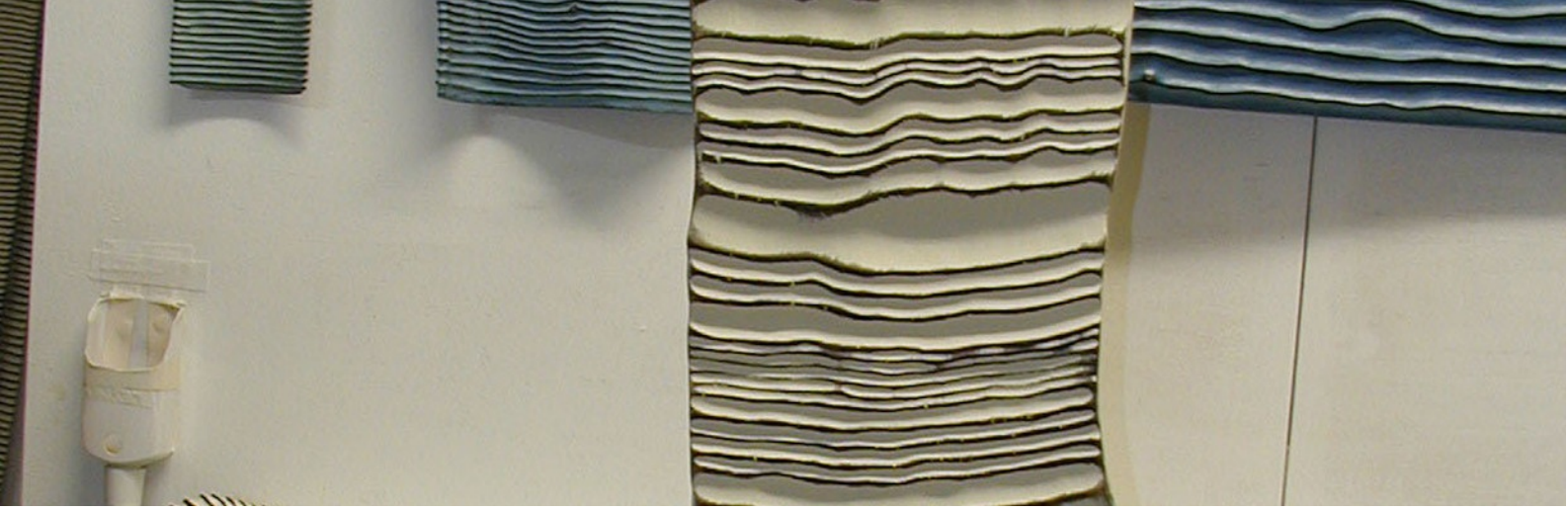

The 1971 War on Cancer Revisited

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THE 1971 WAR ON CANCER REVISITED

Symposium Science, Ethics and Arts

October 14, 2016

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Freiburg University Medical Center

International Master Program of Biomedical Sciences (IMBS)

BIOTHERA-Foundation

JOSHA – Journal of Science, Humanities and Arts

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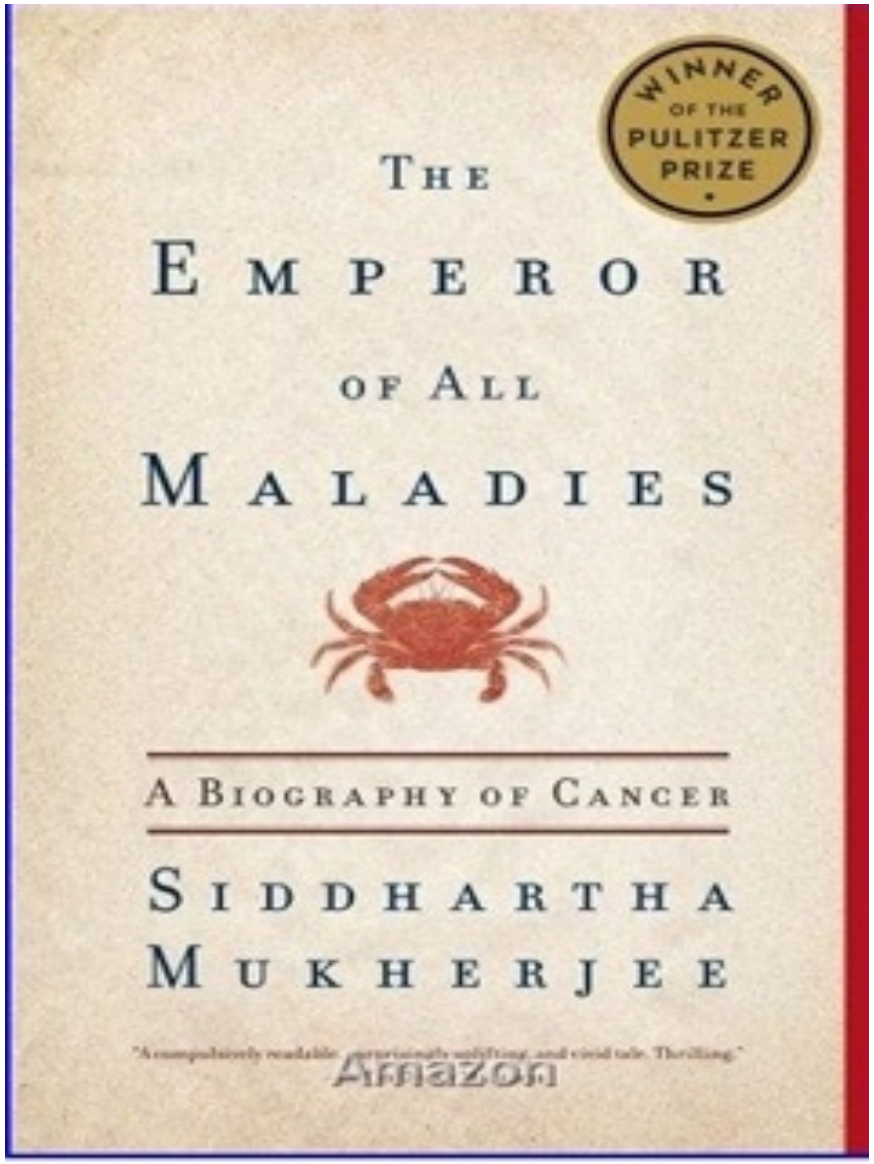
THE WAR ON CANCER
Continues 2016

„For the loved ones we`ve all lost, for the families that we can still save, let`s make America the country that cures cancer once and for all“

President Barack Obama, State of the Union Address, Jan 12, 2016

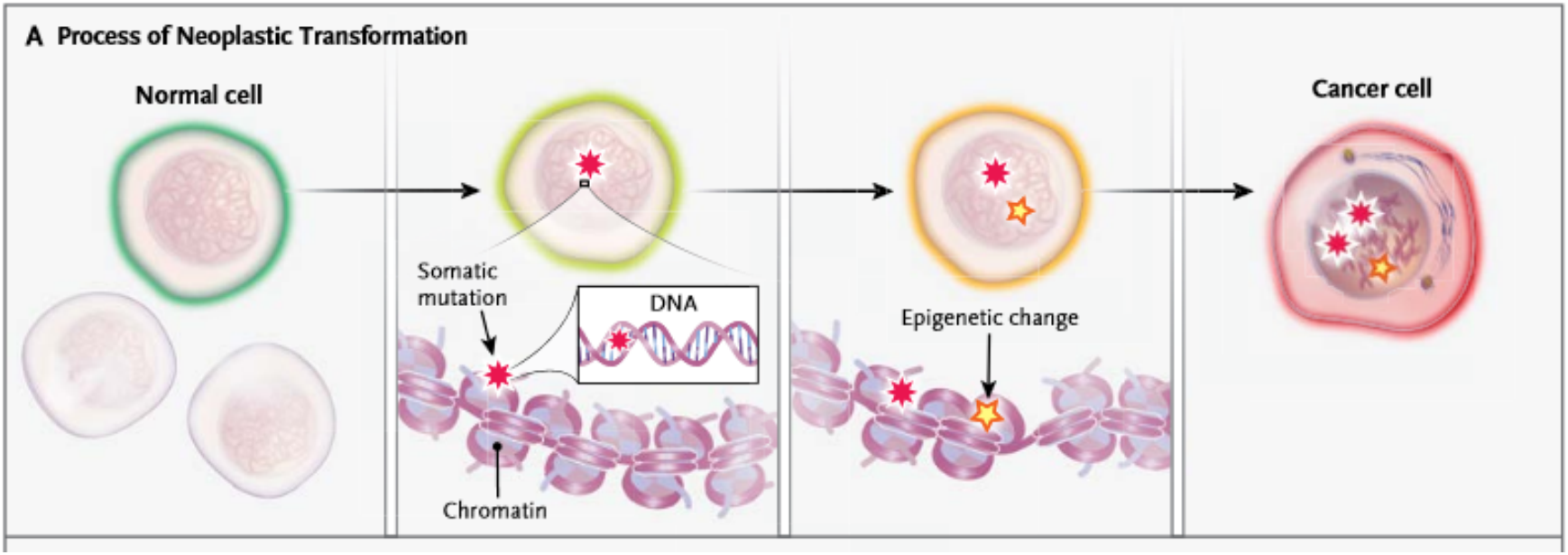
Aiming High – Changing the Trajectory for Cancer
Lowy & Collins, NEJM April 2016

Cancer:
The Emperor of All Maladies



?

Oncogenesis



Increasing autonomy, genetic instability and ....

L. Luzzatto, P.P. Pandolfi,
NEJM 373, 84, 2015

Oncogenesis

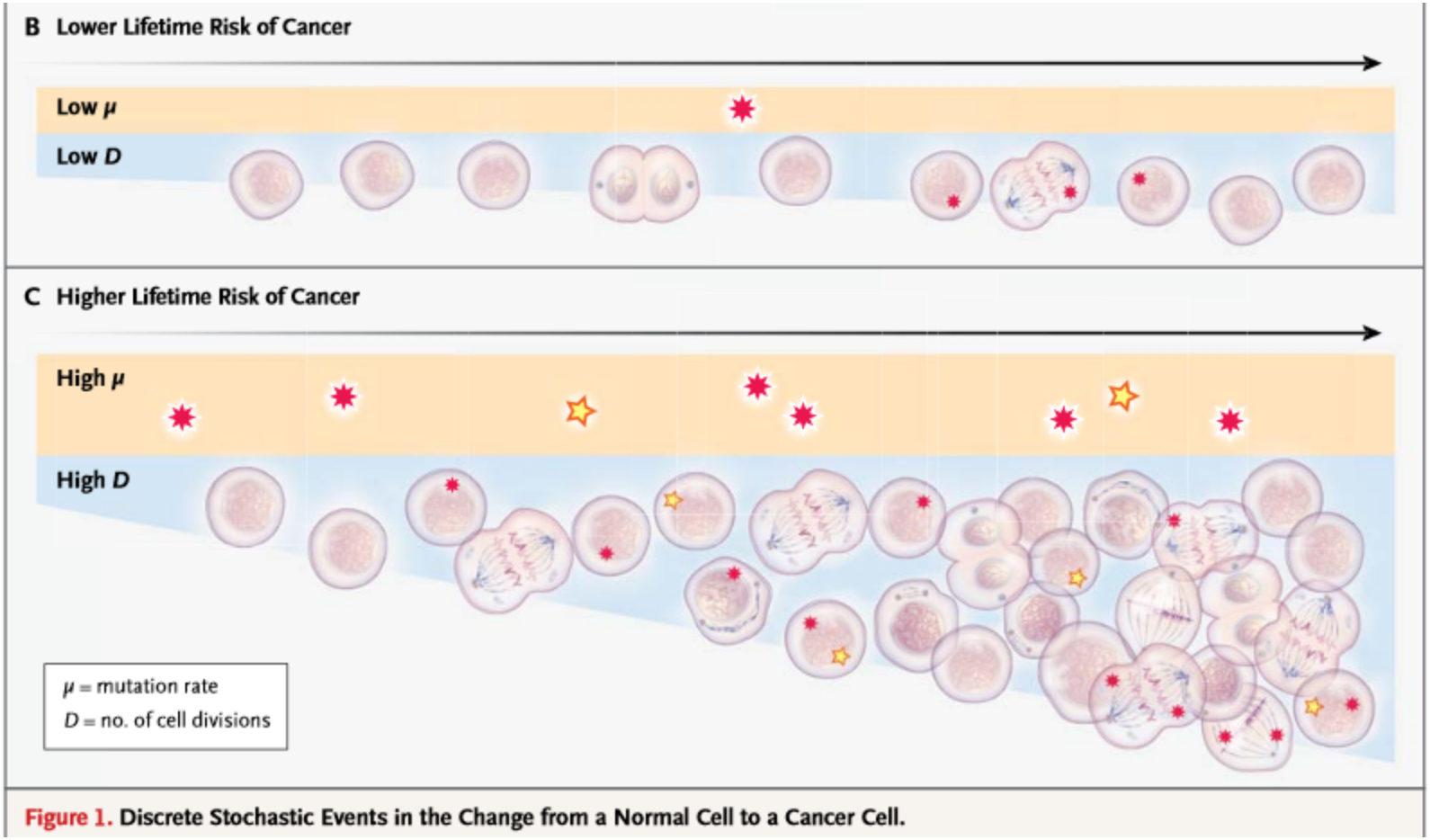


Figure 1. Discrete Stochastic Events in the Change from a Normal Cell to a Cancer Cell.

.....Clonal Evolution

L. Luzzatto, P.P. Pandolfi, NEJM 373, 84, 2015

Evolution and Cancer

Priciples of Evolution

1. **Mutations** by Chance, limited by possible options
2. **Opportunity:** Survival advantage under the given conditions
3. **Selection of the fittest**

Cancer Cells

- **Acquire Immortality**
- **Increasing loss of controls driven by entropy**

Oncogenesis: Conclusion

- Cancer is an aquired genetic disease
- Cancer is the continued evolution of cells within an individuum
- Oncogenesis and the clinical disease follow the Darwinian principles of evolution
- Genetic and epigenetic factors contribute to carcinogenesis and evolution
- **Mutated genes/proteins** may serve as **molecular targets**
  - **for small molecules, antibodies, CART cells**
  - as (neo)antigens for immune system recognition/attack

Pathophysiological hallmarks identify potential therapeutic **pathways**

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Targeted Therapies

- Small (designer) molecules
  - Some Leukemias can now be „cured“
  - Good results also in some solid tumors

- Monoclonal Antibodies
  - Lymphoma, Leukemia: significantly improved survival
  - Lung cancer, colon cancer, others

- Transgenic T Cells (CART Cells)
  - Highly active in leukemias
  - In preclinical models also in solid tumors

Harnessing the Immune System

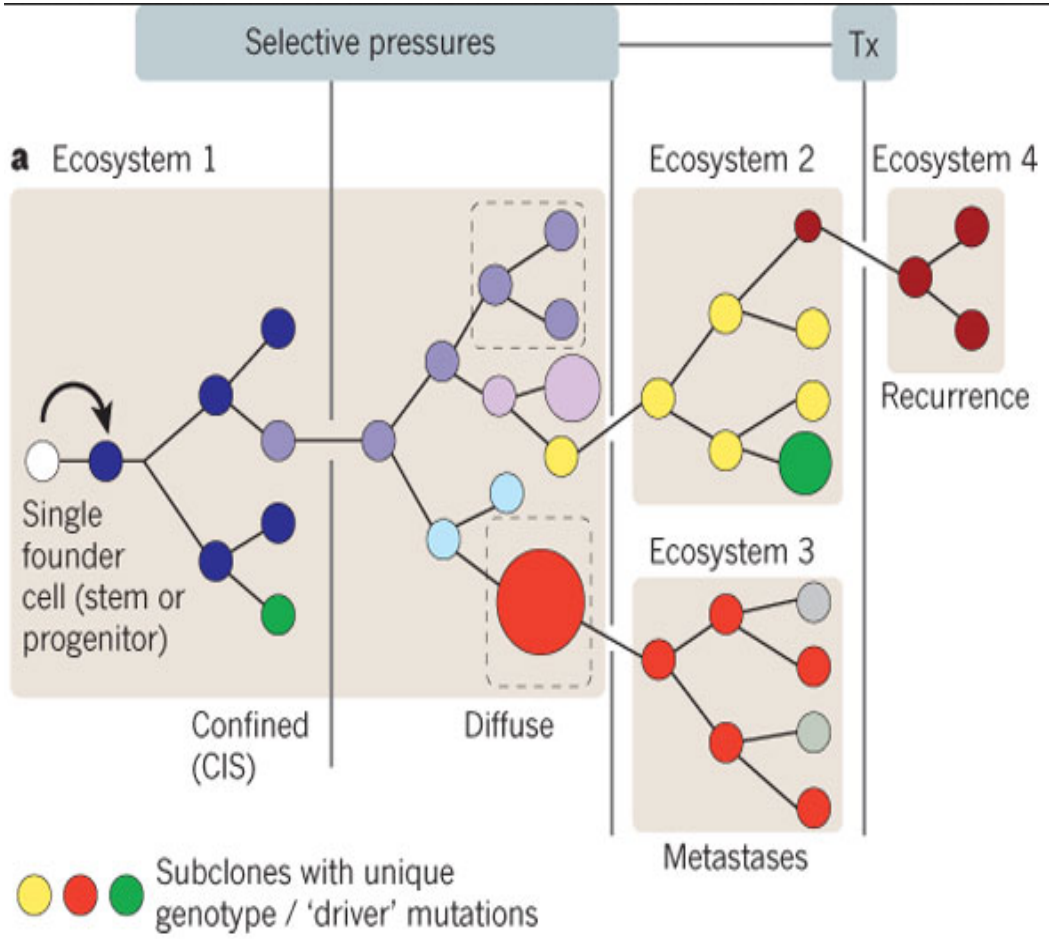
1. non-specific defense mechanisms

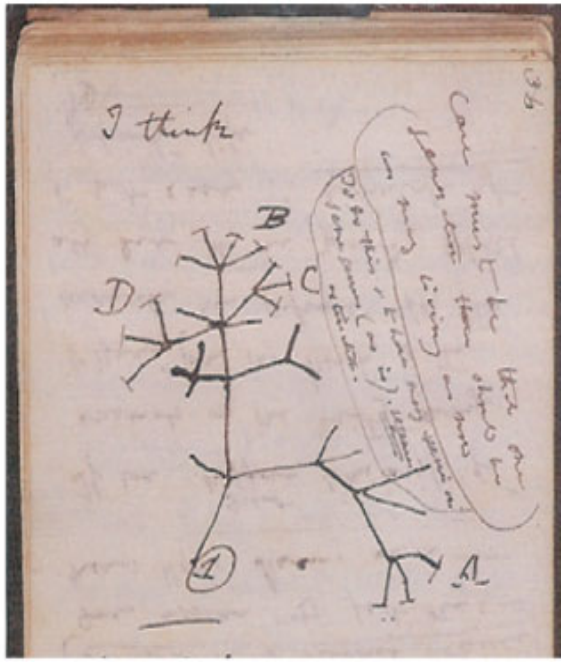
2. Immunisation, Prophylactic - Therapeutic: e.g. HPV

3. Liberating endogenous immunity: **Immune Checkpoint Inhibition**

Clonal Evolution: The Hydra Challenge

Genetic Evolution - Clonal Evolution





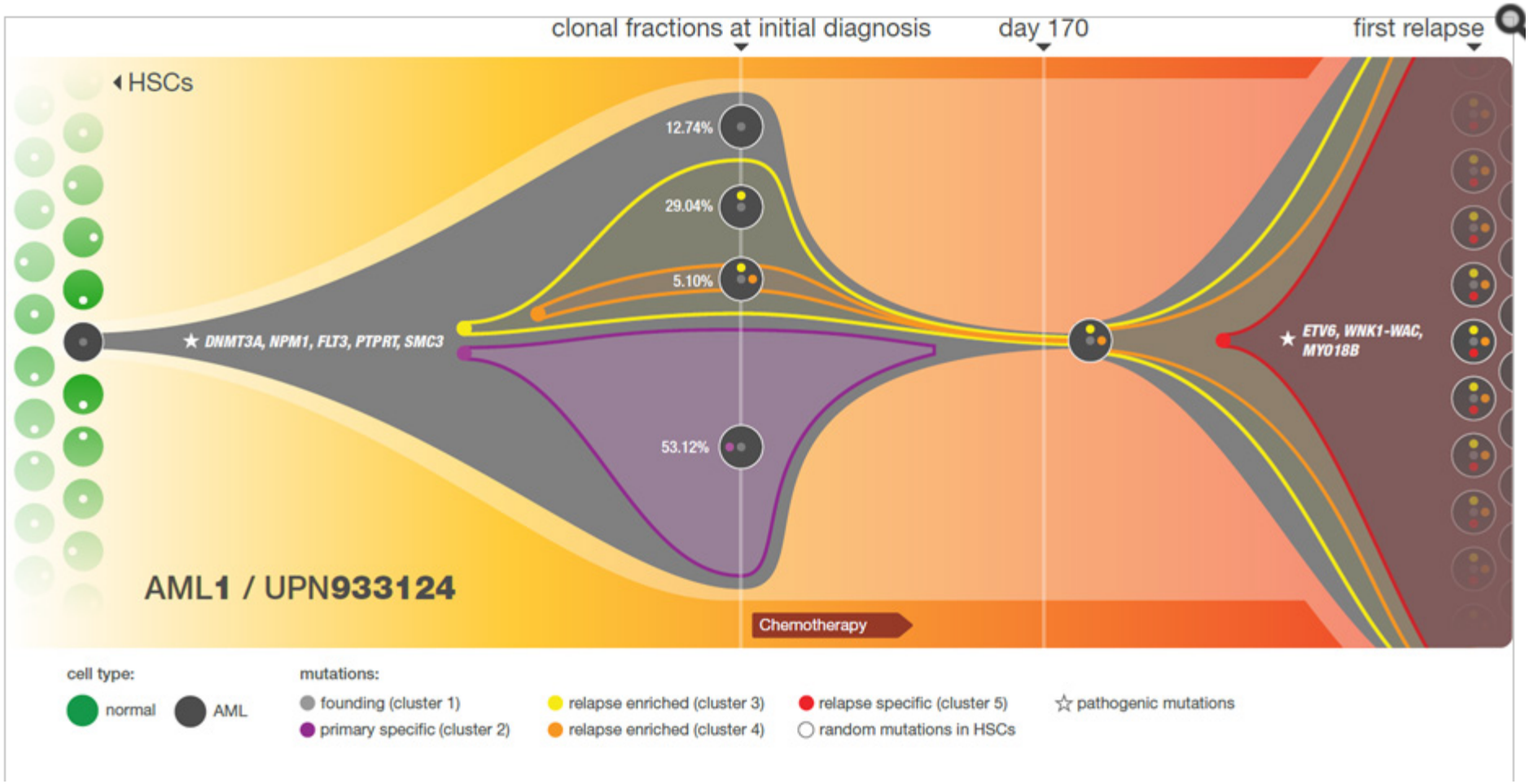
Clonal evolution in cancer, M. Greaves, C.C. Maley, Nature 481, 306–313, 2012

Clonal Evolution

HÄMATOLOGIE & ONKOLOGIE
INNERE MEDIZIN I

UNIVERSITÄTS KLINIKUM FREIBURG

Figure 2



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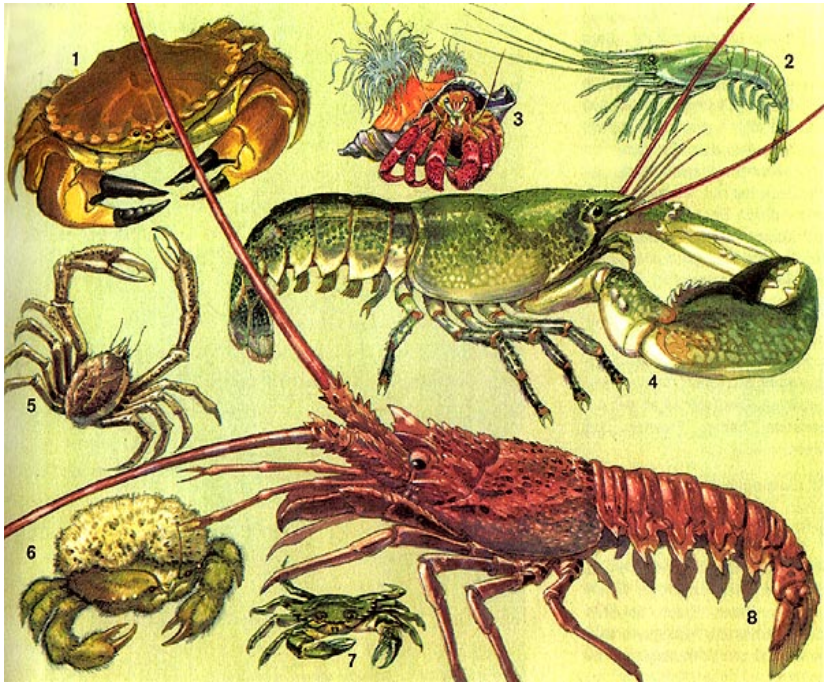
Nature. 2012 Jan 11; 481(7382): 506–510.

Individualized/Personalized Evidence-Based Therapy

Cancers are different

- from Patient to Patient
- within one Patient over Time



Humans differ

- in their genetic program
- in comorbidities
- in their values, dreams and priorities

Variability Necessitates Individual Therapeutic Strategies

Precision Medicine – Bringing it to the Patient
What is „precise“ for the Individual?

The Old Model

1. Phase I, II, III Studies in large, higly selected cohorts of patients aiming for improved response rates

2. Standard of Care in Guidelines for unselected patients focussed on clinical/pathological cancer type and stage

The New Model

Studies in small cohorts aiming for high response rates focussed on Molecular Signature of Cancer

The Innovation Pathway

Focussed on the optimal therapeutic strategy for the Individual Patient
Based on all available evidence
And careful risk – benefit analysis

The 1971 War on Cancer Revisited 2016

1. **Reconnaisance**
   - Understanding cancer: Oncogenesis and Clonal Evolution

2. **Identify Therapeutic Targets**
   - Cancer Pathways, molecular and metabolic
   - Cancer Molecules

3. **Strengthen the Defenses**
   - Activate the immune system

4. **My Strategy for "Winning the War“**

   - Develop the innovation pathway – PEBM
   - Identify novel therapeutic objectives; stable disease vs. Remission
   - Evaluate guidelines and Tumor Boards as management standard
   - In silico experiments, modeling, simulation: Artificial intelligence
   - Search for missing „links“, Phenotype – genotype fallacy

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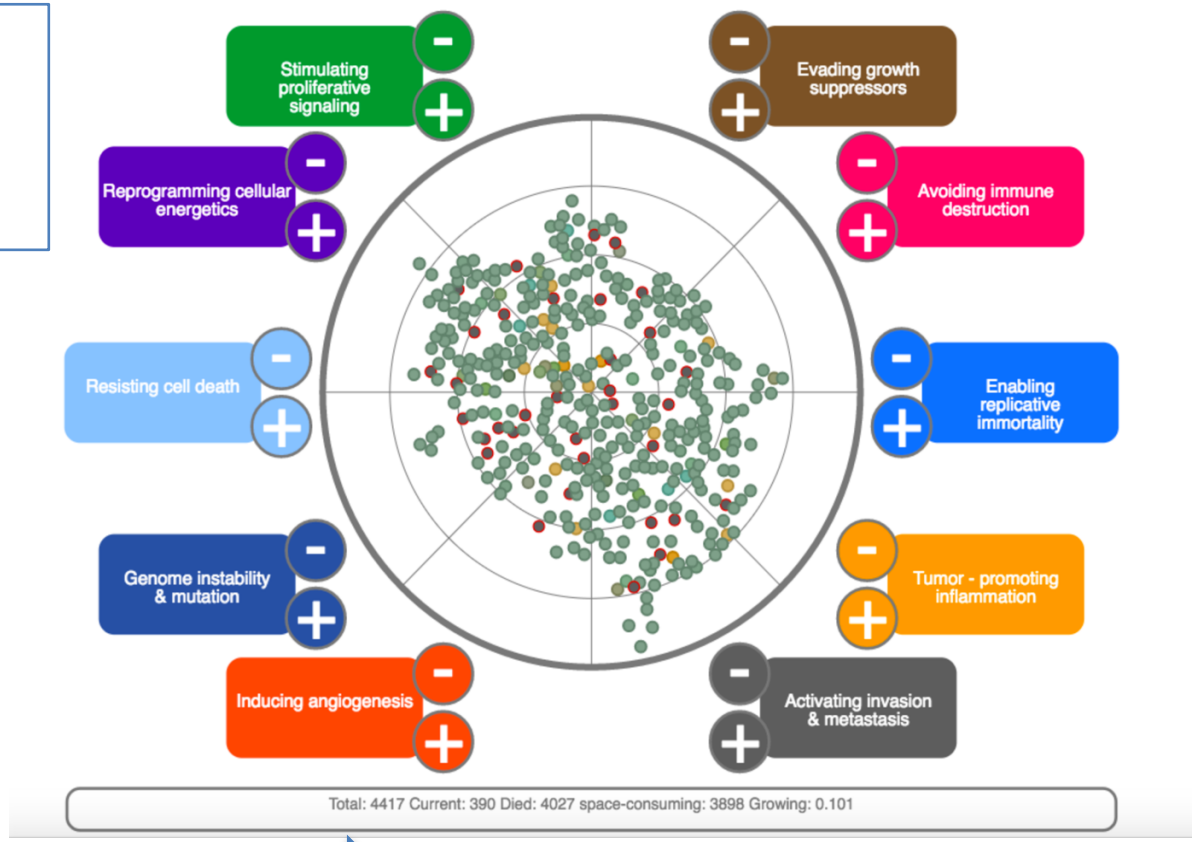
Carcinogenesis: Simulations and Machine Learning

The virtual experiment:
- 10 variables
- With 5 concentrations
- At 10 timepoints
- 10e50 possibilities

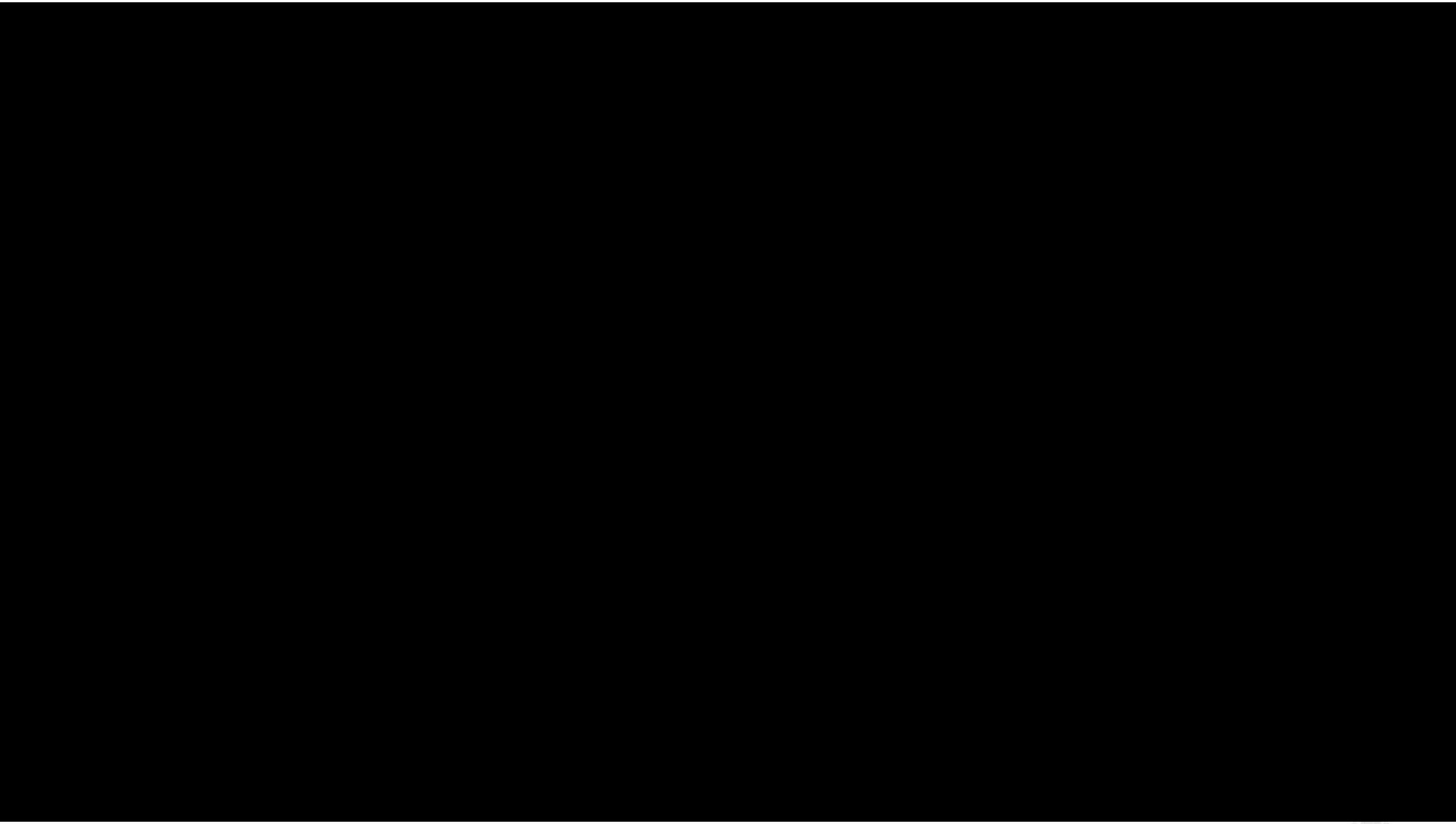


Task: adjust input buttons to provide maximum number of cells
1. In virtual Petri dish
2. In output (Metastases)

manual → Program simulations → machine-learning

1050 experiments, 175 combinations x 6 runs

"Mitosis" Computer Game



2015: 10 Rules to Prevent Cancer

1. Do not smoke.
2. Do not smoke.
3. Do not smoke.
4. Avoid carcinogens: Asbestos, UV-Light, Aflatoxine.
5. Diet: moderate in calories, salt, fat, little Alcohol. .
6. 3x daily fresh fruit and vegetable.
7. Exercise and watch your weight.
8. Vaccination (Hepatitis B, HPV) and Treatment of chronic infections.
9. Good genes.
10. Good luck! !

Paul Kleihues 2007

Oncology – Still fighting Cancer

Thank you to the Speakers and Audience!

My Mentors

My Colleagues

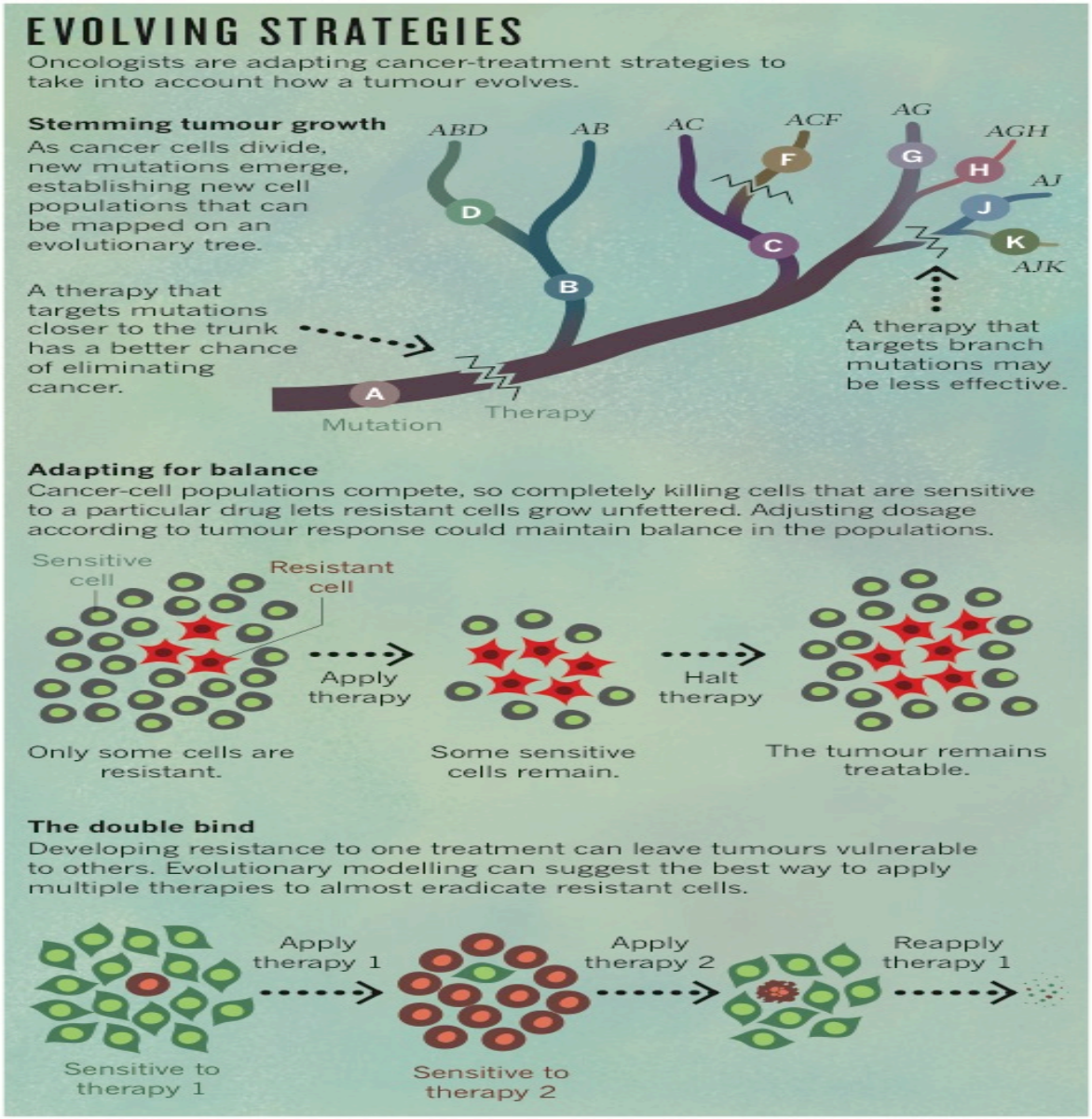
My Mentees and Alumni

Our Patients

The „Symposium“ Team

- Bärbel Schätzle
- Evgenia Alechine
- Stephan Seiler

Clonal Evolution: The Hydra Challenge



Cassandra Willyard

Cancer: An evolving threat

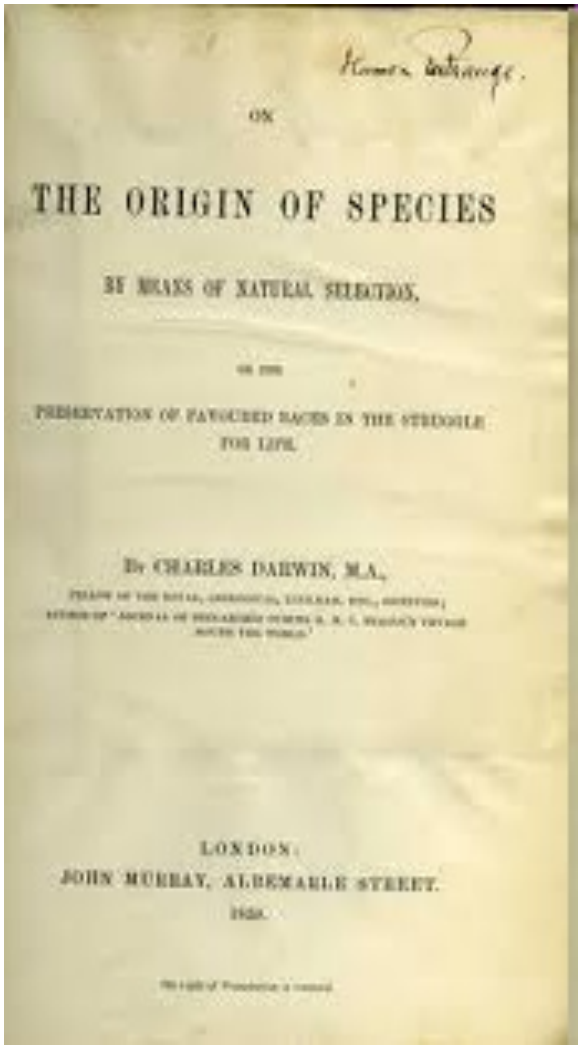
Nature 532, 166, 2016

„Tumours are subject to the same rules of natural selection as any other living thing.“

"CANCER IS CONTINUOUSLY ADAPTING, THEREFORE WE HAVE TO DO SO AS WELL."

Cancer: Evolution und Adaptation

„Survival of the fittest“



ON

THE ORIGIN OF SPECIES

BY MEANS OF NATURAL SELECTION,

OR THE

PRESERVATION OF FAVOURED RACES IN THE STRUGGLE FOR LIFE.

By CHARLES DARWIN, M.A.,

LONDON:
JOHN MURRAY, ALBEMARLE STREET.

Genetic Evolution of DNA assures the long-term survival advantage of cancer cells

"Cancer is a moving target"

Epigenetic Adaptation assures the rapid adaptation to the environment

flexible Phenotype, e.g. MET Transition

Cancer Stem Cell a „Mirage“

Oncogenesis

Factors in Oncogenesis

1. **Chance 30% ?**
2. **Other ?**

Probability of Penetrance dependent on

1. Genetic Predisposition
2. Population Size
3. Proliferative Rate
4. Environmental Factors
5. .....

Harnessing the Immune System
Immune Checkpoint Inhibition

- numerous positive clinical trials demonstrating high efficacy and long-lastin remissions in Melanoma, various ST, HD; others under investigation

- autoimmune side-effects

Oncology – The War on Cancer

Albert Einstein

„Everything should be made as
simple as possible,
but not simpler.“