

# Near-Universal Diagnostic For Malignant Tumors

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## 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 about 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. Onco-Tool Diagnostics Are Designed To Detect Acidic Areas

Onco-tool diagnostics are designed to detect essentially all types of tumors by virtue of their exploiting the near-universal acidic areas in tumors. Onco-tools achieve this detection 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 and this inhibits their exit from that tumor cell. By this means the onco-tools are selectively sequestered in tumors. 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, a gamma-emitting and/or positron-emitting radiohalogen (such as Iodine-124) is attached to the onco-tool diagnostic. After injection of the onco-tool into the subject and waiting for one to a few hours, a gamma ray scan, SPECT scan, or PET scan will then show the position of any tumors in which the onco-tool diagnostic is sequestered.

### C. Design Strategy For Unprecedented Specificity For Acidic Areas

In addition to their ability to detect virtually all tumor types, another advantage of onco-tool diagnostics is they are designed to achieve a specificity for tumors which is many fold greater than afforded by currently available tumor diagnostics. 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 in order to achieve dramatically increased specificity for acidic areas. The underlying design strategy and structural requirements are detailed in Sections C and D of [www.onco-tools.com/diagnostic\\_detailed\\_description](http://www.onco-tools.com/diagnostic_detailed_description)

#### D. Methods For Increasing Specificity And Sensitivity

In addition to an ability to detect most or all tumor types by virtue of targeting the near-universal acidic areas of malignant tumors, and an unprecedented specificity for such acidic areas due to onco-tools' unique molecular design, special methods of using onco-tools can provide further large increases in specificity, as well as providing very high sensitivity. Together these should allow detection of even very small tumors which are still at a stage where treatment can be most successful. These methods of use are detailed in Section E of [www.onco-tools.com/diagnostic\\_detailed\\_description](http://www.onco-tools.com/diagnostic_detailed_description)

#### E. Overview Of Onco-Tool Diagnostics

An onco-tool diagnostic consists of a small non-peptide synthetic molecule with a molecular weight in the range of about 300 to 800 daltons - not counting the radioisotope. An onco-tool contains two or more pH-switch components, each of which includes 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. The structure of a representative onco-tool diagnostic is shown in Section D.4. of [www.onco-tools.com/diagnostic\\_detailed\\_description](http://www.onco-tools.com/diagnostic_detailed_description)

When onco-tools are injected into a subject, if that subject has a malignant tumor larger than about 1 millimeter in diameter (tumors begin to form hypoxic/acidic areas when less than 1 mm in diameter), a portion of the dose will become sequestered within cells in acidic regions of the tumor, with the remainder of the dose being excreted by the kidneys. Thus, onco-tool diagnostics are designed to: a) be repelled from cells in normal tissues; b) be 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 sequestered within a tumor will report the position of that tumor to a suitable scanner.

#### F. A Complication

While an onco-tool diagnostic is expected to detect most or all malignant tumors larger than microscopic size, there remains one serious complication - a number of other pathological conditions have been reported to also generate acidity in interstitial spaces. Such conditions include ischemic stroke, atherosclerotic plaques, and sites of localized inflammation such as arthritis. Thus, the onco-tool diagnostic has the potential to also detect acidic sites which are due to non-tumor pathological conditions.

While a capability for very sensitive detection of non-tumor pathological conditions may have considerable medical value, nonetheless, in the context of a desired near-universal diagnostic for malignant tumors such detection of non-tumor sources of acidity presents a problem, that being if the detected acidic area is in a tumor then an anti-tumor treatment is called for. However, if the detected acidic area is due to some

non-tumor pathological condition, such as an atherosclerotic plaque in an artery or such as an arthritic joint, then instituting an anti-tumor treatment could be damaging or disastrous to the patient. Thus it appears that in order for an onco-tool diagnostic to live up to its full potential as a near-universal tumor diagnostic it will be necessary to devise a means to distinguish between tumor and non-tumor acidic areas.

To this end, simple interventions carried out in conjunction with delivery of the onco-tool diagnostic are expected to adequately distinguish between tumor and non-tumor acidic areas. To illustrate, 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 appears to be due to lactic acid excreted from tumor cells utilizing glycolytic metabolism and so a carbonic anhydrase inhibitor will not cause an increase in pH in acidic areas of tumors.

Accordingly, if a routine onco-tool diagnostic procedure shows the onco-tool diagnostic to be sequestered at one or more sites in a subject (ie., hot spots in the diagnostic scan), the next step will be to do a subsequent diagnostic procedure wherein the subject is first treated with a carbonic anhydrase inhibitor and then the onco-tool diagnostic introduced. If the previously detected hot spots are greatly reduced or absent in this second test, it will indicate that the hot spots were due to some non-tumor pathological condition. Conversely, if the hot spots are of similar magnitude in both the first and second diagnostic tests this will indicate that they are indeed tumor acidic areas. Additional interventions which should also serve to distinguish between tumor and non-tumor acidic areas are described in Section E.6. of [www.onco-tools.com/diagnostic\\_detailed\\_description](http://www.onco-tools.com/diagnostic_detailed_description).

#### G. Summary

Because onco-tool diagnostics are designed to detect virtually all tumor types, because they are designed to achieve very high sensitivity, and because they are uniquely designed for unprecedented specificity for acidic areas, when onco-tool diagnostics are used in routine annual physical exams they are expected to reliably detect nearly all malignant tumors larger than microscopic size.

Prior efforts to exploit acidity in tumors are detailed in: [www.onco-tools.com/diagnostic\\_historical\\_background](http://www.onco-tools.com/diagnostic_historical_background).

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

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