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Creating New Tools to Fight an Old Foe: Cancer Immunotherapy with Alpaca Antibodies

Presented by: Dr. Craig M. Story, Gordon College



Cancer Cell

Talk Outline

- What is cancer?
 - Cancer myths
- What is cancer immunotherapy?
 - It's a little complicated
- Some new tools for cancer immunotherapy.
 - The part having to do with alpaca antibodies.
- Cancer and the Christian faith.

- Cancer is not new
- Term refers to nonbenign growths.
 Benign tumor is not typically called "cancer."



http://www.sciencemag.org/news/2011/10/mummy-has-oldest-case-prostate-cancer-ancient-egypt

 Most forms of cancer arise spontaneously (90-95%) while others result from inheriting a genetic predisposition (5-10%)



https://garlandandpendant.com/category/retinoblastoma/

This photo may save your child's sight or life...



Pay attention to your child's photos. If you see a white image in your child's pupil, contact your primary care doctor, pediatrician, or ophthalmologist immediately.

This public service announcement is brought to you by Florida Society of Ophthalmology, Florida Pediatric Society / Florida Chapter of the American Academy of Pediatrics, and Alcon.





PHOTO PROVIDED COUNTESY OF JOEY BERGINA RETINOBLASTOMA AMARENESS

 Cancer gets worse over time. Decades usually.

From Vogelstein, 1990 Development of metastatic colon cancer takes years



• Diet probably has little to do with cancer compared to other factors Alcohol Antioxidants Artificial Sweeteners

to

Garlic Tea Vitamin D

"RCTs show no conclusive protection or causation"





#10: Prayer and Building Peace

A joyful heart is good medicine, but a broken spirit dries up the bones. Proverbs 17:22

Cancer myths abound

"Sharks don't get cancer"

Contagious cancer found in clams and mussels

As bad as cancer is in humans, at least it's not contagious. The same can't be said for clams, mussels, and other marine bivalves. According to a new study, published online today in *Nature*, **these creatures can suffer from a form of cancer similar to leukemia that appears to be transmitted through the water** and can pass not only between members of one species, but even between two different ones. Genetic analyses





The NEW ENGLAND JOURNAL of MEDICINE



ORIGINAL ARTICLE BRIEF REPORT

Malignant Transformation of *Hymenolepis nana* in a Human Host

Atis Muehlenbachs, M.D., Ph.D., Julu Bhatnagar, Ph.D., Carlos A. Agudelo, M.D., Alicia Hidron, M.D., Mark L. Eberhard, Ph.D., Blaine A. Mathison, B.S.M.(A.S.C.P.), Michael A. Frace, Ph.D., Akira Ito, Ph.D., Maureen G. Metcalfe, M.S., Dominique C. Rollin, M.D., Govinda S. Visvesvara, Ph.D., Cau D. Pham, Ph.D., Tara L. Jones, Ph.D., Patricia W. Greer, M.T., Alejandro Vélez Hoyos, M.D., Peter D. Olson, Ph.D., Lucy R. Diazgranados, M.D., and Sherif R. Zaki, M.D., Ph.D. N Engl J Med 2015; 373:1845-1852 November 5, 2015 DOI: 10.1056/NEJMoa1505892

Cancer is a genetic disease



Normal cell you are born with

Cancer cell that takes over your body

Cancer is a genetic disease



Genetics or environment? BOTH

One mutation or several? SEVERAL

What genes? MANY

What Pathways? NOT AS MANY



Cancer cell that takes over your body

Normal cell you are born with

Strategies to combat cancer typically fail due to selection and genetic/epigenetic instability



"New and improved" cancer is the result. The tumor is now resistant to the drug...

1970's

"War on Cancer" declared

Result: failure

Lack of knowledge and tools



President Richard Nixon signing the National Cancer Act of 1971. Credit: National Cancer Institute

2010's

"Breakthrough of the Year, 2013"

The other "C-word" is being uttered

Avalanche of knowledge and tools

Genetic knowledge, cheap DNA sequencing (Single cell DNA sequencing) Transgenic mice Cancer-specific cell lines Ability to "order a gene" online New insights: Why does chemo kill cancer cells?

And... Alpaca antibodies (of all things)

Video... then, how did it work?



This is the Emily Whitehead story... the result of Carl June and colleagues' work using CAR-T cell therapy. U. Penn.

Link: <u>https://www.youtube.com/watch?v=UE-E-gpUCJ0</u>

ORIGINAL ARTICLE

Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia

Shannon L. Maude, M.D., Ph.D., Noelle Frey, M.D., Pamela A. Shaw, Ph.D., Richard Aplenc, M.D., Ph.D., David M. Barrett, M.D., Ph.D.,
Nancy J. Bunin, M.D., Anne Chew, Ph.D., Vanessa E. Gonzalez, M.B.A., Zhaohui Zheng, M.S., Simon F. Lacey, Ph.D., Yolanda D. Mahnke, Ph.D.,
Jan J. Melenhorst, Ph.D., Susan R. Rheingold, M.D., Angela Shen, M.D., David T. Teachey, M.D., Bruce L. Levine, Ph.D., Carl H. June, M.D., David L. Porter, M.D., and Stephan A. Grupp, M.D., Ph.D.

ABSTRACT

BACKGROUND

Relapsed acute lymphoblastic leukemia (ALL) is difficult to treat despite the availability of aggressive therapies. Chimeric antigen receptor–modified T cells targeting CD19 may overcome many limitations of conventional therapies and induce remission in patients with refractory disease.

RESULTS

A total of 30 children and adults received CTL019. Complete remission was achieved in 27 patients (90%), including 2 patients with blinatumomabrefractory disease and 15 who had undergone stem-cell transplantation. CTL019 cells proliferated in vivo and were detectable in the blood, bone marrow, and cerebrospinal fluid of patients who had a response.

Strategy for Whitehead's blood cancer

Once chemo fails... there was not much that could be done. But now... Adoptive Cell Transfer

- 1. Remove patient's T cells
- 2. Introduce a new a "man made" gene into these cells
 - a. The new protein, a chimaera causes the T cell to "recognize" B-cells and kill them
 - b. "Serial Killer" cells... one T cell kills many tumor cells throughout the body
- 3. Restore normal immune system once the cancer cells are gone. Or use antibody replacement to make up for the lack of antibody-producing cells.

Here, one is using the immune system itself to fight a specific tumor.

"Checkpoint Blockade"



Here, an antibody binds CTLA-4 and blocks the inhibitory signal molecule: the T cell is re-activated.

Breakthrough of the Year Cancer Immunotherapy T cells on the attack

MAAAS

20 December 2013 | \$10

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http://www.retinalphysician.com/articleviewer.aspx?articleID=106236

Summarizes the complexities of this, as well as the different approaches.

Cancer Vaccines Provenge vs prostate feed antigens to dendritic cells so-so results

Adoptive T cell Therapy CAR-T cells good results on leukemia bi-specific T-engagers

Antibody therapies anti-CTLA4



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Liquid vs

Solid tumors

Solid tumors present more challenges to all kinds of cancer therapy, including immunotherapy

New Tools in Cancer Research





Conventional Antibody (mouse, human)

VS



two chains: Light, heavy

binding site made up of 6 loops

cloning requires cloning two separate genes

not easy to produce in bacteria

Camelid Antibody (alpaca, camel)



single chain (HC only) binding domain is one polypeptide large loop and additional S-S bond

easier to clone and select

can be expressed in bacteria

The Immune System is Regulated by a Series of Positive and Negative Signals



Drake, C. G. *et al.* (2013) Breathing new life into immunotherapy: review of melanoma, lung and kidney cancer *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2013.208

Checkpoint inhibitors—antibodies that block normal T cell inhibitory interactions—are effective



anti-CTLA-4

anti-PD1

Hodi et al. NEJM 2010

Robert et al. NEJM 2015

Cancer Immunotherapy—Future Challenges

- Monitoring/predicting anti-tumor immune responses: avoid side effects
 - Distinguish response from progression
 - match therapy to patient/tumor
- Combination therapies: improved efficacy
 - anti-CTLA-4/PD-1
 - Cytokines
 - Fusion proteins

The camelid antibody response



Single domain "nanobodies"

readily modified and expressed in bacteria

no need for glycosylation

folds independent of disulfide bond

deep tissue penetration

rapidly cleared after injection

no FcR or complement engagement

no cross-linking



Adapted from Wesolowski, 2009

Nanobodies are well tolerated in patients



Caplacizumab for Acquired Thrombotic Thrombocytopenic Purpura

Flora Peyvandi, M.D., Ph.D., Marie Scully, M.D., Johanna A. Kremer Hovinga, M.D., Spero Cataland, M.D.,
 Paul Knöbl, M.D., Haifeng Wu, M.D.,* Andrea Artoni, M.D., John-Paul Westwood, M.D.,
 Magnus Mansouri Taleghani, M.D., Bernd Jilma, M.D., Filip Callewaert, Ph.D., Hans Ulrichts, Ph.D.,
 Christian Duby, M.D., and Dominique Tersago, M.D., for the TITAN Investigators⁺

anti-vWF to block aggregation with platelets was effective and did not generate a significant anti-nanobody response

Generation of nanobodies against PD-L1



¹⁸F-B3 immunoPET



WT B3 + B16 tumor

Nanobodies are readily modified as fusion proteins



Benefits of B3-IL2 therapy extends to a mouse pancreatic cancer model







Future Directions

- Other cytokine fusions
 - IFNγ and GM-CSF (undergoing testing now)
 - IL-15, IL-10, and enhanced versions of IL-2
- Combination reagents using additional checkpoint inhibitors
 - There is a growing list of candidates
 - Combinations of these may have synergistic effects

What about death?

Death before the Fall? \rightarrow Re-examination of how to interpret "The Fall"

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Yet... Jesus wept at the premature loss of his close friend, Lazarus

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Cancer as a "result of the fall" strikes me as a **conflict** with science -conceptually, knowing "how cells work" it seems unlikely that cells, in principle, can avoid cancer -I suggest that cancer is **a necessary by-product** of cell biology

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Physical death (on a large scale) is necessary for evolution to happen

The Hope (which I cannot explain)

- SOMEHOW God will overcome death
- Plenty of scripture and biblical teaching, quotes from Christ seem to indicate we will "Be with him." Resurrection is "a thing."
- I don't worry too much about trying to explain this logically.
- To me, the person of Jesus outweighs these doubts. I believe he (God) does provide real strength and power for living <u>right now</u>.

These last slides are important. Other kinds of questions answered by faith are still important questions.

But remember they are not scientific questions.

No amount of science will answer them, yet the science does raise questions that may cause us to reexamine our theology from time to time. This is a healthy thing.

For further reading

Sid Mukherjee's book: "The Emperor of All Maladies: A Biography of Cancer"

For those that want to read a review of cancer with more scientific detail:

Hanahan and Weinberg and Hallmarks of Cancer: The Next Generation (Cell, March 4, 2011)





Raindance



Dr. Jess Ingram

Dr. Stephanie Dougan

Tony Letai (DFCI)

Why does traditional chemo kill cancer cells? some fast-dividing tumors are chemo-resistant some slow-dividing tumors are chemo-sensitive. (Therefore, the reason is not only about killing fast-dividing cells)

What is it?

All cells are "set" at a certain distance from going over the "cliff" of PCD Embryonic-like cells, as well as blood-precursor cells are close to the cliff require a little abuse and "poof" they undergo PCD this sensitivity to PCD of blood cells sets the dosing limit for chemo Tumors that are farther from the cliff are more resistant The distance from the cliff can be directly measured by titrating in peptides