Diagnostic Technologies at the University of Chicago

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Available Diagnostic Technologies

Oncology Diagnostics: Gene signatures and Biomarkers		Page
Conzen: UCHI 2280	Glucocorticoid and Androgen Receptor Expression Predicts Treatment Response to Hsp90 Inhibitors in TNBC Patients	5
Gajewski: UCHI 2232	Diagnosis of Cancer through the EGR2 Transcriptome	5
Lengyel: UCHI 2415	Novel Predictive Factor and Immunogenic Target for High-Grade Serous Ovarian Cancer	6
Rosner: UCHI 2323	Triple-negative Breast Cancer Prognostic Gene Expression Signature for Metastasis	6
Rosner: UCHI 2383	Methods for determining prognosis for Breast Cancer patients	7
Salgia: UCHI 1944	Mutations in c-CBL which Predict Tumor Sensitivity to MET-Targeting Therapies	7
Weichselbaum: UCHI 1374	IRDS: Predictive Seven-Gene Signature for Breast Cancer Therapy	8

Significant Disease Diagnostics		
Ancsin: UCHI 2412	Companion Assays for the Diagnosis of Deficiencies in Triglyceride Clearance for the Treatment of Hypertriglyceridemia (HTG)	10
Noth: UCHI 2049	Peripheral Blood-based Test Predicts Progression of Idiopathic Pulmonary Fibrosis (IPF)	10
Noth: UCHI 2387	Genetic Variants Predict Patient Response to N-acetylcysteine (NAC) Therapy for Idiopathic Pulmonary Fibrosis (IPF)	11

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Oncology Diagnostics: Gene Signatures and Biomarkers

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Conzen UCHI 2280

Glucocorticoid and Androgen Receptor Expression Predicts Treatment Response to Hsp90 Inhibitors in TNBC Patients

- Hsp90 inhibitors have been proposed as potential therapeutics for triple negative breast cancer (TNBC) but require better biomarkers to predict treatment efficacy.
- Dr. Suzanne Conzen has documented that treatment with Hsp90 inhibitors is likely to be most effective in glucocorticoid receptor (GR) and/or androgen receptor (AR) overexpressing TNBC because the activity of these nuclear receptors, which can drive tumor growth, is targeted by Hsp90 inhibition.
- The technology provides a predictive diagnostic where the GR/AR status of the tumor informs patient response to Hsp90 inhibitors.
- Data from TNBC cell lines and mouse models have demonstrated that inhibition of Hsp90 leads to rapid loss of GR/AR activity in tumors, accompanied by tumor cell death.
- A US application has been filed on treating breast cancer patients that have been tested for GR/AR status with Hsp90 inhibitors.
- Clinical trials are underway to further evaluate the predictive validity of GR/AR status in the use of Hsp90 inhibitors for breast cancer.

Gajewski UCHI 2232

Diagnosis of Cancer Through the EGR2 Transcriptome

- Overcoming the immune system's tolerance of cancer cells through ablation of T-cell anergy can increase the efficacy of immunotherapy for cancer.
- Dr. Thomas Gajewski has identified an EGR2-based gene signature that differentiates between immune-responsive and non-responsive tumors.
- The EGR2 transcriptome of anergic T-cells identifies numerous biomarker opportunities.
- Validated studies from three independent genome-wide expression and ChIP-sequencing analyses identified a key set of genes involved in the immune response to cancer.
- National applications have been filed in the U.S. and EPO on methods for diagnosis and treatment of cancer through identification and suppression of T-cell anergy by way of the EGR2 transcriptome.
- The gene expression signature offers opportunities for development of powerful new treatment-enabling diagnostics.

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Oncology Diagnostics: Gene Signatures and Biomarkers

Lengyel UCHI 2415

A Novel Predictive Factor and Immunogenic Target for High-Grade Serous Ovarian Cancer

- Clinicians, patients, and families value the ability to predict whether a patient will respond to chemotherapies, such as platinum-based cytotoxins with potentially harmful side-effects, and emerging immunotherapies.
- Dr. Ernst Lengyel has discovered that overexpression of a certain protein in high-grade ovarian cancers predicts heightened sensitivity to platinum-based therapies, and that novel antigens from the protein are expressed by ovarian cancer cells and represent a new target for T-cell- based immunotherapy.
- Overexpression of the protein enables clinicians to accurately predict whether the patient will respond to a platinum-based therapy, and/or whether an immunotherapy targeting the novel antigen protein will be effective.
- Retrospective clinical study and state-of-the-art proteomic profiling approach identified protein and antigen expression in human high-grade, serous ovarian tissue; mechanistic studies confirmed role in DNA repair and as an HLA-type specific-antigen.
- A provisional patent application has been filed on methods of treating ovarian cancer based on expression of the protein in tissue.
- The investigators are seeking partners for clinical development of these diagnostics.

Rosner UCHI 2323

Triple-Negative Breast Cancer Prognostic Gene Expression Signature for Metastasis

- Identifying the patient subset most at-risk is helpful in finding patients most appropriate for novel therapeutic trials and for determining probable treatment outcome.
- Dr. Marsha Rosner has determined a panel of ~30 genes for identifying patients with the most lethal metastatic forms of triple-negative breast cancer.
- The gene expression signature, named BACH1 Pathway Metastasis Signature or BPMS, works in complement with Mammaprint and Oncotype to identify patients who are most likely to experience metastasis.
- The prognostic power of the thirty-gene signature was validated in a retrospective study of 3600 human breast cancer patients.
- A US application has been filed on methods for determining prognosis for breast cancer patients.
- The investigators are working on determining additional tests for which BPMS provides complementary information.

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Oncology Diagnostics: Gene Signatures and Biomarkers

Rosner UCHI 2383
Methods for Determining Prognosis for Breast Cancer Patients

- Information about tumor-stromal crosstalk can offer insights into the progression of Triple-Negative Breast Cancers (TNBC), which is often refractory to treatment.
- Dr. Marsha Rosner has identified a group of genes from both tumor and stroma whose collective expression is prognostic for metastasis-free survival in TNBC patients.
- The gene expression signature can be used to identify patients who are likely to have poor treatment outcomes.
- In retrospective studies of four independent human breast tumor gene expression datasets, the gene signature stratified high-risk patients with TNBC.
- A PCT application has been filed for using the signature to determine prognosis for breast cancer patients.
- Several of the genes in the signature are potential therapeutic targets in the early stages of testing; the investigators plan to further probe these relationships to determine whether the signature can predict therapeutic outcomes for these drugs.

Salgia UCHI 1944
Mutations in c-CBL which Predict Tumor Sensitivity to MET-Targeting Therapies

- Some types of cancers are resistant to c-MET- or EGFR-targeted therapies, making it hard to design appropriate treatment regimens.
- Dr. Ravi Salgia has identified key mutations in c-CBL (Casitas B-lineage lymphoma), which correlate positively with lung cancer cells' response to c-MET inhibitors.
- Mutations in and expression level of c-CBL can function as a biomarker to provide clinically valuable information in designing treatment plans.
- 14 mutations were identified in human lung cancer cells which successfully predicted response to c-MET inhibition therapy.
- A US utility application has been filed on uses of c-CBL mutations for identifying patients who are likely to respond to a given therapy.
- Validating proof-of-concept studies have been completed using mouse xenograft models and archived clinical trial samples.

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Oncology Diagnostics: Gene Signatures and Biomarkers

Weichselbaum UCHI 1374

IRDS: Predictive Seven-Gene Signature for Breast Cancer Therapy

- In order to avoid unnecessary treatments, it is important to be able to predict whether continued adjuvant therapy would be effective for breast cancer patients.
- Dr. Ralph Weichselbaum's team has performed retrospective studies to demonstrate the ability of seven genes – IFIT3, STAT1, IFIT1, OAS1, IF144, MX1, and G1P2 – to identify responders to adjuvant chemotherapy or radiation.
- The signature – termed the Interferon-Related DNA-damage-resistance Signature (IRDS) – can be used to identify patients who will likely benefit from adjuvant therapy.
- Combined clinical and laboratory data show that the IRDS signature can successfully predict the efficacy of continued adjuvant chemotherapy and local-regional control after radiation.
- A US patent has been issued on predictive markers for assessing risk of local-regional failure, survival, and metastasis in cancer patients.
- The gene signature is compatible with conventional commercial platforms and has been tested on clinically-relevant sample types.

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Significant Disease Diagnostics

Significant Disease Diagnostics

Ancsin UCHI 2412

Companion Assays for the Diagnosis of Deficiencies in Triglyceride Clearance for the Treatment of Hypertriglyceridemia (HTG)

- There is currently no standard clinical assay available to measure lipoprotein function, a key link in the triglyceride (TG) clearance pathway.
- Dr. John Ancsin has developed a set of blood tests to rapidly screen for deficiencies lipoprotein function in patients with hypertriglyceridemia (HTG) in order to identify a treatment strategy.
- Dr. Ancsin has demonstrated that the fluorescence-based lipase assays can assess the activities of lipoprotein lipase (LPL), apolipoprotein, and other plasma factors.
- The lipase assays require only one blood sample to provide patient stratification and can also function as a companion diagnostic to support pharmaceutical development of new HTG therapies.
- A PCT application is pending on methods for the assessment of LpL activity and the triglyceride lowering potential of various HTG therapies.
- The lipase assay is being optimized for better diagnosis of HTG.

Noth UCHI 2049

Peripheral Blood-based Test Predicts Progression of Idiopathic Pulmonary Fibrosis (IPF)

- Current methods of diagnosing IPF (X-ray, CT, echocardiogram) cannot predict disease progression or outcome.
- Dr. Imre Noth has identified a molecular signature of 52 genes in the peripheral blood of patients with IPF that can reliably predict mortality outcome and assess IPF progression rate.
- The technology can serve either as a prognostic or a diagnostic tool by monitoring the expression of the gene signature in peripheral blood mononuclear cells (PBMC).
- A four-gene SmartChip qRT-PCR assay has been developed and successfully tested as a prognostic for IPF progression in 74 people.
- A US nationalized PCT application is pending on methods of using the biomarkers for assessing idiopathic pulmonary fibrosis.
- The assay is ready for use in clinical settings.

Significant Disease Diagnostics

Noth UCHI 2387

Genetic Variants Predict Patient Response to N-acetylcysteine (NAC) Therapy for Idiopathic Pulmonary Fibrosis (IPF)

- N-Acetylcysteine (NAC), commonly used in conjunction with other therapeutic agents to break down mucous and lessen the overall decline in lung function, has historically demonstrated little benefit in patients with IPF.
- Dr. Imre Noth has identified loci in two genes, toll interacting protein (TOLLIP) and mucin 5B (MUC5B) whose SNPs indicate whether NAC therapy will improve or worsen the progression of IPF.
- A simple genetic screen of SNPs in TOLLIP and MUC5B allows the identification of IPF patients who will benefit or be harmed from NAC therapy.
- Out of 341 patients screened, the group receiving NAC showed significantly less risk in progression-free survival when they tested positive for both TOLLIP and MUC5B SNPs.
- A PCT application is pending on methods for treating idiopathic pulmonary fibrosis.
- Additional studies are underway to further evaluate the therapeutic potential of NAC in screened patient populations.

Diagnostic Imaging Technologies

Diagnostic Imaging Technologies

Aydogan UCHI 1849

Novel Imaging Agent Improves Targeting Radiation Therapy and Provides New Tool for Diagnosis and Research

- Current imaging technology does not easily or cheaply provide both anatomical and functional analysis for cancer diagnosis and treatment.
- Dr. Bulent Aydogan has developed a deoxyglucose-labeled gold nanoparticle (AuNP-DG) which provides X-ray contrast to glycolytic cancer cells.
- The AuNP-DG imaging agent enables a standalone CT system to acquire both anatomical and functional information, traditionally acquired by a PET/CT hybrid.
- The internalization of AuNP-DG has been proven in both the A-549 lung cancer cell line as well as a grafted mouse tumor.
- A US Utility application has been issued on methods and compositions for imaging cancer cells
- The imaging agent is being validated in other tumor models.

La Riviere UCHI 2088

3D Imaging Stain Gives More Complete, Accurate View of Pathology

- Histology images provide pathologists with a limited number of thin 2D slices while X-ray-based 3D imaging does not provide the biological specificity of histology stains.
- Dr. Patrick La Riviere has developed X-ray visible stains and computational imaging tools that combine the key benefits of 3D, X-ray-based imaging with histology.
- Method of staining tissues (biological, histological, or pathological samples) with multiple biologically specific heavy metal stains followed by X-ray imaging can generate high-resolution images of 1-2 microns.
- The technique has been validated in zebrafish larvae and juveniles, and can be extrapolated to any tissues traditionally stained with histology stains.
- A US patent is issued on 3D, color histology for multi-stained biological samples.
- The research team is working to scale up the technology to demonstrate it on cm length scales, such as pathology samples.

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Diagnostic Imaging Technologies

Lengyel UCHI 1418
Targeted MRI Imaging Agent for Ovarian Cancer

- Effective early diagnosis of ovarian cancer – typically diagnosed at late stages of metastases to omentum and peritoneum – is critical for its treatment.
- Drs. Ernst Lengyel and Joseph Picirilli have developed an MRI imaging agent molecularly targeted to the prolactin receptor for ovarian cancer diagnosis and monitoring; such an agent would prevent costly, invasive and unnecessary biopsies.
- The targeted imaging agent comprises engineered human placental lectogen (hPL) conjugated to gadolinium; the specificity is increased by the robust expression of the prolactin receptor in 98% of ovarian cancers.
- The first-generation hPL-gadolinium conjugate has been validated both *in vitro* and in mouse models.
- A US patent has been issued on the method of identifying ovarian cancer using the imaging agent.
- Investigators are developing a second-generation conjugate for enhanced detection.

Popko UCHI 2112
PET Imaging Agent for Diagnosis and Monitoring of Multiple Sclerosis and Traumatic Brain Injury

- Readout from MRI correlates imperfectly with MS pathology; tools are needed to more accurately assess disease status.
- Dr. Brian Popko has exploited the exposure of potassium channels upon neuron demyelination as a mechanism by which to visualize the status and progression of MS.
- Derivatives of 4-aminopyridine, which bind to potassium channels, are labeled with an isotope to visualize disease progression or to monitor remyelination during therapy.
- The imaging agent has been demonstrated to highlight demyelination in rodent spines and brains in autoradiography and microPET experiments.
- Applications filed in the US, Europe, Canada, and Australia, with claims issued in the US and Europe, for an imaging agent made of radiolabelled 4-AP or derivatives and uses of the agent for imaging patients with demyelinating disorders.
- The investigators are conducting experiments to test the imaging agent in non-human primates

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Molecular Diagnostic Platform Technologies

Molecular Diagnostic Platform Technologies

Dickinson UCHI 2584

Activity-responsive Split RNA Polymerase Platform for Biosensors

- Detection of key cellular chemical events using current diagnostic strategies have difficulty overcoming the low signal-to-noise ratio, making these tests difficult to implement.
- Dr. Bryan Dickinson has designed a platform using assembled RNA polymerases (ARs) fused to interaction domains that produce amplified, unique transcriptional readouts upon binding of the interaction domains to intracellular signaling molecules or events.
- A sequencing-based test identifies the presence of unique transcripts produced after AR delivery and detection of metabolic events present in diseased cells.
- The specificity of ARs and robustness of signal output have been demonstrated in cell lines in response to light stimulation and detection of a small molecule compound.
- A provisional patent application has been filed on the AR platform technology.
- ARs are being designed and tested in primary cancer cells to evaluate diagnostic and therapeutic use or ARs.

Koide UCHI 2225

Affinity Clamps: A Platform Developing High-Affinity Synthetic Binding Proteins

- Affinity clamp technology could pave the way to understand complex physiological and pathological protein signaling networks and provide unique diagnostic and therapeutic agents.
- Dr. Shohei Koide has created a novel protein engineering platform for developing renewable, high affinity and high specificity antibody-like proteins to diverse and difficult targets in unstructured region of proteins, such as post-translational modifications.
- Current affinity clamps are targeted against phospho-tyrosines and can function as biosesnsors for the diagnosis of chronic myelogenous leukemia and Noonan syndrome.
- The level of affinity achieved with the clamp technology is three-four orders of magnitude greater than that of FLAG/antibody, c-myc/antibody, and 6xHis-tag/immobilized metal systems.
- Pending US patent application on platform technology and issued US patent on specific clamps.
- The affinity clamps have been optimized to bind a variety of small epitopes. Dr. Koide has also developed a novel protein capture system with a unique peptide fusion tag and its corresponding affinity clamp.

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Koide UCHI 2089

First-in-Class Recombinant Antibodies to Histone Post-Translational Modifications for Chromatin-based Diagnostics

- High-quality, reliable antibodies of high specificity are needed for chromatin-based diagnostics.
- Dr. Shohei Koide has created high-quality recombinant antibodies to histone post-translational modifications using tailored phage-display libraries.
- A series of recombinant antibodies have been generated against tri-methylated residues on histones 3 and 4 that may be useful for the diagnosis of breast cancer, renal cell carcinoma, and other cancers, or as companion diagnostics for histone-modifying drugs.
- Lead antibodies were identified from two libraries and validated against commercially available antibodies; the recombinant antibodies showed greater specificity and reproducibility than their commercial counterparts.
- A US patent application is pending on compositions and methods of diagnosis and drug screening.
- Histone antibodies to additional post-translational modifications are in development.

Kossiakoff UCHI 2340

Engineered Protein G for Creating Multivalent, Bispecific Recombinant Affinity Reagents

- Protein G is widely used for the purification of antibodies, but current reagents lack specificity to Fabs and subject the antibodies to harsh conditions that may affect product quality.
- Dr. Anthony Kossiakoff has engineered Protein G (eProtein G) to bind to Fabs with higher affinity and specificity compared to native Protein G or Protein A.
- eProtein G can be used to purify recombinantly produced Fabs in a pH sensitive fashion or covalently tethered together to create multivalent recombinant affinity reagents to desired targets.
- In in vitro binding assays, use of eProtein G tethering of Fabs against a target antigen enhanced binding compared to the same concentration of Fabs alone.
- A PCT application is pending for compositions and methods of use of Protein G variants.
- Dr. Anthony Kossiakoff is expanding the use of the Protein G platform to diagnostic and therapeutic applications.

How to Partner with the University of Chicago

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