Contributions of Gene Variants, Endorphins, and Stress Responsivity to Specific Addictions and Treatment

Mary Jeanne Kreek, M.D.
Patrick E. and Beatrice M. Haggerty Professor
Head of Laboratory
The Laboratory of the Biology of Addictive Diseases
The Rockefeller University
Senior Physician
The Rockefeller University Hospital

October 12, 2011
THS Congress 10
Biarritz, France

funded primarily by NIH-NIDA, NIH-NIMH, NIHCRR
HYPOTHESIS: Heroin (opiate) addiction is a disease – a “metabolic disease” – of the brain with resultant behaviors of “drug hunger” and drug self-administration, despite negative consequences to self and others. Heroin addiction is not simply a criminal behavior or due alone to antisocial personality or some other personality disorder.

Vincent P. Dole, Jr., MD; Marie Nyswander, MD; and Mary Jeanne Kreek, MD

First publications describing methadone maintenance treatment research

1) 1964: Initial clinical research on development of treatment using methadone maintenance pharmacotherapy and on elucidating mechanisms of efficacy performed at The Rockefeller Hospital of The Rockefeller Institute for Medical Research:
   (also recorded in the Association of American Physicians meeting transcription of discussion)

2) 1965: Translational applied clinical research performed at Manhattan General Hospital:

<table>
<thead>
<tr>
<th>Systemic Bioavailability After Oral Administration</th>
<th>Apparent Plasma Terminal Half-life ($t_{1/2}$ Beta)</th>
<th>Major Route of Biotransformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heroin</td>
<td>Limited (&lt;30%)</td>
<td>Successive deacetylation and morphine glucuronidation</td>
</tr>
<tr>
<td></td>
<td>3min (30min for active 6-acetyl-morphine metabolite; 4-6h for morphine and active morphine-6-glucuronide metabolite)</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>Essentially Complete (&gt;70%)</td>
<td>N-demethylation</td>
</tr>
<tr>
<td></td>
<td>24h (48h for active <a href="l">R</a>-enantiomer)</td>
<td></td>
</tr>
</tbody>
</table>

Rate of rise of blood (and presumable brain) levels of drugs of abuse are related positively to their reinforcing effects and rate of fall related to withdrawal and craving.

Methadone Maintenance Treatment for Opiate (Heroin) Addiction – 2010

Number of patients currently in treatment: ~ 1 million worldwide

- USA: ~ 260,000
- Europe: ~ 500,000
- Rest of world: ~250,000

Efficacy in “good” methadone treatment programs using adequate doses (80 to 150mg/d):

- Voluntary retention in treatment (1 year or more): 50 – 80%
- Continuing use of illicit heroin: 5 – 20%

Actions of methadone treatment:

- Prevents withdrawal symptoms and “drug hunger”
- Blocks euphoric effects of short-acting narcotics
- Allows normalization of disrupted physiology

Mechanism of action: Long-acting narcotic provides steady levels of opioid at specific receptor sites.

- Methadone found to be a full mu opioid receptor agonist which internalizes like endorphins (beta-endorphin and enkephalins)
- Methadone also has modest NMDA receptor complex antagonism

Kreek, 1972; 1973; 2011
I. Opiate Addiction (Heroin and Illicit Use of Opiate Medications)
   a. METHADONE (80 to 150 mg/d; 50-80%)**
   b. BUPRENORPHINE (+ NALOXONE) (40-50%)* (***)
   [c. NALTREXONE ( <15%)**]
   [d. SUSTAINED RELEASE NALTREXONE (<15%)**]

II. Alcoholism
   a. NALTREXONE (30-40%)*
   b. ACAMPROSATE (low in USA)

III. Cocaine, Amphetamines and Other Stimulants
     NONE

(%) is % of unselected persons with specific addictions who can be retained voluntarily in treatment for 3 months (*) or 12 months (**), with moderate to high success in eliminating specific drug use.

*** Maximum effective dose, 24 or 32 sl, equivalent to 60 to 80 mg of methadone.

Kreek, 2011
Atypical responsivity to stress and stressors may, in part, contribute to the persistence of, and relapse to self-administration of drugs of abuse and addictions. Such atypical stress responsivity in some individuals may exist prior to use of addictive drugs on a genetic or acquired basis, and lead to the acquisition of drug addiction.

Kreek, 1972; 1981; 1982; 1984 ... 2011
TOLERANCE/ADAPTATION OF STRESS RESPONSIVITY EFFECTS OF COCAINE—Cocaine Self-Administration by Rats Under Extended Access Conditions (18h): Effects on Plasma Corticosterone Levels

**Graph 1:**
- **Y-axis:** pg CRFmRNA/ug total RNA
- **X-axis:** Saline, Day 1, Day 3, Day 14
- **Legend:** Saline, Day 1, Day 3, Day 14
- **Note:** Zhou et al., *J. Pharmacol. Exp. Ther.*, 279:351, 1996

**Graph 2:**
- **Y-axis:** Total Cocaine Intake (18-h session)
- **X-axis:** Self-Administration Day (1-5)
- **Legend:** 0.25, 0.5, 1.0, 2.0
- **Note:** Mantsch et al., *JPET*, 294:239, 2000
Daily Intake of Cocaine During Extended Sessions

Picetti et al., Psychopharmacology, 211:313, 2010
ACTH and CORT Levels 24 h After the Last Extended Self-Administration Session

ACTH (pg/ml)

Fischer Control
Fischer Cocaine
Lewis Control
Lewis Cocaine

Corticosterone (ng/ml)

Fischer Control
Fischer Cocaine
Lewis Control
Lewis Cocaine

Picetti et al., Psychopharmacology, 211:313, 2010
TOLERANCE/ADAPTATION OF STRESS RESPONSIVITY EFFECTS OF ALCOHOL – Plasma ACTH and Corticosterone Levels After Binge Pattern Alcohol Administration (po, 1.5g/kg/h x 3)

**ACTH, pg/ml**

- Control
- 1-d Alcohol: *
- 14-d Alcohol: 

**Corticosterone, ng/ml**

- Control
- 1-d Alcohol: *
- 14-d Alcohol: *

TOLERANCE/ADAPTATION OF STRESS RESPONSIVITY
EFFECTS OF ALCOHOL – Effects of Naltrexone vs. Placebo in Alcoholics: Greater Alcohol-Induced HPA Activation Following Naltrexone Disinhibition of Mu Opioid Receptor Inhibition

O’Malley… Sinha, and Kreek, Psychopharmacology 160:19, 2002
STRESS RESPONSIVITY – Heroin, Cocaine, and Alcohol Profoundly Alter Stress Responsive Hypothalamic-Pituitary-Adrenal (HPA) Axis: Normalization During Methadone Treatment

- Acute effects of opiates
- Chronic effects of short-acting opiates (e.g., heroin addiction)
- Opiate withdrawal effects *
- Opioid antagonist effects
- Cocaine effects *
- Alcohol effects
- Chronic effects of long-acting opiate (e.g. methadone in maintenance treatment)

Suppression of HPA Axis (decrease levels of HPA hormones)
Activation of HPA Axis (increase levels of HPA Hormones)
Normalization of HPA Axis

* Our challenge studies have shown that a relative and functional “endorphin deficiency” develops.

Kreek, 1972; 1973; 1987; 1992 … 2010
Role of Mu Opioid Receptor and Related Endorphin Systems in Normal Physiological Functions*

- Endogenous Response to Pain
- Neuroendocrine Functions
  - Stress responsive systems including hypothalamic-pituitary-adrenal axis
  - Reproductive function including hypothalamic-pituitary-gonadal axis
- Immunological Function
- Gastrointestinal Function
- Cardiovascular Function
- Pulmonary Function
- ? Mood, Affect; Cognition

* All disrupted by chronic abuse of the short acting opiate, heroin

Kreek, 1978; 2010
Genetic Variants of the Human Mu Opioid Receptor: Single Nucleotide Polymorphisms in the Coding Region Including the Functional A118G (N40D) Variant

HYPOTHESIS

Gene variants:

- Alter physiology “PHYSIOGENETICS”
- Alter response to medications “PHARMACOGENETICS”
- Are associated with specific addictions

Bond, LaForge… Kreek, Yu, PNAS, 95:9608, 1998
FUNCTIONAL MOP-r (A118G) VARIANT – Increased Binding and Coupling to G Protein-Activated, Inwardly Rectifying K⁺(GIRK) Channels by Beta-Endorphin at the Prototype A118A and A118G Variant of the Mu Opioid Receptor, but Lower Cell-Surface Receptor Binding and Bmax Levels and Lower Forskolin-Stimulated cAMP Accumulation than MOP-r Prototype (Stably Expressed in AV-12 or HEK293 Cells)

STRESS RESPONSIVITY – High Dose Opiate Antagonist Studies: Nalmefene (mu/kappa Directed) Causes Greater HPA Axis Activation Than Naloxone (mu Directed) in Normal Human Volunteers

FUNCTIONAL MOP-r (A118G) VARIANT – “Physiogenetics” Related to A118G Variant of Human Mu Opioid Receptor Gene – Altered Stress Responsivity in Healthy Control Volunteers

Bart et al., Neuropsychopharmacology, 31:2313-2317, 2006
Wand et al., Neuropsychopharmacology, 26:106, 2002
Chong…Wand, Neuropsychopharmacology, 31:204, 2006
Dissecting the Hypothalamic-Pituitary-Adrenal Axis in Humans: Single-Dose (2.25g) Metyrapone Effects

- Hypothalamus
- Anterior Pituitary
- POMC
- CRF (↑)
- β-End (↑)
- ACTH (↑)

Endogenous Opioids (mu – inhibition) (kappa – ? activation)

Metyrapone

FUNCTIONAL MOP-r (A118G) VARIANT– Metyrapone Testing in Normal Volunteers: Plasma cortisol levels and resultant plasma ACTH levels and AUC at 9 a.m. (prior to metyrapone) and after 4 and 8 hours

Ducat et al., in preparation, 2010
Association Between a Functional (A118G) Polymorphism in the mu Opioid Receptor Gene and Opiate Addiction in Central Sweden

<table>
<thead>
<tr>
<th>Genotype</th>
<th>All Subjects</th>
<th>Swedish with Both Parents Swedish</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls (n=170)</td>
<td>Opiate Dependent (n=139)</td>
</tr>
<tr>
<td>A/A</td>
<td>147</td>
<td>98</td>
</tr>
<tr>
<td>A/G</td>
<td>21</td>
<td>39</td>
</tr>
<tr>
<td>G/G</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

RR = 2.86, $\chi^2(1) = 13.403, P = 0.00025^*$
RR = 2.97, $\chi^2(1) = 8.740, P = 0.0031^*$

Thus, in the entire study group in this central Swedish population, Attributable Risk due to genotypes with a G allele in this population: **18%**
Attributable Risk due to genotypes with a G allele in Swedes w/ Swedish parents: **21%** (with confidence interval ranges from 8.0 to 28.0%)

Association Between a Functional (A118G) Polymorphism in the mu Opioid Receptor Gene and Alcoholism in Central Sweden

<table>
<thead>
<tr>
<th></th>
<th>Swedish with two Swedish parents</th>
<th>Non-Swedish without Swedish Parents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alcohol Dependent (n=193)</td>
<td>Control (n=120)</td>
</tr>
<tr>
<td>A118</td>
<td>158</td>
<td>104</td>
</tr>
<tr>
<td>A118G, G118G</td>
<td>35</td>
<td>16</td>
</tr>
</tbody>
</table>

OR=1.92 $\chi^2_{(1)} = 7.18$, $p = 0.0074$

<table>
<thead>
<tr>
<th></th>
<th>Alcohol Dependent (n=389)</th>
<th>Control (n=170)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G/G; A/G</td>
<td>90</td>
<td>23</td>
</tr>
<tr>
<td>A/A</td>
<td>299</td>
<td>147</td>
</tr>
<tr>
<td>118G Allele Frequency *</td>
<td>0.125</td>
<td>0.074</td>
</tr>
</tbody>
</table>

* Overall 118G Allele Frequency = 0.109

Thus, in the entire study group in this central Swedish population: Attributable Risk due to genotypes with a G allele: **11.1%**

(with confidence interval ranges from 3.6 to 18.0%)

Bart G, Kreek MJ, LaForge KS… Ott J, Heilig M, Neuropsychopharmacology, 30:417, 2005
FUNCTIONAL MOP-r (A118G) VARIANT – “Pharmacogenetics” Related to A118G Variant of Human Mu Opioid Receptor Gene – Altered Stress Responsivity: Naltrexone Treatment of Alcoholics

Oslin et al., Neuropsychopharmacology, 28: 1546, 2003; similar findings by Anton... Goldman et al., Arch Gen Pscyh, 65:135, 2008
### FUNCTIONAL MOP-r (C17T) VARIANT–Association with Alcohol and with Cocaine Dependence in HIV+ or HIV- African American Women (Based on KMSK Cut-Off Scores)

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted Odds Ratio for TT Genotype</th>
<th>Adjusted for HIV-serostatus</th>
<th>Adjusted for HIV, age, income, and education</th>
</tr>
</thead>
<tbody>
<tr>
<td>KMSK alcohol</td>
<td>3.7 (1.6-8.4) <strong>p = 0.003</strong></td>
<td>3.6 (1.5-8.3) <strong>p = 0.003</strong></td>
<td>3.0 (1.1-8.0) <strong>p = 0.03</strong></td>
</tr>
<tr>
<td>KMSK cocaine</td>
<td>2.8 (1.8-6.4) <strong>p = 0.014</strong></td>
<td>2.7 (1.2-6.2) <strong>p = 0.02</strong></td>
<td>2.0 (0.8-5.2) <strong>p = 0.14</strong></td>
</tr>
<tr>
<td>KMSK opiates</td>
<td>1.5 (0.4-5.1) <strong>p = 0.53</strong></td>
<td>1.6 (0.5-5.6) <strong>p = 0.46</strong></td>
<td>1.4 (0.3-6.1) <strong>p = 0.65</strong></td>
</tr>
</tbody>
</table>

Crystal et al., *Addiction Biology*, in press, 2011
GWAS (10K) ARRAY – Genes with Possible Association with Opiate Addiction in Caucasian Subjects: Top Hypothesis-Generated “Hits”

<table>
<thead>
<tr>
<th>Gene</th>
<th>Product</th>
<th>Description</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRY1</td>
<td>Cryptochrome 1 (photolyase-like)</td>
<td>Transports PER proteins to nucleus</td>
<td>0.0040</td>
</tr>
<tr>
<td>GRM8</td>
<td>Metabotropic glutamate receptor subunit 8</td>
<td>Presynaptic cleft in multiple brain regions</td>
<td>0.0052</td>
</tr>
<tr>
<td>OPRM1</td>
<td><strong>Mu opioid receptor</strong></td>
<td>Site of action of opiates/opiods, enkephalin, β-endorphin, morphine, etc.</td>
<td>0.0055</td>
</tr>
<tr>
<td>GRM6</td>
<td>Metabotropic glutamate receptor subunit 6</td>
<td>Post-synaptic cleft of ON-bipolar cells</td>
<td>0.0071</td>
</tr>
<tr>
<td>NR4A2</td>
<td>Nuclear receptor subfamily 4, group A, member 2</td>
<td>Coexpressed with TH Activates DAT</td>
<td>0.0312</td>
</tr>
</tbody>
</table>

## HYPOTHESIS-DRIVEN SNP ARRAY (Using Illumina® GoldenGate Custom Array – 130 Genes, 1350 SNPs) – Study of Heroin Dependence in Caucasians

<table>
<thead>
<tr>
<th>SNP</th>
<th>Gene</th>
<th>nominal P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs510769</td>
<td>mu-opioid receptor</td>
<td>0.0003</td>
</tr>
<tr>
<td>rs3778151</td>
<td></td>
<td>0.0007</td>
</tr>
<tr>
<td>rs6473797</td>
<td>kappa-opioid receptor</td>
<td>0.0009</td>
</tr>
<tr>
<td>rs2236861</td>
<td></td>
<td>0.0029</td>
</tr>
<tr>
<td>rs2236857</td>
<td>delta-opioid receptor</td>
<td>0.0125</td>
</tr>
<tr>
<td>rs3766951</td>
<td></td>
<td>0.0165</td>
</tr>
<tr>
<td>rs1534891</td>
<td>casein kinase 1, epsilon</td>
<td>0.0016</td>
</tr>
<tr>
<td>rs694066</td>
<td>galanin</td>
<td>0.0019</td>
</tr>
<tr>
<td>rs3758987</td>
<td>serotonin receptor 3, subunit B</td>
<td>0.0170</td>
</tr>
</tbody>
</table>

* Allele test
HYPOTHESIS-DRIVEN SNP ARRAY (Using Illumina® GoldenGate Custom Array – 130 Genes, 1350 SNPs) – Study of Heroin Dependence in African Americans

<table>
<thead>
<tr>
<th>SNP</th>
<th>Gene</th>
<th>nominal P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs731780</td>
<td>Solute carrier family 29 member 1</td>
<td>0.0006</td>
</tr>
<tr>
<td>rs1650420</td>
<td></td>
<td>0.0006</td>
</tr>
<tr>
<td>rs6497730</td>
<td></td>
<td>0.0015</td>
</tr>
<tr>
<td></td>
<td>Glutamate receptor 2A</td>
<td></td>
</tr>
<tr>
<td>rs1070487</td>
<td></td>
<td>0.0022</td>
</tr>
<tr>
<td>rs4587976</td>
<td></td>
<td>0.0039</td>
</tr>
<tr>
<td>rs5326</td>
<td>Dopamine D(1) receptor</td>
<td>0.0029</td>
</tr>
<tr>
<td>rs971074</td>
<td>Alcohol dehydrogenase 7</td>
<td>0.0035</td>
</tr>
<tr>
<td>rs1176724</td>
<td>Serotonin receptor 3, subunit A</td>
<td>0.0048</td>
</tr>
<tr>
<td>rs2289948</td>
<td>Diazepam binding inhibitor</td>
<td>0.0170</td>
</tr>
</tbody>
</table>

Levran et al, Genes Brain Behav. 8:531, 2009
Epigenetic Inheritance

- The transmission of information to a daughter cell or from generation to generation that is not encoded in the DNA sequence
- DNA methylation and covalent histone modifications are the primary sources of epigenetic inheritance

Nielsen, Neuropsychopharmacology 34:867-873, 2009
Increased Methylation at Two of Eight CpG Dinucleotides in the OPRM1 Promoter Region in Caucasian Former Severe Heroin Addicts versus Controls

Nielsen, *Neuropsychopharmacology* 34:867-873, 2009
Human prodynorphin gene: Chr 20pter-p12
Exon / intron organization and single nucleotide polymorphisms

- Three 3’UTR SNPs (rs910080, rs910079, and rs2235749) are in complete linkage disequilibrium (LD), and comprise two haplotype blocks: T-T-C or C-C-T;

- The haplotype C-C-T was significantly associated with cocaine dependence and cocaine/alcohol codependence (OR=2.32, experiment-wise p=0.015) in Caucasians.

Yuferov et al, Neuropsychopharmacology, 34:1185, 2009
Preprodynorphin mRNA levels in the caudate from human post-mortem brains stratified by genotypes of PDYN gene

- CC-CC-TT: n=7
- TC-TC-CT: n=21
- TT-TT-CC: n=15

**Genotype Pattern**

- p<0.002
- p<0.005

* Haplotype C-C-T significantly associated with cocaine dependence and cocaine/alcohol codependence (OR=2.32, experiment-wise p=0.015) in Caucasians.

Yuferov et al, Neuropsychopharmacology, 34:1185-1197, 2009
Methylation rate at specific CpG sites of the human PDYN gene promoter in PBMCs and two human post-mortem brain regions

ESME (sequencing) data, n=21

Cloning Data

P-glycoprotein (MDR1, ABCB1)

P-gp is expressed in tissues with barrier function like the endothelial cells lining of the Blood-Brain Barrier

Modified from Tang et al. Pharmacogenetics (2002)

Adapted from Ho et al., Clin. Pharm. Ther., 78: 260, 2005 and Tang et al., Pharmacogenetics, 12: 437, 2002
PHARMACOGENOMICS – P-glycoprotein (MDR1, ABCB1): SNP 1236C>T (and Related Haplotype) Associated with Higher Methadone Doses (>150 mg/day) in Maintenance Treatment Patients

P-gp is expressed in tissues with barrier function like the endothelial cells lining of the Blood-Brain Barrier

Levran... Kreek, Hum. Mol. Genet., 17:2219, 2008
PHARMACOGENETICS – Allelic Variant of *NGFB* Gene Associated with Lower Methadone Dose in Maintenance Treatment Patients (n=72)

NGFB SNP (rs2239622) intron 1 genotypes

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Methadone Dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT</td>
<td>81.7 mg/d</td>
</tr>
<tr>
<td>CT</td>
<td>153.1 mg/d</td>
</tr>
<tr>
<td>CC</td>
<td>139.7 mg/d</td>
</tr>
</tbody>
</table>

Minor Allelic Frequency (MAF) in Controls = 0.30

Levran… Kreek., Pharmacogenetics, in press, 2011
PHARMACOGENOMICS – CYP2B6 SNPs are Associated with Effective Methadone Dose (n=74) (516G>T and 785A>G)

Methadone dose (mg/d)

rs3745274 (516G>T)

G/G  G/T  T/T

Methadone dose (mg/d)

A/A  A/G  G/G

Rs2279343 (785A>G)

Levran … Kreek, Addiction Biology, in press, 2011
Impulsivity* (genetics?)

Risk Taking* (genetics?)

Comorbidity (genetics)

Stress Responsivity-atypical (genetics)

Environmental Factors
(~100% contribution to addiction)

Drug Induced Effects (w/ some genetic factors)
(~100% contribution to addiction)

Genetic Factors for addiction
(30-60% contribution to addiction)

** Relative scale of contributors to stage of drug use/addiction:

0 ↓ ↓ ↓ ↓ ↓

Kreek, Nielsen, Butelman & LaForge, Nat Neurosci., 8:1450, 2005
# The Laboratory of the Biology of Addictive Diseases 2011-2012

<table>
<thead>
<tr>
<th>Laboratory Scientists,</th>
<th>Postdoctoral Fellows &amp; Graduate Students</th>
<th>P60-Center Collaborators/Adjunct Faculty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eduardo Butelman</td>
<td>Collene Lawhorn</td>
<td>Miriam Adelson*</td>
</tr>
<tr>
<td>Yan Zhou</td>
<td>Keiichi Niikura</td>
<td>Gavin Bart *</td>
</tr>
<tr>
<td>Orna Levran</td>
<td>Kate Seip</td>
<td>Paul Casadonte</td>
</tr>
<tr>
<td>Ann Ho</td>
<td></td>
<td>Michael Glass</td>
</tr>
<tr>
<td>Vadim Yuferov</td>
<td></td>
<td>James Kocsis*</td>
</tr>
<tr>
<td>Dmitri Proudnikov</td>
<td></td>
<td>Diane Lane</td>
</tr>
<tr>
<td>Yong Zhang</td>
<td></td>
<td>David Nielsen*</td>
</tr>
<tr>
<td>Brian Reed</td>
<td></td>
<td>David Novick*</td>
</tr>
<tr>
<td>Roberto Picetti</td>
<td></td>
<td>Virginia Pickel*</td>
</tr>
<tr>
<td>Stefan Schlussman</td>
<td></td>
<td>John Rotrosen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ellen Unterwald*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Research Physicians and Nurse Practitioners</th>
<th>Assistants for Research</th>
<th>Administrative Staff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lisa Borg</td>
<td>Adam Brownstein</td>
<td>Kitt Lavoie</td>
</tr>
<tr>
<td>Brenda Ray</td>
<td>Michele Buonora</td>
<td>Rosanna Volchok</td>
</tr>
<tr>
<td>Elizabeth Ducat</td>
<td>Shasha Chen</td>
<td>Susan Russo</td>
</tr>
<tr>
<td></td>
<td>BRANDAN MAYER-BLACKWELL</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory Manager</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Matthew Randesi</td>
<td></td>
</tr>
</tbody>
</table>

*Adjunct Faculty