Our Race for the Cure: Understanding the Future Roles of Immune Therapy, Targeted Therapy and Chemotherapy

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Lombardi Is One of Only 41 NCI-Designated Comprehensive Cancer Centers

**NCI Designation Requires the Center to:**

- Demonstrate excellence in laboratory, clinical, and population-based research
- Conduct high impact transdisciplinary research that bridges these scientific areas
- Demonstrate professional and public education and outreach capabilities, focusing on the communities we serve
- Recently renewed for 5 years of continued support following a rigorous application and review process

NCI: National Cancer Institute
Only NCI Cancer Center Based in DC

• Service to our catchment area is at the core of our mission
• 36% cancer patients in our catchment area are underrepresented minorities, immigrants
  – Challenges for patient care
  – Influences of smoking & obesity
  – Infection-related cancers
  – Different cancer types
Lombardi’s Vision and Mission

*Prevent & Cure Cancer With Local Focus & Global Impact*

*Link Discovery, Patient Care, Education and Community Partnership—Guided by Principle of “Cura Personalis”*

- **Four Research Programs**
  - Cancer Prevention & Control (CPC)
  - Molecular Oncology (MO)
  - Experimental Therapeutics (ET)
  - Breast Cancer (BC)

- **Nine Shared Resources**

- **Research Base**—Georgetown University
- **Clinical Base**—MedStar Health
Fostering Transdisciplinary Research

*Lab Bench to Bedside to Community*

- **Georgetown University**, including Medical School & Medical Center, focuses on research & education
- **MedStar Health** serves Lombardi’s catchment area with five hospitals
  - MedStar Georgetown University Hospital
  - MedStar Washington Hospital Center
  - MedStar Montgomery Medical Center
  - MedStar St. Mary’s Hospital
  - MedStar Southern Maryland Hospital Center
- **Lombardi** is the research engine of the MedStar Georgetown Cancer Network
## Multidisciplinary, Research-Inspired Clinical Care of GI Cancers by World Experts

<table>
<thead>
<tr>
<th>GI Cancer(s)</th>
<th>Leader(s)*</th>
<th>Unique Expertises</th>
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<tbody>
<tr>
<td>Pancreatic Cancer</td>
<td>J. Marshall*, M. Pishvaian*, L. Weiner*, L. Johnson (S), P. Jackson (S), T. Fishbein* (S), N. Haddad (GI), K. Unger (R)</td>
<td>Early diagnosis, neoadjuvant therapy, surgery, management of advanced disease</td>
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<td>Liver Cancer</td>
<td>R. He*, M. Pishvaian*, L. Johnson (S), T. Fishbein (S), K. Unger (R), P. Banovac (IR)</td>
<td>Screening, liver surgery, liver transplant, new drugs</td>
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<td>Esophageal, Stomach and Small Bowel Cancers</td>
<td>J. Marshall, M. Pishvaian, M. Salem, B. Smaglo*, B. Marshall (S), W. Al- Refaie (S)</td>
<td>Surgery, investigational therapy</td>
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<td>Phase I Clinical Trials</td>
<td>M. Pishvaian*, B. Smaglo*, J. Marshall*</td>
<td>New drugs</td>
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</table>

Medical Oncology except where indicated: (S) = Surgery, (R) = Radiation, (GI) = Gastroenterology, IR = Interventional Radiology

* Conducting or collaborating on disease-focused laboratory research
Cancer is Bad

• 1.6 million cases per year will lead to 585,000+ deaths in 2014 in US
  – 3,200 deaths every two days
  – In 1971, 1,000,000 cases (but smaller population) and same number of deaths

• Most cures result from
  – Early diagnosis
  – Surgery
  – Adjuvant treatments (e.g., chemotherapy)

• Survival has improved since 1971, with better quality of life, reduced suffering, but at extraordinary and possibly unsustainable costs

• We are doing better, but have a long way to go
Cancer is Bad

• We still don’t know what causes most cancers and when we do (e.g., tobacco) we don’t know how this happens

• Most treatment decisions rely on anatomic disease “classifiers”, e.g., “colon cancer”

• Strategies to enrich for probability of treatment benefit have inconsistent benefits
  – HER2/neu amplified breast cancer
  – EGFR, KRAS mutations in lung and colon cancers

• Therapy resistance is nearly universal in patients with advanced, metastatic disease
Patient Care Uses Antiquated Methodologies

• Norman Rockwell would find a 21st century cancer clinic to be sadly familiar
  – History/Physical
  – Past History, Social History
  – Physical Exam
  – Laboratories, Radiology Studies
  – “Evidence based” synthesis by a single practitioner who can’t know and read everything, and doesn’t have access to all of the necessary data
Are We Doing Better?

Are We Doing as Well as We Should?
So, What’s the Prescription?
Use **All** of the Information Necessary to Do What is Best for the Patient
Does Information = Power?

- Ask the NSA
- “BIG DATA” = Big Headaches!
- Each patient’s record (especially if linked to complex molecular analyses) generates gargantuan data sets that can lead to many conclusions (most of them wrong)
- **CHALLENGE:** Create tools that help physicians and patients efficiently sift through outcome-based patient-specific data to convert information to clinically actionable knowledge
Systems BioMedicine

- The application of systems biology approaches to biomedical problems
  - Complex computational tools
  - Increasingly high dimensional data
- Sift through complexity to improve understanding of human cancer
- Ultimate goals
  - Improved disease characterization/classification
  - Prevention
  - Cure
  - Precision Medicine – right treatment, right person, right time
Example: AT: Information ≠ Power

• 45 yo female with metastatic cancer of the pancreas
• Cancer rapidly progressed through radiation therapy and chemotherapy
• Tumor sample analyzed by Foundation Medicine
  – 300 genes analyzed for mutations, looking for an actionable drug target
  – 12 different mutations found in genetic panel – none clinically actionable
  – Patient died less than 1 year following diagnosis, leaving behind two young children, husband, parents
Prevention: Can Information Lead to Power?

• Some actions will generally reduce cancer risk – e.g., exercise, weight control, tobacco control
  – Can be applied broadly and safely

• Most actions have potential toxicity (e.g., anti-estrogen chemoprevention or high cost (e.g., colonoscopy, CT scanning) and are best applied to high-risk populations

• **CHALLENGE:** Can high-risk populations be accurately identified?
  – Clinical record and database extractions, combined with genomics?
Cure: Can Knowledge Lead to Power?

• **PROBLEM**: Metastatic disease is rarely cured by targeted therapy or immunotherapy

• **CHALLENGE**: Can treatment resistance be well enough understood to develop effective combinations to attack the heterogeneity of cancer cell populations?

• **OPPORTUNITY**: PERSONALIZED MEDICINE

• **OPPORTUNITY**: CANCER IMMUNOTHERAPY
Individualized Approaches: RP

• 33 yo man with metastatic colon cancer – unknown cause - progressive on chemotherapy – died in October after a nearly three year battle

• Tumor metastasis biopsy at baseline – 12 sublones being grown and characterized for sensitivity to drugs

• But what else could we look at? And how would we make sense of it all?

• **CHALLENGE**: Could systems biomedicine have helped me take care of my next RP?
What We are Doing at Georgetown Lombardi

• Understand resistance to targeted therapies
• Develop informatics infrastructure
  – G-DOC
• Utilize informatics infrastructure to connect patients, molecular aspects and outcomes
  – Colorectal cancer pilot study
• Develop innovative tools to facilitate personalized medicine
• Capture the promise of immunotherapy to better target and destroy cancer
Vision for Georgetown Database of Cancer (G-DOC)

*Knowledge is Power*

An “Informatics Blender” that integrates diverse data elements and links them to clinical outcomes
WELCOME

The Georgetown Database of Cancer (G-DOC) is a cutting-edge data integration platform and knowledge discovery system for the oncology and translational research communities. G-DOC users can access public and proprietary clinical and -omics data aggregated from across the Medical Center, along with a comprehensive set of advanced analysis and visualization tools, to generate and test hypotheses across biomedical disciplines.
Stage 2 Colon Cancer: An 80:20 Call?

- 80% of patients with Stage 2 colon cancer are cured by surgery
- Postoperative (adjuvant) chemotherapy increases cure rates to about 83%
- Treat 100 patients to cure 3 people
  - 80 people treated for no good reason (already cured)
  - 17 doomed to relapse even with chemotherapy

Bottom line: Oncologists bet against the “house” every time. We need to hedge our bets with knowledge, and it is time for informatics to bring the molecular revolution to the bedside.
40 Colorectal Cancer Patients, Stage 2
>10 Years Follow-up

- 20 Relapse-Free Patients
- 20 Relapsed Patients

- DNA, RNA, microRNA, metabolites from tumor, adjacent normal tissue, blood, urine
- Clinical Attributes: >100 all recorded
- Placed into the “informatics blender”

All Samples Obtained on Day of Surgery
Testing a urine sample prior to surgery might predict who is likely to be cured and who is destined to relapse without additional therapy!
Twelve Tumor Gene Abnormalities Defined the Group Destined to Relapse

Madhavan et al, Frontiers Genetics 2013

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Twelve Tumor Gene Abnormalities Defined the Group Destined to Relapse

Gene abnormalities linked to immune function

A hint regarding where to look for future therapies?
CD3 T Cells ("Killers" of the Immune System) found in the tumors of patients who are destined to relapse.
What Did this Mean for RP?

- Nothing
- None of this information was actionable
- I was forced to “fly blind”, relying on broad observations unlinked to his “expected” biology
- He needed me to know his cancer’s unique vulnerabilities and I couldn’t identify them and exploit them
- We need to do more research to make sense of this complex mess we call cancer
Biomedical Informatics for Cancer Research

• **CHALLENGE**: Create tools that help oncologists and patients efficiently sift through outcome-based patient-specific data to convert information to clinically actionable knowledge

• **CHALLENGE**: Create the 21st century physician’s practice based on easily accessed, highly specific, user friendly, clinically useful information gathering and treatment guidance

• **CHALLENGE**: Identify important “signals” that can guide patient management
Biomedical Informatics for Cancer Research

- **CHALLENGE**: When is a mutation driving a cancer and when is it along for the ride?
- **CHALLENGE**: Can high-risk populations be accurately identified?
- **CHALLENGE**: Help me take care of my next AT and RP and all who will follow them.

**CHALLENGES = OPPORTUNITIES!!!**
National Cancer Act: 1971

President Nixon declares a “War on Cancer”
We Have Been at War Against Cancer Throughout Human History

Medieval Saxon man with a large tumor of the left femur
The “War on Cancer”
is fought one person at a time…

- **Primary Combatants:**
  - Malignant cell population
  - Host immune system

- The host immune system is the only active enemy faced by a developing cancer

- All “successful” cancers have solved the challenges of overcoming defenses erected by host immune systems
Cancers Can Overwhelm the Host

• Out-proliferate the immune response
• Acute leukemias
• Burkitt’s Lymphoma

• Solutions
  – Aggressive Chemotherapy
  – Adoptive transfer of activated, tumor-targeting immune cells
Cancers Can Hide from the Immune System

- Antigens (targets of the immune system) lost or not effectively displayed by tumor cells
- Solution
  – Vaccines
Cancers Can Subvert the Immune System

- Local Immune Suppression
  - $T_H^2$ Milieu
  - M2 Macrophages
  - Treg cells
  - Myeloid-derived Suppressor Cells
  - Chemokines
  - Cytokines

- Solutions
  - Block these signals with medicines
Cancers Can Create a Perimeter Defense To Deflect the Immune System

- Decoy antigens
- Immunosuppressive cytokines (e.g., TGF-β)
- Chemokine/cytokine-created defensive perimeter to exclude immune cell infiltration

Solutions
- Block these signals to permit immune infiltration

Establishing a defensive perimeter in World War I
Cancers Can Defend Against Frontal Assaults by the Immune System

• Disable the attackers that actually get to the tumor cells
  – PDL-1
  – Other immune checkpoints – B7H3, B7H4, OX-40L, CD40
  – CD47 – macrophage “don’t eat me” signal

• Solutions
  – Antagonistic antibodies that disable these “immune checkpoints”
Blockade of PD-1 Binding to PD-L1 (B7-H1) and PD-L2 (B7-DC) Revives Exhausted T Cells

- PD-L1 expression on tumor cells is induced by γ-interferon
- In other words, activated T cells that could kill tumors are specifically disabled by those tumors
Phase I Trial of anti-PD1 Antibody

Melanoma is just the tip of the iceberg!

- Melanoma
- Kidney Cancer
- Lung Cancer
- Bladder Cancer
- 

\[\text{Topalian et al, NEJM 2012}\]
Clinical Activity in Patients Who Received the Concurrent Regimen of Nivolumab and Ipilimumab.

Follow Up June 2014
(Proc ASCO 2014)

Overall response rate ~ 70%
Complete response rate ~ 50%

Median survival ~ 40 mos
(expected survival ~ 7 mos)

Few relapses in responders
Is cancer immunology the next great frontier in cancer research?

- Mobilizing the immune system to attack a cancer, remember the enemy and continually target emerging clones may represent the best path to cancer prevention and cure
- PD1 and CTLA4 are just the tip of the iceberg – many other immune regulatory molecules can be attacked to help the immune system destroy cancers
- GI cancers are next!