# 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?

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# Obstacles

- Identifying targets
- Finding medicines for targets
- Moving into the clinic
- Cancer resistance

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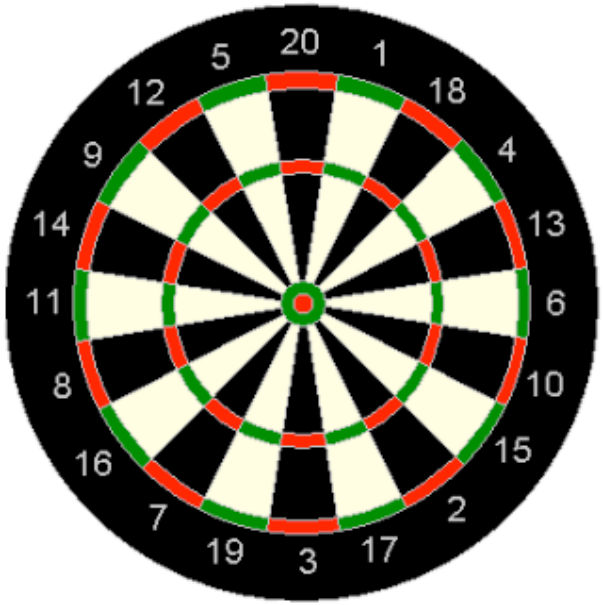
# Obstacle 1: Targeted therapies require targets!




Wikimedia

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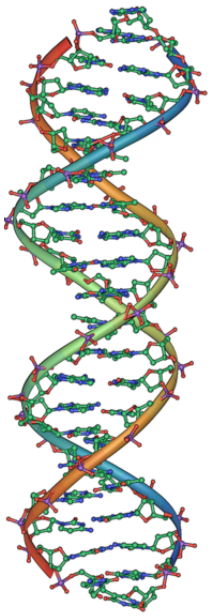
# How do you identify a target?



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

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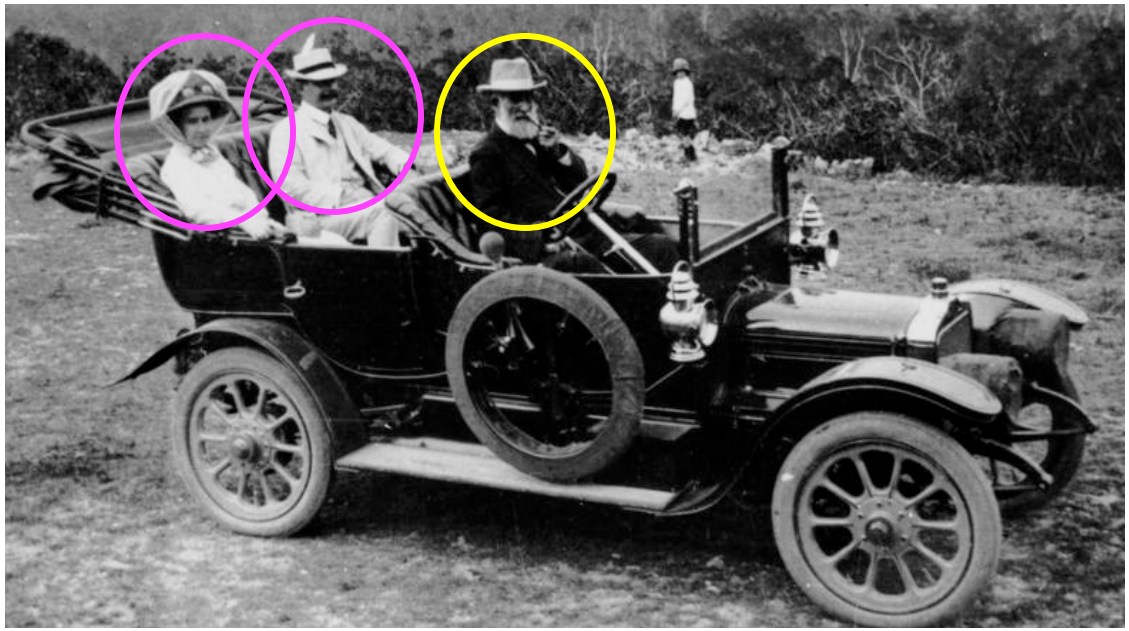
# Driver vs. Passenger Mutations

"Driver" is causing the cancer

"Passenger" is a mutation that happens along the way to becoming cancer, but isn't causing the cancer



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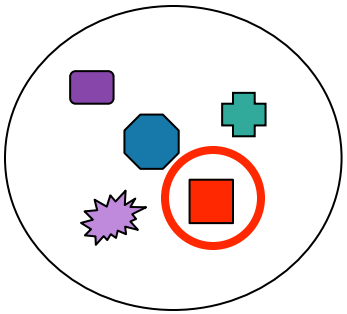
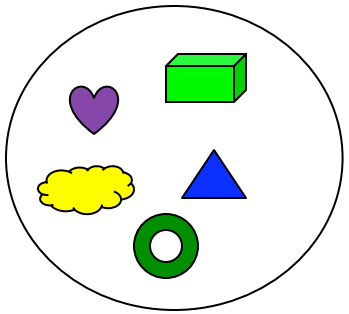
# Which mutations are “drivers”?

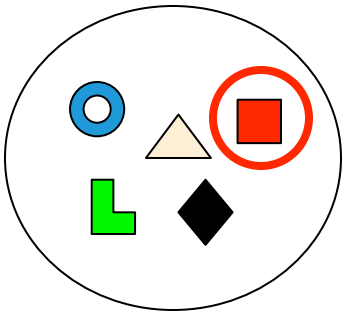
# Solution: Look for common mutations in many tumor samples



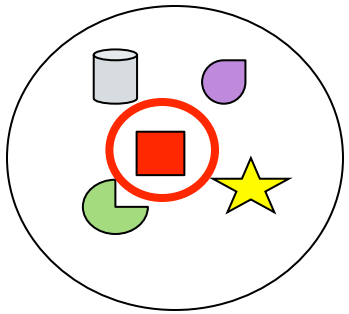
Sample 1



Sample 2



Sample 3



Sample 4

However, rare but important “driver” mutations will be overlooked, and are very difficult to identify

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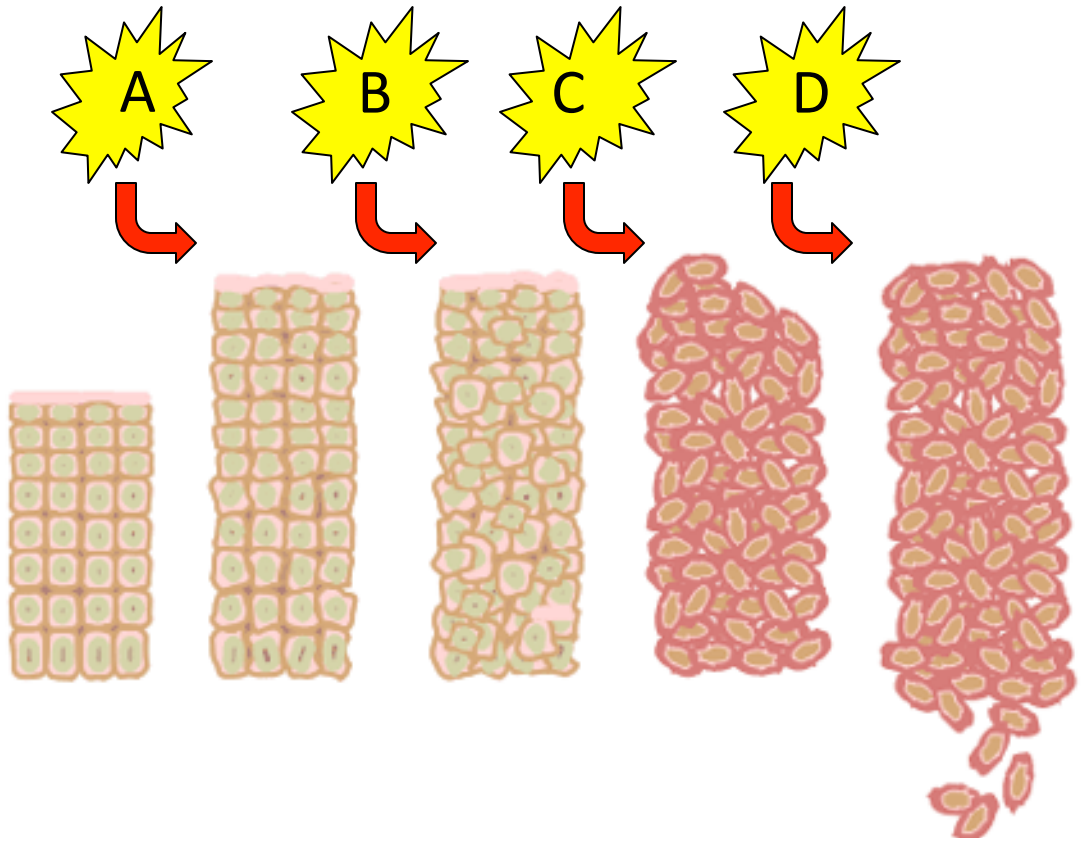
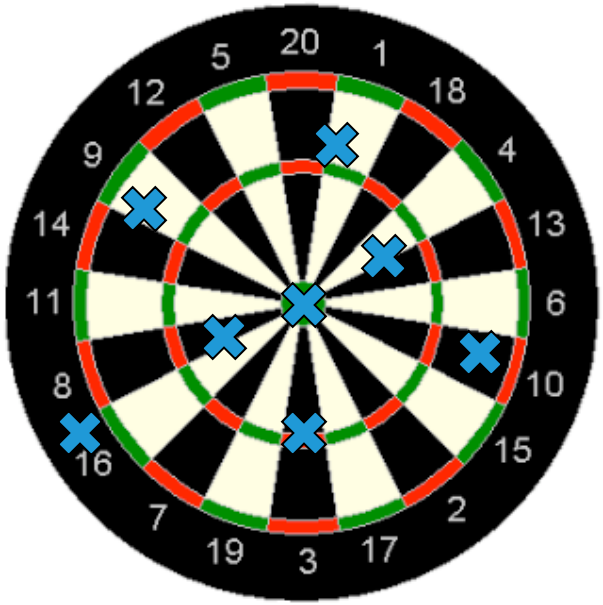
# Not all driver mutations are good targets



# Obstacle 2: Hitting the Target

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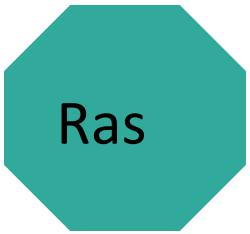
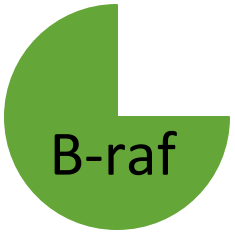
# Which protein has a targeted therapy?

A 


Importance in human cancer discovered in 1982

Mutated in 20-25% of all human cancers

✔ B 


Importance in human cancer discovered in 2002

Mutated in 7% of all human cancers

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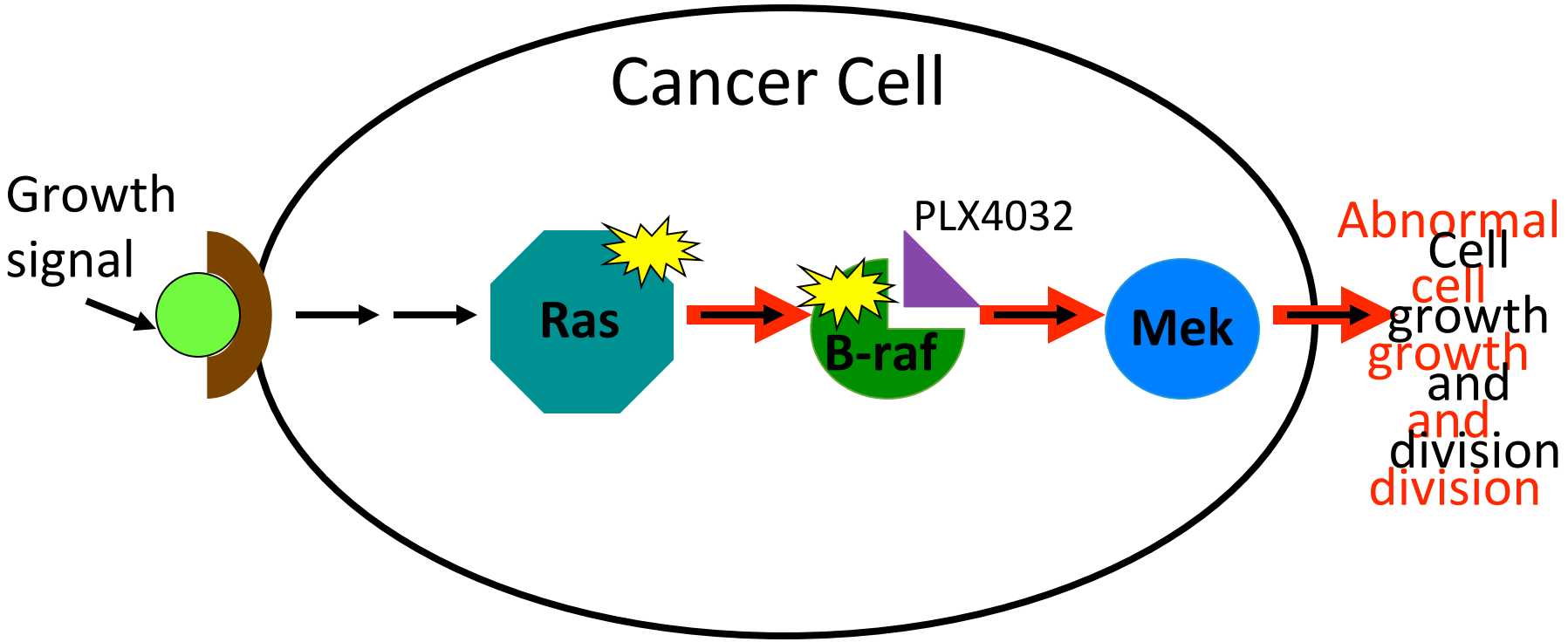
# Cell Growth Example – Ras Pathway




Signal → Receptor → Pathway Component → Pathway Component → Pathway Component → Output

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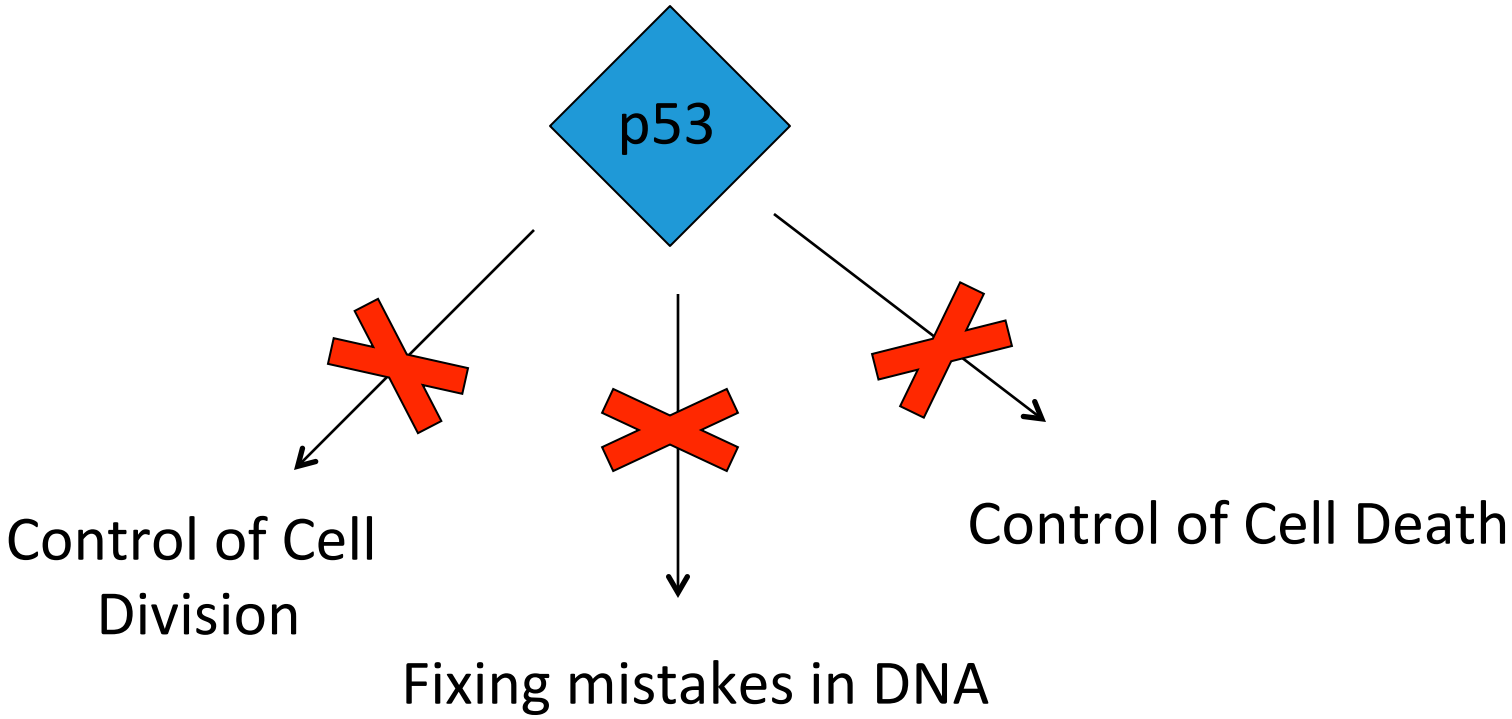
# Tumor suppressors: How do you "target" something that is not there?



# 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

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# Obstacle 3: Moving from the lab to the clinic does not always work

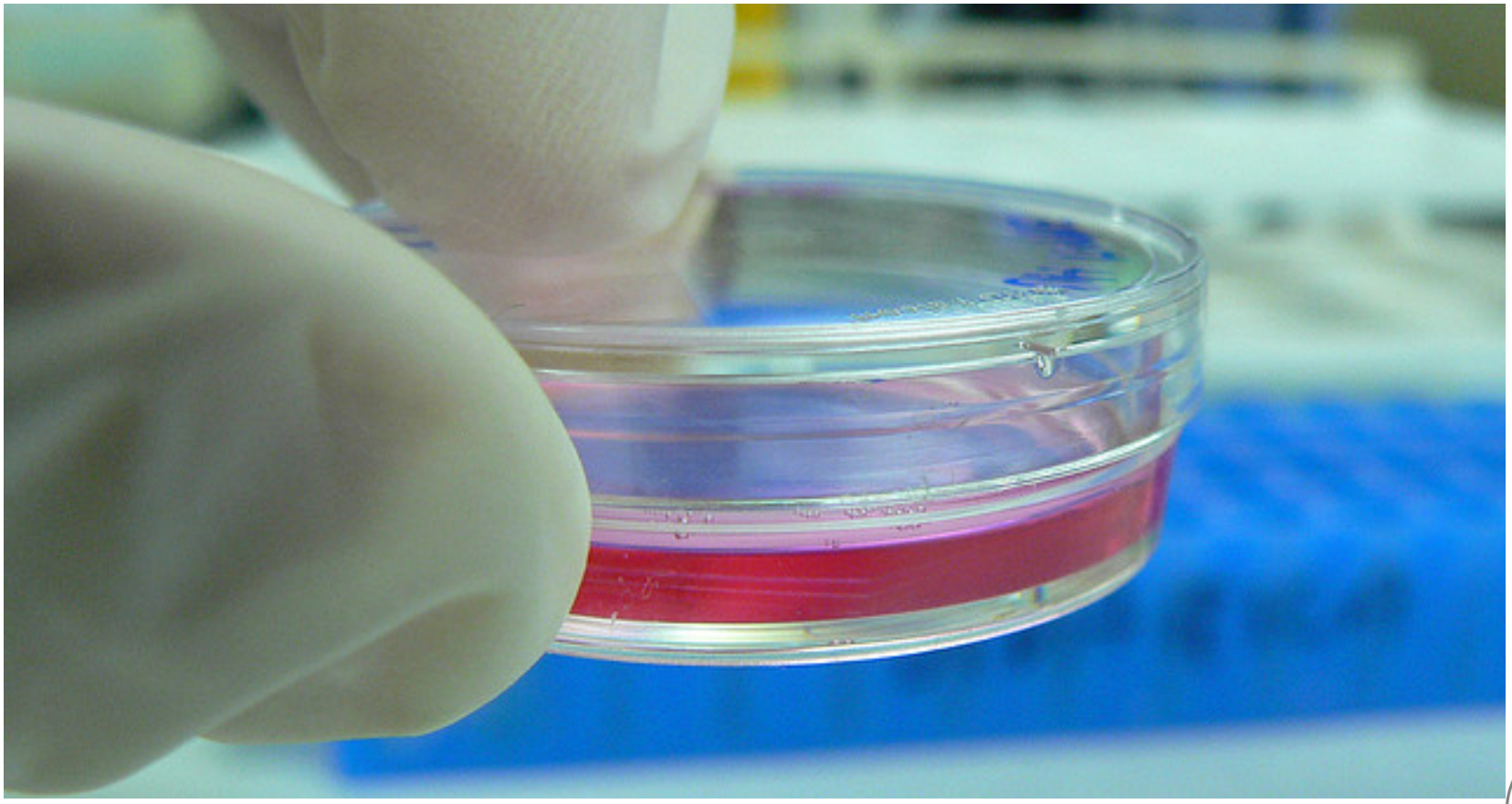

Photo by Umberto Salvagnin http://www.flickr.com/photos/kaibara/3075268200/

# How many potential medicines make it into clinical trials?

A.) 1 in 100

B.) 1 in 1000

C.) 1 in 10,000

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# 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

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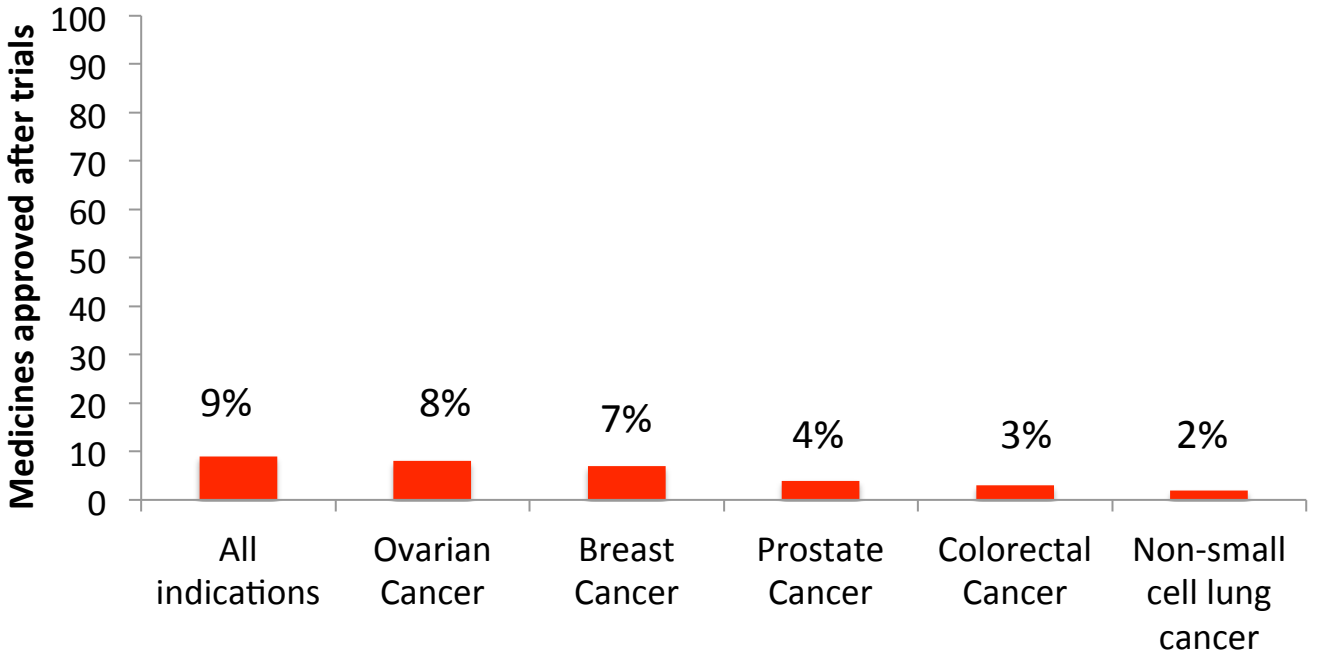
# *Most* potential medicines fail in clinical trials




BioMedTracker BIO study 2011
Insidebiola.com

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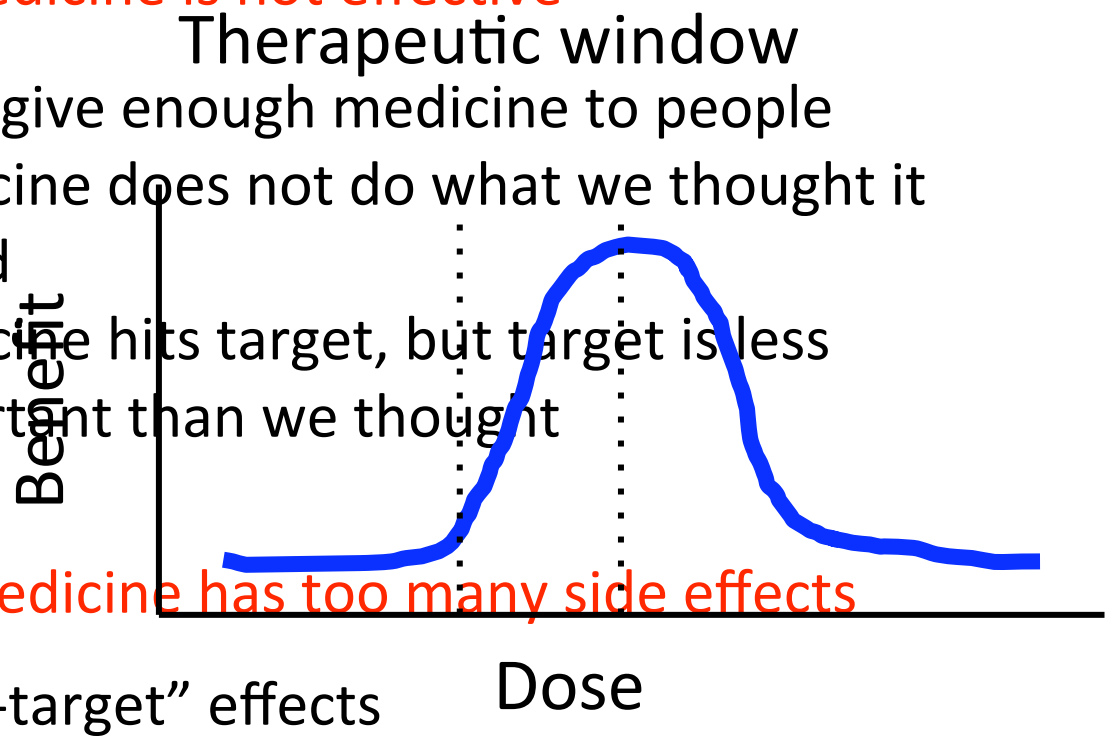
# Why do medicines fail?

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

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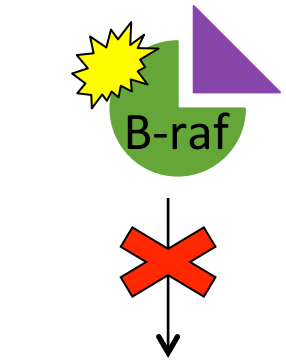
# Targeted therapies *might* have better luck

- 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!

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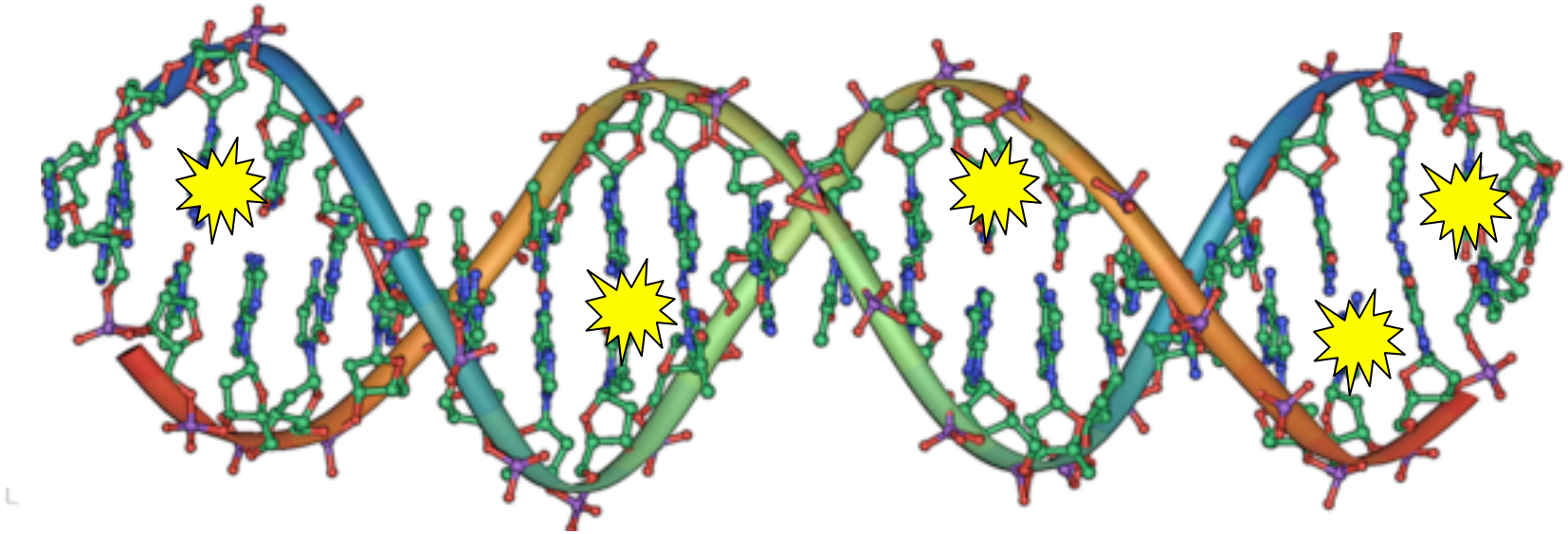
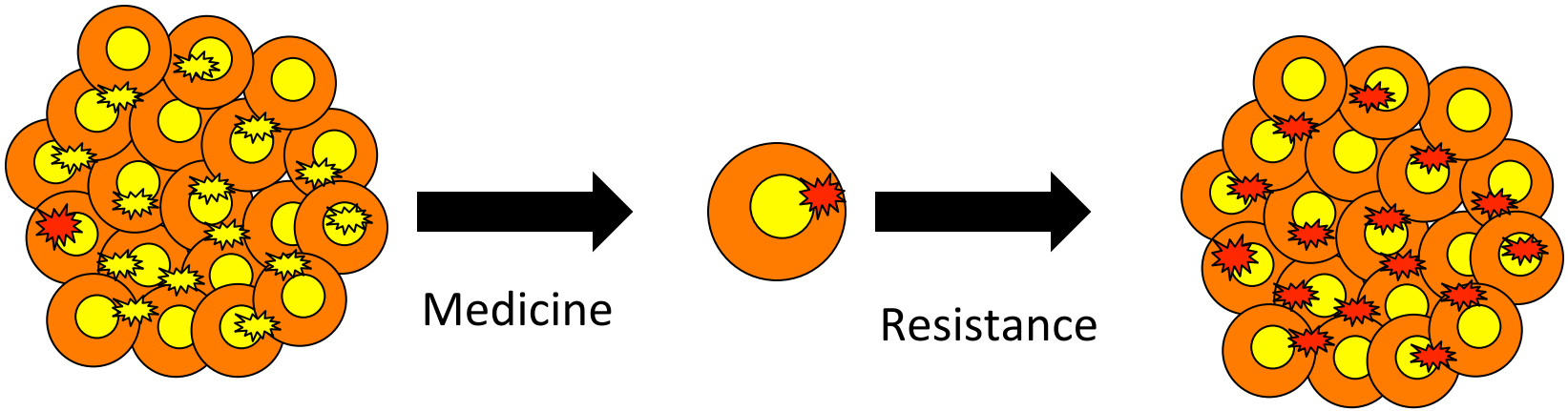
# Obstacle 4: Cancer is always changing



# How does cancer fight back?

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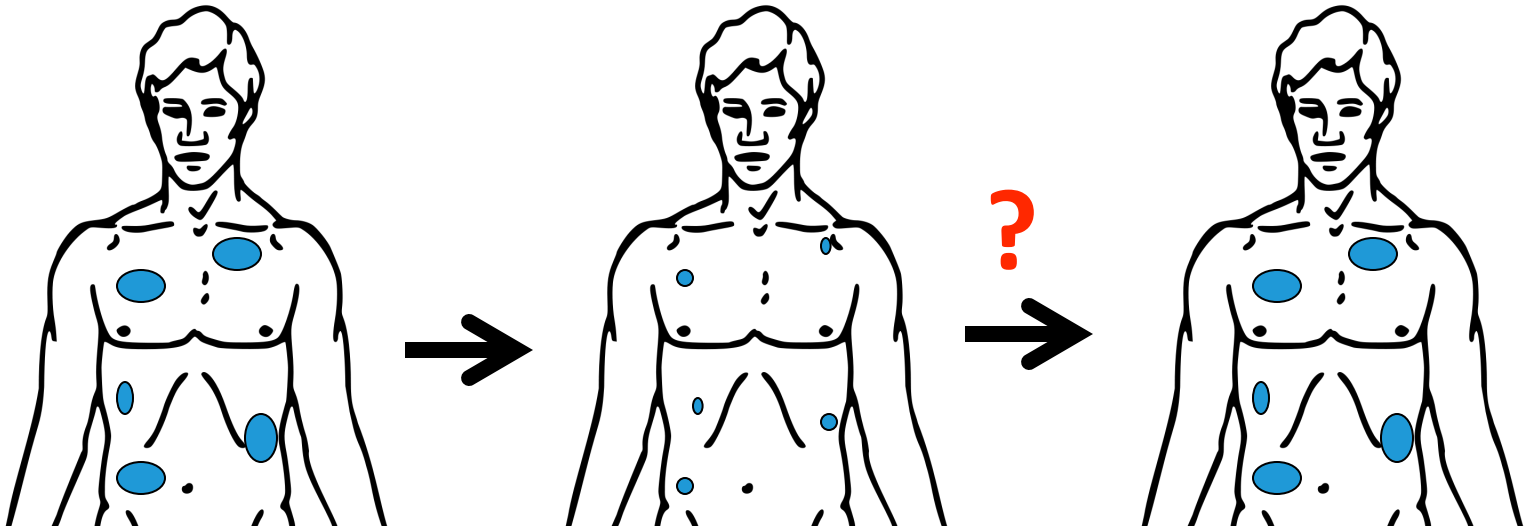
# Resistance to PLX4032



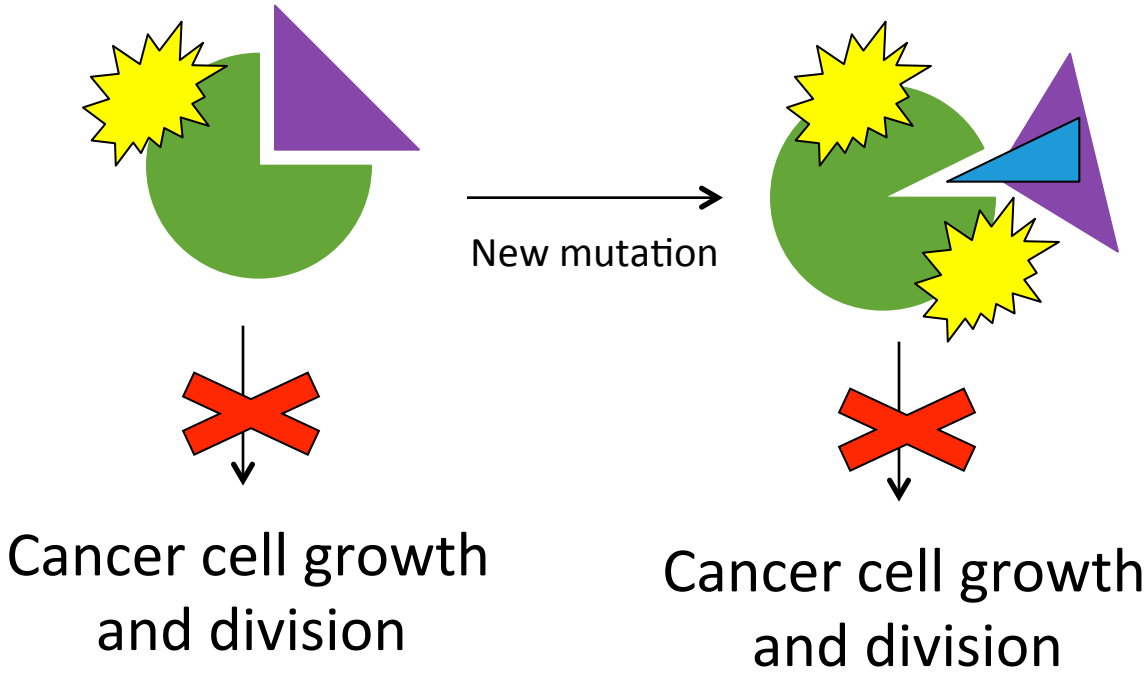

Before therapy

After therapy

Average relapse: 7 months

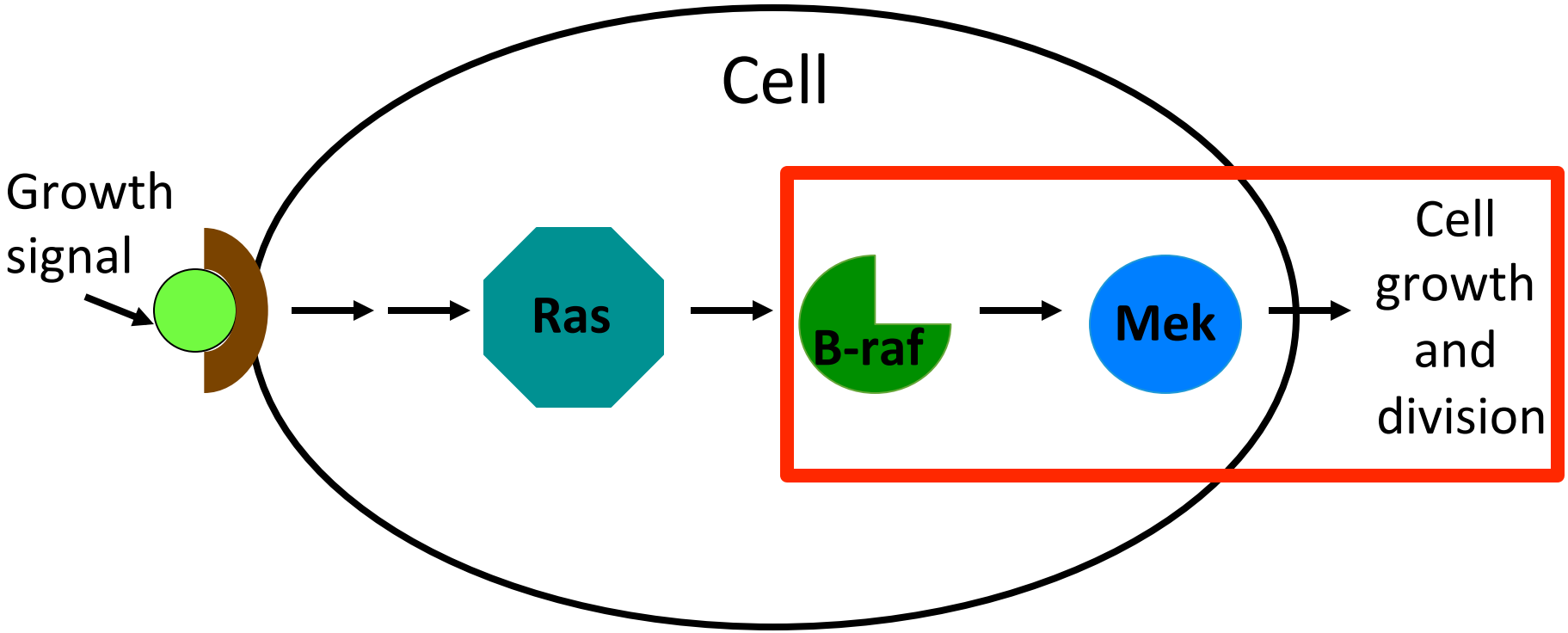
Flaherty et al. N Engl J Med 2010; 363:809-819.

# Mechanism of Resistance #1




Secondary mutation in the target protein

# Ras Pathway

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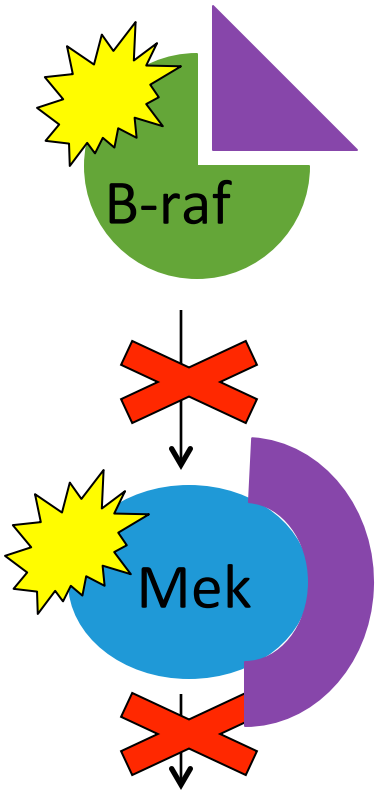
# Mechanism of Resistance #2




Cancer cell growth
and division

Mutation in a downstream protein

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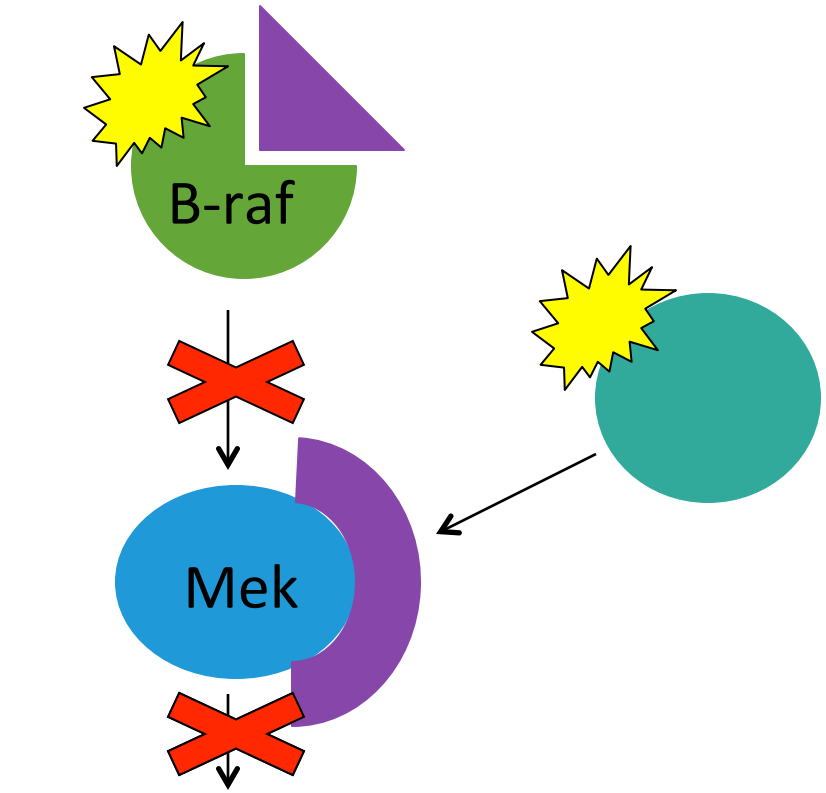
# Mechanism of Resistance #3




Mutation bypasses target protein

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# 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

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# 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

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# Why haven't we won the war on cancer yet?

Because it is not one war, so it requires more than one solution.

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# We *have* made progress in some major battles!

| Cancer Type | 1975 5-year Survival Rate | 2011 5-year Survival Rate |
|---|---|---|
| Promyelocytic Leukemia | 35% | 98% |
| Childhood Leukemias | 30% | 80% |
| Chronic Myelogenous Leukemia | 23.1% | 89% |

Fausel, 2007 Druker NEJM 2006
SEER Cancer Statistics Review. 1975-2008

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# 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

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# Thank you!

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**The Harvard Biomedical Graduate Students Organization (BGSO)**

**The Harvard/MIT COOP**

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