Laboratory Research to Discover New Approaches to Treat Cancer

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Our research is aimed at developing better treatments for cancer

Focus on Metastasis
(spread of cancer cells through the body)

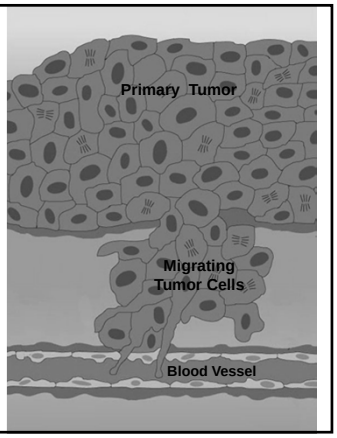
Metastasis is the major cause of death from cancer

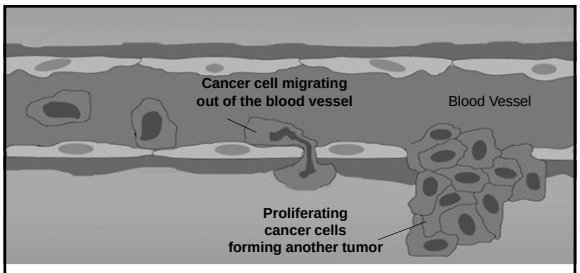
- Primary tumors can be surgically removed
- Metastasis causes multiple tumors to form throughout the body

To develop better treatments, we need to understand how metastasis occurs

The primary tumor consists of proliferating (multiplying) cancer cells

During metastasis, the cancer cells migrate away from the primary tumor, and enter the blood stream

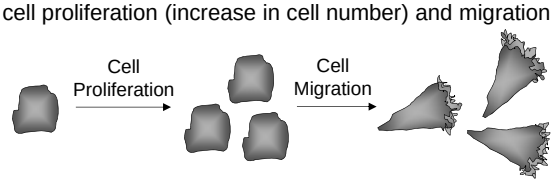




The metastasizing cancer cells
travel in the blood stream
and migrate through the lining of the blood vessels

The cancer cells migrate deeper into tissues,
where they proliferate (multiply) and form more tumors

Metastasis involves both
cell proliferation (increase in cell number) and migration



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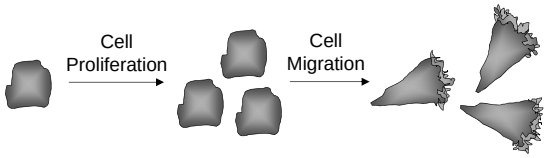

We investigate how metastasis occurs
by studying cancer in the laboratory

Cancer cells isolated from patients' tumors
are grown in our laboratory,
and we examine ways to stop the
proliferation and migration of the cancer cells

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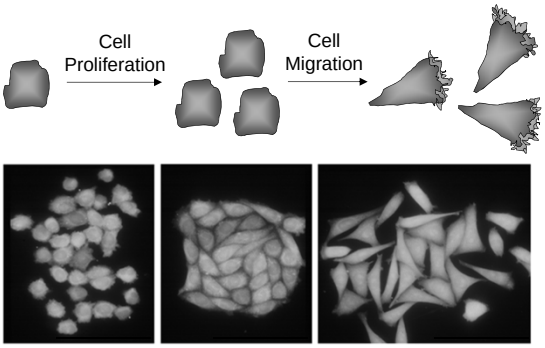

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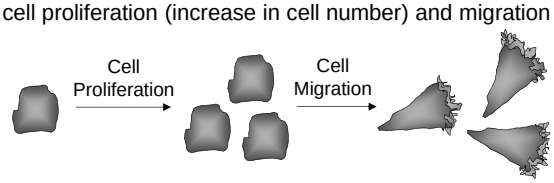
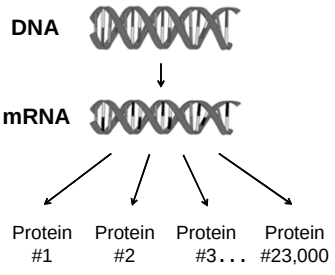


How do we begin to understand
what causes cancer cells to proliferate and migrate
more than normal cells?

We examine the proteins that are made
by the cancer cells

Each cell in our body can make
approximately 23,000 different proteins!

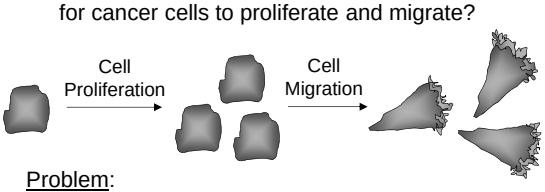


The DNA in each cell
contains about
23,000 different genes

Each of these
23,000 different genes
makes a unique mRNA

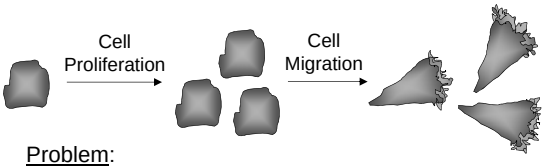
Each of these
23,000 different mRNAs
makes a unique protein

Which of these 23,000 different proteins are needed for cancer cells to proliferate and migrate?



Problem:
Normal cells and cancer cells often use the same proteins to help the cells proliferate and migrate

Which of these 23,000 different proteins are needed for cancer cells to proliferate and migrate?



Problem:
Normal cells and cancer cells often use the same proteins to help the cells proliferate and migrate

Solution:
Cancer cells often make very high amounts of these proteins, so the cancer cells proliferate more and migrate faster than normal cells

Goal:

Identify proteins that are made in abnormally high amounts by cancer cells, because cancer cells might use these proteins for their increased proliferation and migration

Identify ways to block the function or production of these proteins in cancer cells to diminish tumor formation and metastasis

Pipeline to Develop New Ways to Treat Cancer

Identify Therapeutic Targets

- Identify proteins made in higher levels in cancer cells compared to normal cells
- These proteins are called “therapeutic targets”

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Develop ways to Modulate the Target

- Develop drugs to lower the level (or inhibit the function) of the protein in the cancer cells

The multiple steps involved in this approach
can be understood by making the analogy that
rapidly growing cancer cells
are like fast moving joggers!

Identify Therapeutic Targets
↓
Validate the Targets
↓
Develop ways to Modulate the Target

- How can we stop cancer cells from growing faster than normal cells?
- Identify proteins that increase cancer cell growth
- Stop the cancer cells from using those proteins, so the cancer cells grow slower

- How can we stop joggers from running faster than pedestrians?
- Identify items that increase joggers' speed
- Stop the joggers from using those items, so the joggers run slower

Goal: Stop joggers from running faster than pedestrians
- Identify special items that increase the speed of joggers
- Develop ways to take these special items away from joggers, so the joggers move slower

Identify Therapeutic Targets
↓
Validate the Targets
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Develop ways to Modulate the Target

Goal: Stop joggers from running faster than pedestrians
- Identify special items that increase the speed of joggers
- Develop ways to take these special items away from joggers, so the joggers move slower

Identify Therapeutic Targets
- There is more sweat on joggers than on pedestrians

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Validate the Targets
- Diminishing sweat on joggers does not make them run slower
- Sweat is just a consequence of jogging

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Develop ways to Modulate the Target
- Developing ways to alter sweating is not worthwhile, because it will not slow joggers' speed

Goal: Stop joggers from running faster than pedestrians

- Identify special items that increase the speed of joggers
- Develop ways to take these special items away from joggers, so the joggers move slower

Identify Therapeutic Targets

- Special running shoes are worn by joggers

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Validate the Targets

- Joggers run slower when we take away their special running shoes
- Special running shoes are needed to help joggers run faster

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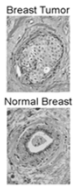
Develop ways to Modulate the Target

- Developing ways to stop joggers from wearing special running shoes is worthwhile, because it will slow joggers' speed

- By comparing joggers and pedestrians, we can identify which items make joggers run faster
- Special shoes help joggers run faster
- Taking away these special shoes make joggers run slower

- By comparing cancer cells and normal cells, we can identify which proteins (among the 23,000 made by cells) cause the cancer cells to grow more quickly
- Can we take away these special proteins from cancer cells, so they grow more slowly?

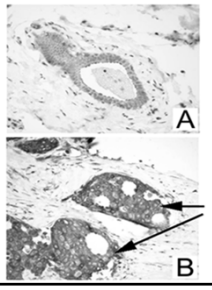


We compare patients' breast tumors with normal breast tissue, to identify proteins that are made more by the tumor cells

We discovered that the protein called **SmgGDS** (pronounced "smidge G D S") is made more in the tumor cells than in the normal cells

Blue Color:
Low SmgGDS level

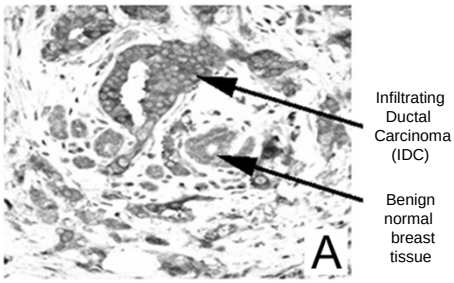
Brown color:
High SmgGDS level



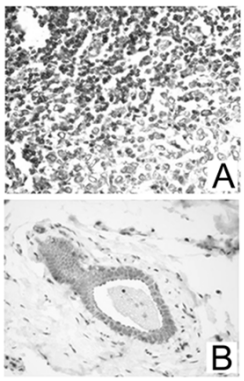
Normal Breast Tissue

Ductal Carcinoma in situ (DCIS)

A later stage breast tumor also has dark brown color, indicating that the breast cancer cells are making high amounts of SmgGDS protein



SmgGDS is made in very high levels in metastatic cancer cells



Metastatic Breast Cancer

Normal Breast Tissue

Brown Color:
High SmgGDS level

Blue Color:
Low SmgGDS level

Developing New Ways to Treat Cancer by Targeting the Protein Called SmgGDS

Identify Therapeutic Targets

- SmgGDS is made more in cancer cells compared to normal cells.
- SmgGDS is a therapeutic target

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Validate the Targets

- Cancer cells proliferate less, and move slower, when we stop them from making SmgGDS
- SmgGDS is a validated target in breast, lung, prostate, and pancreatic cancer

(Google: SmgGDS Williams Cancer [breast, lung, etc.])

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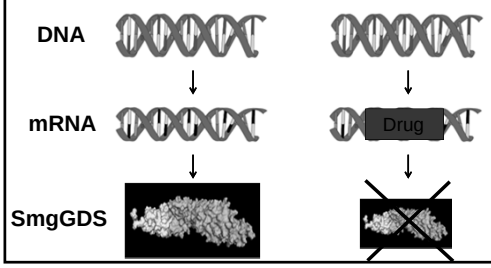
Develop ways to Modulate the Target

- Can we develop drugs to lower the level of SmgGDS in cancer cells?

Collaboration
to develop drugs that block the mRNA that makes SmgGDS

Dr. Mark McNally
Microbiology and Molecular Genetics, Medical College of Wisconsin

Dr. Frank Rigo, Ionis Pharmaceuticals
Carlsbad, California

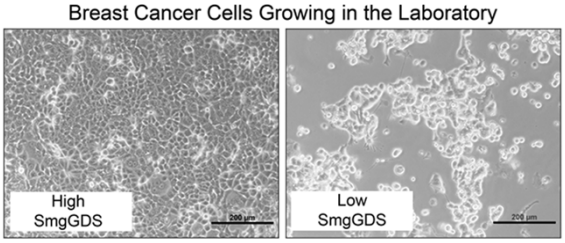


Development of Drugs that Decrease the Level
of SmgGDS in Cancer Cells

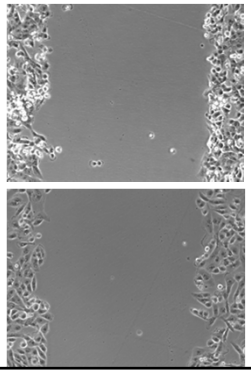
These drugs:

- Decrease the level of SmgGDS in breast cancer cells
- Inhibit the proliferation of breast cancer cells in the laboratory

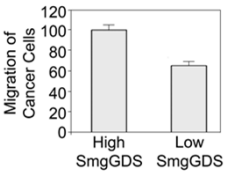
Breast Cancer Cells Growing in the Laboratory



We are currently testing the effects of these
drugs on cell migration



Breast cancer cells
move more slowly
when we inhibit the cells
from making SmgGDS



Cancer researchers are having great success using this approach, but much more research is needed

Erlotinib is an FDA-approved cancer drug that was developed using this approach

Identify Therapeutic Targets
- The protein called the EGF Receptor is on the surface of cancer cells and is highly active

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Validate the Targets
- Blocking the function of the EGF Receptor slows the growth of cancer cells

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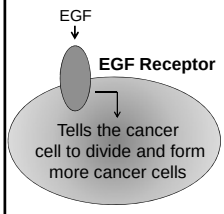
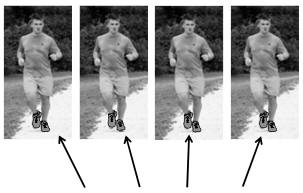
Develop ways to Modulate the Target
- The drug erlotinib inhibits the EGF Receptor and is approved by the FDA as a cancer drug



Returning to the jogger analogy:



The EGF Receptor is like a pair of blue suede running shoes that makes joggers run super fast

There were great expectations when erlotinib was first put on the market

Erlotinib will block the EGF Receptor on all lung cancer cells, and slow lung cancer progression in all patients

Treat with Erlotinib:

In other words…

Erlotinib will remove the blue suede shoes worn by all joggers, and slow the speed of all joggers

But not all of these expectations were met …

Erlotinib slows lung cancer progression, but only in 10 - 20% of patients with lung cancer

- Extensive laboratory research indicated that erlotinib only blocks EGF Receptors that have a special mutation
- Epidemiological and genotyping studies indicated that only 10 - 20% of patients have lung tumors with the mutant form of the EGF Receptor

The different forms of EGF Receptor
are like running shoes that have different colors

Treat with Erlotinib:

All joggers have running shoes, but these shoes come in different colors

- Only blue running shoes are removed by erlotinib

Most lung tumors have EGF Receptors, but these receptors come in different forms

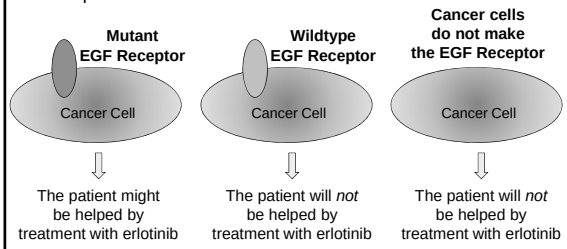
- Only mutant EGF Receptors are inhibited by erlotinib

10 - 20% of patients with lung cancer	80 - 90% of patients with lung cancer
EGF → **Mutant EGF Receptor** → Tells the cancer cell to divide and form more cancer cells	EGF → **Wildtype EGF Receptor** → Tells the cancer cell to divide and form more cancer cells
⇩ **Erlotinib**	⇩ **Erlotinib**
Cancer cells stop growing and form less tumors	The cancer cells keep growing and forming tumors

Personalized Medicine:

Each patient's tumor can be tested to identify the form of EGF Receptor made by their cancer cells

This information can be used to tailor the treatment for each patient



Summary

- Basic laboratory research is required to develop better ways to prevent, diagnose, and treat cancer
- Cancer cell proliferation and migration are often studied, because these characteristics contribute to cancer metastasis
- Scientists compare the features of normal cells and cancer cells to identify which features are abnormal in cancer cells

Summary

- Good therapeutic targets are proteins that
  - are made in abnormally high amounts by cancer cells
  - promote the proliferation and migration of cancer cells
- Scientists develop drugs that stop the abnormal protein (therapeutic target) from functioning or being made in cancer cells
- Clinical trials are conducted to test the ability of newly developed drugs to slow tumor growth and inhibit metastasis