Editorial: Evolution and the Treatment of Cancer

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Evolution and the Treatment of Cancer

Introduction

Exponential progress over the last three decades in basic science has provided deep insights into the genetics, molecular biology and mechanisms of malignancy. The fundamental problem is tumor cell evolution.

Cancer is a hugely diverse, unpredictable, stochastic process\textsuperscript{1} that results from evolution inside the body.\textsuperscript{1,2,3,4,5,6,7} Patients with cancer routinely face the reality of rapid tumor cell evolution. Drug resistance develops and increasingly aggressive cancer cells emerge. Combination chemotherapy was developed to prevent drug resistance and has led to major cure rates for a number of cancers including leukemia, lymphoma, and testicular cancer.\textsuperscript{8,9,10,11} Increasing the number and dose of drugs can improve the response rate, the complete remission rate and the cure rate.\textsuperscript{12} However, toxicity has precluded the routine cure of most cancers. Approximately 570,000 Americans died of cancer in 2005.\textsuperscript{13}

This commentary examines requirements for the specific destruction of an evolutionary population of malignant cells, and proposes a major non-profit initiative to develop a set of drugs that satisfies these requirements.

Three basic requirements must be jointly satisfied for the consistent and specific cure (or control) of cancer:\textsuperscript{5}

- Comprehensiveness
- Specificity
- Knowability

Comprehensiveness refers to the need to destroy (or control) all malignant cells present in the patient.\textsuperscript{14} Comprehensiveness is essential because one malignant cell that evades therapy can potentially cause lethal disease.\textsuperscript{13,15} Specificity refers to the need to kill (or control) cancer cells without significant patient toxicity. Specificity is a measure of the ratio of tumor to host toxicity. Knowability refers to the need to target properties that can be known, or accurately predicted, within the context of the logically sound foundation of scientific knowledge.\textsuperscript{16}

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\textsuperscript{1} A random process in which probabilities depend on outcomes of prior random events
Much about cancer is unknowable.

A patient with metastatic cancer can have billions of cancer cells spread throughout the body. At the genetic and epi-genetic level, each cancer cell can be unique.\textsuperscript{17,18} We can empirically characterize bulk tumor and identifiable metastatic lesions. However, we rarely can identify all the cancer cells present. There is no logically sound way to generalize from the sub-set of observed cancer cells to the set of all cancer cells present.\textsuperscript{ii} Consequently, we generally do not know all that has evolved and cannot know what will evolve in a patient.

The required target

The conclusion is inescapable. The required target for the consistent and specific cure or control of cancer is the set of all malignant cells that could evolve. Targeting a lesser set will fail.

The set of all malignant cells that could evolve is abstract and cannot be directly observed.

Knowledge about the set of all malignant cells that could evolve in a patient must, like all scientific knowledge, be in the form of a well-corroborated scientific theory that is falsifiable, but resistant to the severest attempts at falsification.\textsuperscript{12,19} A malignant cell that contradicted the theory would prove it false. However, as demonstrated by Popper, no amount of evidence can prove a theory true.

The following theory is almost certainly true.

\textit{All malignant cells that could evolve will use normal cellular machinery to carry out the processes of proliferation and invasiveness.}\textsuperscript{iii}

An exception that falsifies the theory has never been observed. On statistical grounds we can be confident that an exception will not be observed. By definition, a malignant cell must at some point in time engage in malignant behavior, which is defined as proliferation and invasiveness in an abnormal context.\textsuperscript{iv} Invasiveness involves the expansion of cells into new space with the destruction of normal tissue architecture and the creation of infrastructure to support the metabolic needs of the cells. Proliferation and invasiveness are highly complex processes that evolved over eons. Darwin’s Theory of Evolution implies that there is not time for the evolution of extensive functional machinery.\textsuperscript{v}

\textsuperscript{ii} Any such generalization is based on the false logic of induction.

\textsuperscript{iii} This machinery includes that made by non-malignant cells in the cancer cell microenvironment that participates in invasive processes.

\textsuperscript{iv} Not all tumor cells are malignant.

\textsuperscript{v} A limited amount of new machinery can evolve (e.g., Bcr-Abl).
In principle, this implies that:

All malignant cells that could evolve can be detected on the basis of a set of patterns\textsuperscript{vi} of normal cellular machinery that effect or reflect proliferation and invasiveness, in an abnormal context.\textsuperscript{vii}

For this to be false would require:

I. The non-existence of a set of patterns of normal cellular machinery that enable the specific detection of proliferation and invasiveness, in an abnormal context; or

II. The evolution of a malignant cell that failed to use normal cellular machinery that comprised any patterns in the set.

Case I would mean that molecular signatures of proliferation and invasiveness do not exist. This is not tenable as the processes exist and occur within the domain of cellular machinery. Case II would mean the evolution of extensive machinery, which is too mathematically improbable to occur.

Patterns of normal cellular machinery that effect or reflect proliferation and invasiveness provide the basis for the detection and destruction of all malignant cells that could evolve.

Normal biomolecules are not tumor specific. Genetic alterations can provide a basis for specificity, but not comprehensiveness. The nearly unlimited potential genetic diversity of cancer generally precludes the requisite knowledge. The situation is summarized below:

### Properties and Classes of Targets

<table>
<thead>
<tr>
<th></th>
<th>Genetic Alterations</th>
<th>Normal Biomolecules</th>
<th>Patterns of Normal Biomolecules\textsuperscript{viii}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Specificity</strong></td>
<td>yes</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td><strong>Comprehensiveness</strong></td>
<td>no\textsuperscript{ix}</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td><strong>Knowability</strong></td>
<td>limited</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td><strong>Targeting Outcome</strong></td>
<td>Partial response, Drug resistance, Disease progression</td>
<td>Toxicity, +/- cure</td>
<td>Specific cure?</td>
</tr>
</tbody>
</table>

The normal machinery that effects proliferation and invasiveness is finite, knowable and already largely known. It is represented in the biochemistry of such activities as DNA synthesis, wound healing, angiogenesis, trophoblast implantation and fetal development.

\textsuperscript{vi} A pattern is a set of at least two types of proteins or other biomolecules (elements of the pattern).

\textsuperscript{vii} At some point in time

\textsuperscript{viii} Related to proliferation and invasiveness

\textsuperscript{ix} Except in those rare cases where the patient’s tumor burden is very low and the cells have little genetic heterogeneity
This implies that:

Any process that can consistently and specifically cure or control cancer needs to target patterns of normal cellular machinery characteristic of proliferation and invasiveness.\textsuperscript{x}

The normal cellular machinery that potentially could carry out proliferation and invasiveness is finite, fixed and essentially the same for all types of solid cancers. This implies that the requirements for the consistent and specific cure or chronic control of all types of solid cancers are essentially identical. In principle, one set of drugs could be developed that would be curative for all types of solid cancers.

A practical simplification

The combination of proliferation and invasiveness is highly restricted within the human body. If cancer therapy is avoided during periods of significant physiological invasiveness, such as pregnancy and wound healing, then patterns of normal cellular machinery characteristic of proliferation and invasiveness, or even invasiveness alone, could provide a practical basis for the detection and destruction of all malignant cells that could evolve.

These considerations imply the following theory:

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

- Each pattern effects or reflects the combination of proliferation and invasiveness, or the potential for proliferation\textsuperscript{xi}, and invasiveness;
- Each pattern is absent from normal tissues not engaged in these processes;
- All malignant cells that could evolve will express at least one of the patterns (either in the cell or in the microenvironment).\textsuperscript{xii}

The smallest set of target patterns for which this theory holds true is the minimum set needed for the consistent and specific cure or control of cancer. The minimum set is also the set of simplest patterns with the fewest elements per pattern. This is the case because pattern AB detects more cells than pattern ABC. Pattern AB detects all cells with both A and B, while pattern ABC detects only cells with all three together, A and B and C.

Patterns

The existence of a common set of patterns that cover all malignant cells that could evolve for all types of solid cancers may seem counter-intuitive given the enormous genetic diversity of cancer. However, the converse contradicts Darwin’s Theory of Evolution.

\textsuperscript{x} Any process that can consistently starve tumor cells of a blood supply must jointly arrest angiogenesis, vascular co-option and vasculogeneic mimicry and will require targeting patterns of normal machinery characteristic of proliferation and invasiveness.\textsuperscript{28, 29, 30}

\textsuperscript{xi} For example, DNA licensing with MCM complexes

\textsuperscript{xii} At some point in time
Consider elements of patterns related to proliferation. The machinery of replication forks and MCM pre-replication complexes are required for, and highly specific markers of, proliferation and DNA licensing, respectively. There is essentially a zero probability of a malignant cell evolving without MCM proteins or replicative DNA polymerase. Since all known pathways of cell proliferation converge, the detection of a small number of proteins is sufficient to comprehensively detect cell proliferation or the potential for proliferation.

By contrast, not all pathways of invasiveness converge. Many different enzymes can degrade basement membranes and promote tumor cell invasion. Markers are needed that can enable the detection of each independent pathway of invasiveness. However, most pathways are not independent. For example, activated c-Met and transforming growth factor β1 trigger programs of gene expression related to invasiveness that share common elements. Another example is the coordinated expression of a set of wound-response genes by fibroblasts exposed to serum. This same set of wound-response genes is over-expressed in cancers. The coordinated expression of sets of functionally related proteins confers robustness to the molecular signatures of invasiveness and makes these processes easy to detect. The major role played by non-malignant stromal cells in invasiveness confers additional stability to the signatures.

There are good reasons to believe that patterns comprised of 2 to 3 different proteins will be sufficient to detect proliferation and invasiveness. The minimal number (and optimal set) of patterns required for comprehensiveness is currently unknown. Based on a survey of published data, we estimate that ~ 5 to 10 patterns will be required.

A comprehensive set of target patterns would provide the information needed to detect all malignant cells that could evolve. To avoid patient toxicity, target patterns should be utilized that are absent from vital normal tissues. Target pattern selection is achievable with existing technology and requires the analysis of known proteins related to proliferation and invasiveness in normal tissues, invasive processes and common pathological conditions. Studies using RNA silencing of target patterns could provide valuable complementary data.

**Pattern recognition tumor targeting (PRTT)**

To specifically cure cancer, the cells that express target patterns must be killed. This requires drugs that engage in pattern recognition tumor targeting (PRTT). The drugs must be designed to kill cells if and only if the cells (or their microenvironment) express the pattern. Targeting specificity must be for the pattern, not for the individual elements of the pattern. In addition, redundant mechanisms of cell killing are required.

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xiii A very large number of patterns exist. However, to achieve comprehensiveness it is not necessary to target all patterns. Most patterns convey redundant information with respect to the detection of proliferation and invasiveness.
A variety of multi-functional, component-based, modular drugs comprised of targeting ligands, triggers, linkers, and effector agents\textsuperscript{xiv} can be developed to perform the logical functions required to target patterns.\textsuperscript{5,27} PRTT is the logical next step in the application of chemistry and nanotechnology to cancer therapy.

The “War on Cancer” has provided the foundation needed to specifically cure or control cancer.

The identification of a comprehensive set of target patterns and the development of drugs to kill cells that express these patterns is well within the scope of existing technology. Achieving these results must become an international priority.\textsuperscript{xv}

The specific cure or control of cancer is a solvable engineering problem. Success will require a convergence of clinical and basic science, in a well-funded, coordinated, goal-oriented, multi-disciplinary, multi-institutional engineering project. To meet this need we propose the formation of a major non-profit initiative --- the Cure Cancer Project.

The Cure Cancer Project

The mission will be to develop a set of drugs for the specific cure or control of metastatic cancer. The primary objective will be to develop a set of approximately 5 to 10 cytotoxic drugs targeted to patterns of normal cellular machinery that effect or reflect proliferation and invasiveness. A set of such drugs given in combination could cure all types of solid cancers, without significant patient toxicity. A secondary objective of the non-profit organization will be to make the therapy affordable to all.

The day will come when cancer is routinely cured without severe side effects. The Cure Cancer Project is designed to hasten that day. However, it will take an open collaborative effort.

We invite comment on the proposed Cure Cancer Project. For further information please contact Dr. Arnold Glazier at \texttt{mailto:arnglazier-mail@yahoo.com}. This editorial was written by A. Glazier and endorsed by the co-signers.

Note:
This editorial has been posted on the Van Andel Research Institute’s website: \url{http://www.vai.org/upload/departments/tumormetastasis/editorial01.pdf}

\textsuperscript{xiv} Cytotoxic drugs or other pharmacological agents
\textsuperscript{xv} Initiatives aimed at prevention and early detection of cancer are also vital.
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