Curing Cancer – Part 8 – Strategic plan for curing cancer (as of February 2020)

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This is my eighth essay about curing cancer based on the principles of complexity theory. Follow my blog at**https://natpernickshealthblog.wordpress.com**.

It has now been 50 years since the war on cancer was announced by President Richard M. Nixon (see **President Nixon's 1971 State of the Union** at 15:03).

Watch Video At: https://youtu.be/peb47Z-jPqc

President Nixon Announcing the War on Cancer at 15:03

Although age adjusted cancer death rates have dropped substantially from 1970 to date (men: 249.3 to 189.5 per 100,000; women: 163.0 to 135.7 per 100,000), the American Cancer Society still projects that 608,570 Americans will die of cancer this year (**Jemal 2010**; **US National Cancer Institute website**, **Cancer Facts & Figures 2021**).

This essay provides a strategic plan for curing cancer. Regular updates are anticipated as our understanding of cancer related networks increases and progress is made in the steps below.

How to define victory in the war on cancer?

I define “curing cancer” as reducing American cancer deaths to 100,000 per year. Further major reductions are unlikely, because some patients will be ineligible for curative treatment due to coexisting medical conditions, some patients will refuse treatment and all of us will eventually die of something.

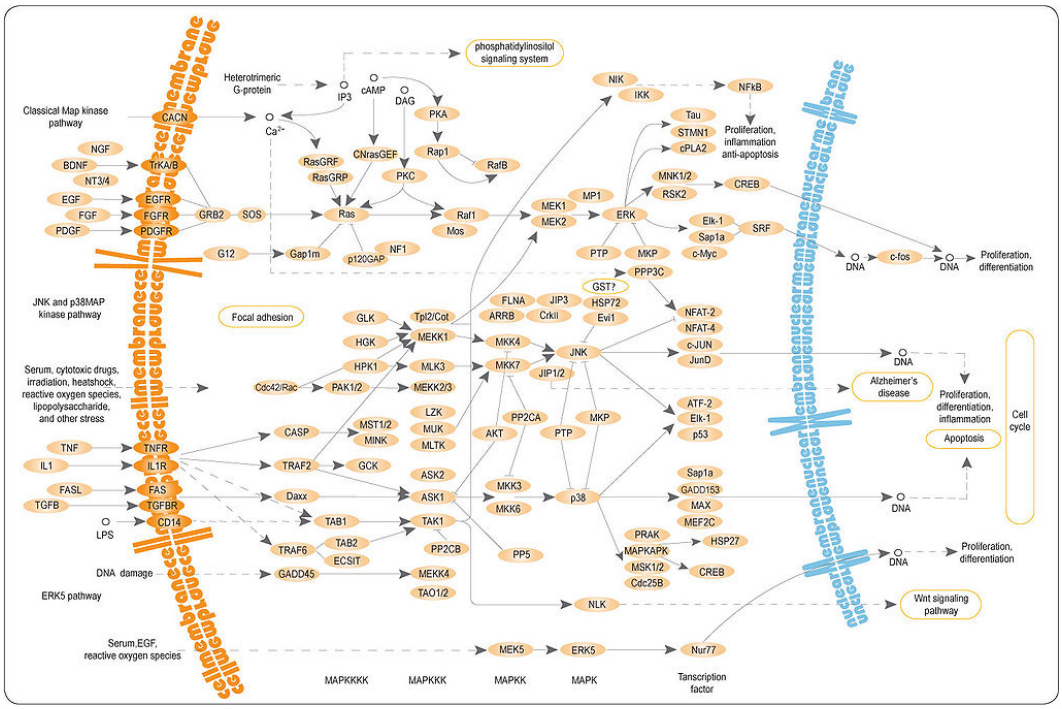
What changes are needed to reduce cancer deaths to this level?

The first step in curative therapy is halting cancer cell growth, which involves several distinct approaches.

1. Institute more effective treatment for the primary tumor.

1a. Develop more effective treatments to kill the cancer cells that damage critical tissues and organs. Some patients need immediate treatment because their cancer is life threatening due to its advanced and aggressive nature. This includes childhood leukemia patients and some adult patients, such as actor **Dustin Diamond**, who died of disseminated small cell lung cancer shortly after diagnosis. We should shift our focus from targeting driver mutations (i.e. specific mutations common in a particular tumor) towards targeting dysfunctional cellular networks which include the driver mutations. This is admittedly more difficult, due to possible alterations in many genes in the network plus all of the components with which the genes and their products interact (**Barabási 2011**).

1b. Curative treatment must attack different aspects of the cancer, requiring combinations of combinations of treatment. Disabling any single cancer attribute, such as rapid cell growth, will likely require combinations of 3-5 drugs or other treatments (radiation therapy, hyperthermia) because each attribute develops through activation of a web of biologic pathways that readily bypasses a single treatment block (**Curing Cancer Blog-Part 4**).



Interactions of cell cycle pathways resemble a web (Wikipedia)

Disabling each additional cancer attribute, such as cell migration (metastatic spread), avoiding programmed cell death (apoptosis) and the systemic networks described below, may require a different combination of treatments, although there may be some overlap. This means that patients must typically receive combinations of combinations of treatments.

1c. Treatments must be extensively tested in clinical trials to optimize their delivery, make them tolerable to patients and ensure that they work well together. Towards this end, every cancer patient should be enrolled in a clinical trial. In addition, computational approaches and modeling methods may be useful to determine the effectiveness of treatment combinations (**Curing Cancer Blog-Part 5**).

1d. It may be important to "normalize" or reduce the malignant traits of tumor cells that survive the above steps. This involves treatments that push tumor cell networks out of their relatively stable "attractor" states towards network states with reduced malignant properties (**Curing Cancer Blog-Part 5**).

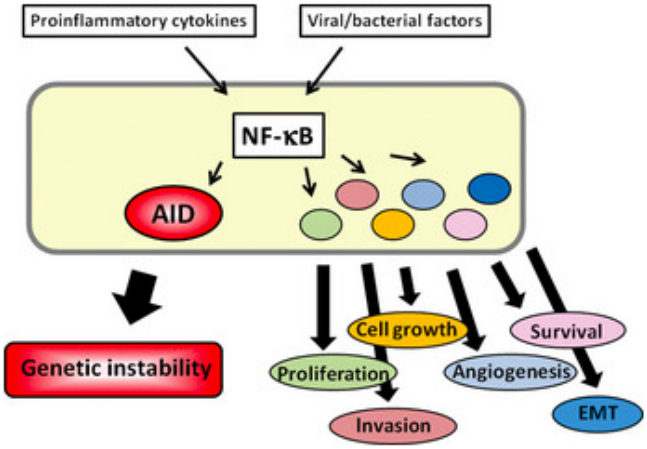
2. Attack and monitor systemic networks that promote malignancy.

Many systemic network changes promote and maintain the primary cancer and produce new malignancies (**Curing Cancer Blog-Part 6**). Curative therapy requires that we attempt to "normalize" or at least block the most harmful aspects of these network changes and that we monitor their status as treatment is given. This monitoring should supplement existing radiologic and clinical studies that determine the size and extent of the known tumor. For each network, we must determine what biological molecules to monitor, how best to do so

and how changes in their values should affect treatment. It may be useful to develop a cancer network score analogous to the TNM staging score for tumors that predicts prognosis and suggests future treatments.

These changes to systemic networks appear to be most important:

2a. Attack the inflammatory process, which has a central role in promoting and sustaining carcinogenesis. Physiologic inflammation activates quiescent networks to initiate sophisticated repair, antimicrobial and antitumor processes and then shuts down, because this activation also triggers pathways promoting its resolution (**Serhan 2005**). However, cancer risk factors trigger inflammation through nonconventional means that do not initiate the resolution process (**Fishbein 2020**). This causes chronic (persistent) inflammation, which may wear down stabilizing factors in inflammatory and adjacent networks, particularly when accompanied by other risk factors, which further drives the malignant process (**Shimizu 2012**, **Morgillo 2018**, **Huang 2009**).



The link between inflammation and carcinogenesis

Chronic inflammation must be treated directly – it has previously been proposed to be one of 5 "super promoters" of cancer (**Curing Cancer Blog-Part 7**).

Possible treatment options for chronic inflammation include: (a) triggering pro-resolution pathways (**Fishbein 2020, Park 2020**); (b) administering anti-inflammatory agents (**Zappavigna 2020**); (c) using agents that mimic physiologic halting mechanisms associated with wound healing (**Shah 2018**) and liver regeneration (**Abu Rmilah 2019**); and (d) countering germline (inherited genetic) changes that promote additional instability in the inflammatory process.

2b. Disrupt the microenvironment that nurtures tumor cells at primary and metastatic sites. Chronic inflammation and cancer risk factors produce a microenvironment that nurtures mutated cells, steers cellular networks towards malignant pathways **(Mbeunkui 2009**), helps them escape immune system surveillance (**Labani-Motlagh 2020**) and activates cancer cells to mimic physiologic "invasion" of wounded epithelium through the extracellular matrix (which provides structural support for cells and a proper microenvironment for optimal function) (**Bleaken 2016**). Tumors require a fertile "soil" for the cancer "seeds" to grow (**Fidler 2003**) and co-opt physiologic control mechanisms (**Coussens 2002**). In the correct microenvironment, tumor cells themselves may produce cytokines (small biologically active proteins) that promote their own survival (**Wang 2019**, **Das 2020**).

Targeting aspects of the inflammatory microenvironment that are active in particular tumors and that provide supportive blood vessels (**Gkretsi 2015**), stroma and extracellular matrix (**Mpekris 2020**) is important. Targeting the microenvironment may also enhance drug delivery and effectiveness (**Polydorou 2017**) and make existing tumors or premalignant states more susceptible to immune system attack (**Mpekris 2020**). It is also important to disrupt the microenvironment of possible metastatic sites. Typically, tumor cells die at secondary sites but the malignant process preconditions this otherwise hostile microenvironment to make it conducive to the growth of disseminated cancer cells (**Houg 2018**, **Kaplan 2005**, **Li 2020**).

2c. Disrupt the microenvironment that promotes embryonic features associated with aggressive tumor behavior. Embryonic cells resemble cancer cells due to their rapid proliferation, tissue invasion and long distance migration (**López-Lázaro 2018**). In the microenvironment of the fertilized egg, coordinated network activity ultimately moves embryonic related networks towards mature, differentiated phenotypes in the newborn. Cancer risk factors also activate these networks to similarly trigger rapid cell division (**Kermi 2017**), cell migration (**Reig 2014**, **Kurosaka 2008**) and changes to cell differentiation (**Li 2014**) but in a destructive manner. Since these risk factors act in a noncoordinated manner, these networks persist in an activated state and do not mature over time. Curative treatment should include agents that promote this maturation, such as retinoids used in acute promyelocytic leukemia (**Madan 2020**), myeloid differentiation promoting cytokines (**McClellan 2015**), other cancer cell reprogramming drugs (**Gao 2019**, **Gong 2019**) or possibly agents that halt rapid cell division in embryogenesis (**Kermi 2017**).

2d. Correct immune system dysfunction that coevolves with carcinogenesis. The immune system consists of a sophisticated web of interacting networks, including the innate immune system (nonspecific defense mechanisms, including macrophages, neutrophils, dendritic cells, natural killer cells, mast cells, eosinophils and basophils), the adaptive immune system (antigen specific immune response involving lymphocytes and antibodies), extracellular matrix, stromal fibroblasts and regulatory molecules. Since malignant

progression systemically degrades the performance of many of these components (**Karamitopoulou 2020**), combinatorial therapy is needed to target multiple aspects of immune dysfunction (**Sodergren 2020**) instead of focusing on just one pathway (**Li 2019**).

2e. Activate gene networks supporting stable, multicellular processes and suppress networks supporting malignant-like unicellular processes. Multicellular organisms evolved from unicellular organisms by adding new genes and more intricate controls to existing networks supporting cell metabolism and replication (**Trigos 2018**, **Trigos 2019**). This enabled greater communication and coordination between cells and made possible higher level functions, such as cell differentiation and programmed cell death (**Trigos 2018**). The new multicellular control mechanisms keep cellular and systemic processes on track and shift the survival focus away from individual cells towards the organism as a whole (**Davies 2011**). Inflammation and DNA alterations damage multicellular controls, activating an existing genetic toolkit of preprogrammed, malignant behavior in unicellular networks based on what has been described as the atavism hypothesis of cancer (**Davies 2011**, **Trigos 2017**, **Bussey 2017**).

Curative treatment should activate multicellular networks and suppress unicellular networks (**Gaponova 2020**, **Hay 1995**). Innovative treatments could also target cancer cell weaknesses by applying a specific cellular stress that is readily dealt with by healthy cells using multicellular programming but not by cancer cells with predominantly unicellular programming (**Lineweaver 2014**). This includes "lethal challenges" of high dose methotrexate with leucovorin rescue (**Howard 2016)** or targeting other aspects of chaotic or unstable states, such as cell-extracellular matrix detachment (**Crawford 2017**).

2f. Antagonize hormones that may promote tumor growth. Physiologic (i.e. normal) levels of estrogens and androgens and elevated levels of insulin are associated with cancers of the breast **(Dall 2017**), endometrium / uterus **(Rodriguez 2019)**, prostate (**Liu 2020**) and pancreas (**Li 2019, Perry 2020**). The primary mechanism may involve promotion of cell growth, particularly during stages in life when these cells are particularly vulnerable to instability.

Simple antagonism of hormonal pathways is possible using tamoxifen for estrogens, antiandrogens for testosterone and metformin for insulin (**Wan 2018)**. One block in these pathways may be adequate for normalization, in contrast to the 3-5 blocks required for other tumor cell networks. Behavioral changes such as weight loss, exercise, a healthier diet and reducing alcohol and tobacco use may also be therapeutic by either altering hormone levels or changing their interaction with other risk factors.

2g. Target germline changes that promote malignant behavior. Genetic testing of nontumor cells (germline testing) is recommended for all patients with pancreatic cancer (**Stoffel 2019**) and select patients with other cancers or family histories of cancer (**Daly 2020**, **Lincoln 2020**). Results are currently used to determine antitumor therapy (**Zhu 2020**) as well as for cancer screenings, reproductive choices and genetic counseling. These

results should also be used to provide treatment that: (a) moves premalignant or malignant cells into less harmful pathways, as discussed above or (b) counters common germline changes that promote malignancy in inflammatory, DNA repair, cell cycle stability, immune system or other networks.

3. Strengthen public health and preventative programs. A curative treatment strategy includes establishing strong public health programs that promote cancer risk reduction, establish effective screening programs and ensure that all patients get adequate medical care.

3a. Public health programs should reduce personal behavior that promotes malignancy. Public health agencies should create professionally crafted messages that promote a culture of being healthy so that everyone is encouraged to make their own health a priority. This includes encouraging behavioral changes, such as reducing smoking, excess weight and alcohol abuse and encouraging a healthy diet, exercise and vaccinations (**European Code Against Cancer**, accessed 16Feb21). At a societal level, our public health and medical care systems act as a behavioral immune system (**Schaller 2015**) to reduce cancer risk factors. Our physiologic immune system prevents numerous cancers from being clinically evident, as demonstrated by the high cancer rate in immunosuppressed patients due to drugs, diseases (HIV) or genetic disorders. Similarly, a well run public health system that promotes risk factor reduction will prevent many cancers from arising.

3b. More effective screening programs are needed to identify premalignant or malignant lesions in both high risk patients and current cancer patients being monitored for relapse. Testing for the presence of chronic inflammation may also be useful, but we must determine what specifically to test for.

3c. Government policy should ensure that all patients have easy access to optimal medical care. At an individual level, optimal medical care promotes the reduction of behavioral risk factors, earlier detection of disease and increased use of effective treatments not available to those with inadequate care, poor performance status or severe comorbidities (**Kelly 2016**). Promoting overall societal health also changes the nature of malignancies that remain and makes it easier to focus on their effective treatment.

4. The next steps to promote this strategic plan include:

(a) Public dissemination of this strategic plan with requests for feedback and collaboration from:

* Medical institutions (medical schools and medical centers, physicians, scientists and researchers)

* Health advocacy organizations (American Cancer Society, American Lung Association, American Medical Association, AARP)

* Elected officials and public health agencies at the city, county, state and federal levels.

(b) Continued analysis of the leading causes of cancer death to determine additional treatment principles or network targets;

(c) Direct funding of research programs to test the principles outlined above.

Please email **NatPernick@gmail.com** to collaborate or for further information.