Evolution and ecology in cancer biology and therapy

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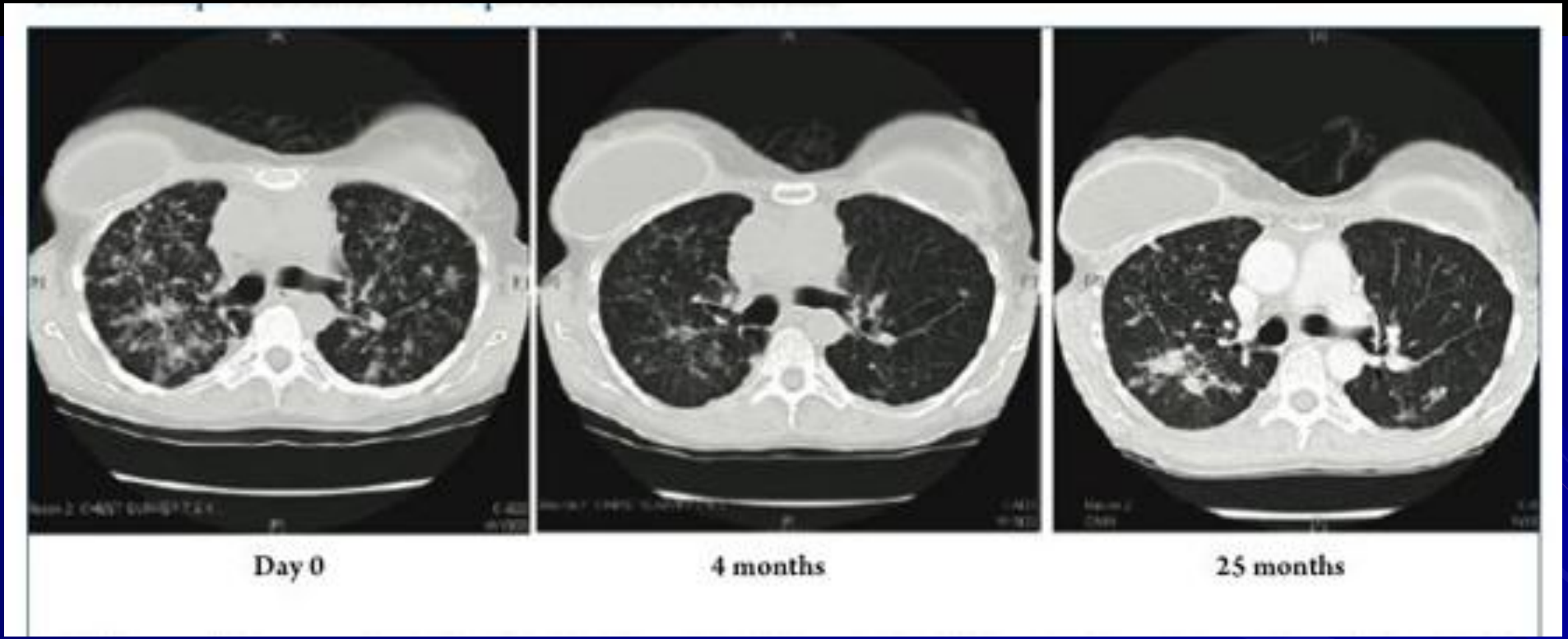
The problem: Disseminated cancer is still usually a fatal disease: Evolution almost always defeats therapy



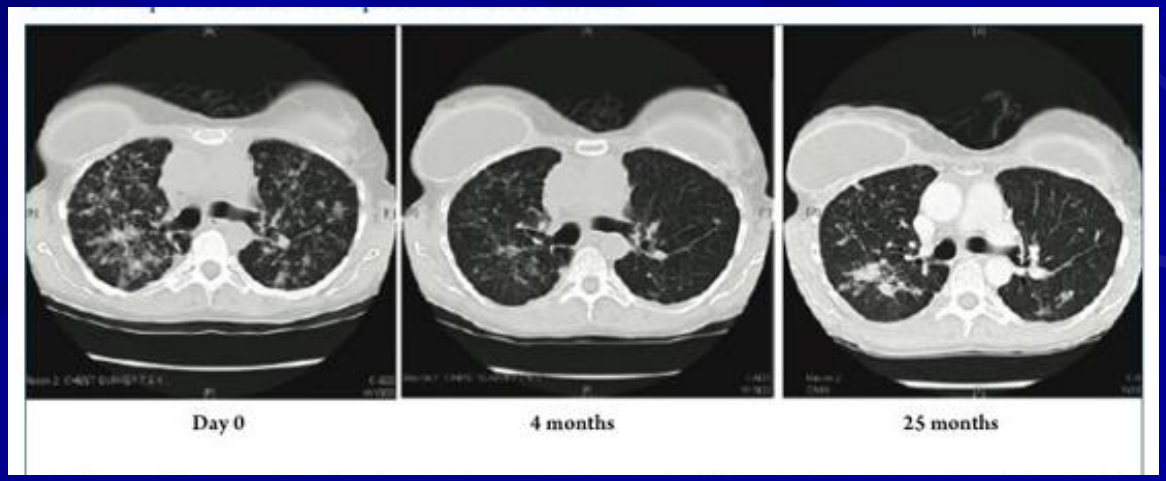
Note:

1. Large number of tumor sites
2. Spatial diversity of response and progression
3. Key role of imaging

Questions

- What was the heterogeneity of EGFR mutation within and between the metastases?
- What other factors affected response?
- Could progression free survival be increased with treatments other than constant maximum dose erlotinib? Was SOC dosing the best strategy available?
- Now what???

  Is first line therapy our only chance for durable control?



Topics

1. Cancer as a complex dynamical system
2. Understanding complex systems requires:
   - First Principles
   - Data
   - Computational methods
3. Clinical applications.

Dear Sir Philada. Feb. 13. 1750

You desire to know my Thoughts about the N.E. Storms beginning to Leeward. Some Years since there was an Eclipse of the Moon at 9 in the Evening, which I intended to observe, but before 8 a Storm blew up at N E. and continued violent all Night and all next Day, the Sky thick clouded, dark and rainy, so that neither Moon nor Stars could be seen. The Storm did a great deal of Damage all along the Coast, for we had Accounts of it in the News Papers from Boston, Newport, New York, Maryland and Virginia. But what surpriz'd me, was to find in the Boston Newspapers an Account of an Observation of that Eclipse made there: For I thought, as the Storm came from the N E. it must have begun sooner at Boston than with us, and consequently have prevented such Observation. I wrote to my Brother about it, and he inform'd me, that the Eclipse was over there, an hour before the Storm began.

Franklin was among the first to recognize the error of applying simple linear thinking to complex, non-linear dynamical systems,

But not the last

Learning from meteorology

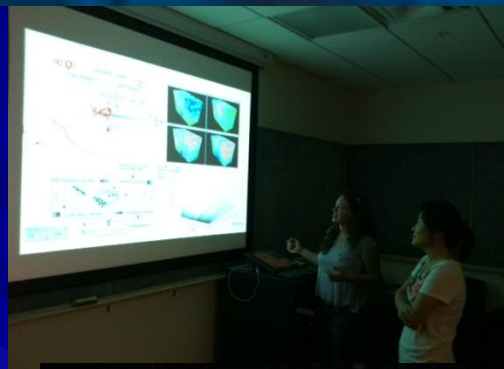
- Weather is a dynamic, complex and non linear system - but predicting weather is mundane
- Forecasting has greatly improved through large data sets, physical first principles (N-S equations), and constant updating of predictions with new data

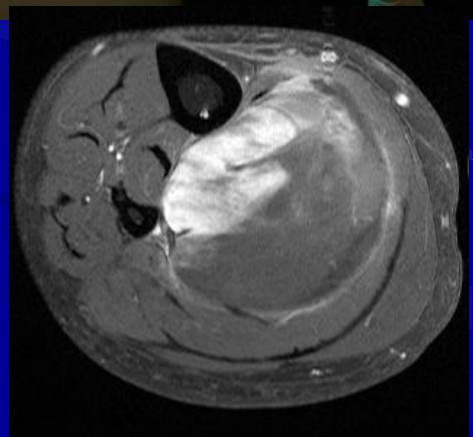
Cancer as a complex, adaptive system – the math/oncology interface

- Human intuition is poorly adapted to predict dynamics in non-linear systems leading to overly simplistic views – e.g. the genetic model of cancer.
- We need computational models but mathematicians typically are distant from biologists lead to modeling that accepts the simplistic biological paradigms
- New proposals for novel biological interactions requires a scientific village.

Integrated Mathematical Oncology (IMO) at Moffitt – Embedding mathematicians in a cancer center

- Cancer is complicated and complex but not incomprehensible!
- First principles will exist
- Quantitative models linked to experimental and clinical data are necessary to define tumor dynamics
- Evolution provides a unifying framework – first principles
- Imaging, by non-destructively defining spatial and temporal heterogeneity, is a key experimental tool and must be used more effectively

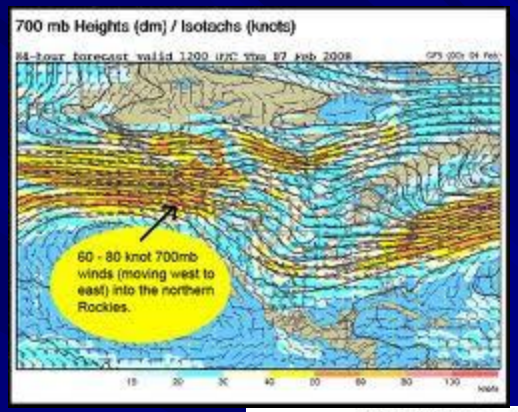


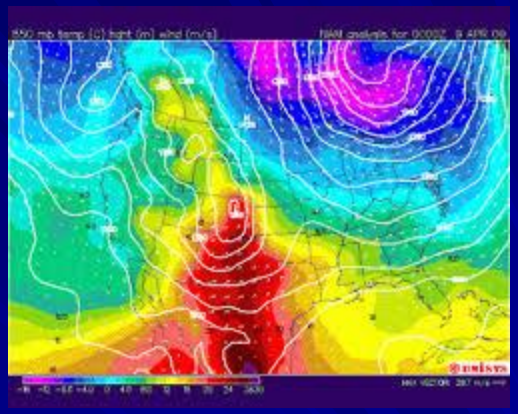


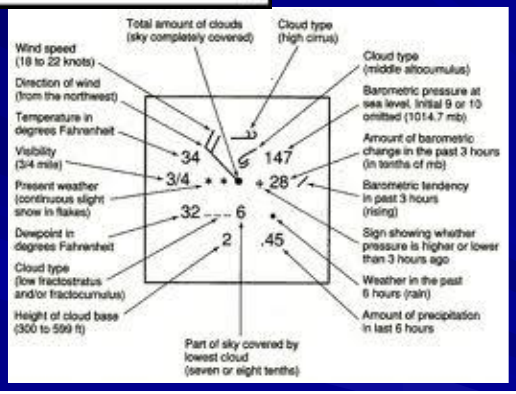
Proposal: a “hurricane model” for every patient’s cancer

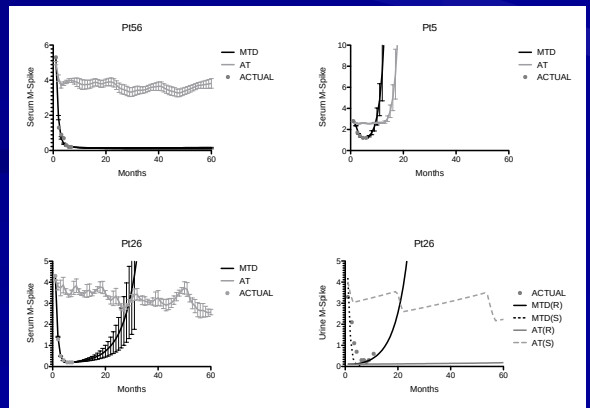
Principle Components:

- Dynamics from first principles
- Big data – spatial and temporal
- Timely and clinically accessible computation models predicting optimal therapy
- Constant feedback comparing prediction to outcomes

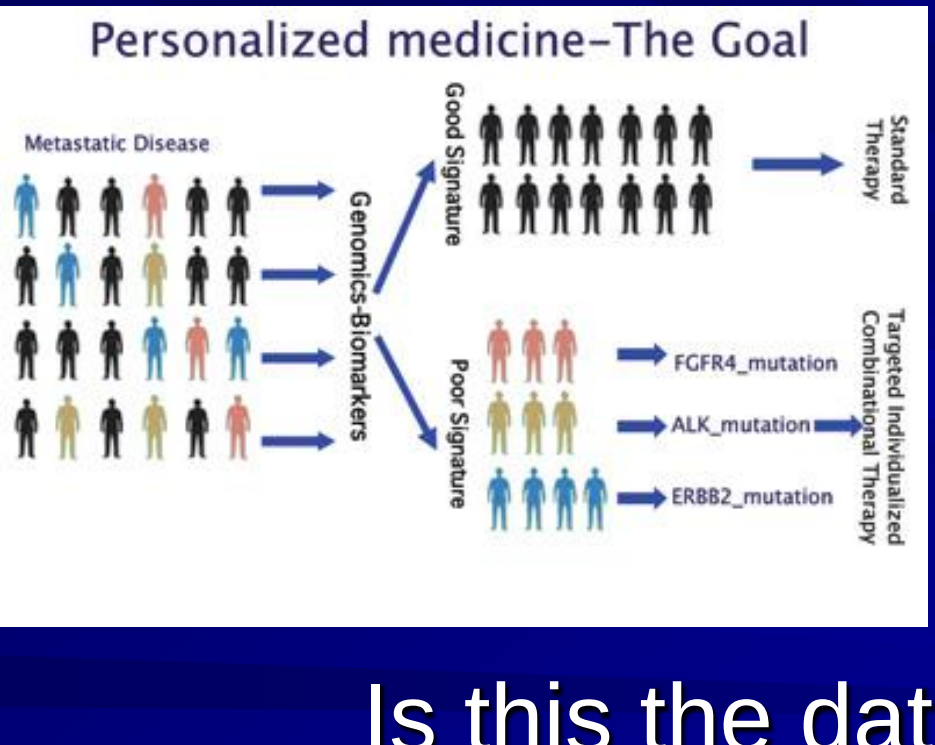






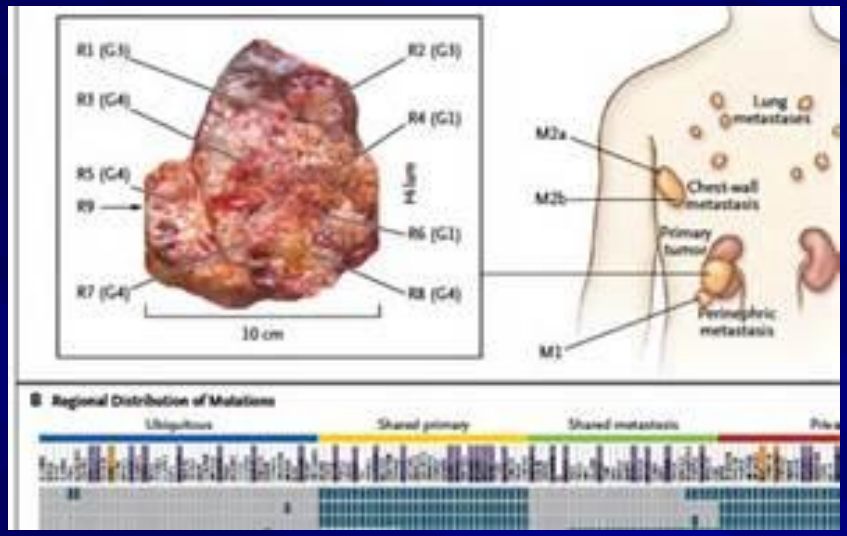


Conventional molecular/genetic approach to “personalized” cancer therapy



Is this the data we need?

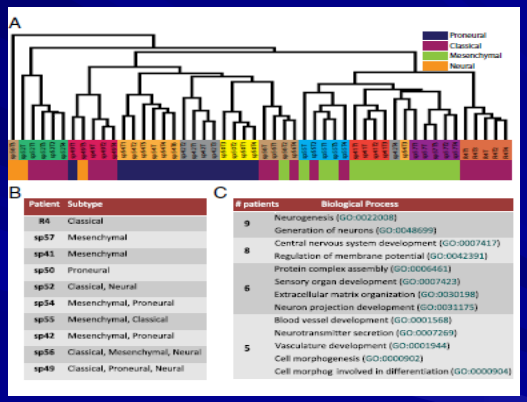
Data: Recent recognition of intratumoral molecular heterogeneity



"Gene-expression signatures of good and poor prognosis were detected in different regions of the same tumor"

Gerlinger, et al. NEJM, 2012

"…extensive intratumor heterogeneity, with most patients displaying different GB subtypes within the same tumor."

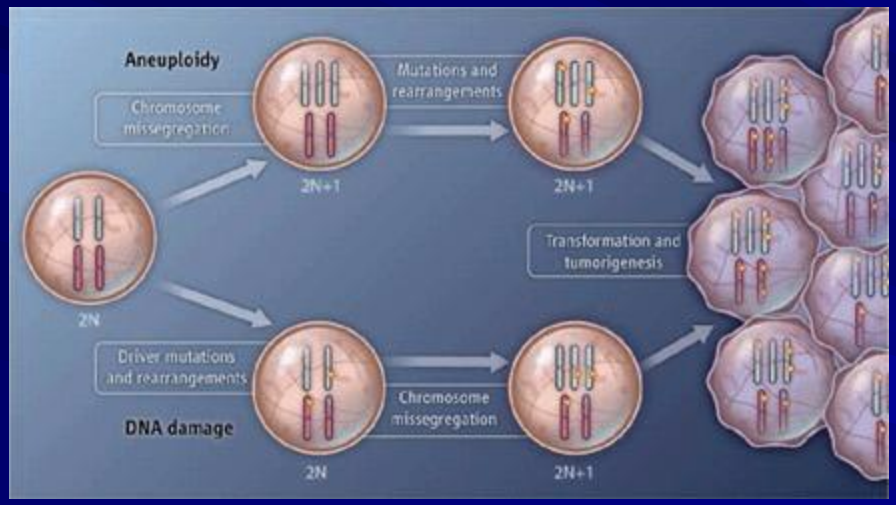


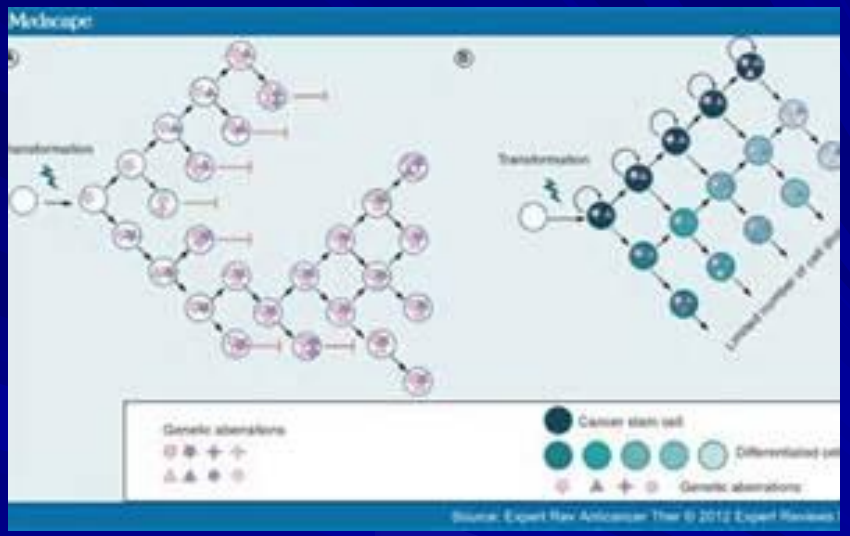
Sottoriva et al. PNAS, 2013

Bad news:

1. Each examined tumor is spatially heterogeneous
2. Each examined tumor is dead

Data and dynamics. What is the source of heterogeneity?: Intratumoral evolution generally ascribed mutations (“mutator phenotype”)





More bad news: If intratumoral evolution is driven by random mutations, spatial heterogeneity in molecular properties is fundamentally stochastic and unpredictable

Darwinian Dynamics can be studied without genetics

- **Heritable Variation in phenotypes (note reaction norms in cancer and normal cells)**
- **Fitness is contextual - depending on environmental selection forces**

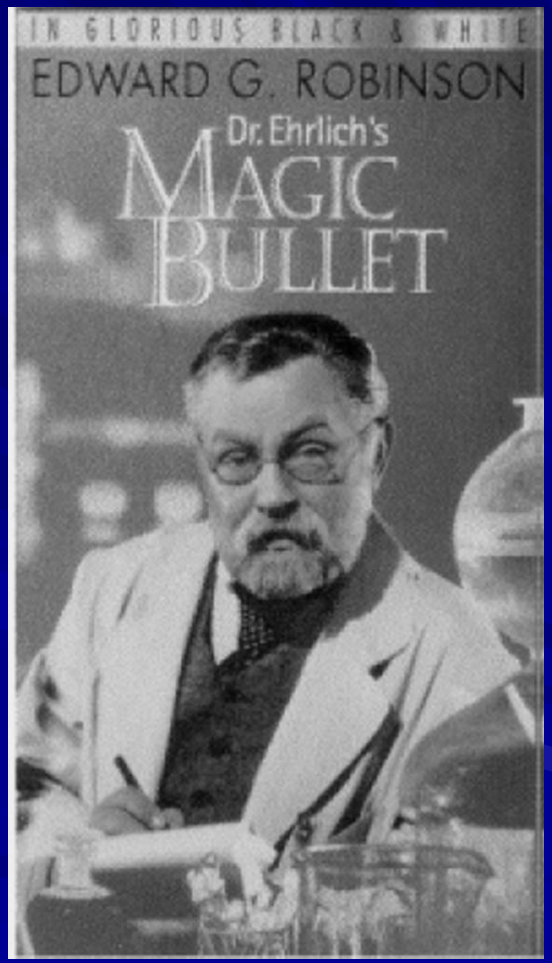
What does genetics tell us and not tell us?

Note : Dandelions are asexual and triploid

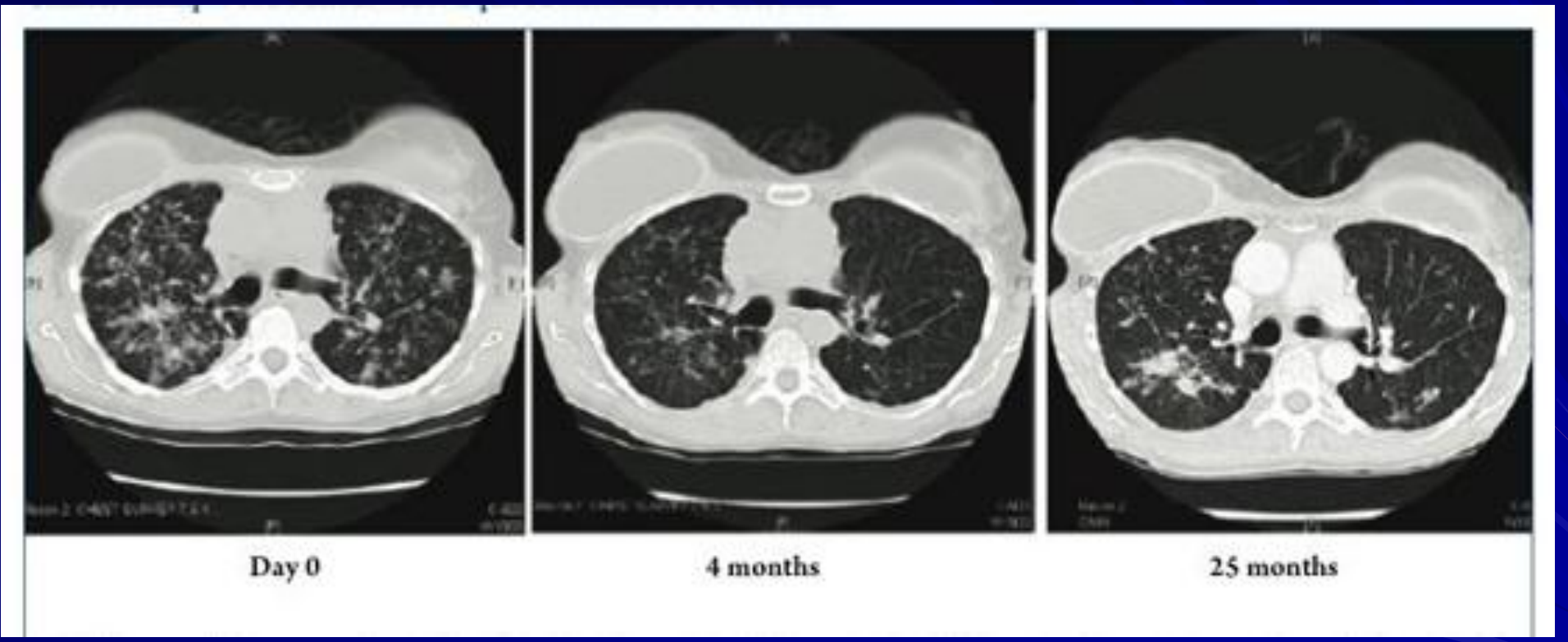
Basic principles: The 40 Years War

- "I will also ask for an appropriation of an extra $100 million to launch an intensive campaign to find a cure for cancer, and I will ask later for whatever additional funds can effectively be used. The time has come in America when the same kind of concentrated effort that split the atom and took man to the moon should be turned toward conquering this dread disease. Let us make a total national commitment to achieve this goal."
- Richard Nixon. State of the Union Speech, 1970

The concept of a cancer cure stems from Paul Ehrlich's magic bullet which proved prophetic in treating infectious diseases



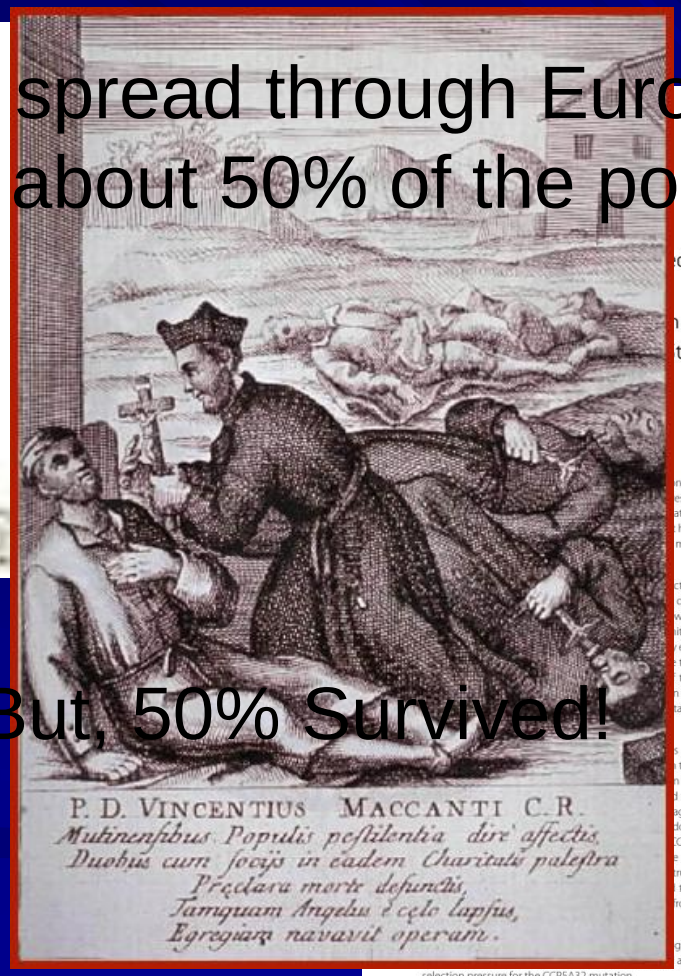
Cancers evolve resistance



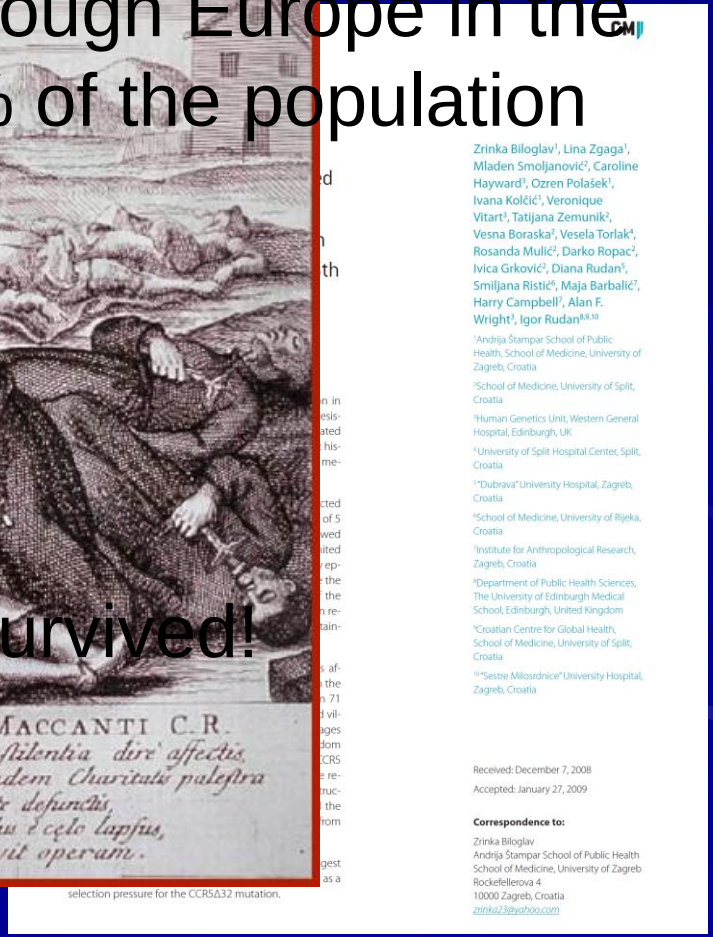
Consider the problem: 10 grams of tumor, modest by oncology standards, contains more cells than there are humans on earth

Could the human population be eradicated without affecting the global ecology?

The bubonic plague, spread through Europe in the 14th Century, killing about 50% of the population



But, 50% Survived!



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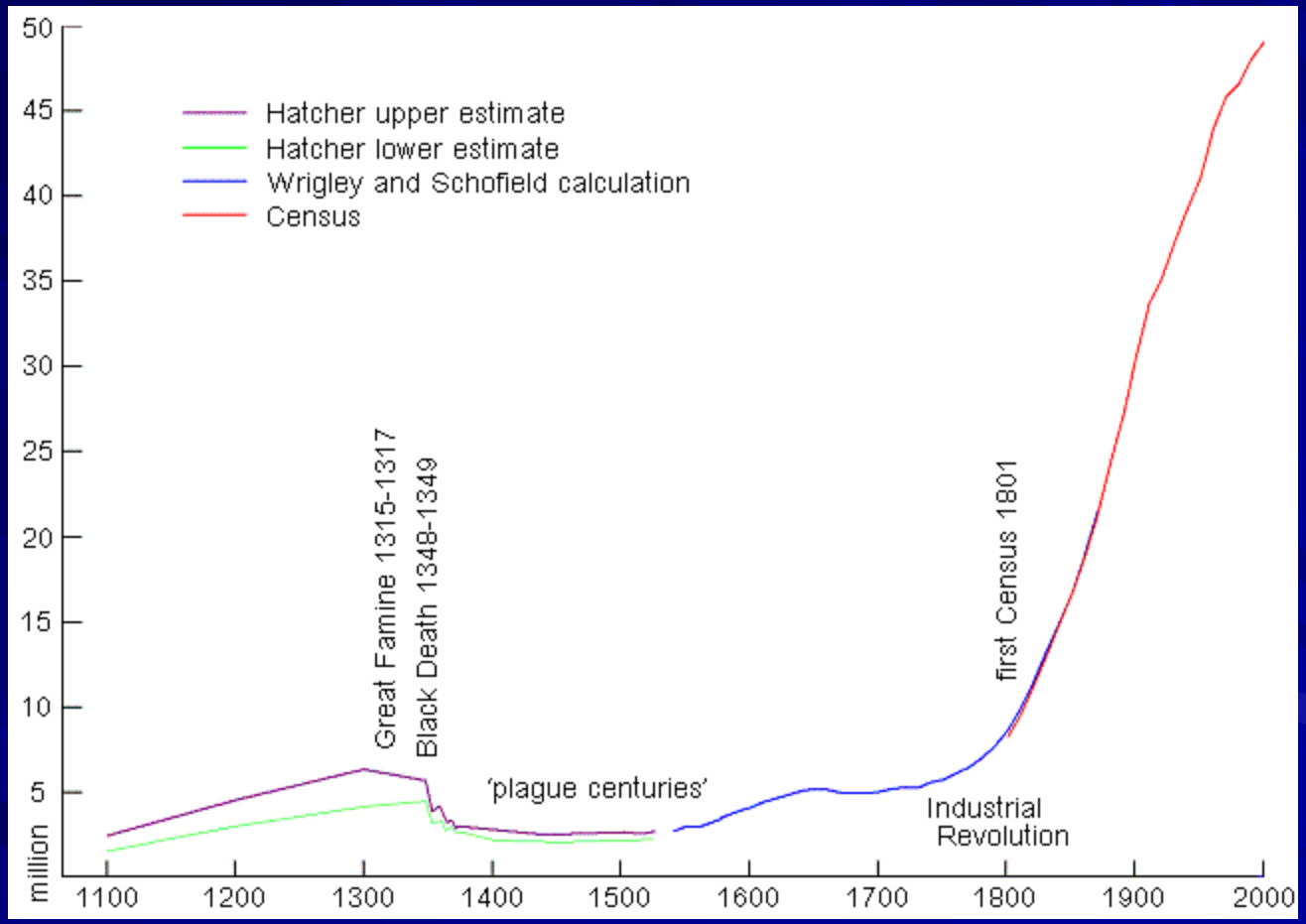
selection pressure for the CCR5Δ32 mutation.

The human population decreased but returned to pre-disease levels



Despite the critical role of evolution therapy failure, evolutionary dynamics virtually never enter clinical design

Overlooking evolution: A systematic analysis of cancer relapse and therapeutic resistance research

C. Athena Aktipis[1,2], Virginia S. Y. Kwan[1], Kathryn A. Johnson[1], Steven L. Neuberg[1], Carlo C. Maley[2]

- Cancer therapy selects for cancer cells resistant to treatment, a process that is fundamentally evolutionary. To what extent, however, is the evolutionary perspective employed in research on therapeutic resistance and relapse? We analyzed 6,228 papers about therapeutic resistance and/or relapse in cancers and found that the use of evolution terms in abstracts has remained at about 1% since the 1980s. However, detailed coding of 22 recent papers revealed a higher proportion of papers using evolutionary methods or evolutionary theory, although this number is still less than 10%. Despite the fact that relapse and therapeutic resistance is essentially an evolutionary process, it appears that this framework has not permeated research. This represents an unrealized opportunity for advances in research on therapeutic resistance.

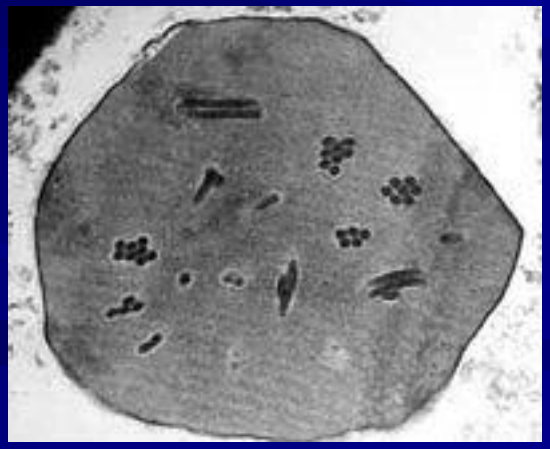
Consider the diamondback moth (Plutella xylostella)

- Probably of European origin - first observed in North America in 1854 in Illinois . Eats cabbage
- The moth has been treated with a wide range of chemicals with transient success
- It has now spread throughout North America causing serious damage to cabbage crops
- In 1988 the moth was reported to be resistant to all known insecticides
- A moth infestation is incurable. Current treatments limit pesticide application to reduce crop damage

Consider the Rhinoceros Beetle (*Oryctes rhinoceros)*

- Significant pest of the coconut palm in islands in the south Pacific
- Rhinoceros beetles are also the strongest animals on the planet in relation to their size
- Rhinoceros beetle larvae are sometimes fried and eaten as a delicacy
- Male beetles are also used for gambling fights since they naturally compete for female beetles with the winner knocking the other off a log
- Pesticides unsuccessful

A biological solution proved effective



- A baculovirus that attacks both the larval and adult stages was discovered in Malaysia
- Introduction of the baculovirus has resulted in successful control of the beetle population for over 20 years
- Despite the fact that a number of beetle phenotypes resistant to infection have been discovered

Invasive pests are now managed using principles of Integrated Pest Management (IPM): lessons from the alfalfa weevil

- “The presence of alfalfa weevils in an alfalfa field does not in itself justify pesticide application.”
- “Chemical control should not be used unless weevil damage approaches the level that will reduce net profit by at least the cost of a pesticide application”
- Several species of wasps and a parasite of the adult weevil (*Microctonus aethiopoides*), have been introduced. In most cases, these natural enemies will help keep infestations below economically damaging levels

Traditional high dose density

Norton-Simon model of high dose density

Maximum tolerable dose in shortest period of time

Minimize probability of mutation conferring resistance.

Three critical assumptions:

1. Resistant populations are not present prior to therapy
2. Resistance is acquired as a step-wise mutation
3. The resistant phenotype rapidly proliferates and results in patient death.

Why does high dose-dense therapy not cure the cancer?

- Resistant cells are present prior to therapy due to phenotypic diversity or microenvironmental factors or both.
- The tumor adapts but the therapy does not. Tumor cells begin adapting immediately upon administration of therapy but treatment protocols rigidly apply the same drugs until the tumor progresses

Sources of resistance in cancer population

1. Reaction norm – individual cells can upregulated defense – i.e. PgP
2. Multiple genetic subpopulations with different phenotype
3. Environmental factors confer resistance to phenotypically sensitive populations
4. Mutation during therapy.

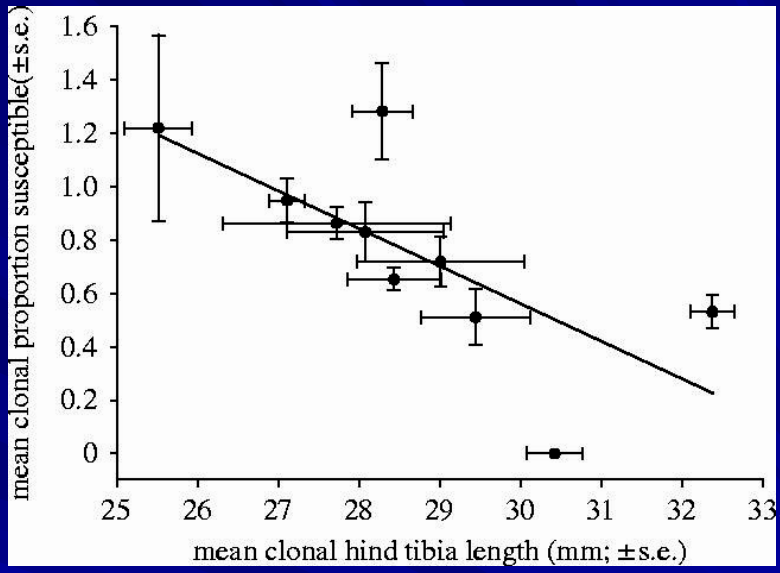
KEY POINT: Cancer therapy is typically applied with a fixed strategy while cancer adapts and evolves with the first dose

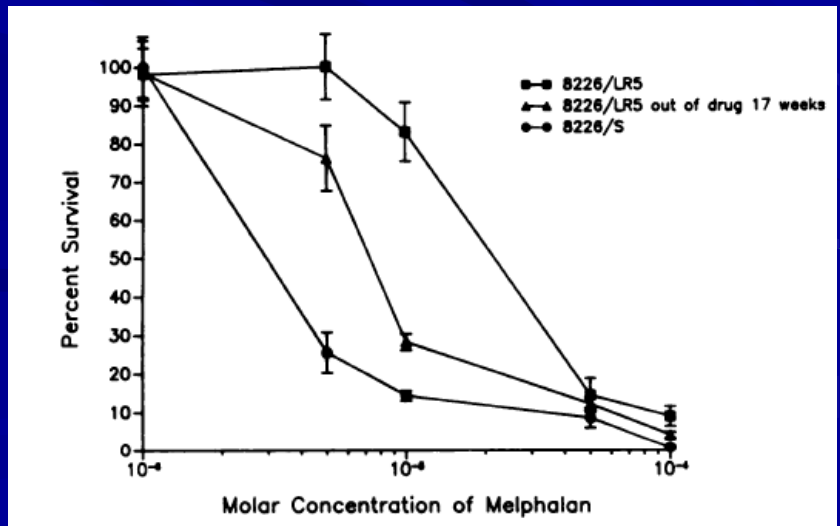
Lessons from Integrated Pest Management – Strategic Therapy

1. Eradication of a disseminated invasive pest is virtually never successful
2. Heterogeneity in pest phenotype and environmental conditions will result in resistance to virtually any therapy.
3. Control is possible but requires treatment strategies explicitly designed for that purpose
4. Kill not the maximum number of pests but the minimum necessary
5. “Biological controls” are more effective than chemical

Key parameter in designing treatment strategies: cost of resistance

- Any resistance mechanisms requires resources
- Resources diverted to resistance are not available for proliferation
- In the absence of therapy, the resistant populations will generally be less fit
- The cost of resistance manifests in various ways depending on the therapy

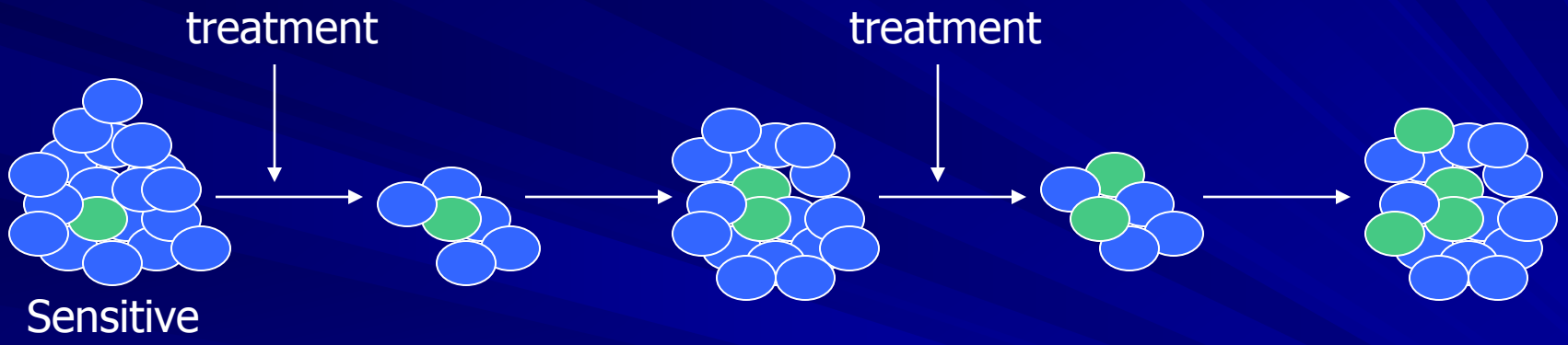




Adaptive therapy – modelled after integrated pest management

- Explicitly abandon the concept of high dose density for cure or control
- The goal is to maintain tolerable tumor burden
- Assume resistant cells are less fit, in the absence of therapy, and are present prior to treatment
- Apply chemotherapy judiciously to maintain a stable population of sensitive cancer cells to suppress proliferation of resistant phenotypes
- Basic principle – retain a cell population that you can control and get them to suppress growth of the population you cannot control

Kill not the maximum possible number of cells, just the minimum necessary

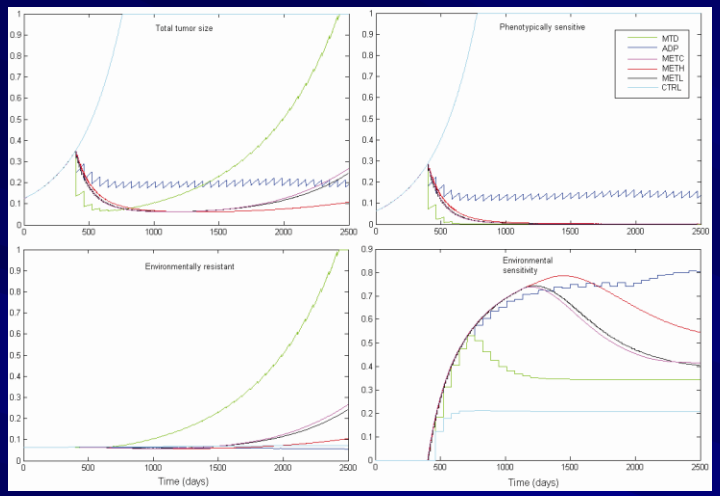


Sensitive Cell

Resistant Cell

- Low dose chemotherapy
  - Less toxicity? Limit sensitive cell death
- Attempt to maintain stable tumor burden
- Chemotherapy sensitive cells suppress resistant cell growth
- Induce near steady state of patient-tumor interaction

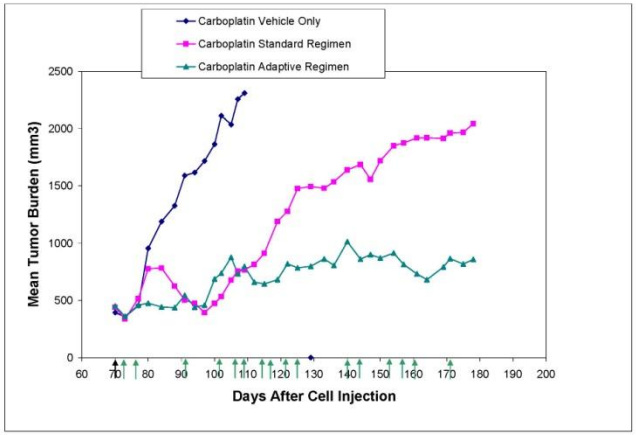
Adaptive therapy



Mathematical Models

High dose density results in shortest patient survival – killing sensitive cells leaves adaptive landscape open to rapid proliferation by resistant phenotype

Adaptive therapy –abandon curative intent - limit therapy to stabilizing sensitive population which then suppresses growth of resistant clones



Experiments:

Adaptive therapy achieves long term survival <u>with decreasing dose of carboplatin</u>

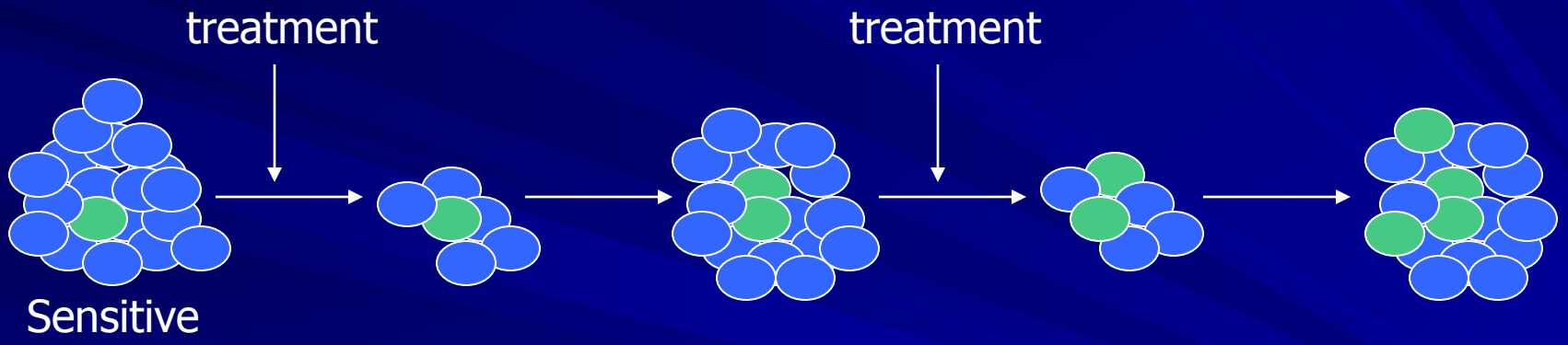
Caveat:

If the resistant phenotype is fitter than the resistant phenotype, you are screwed.

Darwinian First principles in therapy: Consider the diamondback moth (Plutella xylostella)

- Probably of European origin -first observed in North America in 1854 in Illinois . Eats cabbage
- The moth has been treated with a wide range of chemicals with transient success
- It has now spread throughout North America
- In 1988 the moth was reported to be **resistant to all known insecticides**
- Complete eradication of an invasive species is not currently achievable
- General strategy is control.
- Strategies to eradicate are incompatible with strategies to control
- Can control strategies be implemented in oncology?

Evolutionary methods for long term survival with cancer: Kill the minimum necessary and exploit their fitness advantage over resistant phenotypes



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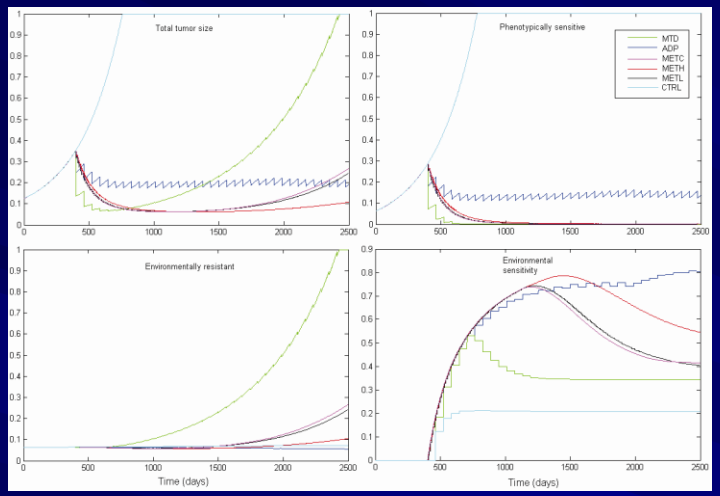

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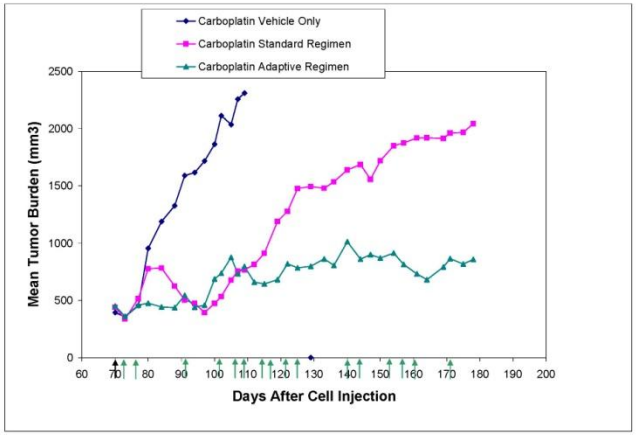

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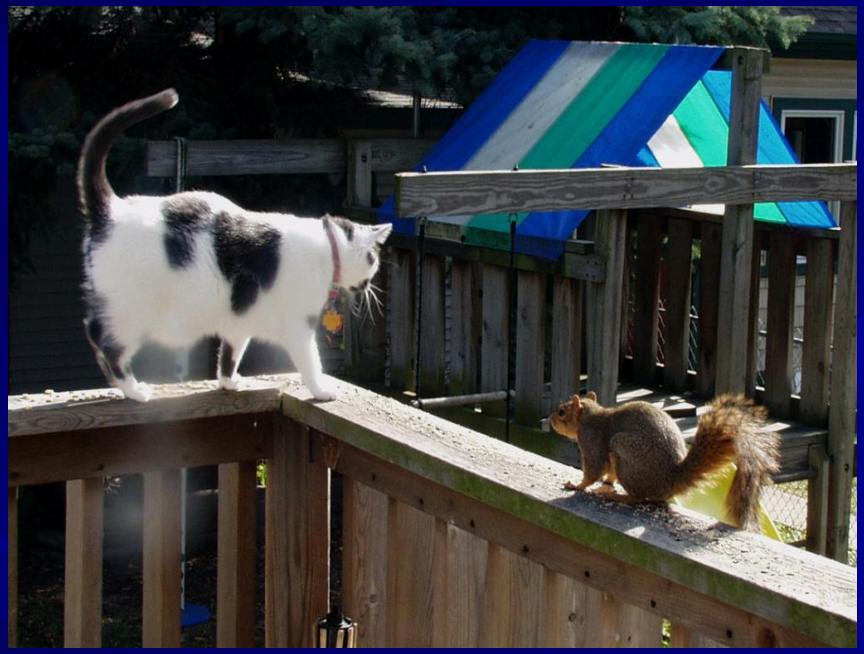
Why are biological controls more effective?

- Hypothesis: the key to pest control is phenotypic cost of resistance
- Adaptation to drugs (like pesticides) usually requires upregulation of extant cellular machinery – relatively inexpensive
- Adaptation to predator may require more extensive phenotypic changes at greater cost.
- The evolutionary double bind – adaptation to initial therapy results in increased sensitivity to a second treatment

Consider a squirrel pest

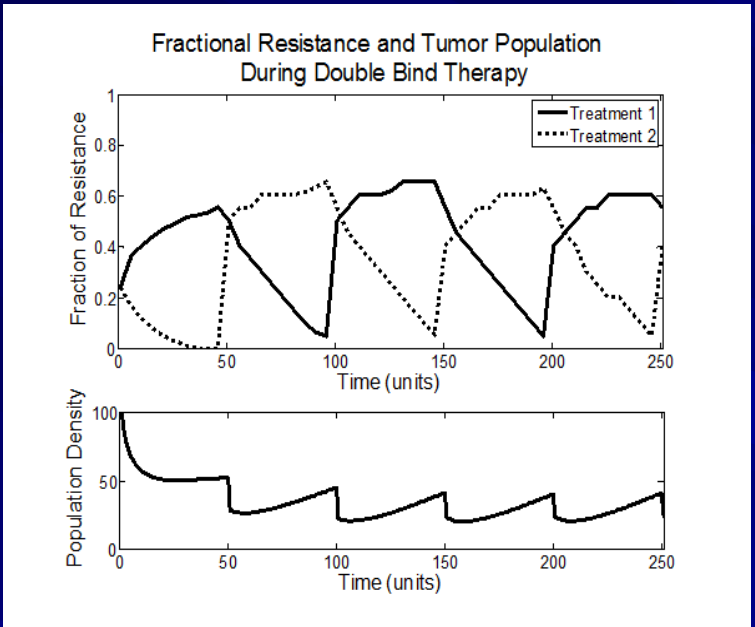
Introduce a cat



The squirrel adapts

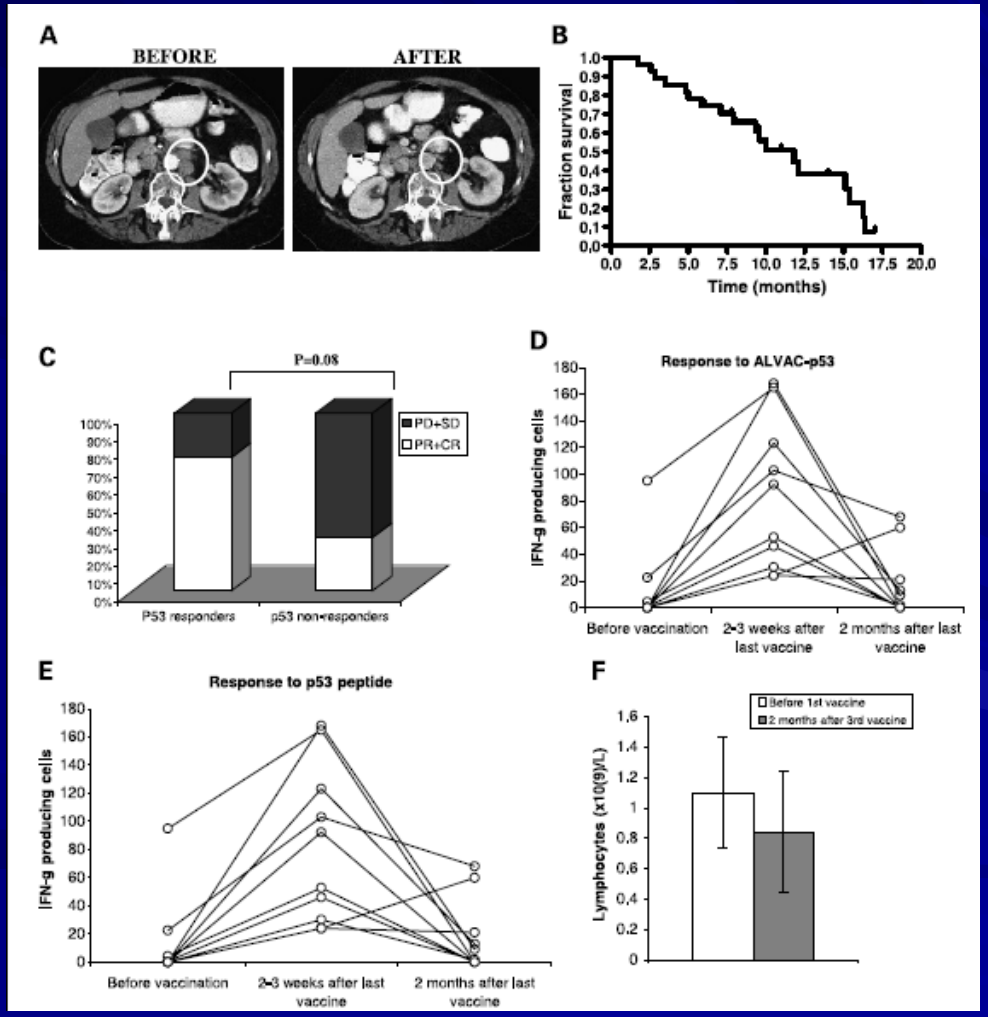
Answer: add a snake

Double bind therapy uses cats and snakes – evolutionarily futile cycle



- Initial therapy kills tumor cell and selects for resistant populations with a known strategy
- Follow with a therapy focused on the adaptation
- Repeat as necessary

Moffitt study: 2nd and 3rd line therapy in small cell lung cancer with vaccine against mutant p53. Results: strong immune response elicited but only one partial clinical response in 29 subjects



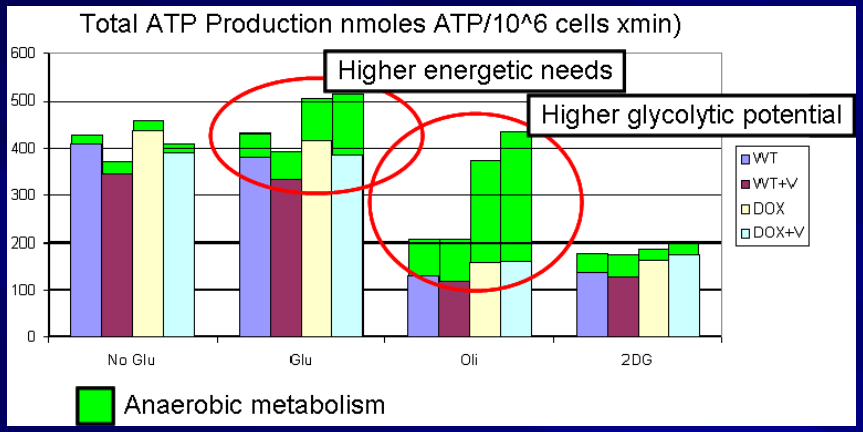
Fortuitously, the patients were followed after exiting the trial. 21 received 2nd or 3rd line chemotherapy. Historical experience predicts a response rate of <5%

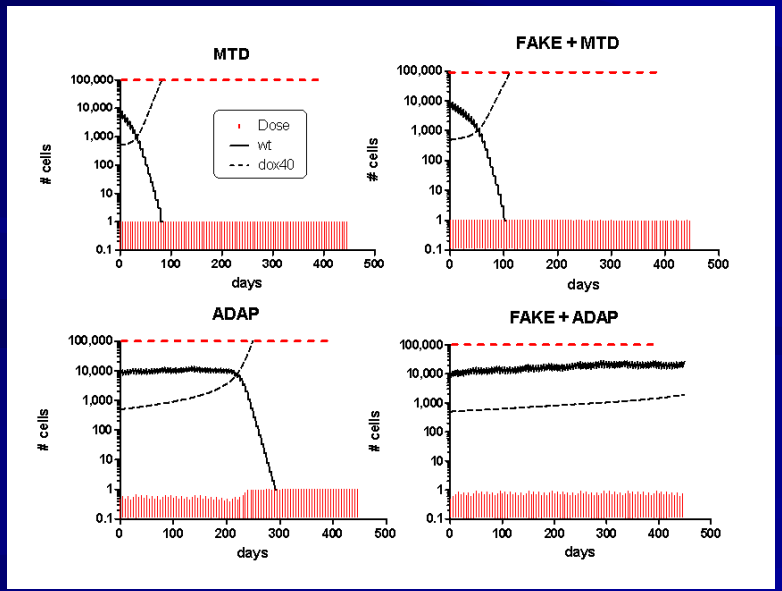
Table 3. Response to second-line chemotherapy in vaccinated patients

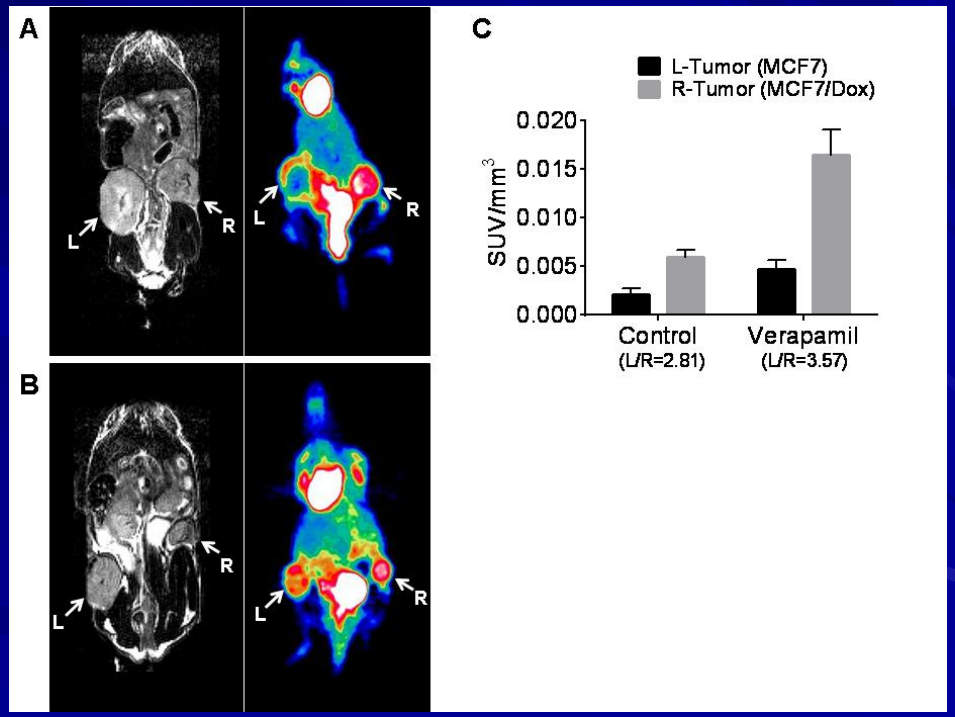
All patients who received chemotherapy after vaccine (n = 21)		Platinum-resistant patients who received chemotherapy after vaccine (n = 13)	
Response	n (%)	Response	n (%)
CR	3 (14.3)	CR	1 (8)
PR	10 (47.6)	PR	7 (54)
SD	4 (19.05)	SD	3 (23)
PD	4 (19.05)	PD	2 (15)
CR + PR	13 (61.9)	CR + PR	8 (61.5)

Abbreviations: PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response (all according to Response Evaluation Criteria in Solid Tumors).

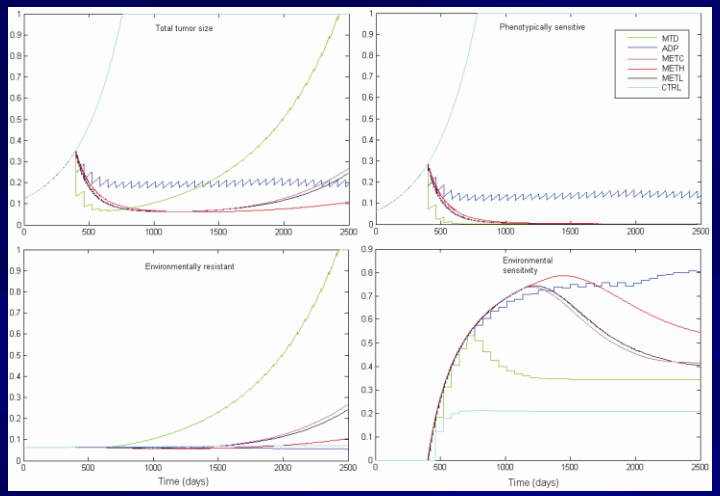
Latest application to breast cancer. Exploit cost of MDR using ersatzdroges!



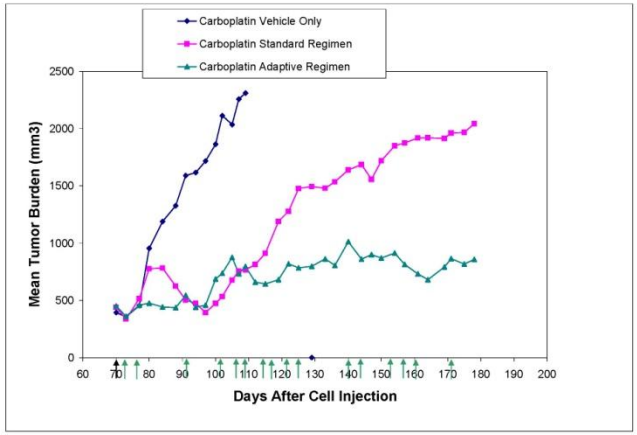




Evolutionary therapy in mice permits indefinite survival with cancer

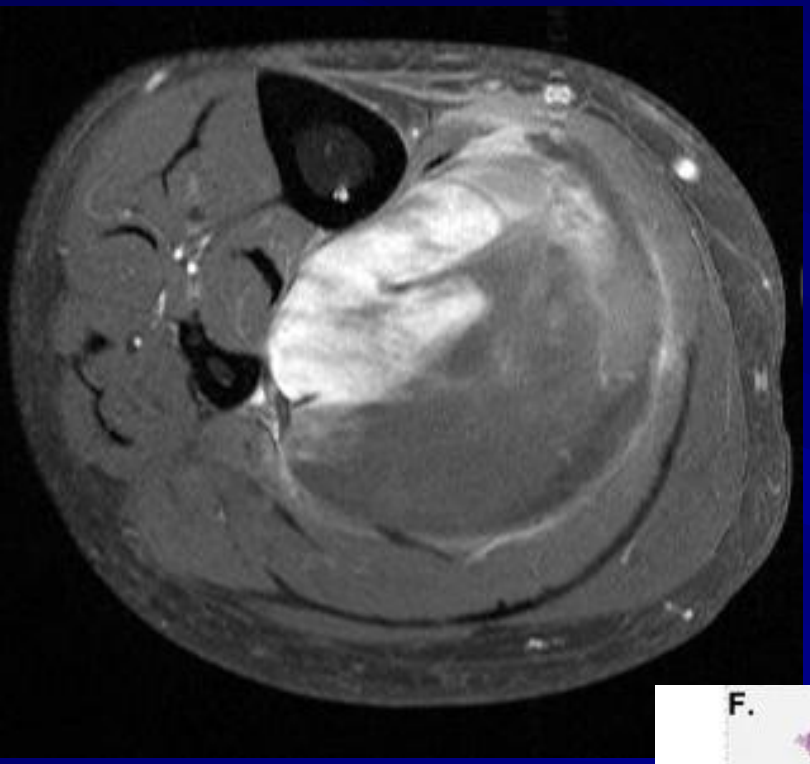


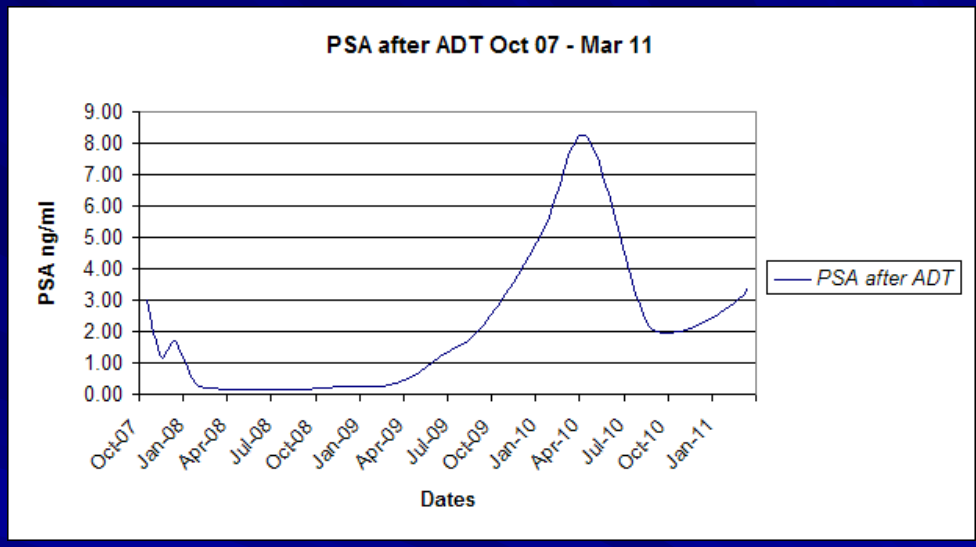
The problem: how to understand these complicated dynamics in patients.

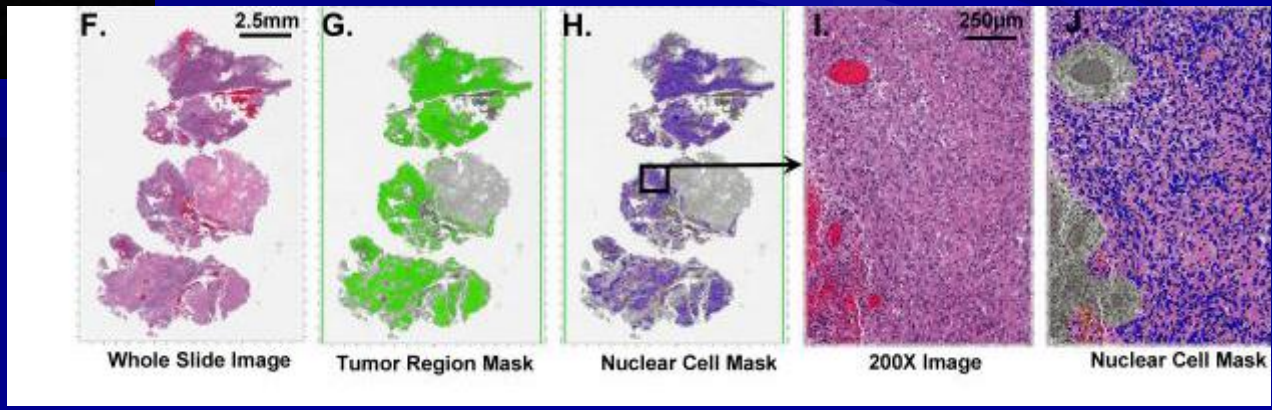


Optimal data is non-destructive, readily available and spatially or temporally explicit

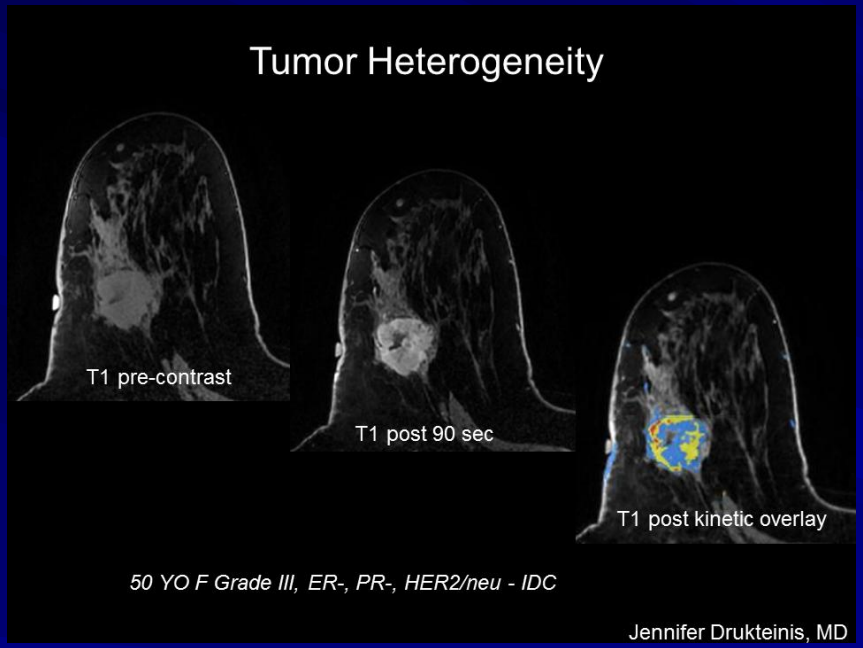
.

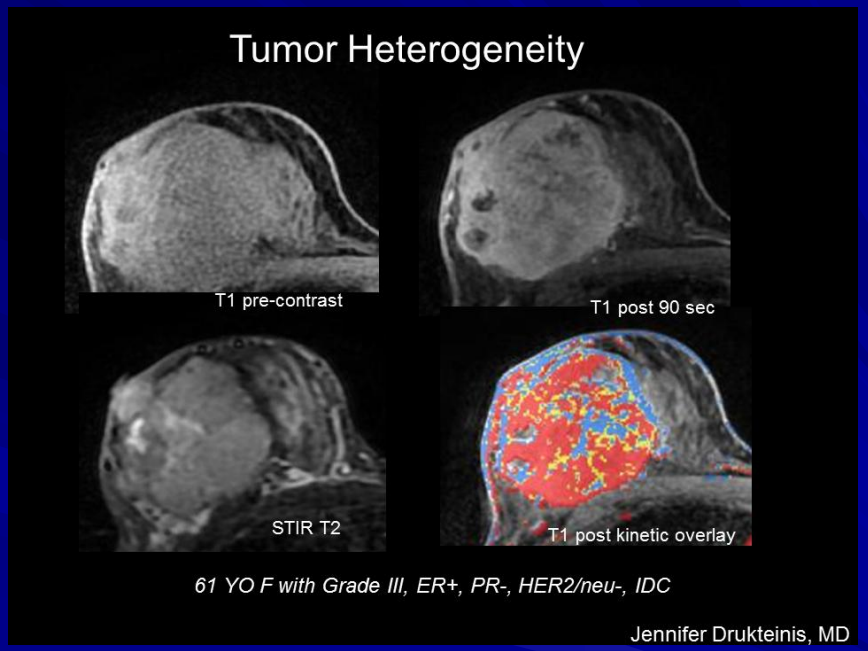






Goal: Maximize value of data.
Intratumoral heterogeneity as a function of variation in environmental selection forces (blood flow)

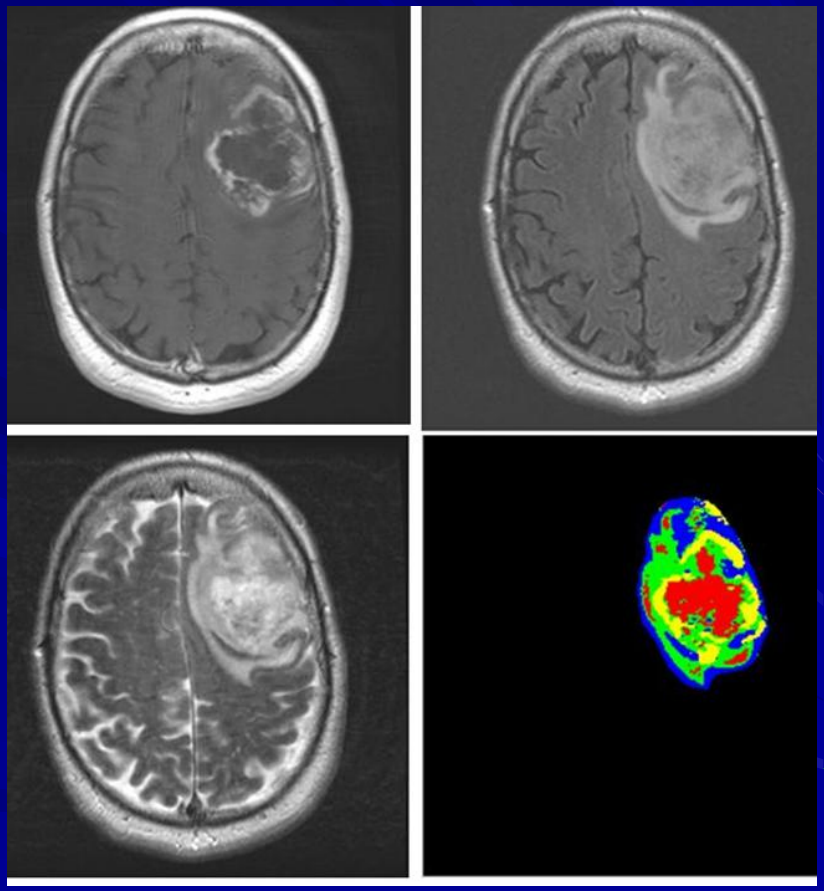


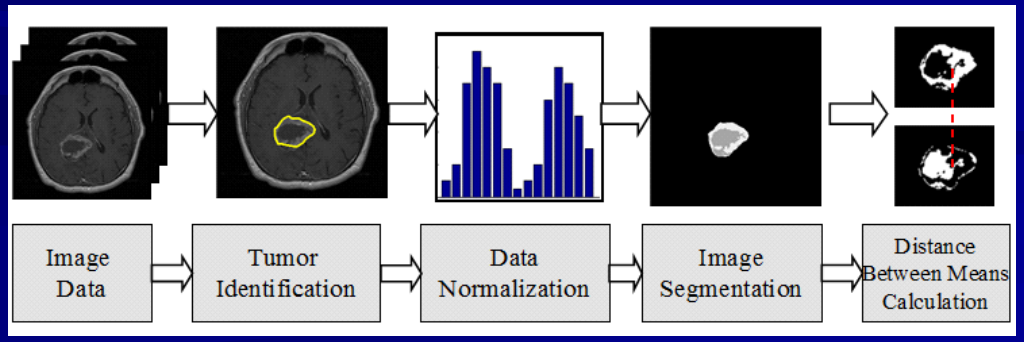


Blood flow and cytotype may be linked using evolutionary principles

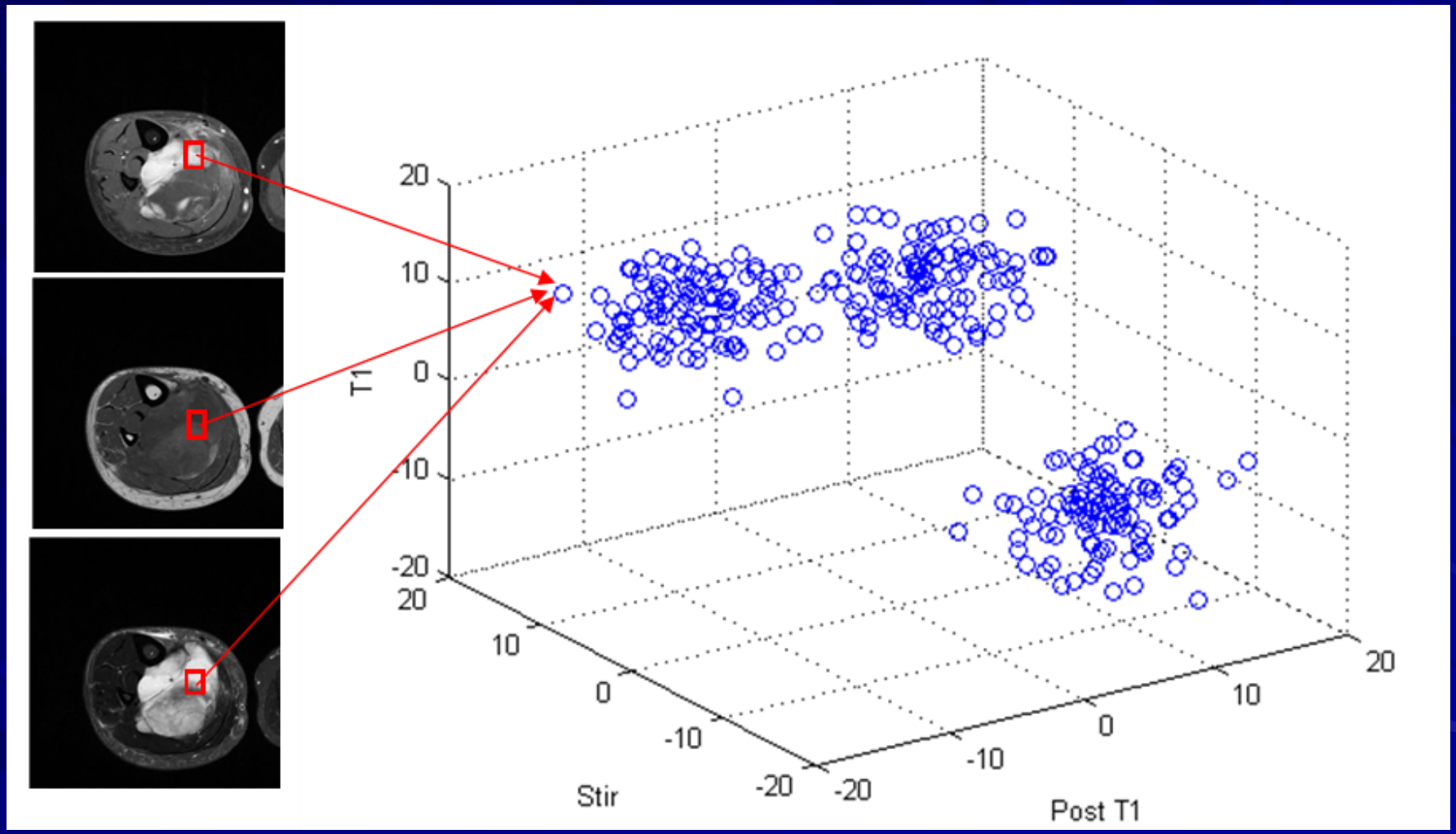
Imaging to define intratumoral ecology (habitats)

- T1-Post gad is a metric of blood flow and substrate availability
- T2, Diffusion weighted, and FLAIR sequences are measures of cellularity and interstitial edema
- Superimposing the images could generate ecological maps of environmental selection forces and size of adapted populations



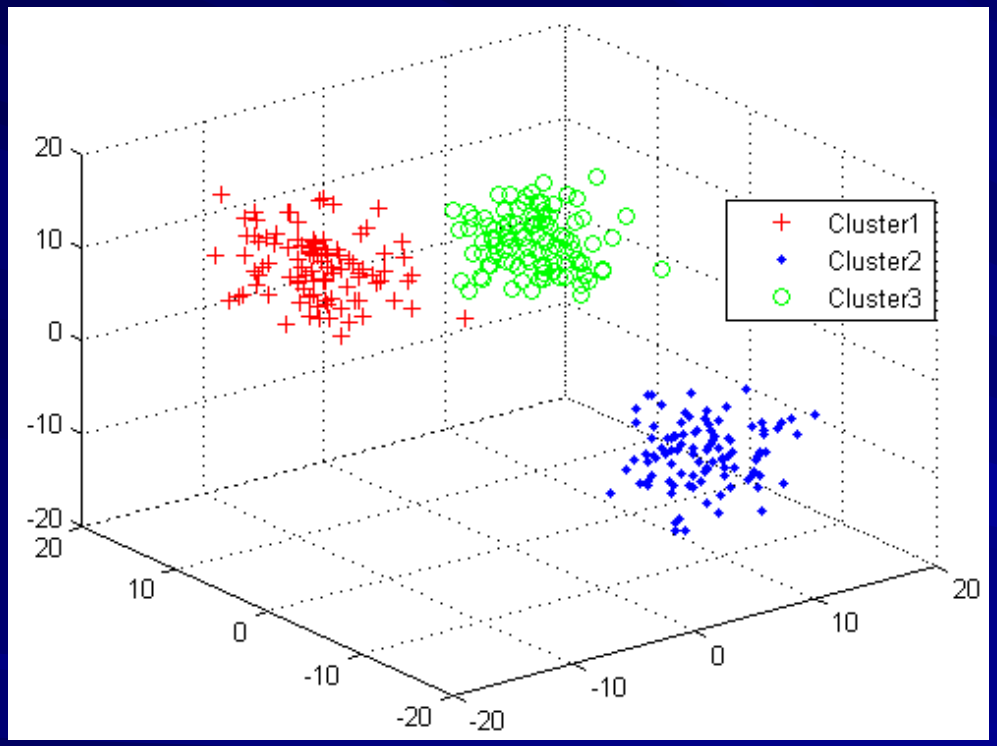


Using clinical imaging to define spatial variations in tumors

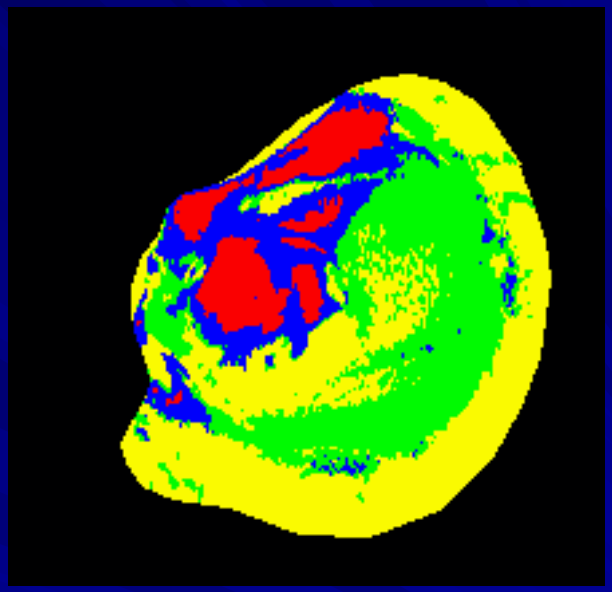


COURTESY OF MU ZHAO

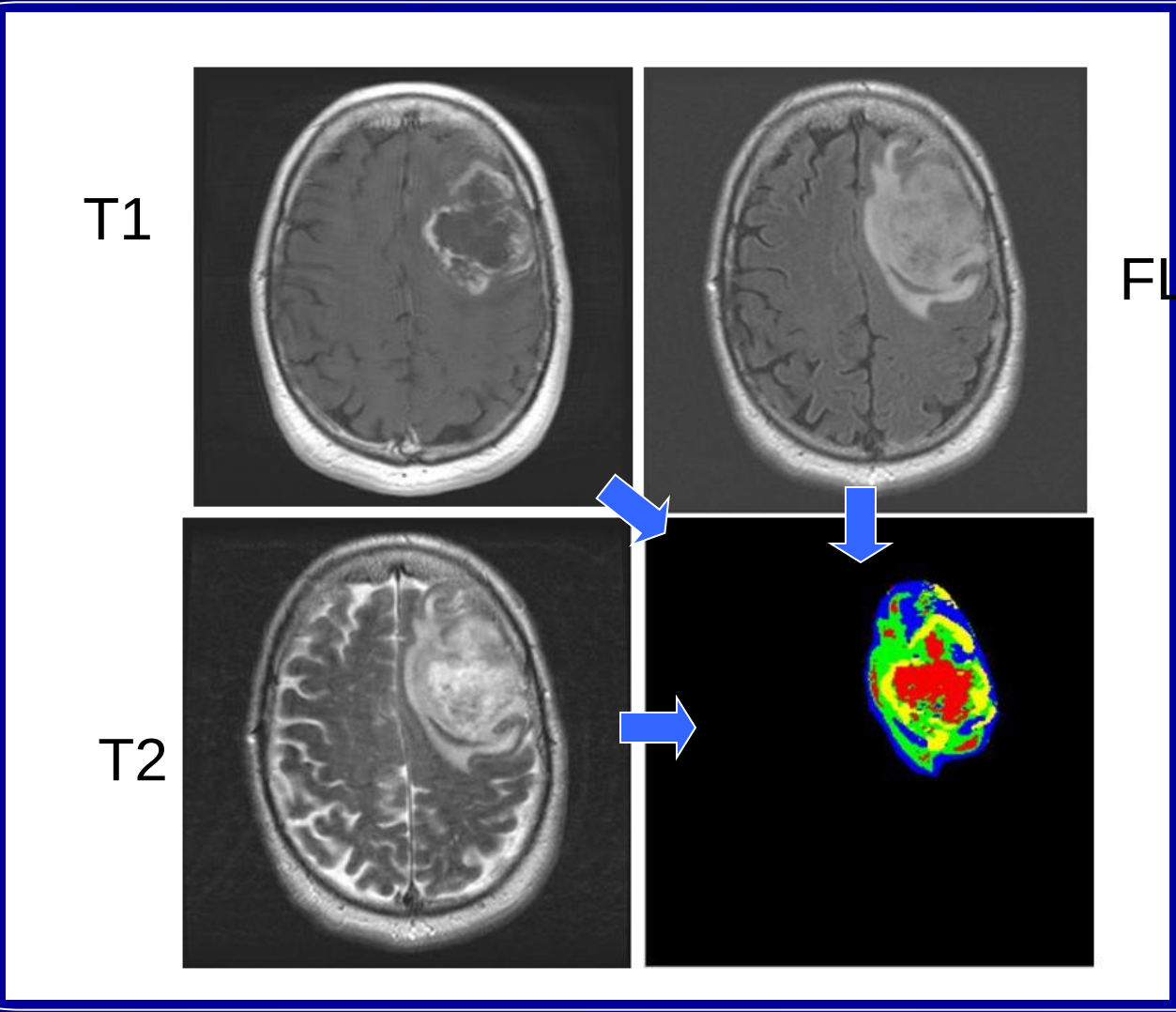
Each habitat can be projected back into the tumor image



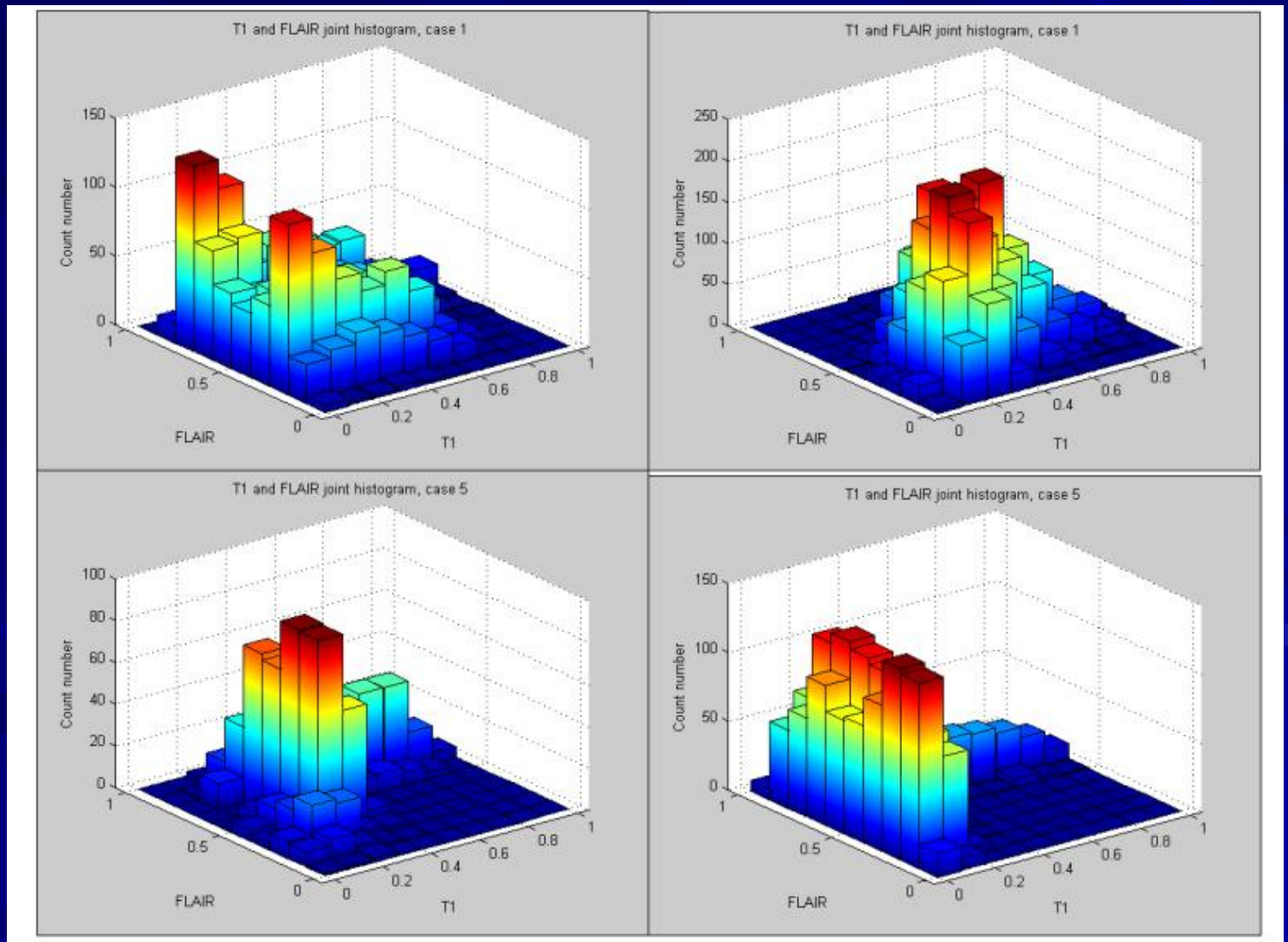
3D SPACE



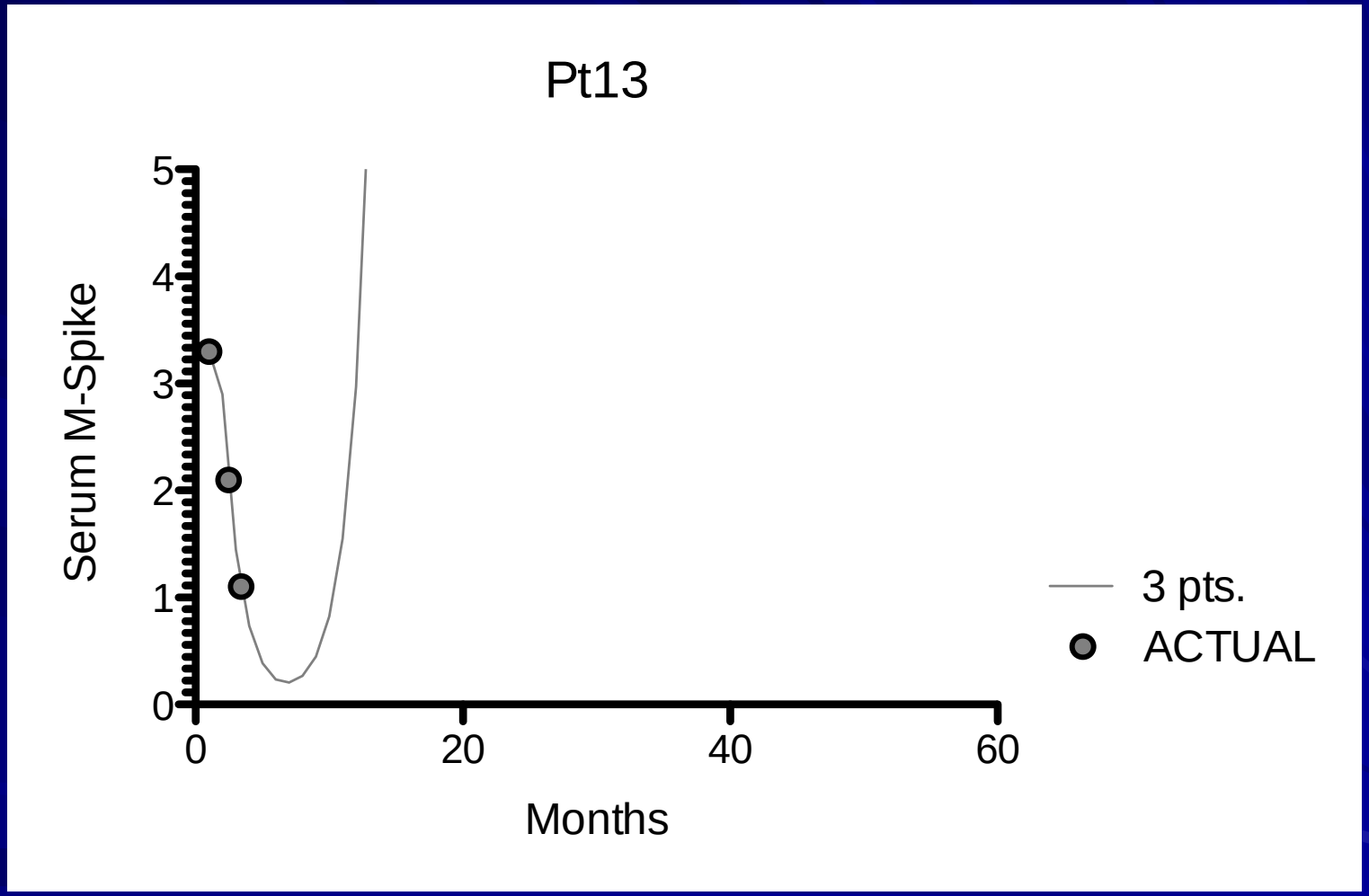
Habitat Imaging in GBM
(fuzzy c-means clustering)



Temporal dynamics: GBM habitats change dramatically after radiation/chemotherapy

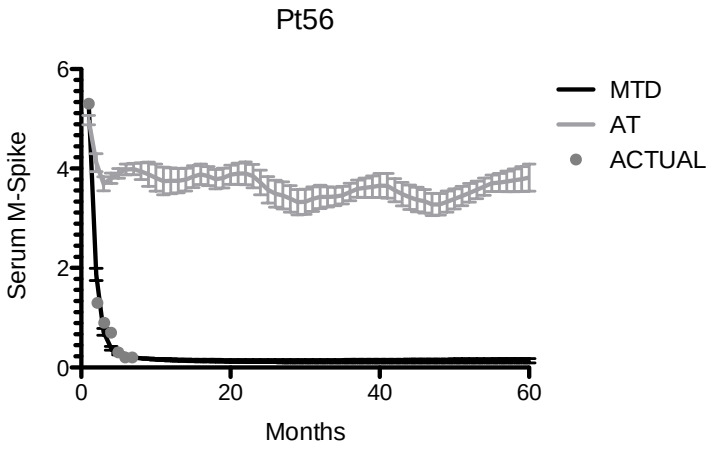


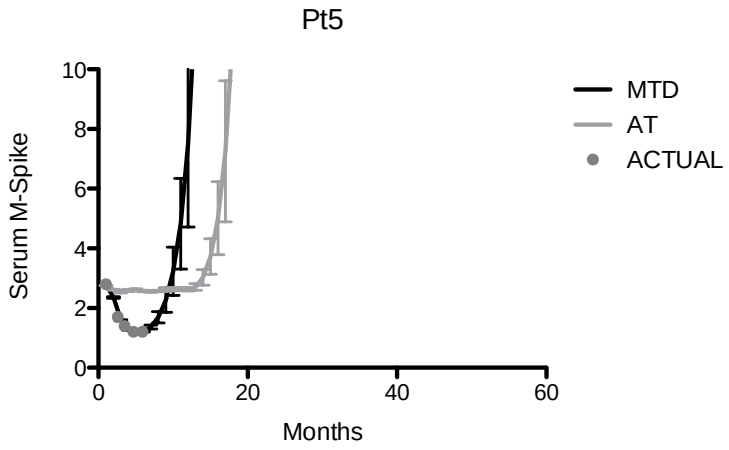
So, how does this work?

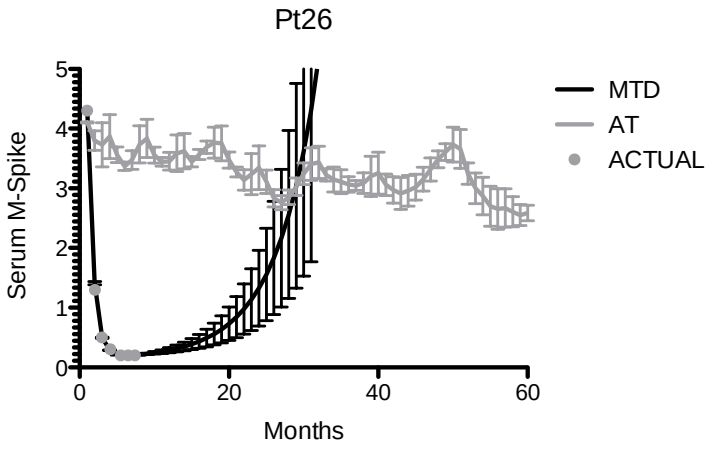


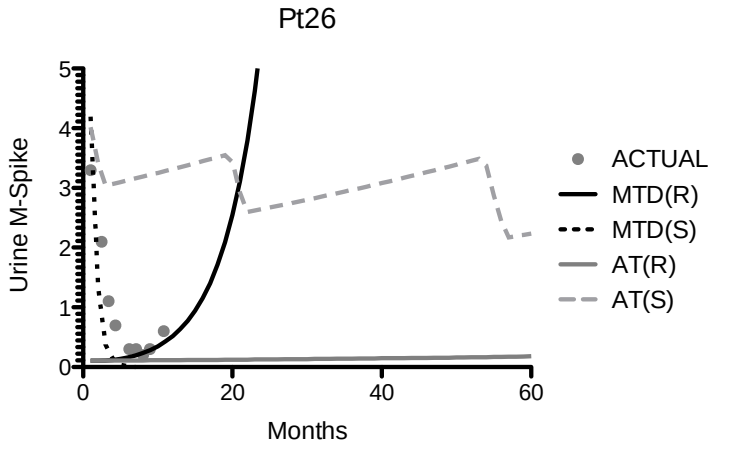
Ariosto Silva, IMO

Within this data set, alternative therapeutic strategies are suggested in some patients but cannot evaluate CR and NR individuals

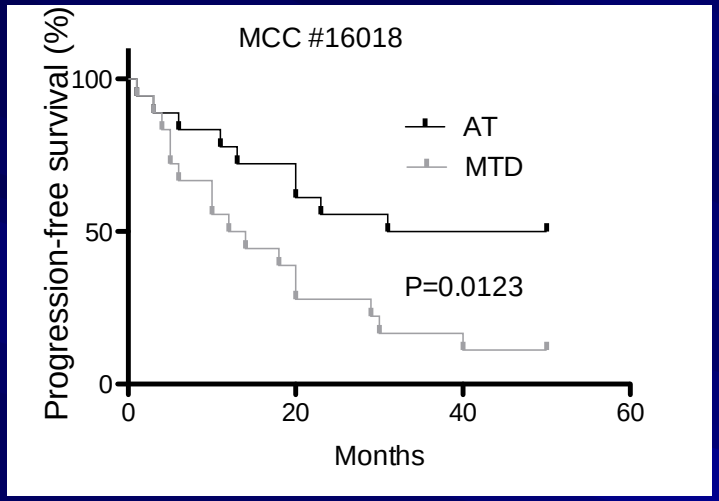


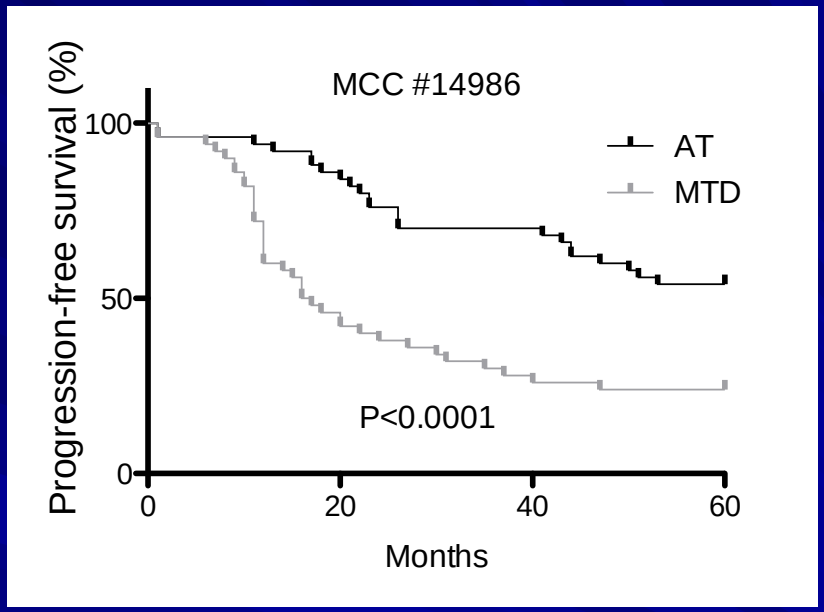


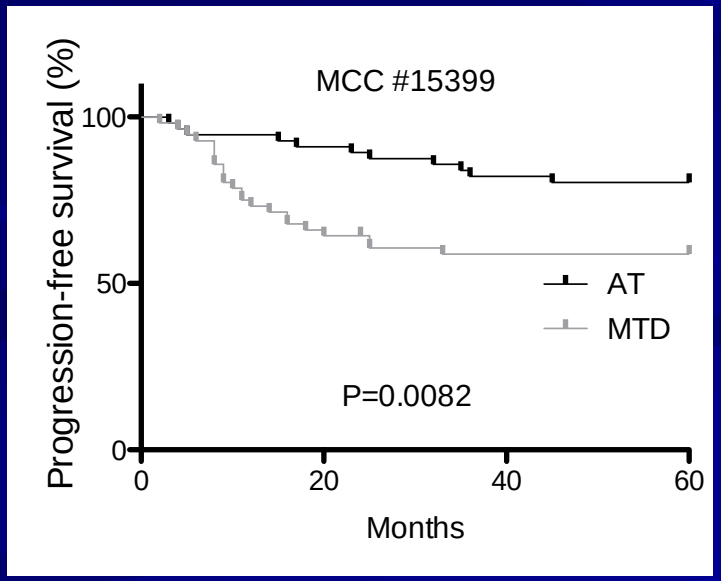




Computational model suggests optimal therapeutic dosing schedule would have improved outcomes in 3 separate trials







Constructing prospective patient-specific computational models using bone marrow biopsies and aspirates

Key parameter estimates:

1. Drug delivery

   Microvessel density

2. EMDR

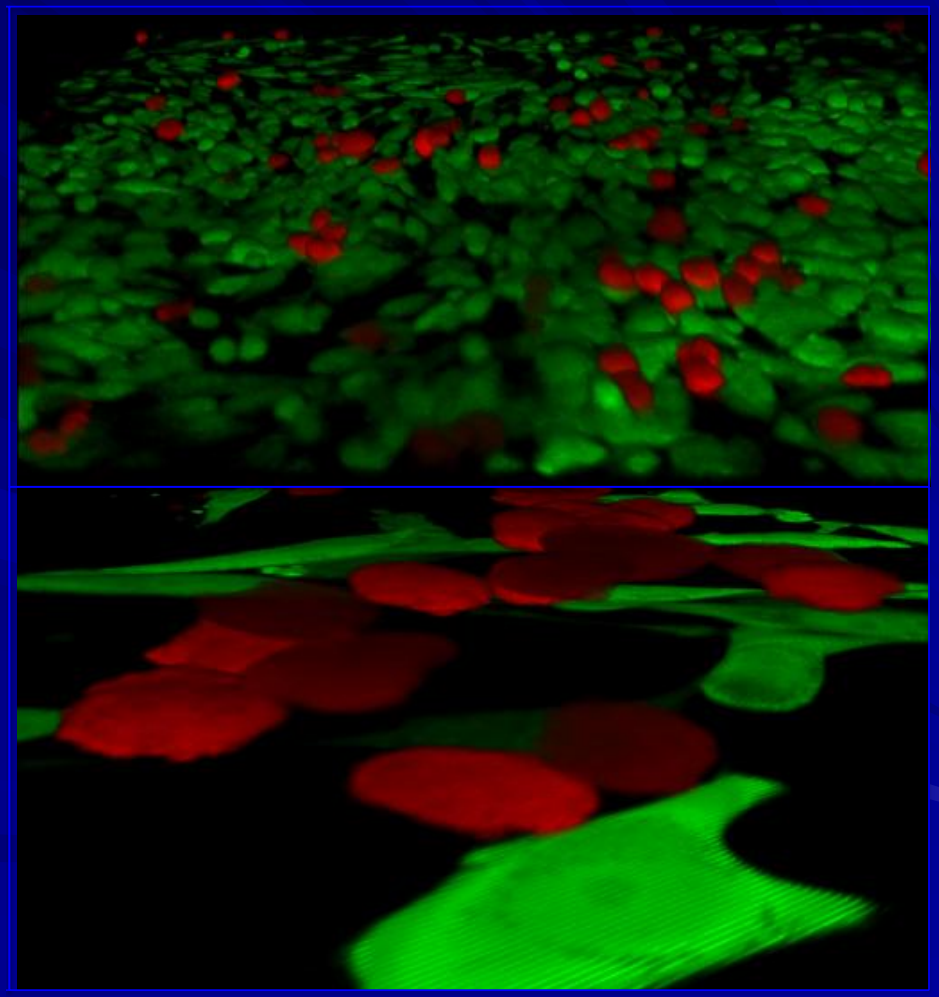
   Fibronectin concentration and spatial distribution

3. Phenotypic resistance

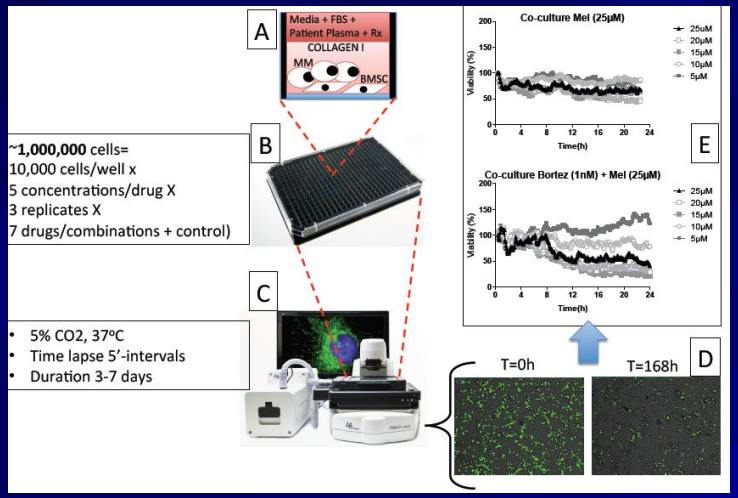
   HR karyotype (FISH)
   PgP expression

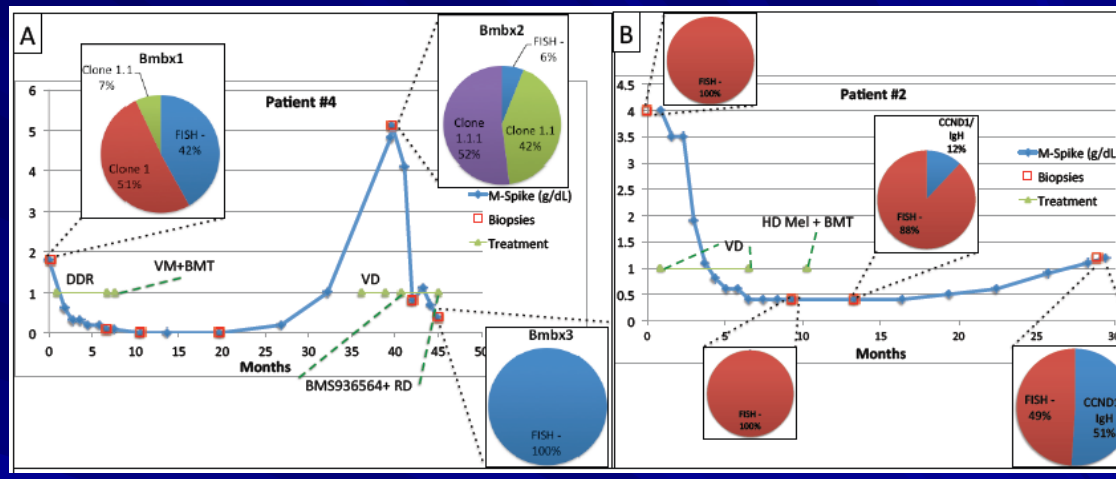
4. Phenotypic resistance

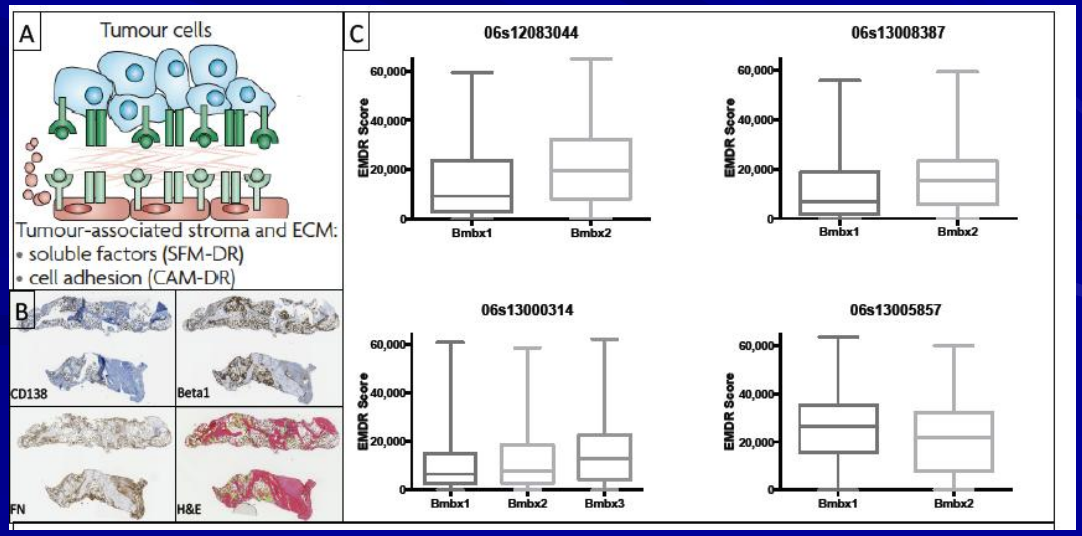
   Microfluidic tesing of aspirated cells



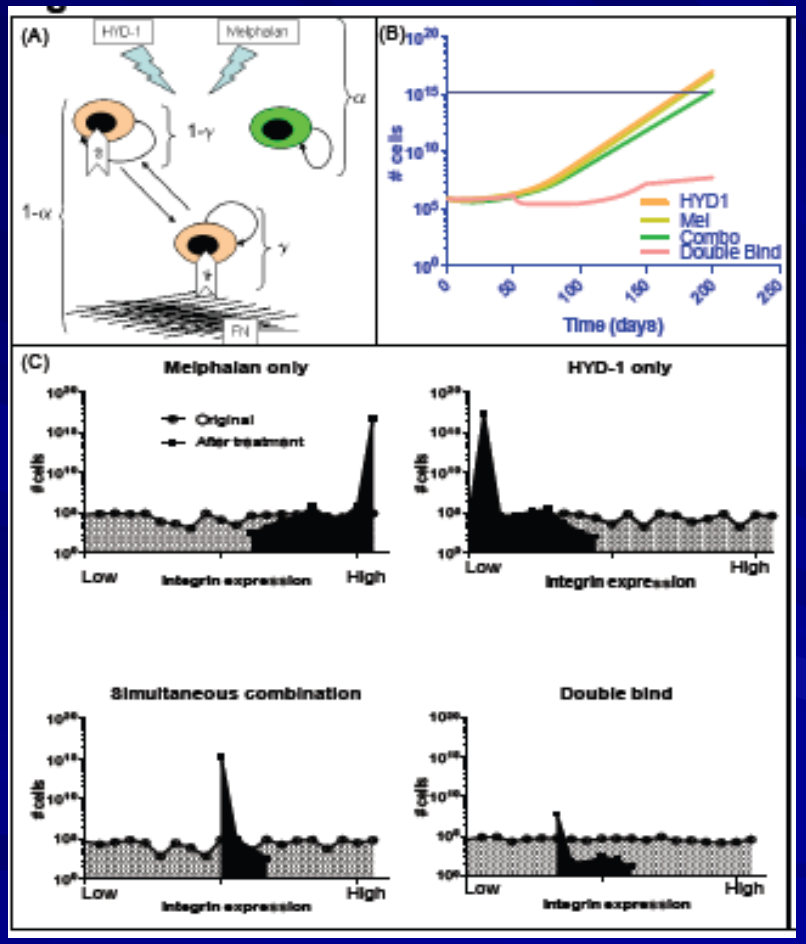
Data: BM environment and cellular dynamics



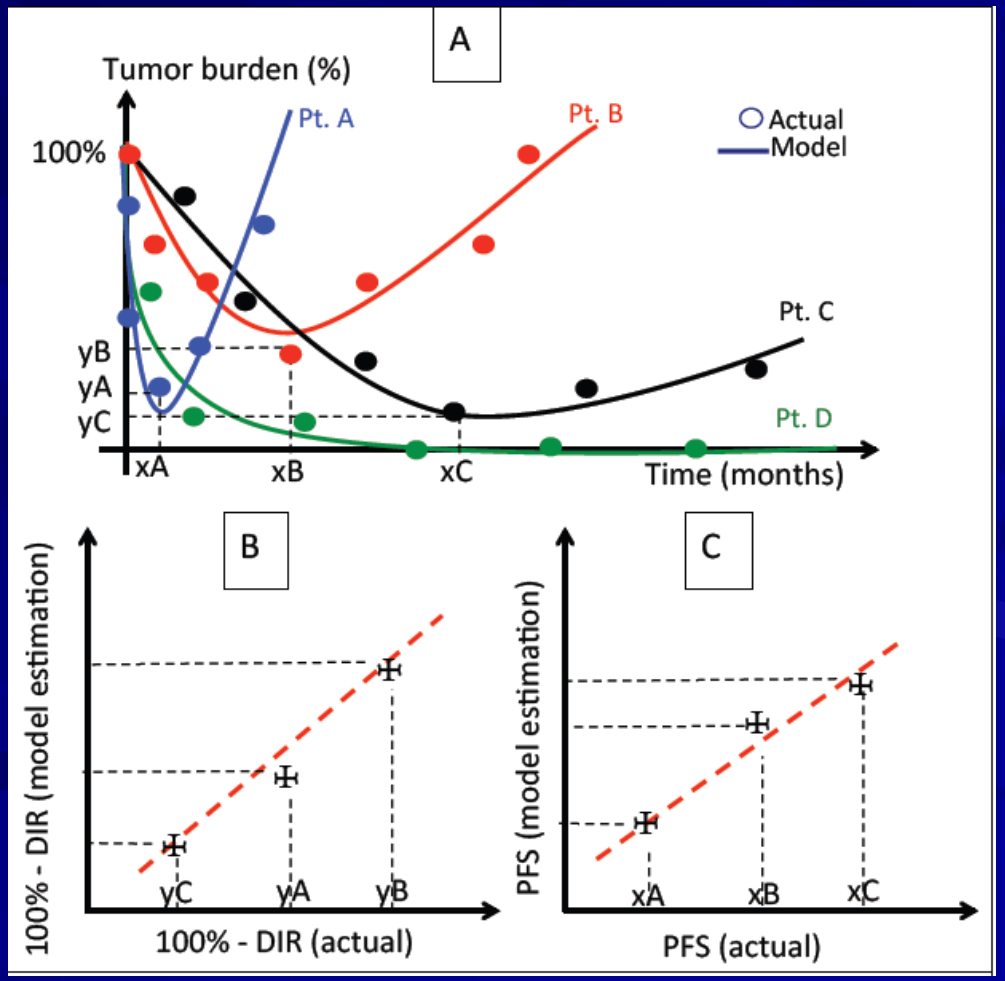




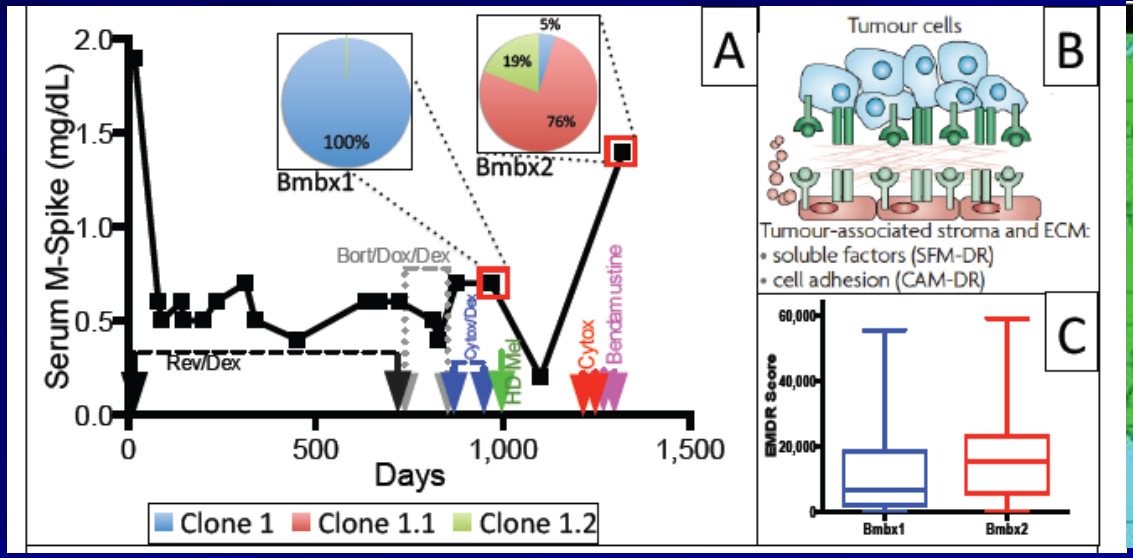
First Principles



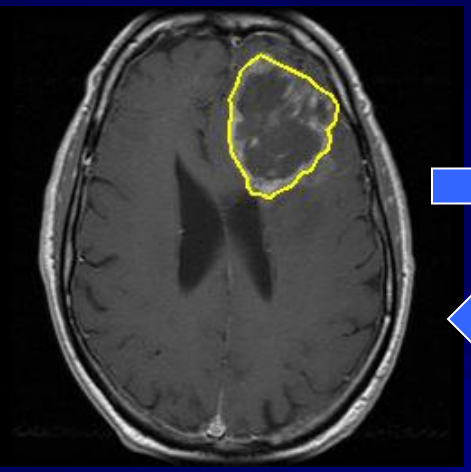
Pre-therapy model predictions for treatment response, validated against data



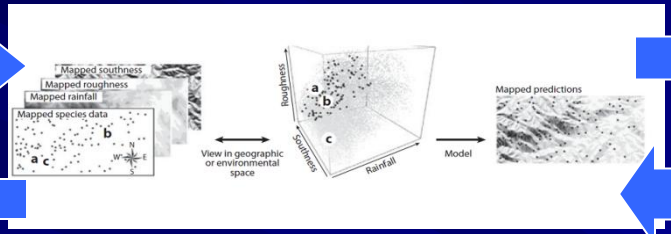
Proposal: A clinical trial based on computational decision support

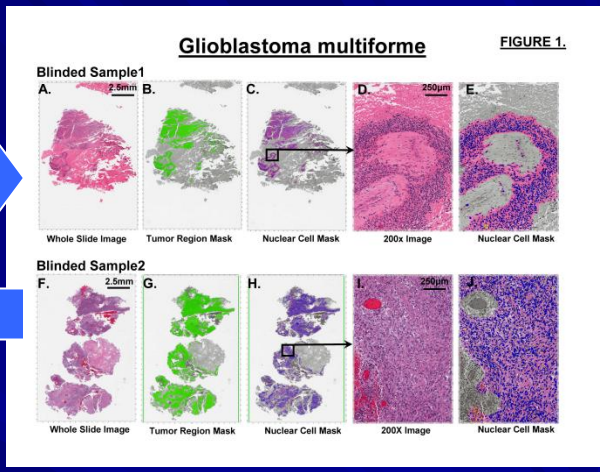


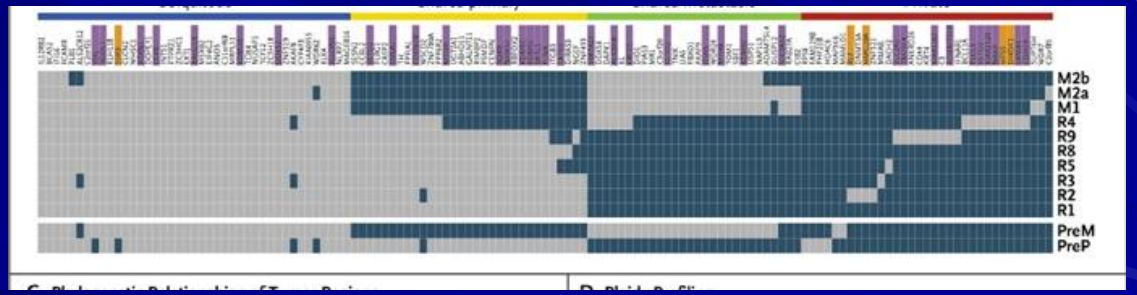
Patient-specific therapy



Computational models







Thank you

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