

Excerpts from Native Cancer 101

Module 8: Biospecimens and Biobanking and “Native Cancer 101 Module 4: The Role of Genes in Cancer”

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Examples of Genetic Traits

 Tongue rolling

 Hand clasp

 Ear lobes

 Arm folding

Revised handout available

<http://www.NatAmCancer.org>

Go to “resources” tab

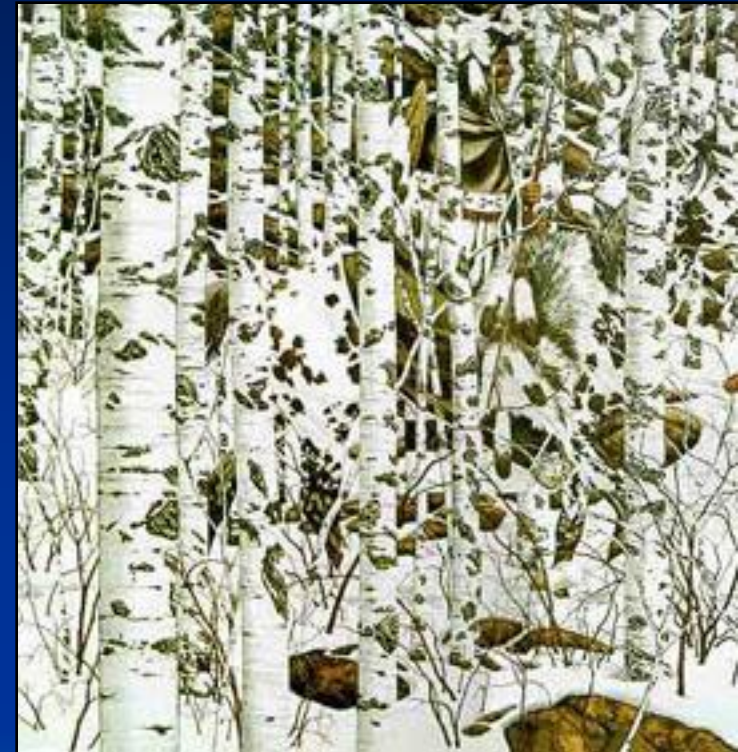
“Handouts”

Section 3a ...

filename begins with “Sanford”

Genetics is not new information for AIANs

- 🥁 Our ancestors knew how to
 - ⊕ Breed horses (Pintos, Appaloosa) so that their coloring blended with rocks, ground or aspens during the winter
 - ⊕ Grow stronger, more disease-resistant crops (e.g., corn and squash)



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Mayo Clinic's "Spirit of EAGLES Community Network Programs 2" [P.I. Kaur; U54CA153605];
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Genetics is not new information for AIANs

- 🥁 The concept of genetics is not new, but:
 - ⊕ How genetics is being used today
 - ⊕ New words created to describe genetic science today
 - ⊕ New cultural issues for protecting privacy of individual and tribal Nations today
 - ⊕ New science that can be generated to help address common health problems (diabetes, cancer) among Natives today...
- 🥁 Those are new ideas and concepts for AIANs

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QUESTION: Why is this important for AI/AN communities?

- 🥁 Cancer = increased among AI/ANs
- 🥁 People may learn their cancer risk, but:
 - ⊕ Is there an effective cure or treatment?
 - ⊕ Are there people trained to explain the cancer risk (is the risk real?)
- 🥁 New treatments are at the genetic and molecular level and the information may impact patient care.



Cancer Care Research

 Every day science makes new progress to:

- ⊕ Find cancer sooner
- ⊕ Find better treatments
- ⊕ Help people live better with cancer
- ⊕ Help people live longer after cancer



Lance White Shirt, MD
Navajo Nation
Lab Discoveries with
Dr. Lynne Bemis,
Cancer Research



Native American Cancer Initiatives, Incorporated (NACI) and Mayo Clinic's "Spirit of
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Mayo Clinic's Spirit of EAGLES Community Network Programs 2 [P.I. Kaur, U54CA153605];
<http://NativeAmericanPrograms.org> / <http://www.NatAmCancerInitiatives.org>



How you can help: Learning more about cancer



Wilma Mankiller
Former Principal Chief,
Cherokee Nation of Oklahoma;
Nov 1945 – April 2010
participant in clinical trials for 2
types of cancer;

*“Native people need to
take charge of your own
health care.”* Mankiller,
2005



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QUESTION: What are biospecimens?

- 🥁 Materials taken from the human body.
- 🥁 Contain information, about the human being and also about their disease
- 🥁 Primarily DNA, RNA and Proteins
 - ⊕ But not all biospecimens contain DNA

Photo credit: Romel Jacinto





QUESTION: What are common sources of biospecimens?

- 🥁 Blood
- 🥁 Saliva
- 🥁 Hair root
- 🥁 Fingernails
- 🥁 Flaked off skin cells (e.g., from clothing)
- 🥁 Biopsy tissue
- 🥁 Bronchoscopy
- 🥁 Sperm
- 🥁 Surgical Procedure




How can research on samples benefit YOU?

Personalized medicine:


- ⊕ Identify genetic differences between people that affect drug response
- ⊕ Develop genetic tests that predict an individual's response to a drug
- ⊕ Tailor medical treatments to the individual
 -  Increase effectiveness
 -  Minimize adverse side effects



Example of Personalized Medicine

 **QUESTION:** How many people die each year in the U.S. from medication side effects?

⊕ 100,000

 **QUESTION:** How many people suffer from serious side effects from medications in the U.S. each year?

⊕ 2,000,000 (2 million)



QUESTION: What factors can influence how a person responds to medication?

- 🥁 Weight
- 🥁 Diet
- 🥁 Food in stomach
- 🥁 Fatigue
- 🥁 Age
- 🥁 Sun exposure
- 🥁 Physical condition / lack of exercise
- 🥁 Drug interactions (i.e., Cross reactivity, synergism)
- 🥁 Genetic make-up

Obviously, many factors affect people's responses to drugs other than genes.



The Enzyme “Cytochrome P-450” contributes to ~ 1/2 of all medications

Examples of medicines ...

- ⊕ Codeine (opiate to treat pain or relieve cough by converting to morphine in the body)
- ⊕ Acetaminophen
- ⊕ Diazepam (dye az' e pam)
- ⊕ Cyclosporin A
- ⊕ Erythromycin



Balance of 3A4 and 2D6 within P-450

- 🥁 You always have 3A4.
 - ⊕ But, if 3A4 is too high in comparison to the amount of 2D6, the liver cannot metabolize codeine into morphine
 - ⊕ Instead = “norcodeine” which cannot be used by the body
- 🥁 Grapefruit juice can reduce your 3A4
- 🥁 Quinidine (used for heart arrhythmia or malaria) reduces 2D6.





3A4

Need ~ 9 volunteers
please



2D6



Grapefruit Juice



Quinidine



Group A



Group B



Group C







Grapefruit
Juice



Quinidine

Will be distributed by workshop faculty shortly

Interactive Activity

-  Please form groups of 4 people each
-  Each group represents one human liver
-  Each group (liver) receives a sack of candies
-  Look at the balance of 3A4 (Hershey's kisses) and 2D6 (peanut butter cups).

Interactive Activity

- ⊕ Can the liver convert codeine into morphine?
- 🥁 Eat or remove a few candies
- ⊕ Now can the liver convert codeine into morphine?
- 🥁 Addition of grapefruit juice or quinidine; how does that affect your metabolism?



2D6



Grapefruit
Juice



3A4



Quinidine

SUMMARY

- 🥁 More 2D6 than 3A4 = can convert codeine into morphine
- 🥁 More 3A4 than 2D6 = cannot convert codeine (makes norcodeine)
- 🥁 Grapefruit Juice = reduces 3A4
- 🥁 Quinidine = reduces 2D6

Read Rx labels

🥁 Many say, “do not drink grapefruit juice”

⊕ **QUESTION:** Why? What does too much grapefruit juice do to the 2D6, 3A4 balance?

🦅 Reduces 3A4 and changes the effectiveness of the medication



Pharmacogenetics Study in Indian Country

- 🥁 University of Montana
- 🥁 Working in partnership with ~5 tribal nations
- 🥁 Examining the P-450 enzyme to learn if American Indians metabolize medications differently than Whites or other racial groups
- 🥁 ~1/2 of Southwestern American Indians have variation in 3A5 (same family as 3A4)
- 🥁 How do MT Tribal Nations differ?



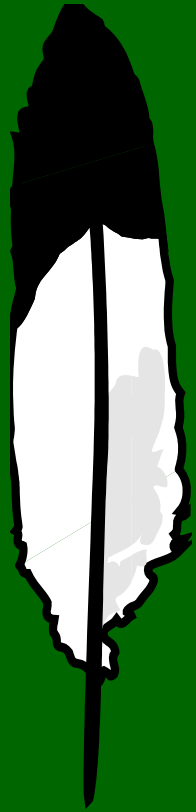
cetuximab



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Module 8, Objective 2:



Discuss ethical, legal, social, spiritual and cultural considerations and policies related to tissue donation for research.

Havasupai Study & Case (1989 – 2010)

🥁 In 2010, the Havasupai Tribal Nation settled a class action lawsuit against Arizona State University and the University of Arizona

⊕ Misuse of blood samples and DNA originally collected for research on diabetes

Indian Tribe Wins Fight to Limit Research of Its DNA



Edmond Tilousi, 56, who can climb the eight miles to the rim of the Grand Canyon in three hours. [More Photos >](#)
By AMY HARMON

Havasupai Study & Case (1989 – 2010)

- 🥁 These research specimens were later used for multiple other purposes including research on “schizophrenia, inbreeding and population migration.”
- 🥁 Insufficient informed consent process
- 🥁 Part of the Havasupai conflict was that the tribe thought their specimens were being used for a single study and the researchers thought the specimens were for biobanking



Havasupai (continued)

- 🥁 Researchers need to be careful about violations of research ethics for individual studies versus biospecimen storage that allows many researchers to access the specimen for studies without subsequent tribal or individual donor approvals
- 🥁 \$700,000 fine paid by Arizona State University and tribal sanctions prohibiting research studies with ASU
- 🥁 What happened to the PI? New job, promoted

Native American Cancer Initiatives, Incorporated (NACI) and Mayo Clinic's "Spirit of EAGLES Community Network Programs 2" [P.I. Kaur; U54CA153605]

<http://www.NativeAmericanPrograms.org> / <http://www.NatAmCancerInitiatives.org>



Based on Tribal Discussion Groups conducted through “Genetic Education for Native Americans” (GENA®)

🥁 According to GENA® participants (>3,000 AIANs), most tribes and urban Indian programs ARE interested in taking part in research that addresses:

🥁 Diabetes

🥁 Cancer

🥁 Obesity

🥁 Heart conditions

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Based on Tribal Discussion Groups conducted through “Genetic Education for Native Americans” (GENA®)

(1999-2004; PI: Burhansstipanov, HG01866):

- 🥁 Tribal Nations differ greatly on their perspectives about:
 - ⊕ The storage of biospecimens
 - ⊕ Inclusion within repositories that do not require individual informed consent processes



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Issues Identified through GENA®

- 🥁 Ownership of the specimens / data
 - ⊕ Most tribes / urban programs want to own study data
 - 🌐 Access it for additional programs/services



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Issues Identified through GENA®

- 🥁 Storage of data or specimens
 - ⊕ Storage of specimens requires a minus 80 degree freezer with back-up generators ... ~\$100,000 for the freezer



Issues Identified through GENA®

- 🥁 Cultural perspectives about specimens
 - ⊕ Such hair, hair roots/ follicles or blood for certain tribes is prohibited
 - ⊕ Blood tests for prenatal health is usually acceptable



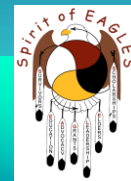
Issues Identified through GENA®

Uses of specimens

- ⊕ For research *on a single disease* (e.g., dedicated use of specimens only for cancer, heart disease, HIV)
- ⊕ Specimens *should not be used to create patents for drugs or devices*
 - 🌐 Some tribes have brokered agreements to have access to new patented drugs and devices

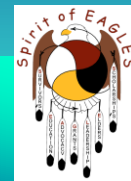
Issues Identified through GENA®

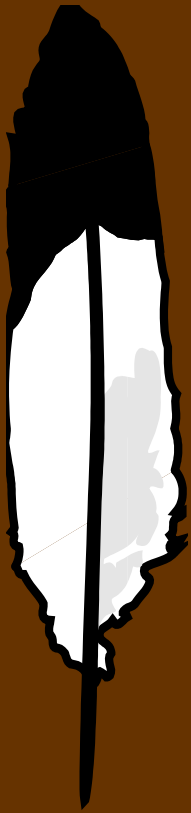
- 🥁 Research on topics of little to no interest to the tribal nation
 - ⊕ Mitochondria DNA to trace roots to Africa of little to no interest to AI/ANs
 - ⊕ Genetic / specimen research on diabetes, substance abuse, mental conditions such as depression = high interest by many tribal Nations



Issues Identified through GENA®

- 🥁 Publication of genetic research findings without obtaining previous tribal approvals
 - ⊕ Most tribal groups have policies requiring review of findings prior to submission as abstract for conferences, publication
- 🥁 Tribal sanctions: scientific inadequacy to appropriately protect cultural mores, privacy and confidentiality





Summary

Take Home
Messages

Summary / Take Home Messages

- 🥁 Tribal Nations and urban Indian programs differ in their opinions about biospecimens and biobanking
- 🥁 You need to understand if your tribal Nation has a formal position about taking part in biospecimen research
- 🥁 If you choose to take part, you have rights (informed decision-making)



Summary / Take Home Messages

- 🥁 A biobank / repository CAN be limited to a single study ... but you need to ask to confirm this is true if that is important to you or your tribal Nation
- 🥁 Some specimens (e.g., hair or blood) may have tribal sanctions prohibiting donations to biobanks



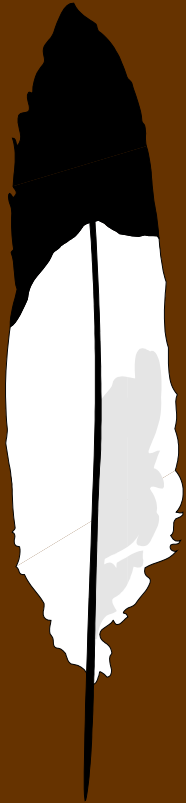
Summary / Take Home Messages

- 🥁 There are both potential benefits and drawbacks to taking part in genetic tests and research.
- 🥁 The individual needs to understand one's tribal Nation's perspectives and review the potential impacts to make an informed choice.



Thank you for allowing
us to share this excerpt
from Native Cancer 101
modules with you





As time allows

Module 4, Objective 2:
Describe role of genes in
cancer

Role of genes in cancer

- 🥁 Only a small group of mutations directly associated with cancer risk are inherited from the parents
- 🥁 Other (i.e., “most”) mutations are acquired over the life span
- 🥁 Multiple injuries occur to the same cell to evolve or result in cancer
 - ⊕ “Injuries” can be from alcohol abuse, exposure to commercial tobacco, bacteria, virus, inactivity, unhealthy diet

Role of genes: mutations


- ⊕ The injury is a mutation resulting in damage that is passed on from the first body (somatic) cell as it divides into additional cells
- ⊕ It gives the cells harboring the mutation an advantage to outgrow other cells
 - ⊙ For example in lung cancer the carcinogens in cigarette smoke may cause damage in several genes

Role of genes: mutations (continued)

- ① One change may allow the cells to grow out of control while another may cause the cells to be resistant to therapy
- ① Multiple injuries are required before the cells are changed enough to allow them to grow out of control
- ① For most solid tumors, 5-10 separate “injuries” occur before the cell becomes cancer

Interactivity: Chromosome Ropes

Longest chromosome = 1;
Shortest chromosome = 22
Germ (sex) cells (2)

 Rope chromosomes
(100,000 of times larger
than actual chromosomes)

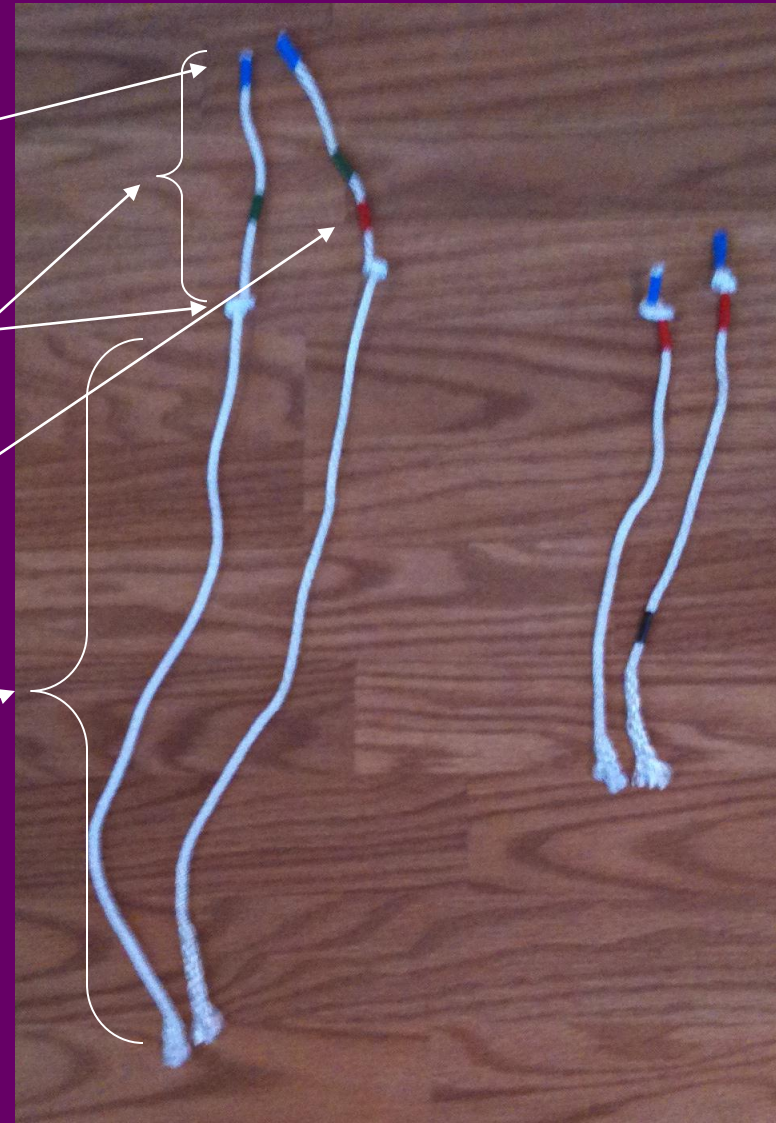
⊕ Telomere

⊕ Centromere

⊕ "Single Nucleotide
Polymorphism" (SNP) /
mutation

⊕ p segment

⊕ q segment



Role of genes in cancer (continued)

- 🥁 A variety of genes are known to be ‘injured’ in cancer.
- 🥁 Two overall types of injuries occur
- 🥁 Those that block the expression of “**Tumor suppressor**” genes like
 - ⊕ p53, BRCA1 and BRCA2
- 🥁 Those that activate **oncogenes** (genetic markers / SNPs that contribute to cancer)
 - ⊕ KRAS, BRAF, EGFR

Tumor Suppressors

 Those genes whose normal function is to suppress the overgrowth of cells.

 For example:

⊕ p53 is known as the guardian of genome

⊕ p53 is a guardian because it protects the cell from damages such as radiation or other stress

⊕ p53 Families and Li-Fraumeni

Tumor Suppressors

- ⊕ People who have a disease called Li Fraumeni generally inherit a mutation in p53 and their cancer rate is much higher than the rest of the population
 - ⊙ It is thought that treating a patient who has a mutation in p53 with radiation increases their risk for additional cancer incidence
 - ⊙ If a patient has Li-Fraumeni (p53) damage, would they receive radiation?

Oncogenes and Adapted Cancer Treatments

- 🥁 Oncogenes are genes that are over-expressed, allowing the growth of the tumor or increases the aggressive nature of a tumor.
- ⊕ Mutations in BRAF are a good example in melanoma because it allows for the uncontrolled growth of melanoma cells.

Oncogenes and Adapted Cancer Treatments

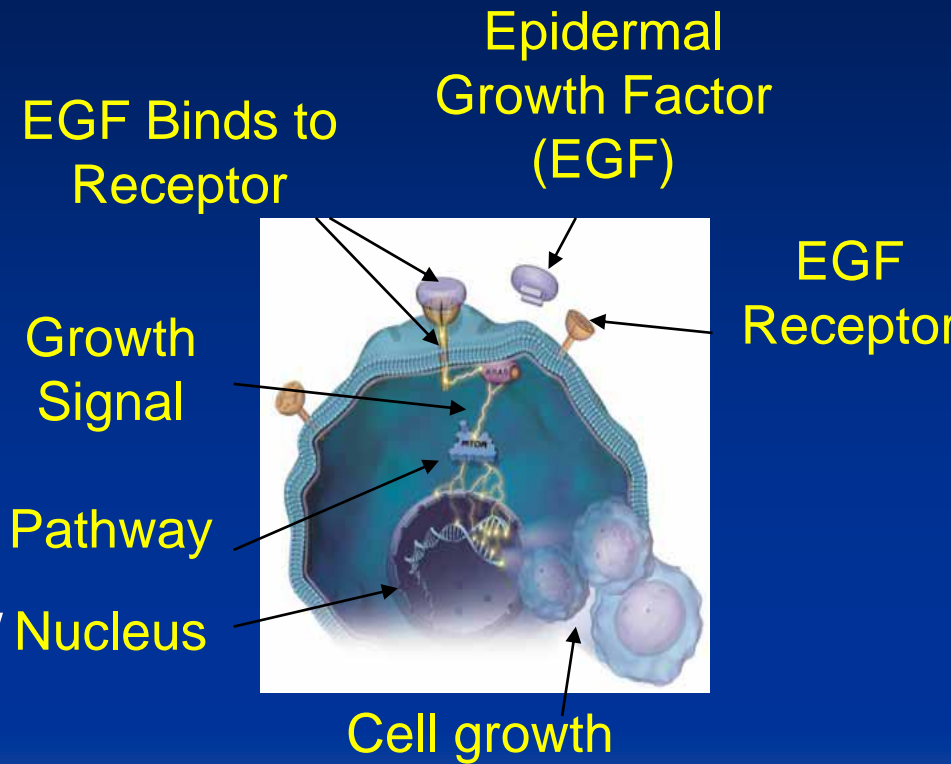
⊕ Mutations must be detected for patient to receive drug targeting BRAF because if given to patients without a BRAF mutation they may become more sick due to the effects of the drug

🥁 Obviously learning more about these oncogenes can predict more effective cancer treatments with fewer side effects

Researchers Study Molecular Pathways

🥁 Researchers study “pathways” for how oncogenes reach the cancer tumor cells

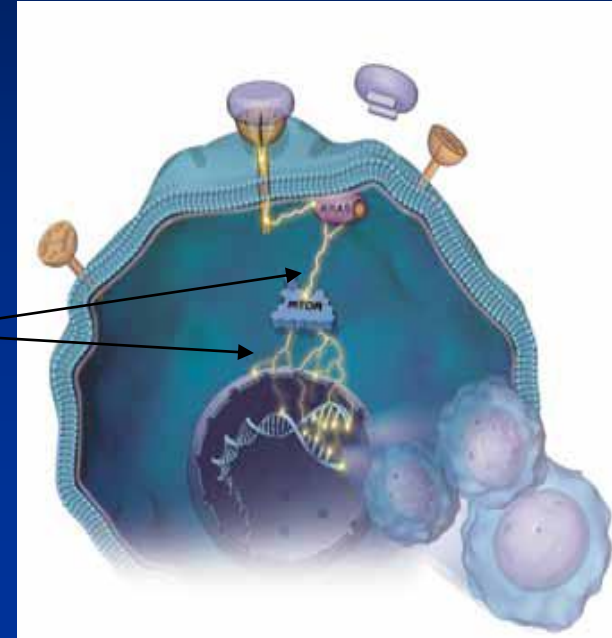
🥁 These are molecular pathways that tell the tumor cell to grow grow grow (also called “amplification”)



Researchers Study Molecular Pathways

🥁 Researchers try to find other molecules that would block that pathway so that the cell never receives the signal to grow grow grow

Pathways



Cancer Treatment: cetuximab

- 🥁 cetuximab is an antibody (protein acceptable to human body) that attacks receptors on cancer cell so that the cancer cell cannot multiply
- 🥁 Attacks oncoproteins such as Epidermal Growth Factor Receptor (EGFR)



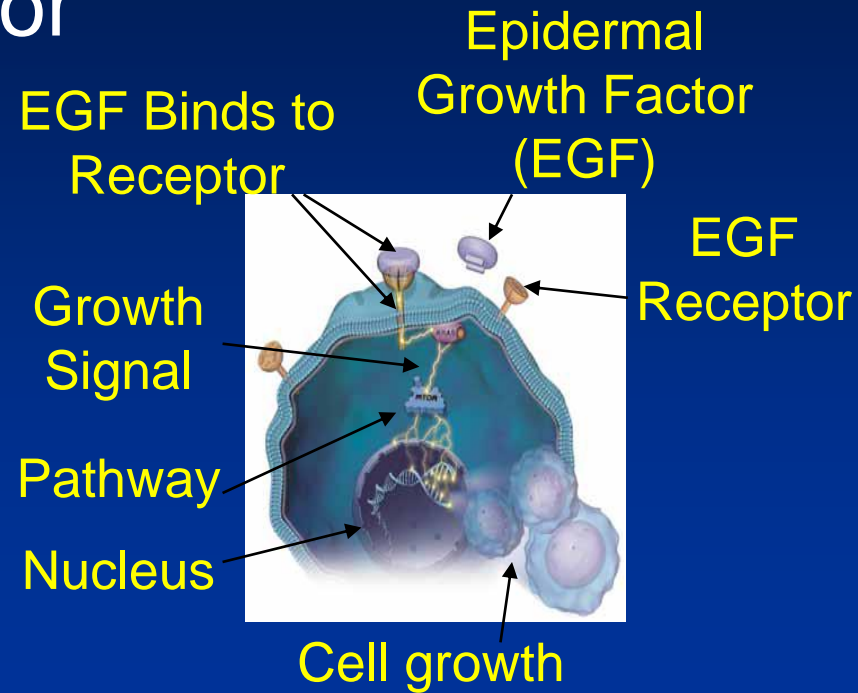
Pathway blocks binding of EGF and prevents growth signal

cetuximab

⊕ Epidermal Growth Factor Receptor EGFR is a receptor on the cell's surface

⊕ Found on many cancer cells (lung, CRC)

🥁 The EGFR protein gives improper signals to the tumor cell to grow grow grow



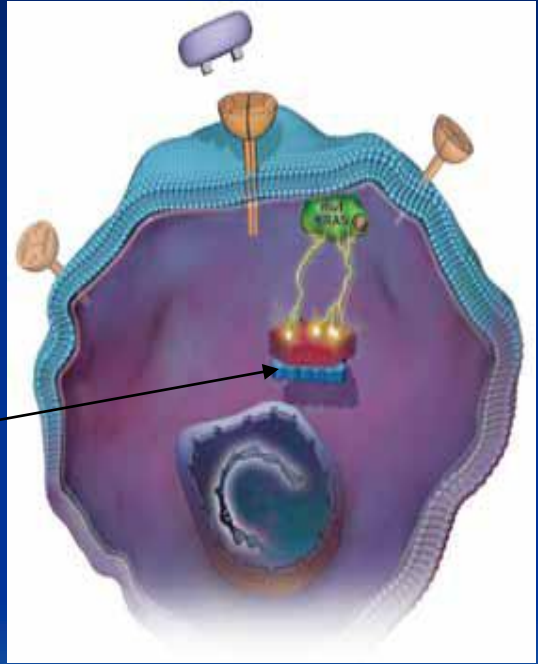
Based on this type of Research

- 🥁 If you give the patient cetuximab, the cetuximab goes to the EGFR protein and blocks its ability to send “grow grow grow” signals
- 🥁 Patient is tested for KRAS mutation prior to CRC treatment
 - ⊕ Currently the clinical lab needs a biopsy of the tumor
 - ⊕ The test for KRAS is a blood test

95% of pancreas cancers have KRAS Mutation

This is why cetuximab cannot be used to treat pancreas cancer

Likely to need a different drug (e.g., mTOR inhibitors) to target this signal



Chromosomal changes in Cancer

- 🥁 There are frequent mutations in cancer cells
- 🥁 Sometimes there are large rearrangements
- 🥁 Sometimes there are deletions of part of a chromosome
- 🥁 Sometimes there are small changes that may only be detected with PCR or other genetic tests.

NOTE: PCR stands for polymerase chain reaction. This is the method that allows researchers to copy and amplify almost any piece of DNA to better understand it. Many of the genetic tests currently in use require PCR as part of the process of determining if the patient has a SNP

Chromosomal Changes in Cancer

- ☞ Sometimes a test can be developed that looks at large regions of DNA changes
- ☞ Other times a few regions of a gene are examined
- ☞ BRCA1 and BRCA2 are very large genes known to harbor many mutations that may be passed from the parent to child

QUESTION: What is a BRCA2 mutation?

- 🥁 BRCA2 is a protein that helps to repair certain kinds of damage to DNA
- 🥁 BRCA2 is a very large gene composed of 84,188 base pairs
- 🥁 Hundreds of mutations have been discovered in BRCA2 and some are associated with certain ethnic groups



SEE YELLOW LAMINATED SHEETS WITH BRCA2 SUMMARY INFO (or use the following yellow slides end of module)