Part 3: Obstacles to Developing Targeted Cancer Therapies

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If targeted therapies are so great, why can’t we treat all cancers?
Obstacles

- Identifying targets
- Finding medicines for targets
- Moving into the clinic
- Cancer resistance
Obstacle 1: Targeted therapies require targets!
How do you identify a target?

Discover differences between normal cells and cancer cells:

- DNA mutations
- Protein levels

**Problem:** Most cancer cells have DNA that looks like someone exploded their DNA and then put it back together randomly
Driver vs. Passenger Mutations

“Driver” is causing the cancer

“Passenger” is a mutation that happens along the way to becoming cancer, but isn’t causing the cancer
Which mutations are “drivers”?

geograph.org.uk
Solution: Look for common mutations in many tumor samples

However, rare but important “driver” mutations will be overlooked, and are very difficult to identify
Not all driver mutations are good targets
Obstacle 2: Hitting the Target
Which protein has a targeted therapy?

A  Ras

Importance in human cancer discovered in 1982
Mutated in 20-25% of all human cancers

B  B-raf

Importance in human cancer discovered in 2002
Mutated in 7% of all human cancers
Cell Growth Example – Ras Pathway

Cancer Cell

Growth signal → Ras → B-raf → Mek → PLX4032 → Abnormal cell growth and division

Signal → Receptor → Pathway Component → Pathway Component → Pathway Component → Output
Tumor suppressors: How do you “target” something that is not there?

- Control of Cell Division
- Fixing mistakes in DNA
- Control of Cell Death

p53
So far we’ve learned...

1. It can take years of research to identify promising targets

2. It can be difficult or impossible to find medicines that alter promising targets
Obstacle 3: Moving from the lab to the clinic does not always work

Photo by Umberto Salvagnin http://www.flickr.com/photos/kaibara/3075268200/
How many potential medicines make it into clinical trials?

A.) 1 in 100

B.) 1 in 1000

C.) 1 in 10,000
Why don’t they make it to clinical trial?

• Cannot be effectively delivered to patient (oral, IV etc)

• Not stable enough for use in the clinic

• Not specific for target

• Toxic to normal cells
Most potential medicines fail in clinical trials

Medicines approved after trials

- All indications: 9%
- Ovarian Cancer: 8%
- Breast Cancer: 7%
- Prostate Cancer: 4%
- Colorectal Cancer: 3%
- Non-small cell lung cancer: 2%

BioMedTracker BIO study 2011
Insidebiola.com
Why do medicines fail?

1.) Medicine is not effective
   • Can’t give enough medicine to people
   • Medicine does not do what we thought it would
   • Medicine hits target, but target is less important than we thought

2.) Medicine has too many side effects
   • “Off-target” effects
   • Hitting target not safe
Targeted therapies *might* have better luck

- More is understood about the biology before trials are started (better efficacy)
- Risk of serious side-effects is expected to be lower (safer)

This means a **wider** therapeutic window, so it is easier to achieve effective doses safely!

PLX4032’s end-stage clinical trial is the shortest on record!
Obstacle 4: Cancer is always changing
How does cancer fight back?

Medicine → Resistance
Resistance to PLX4032

Before therapy

After therapy

Average relapse: 7 months

Mechanism of Resistance #1

New mutation

Cancer cell growth and division

Secondary mutation in the target protein
Ras Pathway

Growth signal → Growth signal receptors → Ras → B-raf → Mek → Cell growth and division
Mechanism of Resistance #2

Mutation in a downstream protein

B-raf

Mek

Cancer cell growth and division
Mechanism of Resistance #3

Mek

Cancer cell growth and division

Mutation bypasses target protein
Cancer resistance to targeted therapies

- Resistance is a common problem in targeted therapies

- Some common mechanisms include:
  - Second mutation in the target protein
  - Mutation in a protein downstream of the target
  - Mutation that bypasses the target protein

- Combination therapies may help combat resistance
What we learned tonight:

Adrianna: Principles of cancer
- How cancer cells are different from normal cells
- Why is not one disease

Leah: Cancer therapeutics
- Chemotherapy and radiation
- Targeted therapies

Clare: Obstacles to developing cancer therapies
- Identifying and hitting targets
- Translating discoveries to the clinic
- Cancer resistance to therapy
Why haven’t we won the war on cancer yet?

Because it is not one war, so it requires more than one solution.
We *have* made progress in some major battles!

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>1975 5-year Survival Rate</th>
<th>2011 5-year Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Promyelocytic Leukemia</td>
<td>35%</td>
<td>98%</td>
</tr>
<tr>
<td>Childhood Leukemias</td>
<td>30%</td>
<td>80%</td>
</tr>
<tr>
<td>Chronic Myelogenous Leukemia</td>
<td>23.1%</td>
<td>89%</td>
</tr>
</tbody>
</table>
What does the future of cancer therapy look like?

Near Future:
• More targeted therapies
• Second- and third-line therapies to combat resistance

Distant Future:
• Combination of medicine specific for patient
• Manageable chronic disease
Thank you!

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