Hereditary Non-Polyposis Colorectal Cancer

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Pd 3

Physiology

- HNPCC, or Lynch syndrome is a genetic condition that puts you at an increased risk for colon cancer as well as various other diseases of the digestive and reproductive tract
- As the main cancer that is associated with this condition is colon cancer, the primary target tissue is the colon
- HNPCC has an late onset, usually when one is in their 30s or 40s
- HNPCC consists of three stages:
  - The early stage, which if detected allows those diagnosed the highest chance of survival, is asymptomatic
  - The second stage may show a formation of adenomatous colon polyps which proves to be an inconclusive system as they form at a similar rate to that of the general public
  - Finally, the late stage is when most people notice that they may have a condition as symptoms include rectal bleeding, constipation, diarrhea, change in stool size, and a significant loss of weight

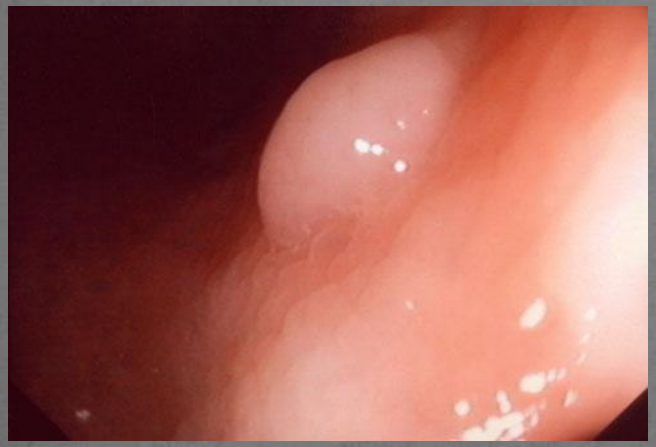

Figure 1

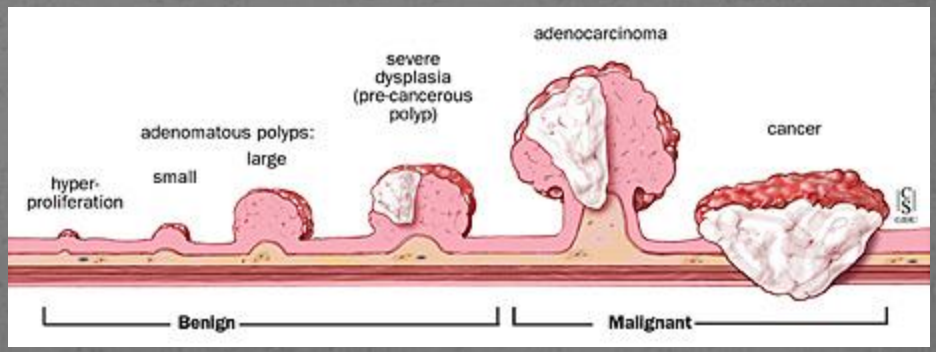

Figure 2

Molecular Cause

- Lynch Syndrome is autosomal dominant and has no gender bias
- The nature of this lesion is a point mutation in 1 of the 4 following genes : MLH1, MSH2, MSH6, PMS2
- The affected chromosomes are 2,3 and 7
- Basically, the point mutation is in one of the aforementioned mismatch repair genes which is responsible for the critical process of mismatch repair during DNA replication
- The genes are responsible for creating proteins that identify and fix the mismatched bases in the cell
- The point mutation causes these proteins to be dysfunctional, thus not being able to carry out tasks, mistakes that would usually be fixed are not and passed on to the daughter cells
- These abnormal cells replicate , leading to an uncontrollable cell growth which can possibly lead to cancer if left unchecked
- The key molecules here are the proteins that facilitate mismatch repair, which is what I will be dealing with for my proposed cure

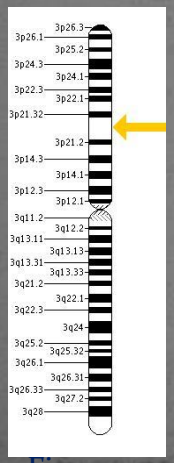

Figure 3

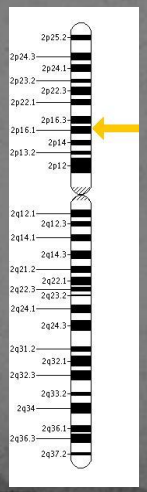

Figure 4

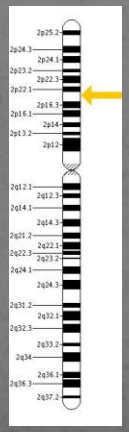

Figure 5

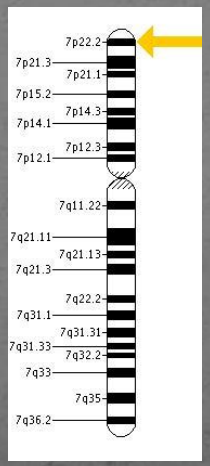

Figure 6

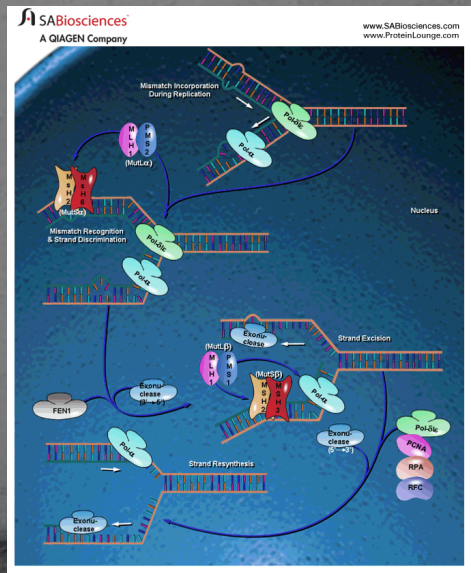

Figure 7 →

Treatments

- As of now there are no cures for HNPCC
- Currently one of the recommended procedures for those at risk or who have HNPCC to have frequent screenings and to remove any polyps I found as they can develop into malignant tumors
- The most common procedure is the colonoscopy which allows doctors to check for the presence of polyps in the colon
- However, most patients discover the disease in its late phase
- As a result, drastic procedures may be taken such as a removal of part or all of the colon with an ileorectal anastamosis, a proctocolectomy or even an ileostomy if diagnosed with rectal cancer as well
- However such actions only prevent those two specific cancers, and HNPCC can cause a much wider array of cancers
- Measures such as chemotherapy and high dose radiotherapy on tumors are being suggested in order to avoid invasive surgical procedures
- Chemotherapy drugs specifically to target colorectal cancer includes 5-Fluorouracil with leucovorin, capecitabine, irinotecan, and oxaliplatin
- However such procedures do little to improve the survival rate in contrast with the colectomy or ileostomy

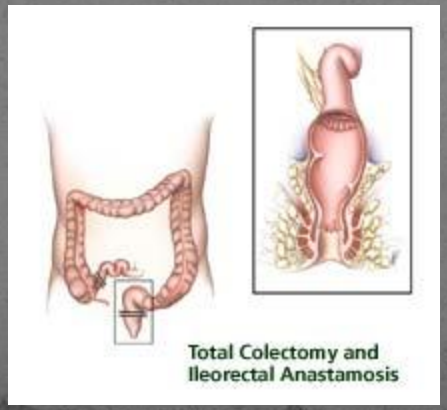

Figure 8

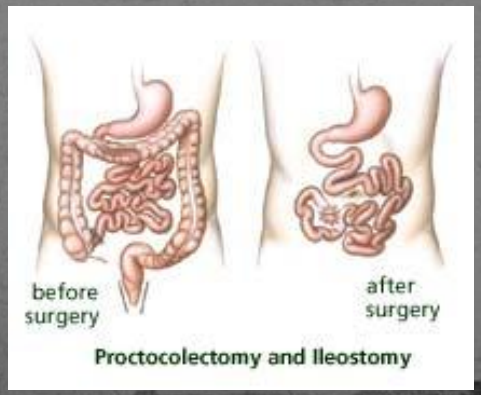

Figure 9

Proposed Cure and Limitations

- Since the main problem is that you have 1 or more dysfunctional mismatch repair protein, perhaps implanting the necessary protein would do the work
- The proteins would be contained in vesicles that would enter the cell via endocytosis
- The vesicles would be held in nanobots composed of DNA which would enter the cell via an injection and targeted to the colon or rectum
- These nanobots are made up of DNA chains folded into a barrel type structure which use aptamers
- The aptamers can be engineered to respond to a specific biomarker that is associated with colorectal cancer cells which is guanylyl cyclase C and target those if desired
- Once the nanobot reaches the cell, it releases its contents and after the proteins are inside, they travel to the nucleus via NLS and do their job in fixing the DNA
- Some of the limitations is that this method has not been actually tested according to my research, so there is no definitive proof if it will all go smoothly
- In addition, a great number of nanobots is needed to "cure" the patient so until self-replicating nanobots become a thing or some other method is discovered, this cure is unfeasible
- However if all goes well, injections would be given in the hospital so patients can be monitored
- It may take a long time or maybe your whole life depending on how successful the nanobots are

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- **IMAGES**
- Figure 1: http://www.mightyharvest.com/images/Mighty%20Harvest/health/Understanding%20Colorectal%20Cancer/2_Colon_lining.jpg
- Figure 2: http://www.hopkinscoloncancercenter.org/Upload/200812051423_11416_000.jpg
- Figure 3: http://ghr.nlm.nih.gov/dynamicImages/chromomap/MLH1.jpeg
- Figure 4: http://ghr.nlm.nih.gov/dynamicImages/chromomap/MSH2.jpeg
- Figure 5: http://ghr.nlm.nih.gov/dynamicImages/chromomap/MSH6.jpeg
- Figure 6:http://ghr.nlm.nih.gov/dynamicImages/chromomap/PMS2.jpeg
- Figure 7: http://www.sabiosciences.com/images/MismatchEukaryotes680.gif
- Figure 8: http://my.clevelandclinic.org/PublishingImages/Digestive_Disease/ileorectal.jpg
- Figure 9: http://my.clevelandclinic.org/PublishingImages/Digestive_Disease/colectomy.jpg