Summary of Evolution and the Requirements for the Specific Cure of Cancer

The definition of cancer

Cancer is defined by malignant behavior, (e.g. cell proliferation and invasiveness in an abnormal context. Not all tumor cells are malignant (or cancer cells). [i] Many tumor cells are dead end, and cannot sustain the disease of cancer. Only malignant cells can sustain the disease of cancer.

The cure of cancer requires the destruction of all malignant cells

One malignant cell that evades therapy can after forty population doublings give rise to a population of one trillion cancer cells and cause fatal disease.

Cancer is an enormously diverse, stochastic, unpredictable, evolutionary process.

At the genetic and epi-genetic level every cancer cell can be unique. The potential genetic and epi-genetic diversity is for all practical purposes infinite.

Cancer is first and foremost about the growth of an evolutionary population of cancer cells

The importance of the words *evolutionary population* cannot be over-emphasized. There is a big difference between *a cancer cell* and an *evolutionary population* of cancer cells. The failure to recognize and fully accept this difference has caused the problem of cancer to be inadequately defined and has frustrated attempts to specifically cure or control cancer.

Tumor cell evolution limits what can be known about cancer in a patient

A patient can have billions of different cancer cells spread throughout his or her body. Bulk tumor and identifiable metastatic lesions can be experimentally characterized. However, we generally cannot identify all cancer cells that are present in a patient with metastatic disease and we cannot know what will evolve. There is no logically valid way to generalize from observed cancer cells to all cancer cells present in the patient, nor is it possible to formulate a scientific theory that can predict the unpredictable.

The required target for the cure of cancer is the set of all malignant cells that could realistically evolve in the patient

Therapy that targets a lesser set cannot consistently cure or control cancer. It should be noted that the set of all malignant cells that could realistically evolve in the patient is abstract, has no real world existence, and cannot be characterized by observation. However, critical properties of the set can be known by means of a well-corroborated scientific theory that resists empirical falsification. [ii]

Only known or knowable properties can be targeted

Very little can be known that about properties that characterize the set of all malignant cells that could evolve. What little can be known sharply defines requirements for the consistent and specific cure of cancer.

The essential targets of curative cancer therapy must be knowable properties of the set of all malignant cells that could realistically evolve

This follows as a matter of deductive logic.

Tumor cell evolution implies that cancer is not about any particular:

- Tumor cell type
- Antigen
- Genetic alteration
- Epi-genetic alteration
- Oncogene
- Metabolic abnormality
- Mechanism of tumor vascularization [iii]
- Mechanism of malignancy
- Pathway of tumor cell evolution

Such properties can provide a basis for tumor-specific targeting but cannot provide a basis for the comprehensive detection and destruction of the set of all malignant cells that could realistically evolve. There is a clinically significant and realistic probability that any particular genetically encoded molecular target will be lost or modified by mutation during tumor cell evolution. According such properties are generally irrelevant to the consistent and specific cure or control of cancer. [iv]

Malignant behavior is one property that is characteristic of the set of all malignant cells that could realistically evolve

This is by true by definition.

All malignant cells that could realistically evolve will use normal cellular machinery to carry out malignant behavior, proliferation and invasiveness in an abnormal context

- Cancer cells that violate this rule have never been observed. On statistical grounds we can be confident that they will not evolve.
- Proliferation and invasiveness are highly complex normal cellular activities.
- Darwin's Theory of Evolution implies that there is not time for extensive, new, functional cellular machinery to evolve during the short life span of a patient.
- It took hundreds of millions for years for the machinery required for proliferation and invasiveness to evolve.

The normal cellular machinery that effects or reflects proliferation and invasiveness is finite, knowable and largely already known

This machinery is represented in the biochemistry of activities, such as DNA synthesis, cell division, tissue remodeling, wound healing, blood vessel formation, and trophoblast implantation during formation of the placenta, and fetal development.

The combination of proliferation and invasiveness can only be detected on the basis of a pattern of cellular machinery, furthermore, multiple such patterns exist

Proliferation and invasiveness involve a complex series of events involving many different types of normal cellular machinery. They are different processes and, are detectable on the basis of different cellular machinery. No single molecular entity is diagnostic for the combination of proliferation and invasiveness.

The combination of proliferation and invasiveness is highly restricted and not expressed in most normal tissues

It is in expressed in processes such as trophoblast implantation; fetal development; angiogenesis; mammary gland development; the menstrual cycle; ovulation; inflammatory processes such as abscess formation; and wound healing.

If we exclude these physiological invasive processes then in principle:

All malignant cells can be specifically detected on the basis of patterns of normal cellular machinery that effect or reflect the combination of proliferation and invasiveness.

As a practical matter, the avoidance of cancer therapy during pregnancy, major wound healing, and infections should generally not be overly problematic. (This restriction is not necessary but hugely simplifies drug design considerations.)

Cancer is essentially one disease

Although, every patient's cancer is different, and every cancer cell can be different, cancer is essentially one disease. The normal cellular machinery that potentially can carry out proliferation and invasiveness is the same for all malignant cells, for all types of solid cancers. This implies that the requirements for the specific cure or chronic control of all solid cancers are identical. It also means that one set of drugs could be developed that would be effective against all forms of solid cancers.. (i.e., breast, colon, prostate, lung, ovarian…)

Any genetically encoded protein or biomolecule can potentially be lost, or mutated during tumor cell evolution

This means that any given pattern of normal cellular machinery that effects or reflects malignant behavior can be lost by some malignant cells that could evolve. No single pattern of normal cellular machinery is characteristic of the set of all malignant cells that could realistically evolve.

Multiple patterns are required to be able to detect the set of all malignant cells that could evolve

A sufficient number of patterns must be targeted such that the probability of a malignant cell evolving without at least one pattern is clinically insignificant, (i.e., on the order of 10^{-15}

per cell division or lower. The role of the patterns is to enable the detection of any malignant cell. The destruction of any malignant cell is a separate issue.

Redundant mechanisms of cell killing must be employed to kill malignant cells

It is unknowable if a particular drug will kill a particular cancer cell. Resistance could develop to any given drug or virtually any particular mechanism of cell killing. However, it is possible to select a set of drugs for which the development of resistance is too improbable to be of clinical significance.

Summary of key requirements for the specific cure or control of cancer

The consistent and specific cure or control of metastatic cancer will require multiple drugs, administered in combination, targeted to abnormal patterns of normal cellular machinery that effect or reflect malignant behavior (i.e., proliferation and invasiveness).

A sufficient number of patterns must be targeted such that the probability of a malignant cell evolving without at least one pattern is clinically insignificant, (i.e., on the order of 10^{-15} per cell division or lower).

Redundant mechanisms of cell killing must be employed. In practical terms, we estimate that approximately 5 to 10 drugs, in combination, will be required. [v]

Pattern Recognition Tumor Targeting (PRTT)

The translation of the above requirements into the language of molecular biology, chemistry, and drugs is what we call PRTT. The concept of targeting patterns is simple. Targeting specificity is for a pattern, not the individual proteins (or biomolecules) that comprise the pattern. For example, a cytotoxic drug targeted to a pattern of two proteins would only kill cells that express both proteins. Cells that express only one of the proteins would be spared.

There is a requirement for some form of PRTT for the consistent and specific cure or chronic control of metastatic cancer.

A general unifying theory of cancer

There exists a set of patterns of normal cellular machinery such that:

- Each pattern effects or reflects the combination of proliferation and invasiveness; [vi]
- Each pattern is absent from normal tissues not engaged in these processes;
- All malignant cells that could realistically evolve will express at least one of the patterns [vii].

A rational approach to the development of a specific cure or control of cancer:

- Identify the smallest set of patterns for which the above theory resists falsification. [vii]
- Develop a set of drugs with PRTT capabilities to kill cells that express these patterns.

Footnotes

[i] The term malignant cell and cancer cell will be used interchangeably

[ii] The observation of a malignant cell that contradicted the theory would falsify it.

[iii] For example, angiogenesis, vasculogenic mimicry, blood vessel co-option

[iv] This will not be the case if the number of metastatic tumor cells present in the patient is so low that all the cancer cells express the particular property. However, this is not generally the case.

[v] The exact number needs to be determined empirically.

[vi] Or the potential for proliferation and invasiveness

[vii] The pattern can also be in the microenvironment of the malignant cell including stromal cells.

[vii] The smallest set is also the simplest set. It is probable that patterns will be comprised of 2 or 3 elements.