Curing Cancer – Part 4 – Principles of curative treatment

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This is my fourth essay about curing cancer based on complexity theory – follow my blog at **https://natpernickshealthblog.wordpress.com**. In part 3, I summarized my recommendations on curative treatment for advanced adult cancers with a poor prognosis, such as lung and pancreatic cancer. In this essay, I discuss the principles of curative treatment in greater depth.

I. Network medicine. Adult cancer is a systemic disease. It arises and is maintained due to dysfunctional cellular networks, not just mutated genes in a simple pathway. A network is defined as a complex set of interactions or relationships between different entities. By contrast, a simple pathway is a linear process with changes that occur one step at a time, such as an automobile assembly line. Scientists often think about biological pathways as a circular assembly line with small changes at each step until the pathway's function is completed, such as activating an enzyme; then the pathway begins again. Complex biological pathways, such as those related to cell division, interact with each other at many steps, resembling sets of intersecting circles forming a network web of pathways that, when viewed as a whole, may perform a higher level function. The concept of "network medicine" emphasizes this point of view (**Barabási 2011**, **Parini 2020**).

Adult tumors may begin with local changes but large tumors are sustained by years or decades of supportive network changes throughout the body, called an altered systems biology **(Koutsogiannouli 2013**). Even if the tumor is destroyed by surgery, radiation or otherwise, networks outside the tumor typically will not revert to normal and may create new tumors.

II. Blocking multiple pathways. Disabling the activity of some dysfunctional networks requires combinations of treatments to block multiple pathways because these networks interact in a weblike manner and can readily bypass a single block in a particular pathway. The most consistent property of cancer cells is uncontrolled cell division, the target of most anticancer drugs. In the 1940s, Dr. Sidney Farber, a Harvard pathologist, gave his childhood leukemia patients a new drug, aminopterin, which blocked the effect of folic acid, which is needed for cells to divide (**Dana-Farber Cancer Institute**, accessed 2Jan21). Amazingly, these children, who usually died within weeks of diagnosis, went into remission. But their cancer soon relapsed, most likely because tumor cells bypassed this block through the web of reactions relating to cell division. We now know that it may take 3-5 drugs with different mechanisms of action to create enough blocks to completely disable these specific tumor networks **(Mukherjee: The Emperor of All Maladies 2010**).

III. Combinations of combinations of treatment. Adult tumors are due to network dysfunction in the local tumor as well as in many key systemic networks affecting the tumor, including inflammation and the immune system and may be promoted by hormones such as estrogen, testosterone or insulin. Normalizing or antagonizing each network may require a distinct treatment or combinations of treatments. Thus, curative therapy that affects all of these networks supporting the tumor may require combinations of combinations of treatment. This is more complicated than for childhood tumors, which are typically caused by inherited mutations **(Kentsis 2020**) and lack key systemic network changes.

IV. Monitoring key networks. It may be important to target these key networks which nurture and maintain the tumor and to monitor their status as treatment is given: the inflammatory process in general, the immune system's antitumor capabilities, the microenvironment of the tumor and metastatic sites, unicellular type networks that promote malignant properties, embryonic networks that promote lack of cell differentiation and rapid growth, hormones that promotes tumor growth and germline (inherited) changes that promote malignant behavior directly or indirectly by affecting other networks. These key networks will be discussed in more depth in future essays. This monitoring, analogous to therapeutic drug monitoring of antibiotics and other antimicrobials for infectious diseases, 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.

V. Clinical trials. Extensive clinical trials will be needed to determine the effectiveness of individual treatments, combinations of treatments and combinations of combinations of treatments affecting these key networks. Additional studies will determine how to reduce side effects and what adjustments to make for particular patients. Towards this end, every cancer patient should be enrolled in a clinical trial.

VI. Strong public health programs. A curative treatment strategy includes strong public health programs to promote cancer risk reduction, effective screening programs and ensuring that all patients get adequate medical care. Risk factor reduction includes behavioral changes such as reducing smoking, excess weight and alcohol abuse and encouraging a healthy diet and exercise (**European Code Against Cancer**, accessed 2Jan21). 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 and early detection prevents many cancers from arising. We should also develop more effective programs for identifying premalignant or malignant lesions in both high risk patients and current patients being monitored for relapse. 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, Maclay 2017**).

The next essay will discuss the key treatment issues affected by these principles in more detail.