Modeling Cancer Complexity (Fragile Proteins and the Origins of Cancer)

Robert Austin
Dept. of Physics
Princeton University

I'm not going present any answers or, for that matter, any of our own data.

As I stand in the ashes of the PSOCs I'm going to talk about what I am thinking about right now about the origins of cancer, and what I think we are doing wrong. That includes me.

(A) Cancer is 90% environmentally caused: Preventable in many cases.

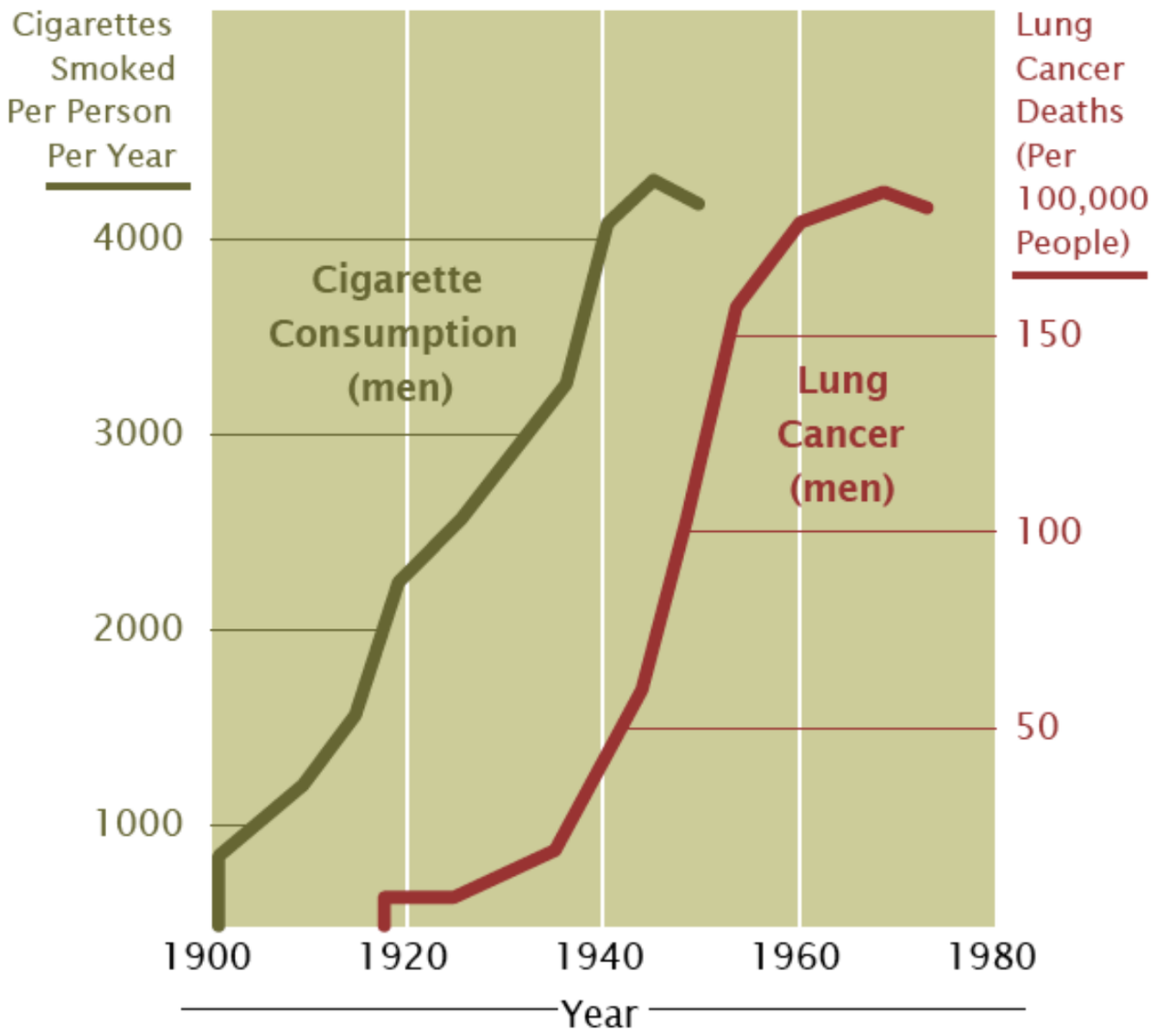
(B) It is not initially a genetic problem. We are missing the point.

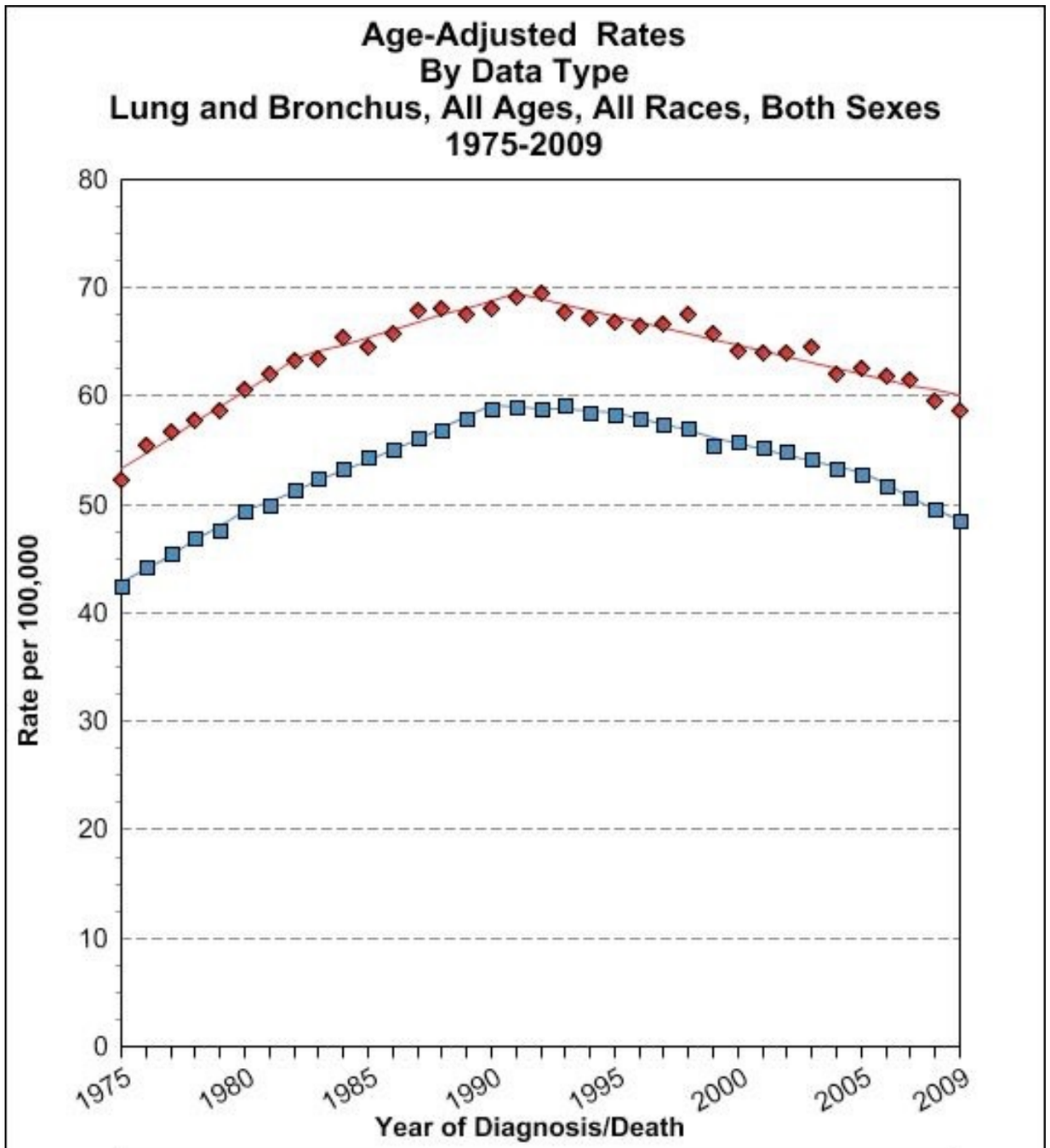
(C) Stop doing experiments with cancer cells. Misses the point.

Note: does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health.

I) Cancer is 90% environmentally caused.

1) 50% is easy: smoking kills. Lung cancer used to be quite rare, now it is #1, and 95% preventable, 10% curable.





The tobacco industry, which is responsible for about 50% of all cancer mortalities in the US, is a $100 billion/yr business.

Note that the tobacco industry advertising and promotional budget is $8.4 billion/yr, almost x2 entire NCI budget.

This is totally insane.

Alas, China going down the same crazy road, and will pay a terrible price.

2) Many cancers appear to be highly environmentally linked and not spontaneous.

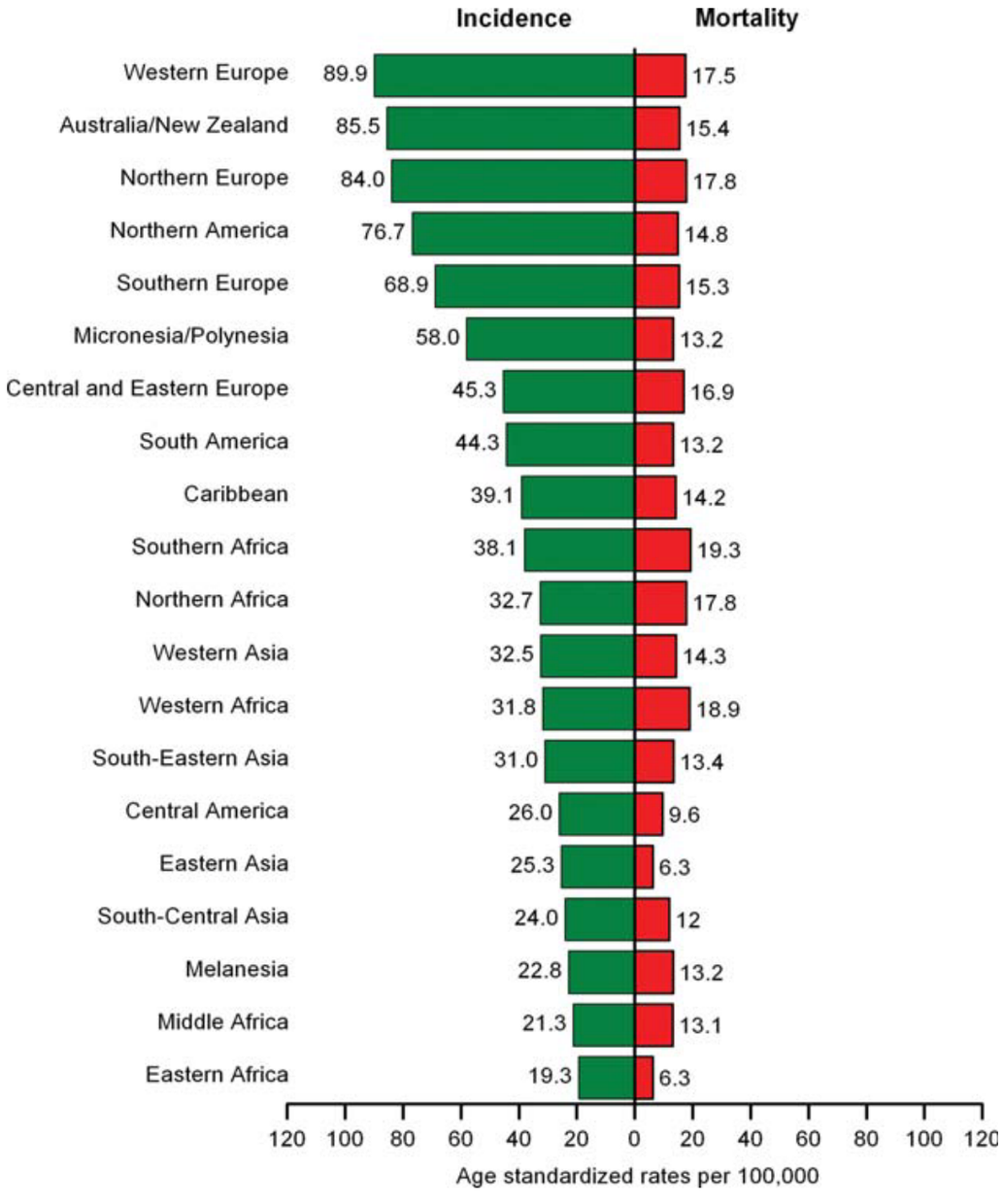


FIGURE 4. Age-Standardized Breast Cancer Incidence and Mortality Rates by World Area. Source: GLOBOCAN 2008.

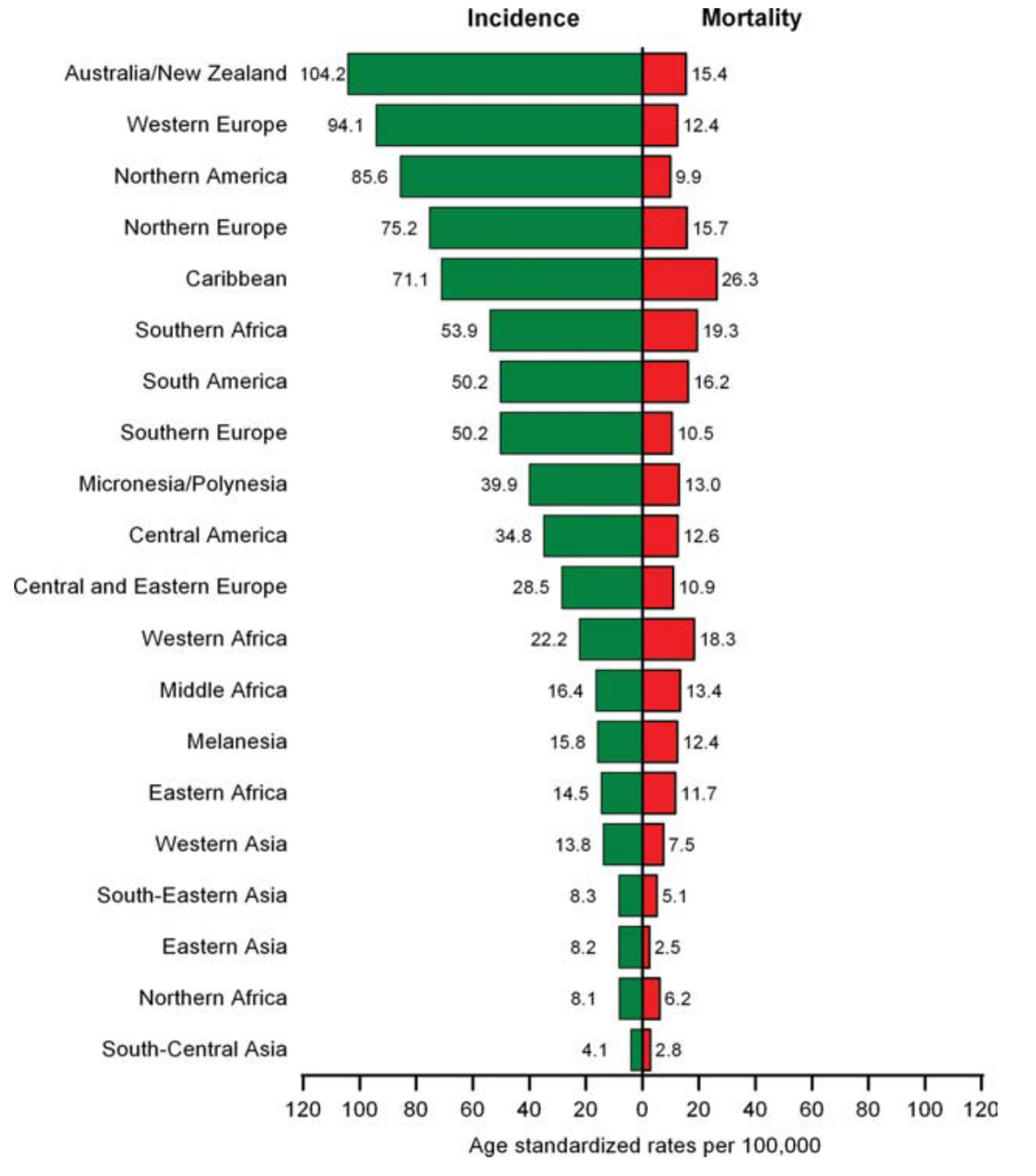


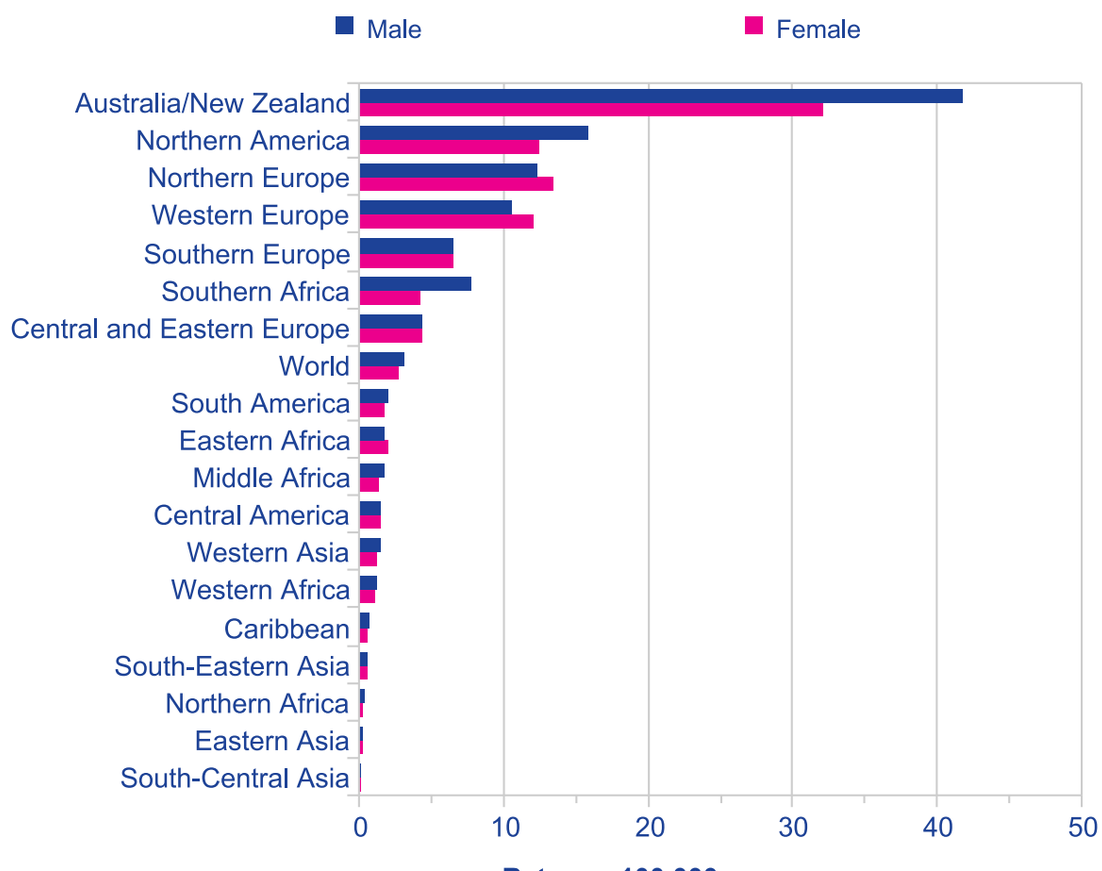
FIGURE 7. Age-Standardized Prostate Cancer Incidence and Mortality Rates by World Area. Source: GLOBOCAN 2008.

Mad dogs and Englishmen go out in the noon-day sun.

Malignant Melanoma (C43): 2008 Estimates

World Age-Standardised Incidence Rates per 100,000 Population, World Regions

World Region	Male	Female
Australia/New Zealand	41.8	32.1
Northern America	15.8	12.5
Northern Europe	12.3	13.4
Western Europe	10.6	12.0
Southern Europe	6.5	6.5
Southern Africa	7.7	4.2
Central and Eastern Europe	4.4	4.3
World	3.1	2.7
South America	2.1	1.8
Eastern Africa	1.7	2.0
Middle Africa	1.7	1.4
Central America	1.5	1.5
Western Asia	1.5	1.2
Western Africa	1.2	1.1
Caribbean	0.7	0.6
South-Eastern Asia	0.6	0.5
Northern Africa	0.4	0.3
Eastern Asia	0.3	0.3
South-Central Asia	0.2	0.2



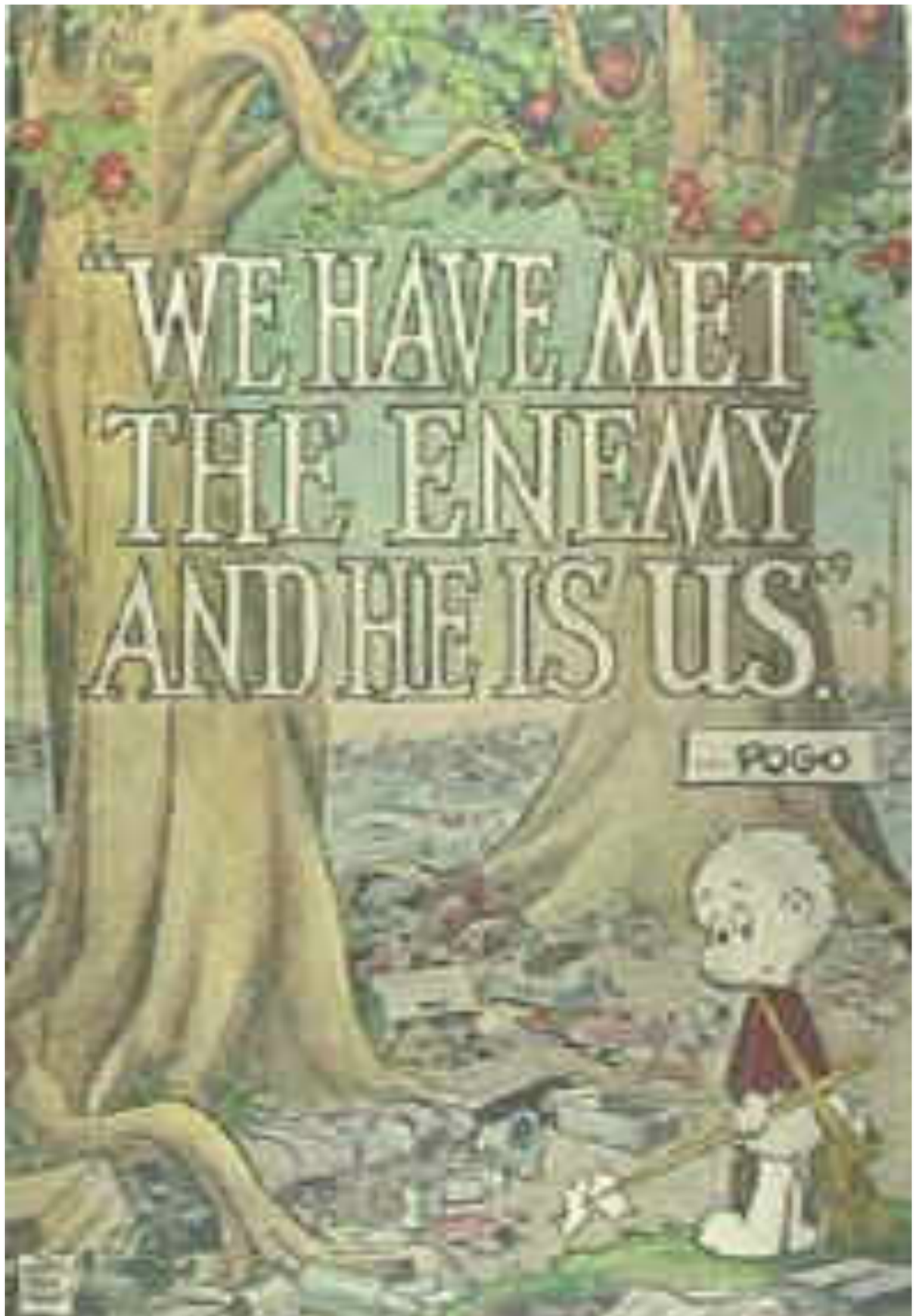
I believe these 客家 women are picking tobacco leaves. This called "irony".

That's a Modest Proposal, but I am being as satirical as Jonathan Swift, because it **Will Not Happen.**

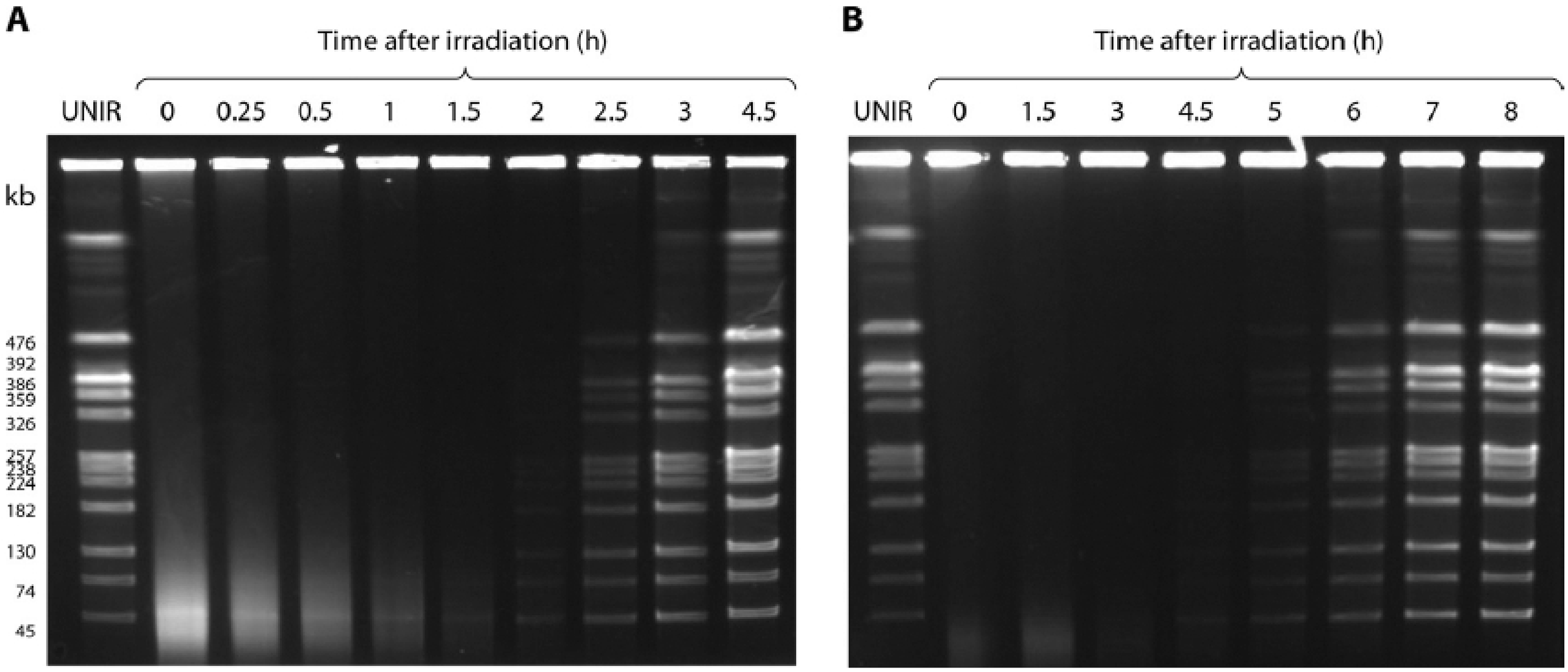
This is because of the Medical-Industrial Academic Complex, where cancer is a huge 130 billion dollar a year business.

There is far too much money at stake to expect us to do the obvious: PREVENT CANCER, not CURE IT.

End of Screed



B) Cancer is not initially a genetic problem. It is a protein problem.



Deinococcus radiodurans: bacteria that can take 7,000 Gy dose. Lethal dose for humans is 8 Gy! Nothing magic about the DNA, it gets shredded. The magic is in the proteins that REPAIR the DNA damage. Proteins are minding the store.

D. radiodurans is fully capable of repairing DNA lesions as long as the complex DNA repair proteins are functional.

I believe that in a "healthy" cell that the genome can be maintained in an undamaged state as long as the DNA repair proteins are functional.

If you damage the repair proteins, then genomic damage begins.

So, cancer emerges from a damaged proteome, not a damaged genome.

I am beginning to think that Cyrus Leventhal did NOT find a paradox:

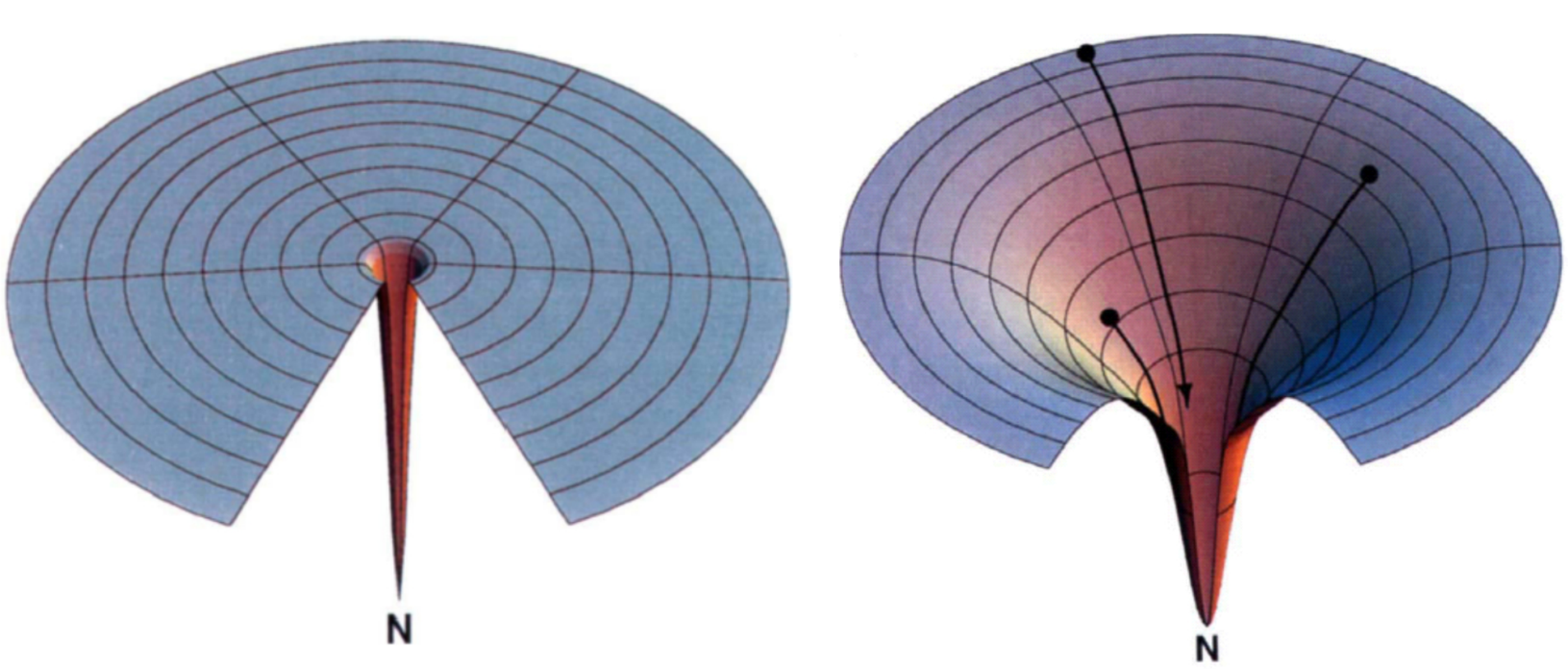
(Large) proteins CANNOT fold graciously.

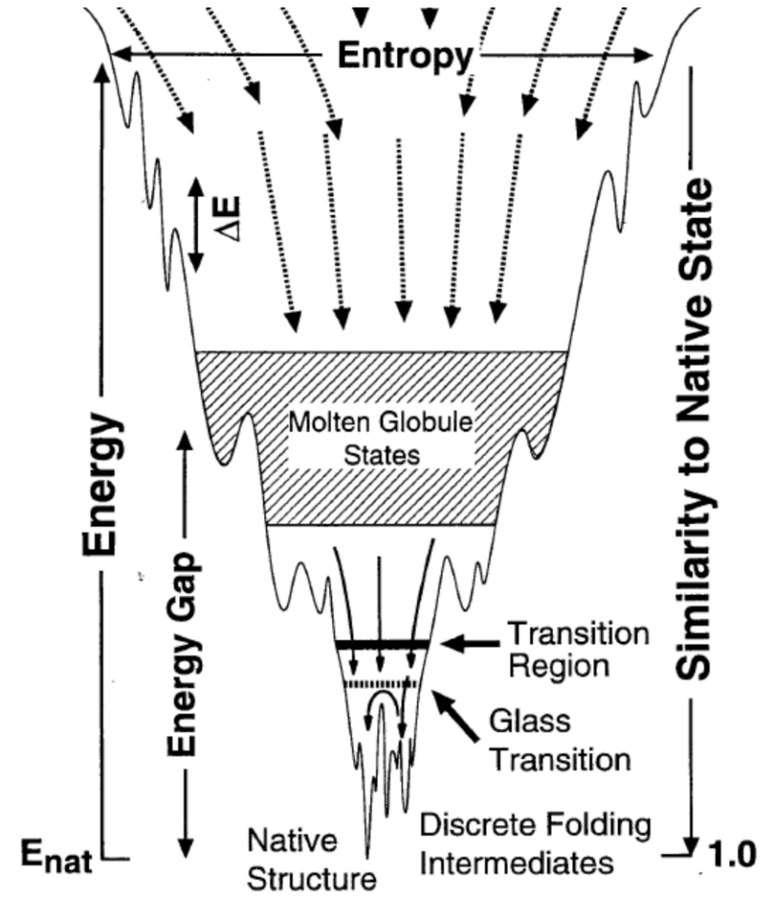
Perhaps the physicists have been wrong, (large) proteins CAN'T fold into active conformations at thermodynamic time scales, OR the functional state is non-thermodynamic.

The Protein Folding "Problem": Not Even Wrong

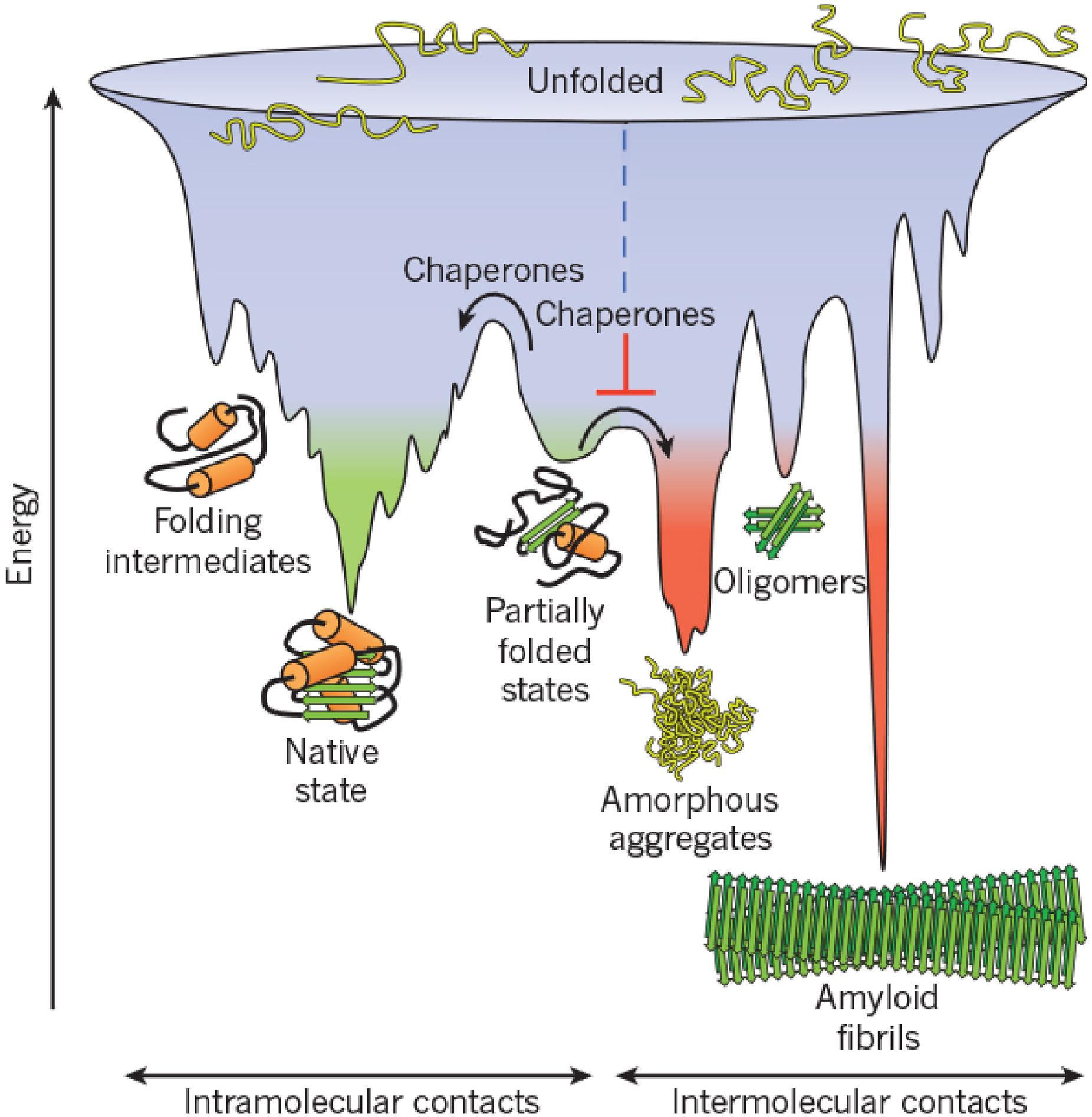
$$\mathcal{H} = -1/2 \sum_{ij} J_{ij} S_i S_j - H \sum_i S_i$$

The irony is that the spin-glass hamiltonian has no unique ground state because of frustration.





None of these correspond to reality


Unfolded
Chaperones
Chaperones
Folding
intermediates
Partially
folded
states
Oligomers
Native
state
Amorphous
aggregates
Amyloid
fibrils
Energy
Intramolecular contacts
Intermolecular contacts

Fundamental questions:

(A) Can large proteins really fold? That is, can they truly find the functional subset of the conformational distribution on a biologically relevant timescale? Ever?

(B) Are chaperones absolutely essential, and who then folds the chaperone proteins?

(C) How can we experimentally characterize the functional state of the proteome, the landscape of generically folded, functionally folded, and aggregated proteins?

(D) How is the emergent complexity of the functional proteome connected to the state of the organism?

So: cells respond to stresses, like heat shock or oxidative agents, which lead to protein aggregation, by activating the protein quality control (PQC) and attenuating translation.

The PQC consists of molecular chaperones and degradation systems and is an essential player of the proteotoxic stress response.

To minimize protein aggregation, chaperones assist protein folding; when this is not effective, chaperones assist in targeting damaged substrates for clearance

Screening for direct DNA mutagens rather than cross-linkers of misfolded proteins misses the point.

We should be screening for loss of chaperone re-folding function.

Conformational Stability and Catalytic Activity of PTEN Variants Linked to Cancers and Autism Spectrum Disorders

Sean B. Johnston[†] and Ronald T. Raines*[,†,‡]

[†]Department of Biochemistry and [‡]Department of Chemistry, University of Wisconsin—Madison, Madison, Wisconsin 53706, United States

Supporting Information

ABSTRACT: Phosphoinositides are membrane components that play critical regulatory roles in mammalian cells. The enzyme PTEN, which catalyzes the dephosphorylation of the phosphoinositide PIP_3, is damaged in most sporadic tumors. Mutations in the *PTEN* gene have also been linked to autism spectrum disorders and other forms of delayed development. Here, human PTEN is shown to be on the cusp of unfolding under physiological conditions. Variants of human PTEN linked to somatic cancers and disorders on the autism spectrum are shown to be impaired in their conformational stability, catalytic activity, or both. Those variants linked only to autism have activity higher than the activity of those linked to cancers. PTEN-L, which is a secreted *trans*-active isoform, has conformational stability greater than that of the wild-type enzyme. These data indicate that PTEN is a fragile enzyme cast in a crucial role in cellular metabolism and suggest that PTEN-L is a repository for a critical catalytic activity.

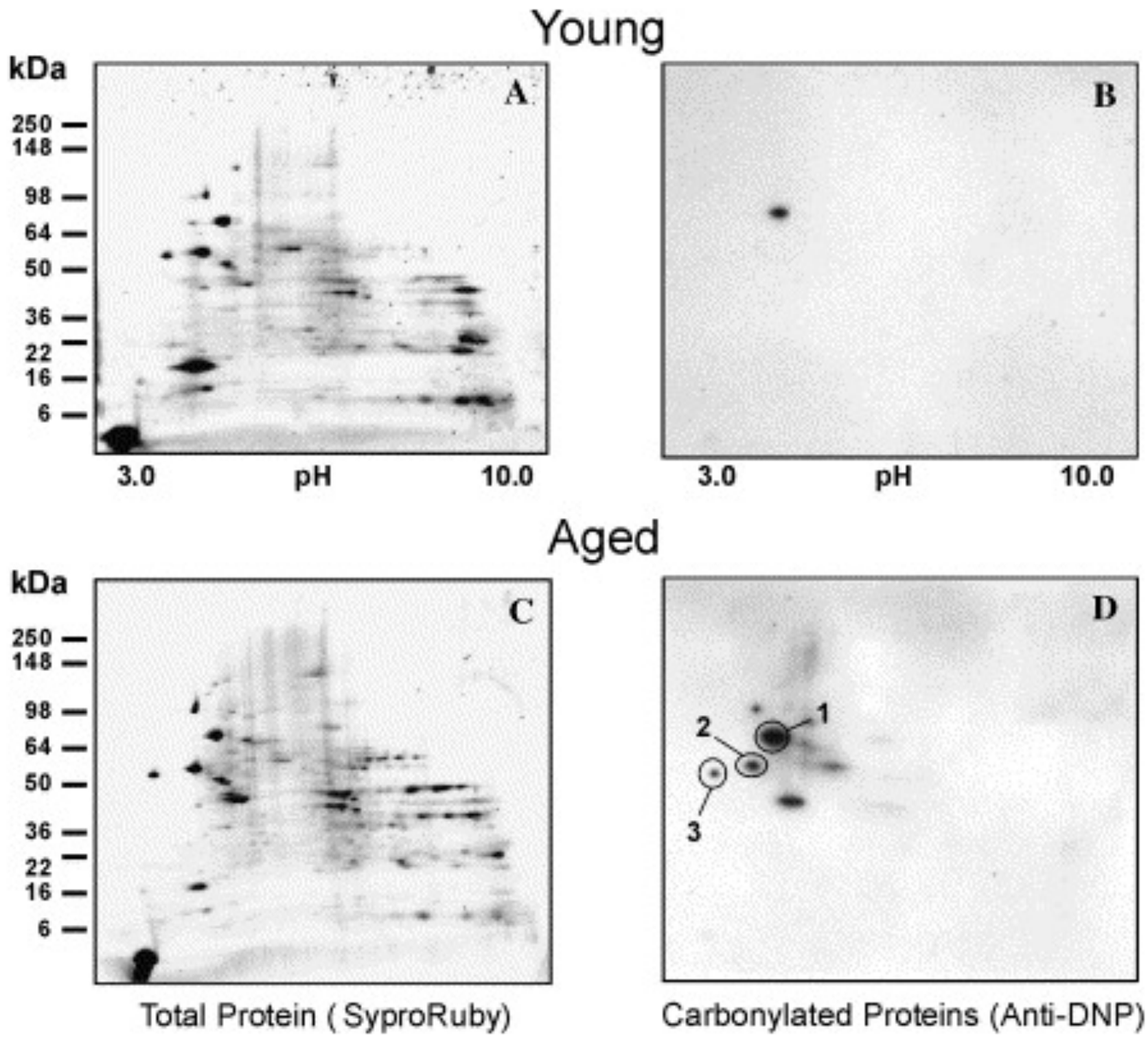
III. Stop doing experiments with cancer cells. Misses the point. Work with precancerous cells and seek prevention of protein damage/regression to functional proteome.

1) We do not understand the progression that environment causes in the induction of genetic lesions via the failure of DNA repair proteins.

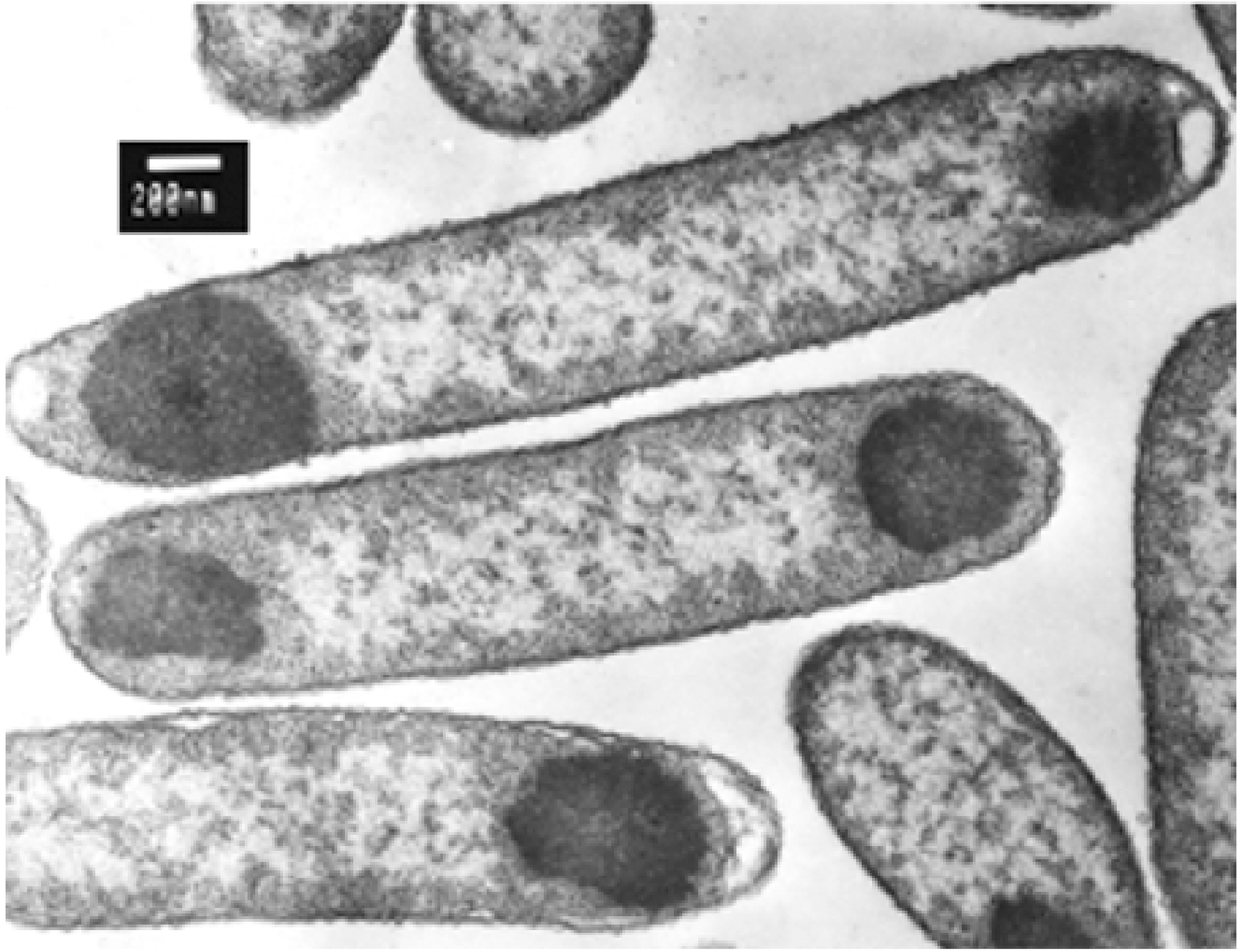
2) Take "normal" cell metapopulations on some sort of a complex stress landscape and map out first the time scale of protein damage and then the beginnings of genomic lesions: emergent cancer.

ROS stress, generated by oxidative glycolysis byproducts, irreversibly damages proteins due to the formation of carbonyl bonds within the protein, and between proteins.

Protein carbonyl bonds between amino acids is then the critical first stage. Carbonyl bonds, particular between the amino acids proline, arginine, lysine, and threonine result in dysfunctional proteins, and cross-linked proteins.



2D gel analysis of carbonylated proteins from liver ER/mitochondria of young and aged mice.

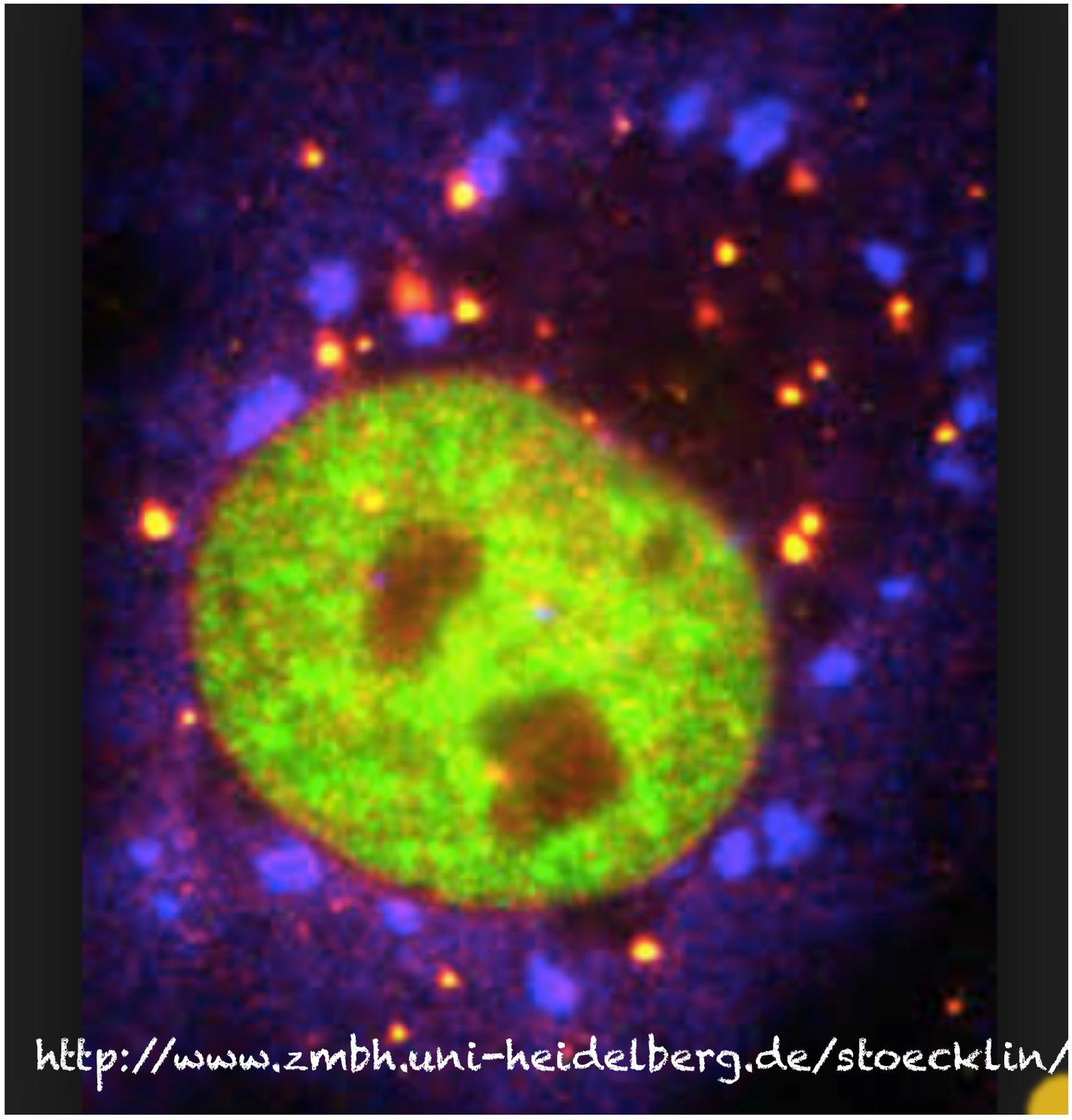


Occlusion bodies in bacteria due to build-up of misfolded proteins.

There is a related, very strange kind of nanoscale assembly that forms in mammalian cells under stress called stress granules.

Stress granules are about 100 nm in diameter, they consist of mRNA-protein aggregates and are induced during stress.

They accumulate in many neurodegenerative diseases, and in cancer.



Stress granules are transient, intracellular, dense aggregations of proteins and RNAs that accumulate as a stress response, protecting cells from apoptosis.

The Protein Quality Control (PQC) network may survey and/or assist in stress granule dynamics.

However, it is currently unknown whether the PQC actively participates in stress granule assembly.

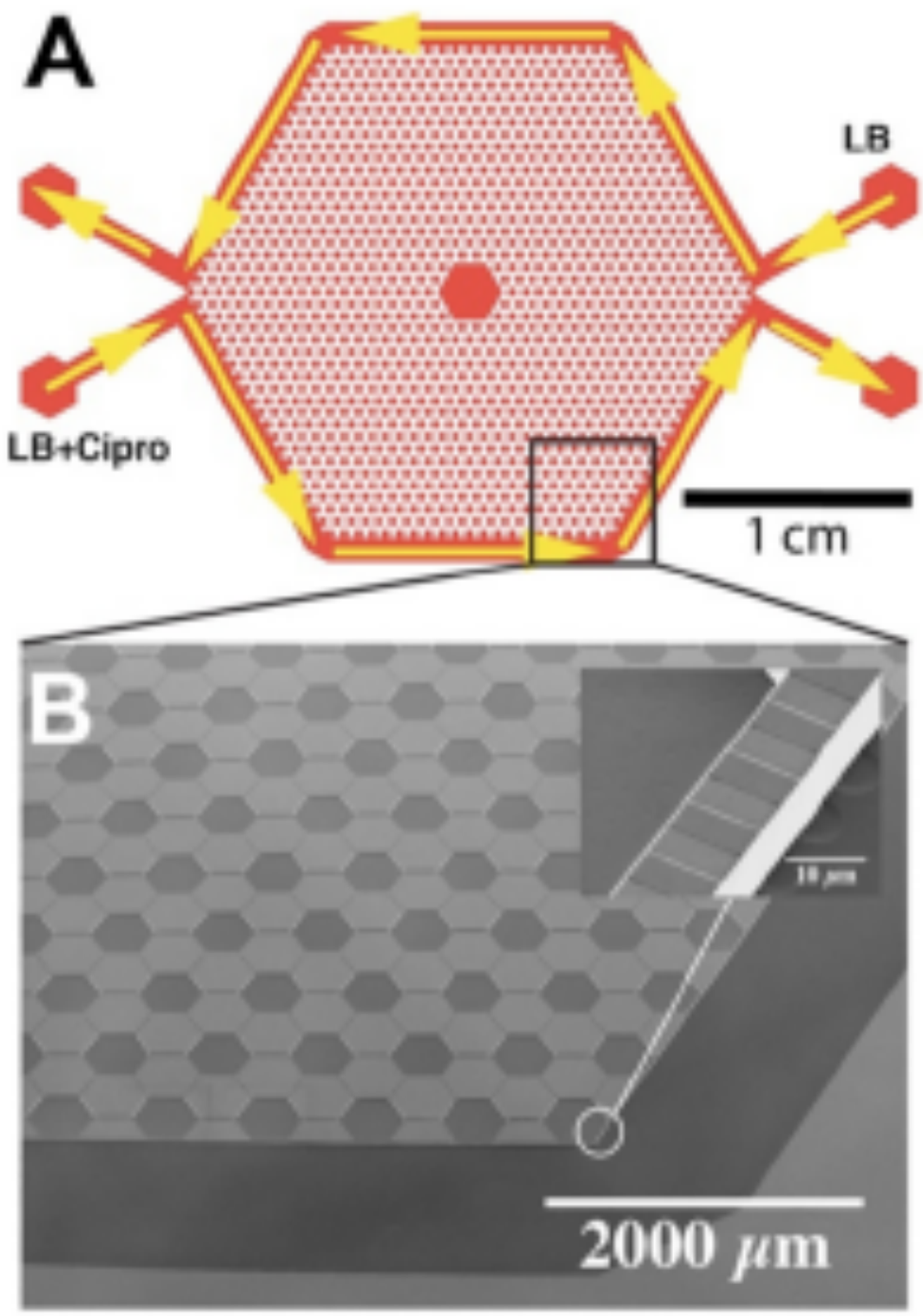
It is known that inhibition of autophagy is connected stress granules, and that radiotherapy, which is used in 50% of all cancer patients, also results in the generation of stress granules.

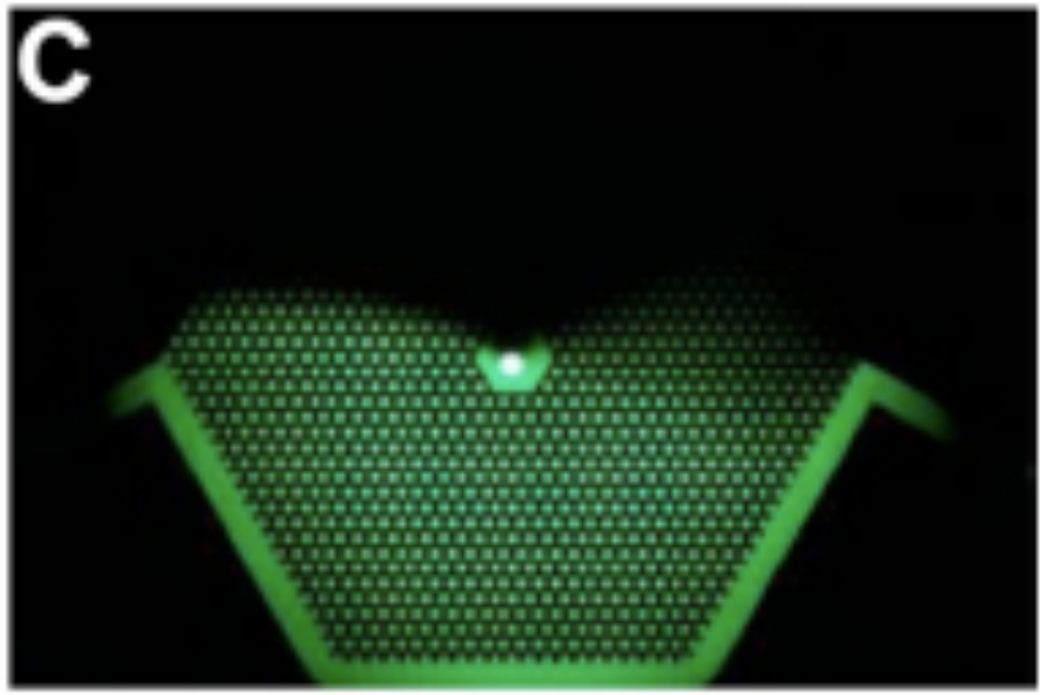
I think understanding
the origins of cancer will be
accomplished by assaying the
proteome, not genome, of complex
3-D ecologies of normal cellular
communities under conditions of
environmental stress.

In particular, generating stress
granules, extracting cells that have
stress granules and analysing the
contents of the stress granules.

IV. Plans for the Future

Construct complex,
metapopulation microecologies
with high ROS stress gradients
to drive forward the accumulation
of misfolded protein populations
within cells and cells adapted to
the dysfunctional state


A
LB
LB+Cipro
1 cm
B
2000 μm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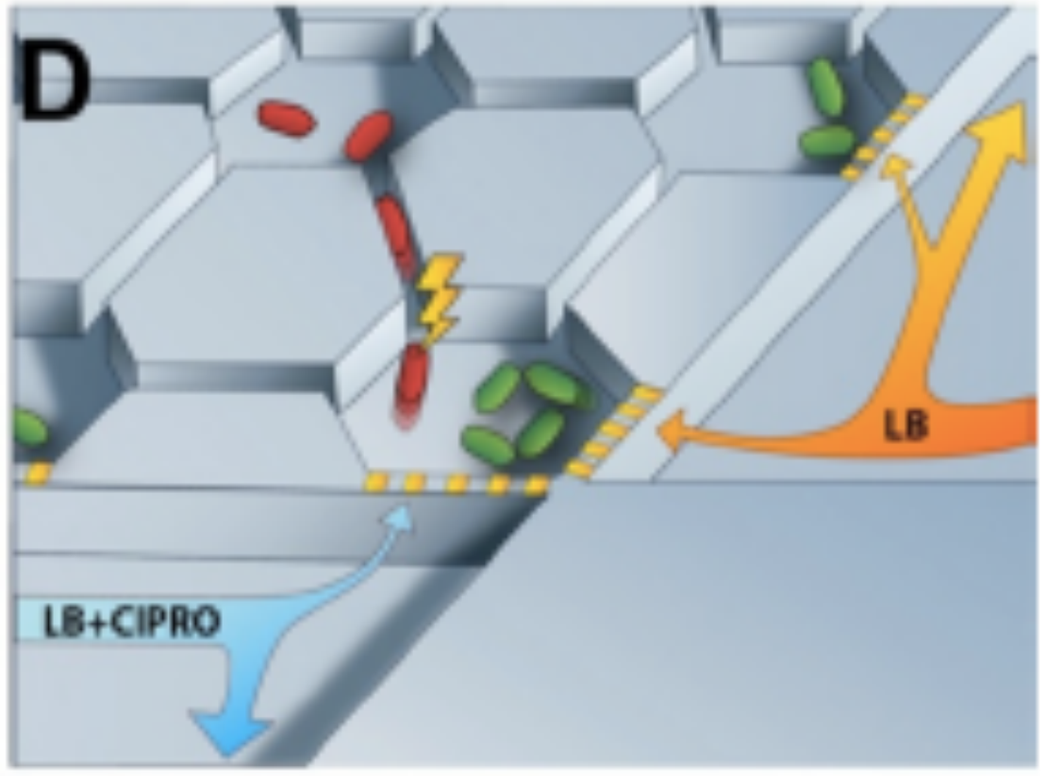
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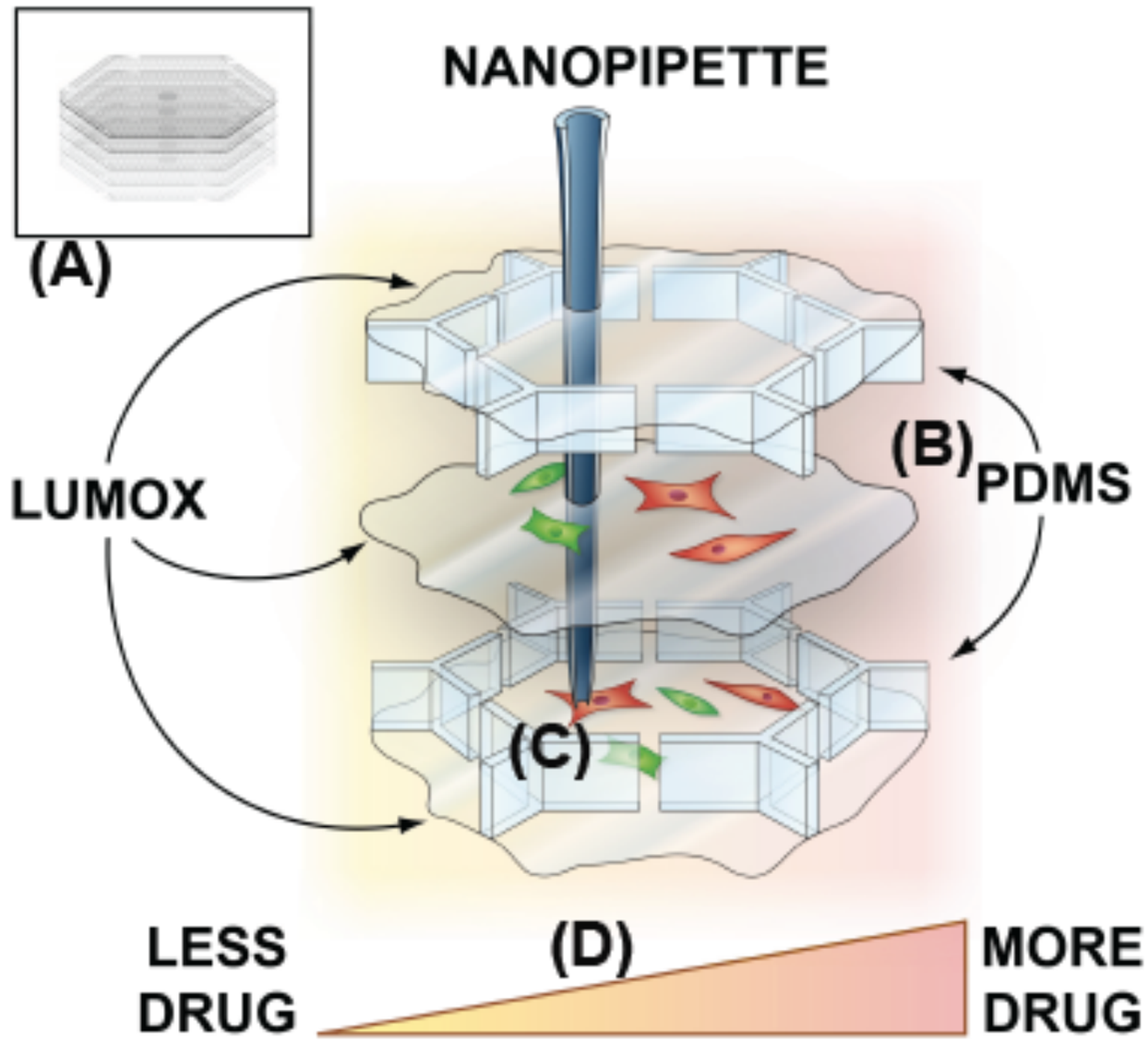
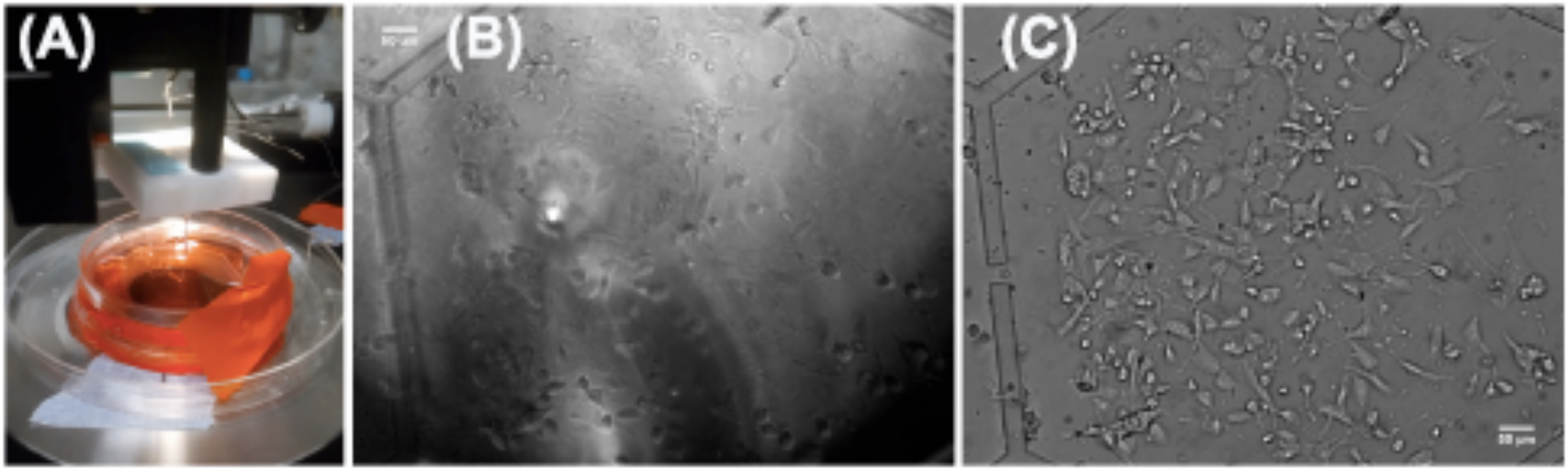
LB
LB+CIPRO

Develop single-cell microfluidic techniques to analyze the proteome contents of single cells extracted from a complex ecology.





With Nader Pourmand, UC Santa Cruz

V. Conclusions

In a sense, cancer not a disease.

1) 90% of cancers are due to our own environment: self inflicted for many cases. We could do much more prevention.

2) The origins of cancer lie deeper than genetic damage: accumulation of misfolded proteins. Chasing the wrong dog, after the damage is done.

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Since we are obsessed with "curing" cancer as a genetic problem rather than preventing cancer from it's misfolded protein origins driven by the environment, we have a good business but bad science.


HEALTH CARE
EUROPEAN STYLE:
HEALTHY PATIENTS ABOVE ALL
DOCTORS
NURSES
NURSING ASSISTANTS
MEDICAL ASSISTANTS
VS.
AMERICAN STYLE:
HEALTHY PROFITS ABOVE ALL!
ACCOUNTANTS
LAWYERS
$$$
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