James Watson, co-discoverer of DNA’s double-helix structure recently called for a back to basics approach in dealing with cancer. In previous post threads I’ve discussed cancer’s complexity and in particular the confounding and scary implications of somatic evolution, which underscores some of the reasons we are not winning the “war on cancer.” Here I will discuss some cutting edge approaches to treating and preventing cancer and how they might pan out in light of the complexities of the disease. The categories below are not mutually exclusive, and the examples cited are nowhere near exhaustive, but this should give you some food for thought. If you have ideas, questions or know of approaches that should be highlighted, please comment.

Target&Kill Approaches

Biris and Zharov are making some exciting progress in using nanotubes to tag and then track cancer cells inside the body as they move around. They propose to kill the cancer cells by heating up the nanotubes using lasers, while others are using nanomagnets and still others siRNA. Glazier is in agreement with the target and kill approach and outlines a number of such methods in his book, Cure, in which he also argues forcefully for the importance of taking somatic evolution seriously in our approaches to treating cancer.

One potential problem with target and kill, as Glazier points out, is that if you don’t get all cancer cells, you run a high risk of recurrence. Which belies an even bigger problem: how do
you detect which cells are cancerous and which are not? Glazier calls for behavioral pattern recognition, i.e. looking for cells that are proliferating and also exhibiting invasive behavior at the same time. But it remains to be seen whether such pattern recognition is possible in practice. A possible way to keep tabs on cell behavior is to do continuous in situ monitoring or ultrasonic nanotech.

Enhance Immune Response

The immune system is really good at identifying and killing cells behaving badly (although the majority of the time the immune system’s targets are foreign invaders like viruses). But what if we could boost the immune system so that it was better able to deal with cancer cells? Essentially create a vaccine for cancer.

The difficulty with immunotherapies for cancer has always been that it’s not in the “charter” of the immune system to fight the body’s own cells; when it does we can get what are know as autoimmune diseases.

Reiter, et al are working on a clever hack of the a class of immune cells called tumor-infiltrating lymphocytes (TILs) wherein they extract TILs from a tumor, enhance their tumor-fighting potential and reinject the enhanced TILs back into the tumor.

The achilles heel of immune enhancement will always be comprehensiveness. That is, if you don’t get everything, cancer can eventually evolves resistance by becoming too hard for the immune system to detect or by learning how to fight off the immune response. And if you get overly aggressive, you risk harming the patient in other ways. And cancer has proven to be extremely tricky in outwitting the immune system.

Genetic Modification Approaches

Modifying genes, either by enhancing tumor suppressors or reducing tumor promotors, has been a popular appoach in recent years. Often the approach has been to focus on individually important genes or to try to find exhaustive sets of genes which, when modified appropriatly, stop cancer progression.
One problem is that genetic information is not organized into atomic functions or even sets of functions, but rather in complex, multi-scale functional networks with built-in redundancy. In such networks, you can modify, add or delete many nodes and links without changing the overall network behavior significantly. Still, recent advances do show promise, as with microRNA replacement.

Another confounding factor is genetic modification is that the genetic code seems to be organized a bit like a toolbox of mix-and-match parts that get shuffled around by evolution. Thus if a trait or function is adaptive, it might emerge by more than one evolutionary path using different arrangements of genetic code and entirely different mechanisms (this is known as convergent evolution). Theoretically the malignant behaviors that characterize cancer — unregulated proliferation and invasiveness — could re-evolve, just as happens in organismal evolution; after all, to the cancer cells malignant behaviors are are adaptive, it’s just us multacellular beings that view the behavior as bad. What I mean by this is the following; vision has been achieved a number of different ways by organismal evolution with the genetic toolbox, so what’s to stop somatic evolution from achieving proliferation and invasiveness in different ways than is normally seen in human physiology?

Viewing the problem from a slightly different angle still, consider the following. Cancer itself works by making massive numbers of changes to individual cells’ genetic networks. This source of heterogeneity is what provides the grist for the evolutionary mill. The vast majority of these mutations don’t work out and the cells die off or — more problematically — the mutations remain dormant in successive generations of the cell line. But every once in a while you end up with a rearrangement of the network that is viable and which creates cells who don’t “play nice” with their neighbors (i.e. cancer). Thus, if you have created a therapy targeted to a particular gene, there’s a good chance it won’t work anymore because the gene now sits in a different functional context; the original function you were targeting may now be served via different mechanisms.

A more harmonious variant of genetic modification is to replace entire cells with stem cells and allow them to differentiate into the appropriate cell type, effectively cleansing the genome. This type of work is being done but is very preliminary and the stems cells themselves are
prone to becoming cancerous, presumably due to their pluripotency and robust replicative potential. Still, this line of inquiry seems promising to me, because it honors the body’s own developmental programming to replace badly acting cells with good ones, instead of just, say, killing bad cells and leaving a physical (and behavioral/ecological) void for surrounding cancer cells to exploit. While currently solid tissue cell replacement requires surgery, down the road we can expect a veritable Cambrian explosion of nanobots that will be able to precisely navigate to targeted areas and do the work of cell replacement and genetic modification.

Prophylactic / Preventative Approaches

Aubrey de Grey works on the radical extension of the human lifespan and believes that there’s no theoretical limit to how long we can live if we hack our biological inheritance appropriately (BTW, many others agree, including Ray Kurzweil). Organ replacement and regrowing failed body parts is a forgone conclusion (it’s happening already), and de Grey says that the only disease that presents a problem long-term is cancer, due to the relentlessness and “cleverness” of somatic evolution. De Grey proposes therefore that the only real approach is one of indefinite prophylaxis, i.e. take specific steps to intervene on a regular basis so that somatic evolution stays in check and we don’t get the unregulated proliferation and invasiveness that is cancer. His WILT approach argues we achieve this by regulating the length of telomeres which are critical to the proliferation process.

Carlo Maley says that the WILT approach should work, but the technology is a far way off and it’s hard work to go this route. Maley believes that we may be closer on the prophylactic front with by boosting cancer-suppression genes, as in the super p53 approach. But recent research suggests this approach is problematic too.

Last year I started asking cancer researchers the following question: if we were somehow magically able to replace the DNA in every cell in your body with a clean copy at regular intervals, would that prevent cancer entirely? While most who answered thought that in theory this would work, some startling research recently has me wondering whether it would. The discovery of non-genetic forms of persistent heterogeneity (Brock, et al, Spencer et al, and Sigal et al), combined with the logic of somatic evolution and the genetic toolbox, leads me to be fearful that unregulated proliferation and invasiveness might re-emerge without genetic
(or genomic) heterogeneity. Even if non-genetic heterogeneity is not broad enough to provide an “escape hatch” from full DNA replacement, it might be broad enough to thwart a WILT or super p53 approach.

Other preventative approaches focus on detecting pre-cancerous cells — ones that are most likely to turn malignant at some point — and removing them either surgically or with more advanced technology like radio waves.

**Hijacking Microorganisms**

Then there’s the approach of co-opting existing viruses and bacteria (also here, here, and here) since these microorganisms have exquisitely evolved to be effective at targeting and dismantling individual cells and cell types in multicellular organisms like humans. There are several issues with this approach though. First is that in order to “repurpose” these critters to do our therapeutic bidding, we have to simultaneously help them outsmart our immune system while making sure they don’t harm normal cells; not such an easy task. Second, there is a danger in messing with viruses and bacteria in that these are populations with the potential to evolve (despite whatever measures are taken to avoid this) and as such could get out of control. Third, there are always unintended and unpredictable consequences when injecting a body with foreign substances, especially ones that are alive….

**Fighting Evolution with Evolution**

There are a number of ways to approach fighting cancer “with” evolution, one of which was mentioned already (the TIL approach). Another is to use evolution as a mad tinkerer/designer to create sophisticated biological agents that empirically do the job well.

Maley and Pepper are looking at changing the microenvironment to shape somatic evolution so that there is less selective pressure for cells to compete with one another. David Basanta and his colleagues at the Moffitt Research Center modeling various aspects of evolution in the hopes to be able to one day shape it’s direction.

David Rasnick suggests that if we are to really take somatic evolution seriously we need to recognize that normal human cells are vastly more robust than cancer cells and that most
cancer cells die off with the smallest perturbation to their environment. The problem is that they mutate and adapt very quickly. Rasnick’s “perturbation theory” says we should look to induce stresses into the body that normal cells are equipped well to deal with and on a relative basis, cancer cells are not. While one could think of chemo and radiation in this regard there are two problems: (1) they can damage DNA making the heterogeneity worse; (2) normal cells are not equipped to deal with these perturbations either. Examples of perturbations normal cells are equipped to deal with include radical changes in various lifestyle dimensions (extreme exercise, extreme diet changes) or inducing natural stress reactions. Rasnick notes that many cases of “spontaneous remission” occurred after prolonged periods of extremely high fever. One thing that’s for sure, as technology advances we will have more and more ways to cleverly perturb cells.

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