An Overview on Requirements for the Prevention and Cure of Cancer

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Introduction

This document defines and explains requirements that must be satisfied for the prevention, cure or control of cancer.

It expands upon the three part series of webcasts on the New Cancer Mentality website titled: **Cancer in the Post-Genomic Era: Where do we go from here? How can we prevent and cure or control cancer?**

These requirements are logical consequences of the evolutionary nature of cancer. The requirements:

- Apply to all types of cancers, including metastatic cancers
- Are independent of genetic and epigenetic alterations
- Are independent of pathways of tumor cell evolution
- Are independent of the properties of individual tumor cells, per se
- Relate to knowable properties of all malignant cells that could evolve
- Relate to the information required to detect all malignant cells that could evolve
- Imply that at an important level cancer is one disease
- Sharply define practical solutions to the cure or control of all types of cancers

If these requirements are satisfied, the consistent and specific cure or control of cancer is achievable.

Within the context of these requirements the cure or control of cancer is a practical engineering solution.

For the sake of clarity and brevity, the extensive experimental evidence and analytic details underlying these conclusions have been omitted from this summary document.

The book: **Cure: Scientific, Social and Organizational Requirements for the Specific Cure of Cancer,** provides additional information and can be downloaded for free as a pdf document by clicking on the following link.

http://www.lulu.com/product/paperback/cure-scientific-social-and-organizational-requirements-for-the-specific-cure-of-cancer/2299550

I would be please to provide a free pdf copy of a draft, new, yet to be published book titled: **Cancer: Requirements for Cure,** which provides much more scientific and technical details, (provided that the book is used only for academic research and scholarly purposes). Please contact me by email at arnglazier-mail@yahoo.com if you would like a copy, or have any questions or comments. Thank you. – Arny Glazier

Requirements for the Prevention and Cure of Cancer

1. Cancer is defined by malignant behavior: proliferation and invasiveness in an abnormal context or site in the body

- Proliferation involves cellular replication and an increase in cell numbers.
- Invasiveness is the expansion of cells into new space with the remodeling or destruction of existing tissue architecture and the creation of infrastructure to support the metabolic needs of the cells.

2. Cancer is first and foremost about the growth of an evolving population of cells

There is a big difference between the properties of a cancer cell and those of an evolving 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 cure or control the disease.

3. Evolution

There are four necessary and sufficient conditions for evolution:

- Random variation
- Reproduction
- Heredity, or transmission of variations to offspring
- Selective pressure, which results in competition for survival and natural selection

Random variations that confer a reproductive or survival advantage are naturally selected for and become enriched in the population.[*] New random variations arise and the process repeats. The cumulative effect of a very large number of these selection cycles generated the complex machinery of life.

4. Cellular Information

Genetic information, which provides the basis of heredity and blueprints for the machinery of life, is encoded within the sequences of approximately 6 billion DNA base pairs. Epigenetic information resides outside the DNA sequence.

5. Cells accumulate random genetic and epigenetic alterations

It is inevitable that cellular information becomes damaged or altered during storage and replication. Oxygen alone is estimated to damage about ten thousand DNA bases per cell per day.[†] The net result is variation within populations of cells in the body.

[*] More precisely, variations that impart a survival or reproductive disadvantage are selected against.
[†] Agents such as tobacco smoke and radiation markedly increase the damage to cellular information.

6. Evolution occurs within cell populations in the human body

The four necessary and sufficient conditions for evolution exist within populations of cells in the human body.

- Genetic and epigenetic variation occurs.
- Reproduction occurs (cell proliferation).
- Heredity is hardwired into cells.
- Selective pressure is inevitable; resources vital to cell growth and cell survival are finite.

7. Cancer can result from "runaway" evolution within cell populations in the body

- The "fittest", most "aggressive" cells survive and pass onto the next generation information helpful for cell survival and reproduction.
- Repetitive cycles of this process of random mutation and natural selection can lead to cancer.
- Continuation of the process generates a constantly changing population of increasingly aggressive cancer cells that can evade therapy and cause progressive disease.

8. To prevent cancer it is necessary to halt evolution in cell populations in the body

This requires eliminating at least one of the four necessary and sufficient conditions for evolution, which is generally not possible (with limited exceptions).

- Genetic and epigenetic variation: cannot be eliminated.
- Cell proliferation: cannot be safely eliminated in <u>most</u> sites in the body.*
- Heredity: cannot be eliminated.
- Selective pressure: cannot be eliminated.

9. To reduce the risk of cancer it is necessary to slow the rate of evolution

This requires one or both of the following:

- Decreasing the rate and extent of genetic and epigenetic variation.†
- Slowing the rate of cell proliferation.

Interventions that decrease cell proliferation can act as selective pressures and lose effectiveness as variant cells arise that can escape growth inhibition.

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* In most tissues, with limited exceptions, proliferation is vital to life and health and could not be safely eliminated.

† Examples include: minimizing exposure to agents such as tobacco smoke, radiation, and viruses that trigger genetic and epigenetic damage and surgically removing precancerous lesions.

10. Special case for prevention --- cell proliferation is not essential for general health in the following special sites:

- Prostate
- Breast
- Brain and spinal cord
- Retina

11. Permanently abolishing cell proliferation at these sites would:

- Prevent the evolution of cancer at these locations.
- Eradicate localized cancer present at these sites.
- Prevent and halt other proliferative diseases at these sites.[*]

12. To cure or control cancer, it is necessary to satisfy jointly three basic requirements: [†]

- **Comprehensiveness:** Refers to the need to kill (or control) all malignant cells present in the patient; one malignant cell that evades therapy can potentially cause lethal disease.
- **Specificity:** Refers to the need to kill (or control) cancer cells without significant toxicity to the patient.
- **Knowability:** Refers to the need to target properties that can be known, or accurately predicted, within the context of the logically sound method of scientific knowledge as articulated by Karl Popper.

13. Cancer is an extremely diverse, unpredictable, stochastic[‡] (random), and complex evolutionary process

- Genetic and epigenetic alterations are largely stochastic.
- Natural selection is a stochastic process.
- The number of different combinations of genetic and epigenetic alterations that could arise is essentially unlimited.
- Every patient examined to date with solid cancer has had a different set of genetic and epigenetic alterations.
- Every cancer cell can be unique at the genetic and epigenetic level.
- Extensive genetic and epigenetic differences occur within tumors and between metastatic lesions and primary tumors.
- Cancer is characterized by nearly unlimited genetic and epigenetic chaos.

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[*] Such as BPH (benign prostatic hypertrophy or prostate enlargement) and proliferative retinopathies

[†] The immune system response against cancer is *not* an exception to these requirements, cannot satisfy these requirements and frequently fails to cure or control cancer.

[‡] A stochastic process is a random process in which the outcome depends on the outcomes of prior events and the probabilities change in time. For example, Brownian motion is a stochastic process.

14. Tumor cell evolution limits what can be known about cancer in a patient with metastatic cancer

- A patient can have billions of different cancer cells spread throughout his or her body.
- We generally cannot identify all cancer cells that are present in a patient with metastatic disease.
- We cannot know what will evolve.
- We cannot have comprehensive knowledge of the genetic and epigenetic alterations and pathways of tumor cell evolution.

15. Cancer is a disease of statistical extremes and outliers, "black swans"

- One cell out of billions can profoundly influence the clinical course of cancer.
- A single malignant cell resistant to therapy can potentially give rise to progressive metastatic disease.

It is the exceptions that disprove theories, cause treatment failures, and result in progressive disease.

16. Targeting specific pathways of tumor cell evolution cannot satisfy the requirements for cure or control of cancer

- Genetic and epigenetic alterations can provide a basis for targeting specificity, but cannot provide a basis for comprehensiveness.
- Resistance and treatment failures have been observed with all anticancer drugs that target particular genetic alterations.

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

- Tumor cell type
- Antigen
- Genetic or epigenetic alteration
- Oncogene (cancer causing gene)
- Metabolic abnormality
- Mechanism of tumor vascularization
- Mechanism of malignant transformation
- Pathway of tumor cell evolution

Such properties can provide a basis for tumor-specific targeting but cannot provide a basis for comprehensiveness. Virtually any genetically encoded molecular property or target can be lost or modified by mutation during tumor cell evolution.

18. The extremely diverse, unpredictable, stochastic, evolutionary nature of cancer implies that:

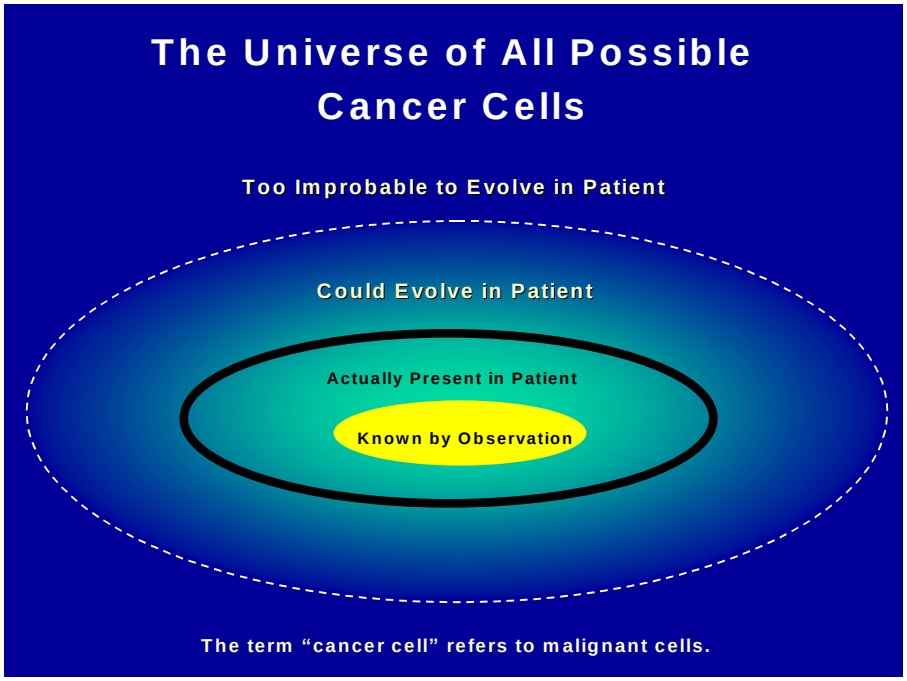
- The essential features of therapy for the cure or control of cancer must be independent of the pathways of tumor cell evolution, and independent of the genetic and epigenetic alterations.

19. What population of cells must therapy target to cure or control cancer?

- The obvious answer is all malignant cells in the patient. However, this answer is false. It presupposes knowledge that cannot be known.
- Targets must be knowable and known.
- What is actually present is not what matters. What matters is what can be known about what is present and what can be known about what could evolve in the patient.
- Unknown and unknowable, chaotic, changing features of cancer cannot be targeted.
- If we could know all that is present and what will evolve in a patient with metastatic cancer, then at least in principle we could target it. But we can't know. So we must target everything that could evolve.

20. The set of all malignant cells that could evolve is the required target for the cure or control of cancer

- It is instructive to think in terms of *sets* of cancer cells. The following picture represents the universe of all possible malignant cells with all possible genetic and epigenetic alterations.



- The set of cells that are actually known by observation is contained within the yellow oval and changes with time. Not all cancer cells that are actually present in the patient are known or knowable by observation (except, as a practical matter, in some cases of localized disease).
- The set of cancer cells actually present in the patient is contained within the black oval. This set changes with time. The changes are stochastic and predictable only to the extent that the set will (almost always) remain inside the dashed oval.
- As the distance from the set "Actually Present" increases, the cells become increasingly less probable to evolve. The probability value is 1 inside the black oval and approaches 0 at the dark blue periphery. The exact probability function or distribution is unknown, variable and unknowable.
- Inside the dashed line is the set of all cancer cells that could evolve in a patient. This set is fixed and does not change with time.[*] Outside the dashed oval is the set of cells that are too improbable to realistically evolve in a patient.
- Except in some cases of localized disease, it is not possible to know by observation or accurately predict by theory the content of the black oval (i.e., the malignant cells actually present). The content is the output of an enormously diverse, stochastic, unpredictable, evolutionary process. The formulation of a theory that can consistently predict the unpredictable is a logical contradiction. Consequently, the content of the black oval is generally unknowable and is not a suitable target.
- By contrast, in principle we can formulate a true scientific theor*y* that defines the set of all malignant cells that could evolve.[† ‡]
- The set of all malignant cells that could evolve is the smallest knowable set of cancer cells that is comprehensive. Therapy that targets a smaller set will fail.
- Terms like "*could evolve*" are ill defined and nonquantitative. However, when translated into practice these terms acquire clinical meaning.
- Individual cancer cells with particular genetic and epigenetic alterations are like microscopic pixels in the big picture. We cannot know and cannot target the almost unlimited number of individual pixels. They are irrelevant. What matters are the properties of the set of all cancer cells that could evolve.

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[*] The extent of the set of all malignant cells that could evolve is dependent upon our choice of what we consider a realistically probable chance (e.g., one in a thousand, one in a million, one in a billon) to evolve in the patient. Graphically speaking, the smaller the probability we chose, the further the dashed boundary line (all that could evolve) is from the black oval (actually present).

[†] The term *true scientific theory* means a theory that is potentially falsifiable, internally logically consistent, consistent with other well-established "principles of nature", and that resists the severest attempts at falsification. In other word, the theory will be true for any malignant cell ever observed. An exception would disprove the theory.

[‡] The simplicity or complexity of the theory is, for the moment, not the issue.

21. The set of all malignant cells that could evolve cannot be characterized by direct observation

- The set is metaphysical; it has no real world existence.
- Properties of the set can be "known" by means of a true scientific theory.
- Observation of a single malignant cell with properties that contradicted the theory would falsify the theory.

22. Only known or knowable properties can be targeted

- Very little can be known 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.

23. Malignant behavior is the only property common and specific to all malignant cells, regardless of the pathways of tumor cell evolution

- Malignant behavior is defined as: proliferation and invasiveness in an abnormal context.*
- A cell is a malignant cell if and only if the cell engages in malignant behavior.
- Only cells that engage in malignant behavior can sustain the disease of cancer.
- Not all tumor cells are malignant. Many tumor cells are dead-end and cannot sustain the disease of cancer.

24. All malignant cells use normal cellular machinery to engage in malignant behavior

- An exception has never been reported.
- The normal cellular machinery that carries out malignant behavior is expressed by malignant cells and also by non-cancer cells in the microenvironment.

25. There is not sufficient time for the evolution of extensive new functional machinery

- The complexity of the requisite interdependent biochemical processes is too great, the joint probabilities are too small, and the human life span far too short for a tumor cell to evolve that violates this rule.

26. The nearly unlimited genetic and epigenetic chaos of cancer is constrained

* These processes of proliferation and invasiveness need not to be expressed at the same time. However, invasiveness and the potential for proliferation are expressed concurrently.

- A malignant cell will result if and only if the genetic and epigenetic alterations cause normal cellular machinery to carry out the processes of proliferation and invasiveness.
- Genetic and epigenetic lesions that do not fulfill this criteria result in dead end tumor cells that are not malignant.
- This imparts a simplicity to cancer; the nearly unlimited genetic and epigenetic complexity of the disease becomes irrelevant.

27. The set of normal cellular machinery that is required for (or characteristic of) proliferation and invasiveness is fixed, finite, and encoded in the normal human genome

- The set of normal cellular machinery is represented in the biochemistry of DNA synthesis (a component of proliferation), cell division, wound healing, blood vessel formation, placental growth and fetal development.
- This cellular machinery is largely known.

28. The set of normal cellular machinery that could carry out malignant behavior is:

- The same for all types of cancers
- Independent of the pathways of tumor cell evolution
- Comprehensive
- Knowable*

29. Patterns

- A pattern is a set of at least two different types of proteins (or other biomolecules) that are expressed by malignant cells and/or their microenvironment.
- For the pattern to be present, all elements of the pattern must be present.
- Elements that comprise a pattern can be expressed by cancer cells and/or by non-cancer cells in the microenvironment.

30. Malignant behavior is always accompanied by the expression of patterns of normal cellular machinery in an abnormal context or setting

- Normal cellular machinery is absolutely required to carry out malignant behavior.

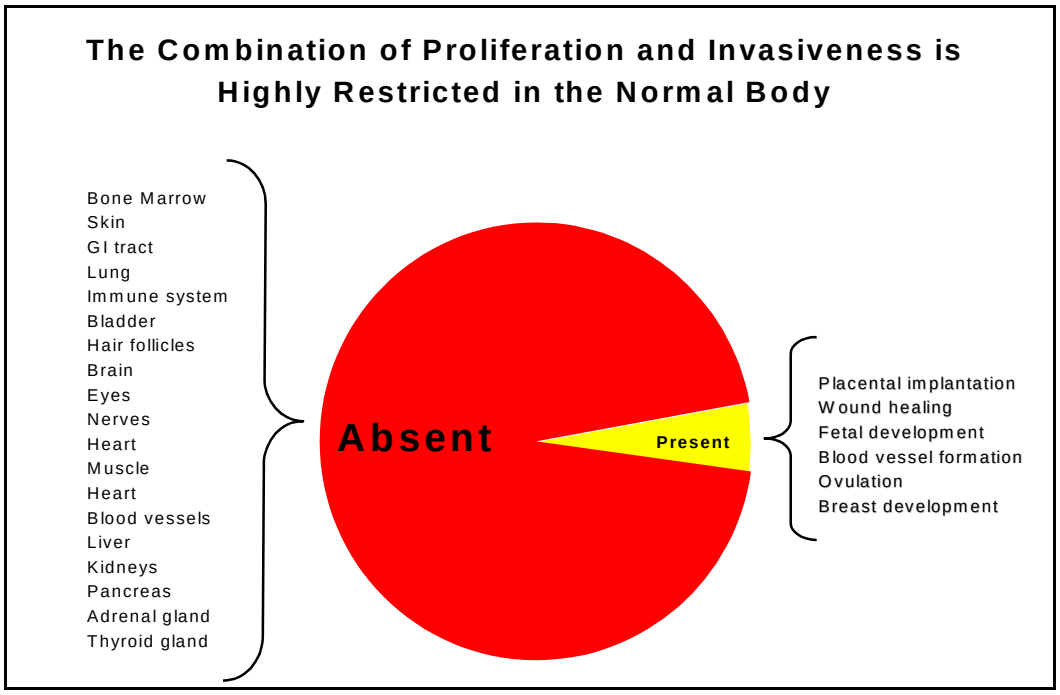
* By contrast, the sub-set of normal cellular machinery that actually carries out malignant behavior in a particular patient is dependent upon the pathways of tumor cell evolution, and is unpredictable and unknowable. Short of examining every cancer cell present in the patient, at least a practical impossibility, we cannot know exactly which normal cellular machinery is actually used by all of the malignant cells in a patient to engage in malignant behavior.

31. Malignant behavior can only be detected on the basis of <u>patterns</u> of normal cellular machinery related to proliferation and invasiveness

- No single molecular entity can enable the detection of both proliferation and invasiveness, nor provide contextual information.
- To detect the combination requires the detection of a pattern.
- There are good reasons to believe that patterns comprised of 2 to 3 different proteins will be sufficient to detect proliferation and invasiveness.

32. The combination of proliferation and invasiveness is highly restricted and not expressed in most normal tissues of the body

- It is expressed in processes such as placental and fetal development, new blood vessel formation, mammary gland development, the menstrual cycle, ovulation, inflammatory processes such as abscess formation, and wound healing.



33. If we exclude instances of these normal combinations, then in principle:

- Malignant cells could be specifically detected on the basis of a set of <u>patterns</u> of normal cellular machinery that effect or reflect:
  - The combination of proliferation and invasiveness; or
  - Invasiveness and the potential for proliferation; or
  - Invasiveness alone.
- The avoidance of cancer therapy during pregnancy, major wounds and infections is standard practice and is generally not a problem.

34. The comprehensive detection of malignant cells requires the ability to detect multiple patterns of normal cellular machinery related to proliferation and invasiveness

- Any genetically encoded protein or biomolecule could be lost or mutated during tumor cell evolution.
- This means that any given pattern of normal cellular machinery that effects or reflects malignant behavior could be lost by some malignant cells that could evolve.
- The minimal number of patterns required for comprehensiveness is currently unknown.
- We estimate, based on existing data, that approximately 5 to 10 patterns will be needed to enable the comprehensive detection of malignant behavior and all malignant cells that could evolve.

35. To achieve comprehensiveness it is not necessary to be able to detect and target all patterns of this normal cellular machinery

- The coordinated expression of a large number of proteins is involved in proliferation and invasiveness; an even larger number of patterns is possible.
- However, most patterns convey redundant information with respect to the detection of proliferation and invasiveness.*

36. There is a common and comprehensive set of patterns for all solid cancers

- The normal cellular machinery that could carry out malignant behavior is the same for all malignant cells, for all types of solid cancers.
- One set of patterns would be able to detect all malignant cells for all types of solid cancers (e.g., breast, prostate, lung, ovarian, pancreatic, etc.).†
- This means that that one set of drugs could be developed that would be effective against all forms of solid cancers.
- At very important level cancer is one disease. (See Table 3)

37. A comprehensive set of patterns would enable the detection of all malignant cells

- The patterns provide the information needed to detect malignant behavior and all malignant cells that could evolve.
- The comprehensive destruction or inactivation of malignant cells detected by the patterns is a separate issue.

* For example, about 800 proteins are involved in DNA synthesis; however the detection of a single key protein as an element of a pattern is sufficient to identify proliferating cells.

† The leukemias and lymphomas could require a different set of patterns.

38. To target and destroy malignant cells detected by patterns requires: Pattern Recognition Tumor Targeting (PRTT)

- To target patterns requires PRTT-based drugs* that kill (or inactivate 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.
- The objective of PRTT is not to inhibit the machinery that carries out malignant behavior; it is to kill or inactivate malignant cells.

39. PRTT is fundamentally different from using combinations of conventionally targeted anticancer drugs

- Consider the pattern "AB" comprised of two proteins, A and B.
- PRTT-based drugs would only kill cells that express both A and B.
- Cells that express A alone or B alone would be spared.
- By contrast, a combination of conventionally targeted anticancer drugs would target and kill cells that express A alone, B alone, and AB; this leads to a lack of specificity and to toxicity.

40. Redundant mechanisms of cell killing or inactivation are required

- 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.

41. Targeting patterns of normal cellular machinery related to proliferation and invasiveness provides the <u>only</u> basis for the detection and destruction of all malignant cells that could evolve

- There are three basic classes of targets:
  i. Mutant molecules that arise from genetic alterations
  ii. Normal biomolecules
  iii. Patterns of normal biomolecules
- Mutant molecules can provide a basis for specificity, but cannot provide a basis for comprehensiveness. The nearly unlimited potential genetic diversity of cancer generally precludes the requisite knowledge.
- Normal biomolecules are not tumor specific, but can provide a basis for comprehensiveness.
- Patterns of normal cellular machinery characteristic of proliferation and invasiveness provide the only molecular basis that can satisfy the joint requirements of comprehensiveness, specificity, and knowability needed for the cure of cancer.

* Or technologies

Table 1

Classes and Properties of Targets

	Genetic Alterations	Normal Biomolecules	Patterns of Normal Biomolecules Related to Proliferation and Invasiveness
Independent of pathways of tumor cell evolution	No	Yes	Yes
Specificity	Yes	No	Yes
Comprehensiveness	No	Yes	Yes
Knowability	Limited	Yes	Yes
Targeting Outcome	Partial response, drug resistance, disease progression	Toxicity, +/- Cure	Specific cure?

42. In practical terms, the 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.
- 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.
- Redundant mechanisms of cell killing must be employed.

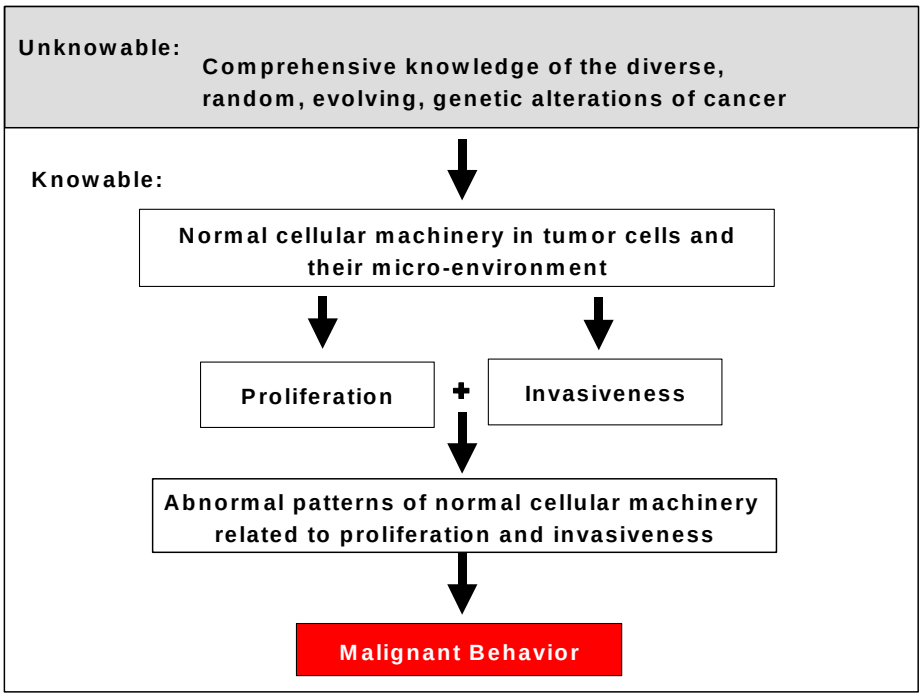
We estimate that approximately 5 to 10 drugs, in combination, will be required.

43. A focused, well-funded, coordinated engineering enterprise is needed to:

1. Identify and select a comprehensive set of target patterns
2. Develop PRTT platform technology to enable drugs to kill cells if and only if the cells and/or or their microenvironment express the target pattern
3. Develop PRTT-based drugs targeted to specific patterns
4. Develop a set of PRTT-based drugs that can be given in combination for the specific cure or control of all types of solid metastatic cancers

Summary

An Evolutionary Model of Cancer



Cancer is defined by malignant behavior: cell proliferation and invasiveness in an abnormal context or site in the body.

A set of patterns of normal cellular machinery related to proliferation and invasiveness exists that is used by all malignant cells regardless of the underlying genetic and epigenetic alterations. The set is comprehensive; i.e., no malignant cell will fail to use at least one pattern in the set to engage in malignant behavior. Targeting such a set enables the detection and destruction of all malignant cells that could evolve.

In practical terms, the specific cure or control of metastatic cancer will require:

- Multiple target patterns of normal cellular machinery that effect or reflect malignant behavior.
- Multiple drugs, administered in combination, which kill or inactivate cells if and only if the cells and/or their microenvironment express the target patterns (estimated that approximately 5 to 10 drugs will be needed).
- Redundant mechanisms of cell killing or inactivation.

Table 2

A Comparison of Cancer Models

Standard Cancer Models	Evolutionary Model -- PRTT
Inconsistent with the evolutionary nature of cancer	Consistent with the evolutionary nature of cancer
Tumor cells that are actually present in the patient are the cellular targets.	The required target is the set of all malignant cells that could evolve in the patient.
A tumor-specific marker is validated as a drug target by its presence in tumor cells.	A tumor-specific marker is invalidated by its absence in a malignant cell.
The genetic and epigenetic lesions that cause a patient's cancer can be experimentally characterized.	Only bulk tumor and *identifiable* metastatic lesions can be experimentally characterized. What will evolve is unknowable.
Specific curative cancer therapy is dependent on particular genetic and epigenetic alterations.	Specific curative cancer therapy must be independent of any particular genetic and epigenetic alterations.
Rational cancer therapy is dependent on the pathway of tumor cell evolution.	Specific curative therapy must be independent of any particular pathway of tumor cell evolution.
Cancer is hundreds of different diseases.	Cancer is essentially one disease.
Different types of solid cancers will require different types of therapy.	One therapy could specifically cure or chronically control all types of metastatic cancers.
Cancer therapy must be tailored to the individual patient.	Specific curative therapy cannot be tailored to the individual
The immune system is a solution.	The immune system is a selective pressure.
Signal transduction inhibitors are a solution.	Drug resistance frequently develops.
Cancer is dependent upon angiogenesis.	Cancer cells require oxygen, not new blood vessels (e.g. vascular co-option).
Current chemotherapy regimens are toxic. Drug combinations are selected by educated guesses and trial and error.	Drug combinations will be based on rational scientific theory and empirical data. The drugs will be non-toxic or minimally toxic.
Targeting specificity is for a single type of molecular target.	Targeting specificity is for abnormal patterns of normal biomolecules that effect or reflect malignant behavior.
Current models cannot provide both specificity and comprehensiveness.	PRTT can provide both comprehensiveness and specificity.
Current models cannot provide a basis for the specific cure or chronic control of metastatic cancer.	PRTT provides a practical basis for the specific cure or chronic control of all types of metastatic cancers.*

* The technologies can be adapted for leukemias and lymphomas. However, it may be necessary to target different patterns.

Table 3

Expression Rates of Common Patterns in Cancer

Pattern	Type of Cancer	%	# Patients	Ref.	Comments
MMP-2 + MT1-MMP + EMMPRIN	Breast	**100 %**	17 out of 17	1	mRNA was measured
MMP-2 + MT1-MMP	Breast	**91%**	104 out of 114	2	68% MMP-9 +
MMP-2 + EMMPRIN	Breast	**100%**	20 out of 20	3	
MMP-2 + EMMPRIN	Lung	**100%**	20 out of 20		14 squamous cell 6 adenocarcinoma
MMP-2 + MT1-MMP	Breast	**100%**	32 out of 32	4	
Activated MMP-2 + MT1-MMP	Breast	**97%**	31 out of 32		
MMP-2 + MT1-MMP	Pancreatic	**85 %**	23 out of 27	5	mRNA
MMP-2 + MMP-9 + MT1-MMP + gelatinolysis	Lung	**100 %**	14 out of 14	6	mRNA
MMP-2 + MT1-MMP	Invasive lung adenocarcinoma	**93%**	25 out of 27	7	
MMP-2 + MMP-9	Colon	**100%**	10 out of 10	8	Cathepsin B also expressed in 60%
Activated MMP-2*		**100%**	10 out of 10		Averaging 10 X > than normal colon
Activated MMP-2*	Pancreatic	**100%**	33 out of 33	9	(MT1-MMP activates MMP-2)
Activated MMP-2*	Lung	**94%**	34 out of 36	10	Averaging 17 X > than normal lung
Activated MMP-2*	Colon	**99%**	265 out of 269	11	Averaging 10 X > than normal colon
MMP-2 + MT1-MMP	Papillary thyroid	**100%**	26 out of 26	12	
MMP-1 + MMP-3	Renal cell	**90%**	9 out of 10	13	
MMP-1 + MMP-2	Renal cell	**90%**	9 out of 10		
(MMP-1 + MMP-3) or (MMP-1 + MMP-2)	Renal cell	**100%**	10 out of 10		

* While not a pattern, activated MMP-2 reflects the presence of MMP-2 and an activator, (typically MT1-MMP).

Table 3 (cont.)

Expression Rates of Common Patterns in Cancer (cont.)

Pattern	Type of Cancer	%	# Patients	Ref.	Comments
MMP-2 + urokinase	Invasive meningiomas	**86%**	6 out of 7	14	All expressed at least one of the patterns
MMP-9 + urokinase		**86%**	6 out of 7		
MMP-2 + MMP-9	Glioblastoma	**100%**	6 out of 6	15	Gelatinolytic activity: 100%
MMP-2 + MMP-9	Glioblastoma	**100%**	3 out of 3	16	Gelatinolytic activity: 100%
MMP-2 + MMP-9 + MT1-MMP	Glioblastoma	**83%**	5 out of 6	17	
MMP-2 + MT1-MMP	Brain	**86%**	49 out of 57	18	All are absent in normal brain
MMP-2 + MT1-MMP + + Lam5-γ2 + Ang2	Brain	**82%**	47 out of 57		
MMP-2 + MT1-MMP	Glioblastoma	**100%**	15 out of 15	19	Absent normal brain
MMP-2 + MT1-MMP	Brain mets	**100%**	4 out of 4	20	
MMP-13 + uPAR + Urokinase	Breast (DCIS micro-invasive)	**100%**	9 out of 9	21	mRNA MMP-13 mRNA urokinase
MMP-11 + MMP-13 + MMP-14 + MMP-2	Breast (DCIS micro-invasive)	**75%**	3 out of 4	22	mRNA Stromal cells +
MMP-2 + MMP-9	Endometrial	**100%**	29 out 29	23	Gelatinase + % not specified
MT1-MMP + TIMP-1	Endometrial (Grade II and III)	**90%**	9 out of 10	24	mRNA
MMP-1 + MMP-2	Kaposi Sarcoma	**89%**	8 out of 9	25	
MMP-1 + MMP-9		**89%**	8 out of 9		
MMP-1 + MMP-7		**78%**	7 out of 9		
MMP-1 + MMP-7	Prostate cancer metastatic to bone	**100%**	7 out of 7	26	
Urokinase + uPAR	Breast	**90%**	9 out of 10	27	
MMP-2 + MMP-1	Breast, invasive	**83%**	20 out of 24	28	mRNA, stromal cells +

* Most breast cancers concurrently express MMP-1, 2, 3, 7, 9, 11, 13, 14, 17, 19, 23 and 28.29

Expression Rates of Common Patterns in Cancer (cont.)

Pattern	Type of Cancer	%	# Patients	Ref.	Comments
MT1-MMP + MMP-2 + MMP-9	Prostate cancer metastatic to bone	**100%**	18 out of 18	30	In a separate study 20 out of 20) prostate cancers metastatic to the bone were positive for MT1-MMP. 31
MMP-13 + MT1-MMP	Esophageal	**77%**	27 out of 35	32	
MT1-MMP + MMP-2	Transitional Cell Carcinoma	**100%**	102 out of 102	33	
MMP-2 + uPAR	Pancreatic cancer	**90%**	18 out of 20	34	
MMP-2 + MMP-9	Pancreatic cancer	**65%**	13 out of 20		
MMP-2 + Urokinase	Pancreatic cancer	**85%**	17 out of 20		
uPAR + Urokinase	Pancreatic cancer	**85%**	17 out of 20		
(MMP-2 + uPAR) or (MMP-2 + MMP-9)	Pancreatic cancer	**100%**	20 out of 20		
uPAR + PAI-1	Colorectal	**100%**	22 out of 22	35	
EMMPRIN + MMP1+ MMP-2+ MT1-MMP	Melanoma with metastasis	**100%**	10 out of 10	36	
Cathepsins B +D + L	Melanoma	**100%**	16 out of 16	37	
MMP-2 + MMP-9	Cervical Adenocarcinoma	**89-94%**	(16 or 17) out of 18	38	MMP-2 + (17/18) MMP-9 + (17/18)
Urokinase + uPAR	Hepatocellular carcinoma	**100%**	26 out of 26	39	Stromal cells at invasive front +
MMP-1 + MMP-3	Hepatocellular carcinoma	**73%**	8 out of 11	40	
ADAM9 + ADAM12 + ADAM17	Breast cancer	**100%**	16 out of 16	41	
MMP-2 + MMP-9	Colorectal cancer metastases in liver	**100%**	32 out of 32	42	29 had active MMP-9. 22 had active MMP-2 averaging > 15 times normal.
MMP-2 + MT1-MMP	Ovarian (clear cell)	**94%**	17 out of 18	43	
MMP-2 + MMP-9	Osteosarcoma	**92%**	11 out of 12	44	mRNA
MMP-1 + CXCR4	Breast cancer	**100%**	85 out of 85	45	

Expression Rates of Common Patterns in Cancer (cont.)

Pattern	Type of Cancer	%	# Patients	Ref.	Comments
MMP-2 + α5β3 integrin	melanoma	**100%**	36 out of 36	46	% + increased in metastatic lesions
MT1-MMP + MMP-2	Colon cancer	**100%**	24 out of 24	47	mRNA, mostly stromal
MT1-MMP + MMP-2 + MMP11	Colon cancer	**96%**	23 out of 24		
MT1-MMP + MMP-2 + MMP11	Breast cancer	**100%**	34 out of 34	48	mRNA, mostly stromal
MT1-MMP + MMP-2 + MMP11	Head and Neck cancer	**100%**	18 out of 18		mRNA, mostly stromal
Urokinase +MMP-1	Invasive meningioma	**71%**	5 out of 7	49	
Urokinase + MMP-2		**86%**	6 out of 7		
Urokinase + MMP-9		**86%**	6 out of 7		
(Urokinase + MMP-2) or (Urokinase + MMP-9)		**100%**	7 out of 7		
MMP-11 + MMP-12 + Cathepsin F	Cervical	**100%**	15 out of 15	50	mRNA
MMP11 + MMP-12	Cervical	**100%**	15 out of 15		Protein
MMP-1 + MMP-9	Cervical	**90%**	9 out of 10	51	
MMP-2 + MT1-MMP	Oral squamous cell carcinoma	**96%**	23 out of 24	52	
VEGF-C + Furin	Oral squamous cell (tongue)	**100%**	15 out of 15	53	46 were examined for furin; all were +
uPAR+ PAI-1+ Lam5γ2	Oral squamous cell (invasive)	**100%**	12 out of 12	54	
Collagen Type I + Fibronectin	Invasive breast cancer	**~ 100%**	35 out of 35 ?	55	mRNA in stromal cells, *see data in ref.
MMP-2 + MT2-MMP	Dermatofibroma and malignant fibrous histiocytoma	**100%**	8 out of 8	56	Gelatinolytic in activity 100%
MMP-2 + EMMPRIN	Malignant fibrous histiocytoma	**88%**	7 out of 8	57	
MMP-9 + Cox2 + Osteopontin	Prostate cancer	**100%**	10 out of 10	58	

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