Cancer Genetics: Cracking Cancer’s Code

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Disclosures

• I have no actual or potential conflict of interest in relation to this program/presentation.

• I am a co-founder, consultant, and co-owner of NeoClone Biotechnologies, Inc., Discovery Genomics, Inc., (recently acquired by Immusoft, Inc.), B-MoGen Biotechnologies, Inc. (recently acquired by Biotechne, Inc.), and Luminary Therapeutics, Inc. This presentation is not directly related to the business of these companies and I obtain no funds for my laboratory research from these companies.

• Some of my laboratory’s work is funded by Genentech, Inc. That work will not be discussed today.

• I hold equity in and serve as the Chief Scientific Officer of Surrogen, a subsidiary of Recombinetics, a genome-editing company. That work will not be discussed today.
Learning Objectives

- All cancer has a genetic cause – but that doesn’t (usually) mean the genes you’re born with cause cancer, instead cancer is primarily caused by mutations occurring in rare cells in your body.
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• Cancer cells typically have many, many gene mutations and about 6 or more of these “drive” the abnormal behavior of the cancer cells, while the rest are merely “passengers”.

• It is thought that the genes mutated in a cancer can produce abnormal proteins allowing the immune system to kill off the cancer cells. This is how “immunotherapies” like Keytruda can work for some cases of cancer.

• The specific genes that are mutated in a tumor or leukemia may determine the prognosis of the patient and dictate the best therapy for the physician to choose.
All Cancer is “Genetic” Because:

- ALL cancer cells have altered genomes compared to a normal cell
- Those DNA alterations are called mutations
Cancers Are Genetic Diseases that Result from Alterations in DNA Sequence &/or Expression

- Cancers result from the corruption or misuse of DNA.
  - Corrupt results from changes in DNA that can be small (single nucleotide changes/mutations) or large (chromosomal abnormalities).
  - Misuse results from changes in when and what genetic information is accessed (epigenetics).

- Cancers are often genetically unstable.
  - DNA copying/repair machinery is compromised leading to greater accumulations of DNA mistakes during cell division.
Consider How Much Information is Stored in Every Human Cell

- All the DNA in one cell, if stretched out, would be over 2 meters long!
- The human genome would take 6,000,000 pages of 500 words each just to print out
A page a second for 23 days!
A new gene about every minute

ATGTTGAATCTGTGTCATGTCTCTCGAGGGCTACGTCAATTTTTCTCTGTTCTGGATTGGA
AAAGTGAATGCGTCATGGTTCTCATAAAAACCTACAGGGATCGACTCAGTTAAACCAGGA
TATATACGAAAGGAGTCTACCGGACTAAAAACTTTATCTGACTCCCAAGATCTGGAA
AGATATTTTGCATTTACGTCAGAACACATACACGCTCTGGAACAGGGCACTCAAATATTGATCT
GACCTCAAAAACAAAAGAGATTTACATTTGAGTATTGTGGCAAAAAGGSGCTAGTAATGCA
CTTTACATCAAAAATTTATACCCGGAAGATTTTCCCCGAAGACATTTAAATGATATTTCTG
AATCTACGCCAGTACAAAATTTGTACATTTGGCTCCCTTTGATAGAATTTCCTCTTA
CATTAGACCCCAATGTGTTTTGAAAAGCAGAATTGGATTTAGATACATCAATTAGTGGTAAACGA
AGGATCAAGTTTTTTAAGATATAAAAAATGTCGTACGCAAAAAAGGTCTCTATATTTCTAGGA
CAATTATTAAAGAACACATTTAAGAATTTGACCTAAATAAAACACATTGCCATATCCTGCGCT
AAAACATTGGAAACATCCATCTATTTTACAATCACTATTCTTTAATAACATCAAGATTTTGATG
AAGGTAAAAATTGATCTCTACTGGAAAATATTACTCCCTCTCTGGAAGAATTGTGAATACAA
GCTTTTACGCAAGGCTGCTGCTGCTGCAGTCTGGATCTGGATGCAAAAGGAA
CAAAAGGGTCGGAAGGAGTATTATTCCAAATCGGAAGCATAATAAAACAGAAAGACTTATTGAG
TCTATGAAGGCGACATCACAGGAGGCTTTATACCGGTGGAGGATTTCTAACCCTGTA
CCCTGGAAGAGGACATAAAAATACAGATGTGGAATATACATACCAGGACACATCAAAAAACATT
AAGAAACATTGAAGAGGTATTGTATTTCAAATCTCAGTTCGAAATCTCATTCTCAGCACAT
CGTTATACTAGGGTATGGAAATTTAAAGGCTTTATTATTTGAAAAGCTGAAATCCATTTATT
TTAATAGAGGCAACTCTGAGGATGATGGCTTCAAAGGACTTACATGAGATTGATCATTTG
AGTTATACGAAATGTATTATAAGGGAAGCGTAGAAGAAACCTTTGATTGATGTTGCTGTACAGCT
TACATGGAACAAATGGTTAAGAGTGCAAGCTGGTCCAGAGATAGACCCGATATCAGTCA
CTCTGTATAGTAGATGGCGCCGAGTAAACGTDAAGCTCATTAAGGCGCTGGAAGCTGTTATA
GAAAAAGCGAGAACATTTACTGCTAGAAGATTTGTGACGATGACTCCTTTATATTGATTTTG
GTTCAACAACCTATGAAAGAAAAAAAAGAATCCCTATTTGTTGACTACAAATGGA
That’s a lot of information to copy!
Each DNA Strand is Copied During Replication
Each DNA Strand is Copied During Replication
Radiation Can Break DNA
Errors in DNA Repair Cause Mutations
Carcinogens Can Alter DNA
Carcinogens Can Alter DNA

ADDUCT
*(add a duck)*

G G A A T T
A A C G T T G C C T A A C T C T T T G A T T G A T
Mutations Allow Cells to Overcome Barriers to Cancer
If Cancer is Caused by DNA Damage During our Lifetimes, Then Why Does Cancer “Run in the Family” Sometimes?
How Much of Cancer is Hereditary?

- Sporadic: 70-80%
- Family clusters: 15-20%
- Hereditary: 5-10%
**Sporadic**
70-80% of cancer in families

**Familial**
15-20% of cancer in families

- Acquired mutations in the tumor
- Single or Unilateral Tumor
- Later age of onsets

- Germline Mutation??
- Single or Unilateral Tumors
- Early/late age of onset
“Red Flags” for Hereditary Breast and Ovarian Cancer?

- Breast cancer before age 50
- Ovarian cancer at any age
- Male breast cancer at any age
- Multiple primary cancers
- Ashkenazi Jewish ancestry
- Relatives of a mutation carrier
Cancer Risk Spectrum

**HIGH**
- Multiple generations affected (AD inheritance)
- Early onset
- Multiple primary tumors

**MODERATE**
- Several family members affected
- No single gene pattern
- Variable onset

**LOW**
- No family history
- Late onset
Hereditary Cancer is Usually Inherited as Dominant Trait

- Penetrance is often incomplete
- May appear to “skip” generations
- Individuals inherit altered cancer susceptibility gene, not cancer
What if You’re Concerned your Family is Affected?

- Cancer management clinic contact information thru M Health: [https://www.mhealth.org/care/services/cancer-risk-management-program](https://www.mhealth.org/care/services/cancer-risk-management-program)

- There are hereditary cancer clinics in all the major health systems

- There are online telehealth genetic counseling options like GeneMatters or Genome Medical that consumers can use as a resource.
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• Cancer cells typically have many, many gene mutations and about 6 or more of these “drive” the abnormal behavior of the cancer cells, while the rest are merely “passengers”.

• It is thought that the genes mutated in a cancer can produce abnormal proteins allowing the immune system to kill off the cancer cells. This is how “immunotherapies” like Keytruda can work for some cases of cancer.

• The specific genes that are mutated in a tumor or leukemia may determine the prognosis of the patient and dictate the best therapy for the physician to choose.
Large Study of Twins Suggests Lifestyle Choices have a Strong Role in Determining Cancer Risk

FOR MOST PEOPLE!
Determined Concordance Rate for Cancer in Identical Twins Versus Fraternal Twins

- How often did both get cancer?
  - For fraternal twins:
  - How often did just one of the two get cancer?
- How often did both get cancer?
  - For identical twins:
  - How often did just one of the two get cancer?

- Allows estimate of heritability
- If fraternal twins are concordant as often as identical twins, then it suggests shared environmental effects important in cancer risk
- If identical twins are concordant more often than fraternal twins, then it suggests shared heritable effects important in cancer risk
Conclusions  Inherited genetic factors make a minor contribution to susceptibility to most types of neoplasms. This finding indicates that the environment has the principal role in causing sporadic cancer. The relatively large effect of heritability in cancer at a few sites (such as prostate and colorectal cancer) suggests major gaps in our knowledge of the genetics of cancer. (N Engl J Med 2000;343:78-85.)
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Epidemiologic Studies Have Shown that **Age** is a Surprisingly Large Factor in the Incidence of Cancer

- Late age of onset indicates that the development of most cancers requires an extended period of time.

Figure 11.1  *The Biology of Cancer* (© Garland Science 2007)
How Much More Likely is Cancer in Aged Versus Young People?

THE REAL ANSWER IS FAR MORE THAN 10X MORE COMMON!
How Much More Likely is Cancer in Aged Versus Young People?

STUDIES LIKE THESE SUGGEST 6 OR 7 "STEPS" REQUIRED TO GET CLINICALLY EVIDENT CANCER
Histopathology Provides Evidence of Multi-Step Tumor Formation

Figure 11.6  The Biology of Cancer (© Garland Science 2007)
Genetic Alterations Cause These Multiple Steps

Figure 11.9  The Biology of Cancer (© Garland Science 2007)
Why is this Important to Know?

- We can detect cancer at early stages!
- We can intervene in the process!
  - Remove it
  - Prevent progression
- Knowing the specific mutations that are present informs therapy
Remember All Mutations Are Not Created Equal

- Many mutations discovered in cancer cells are **neutral passengers** that merely accompany **functionally important drivers** that have been subject to selective pressure.

- These mixtures of passenger and driver mutations together comprise the mutated gene sets of the tumors in question.
Basic Research Has Revealed Many of These Cancer Drivers

- In 1970’s we didn't know that cancer was caused by mutated genes
- The first cancer gene discovered in 1982 – HRAS
- The first hereditary cancer gene identified in 1986 – RB1
- Now hundreds of cancer genes known
- The first cancer genome sequenced completely in 2008
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KEYTRUDA® (pembrolizumab) Injection 100 mg

KEYTRUDA will not work for everyone. Results may vary.

Masonic Cancer Center
University of Minnesota
Comprehensive Cancer Center designated by the National Cancer Institute
Our Immune System is Highly Regulated

Mechanisms to Activate Immune Reaction

Mechanisms to Suppress Immune Reaction
Autoimmune disease

Our Immune System is Highly Regulated

Mechanisms to Activate Immune Reaction

Mechanisms to Suppress Immune Reaction
Our Immune System is Highly Regulated

Mechanisms to Activate Immune Reaction

Keytruda hyper-activates the immune system

Anti-cancer effect?
If Tumors Express Many Non-normal Proteins, Due to Mutations, They May Respond to this Kind of Immunotherapy

The Conversation, May 26, 2015
The More Mutations Present the Better the Chance to Respond to Immunotherapies like Keytruda

Aurora et al., Adv. Ther., 2019
Abnormal architecture & arrangement

LOTS OF MUTANT PROTEINS

Normal

Image source: http://library.med.utah.edu/WebPath/FEMHTML/FEM008.html
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A picture is worth a thousand words…true

But…you can’t judge a book by it’s cover either
Altered Genes = Altered Proteins

- Despite cancers being genetic diseases, aberrant and dysregulated genes **indirectly** cause pathology.
  - *That is, genes underlie the pathology but are not themselves the causative agents.*

- Altered gene products –**altered proteins** - are the direct causes of pathology.
Form = Function

...AAA  GGG  ACT  GCC  TGG  CAT  TGC  GTT  GAC...
...Lys  Gly  Thr  Ala  Trp  His  Cys  Val  Asp...
Mutations Disrupt Form/Function

...GAA GGG ACT GCC TGG CAT TGC GTT GAC...

...Asp Gly Thr Ala Trp His Cys Val Asp...
Identifying cancer drivers has had profound implications for therapy.

Chronic myelogenous leukemia
Identifying cancer drivers has had profound implications for therapy.

Breast cancer

Precision Medicine
Cancer Driver Gene Identification is an FDA Approved Concept for Precision Medicine

FoundationOne CDx™, the First FDA-Approved Comprehensive Genomic Profiling Assay for All Solid Tumors Incorporating Multiple Companion Diagnostics

-- FoundationOne CDx is the First Next Generation Sequencing Test for All Solid Tumors to Complete the FDA/CMS Parallel Review Process and Launch with National Medicare Coverage --

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Foundation Medicine, Inc. (NASDAQ:FMRI) today announced that FoundationOne CDx™, the first U.S. Food and Drug Administration (FDA) approved comprehensive genomic profiling (CGP) assay for all solid tumors incorporating multiple companion diagnostics, is now available in the United States. FoundationOne CDx is a first-of-its-kind test for individuals with advanced cancer that is offered as a nationally covered benefit across all solid tumors for Medicare and Medicare Advantage beneficiaries who meet eligibility requirements.

"Now that FoundationOne CDx is widely available in the U.S., oncologists can begin using this valuable test to help guide and simplify personalized treatment decisions for their patients," Vincent Miller, M.D., chief medical officer at Foundation Medicine. "By integrating FoundationOne CDx early into routine clinical care, oncologists can create treatment efficiencies and expand access to biomarker-driven medicines for patients, with the potential to validated genomic profiling may establish a path toward improved patient outcomes. Personalized, biomarker-driven clinical benefit across tumor types and biomarkers, making therapy selection ever more complex, single, FDA-approved comprehensive platform for all solid tumors to detect specific genomic alterations in decisions, while reducing the time and tissue needed when testing for biomarkers one at a time.

FoundationOne CDx, assesses genomic alterations in 324 genes known to drive cancer growth, providing treatment options. FoundationOne CDx is also FDA-approved as a broad companion diagnostic for patients with melanoma, colorectal cancer, ovarian cancer or breast cancer to identify those patients who may benefit from therapies, 12 of which are approved as first line therapy for their respective indications. FoundationOne microsatellite instability (MSI) and tumor mutational burden (TMB), that can help inform the use of other therapies and relevant clinical trial information. In all of these ways, FoundationOne CDx is available to form for clinical research and as a CGP platform for biopharma companies seeking to develop companion
Old Situation for Lung Cancer

Everyone gets the same therapy
Surgery, radiation, Chemotherapy (anti-folates, platinum drugs, gemcitabine)
Personalized Therapy for Lung Cancer

Pakala and Ramalingam, JCI Insight, 2018
Personalized Therapy for Lung Cancer

Molecular testing: EGFR, ALK, ROS1, BRAF, RET, MET, HER2
Personalized Therapy for Lung Cancer

Molecular testing:
- EGFR
- ALK
- ROS1
- BRAF
- RET
- MET
- HER2

Specific Drug:
- EGFR
- ALK
- ROS1
- BRAF
- RET
- MET
- HER2
Reversing the "Altered Function" of an Oncogene

Cheng et al., Pharma. Rev., 2019
Reversing the “Altered Function” of an Oncogene

Reversing the "Altered Function" of an Oncogene

- Inhibits activated, mutant ALK
- Used once crizotinib fails
Cost of DNA Sequencing

Cost per Genome

Moore's Law

$100M $10M $1M $100K $10K $1K


NIH National Human Genome Research Institute

genome.gov/sequencingcosts

Masonic Cancer Center
University of Minnesota
Comprehensive Cancer Center designated by the National Cancer Institute
The Future of Cancer Prevention and Care

- We all get sequenced?
- DNA from blood monitored for mutant DNA to detect cancer early
- Our tumors get completely sequenced – every few months during course of disease
- More “matched” therapies
- Immune therapy versus mutant proteins
• The Largaespada lab
  ◦ Bryant Keller
  ◦ Sue Rathe
  ◦ Flavia Popescu
  ◦ Kyle Williams
  ◦ Pauline Beckmann
  ◦ Sara Isakson
  ◦ Julia Nikrad
  ◦ Emily Pope
  ◦ Minu Bhunia
  ◦ Garrett Draper
  ◦ Wendy Hudson
  ◦ Alex Larsson
  ◦ Sandi Wagner
  ◦ Eunice Orimabisi
  ◦ Mahathi Patchava

• Collaborators
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  ◦ Nancy Ratner (Cincinnati Children’s)
  ◦ Gelareh Zadeh (U of Toronto)

• Funding
  ◦ NIH/NCI, DOD
  ◦ Children’s Cancer Research Fund, American Cancer Society, Children’s Tumor Foundation, Rein in Sarcoma
  ◦ Masonic Cancer Center
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