I will be discussing off-label uses of cancer therapeutics.

**Disclosures**

<table>
<thead>
<tr>
<th>Company</th>
<th>Activity</th>
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<tr>
<td>Ion Torrent/Fisher</td>
<td>Travel support; reagents</td>
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<tr>
<td>Ventana/Roche</td>
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<td>Genentech/Roche</td>
<td>Honoraria</td>
</tr>
<tr>
<td>Novartis</td>
<td>Consulting fees</td>
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**Chronic Myelogenous Leukemia**

- Before 2000, the 5-year survival rate was 30%, and most patients died of their disease.
- Imatinib was approved by the FDA in 2002.
- By 2006, the 5-year survival rate was 89%.
- By 2011, the 5-year survival rate was 95.2%, equivalent to the general population for this age group.
- Today, only 1% of CML patients will die of their leukemia.

**Individualized Cancer Medicine - An Example -**

- 42 year old male with 'glioblastoma' treated with surgery, temozolomide and radiation
- Bone and lymph node mets appeared at 20 months (what is this tumor?)
- Admitted to OHSU to manage pain, monitor pending cord compression
- Another round of chemo failed
- BRAF V600E mutation identified
- Patient started on dabrafenib
- Excellent clinical response

**Evolution of Cancer Treatment**

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Treatment</th>
<th>Cancer</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>CML</td>
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<td>BCR-ABL inhibitor</td>
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<td>Chemotherapy</td>
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<td>KIT inhibitor</td>
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<tr>
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<td>Chemotherapy</td>
<td>Melanoma</td>
<td>BRAF inhibitor</td>
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<tr>
<td>Renal cancer</td>
<td>Chemotherapy</td>
<td>Renal cancer</td>
<td>VEGFR inhibitor</td>
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<tr>
<td>Lung cancer</td>
<td>Chemotherapy</td>
<td>Lung cancer</td>
<td>EGFR inhibitor</td>
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**The Future**

<table>
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<th>Cancer</th>
<th>Treatments</th>
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<tr>
<td>All Types</td>
<td>• Combinations of targeted therapies, immune-based therapies and chemotherapies</td>
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</table>

**GI Stromal Tumor (GIST)**

- 5000 – 6000 new cases per year in the U.S.
- 70% harbor KIT gene mutations
Effect of the Tyrosine Kinase Inhibitor STI571 in a Patient with a Metastatic Gastrointestinal Stromal Tumor

Heikki Joensuu, M.D., Peter J. Roberts, M.D., Maarit Sarlomo-Rikala, M.D., Leif C. Andersson, M.D., Pekka Tervahartiala, M.D., David Tuveson, M.D., Ph.D., Sandra L. Silberman, M.D., Ph.D., Renaud Capdeville, M.D., Sasa Dimitrijevic, Ph.D., Brian Druker, M.D., and George D. Demetri, M.D.

Before Tx

1 Month of Tx


GI Stromal Tumor Response To Imatinib

Baseline                  24 hours           7 days            2 months         5.5 months

Courtesy of Dr. Annick van den Abbele, DFCI

Growth Signaling in GI Stromal Tumors

KIT Mutation

Targeted Therapeutics

Receptor tyrosine kinases

Trastuzumab
Cetuximab
Panitumumab
Sorafenib
Imatinib
Sunitinib
Afatinib
Dovitinib
Vemurafenib
Dabrafenib
LGX818
Trametinib
Selumetinib
Benitinib
Everolimus
Temsirolimus
Buparlisib
BGT226
BYL719

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BGT226
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Growth Signaling in GI Stromal Tumors

KIT Mutation

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Trametinib
Selumetinib
Benitinib
Everolimus
Temsirolimus
Buparlisib
BGT226
BYL719

Growth Signaling in GI Stromal Tumors

KIT Mutation

Targeted Therapeutics

Receptor tyrosine kinases

Trastuzumab
Cetuximab
Panitumumab
Sorafenib
Imatinib
Sunitinib
Afatinib
Dovitinib
Vemurafenib
Dabrafenib
LGX818
Trametinib
Selumetinib
Benitinib
Everolimus
Temsirolimus
Buparlisib
BGT226
BYL719
DNA Sequencing

Traditional Sanger Method

Initial Output

Final Sequence

Next-Generation DNA Sequencing

- Definition
  - Massively parallel sequencing (many sequencing reactions performed simultaneously)

NGS Sequencers in Clinical Labs

Next-Gen Sequencing Tests

<table>
<thead>
<tr>
<th>Panel</th>
<th># Genes</th>
<th>Availability</th>
<th>Notes</th>
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<td>Non-small cell lung ca panel</td>
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<tr>
<td>GI stromal tumor panel</td>
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<td>Available</td>
<td></td>
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<tr>
<td>AML / MDS panel</td>
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<td>General solid tumor panel</td>
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<tr>
<td>AML / Lymphoma panel</td>
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<td>20</td>
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<tr>
<td>Whole exome</td>
<td>~20K</td>
<td>July, 2015</td>
<td></td>
</tr>
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</table>
Would imatinib work in melanoma?

Updated from Beadling et al. J Molec Diag, 2011 Sep;13(5):504-13

**Cutaneous Melanoma Cases (n=140)**

- **AKT1**: 1%
- **BRAF**: 44%
- **CTNNB1**: 2%
- **GNAQ**: 1%
- **KIT**: 1%
- **MAP2K1**: 1%
- **NRAS**: 16%
- **PIK3CA**: 1%
- **TP53**: 1%
- **No Mutation**: 34%

**Best Response to Vemurafenib in Metastatic BRAF<sup>V600E</sup> Melanoma**


**Targeting KIT-Mutant Melanoma**

<table>
<thead>
<tr>
<th>Phase II Clinical Trials</th>
<th>Drug</th>
<th># Pts</th>
<th>Clinical Benefit Rate</th>
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</thead>
<tbody>
<tr>
<td>Carvajal et al. JAMA 2011;305(22):2327-2334</td>
<td>Imatinib</td>
<td>25</td>
<td>72%</td>
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<td>Guo et al. JCO 2011;29(21):2904-2909</td>
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<td>43</td>
<td>53%</td>
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<tr>
<td>Hodi et al. JCO (epub Jul 8, 2013)</td>
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<td>13</td>
<td>77%</td>
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</table>

**Metastatic BRAF<sup>V600E</sup> Papillary Thyroid Carcinoma Treated With Vemurafenib**
NSCLC Case Example

- 47 y/o woman with treatment refractory bronchioalveolar carcinoma
- Genotyping: BRAF V600E mutation
- Phase I study combining BRAF + MEK inhibitors: 6 month response

Baseline 2 months

Interim results of phase II study BRF113928 of dabrafenib in BRAF V600E mutation-positive non-small cell lung cancer (NSCLC) patients.

J Clin Oncol 31, 2013 (suppl; abstr 8009)

Emerging Theme

- The same growth-promoting mutations can occur in different tumors:
  - KIT gene mutations in GISTs and melanomas
    - generally responsive to KIT inhibitors
  - BRAF gene mutations in melanomas, lung cancers and brain tumors – generally responsive to BRAF inhibitors
- Other examples include:
  - ERBB2 mutations in breast, ovarian and lung cancer
  - RET mutations in thyroid and lung cancer
Cerizatinib-Overcomes Cerizatinib Resistance in ROS1 Fusion-Positive Cancer


ROS1 fusions in lung adenocarcinoma
• Discovery published in Jan. 2012
• Trial published Nov. 2014
• FDA-approved in Apr. 2015
• 2nd Line therapy published in Oct. 2014

Detecting Actionable Gene Fusions in NSCLC

<table>
<thead>
<tr>
<th>Kinase Fusion</th>
<th>IHC</th>
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<tbody>
<tr>
<td>ALK</td>
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<tr>
<td>AXL</td>
<td>??</td>
</tr>
<tr>
<td>BRAF</td>
<td>No</td>
</tr>
<tr>
<td>FGFR1</td>
<td>No</td>
</tr>
<tr>
<td>FGFR2</td>
<td>No</td>
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<tr>
<td>FGFR3</td>
<td>No</td>
</tr>
<tr>
<td>MET</td>
<td>No</td>
</tr>
</tbody>
</table>

Result: Positive for AXL (or ROS1) Rearrangements

Fusion Detection Using Next-Generation Sequencing

- Identify fusion partners
- Sensitivity down to 1%
- Estimate expression level
**EGFR Amplification in Breast Carcinoma**

68 year old F
Tumor metastatic to the liver
HER2-negative

[6% of breast carcinomas have EGFR amplification]

Bhargava et al. Mod Pathol. 2005 Aug;18(8):1027-33

---

**Example of Variant List For a 37-Gene Panel**

**Head & Neck Squamous Cell Carcinoma**

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<tr>
<th>Chrom</th>
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<th>Position_End</th>
<th>Ref</th>
<th>Var</th>
<th>Type</th>
<th>Consequence</th>
<th>Zygosity</th>
<th>Var_Freq</th>
<th>Gene</th>
<th>p_AA_change</th>
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**Amino acid Change**

- **KDR K747N**
- **CDKN2A E88*(stop)**
- **TP53 G245G**
- **TP53 C242G**

KDR encodes VEGFR2

---

**Head & Neck SQCC**

**Table 1:**

<table>
<thead>
<tr>
<th>Head &amp; Neck SQCC</th>
<th>Before Treatment</th>
<th>Treatment Day 15</th>
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<tbody>
<tr>
<td>TKI With VEGFR2 Activity</td>
<td>TKI With VEGFR2 Activity</td>
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</tbody>
</table>

---

**Whole Exome Sequencing**

(Sequencing All Protein-Coding Regions Across 20,000 Genes)

**Exacloud Computing Center**

OHSU/Intel Collaboration

- Intel is interested in projects that require a lot of computing power
- OHSU needs computing power for:
  - DNA sequence analysis (whole exome / genome)
  - RNA sequence analysis (whole transcriptome)
  - Image analysis (new microscopes in CLSB)
- Both parties want to find ways to share data with other institutions

**Variant Annotation**

- Sequence alignment
- Variant calling

**Clinical Sequence Data**

- Exacloud Computing Center
- Variant Annotation

**Clinical Genomics Database**

**Data Reporting**

- 7,000 Processors for data crunching
- 220 Terabytes of storage for clinical datasets
- 1200 Terabytes of storage for research samples
‘Liquid’ Biopsies

DNA in Plasma and Urine

- Small fragments of DNA are present in normal plasma and urine
- Increased levels occur in patients with advanced cancer
- New, high sensitivity tests based on next-gen sequencing can be used to detect mutations in such samples
- May be useful in monitoring treatment responses

**Commercial Labs**

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**Clinical Genomics Database**

**Summary**

- Advances in DNA sequencing technology are supporting the new era of ‘precision’ cancer care
- Panels of genes can now be screened quickly and cheaply by NGS
- In coming years molecular subtyping will likely be expanded to nearly all tumor types

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