The Dynamics of Drug Resistance in Cancer

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Joint work with

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  Hematology, COH

- Michael Gottesman, MD
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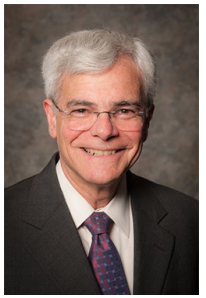

- Peter Kim
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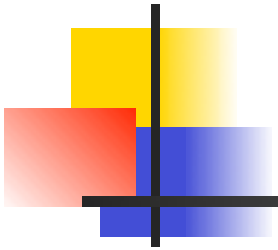


Outline

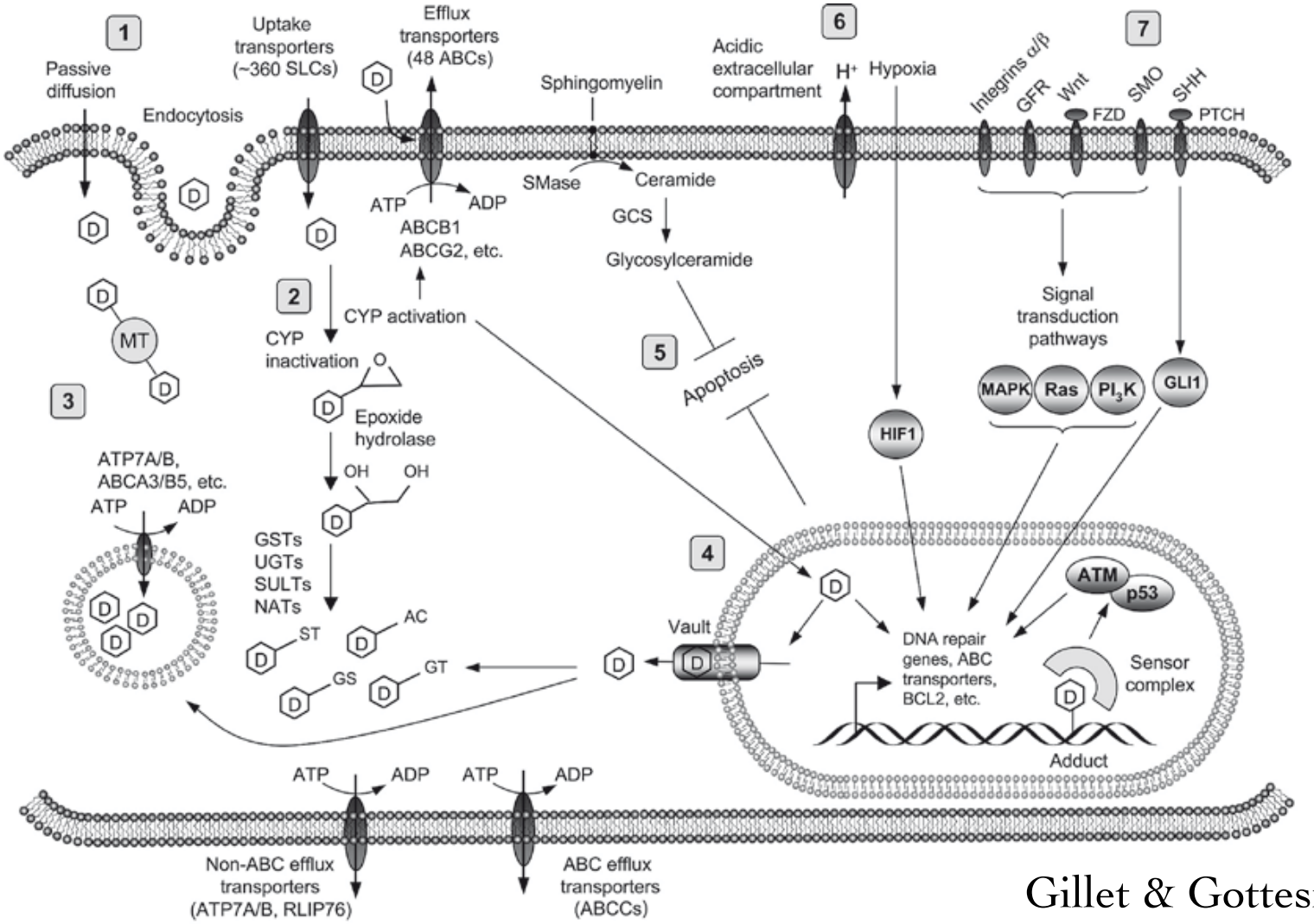
- Drug Resistance in Cancer
  - Mechanisms of MDR
  - Mathematics & Drug Resistance
- A Specific Example
  - Chronic Myelogenous Leukemia
  - Modeling the role of the immune response
  - Drug resistance and cancer stem cells
- Heterogeneity and Resistance
  - Selection process

American Cancer Society – 2013

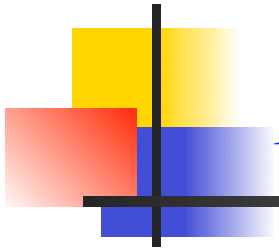
Estimated Number* of New Cancer Cases and Deaths by Sex, US, 2013

	Estimated New Cases			Estimated Deaths		
	Both Sexes	**Male**	**Female**	**Both Sexes**	**Male**	**Female**
All Sites	1,660,290	854,790	805,500	580,350	306,920	273,430
Oral cavity & pharynx	41,380	29,620	11,760	7,890	5,500	2,390
Tongue	13,590	9,900	3,690	2,070	1,380	690
Mouth	11,400	6,730	4,670	1,800	1,080	720
Pharynx	13,930	11,200	2,730	2,400	1,790	610
Other oral cavity	2,460	1,790	670	1,640	1,260	380
Digestive system	290,200	160,750	129,450	144,570	82,700	61,870
Esophagus	17,990	14,440	3,550	15,210	12,220	2,990
Stomach	21,600	13,230	8,370	10,990	6,740	4,250
Small intestine	8,810	4,670	4,140	1,170	610	560
Colon†	102,480	50,090	52,390	50,830	26,300	24,530
Rectum	40,340	23,590	16,750			
Anus, anal canal, & anorectum	7,060	2,630	4,430	880	330	550
Liver & intrahepatic bile duct	30,640	22,720	7,920	21,670	14,890	6,780
Gallbladder & other biliary	10,310	4,740	5,570	3,230	1,260	1,970
Pancreas	45,220	22,740	22,480	38,460	19,480	18,980
Other digestive organs	5,750	1,900	3,850	2,130	870	1,260
Respiratory system	246,210	131,760	114,450	163,890	90,600	73,290
Larynx	12,260	9,680	2,580	3,630	2,860	770
Lung & bronchus	228,190	118,080	110,110	159,480	87,260	72,220
Other respiratory organs	5,760	4,000	1,760	780	480	300
Bones & joints	3,010	1,680	1,330	1,440	810	630
Soft tissue (including heart)	11,410	6,290	5,120	4,390	2,500	1,890
Skin (excluding basal & squamous)	82,770	48,660	34,110	12,650	8,560	4,090
Melanoma-skin	76,690	45,060	31,630	9,480	6,280	3,200
Other nonepithelial skin	6,080	3,600	2,480	3,170	2,280	890
Breast	234,580	2,240	232,340	40,030	410	39,620
Genital system	339,810	248,080	91,730	58,480	30,400	28,080
Uterine cervix	12,340		12,340	4,030		4,030

Mechanisms of MDR



Gillet & Gottesman, 2010



Mathematics and Drug Resistance

Lavi, Gottesman, Levy.

The dynamics of drug resistance: A mathematical perspective.

Drug Resistance Updates 15, 2012, pp.90-97.

- Overcoming multidrug resistance in cancer: 35 years after the discovery of ABCB1
- Contribution of tumoral & host solute carriers to clinical drug response
- Epigenetic mechanisms in tumorigenesis, tumor cell heterogeneity and drug resistance
- The tumor microenvironment is a dominant force in MDR
- Targeting MDR in breast and lung cancer
- Drug resistance in the mouse cancer clinic

Mathematics and Drug Resistance

- **Q1: What is the optimal protocol for drug scheduling in terms of dose and timing?**

  - **Goal**: maximize the control of the tumor while minimizing toxicity.

  - **Solution 1**: **Norton & Simon**. Based on kinetic resistance (phase of the cell cycle). Deliver the most effective level of drug over as short time as possible. Tumors given less time to grow between treatments are more likely to be eradicated.

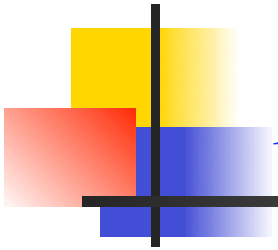
  - **Solution 2**: **Goldie & Coldman**. Minimize the development of drug resistance based on the occurrence of mutations. When more than one (non cross-resistance) drug is used – treatment should alternate between drugs as quickly as possible.

Mathematics and Drug Resistance

- **Continuous infusion vs. short pulses** (Gardner, Panetta, Smieja,...). Continuous infusion prevents tumor regrowth between treatment. Exposes more cells to the drug when they are in the sensitive phase of the cell cycle.
- Problem: if the drug is applied too quickly, cells that are in an invulnerable part of their cell cycle may escape. If the drug is applied too slowly, drug resistance may develop.

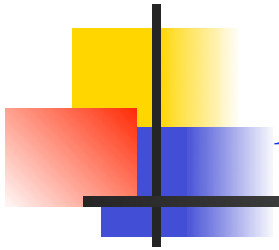
★ **Q2: When several drugs are available, how many drugs should be used? Should they be used in combination or sequentially?**

- **Komarova & Wodarz**. Study the number of the drugs that should be used based on the size of the tumor. Generally, conclude that combination therapy is less likely to yield an advantage over single-drug therapy.



Mathematics and Drug Resistance

- Q3: How effective is chemotherapy in eradicating a tumor?
- Q4: How is early detection and early therapy connected with the development of drug resistance?
- **Q5: What is the probability that at the time of diagnosis resistant cancer cells are already present?**
- Q6: How fast does the subpopulation of cells that develop drug resistance grow?
- **Q7: What function best describe the "growth law" of cancer?**



Modeling Drug Resistance

The simplest possible (mathematical) model…

An elementary approach to modeling drug resistance in cancer (Tomasetti + DL, 2010)

- **A deterministic approach**: the single drug case.
- Assuming (i) an exponential cancer growth (ii) a wild-type cell differentiates into one wild-type and one mutant cell:

$$\begin{cases} N'(t) = (L-D)N(t), \\ R'(t) = (L-D)R(t) + uN(t). \end{cases} \qquad t \le t^*.$$

$$\begin{cases} N'(t) = (L-D-H)N(t), \\ R'(t) = (L-D)R(t) + uN(t). \end{cases} \qquad t > t^*.$$

  - N(t) = # of wild-type cancer cells
  - R(t) = # of mutated cells
  - L = birth rate
  - D = natural death rate; H= drug induced death rate.
  - u = mutation rate
- Initial conditions: R(0)=0, N(0)=N_0

The single-drug case

- t^* = Time treatment starts
- M = Total # of cancer cells at the beginning of the treatment

★ Assuming small mutation rate:

$$t^* \approx \frac{1}{L-D} \ln \frac{M}{N_0}.$$

The amount of resistance present at the time when the treatment starts:

$$R(t^*) = N_0 u t^* e^{(L-D)t^*} \approx \frac{Mu \ln(M/N_0)}{L(1-D/L)}$$

- R depends on the turnover rate (!)

The 2-drug case

$$\begin{cases} N'(t) = (L-D)N(t), \\ R_1'(t) = (L-D)R_1(t) + uN(t), \\ R_2'(t) = (L-D)R_2(t) + uN(t), \\ R'(t) = (L-D)R(t) + uR_1(t) + uR_2(t). \end{cases} \qquad t \le t^*.$$

$$\begin{cases} N'(t) = (L-D-H)N(t), \\ R_1'(t) = (L-D-H)R_1(t) + uN(t), \\ R_2'(t) = (L-D-H)R_2(t) + uN(t), \\ R'(t) = (L-D)R(t) + uR_1(t) + uR_2(t). \end{cases} \qquad t > t^*.$$

- Ri(t) = resistant to drug i. R(t) = resistant to both drugs

The amount of resistance present at the time when the treatment starts:

$$R(t^*) = N_0(ut^*)^2 e^{(L-D)t^*} \approx M\left[\frac{u\,\ln(M/N_0)}{L(1-D/L)}\right]^2$$

How much resistance originates before the treatment?

- **Pre-treatment resistance** = the progeny of the resistance generated before therapy started. In the single drug case:

$$R^p(t) = \frac{Mu\,\ln(M/N_0)}{L-D}e^{(L-D)t}.$$

- **During-treatment resistance** = resistance generated exclusively by mutations that occur during treatment. In the single drug case:

$$R^d(t) = M\frac{u}{H}[e^{(L-D)t} - e^{(L-D-H)t}].$$

- time zero corresponds to the beginning of treatment

- initial conditions: $\mathrm{N}(0) = \mathrm{M}$ and $\mathrm{R}(0) = 0$

How much resistance originates before the treatment?

- **Main Conclusion:**

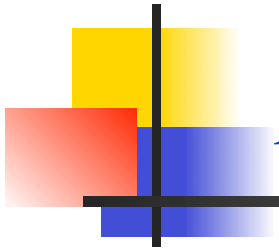
$$\boxed{R^p(t) \geq R^d(t)}$$

- The amount of resistance generated before the beginning of the treatment depends on the turnover rate
- Similar results hold for more drugs. Generally, it is assumed that

$$(L - D) < H \text{ and } M/N_0 \geq C$$

where C is a constant that depends on the dimension.

- Generalizations: different drug-induced death rates for different drugs,...



Application

CML

June '08

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PLoS COMPUTATIONAL BIOLOGY

Dynamics and Potential Impact of the Immune Response to Chronic Myelogenous Leukemia

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Abstract

Recent mathematical models have been developed to study the dynamics of chronic myelogenous leukemia (CML) under imatinib treatment. None of these models incorporates the anti-leukemia immune response. Recent experimental data show that imatinib treatment may promote the development of anti-leukemia immune responses as patients enter remission. Using these experimental data we develop a mathematical model to gain insights into the dynamics and potential impact of the resulting anti-leukemia immune response on CML. We model the immune response using a system of delay differential equations, where the delay term accounts for the duration of cell division. The mathematical model suggests that anti-leukemia T cell responses may play a critical role in maintaining CML patients in remission under imatinib therapy. Furthermore, it proposes a novel concept of an "optimal load zone" for leukemic cells in which the anti-leukemia immune response is most effective. Imatinib therapy may drive leukemic cell populations to enter and fall below this optimal load zone too rapidly to sustain the anti-leukemia T cell response. As a potential therapeutic strategy, the model shows that vaccination approaches in combination with imatinib therapy may optimally sustain the anti-leukemia T cell

What is Leukemia?

- **Normal state:**

  Stem cells turn into mature cells

- **Leukemia:**

  A malignant transformation of a stem cell or a progenitor cell

  - Myeloid or Lymphocytic
  - Acute or Chronic

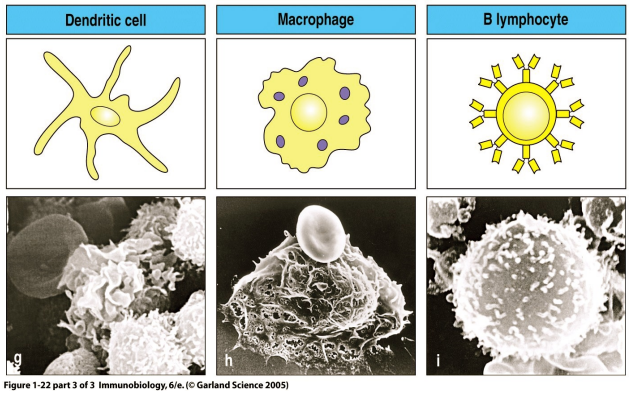


Figure 1-22 part 3 of 3 Immunobiology, 6/e. (© Garland Science 2005)

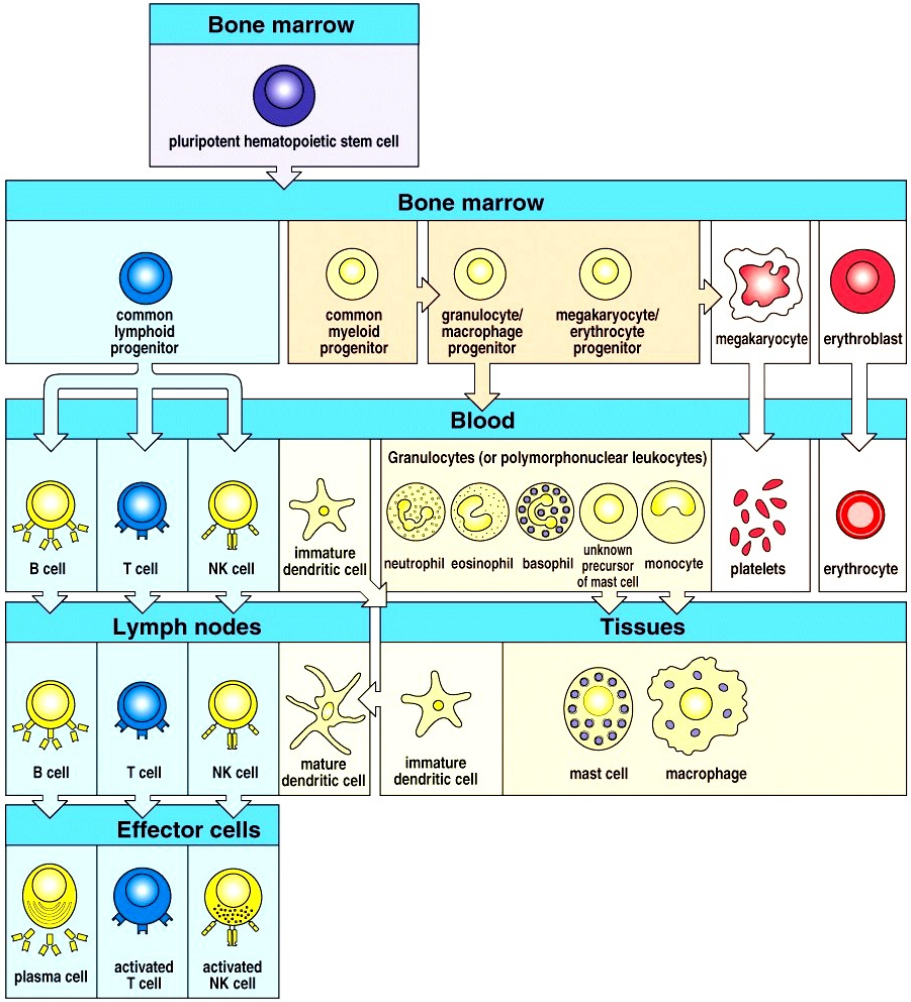
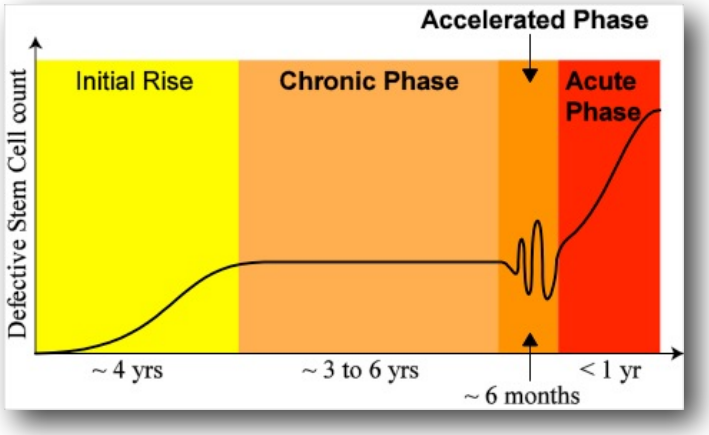


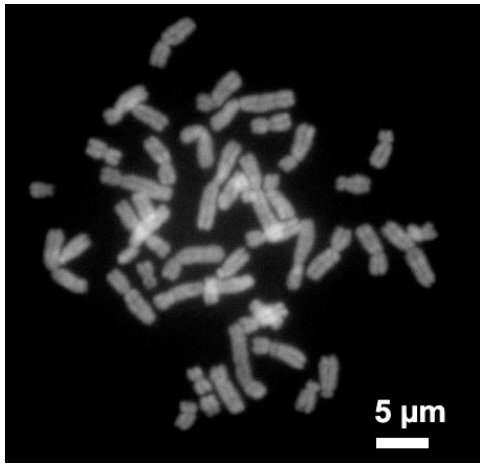
Figure 1-3 Immunobiology, 6/e. (© Garland Science 2005)

CML

- 3 phases
  - Chronic: uncontrolled proliferation
  - Accelerated
  - Acute: Aggressive. Uncontrolled proliferations. Cells do not mature



- Philadelphia chromosome
  - Translocation (9;22)
  - Oncogenic BCR-ABL gene fusion
  - The ABL gene expresses a tyrosine kinase. Growth mechanisms
  - Easy to diagnose
  - Drug targeting this genetic defect (a tyrosine kinase inhibitor)

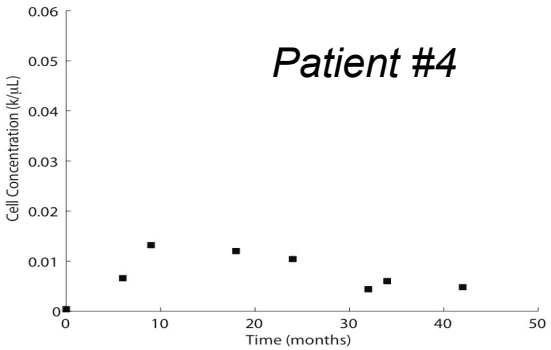


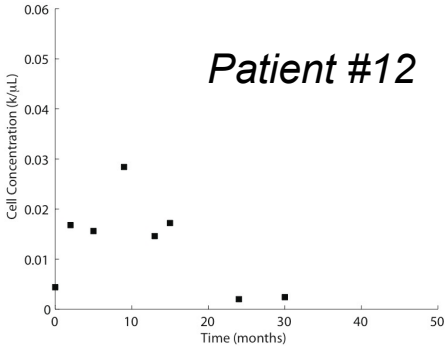
Treating Leukemia

- **Chemotherapy**
- **Bone Marrow / Stem Cell transplant**
  - Chemo + radiotherapy + transplantation
- **Imatinib** (Gleevec)
  - Molecular targeted therapy - suppresses the corrupted control system
  - $30K/yr ('01) – $98K/yr ('13)

May 28, 2001

Incorporating the immune response

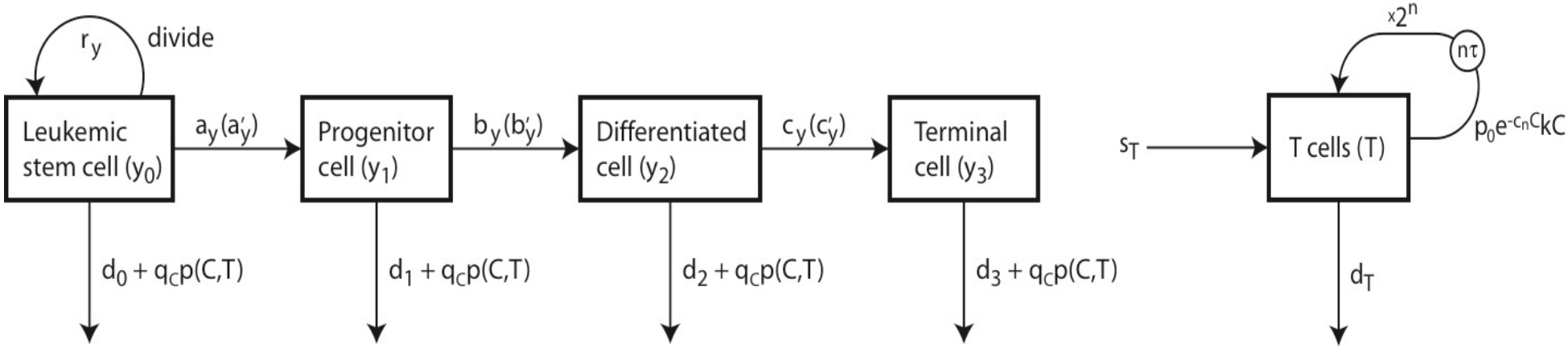




- ★ Shown: the specific anti-leukemia immune response
  - Different patients, Imatinib, 50 months, each dot = one blood test
- ★ A different immune response for each patient. However:
  - At the beginning of the treatment: no immune response
  - Peak: around 6-12 months (after starting the drug treatment)
  - Later: waning immune response

Question: What is the relation between the dynamics of the cancer, the drug, and the immune response?

A mathematical model



- Ingredients:
  - Leukemia cells: stem cells, …, fully functional cells
  - Mutations
  - Drug (Imatinib)
  - Anti leukemia immune response
- *Michor et al. (Nature '05)* + immune response

Cronkite and Vincent (69), Rubinow (69), Rubinow & Lebowitz (75), Fokas, Keller, and Clarkson (91), Mackey et al (99,...), Neiman (00), Moore & Li (04), Michor et al (05), Komarova & Woodarz (05).

Michor's model + immune response

$$\dot{y}_0 = [r_y(1-u) - d_0]y_0 - q_c p(C,T)y_0$$
$$\dot{y}_1 = a_y y_0 - d_1 y_1 - q_c p(C,T)y_1$$
$$\dot{y}_2 = b_y y_1 - d_2 y_2 - q_c p(C,T)y_2$$
$$\dot{y}_3 = c_y y_2 - d_3 y_3 - q_c p(C,T)y_3$$

- Cells without mutations

$$\dot{z}_0 = [r_z - d_0]z_0 - q_c p(C,T)z_0$$
$$\dot{z}_1 = a_z z_0 + d_1 z_1 - q_c p(C,T)z_1$$
$$\dot{z}_2 = b_z z_1 + d_2 z_2 - q_c p(C,T)z_2$$
$$\dot{z}_3 = c_z z_2 + d_3 z_3 - q_c p(C,T)z_3$$

- Cells with mutations

$$\dot{T} = s_t - d_t T - p(C,T)C + 2^n q_T p(C_{n\tau}, T_{n\tau})C_{n\tau}$$

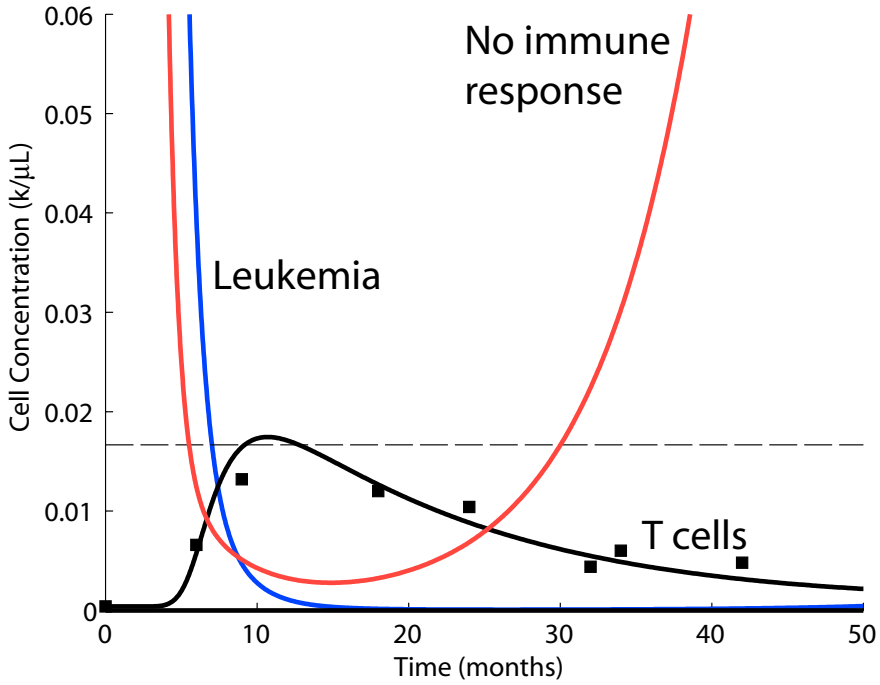
- Anti-Cancer T cells

$$p(C,T) = p_0 e^{-c_n C} kT, \;\; C = \sum(y_i + z_i), \;\; C_{n\tau} = C(t - n\tau)$$

Accounting for the immune response

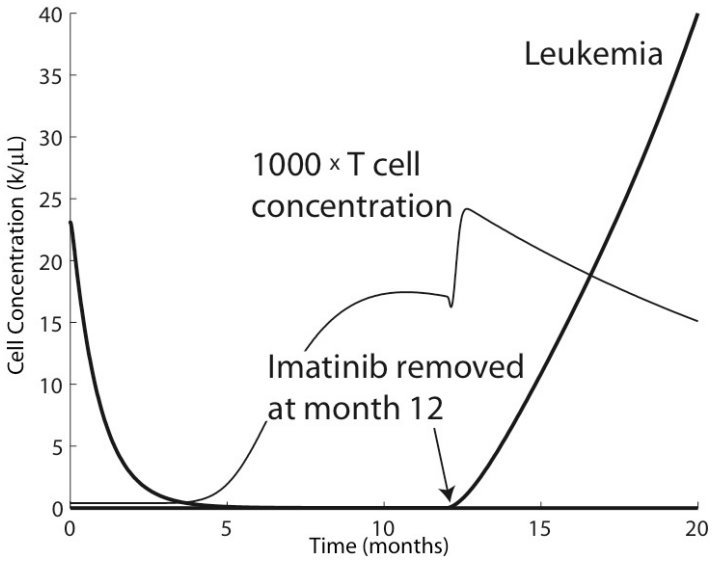
- Dots: data from a patient
- Dashed line: remission

- Results of mathematical simulations
  - 50 months
  - Cancer load without an immune response
  - Cancer load with an immune response
  - The immune response



Stopping imatinib (simulation)

- Stopping Imatinib treatment after one year
- The disease relapses within months
- Validation: The mathematical simulation agrees with the medical experiments



Biological conclusion from the math

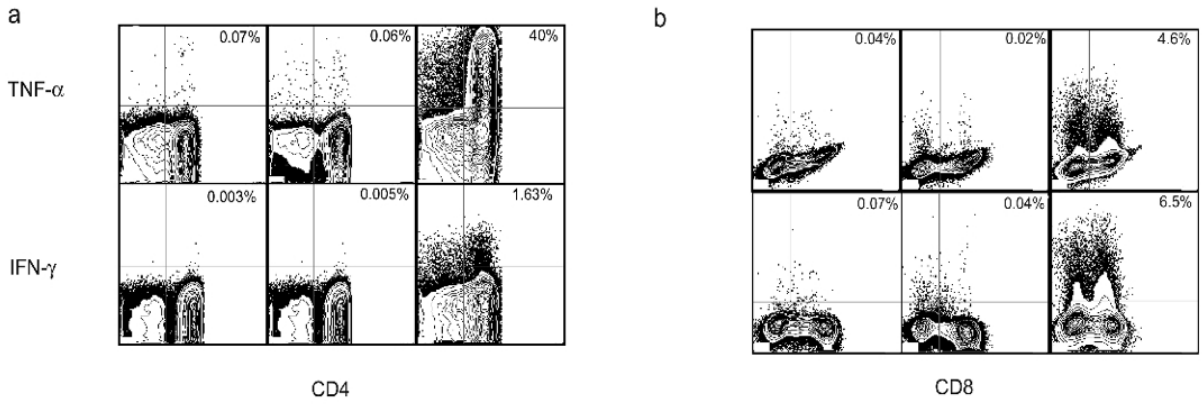
Conclusion: remission is the result of a complex interaction between cancer, imatinib, and the immune response

- Surprising
  - The role of the immune response
  - Non-intuitive conclusion of the mathematical analysis

Questions: Why does the immune response not cure the disease? Can we do something to cure it?

Idea: augment the immune response

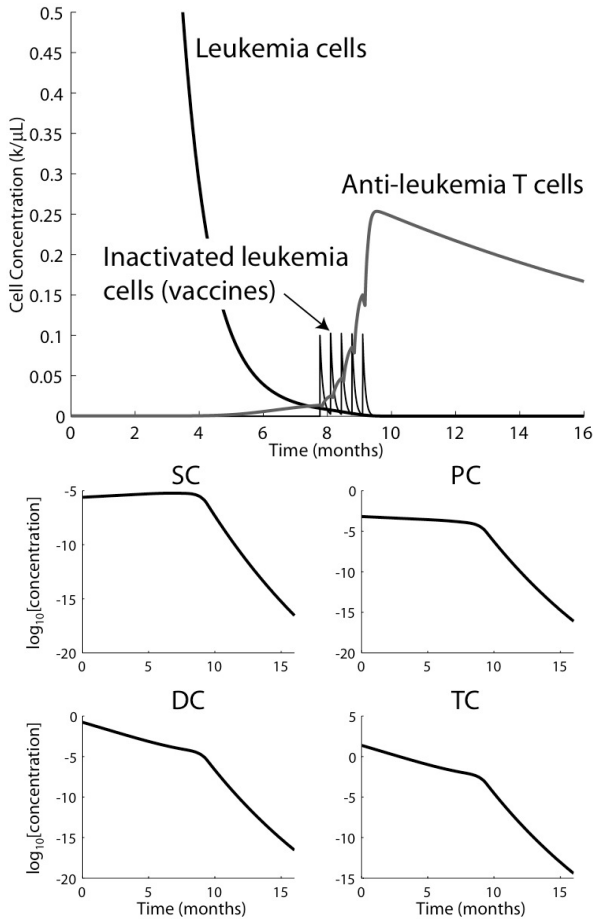
Stimulating the immune response



- Experimental design:
  - Irradiate the blood of the patient that was frozen when the disease was diagnosed
  - Mix it with blood taken from the patient at a later time point after the treatment has started
  - Measure the anti-leukemia immune response
- Result:
  - It works. Consequently we propose "Cancer vaccines"

Cancer Vaccines: a mathematical design

- A vaccination plan
- Solving a mathematical optimization problem:
  - Dosage
  - Timing
- Individual planning: based on the immune response of each patient
- Remission / cure

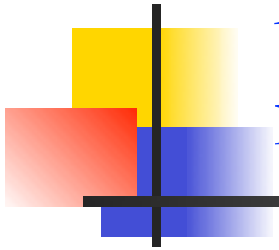


- Inactivated leukemia cells

$$\dot{V} = -d_V V - q_c p(C,T)V + s_V(t)$$

- Anti-Cancer T cells

$$\dot{T} = s_t - d_t T - p(C,T)(C+V) + 2^n p(C_{n\tau}, T_{n\tau})(q_T C_{n\tau} + V_{n\tau})$$

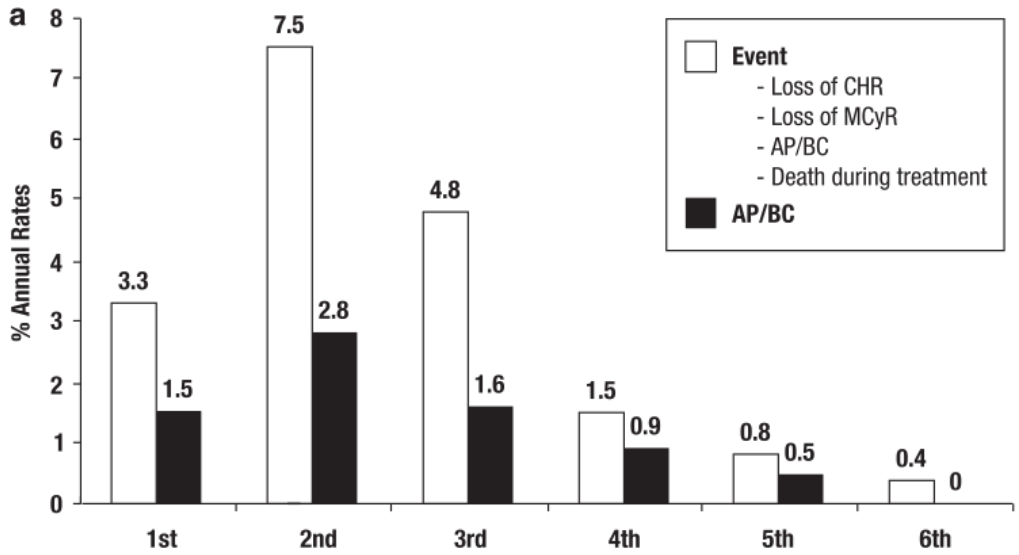


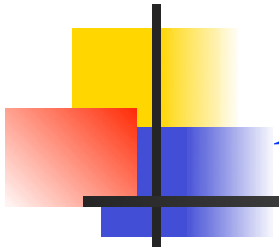
Mathematical models of drug resistance in cancer (Tomasetti + DL, PNAS 2010)

A Tale in 3 Acts

CML: studying drug resistance

"Six-year follow-up of patients receiving imatinib for the first-line treatment of chronic myeloid leukemia", *Hochhaus et al. (Leukemia 2009)*





Act I

On the probability of developing drug resistance by the time a tumor is diagnosed

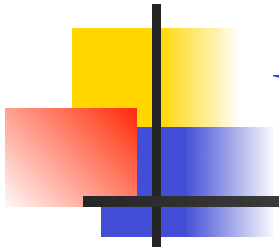
Mathematical models of drug resistance in cancer

- Goldie & Coleman; Iwasa, Nowak, & Michor; Komarova; Roeder; ...
- **Iwasa, Novak, & Michor (Genetics, 2006):**
  - The probability of developing resistance by the time a tumor is diagnosed:

$$P = 1 - \exp\left(-\frac{MuL}{D}\ln\frac{L}{L-D}\right)$$

    - L & D = birth & death rates; u = mutation rate
    - M = total number of cancer cells (!)
  - The expected # of resistant cancer cells that are present at detection (when $Mu \ll 1$)

$$\bar{Y} \approx \frac{\ln M}{(L/D-1)\ln\left(L/(L-D)\right)}$$



What is wrong with these estimates?

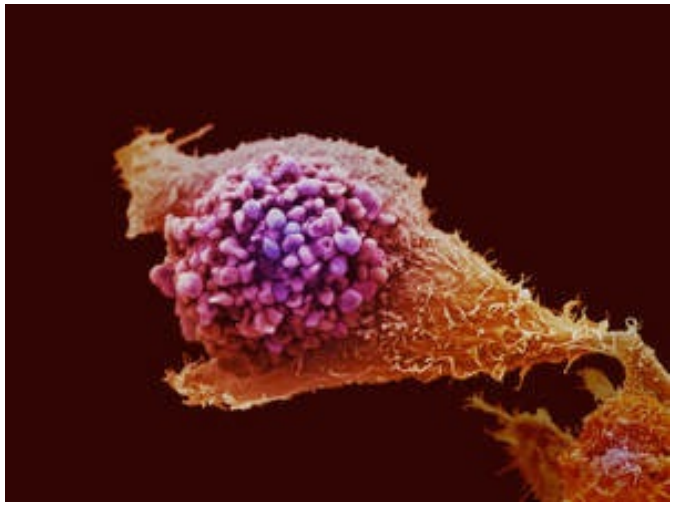
- **Actual values:** $M = 10^9, \quad u \geq 10^{-8}$

  - The probability of developing resistance by the time a tumor is diagnosed is greater than 0.9999
  - The expected number of resistant cancer cells that are present at detection is of the order of thousands
  - Conclusion: resistance should always be present in large numbers.
  - This must be wrong

Cancer Stem Cells

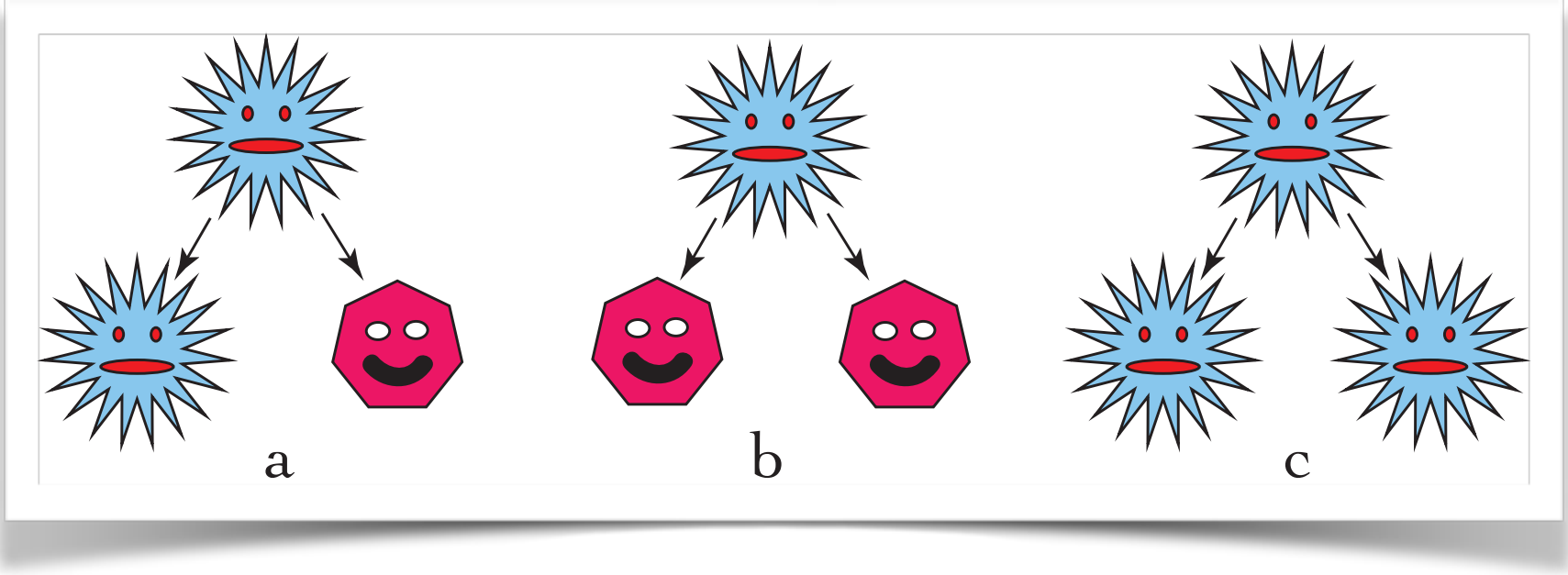
- **Leads to the Stem-Cell Hypothesis**

  - Cancer cells (just like healthy cells) are not all alike
  - The tumor population is heterogeneous: it is comprised from stem cells and other cells
  - Stem cells have the ability of self-renewal. They are very long lived.
  - **From the point of view of drug resistance – it is only the long lived cells we should care about**



Cancer stem cells

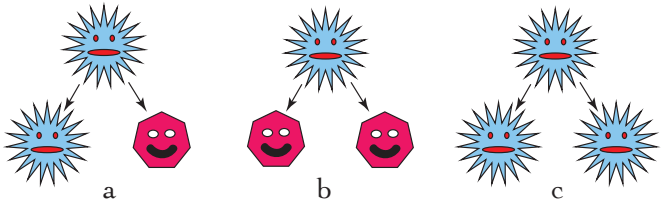
- A stem cell divide in one of the following ways:
  - Asymmetric division with probability *a*
  - Symmetric differentiation with probability *b*
  - Symmetric renewal with probability *c* = *1-a-b*



Drug resistance & cancer stem cells

- **Modified Question**: What is the probability that at the time of detection there are cancer stem cells that developed resistance to the drug?
- **Answer (Tomasetti+DL):**

$$P_R = 1 - \exp\left(-uM\left(\frac{1-\frac{a}{2}-b}{1-a-b}\right)\right)$$

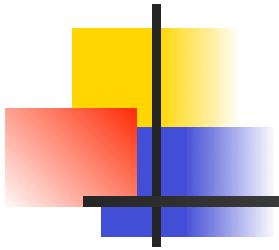


or (for nonzero D):

$$P_R = 1 - \exp\left(-uM\left(\frac{1-\frac{a}{2}-b}{1-a-b}\right)\frac{1}{C}\ln\left(\frac{1}{1-C}\right)\right)$$

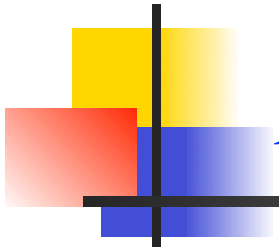
$$C = \frac{D+Lb}{L(1-a-b)}$$

M=CSCs, u=mutation rate, D&L=birth&death rates



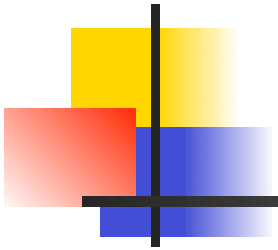
Our result

- Extension of the Iwasa result
- It is possible to calculate the refined estimates that take into account stem cells, due to different mathematical tools
- Brings cancer stem cells into the picture
- Key to obtaining the result: SIMPLIFY THE MATH



Act II

On symmetric vs. asymmetric differentiation



Case study: CML

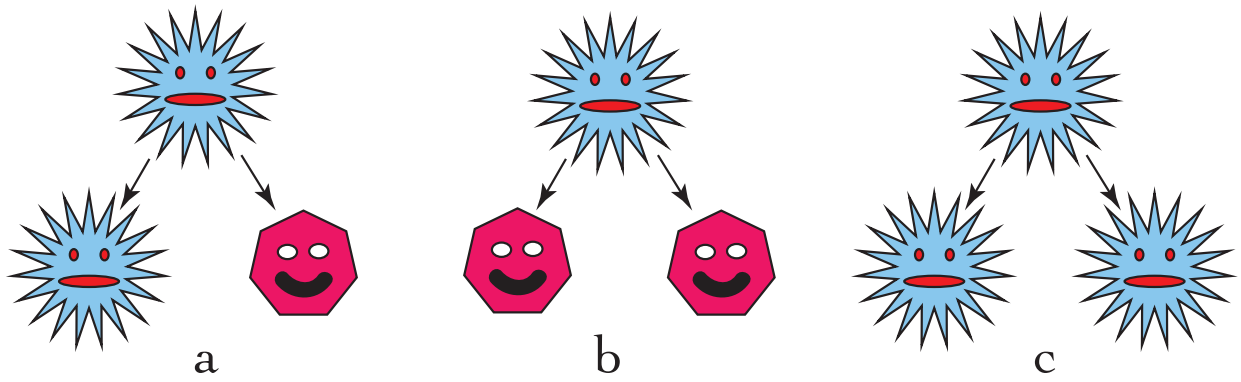
- **Question**: what is the probability of developing resistance at detection?
  - Stem cell population at detection: $M \approx 2.5 \times 10^5$
  - The mutation probability: $u \approx 4 \times 10^{-7}$

- **Answer**: Michor et al (Nature, 2005): 13%
  - **Good yet bad**: fits the data but is based on the wrong formula (homogeneous tumor population)

How do leukemia stem cells divide?

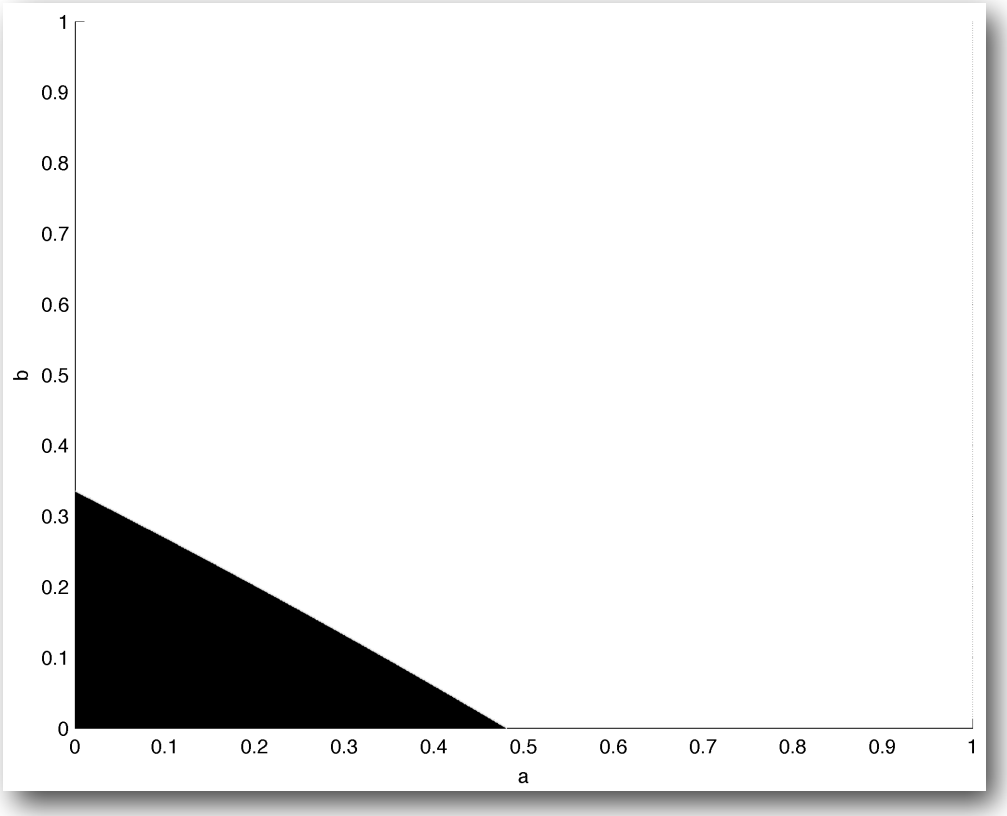
- For healthy hematopoietic stem cells the probability of an asymmetric division, *a,* is in the range 0.5-0.9 (Wu et al. Cell Stem Cell 2007)
- Tipping *et al.* (Blood 2001), $D/L \approx 0.1 - 0.5$
- The probability of developing resistance by the time of detection (our estimates):

$$P_R \approx 73\% \quad \text{if} \quad a = 0.87,\ b = 0.01$$
$$P_R \approx 12\% \quad \text{if} \quad a = 0.2,\ b = 0.05$$



How do leukemia stem cells divide?

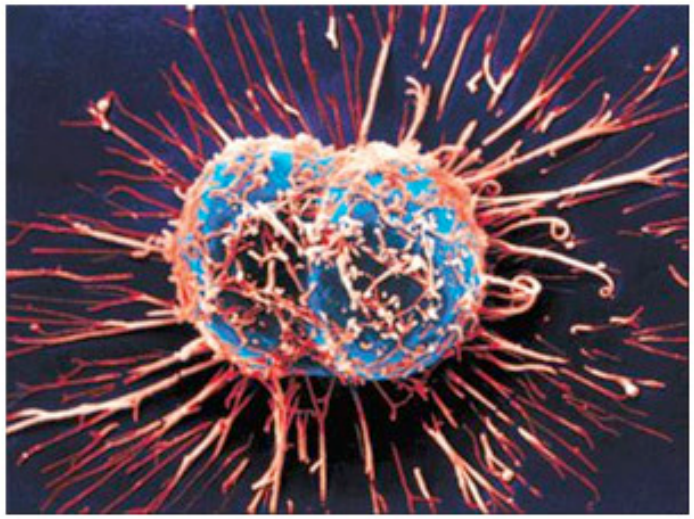
- The range of a and b for which $P_R < 0.15$. The turnover rate is $D/L = 0.1$



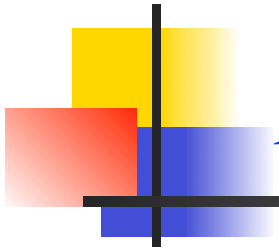
How do leukemia stem cells divide?

- **Conclusion**: leukemia stem cells should have a lower tendency than healthy stem cells to divide asymmetrically.

Cancer Stem Cells must shift towards an increased symmetric renewal



(Cancererous cells splitting apart)

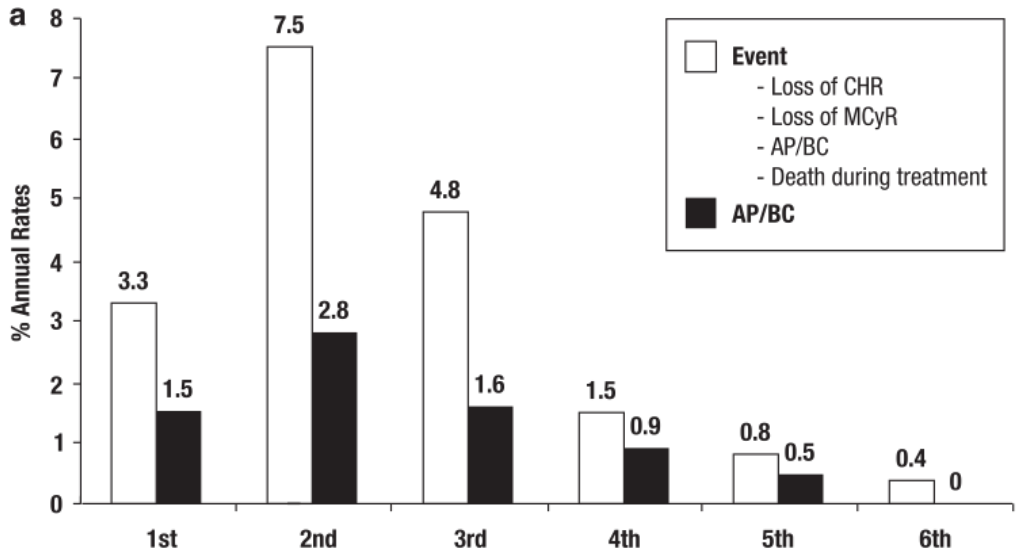


Act III

A surprising finalé

CML: studying drug resistance

"Six-year follow-up of patients receiving imatinib for the first-line treatment of chronic myeloid leukemia", *Hochhaus et al. (Leukemia 2009)*



Why do relapses stop?

Hypothesis: relapses are related to the drug response

- Two points of view in the literature:
  - Cancer Stem Cells are the only sub-population that is resistant to the drug (Michor & Novak)
  - Cancer Stem Cells are sensitive to the drug but shift rapidly between active and dormant states (Roeder)

Our hypothesis: Cancer Stem Cells must be affected by the drug. The drug keeps the CSCs in a dormant state

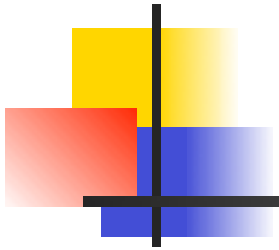
- Explains:
  - Why there is an immediate relapse when stopping Imatinib
  - Patients eventually relapse if they have CSCs that do not respond to the drug
  - Explains why there are no further relapses after 5-6 years

When did the resistance develop?

- If resistance developed, it must have happened by the time of detection
- **The results of the the mathematical calculation:**
  - On average, resistance must have developed in the 3-4 months prior to detection

Finalé – Clinical consequences:

- **Early detection of CML will increase the chances of survival.**
- **Patients should be treated immediately.**



Conclusion

- **Medical Applications:**
  - Quantitative approach
  - Should be used in conjunction with clinical & experimental data
  - A complex biological setup – the tip of the iceberg

- **Math:**
  - New challenges
  - New math
  - Can potentially be useful