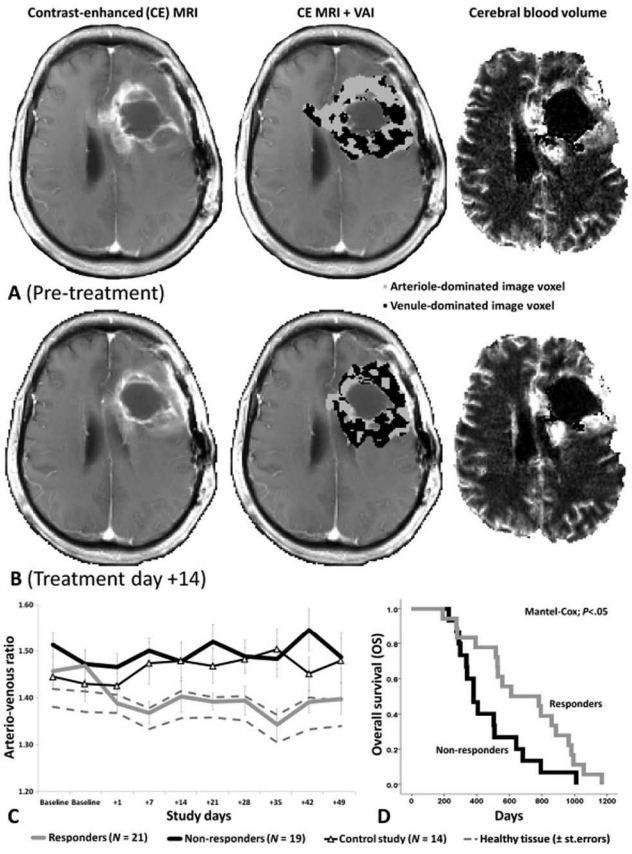

Figure 1. Vessel architectural imaging. (A) Pre-treatment MRI including VAI for identification of vessel type. (B) Corresponding MRI during therapy. Note the change in the arterio-venus ratio compared to pre-treatment. (C) Average arterio-venous ratios for *responding* and *non-responding* patients. Responders mimic the arterio-venous ratios of healthy tissue during therapy. Similar to *non-responders*, a collective vascular normalization is not observed in the control study. (D) Patients with arterio-venous normalization have prolonged OS.

Results: Twenty-one patients were identified as *responders* by the tumor arterio-venous ratios overlapping that of reference tissue at a minimum of two time points during therapy (Fig. 1). Responding patients had prolonged overall survival (OS) compared to 19 *non-responding* patients (median OS = 696 d vs. 381 d, Cox; $P<0.01$, corrected for MGMT methylation status). At day +21, the median ΔSO_2 level of non-responders was 20% higher than pre-treatment, compared to –10% for responders (Mann-Whitney; $P<0.05$), indicating more hypoxia in non-responding tumors.
Conclusions: Using VAI we show for the first time *in humans* that anti-angiogenic therapy induce vascular normalization in nGBM by arterio-venous remodeling and improved oxygenation. Patients who responded to therapy by mimicking the vessel architecture of normal tissue had prolonged survival.
References:
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MC13-0063

MicroRNA-mRNA networks for identification of biomarkers for breast cancer

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Background: MicroRNAs (miRNAs) are highly conserved small non-coding molecules (~22 nt) involved in post-transcriptional regulation. These molecules are playing important role in a range of disease, especially in cancer. Considering the importance of miRNAs as non-invasive biomarkers, the identification of mRNA targets is important to elucidate molecular mechanisms for future target therapies.
Purpose/Objective: Our aim was to identify microRNAs biomarkers by integration of mRNA and miRNAs expression profiles using bioinformatics tools.
Materials and Methods: In this study we performed mRNA and miRNA Agilent microarrays of breast cancer cell lines, classified in different molecular subtypes, such as luminal (T47D, MCF-7 and MCF-7/AZ), Her2 overexpression (SK-BR3 and BT-20), triple negative (MDA-MB-231 and Hs578T) and normal phenotype (HB4A). All the microarray data analyses were performed using the R environment. The anti correlated expression profiles of differentially expressed miRNAs and mRNAs were considered and integrated networks were constructed using GenMiR algorithm. The targets identified were compared with those predicted by miRDip tool and functional analyses were performed using DAVID and Panther databases.
Results: Unsupervised analysis revealed separation according to molecular subtype in both mRNA and miRNA expression profiles. It was constructed miRNA-mRNA networks for each one of the 70 miRNAs differentially expressed, identified according to ANOVA $p<0.01$ bonferroni-corrected, some of them previously associated with breast cancer progression, such as miR-10, miR-21 miR-31, miR-221/222 and let7a. Their targets could be grouped according to biological mechanisms, pathways in cancer and breast cancer molecular subtype.
Conclusions: In conclusion, the present study identified several miRNA biomarkers and targets of interest in miRNA-mRNA networks. Financial support: FAPESP.

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Identification of a putative precursor lesion of papillary thyroid carcinoma by cyclin D1 overexpression and p38 MAPK phosphorylation

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Background: Papillary thyroid cancer (PTC) is the commonest endocrine malignancy. Though significant progress has been made to understand the pathways involved in the tumorigenesis of PTC, no precursor lesion has been identified yet.
Purpose/Objective: The present study aims to identify and understand the precursor lesion of PTC and its molecular markers.
Materials and Methods: Thirteen cases of metastatic PTC, papillary microcarcinoma and follicular variant of PTC (FVPTC) were identified from