

Near-Universal Cure For Malignant Tumors

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17 December 2007

EXECUTIVE SUMMARY

A. Acidic Areas In Tumors

In 1930 Otto Warburg reported that one of the most universal properties of malignant tumors is their acidic areas. Subsequent research has shown that such areas arise because for a tumor to grow larger than 1 millimeter in diameter it must induce new blood vessels. Such tumor-induced blood vessels are poorly spaced and abnormal. As a result, areas of tumors more than a few tens of microns from tumor capillaries become hypoxic. Cells in such hypoxic areas either die or switch to glycolytic metabolism - resulting in their excreting lactic acid. Because of the poor circulation in a tumor that excreted lactic acid builds up in the interstitial space surrounding cells in the hypoxic areas. This results in an acidic pH as low as 6.0 in areas distant from capillaries, up to pH 7.0 close to capillaries. For comparison, the pH in the interstitial space in normal tissues is tightly regulated between pH 7.3 and 7.5.

B. Role of Hypoxic/Acidic Areas In Post-Treatment Relapses

Tumor cells at near-normal pH close to capillaries, which are well-oxygenated and fast dividing, are readily killed by conventional cancer therapies. In contrast, tumor cells in hypoxic/acidic areas distant from capillaries divide slowly or not at all and these quiescent tumor cells are appreciably more resistant to killing by conventional cancer therapies. Therefore, cancer treatments predominantly kill the well-oxygenated fast-dividing tumor cells while sparing the more treatment-resistant quiescent cells in hypoxic/acidic areas of that tumor. This killing of the fast-dividing cells causes the tumor to go into remission while the killed cells are disposed of by the body's cleanup processes. However, during this post-treatment cleanup process all too often surviving treatment-resistant quiescent cells in acidic areas of the tumor slowly regain access to adequate oxygen, nutrients, and waste disposal - eventually allowing them to revert to rapid cell division, with attendant tissue invasion, metastatic spread, and often enhanced resistance to subsequent cancer therapies. A common result of this rejuvenation of the previously-quiescent tumor cells is the post-treatment relapse that causes most deaths from cancer.

C. Onco-Tool Therapeutics Target Acidic Areas

Onco-tool therapeutics are designed to target essentially all types of tumors by virtue of being sequestered in the acidic areas present in nearly all malignant tumors. This selective sequestering occurs as follows. In normal tissues (pH 7.4) onco-tools exist almost completely in their negatively-charged hydrophilic form which is repelled from the negatively-charged surfaces of cells. However, when onco-tools perfuse into an acidic area of a tumor a portion of the onco-tool molecules undergo an acid-induced switch to their non-ionic lipophilic cell-penetrating form which then enters nearby tumor

cells. Once they pass into the neutral cytosol of a tumor cell they are re-ionized, which inhibits their exit from that tumor cell. Because of their high water solubility and repulsion from cells at the pH in normal tissues, any onco-tools not sequestered in tumors will be rapidly excreted from the body by the kidneys. Prior to use, alpha-emitting and beta-emitting radiohalogens are attached to the onco-tool therapeutics. The emitted alpha particles serve to destroy the treatment-resistant quiescent cells in hypoxic/acidic areas, while the emitted beta particles serve, via a crossfire effect, to destroy the better-oxygenated fast-dividing cells closer to tumor capillaries. Together they completely destroy the entire tumor in which the onco-tool therapeutics are sequestered - thereby preventing the relapses that commonly occur after current cancer treatments.

D. Design Strategy For Unprecedented Specificity For Acidic Areas

Onco-tool therapeutics are specially designed to achieve a specificity for tumors which is many fold greater than afforded by current tumor therapies. This unprecedented specificity is a consequence of a novel multi-acid molecular design which incorporates unique internal acid-specific hydrogen bonding structures and carefully adjusted lipophilicities. The design strategy and structural requirements which underlie this dramatically increased specificity for acidic areas are detailed in Sections D and E of www.onco-tools.com/therapeutics_detailed_description.

Special methods of using onco-tools also provide further large increases in efficacy and specificity. These methods are detailed in Section F of www.onco-tools.com/therapeutics_detailed_description.

E. Onco-Tool Structure

Onco-tool therapeutics are small non-peptide synthetic molecules with molecular weights in the range of 300 to 1000 daltons - not counting the radioisotope. Each onco-tool contains two or more pH-switch components which include a weak-acid moiety that readily converts between an anionic hydrophilic form at a higher pH and a non-ionic membrane-penetrating form at a lower pH. Each onco-tool also contains a cargo component which is effective to bind a radiohalogen, or which contains a radiohalogen. These structural components give the onco-tool therapeutic the special properties of: a) being repelled from cells in normal tissues; b) being sequestered in acidic areas of tumors; c) any onco-tool not sequestered in an acidic area is designed to be cleared from the body by the kidneys; and, d) onco-tool therapeutics sequestered within acidic areas of a tumor are designed to destroy the entire tumor by a combination of alpha and beta emissions. The structure of a representative onco-tool therapeutic is shown in Section E.5. of www.onco-tools.com/therapeutics_detailed_description.

F. Target only acidic areas in tumors

In addition to acidic areas in tumors, a number of non-tumor pathological conditions also cause acidity in interstitial spaces. Acid-causing conditions include ischemic stroke, atherosclerotic plaques, and areas of localized inflammation, such as arthritis. This can present a possible problem in the context of curing a patient's malignant tumor(s) using onco-tool therapeutics. The problem arises if a cancer patient is also suffering from additional pathological conditions which generate non-tumor acidic areas.

For instance, the cancer patient might also have an atherosclerotic plaque in an artery as well as several arthritic joints. If those non-tumor pathological conditions have areas of sufficient acidity then the onco-tool therapeutic being used to cure the tumor would be expected to also damage the artery at the site of the atherosclerotic plaque and damage the cartilage-producing cells in acidic areas of the arthritic joints.

To avoid damage to such non-tumor acidic areas selected interventions will be carried out in conjunction with the onco-tool therapeutic treatment needed to cure the patient's malignant tumors. Specifically, certain interventions appear to affect the pH in tumor acidic areas quite differently than they affect the pH in non-tumor acidic areas, and it is expected that these differential effects on the two types of acidic areas (tumor versus non-tumor) can be successfully exploited for the patient's benefit.

For example, it has been noted that acidity associated with inflammation is due to carbonic acid and it has been demonstrated that treatment with the carbonic anhydrase inhibitor Acetazolamide substantially increases the tissue pH at sites of inflammation (Radhakrishnan & Sluke (2005) J. Pharm. & Expt. Therapies 313 921). In contrast, the acidity in hypoxic areas of tumors is due to lactic acid excreted from tumor cells utilizing glycolytic metabolism and so it is expected that a carbonic anhydrase inhibitor will not generate a corresponding increase in pH in acidic areas of tumors. Thus, treatment of the patient with both the onco-tool therapeutic and with a carbonic anhydrase inhibitor should raise the pH in areas which are acidic due to inflammation (ie., non-tumor acidic area) and so preclude sequestering of onco-tools in those non-tumor areas. Conversely, that same treatment with a carbonic anhydrase inhibitor should not affect the pH in tumors and so the onco-tool therapeutic should carry out its intended destruction of the patient's malignant tumors.

Additional interventions which are expected to lower the pH in tumors and/or raise the pH in non-tumor acidic areas are described in Section F.9. of www.onco-tools.com/therapeutics_detailed_description.

G. Summary

Because onco-tool therapeutics are designed to be effective against all tumor types, because they are designed to be highly effective against both the treatment-resistant quiescent cells in hypoxic/acidic areas and the treatment-sensitive fast-dividing cells in better oxygenated areas of tumors, and because they are uniquely designed for unprecedented specificity for acidic areas, onco-tool therapeutics hold the promise of effective cures for most or all malignant tumors, without the post-treatment relapses that commonly occur after current cancer treatments.

[The first onco-tool will be available as a research reagent in 2008.]

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