Precision Medicine: Genomic Profiles to Individualize Therapy

Charles R. Drew University of Medicine and Science
Friday Noon Lecture Series

January 26, 2018

Presenter: Oscar E Streeter, Jr, MD, FACRO
BACKGROUND:

• Last Year – More than 1.7 million people were diagnosed with cancer in the United States

• It is difficult to treat – Because each tumor is unique, treating patients by the site where it originates, e.g. lung or colon as if all tumors are the same by specific histology is to deny tumor heterogeneity and the unique genetic mutations of each patient

• In the last decade researchers have started and continue to define those genetic mutations and technology has developed to analyze rapidly at low cost those genetic differences and therapies have developed to respond to those genetic mutations to shrink tumors

Epigenetic Changes from DNA Methylation

Writer: Rachel Saslow.
Date: Tuesday, December 15, 2009

Source: Randy Jirtle, director of the Epigenetics and Imprinting Laboratory, Duke University; gene images copyright 2005 National Academy of Sciences

Accessed online on August 5, 2015.

http://www.washingtonpost.com/wp-dyn/content/graphic/2009/12/15/GR2009121500588.html
Definitions:

• Next Generation Sequencing (NGS) — Genome sequencers that with a single run of material can analyze more than 1.8 terabases (the amount of genetic sequence data equivalent to $10^{12}$ base pairs), decreasing the cost of sequencing per base pair about 10-fold with improved accuracy and speeding generating sequence data.

• Whole Exome Sequencing (WES) — Sequences the protein-coding region of the genome to identify mutation identification in patients.

• Base pairs — two nucleotides on opposite complementary DNA of RNA strands that are connected by hydrogen bonds.

• Sequencing — a method of detecting single bases as they are incorporated into DNA template strands.

• SNPs — single nucleotide polymorphism.

• Indel — insertion-deletion identification.

• Data Analysis — is where newly identified sequences are then aligned to a reference genome. Many variations of analysis can take place of SNPs, Indels, RNA analysis, and other analysis.

• CRISPR — C{lustered} R{egularly} I{nterspaced} S{hort} P{alindromic} R{epeats}, provides a method to edit genomes with molecular tools. It relies on an enzyme called Cas9 that uses a guide RNA molecule to home in on its target DNA, then edits the DNA to disrupt genes or insert desired sequences.
What is Precision Medicine

• Means treating patients based upon the molecular characteristics of their tumor. It is “Delivery of the Right Therapy at the Right Time”.

• It is not treating patients based upon the tumor characteristics of disease subtypes determined by histology or assessing markers by immunohistochemistry; however still start with classic histology analysis and markers because of their clinical treatment value.

• Implies that therapeutics are directed precisely toward the identified molecular defect.

• The first and best example so far of the success of precision medicine in oncology is imatinib mesylate (Gleevec) to treat chronic myeloid leukemia with the BCR-ABL translocation. The daily dosing is 400 mg daily that can be increased to 600 mg/day.

• CML was so successful because of it’s clonal evolution, starting with acquisition of the t(9;22)(q34;q11) translocation (Ph chromosome), which creates a fusion between the BCR and ABL1 genes.

• Imatinib works on CML because it is an inhibitor of ABL family kinases including the BCR-ABL fusion gene.

Ref: ascopost.com, vol. 6, issue 11, June 25, 2015 (p. 1, Michael Green, MD)
Caveats of Precision” Medicine

- It is evolving as a multi-disciplinary approach that combines people, behaviors, social determinates of health ("patients’ zip code have as much influence on a patient’s health as their genetic code"), i.e. phenotypic data.

- While genomics at the point of care is fundamental to precision medicine, care at the bedside (in the facility or at home) also requires the acquisition, management, integration, clinician validation, and use of data from disparate sources such as:

  1. Clinical Care (Imaging, Clinical Narrative, EMR, and sensor/device data)

  2. Research (research trials, publications, results of data discovery)

  3. Financial (cost, charges, affordability, income disparities, or credit scores)

  4. External & patient-reported data that encompasses patient self-reported data on the web via smart phones; family & disease history/lore, environmental variables; behavior/sentiment data; and increasingly income/educational/cognitive disparities
Precision Medicine and Big Data

Patient Engagement & Behavior

Imaging & Devices

Research & Clinical Care

Thoughts

Things

Activities

Healthcare Big Data: OMICS and Much More

The Growth of Big Data

**Significant reduction in cost of genome sequencing**

**Increase in real-world data**

<table>
<thead>
<tr>
<th>Will you use secondary health data within the next 2 years?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provider: 70%</td>
</tr>
</tbody>
</table>

**Aggregation and analysis of All Data Important**

**More than half of clinical trials already have a molecular biomarker component**

**Patient stratification to identify population subsets most likely to respond to a therapy**

**Enhance Collaboration between research and medicine**

Mining old data for new insights through automated image management, analytics, and co-registration

Precision Medicine for:
1. Cancer
2. Infectious Diseases
3. Public Health

Key takeaways:
1. Precision medicine and population health are two sides of the same coin.
2. In healthcare, it is not always about searching for the needle in the haystack.
3. Big data analytics in precision medicine allows us to burn the hay to find the needle.

How Is “BIG DATA” Obtained at the Genome Level?

- Big data at the genomic level is now possible with high-output next-generation sequencing (NGS), which identifies molecularly defined tumor subtypes, identifies new drug response targets, and defining tumor heterogeneity\(^1\).

- Metastatic tumors often undergo genomic evolution during progression and resistance, and therefore drivers may not always be evident in the primary tumor.

- Using whole-exome sequencing (WES) clinical testing, you can analyze thousands of genes of the cancer exome rather than a targeted hot-spot approach.

- This is important for patients who have not responded or have become resistant to first line therapy.

- This means incorporation of: 1) serial biopsies, 2) use of fresh/paraffin-fixed tissue, 3) development of patient-derived organoids and 4) xenografts for co-clinical trials.

- This requires a comprehensive pipeline of categorized mutations.

Origin of ctDNA and circulating tumor cells (CTCs) in the bloodstream

cfDNA
Detection of cell free DNA mutations

Circulating Tumor Cells (CTCs)
Capture, detection and defined through molecular analysis in blood samples

Plasma
55% of total blood

Buffy Coat of leukocytes & platelets (<1% of total blood)
Contains CTCs

Erythrocytes (red blood cells)
(45% of total blood)

Liquid Biopsies of cfDNA and CTCs

Circulating Tumor Cells (CTCs)

Cancer cells escape from the primary tumor and circulate in the bloodstream.

CTCs may be detected in a blood sample.

CTCs may exit the bloodstream, enter other organs, and grow into new tumors.

Metastatic tumors in the liver.
Using somatic mutations to guide treatment decisions - Context matters [In the Clinic]

Authors: HH Horlings, SP Shah, DG Huntsman
Online first 03.12.2015, JAMA Oncology (oncology.jamanetwork.com): Accessed online 05.12.2015
National Cancer Institute’s NCI-MATCH Clinical Trial (NCI-Molecular Analysis for Therapy Choice)  
www.cancer.gov/nci-match

• This Precision Medicine Trial explores treating patients based on the molecular profiles of their tumors.
• Inclusion Criteria:
  • Adult patients
  • Solid Tumors (including Rare Tumors) and Lymphomas
  • Tumors that no longer respond to standard treatment
• Accrual Goal: ~3,000 Cancer Patients Screened with a Tumor Biopsy

• The biopsied Tumor Tissue will undergo Gene Sequencing, Looking for Changes in 143 Genes
If a Patient’s Tumor has a Genetic Abnormality that Matches One Targeted by A Drug Used in the Trial,

The Patient will be Eligible to Join the Treatment Portion of NCI-MATCH

Not All Patients will have an Abnormality that Matches a Drug Being Tested

While Patients with Tumors that Share the Same Genetic Abnormality, Regardless of Tumor Type, Will Receive the Drug that Targets That Abnormality
FDA-Approved in December 2017 Broad Genomic Testing Analysis For Solid Tumors for NSCLC, Colorectal, Breast, Ovarian and Melanoma

- Same process at the NIH-MATCH Trial
- FoundationOne CDx™ is designed to provide physicians with clinically actionable information for all solid tumors, 17 FDA-approved targeted therapies and 2 immunotherapy biomarkers.
- Based on the patients genomic profile that can be analyzed for therapies and resistance.
- Every test result includes:
  1) Microsatellite instability (MSI) for colorectal cancer
  2) Tumor mutational burden (TMB) to help inform immunotherapy choices
  3) PD-L1 immunohistochemistry (IHC) testing

References:

Overview: https://www.foundationmedicine.com/genomic-testing/foundation-one-cdx

Companion diagnostic indications: https://www.foundationmedicine.com/genomic-testing/foundation-one-cdx#overview
What is Immunotherapy?

A method of treatment in which a person receives substances designed to boost the immune system and help fight off disease such as cancer.

Reference: American Cancer Society online dictionary under Coley’s Toxin: www.cancer.org
**Immune Checkpoint Inhibitors**

**How do immune checkpoint inhibitors work?**

Tumor cells turn off activated T cells when they attach to specific T-cell receptors.

Immune checkpoint inhibitors prevent tumor cells from attaching to T cells so T cells stay activated.

Immune checkpoint inhibitors target either T cells (ϒ) or tumor cells (ϒ).

**Response to immune checkpoint inhibitor treatment with brief increase in tumor size (pseudoprogression)**

- Tumor cell
- T cell

**Graph:**
- **Tumor Size**
- **Activating T cells enter tumor**
- **Start of treatment**
- **Time**
- **Pseudoprogression**
Review Article

Molecular and Biochemical Aspects of the PD-1 Checkpoint Pathway

Vassiliki A. Boussiotis, M.D., Ph.D.

N Engl J Med
Volume 375(18):1767-1778
November 3, 2016
Summary

• The PD-1 pathway plays an essential role in maintaining immunologic self-tolerance.

• However, cancers can subvert the role of this pathway and blind the immune system to their presence.

• The molecular details of the pathway are discussed.
Effects of PD-1 on Major Signaling Pathways in T Cells.

Alteration of Metabolism by the PD-1 Checkpoint Pathway.

Inhibition of Tumor-Specific T-cell Function by the Expression of PD-1 and Its Ligands in the Tumor Microenvironment.

Classic Article on Using a PD-1 Inhibitor to Treat Melanoma

Safety and tumor responses with Lambrolizumab (Anti–PD-1) in melanoma

Authors: Omid Hamid, M.D.¹. Caroline Robert, M.D., Ph.D., Adil Daud, M.D., F. Stephen Hodi, M.D., Wen-Jen Hwu, M.D., Ph.D., Richard Kefferd, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D., Peter Hersey, M.D., Ph.D., Richard W. Joseph, M.D., Jeffrey S. Weber, M.D., Ph.D., Roxana Dronca, M.D., Tara C. Gangadhar, M.D., Amita Patnaik, M.D., Hassane Zarour, M.D., Anthony M. Joshua, M.B., B.S., Ph.D., Kevin Gergich, M.A., Jeroen Elissaiss-Schaap, Ph.D., Alain Algazi, M.D., Christine Mateus, M.D., Peter Boasberg¹, M.D., Paul C. Tumeh, M.D., Bartosz Chmielowski, M.D., Ph.D., Scot W. Ebbinghaus, M.D., Xiaoyun Nicole Li, Ph.D., S. Peter Kang, M.D., and Antoni Ribas, M.D., Ph.D.

¹Angeles Clinic (Cedars-Sinai Affiliate Practice), medical oncologist

²Keck School of Medicine, USC Norris Cancer Hospital, surgical oncologist

Note: Pembrolizumab (Keytruda) was formerly MK-3475 or lambolizumab for clinical trial evaluation
Study Overview

- Antibodies to PD-1 appeared to unblock T-cell responses to melanoma in a sizeable fraction of patients with antitumor responses, some of which were long-lasting.

- Toxic effects were mainly grade 1 or 2 fatigue, rash, pruritus, and diarrhea.

N Engl J Med
Volume 369(2):134-144
July 11, 2013
Antitumor Activity of Lambrolizumab.

A  Best Objective Response

<table>
<thead>
<tr>
<th>Percent Change from Baseline in Longest Diameter of Target Lesion</th>
<th>Prior ipilimumab treatment</th>
<th>No prior ipilimumab treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>160</td>
<td></td>
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<tr>
<td>140</td>
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<tr>
<td>120</td>
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<td>-100</td>
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</table>

Individual Patients Treated with Lambrolizumab

B  Time to Response and Duration of Study Treatment

<table>
<thead>
<tr>
<th>Individual Patients Treated with Lambrolizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior ipilimumab treatment</td>
</tr>
<tr>
<td>No prior ipilimumab treatment</td>
</tr>
<tr>
<td>Complete response</td>
</tr>
<tr>
<td>Partial response</td>
</tr>
<tr>
<td>Still receiving treatment</td>
</tr>
</tbody>
</table>

Weeks

0  10  20  30  40  50  60  70
Tumor Responses with Lambrolizumab

Hamid O et al.  
Conclusions

In patients with advanced melanoma, including those who had had disease progression while they had been receiving ipilimumab, treatment with lambrolizumab (now known as pembrolizumab of Keytruda) resulted in a high rate of sustained tumor regression, with mainly grade 1 or 2 toxic effects.

N Engl J Med
Volume 369(2):134-144
July 11, 2013
Approved Indications for the PD-1 Drug pembrolizumab

- Progressive Non-small cell lung cancer, with not EGFR or ALK genomic tumor aberrations.
- Melanoma, metastatic or unresectable
- Squamous cell head/neck cancer, recurrent or metastatic
- Hodgkin lymphoma, relapsed or refractory
- Urothelial carcinoma, locally advanced or metastatic
Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer:

a secondary analysis of the KEYNOTE-001 phase 1 trial

Narek Shaverdian, MD (UCLA RadOnc), Aaron E Lisberg, MD, Krikor Bornazyan, MD, Darlene Veruttipong, MPH, Jonathan W Goldman, MD, Silvia C Formenti, MD, Edward B Garon, MD, Dr Percy Lee, MD (UCLA RadOnc)

The Lancet Oncology
Volume 18, Issue 7, Pages 895-903 (July 2017)
DOI: 10.1016/S1470-2045(17)30380-7
Types of Targeted Therapies Available:

- **Hormone Therapies** – slow or stop the growth of hormone-sensitive tumors.

- **Signal transduction inhibitors** – blocks the activities of molecules that participate in signal transduction, the process by which a cell responds to signals from its environment.

- **Gene expression modulators** – modify the function of proteins that play a role in controlling gene expression.

- **Apoptosis inducers** – cause cancer cells to undergo a process of controlled cell death.

- **Angiogenesis inhibitors** – block the growth of new blood vessels to tumors.

- **Immunotherapies** – trigger the immune system to destroy cancer cells.

- **Monoclonal antibodies that deliver toxic molecules** – once the antibody has bound to its target cell, the toxic molecule that is linked to the antibody – such as a radioactive substance or poisonous chemical – is taken up by the cell, ultimately killing that cell while not affecting cells that lack the target for the antibody.

- **Cancer Vaccines** – work by activating B cells and killer T cells and directing them to recognize and act against specific types of cancer.

References accessed on-line from the National Cancer Institute website on 09/08/2015:
More Cutting Edge Research in Viral Oncolytic Therapy: ‘Vice Special Report: Killing Cancer’ on HBO™

1) The viral treatment of leukemia (using a chimeric antigen receptor T-cell molecule) manipulated by using HIV infecting cells to reprogram T-cells to recognize normal cells from leukemia cells resulting in 90% remission in relapsed and stem cell transplant failed patients with ALL¹.

2) A host of human tumors using an engineered and armed poxvirus that acts as an oncolytic toxin replicating inside the tumor cell².

3) Using an engineered measles virus (MV-NIS) that was originally isolated from the throat of a boy in 1954 had a measles infection to treat multiple myeloma patients that have exhausted all other options³; multiple myeloma is a disease that kills half of the patients in five years. However, the majority of the patients relapse in one year.

4) A phase I trial that injects a genetically modified adenovirus (DNX-2401 formerly known as Delta-24-RGD) directly into glioblastomas (a dose of $3 \times 10^{10}$ of viral particles) while the patient is awake for patients that have failed intensive treatment with chemotherapy and radiation therapy in the past⁴,⁵.

References:


⁵ClinicalTrials.gov Number: NCT00805376 [DNX-1240 (Formerly Known as Delta-24-RGD-4C)] for Recurrent Malignant Gliomas, PI: Frederick F. Lang, MD, UT MD Anderson Cancer Center
What is CAR-T Therapy and Cost

- CAR-T stands for chimeric antigen receptor T-cell molecule
- It can be likened to a transplant rather than drug therapy
- Effective treatment for patients with certain blood tumors (refractory lymphomas for example)
- **How it works:** A patient’s T cells are removed, frozen, shipped to a lab, reengineered to reprogram T-cells to recognize normal cells from blood cancer cells in relapsed and stem cell transplant failed patients with ALL relapsed or refractory diffuse large B-cell lymphoma and follicular lymphoma
- The reengineered cells are reinserted into the patient, where the reengineered cells attack cancerous cells. The process can take weeks and involves multiple facilities, supported by different types of manufacturing and clinical staff.
- Cost for a course of treatment: **Novartis’s Kymriah**, the first CAR-T treatment to receive approval, costs $475,000, while **Kite Pharma’s Yescarta costs $373,000.**
Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas


N Engl J Med
Volume 377(26):2545-2554
December 28, 2017
Study Overview

- Among 38 patients with refractory diffuse large B-cell lymphoma or follicular lymphoma, 28 were able to receive CAR-T cells
- 16 had complete remission
- None of those who had had a complete response at 6 months had a relapse at 28 months of follow-up.
Progression-free Survival, Response Duration, and Overall Survival

A  Diffuse Large B-Cell Lymphoma, Progression-free Survival

B  Follicular Lymphoma, Progression-free Survival

C  Diffuse Large B-Cell Lymphoma, Response Duration

D  Follicular Lymphoma, Response Duration

E  Diffuse Large B-Cell Lymphoma, Overall Survival

F  Follicular Lymphoma, Overall Survival

Conclusions

• CTL019 cells can be effective in the treatment of relapsed or refractory diffuse large B-cell lymphoma and follicular lymphoma.

• High rates of durable remission were observed, with recovery of B cells and immunoglobulins in some patients.

• Transient encephalopathy developed in approximately one in three patients and severe cytokine-release syndrome developed in one in five patients.
Possible Mechanisms Underlying Immune-Related Adverse Events.
Immune Checkpoint–Blocking Antibodies Approved by the Food and Drug Administration.

**Table 1. Immune Checkpoint–Blocking Antibodies Approved by the Food and Drug Administration.***

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>CTLA-4</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>PD-1</td>
<td>Melanoma, non–small-cell lung cancer, renal-cell carcinoma, hepatocellular carcinoma, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, colorectal cancer with high microsatellite instability or mismatch-repair deficiency</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>PD-1</td>
<td>Melanoma, non–small-cell lung cancer, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, gastric cancer, solid tumors with high microsatellite instability or mismatch-repair deficiency</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>PD-L1</td>
<td>Non–small-cell lung cancer, urothelial carcinoma</td>
</tr>
<tr>
<td>Avelumab</td>
<td>PD-L1</td>
<td>Merkel-cell carcinoma, urothelial carcinoma</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>PD-L1</td>
<td>Urothelial carcinoma</td>
</tr>
</tbody>
</table>

* CTLA-4 denotes cytotoxic T-lymphocyte antigen 4, PD-1 programmed cell death 1, and PD-L1 programmed cell death ligand 1.

Ten Questions Relevant to the Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Blockade.

<table>
<thead>
<tr>
<th>Questions about Immune-Related Adverse Events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Why do they occur?</td>
<td>The precise pathophysiology is unknown. Translational studies in patients with immune-related adverse events have shown that T-cell, antibody, and cytokine responses may be involved.</td>
</tr>
<tr>
<td>How are they generally treated?</td>
<td>No prospective trials have defined the best treatment approaches, and recommendations are based on consensus opinion. Immunosuppression is used to reduce the excessive state of temporary inflammation. Glucocorticoids are usually the first-line immunosuppressive agent. Additional immunosuppressive agents can be used if glucocorticoids are not initially effective.</td>
</tr>
<tr>
<td>When do they occur?</td>
<td>Immune-related adverse events usually start within the first few weeks to months after treatment but can occur anytime, even after treatment discontinuation. Dermatologic adverse events are usually the first to appear.</td>
</tr>
<tr>
<td>Why do they occur in some patients and not others?</td>
<td>The reason for the occurrence of immune-related adverse events only in certain patients is unknown. Some studies are investigating whether such factors as germline genetics and the composition of host microbiota are related to risk.</td>
</tr>
<tr>
<td>Are they associated with the efficacy of immune checkpoint blockade?</td>
<td>Conflicting data are available regarding whether the occurrence of immune-related adverse events is associated with improved treatment efficacy. The development of immune-related adverse events is not required for treatment benefit. Specific adverse events (e.g., vitiligo) may be more clearly associated with treatment efficacy.</td>
</tr>
<tr>
<td>Does immunosuppression to treat such adverse events reduce the antitumor efficacy of treatment?</td>
<td>Clinical outcomes are similar in patients who require immunosuppression to treat immune-related adverse events and in those who do not require such treatment. Beneficial responses can persist despite the use of immunosuppression to treat immune-related adverse events.</td>
</tr>
<tr>
<td>Are there unintended effects of immunosuppression to treat adverse events?</td>
<td>Side effects of glucocorticoid use (e.g., hyperglycemia, edema, anxiety, and iatrogenic adrenal insufficiency) can occur. Immunosuppression is a risk factor for subsequent opportunistic infections.</td>
</tr>
<tr>
<td>Is it safe to restart treatment after a major adverse event?</td>
<td>Retrospective studies have shown that immune-related adverse events associated with one class of agent (e.g., anti-CTLA-4) may not necessarily recur during subsequent treatment with another agent (e.g., anti-PD-1). The safety of retreatment probably depends on the severity of the initial immune-related adverse event.</td>
</tr>
<tr>
<td>Is it necessary to restart treatment after resolution of an adverse event?</td>
<td>Retrospective data suggest that patients who have had a favorable response to immune checkpoint blockade and then discontinue treatment because of immune-related adverse events generally maintain responses. Prospective data are needed to address whether restarting immunotherapy is necessary.</td>
</tr>
<tr>
<td>Is it safe to treat patients at potentially increased risk for such adverse events?</td>
<td>Patients at increased risk for immune-related adverse events (e.g., preexisting autoimmune disease) may still benefit from immune checkpoint blockade. Age alone should not be used to exclude patients from treatment, since benefit appears to be similar regardless of age.</td>
</tr>
</tbody>
</table>