February, 2015

**Potential of Immunotherapy for Solid Tumors including Cancers of the Bile Duct**

Lei Zheng, M.D., Ph.D.
Tumor Immunology Program and GI Cancer Program
Sidney Kimmel Cancer Center at Johns Hopkins
GVAX – Under a licensing agreement between Aduro BioTech, Inc. and the Johns Hopkins University, the University is entitled to milestone payments and royalty on sales of the vaccine product.
Cancer Immunotherapy Comes of AGE

• FDA-approved prostate cancer vaccine (sipuleucel-T) targeting a specific cancer antigen

• FDA-approved checkpoint inhibitor ipilimumab targeting the T cell inhibitory signal CTLA-4

• Efficacy of PD-1/PD-L1 pathway blockade in solid tumors – recently FDA-approved pembrolizumab and nivolumab for melanoma
Immune checkpoint blocking agents release the break on the immune “engine”, but this “engine” needs to be fueled first

- Immune checkpoint agents act on T cells

- Only a minority of tumors have naturally infiltrated effector T cells
  - 50% of melanomas
  - 20-30% renal cell carcinoma (RCC)
  - ~20% lung
  - 10-20% colorectal tumors (particularly MSI)

- For most cancers, immune modulation alone is not enough – a T cell generating agent is also needed
50% of Melanomas have spontaneous infiltration of effector T cells

Explains why immune checkpoint inhibitors as a single agent work more often in this cancer
Response of metastatic melanoma to re-induction of anti-PD-1 therapy

**A**

Metastatic sites
- LN1
- LN2
- LN3
- LN4
- LN5
- LN6
- Liver 1
- Liver 2

**B**

H&E
PD-L1
CD8
PD-1

**C**

August 2007
December 2010
November 2011

Melanoma recurrence
4 months after starting reinduction therapy

**D**

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Response of metastatic colorectal cancer to anti-PD-1 therapy

Regression of metastatic RCC following anti-PD-1 therapy, with “immune-related” response characteristics.
Immune-Modulatory Receptors & Ligands Regulating T Cells: Emerging and in the Clinics

Activating receptors:
- CD28
- OX40
- GITR
- CD137
- CD27
- HVEM

Inhibitory receptors:
- CTLA-4
- PD-1
- TIM-3
- BTLA
- VISTA
- LAG-3

Agonistic antibodies
- T-cell stimulation

Blocking antibodies

Biologic roles
NOT redundant

Differential up-regulation by different tumor types
In all those anti-PD-1/PD-L1 therapy sensitive tumors, infiltration of CD8^+ T cells is correlated with the PD-L1 expression.

However, many signals within the tumor microenvironment that inhibit effective T Cell trafficking and function into tumors.
What makes immunologically quiescent tumors different from immunologically active cancers like melanoma that respond to immunotherapy?
Effector T cell infiltration NOT usually a natural response to cancers like pancreatic cancer, a malignant disease clinically similar to cholangiocarcinoma.
But even in cancers like pancreatic cancer the immune system can be provoked!
GVAX: GM-CSF Secreting, Allogeneic, Whole Tumor Cell Vaccine

- Allogeneic pancreatic cancer cell vaccine expressing GM-CSF
- Developed by JHU (Jaffee)
- Off-the-shelf product produced at JHU GMP
- Excellent safety profile in people
- Induces mesothelin-specific cellular immunity

Vaccines are the most efficient way to induce T cells.
A (Neo)adjuvant Pancreatic Ductal Adenocarcinoma (PDA) Vaccine Study

<table>
<thead>
<tr>
<th>Pre-study Screen/randomization</th>
<th>1st Vaccine</th>
<th>Surgery (PD)</th>
<th>2nd Vaccine</th>
<th>Adjuvant Chemoradiation and Chemotherapy</th>
<th>3rd Vaccine</th>
<th>4th Vaccine</th>
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<td>4</td>
<td>8</td>
<td>12</td>
<td>16</td>
<td>20</td>
<td>24</td>
</tr>
</tbody>
</table>

**Week**

**Arm A:** Vaccine alone

**Arm B:** Vaccine plus a single low dose IV Cyclophosphamide

**Arm C:** Vaccine plus daily oral metronomic cyclophosphamide

Zheng and Edil

Intratumoral Lymphoid Aggregates Form in 85% PDAC Tumors within Two Weeks Following Vaccination

<table>
<thead>
<tr>
<th>Vaccinated</th>
<th>Unvaccinated</th>
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<tbody>
<tr>
<td>H&amp;E</td>
<td>H&amp;E</td>
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<tr>
<td>CD3</td>
<td>CD3</td>
</tr>
<tr>
<td>CD20</td>
<td>CD20</td>
</tr>
</tbody>
</table>

Elaine Bigelow
Lutz, Zheng et al. CIR 2014
Vaccine-induced Intratumoral Lymphoid Aggregates are Characteristic of Germinal Centers

Elaine Bigelow
Lutz, Zheng et al. CIR 2014
Development of Lymphoid Aggregates Involves Lymphoid Neogenesis

D2-40 (Lymphatic vessel marker)

CCL21 (Chemokine involved in Lymphoid Neogenesis)

Elaine Bigelow

Lutz, Zheng et al. CIR 2014
Microdissection of Intratumoral Lymphoid Aggregates for Microarray Analysis

Elaine Bigelow, Annie Wu

Lutz, Zheng et al. CIR 2014
Decreased Tregs - increased Th17 - decreased PD-L1 correlate with improved survival

Elaine Bigelow, Annie Wu
Lutz, Zheng et al. CIR 2014
**Decreased Treg/TGFβ and Increased TH17 Intratumoral Gene Signatures are Associated with Improved Vaccine Response**

**Regulatory T cells (Tregs)**

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>OS&gt;3yr vs. OS&lt;1 yr</th>
<th>Enh T cell vs. not Enh</th>
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<tbody>
<tr>
<td>TGFβ1</td>
<td>1.66</td>
<td>1.33</td>
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<tr>
<td>TGFβ11</td>
<td>-13.22</td>
<td>-1.65</td>
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<tr>
<td>TGFβ2</td>
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<td>TGFβ3</td>
<td>-1.34</td>
<td>1.44</td>
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<td>TGFβ1</td>
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<td>1.06</td>
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<td>Smad3</td>
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<td>IL10</td>
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<tr>
<td>stat5</td>
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<td>-1.5</td>
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<td>FOXP3</td>
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**TH1**

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<tr>
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<th>OS&gt;3yr vs. OS&lt;1 yr</th>
<th>Enh T cell vs. not Enh</th>
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<td>IL12A</td>
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<td>IL12B</td>
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<td>IL18</td>
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<td>1.71</td>
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<td>IFNG</td>
<td>-2.14</td>
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<td>IFNGR1</td>
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<td>TNF</td>
<td>1.48</td>
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<td>1.45</td>
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**TH17**

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<tbody>
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<td>IL17A</td>
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<td>IL17C</td>
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<td>IL17F</td>
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<td>IL17RA</td>
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<td>IL17RC</td>
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<tr>
<td>IL17RE</td>
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<tr>
<td>stat3</td>
<td>-8.22</td>
<td>-7.28</td>
</tr>
</tbody>
</table>

**Up ≥ 1.5X in responders**
**Down ≤ 1.5X in responders**

Can we enhance vaccine-induced immune response by targeting lymphoid aggregate associated immune signatures such as the TGFβ pathway?
Syngeneic Mouse Hepatic Metastasis Model by Hemispleen Injection


Soares, Zheng et al. JoVE. 2014
Anti-Tumor Effect of GVAX in Combination with Anti-TGF-β Blockade Antibody

Soares K. et al. Unpublished
Anti-TGFβ Blockade Antibody Enhances Effector T Cells to Treg Ratio in Tumors in an Vaccine-dependent Manner

CD8:Foxp3⁺ TIL Ratio

CD8 IFNγ:Foxp3⁺ TIL Ratio

Kevin Soares
Soares K. et al. Unpublished
Upregulation of PD-1 and PD-L1 (B7-H1) in All Vaccine-induced Intratumoral Lymphoid Aggregates

Co-localization

Elaine Bigelow, Annie Wu
Lutz, Zheng et al. CIR 2014
PD-L1 membranous expression is seen in less than 20% of PDAs and is enhanced in patients receiving GVAX vaccines.

Elaine Bigelow, Annie Wu
Soares, Zheng et al. Journal of Immunotherapy 2015

Bigelow et al. JoVE, 2013
GVAX induces PD-L1 expression on the cell membranes of the murine Panc02 tumors formed in the hemispleen model

Annie Wu
Soares, Zheng et al. Journal of Immunotherapy 2015
Anti-Tumor Effect of GVAX in Combination with Anti-PD1 Blockade

Days after tumor implantation

Percent survival

Cy: low dose cyclophosphamide

Kevin Soares
Soares, Zheng et al. Journal of Immunotherapy 2015
PD-1 or PD-L1 blockade coordinates with GVAX to enhance infiltration of tumor-targeting IFNγ+ CD8 cells into murine PDAs

Kevin Soares
Soares, Zheng et al. Journal of Immunotherapy 2015

Cy: low dose cyclophosphamide
Evidence supporting the combination of vaccines and immune checkpoint inhibitors in human studies
**Phase Ib: Ipilimumab 10 mg/kg Alone (Arm 1) or Ipi + GVAX (Arm 2)**

<table>
<thead>
<tr>
<th>INDUCTION PHASE</th>
<th>MAINTENANCE PHASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 2 3 4</td>
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<tr>
<td></td>
<td></td>
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<tr>
<td>1* 4 7* 10 14* 18 22* 34* 46* 58*</td>
<td></td>
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<tr>
<td>Weeks</td>
<td></td>
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</table>

- **Vaccine** = $2.5 \times 10^8$ Panc 6.03 + $2.5 \times 10^8$ Panc 10.05 tumor cells
- *Tumor assessments (TA)*
- Maintenance phase dosing and/or TA q 12 weeks if SD or better at week 22

*Le et al. Journal of Immunotherapy 2013*
Ipilimumab + Vaccine Improves Survival In Advanced Pancreatic Cancer Patients

- Metastatic patients having failed >2 chemotherapies
- Phase II multicenter study is ongoing
- 7/15 patients in the ipi+GVAX combo arm with clinical and/or biomarker response
- 0/15 in the Ipi alone arm with clinical and/or biomarker response

Le et al. Journal of Immunotherapy 2013
Radiographic Regressions After 14 Weeks of Treatment with Ipilimumab (Ipi) + Vaccine

Baseline

Week 7 Ipi/Vaccine

Week 14 Ipi/Vaccine
Baseline: local recurrence and peritoneal carcinomatosis 10 months following neoadjuvant GVAX and surgery.

Week 14 (4 weeks post dose 4), Week 7 both showed growth from baseline & narrowing at portal/splenic confluence.

Week 34 (2nd maintenance dose), Week 22 appeared similar.

- 5 years since the recurrence
- 40 months off ipilimumab/GVAX treatment

Le, Zheng, Jaffee et al. Journal of Immunotherapy 2013
Reprogram TME to Optimize Immunotherapy

**Antigen Presentation**
- Activate Dendritic Cells
  - GM-CSF Vaccine
- Chemotherapy
- Epigenetic modifier/Neoantigens
- Combination of GVAX and listeria-vaccine (Prime-boost)
- CDN-STINGVAX

**Suppress Immune Tolerance**
- Blockade of immune checkpoints in tumor microenvironment
  - Anti CTLA-4
  - Anti PD-1/PD-L1
  - Targeting Tregs (?TGFβ inhibitors)
- Manipulation of innate response in tumor microenvironment
  - Stromal fibroblast targeting agents?

More Effective Cancer Immunotherapy

Modified from Soares, Zheng, Edil, and Jaffee Cancer J. 2012
Epigenetic modifiers can reprogram immune TME

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- Epigenetic modifier/Neoantigens
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  - Anti PD-1/PD-L1
  - Targeting Tregs (TGFβ inhibitors)
- Manipulation of innate response in tumor microenvironment
  - Stromal fibroblast targeting agents?

These strategies lead to a more effective cancer immunotherapy.

Modified from Soares, Zheng, Edil, and Jaffee Cancer J. 2012
DNA Demethylating Agents May Prime Cancers for Checkpoint Inhibitor Therapies and Also Induce Neoantigens – Cancer Testis Antigen Expression in Colorectal Cancer Cells

Li, Ahuja, et al. Oncotarget 2014
Chemotherapy can reprogram TME

**Antigen Presentation**
- Activate Dendritic Cells
  - GM-CSF Vaccine
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More Effective Cancer Immunotherapy

Modified from Soares, Zheng, Edil, and Jaffee Cancer J. 2012
Certain chemotherapy agents may also prime pancreatic cancer for anti-PD-1/PD-L1 therapies

PDAC cells treated by 5FU, Oxaliplatin, or Abraxane

IHC of PD-L1

Edil (University of Colorado)
& Zheng (JHU)
IT'S A BALANCE: NOT AN ALL OR NONE SITUATION!

The balance between pro-carcinogenic versus anticancer inflammation currently favors cancer growth. New advances are beginning to tip the balance in favor of a potent anti-cancer immune response.
Both Pancreatic Adenocarcinoma and Cholangiocarcinoma are associated with Stromal Fibrosis

Pancreatic adenocarcinoma

Intrahepatic Cholangiocarcinoma
Carcinogenesis of the Bile Duct is associated with Inflammatory Processes

Cadamuro et al. Translational GI Cancer, 2013
Phenotyping the tumor reactive stroma in cholangiocarcinoma

A. SMA
B. fibronectin
C. CD45
D. CD206 (TAM)
E. Podoplanin
F. CD34
## Limited Clinical Research in Immunotherapy for Cholangiocarcinoma

<table>
<thead>
<tr>
<th>Drug</th>
<th>Treatment type</th>
<th>Treatment timing</th>
<th>Disease stage</th>
<th>Phase</th>
<th>PFS (month)</th>
<th>OS (month)</th>
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<tr>
<td>Cetuximab</td>
<td>anti-EGFR antibody</td>
<td>first line</td>
<td>Metastatic BTC</td>
<td>II</td>
<td>2.0</td>
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<td>Metastatic BTC</td>
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<td>vaccine</td>
<td>adjuvant</td>
<td>Advanced BTC</td>
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<td>NA</td>
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<td>MUC1 peptide-loaded DCs</td>
<td>vaccine</td>
<td>adjuvant</td>
<td>Resected BTC</td>
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<td>NA</td>
<td>NA</td>
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<td>WT1 peptide</td>
<td>vaccine</td>
<td>first line</td>
<td>Advanced BTC</td>
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<td>Tumor lysate-pulsed DCs plus activated T cell transfer</td>
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<td>adjuvant</td>
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<td>Personalized peptide vaccine (PPV)</td>
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<td>chemo-resistant</td>
<td>Resected BTC</td>
<td>II</td>
<td>NA</td>
<td>6.9</td>
</tr>
</tbody>
</table>
Immunotherapy is Promising for Cholangiocarcinoma

Tran, Rosenberg, et al. Science 2014
Tumor regression after treatment with a highly pure population of Vβ22+ ERBB2IP mutation–reactive CD4+ T cells

Tran, Rosenberg, et al. Science 2014
Is Cholangiocarcinoma an Immune Quiescent Tumor like Pancreatic Cancer or an Immune Active Tumor like Melanoma?
Infiltration of CD8+ T cells is inversely associated with the expression of PD-L1; high PD-L1/low CD8+ is associated with advanced stages of intrahepatic cholangiocarcinoma

How should we design the immunotherapy for cholangiocarcinoma after having learned from the experience in other solid tumors?

Identify the patient population that is suitable for the single agent checkpoint inhibitor treatments

However, even for those patients who respond to the single agent immunotherapy, combinational therapy may be more potent and lead to more durable response.
Lessons Leaned From Other Solid Tumors: Improving Survival with Combination Therapy

Combinations needed for the big therapeutic leap!
Combinations are needed to achieve the full potential of the immune system to recognize and kill all cancers

- Understand the signaling networks that regulate immune responses to cholangiocarcinomas: Is ICC the same as ECC or GBC?

- What are the right combinations?

- Need to selectively control cancer specific T cells to avoid immune mediated adverse events
Vaccines targeting multi-neoantigens

1. Identify mutations
   - Pool (unbiased)
   - Use epitope predication algorithms
2. Select epitopes
3. Formulate vaccine
   - Synthesize peptides
   - Recombinant DNA
   - Other
4. Add immune modulation
   - Immune adjuvant
   - Checkpoint blockade

Adoptive T Cell Transfer

- Isolate tumour cells
- Test for autologous tumour recognition
- Select T cells expressing tumour-specific TCRs
- Clone TCR gene into viral vector
- Culture in vitro with peptides to expand T cell populations derived from TIL isolates or peripheral blood
- Immunize MHC-transgenic mice to create new TCRs
- Use tetramers to identify or sort naturally occurring T cells
- Process data using software
- Mutated DNA sequence
- Mutated protein sequence
- DNA
TIP THE BALANCE IN FAVOR OF A POTENT ANTI-CANCER IMMUNE RESPONSE!

- Vaccines
- Immune modulating agents
- Adoptive transfer

Antigen specific T cells
Dendritic Cells
Th1 T cells
TLR ligands
Activated monocytes
Cancer specific antibodies

TUMOR INFLAMMATION

Regulatory T cells
Th17 T cells
Regulatory Dendritic Cells
Regulatory Monocytes
Regulatory Mast Cells
Regulatory Granulocytes
Inhibitory Cytokines/Chemokines
Vascular Factors (VEGF)
Stromal Factors
Tumor Factors (STATS, TGF-beta)
Preclinical Models of Bile Duct Cancers are needed for Immunotherapy Research

Education

Nobel Prizes
1905 - Transmission and treatment of TB
1906 - Structure of Nervous System
1907 - Role of protozoa in disease
1908 - Immunity to infectious diseases
1928 - Investigations on typhus
1929 - Importance of dietary vitamins
1939 - Discovery of antibacterial agent, Prontosil
1945 - Discovery of penicillin
1951 - Yellow fever vaccine
1952 - Discovery of streptomycin
1954 - Culture of the polio virus
1960 - Understanding of immunity
1970 - Understanding of neurotransmitters
1974 - Structural & functional organisation of cells
1975 - Tumour-viruses and genetics of cells
1977 - Hypothalamic hormones
1984 - Techniques of monoclonal antibody formation
1986 - Nerve growth factor and epidermal growth factor
1990 - Organ transplantation techniques
1992 - Regulatory mechanisms in cells
1996 - Immune-system detection of virus-infected cells
1997 - Discovery and characterisations of prions
1999 - Discovery of signal peptides
2000 - Signal transduction in the nervous system
2004 - Odour receptors and organisation of olfactory systems
2008 - Role of HIV and HIV in causing disease
2010 - Development of in vitro fertilization
2011 - Discoveries around innate and adaptive immunity
2012 - Reprogramming mature cells to pluripotent ones

Overview
- Involved in around 75% of research
- Short life-span and fast reproductive rate means mice are suitable for studying disease across whole life cycle
- 98% of genes have comparable genes in humans
- Similar reproductive and nervous systems and suffer many of the same diseases as humans including cancer, diabetes and anxiety
- Can be genetically modified to include human genes in enhance biological relevance
- Can act as an avatar for a human cancer to allow drug therapies to be trialled safely

Research Areas
- Alzheimer’s disease, anaesthetics, AIDS & HIV, anticoagulants, antidepressants, asthma, blindness, bone and joint disease, brain injury, breast cancer, cardiacc arrest, cystic fibrosis, deafness/hearing loss, Down’s syndrome, drugs for high blood pressure, transplant rejection, Hepatitis B, C & E, Huntington’s disease, influenza, leukaemia, malaria, motor neurone disease, multiple sclerosis, muscular dystrophy, Parkinson’s disease, prostate cancer, schistosomiasis, spinal cord injury, stroke, testicular cancer, tuberculosis,

Contact
www.understandinganimalresearch.org.uk
www.animalresearch.info
www.animalprogress.org
www.speakingofresearch.com

Cancer Immunotherapy: A breakthrough made through animal research
Posted on December 20, 2013 by Blue Sky Science
Acknowledgement

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Katie Bever*
Wei Gong*

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Eric Lutz*
Guanglan Mo*
Todd Armstrong
Sara Solt*

University of Colorado
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Rich Schulick*

JHU Pathology
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Masamichi Mizuma
Chris Iacobuzio (MSKCC now)
Bob Anders*
Peter Illei
Rajni Sharma*
Ralph Hruban*

Mastui/Rasheed Labs
Zeshaan Rasheed

JH Neuroscience
David Ginty Lab (Harvard now)
Alex Kolodkin Lab

Connell Med
Katherine Hajjar

Baylin/Ahuja Labs
Nita Ahuja
Kate Chiappineli
Lifeng Sun

Gamper/Ladle Labs
Brian Ladle
Christopher Gamper

Amplimmune
Sheng Yao*
Linda Liu*

Aduro Biotech
Dirk Brockstedt
Tom Dubensky

Yale
Lieping Chen*

Clinical Research
Daniel Laheru*
Chris Wolfgang*
Matt Weiss*
Carol Judkins*
Joseph Herman*
Nilo Azad
Dung Le*
Ana De-Jesus
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