Potential Impact on Estimation of Human Health Risk

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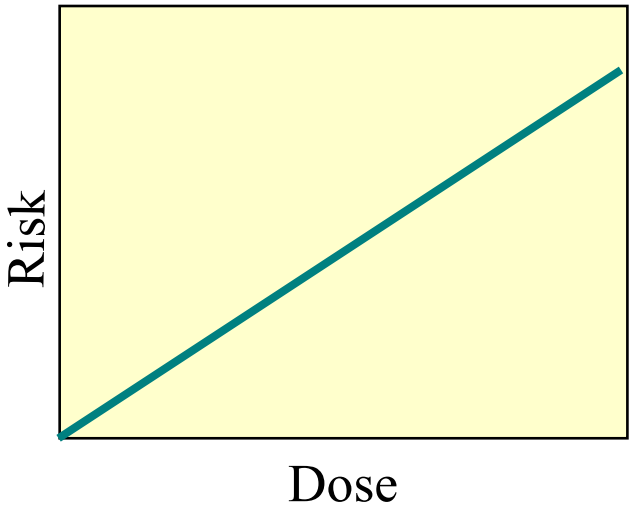
My Background

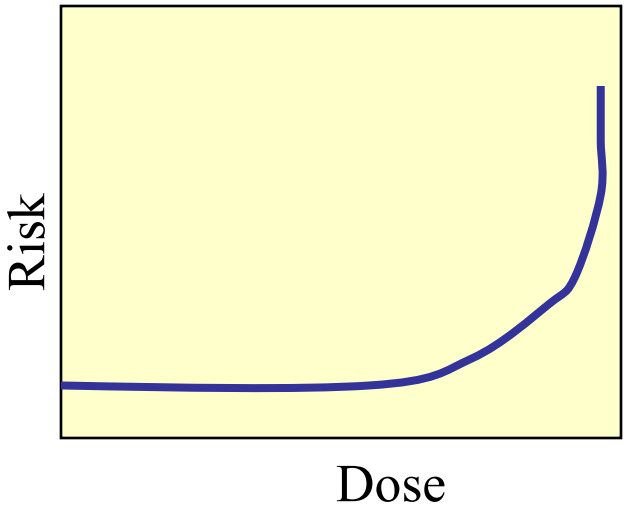
- Early interest in radiation
  (Watching atomic weapons in southern Utah)
- MS in radiation ecology (Chasing fallout)
- PhD in radiation biology in genetics
  (Trying to discover what radiation is actually doing inside people)
- Investment of my life in research on health effects of low doses of radiation

Risk Models

Linear No Threshold



Non-Linear Threshold



Is risk always proportional to dose?

Can any amount dose increase risk?

Can a single radioactive ionization can cause cancer?

Problems Associated with Estimating Health Risks of Radiation

- Background radiation
- Background cancer

Normal annual exposure from natural radiation

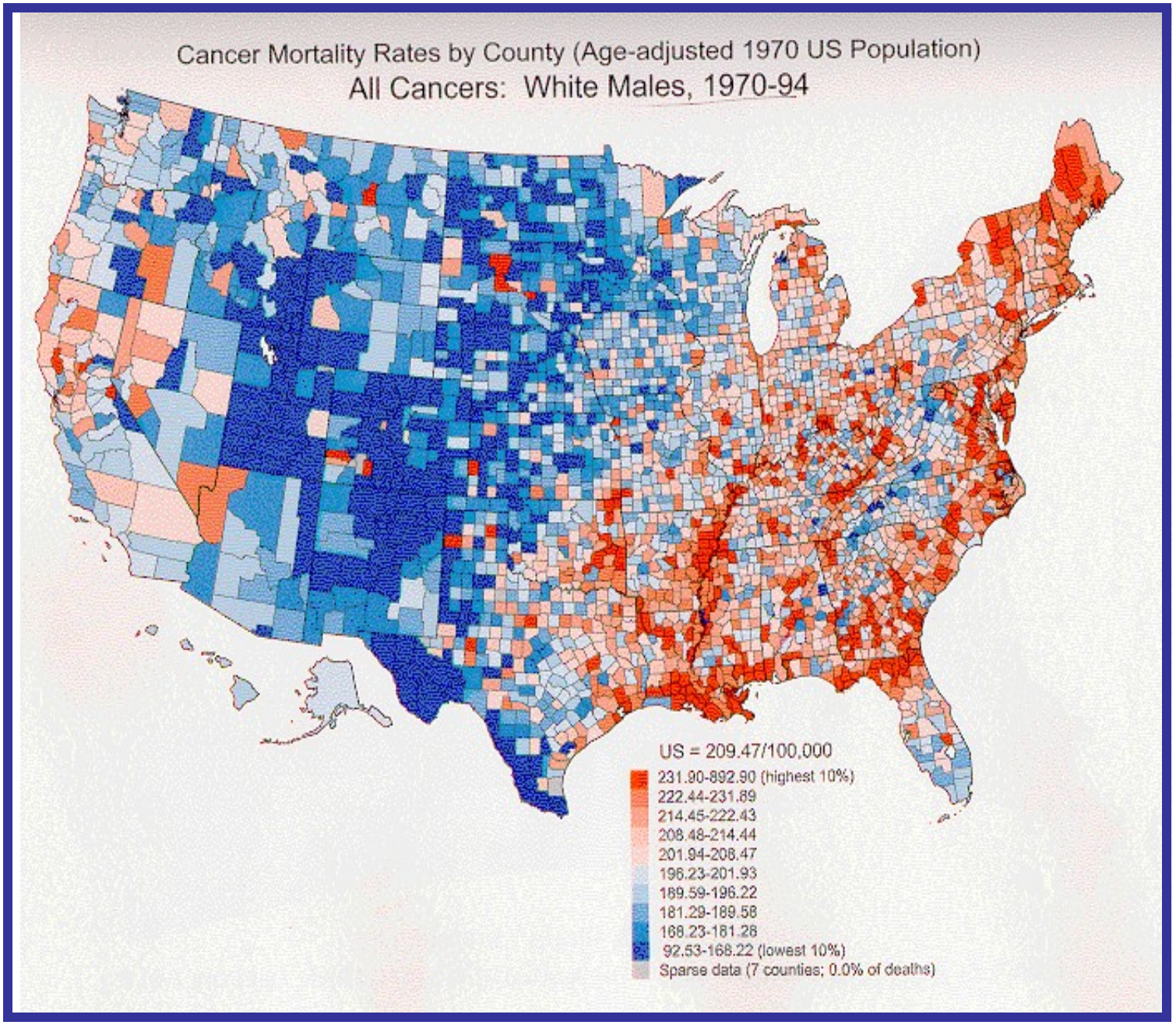
300 mrem/yr

Radon gas	200 mrem
Human body	40 mrem
Rocks, soil	28 mrem
Cosmic rays	27 mrem

Normal annual exposure from man-made radiation

70 mrem/yr

Medical procedures	53 mrems
Consumer products	10 mrems
One coast to coast airplane flight	2 mrems
Watching color TV	1 mrem
Sleeping with another person	1 mrem
Weapons test fallout	less that 1 mrem
Nuclear industry	less than 1 mrem


Cancer Mortality Rates by County (Age-adjusted 1970 US Population)
All Cancers: White Males, 1970-94
US = 209.47/100,000
231.90-892.90 (highest 10%)
222.44-231.89
214.45-222.43
208.48-214.44
201.94-208.47
196.23-201.93
189.59-196.22
181.29-189.58
168.23-181.28
92.53-168.22 (lowest 10%)
Sparse data (7 counties; 0.0% of deaths)

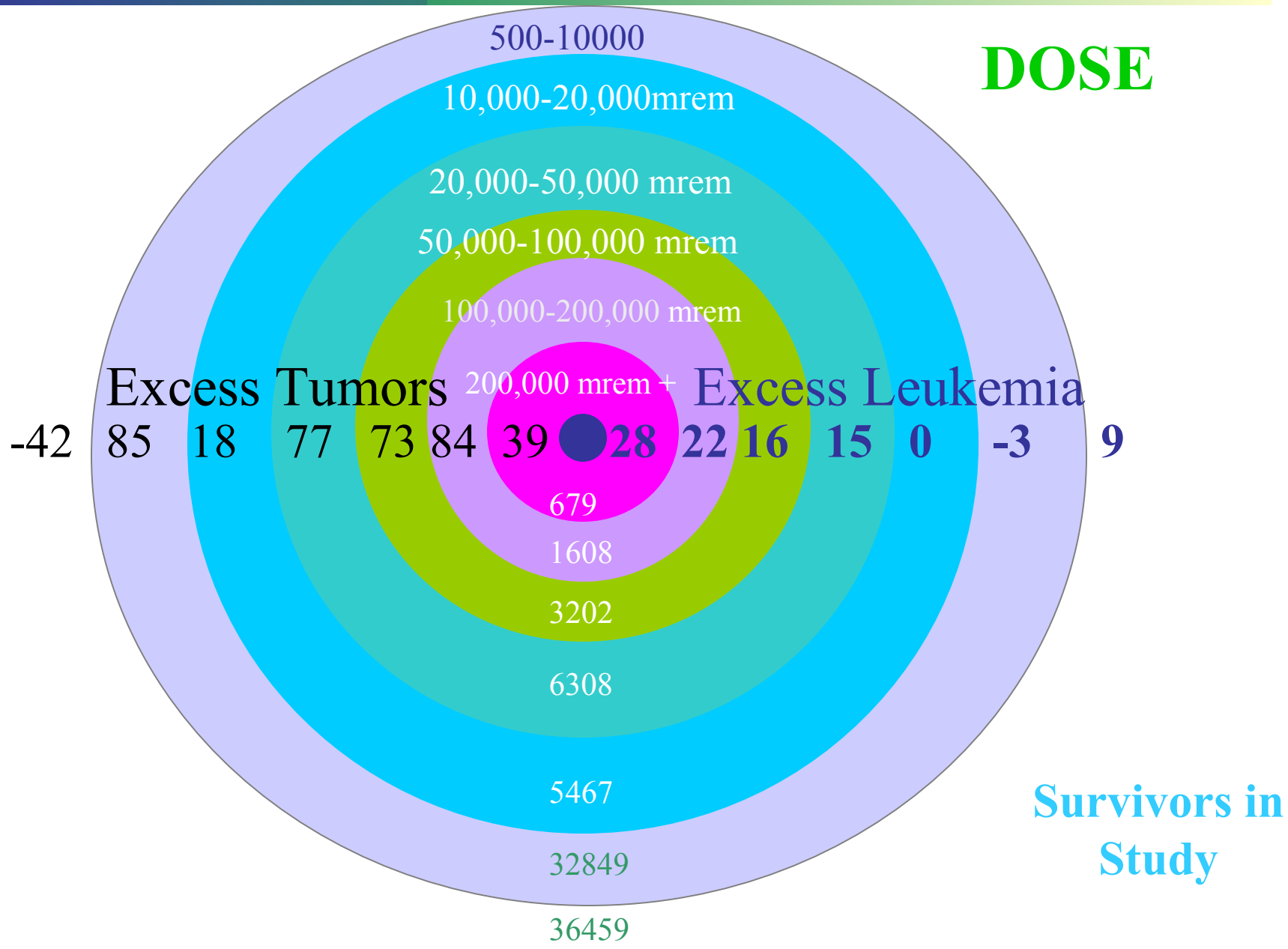
Nuclear “Disasters”

A-BOMB

- BAD!!!
- Over 200,000 mrem on a highly populated city

- Intent to kill and do as much damage as possible

Atomic Bomb Survivor Excess Cancer



Effects of Atomic Bomb

Killed outright by the bomb or acute radiation effects.	**200,000 people**
Survived for life-span study	**86,572 people**
Expected cancers	**21,643 cancers (10,721 cancers to date)**
Total observed cancers	**11,445**
Observed cancers	**11,445 - 10,721=724 (excess cancers from the A-bomb)**

Understanding Biological Response to Radiation

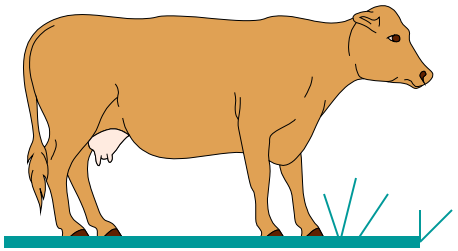
Hanford Thyroid Study (Dose)

- Few human measurements
- Identifying exposed people
- Estimating dose from lifestyle
- Reconstructing dose 50 years later

Understanding Biological Response to Radiation

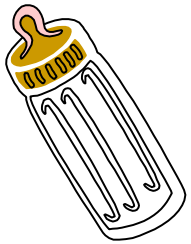
Normal population

- 5000 people
- 25 (20-30) thyroid cancers expected



Downwinders

- 5000 people
- 25 cancers
- No dose-response



Conclusion- no effect?

–Radiation induced disease

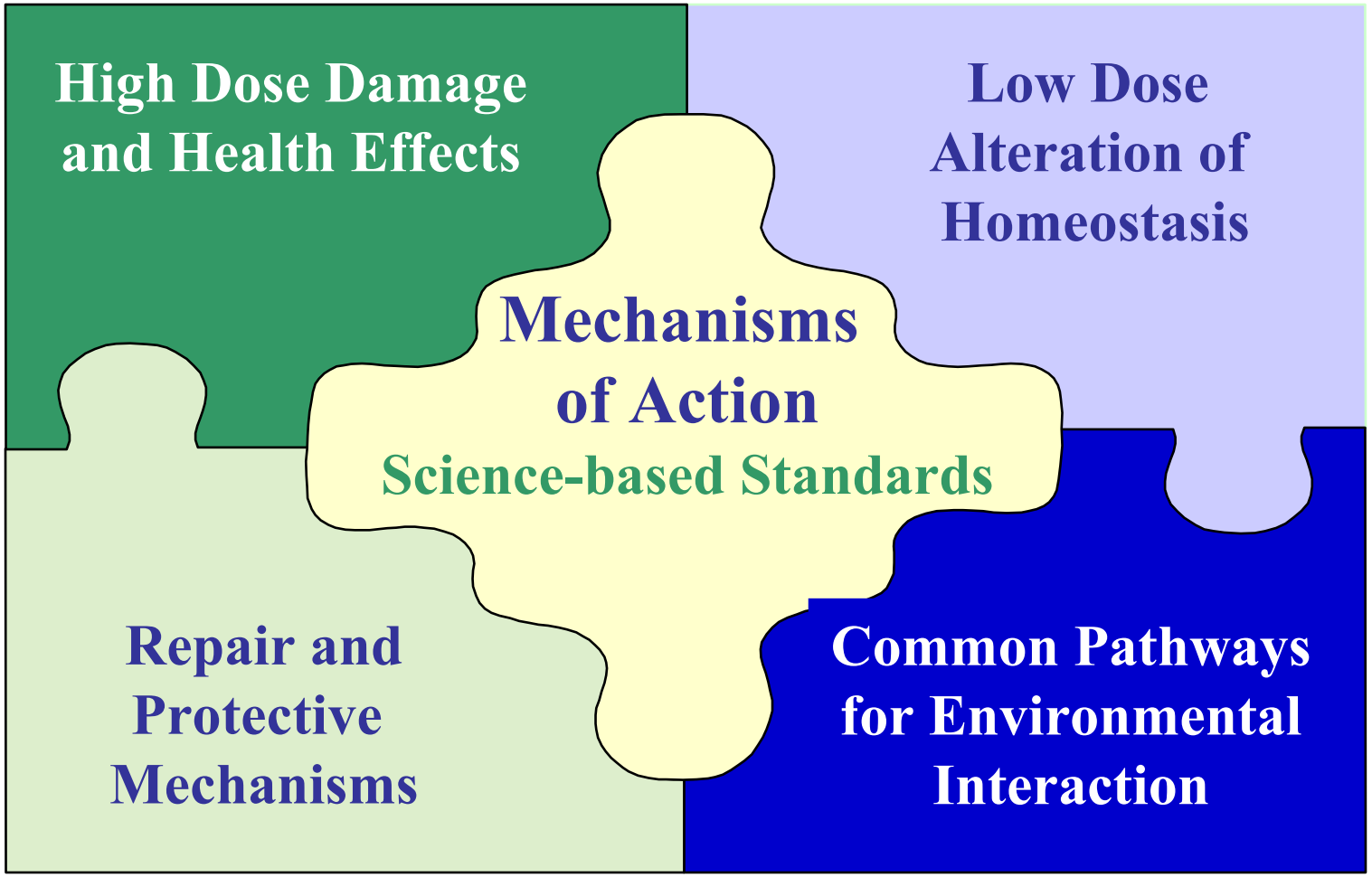
–Sensitivity

Why now?

- Standards have been set from high dose effects, but low dose effects have not been measurable until now

- New technological developments and biological discoveries have made it possible to study low dose effects

Needed Shift in Research Emphasis



DOE Low-Dose Radiation Research Program

- A 10 year program
- Focused on biological mechanisms of low-dose (< 0.1 Gy) and low dose-rate (< 0.1 Gy / Yr) radiation
- International in scope (currently 49 projects)
- To develop radiation standards based on risk
- We are interested in your ideas or proposals

http://lowdose.tricity.wsu.edu

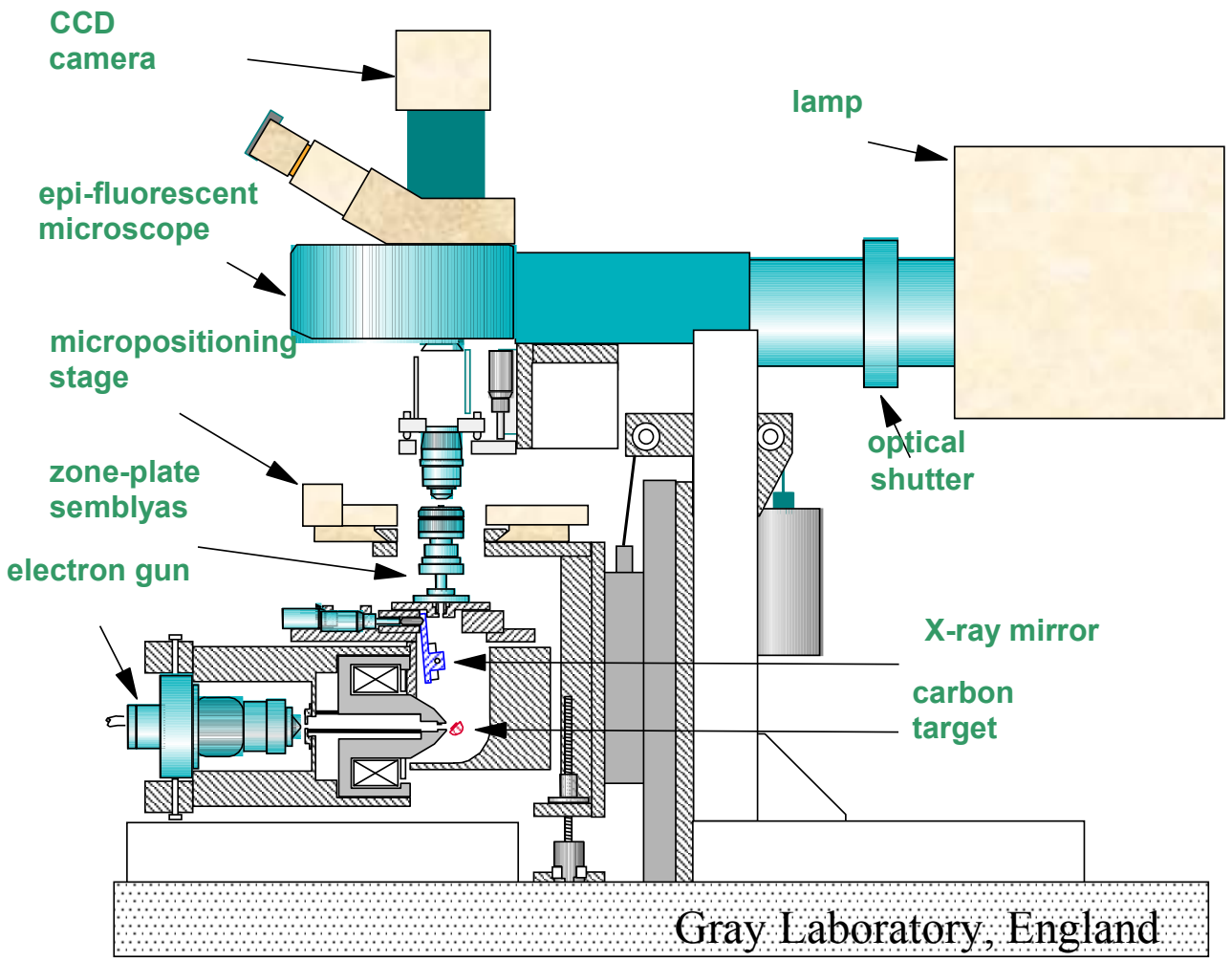
Low Dose Radiation Research Programatic Interest

- Bystander Effects
- Oxidative vs Radiation-induced Damage
- Radio-adaptive Responses
- Genetic Susceptibility

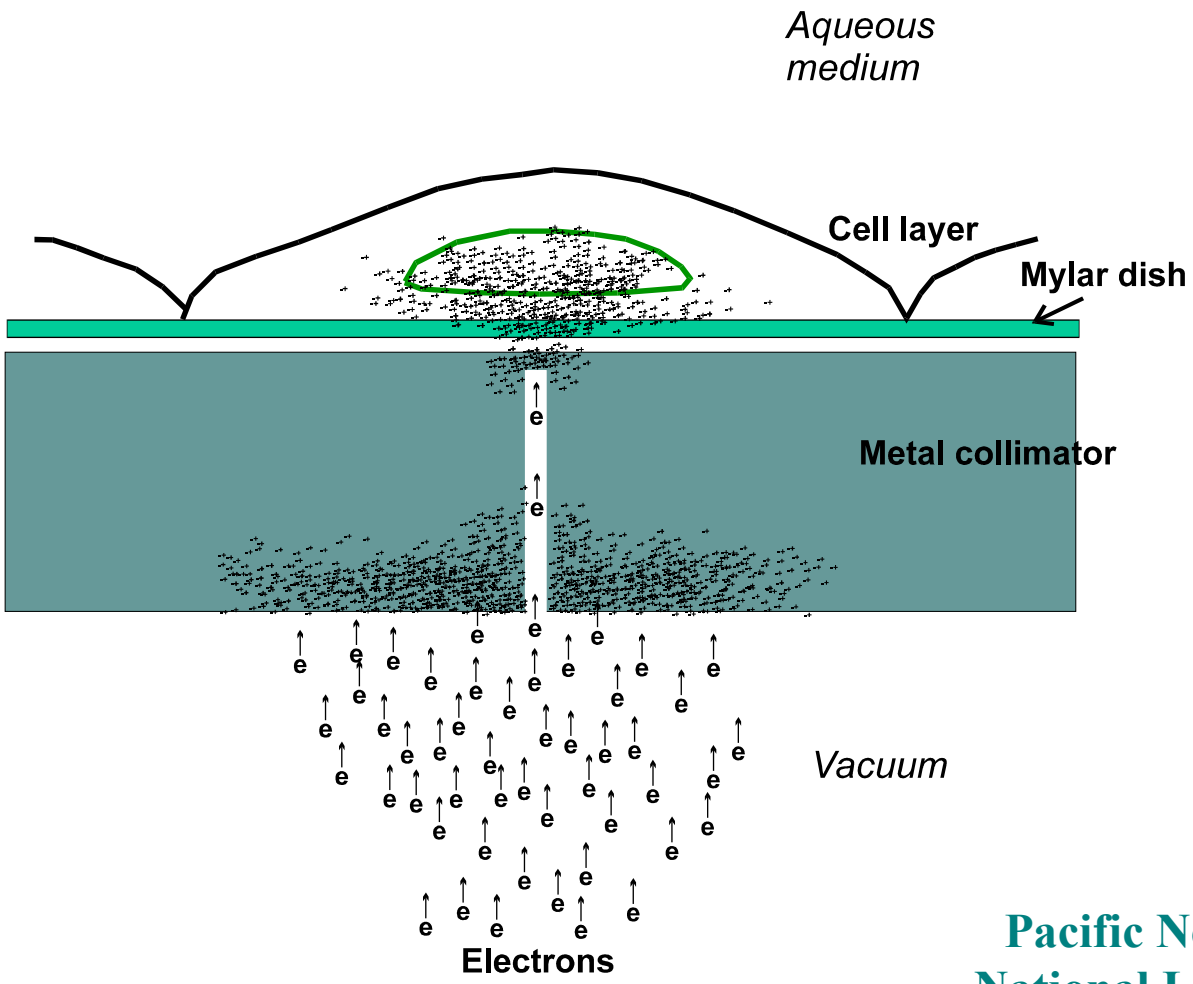
Key Research Areas

- Technological Advances
- Biological Advances

Microbeam

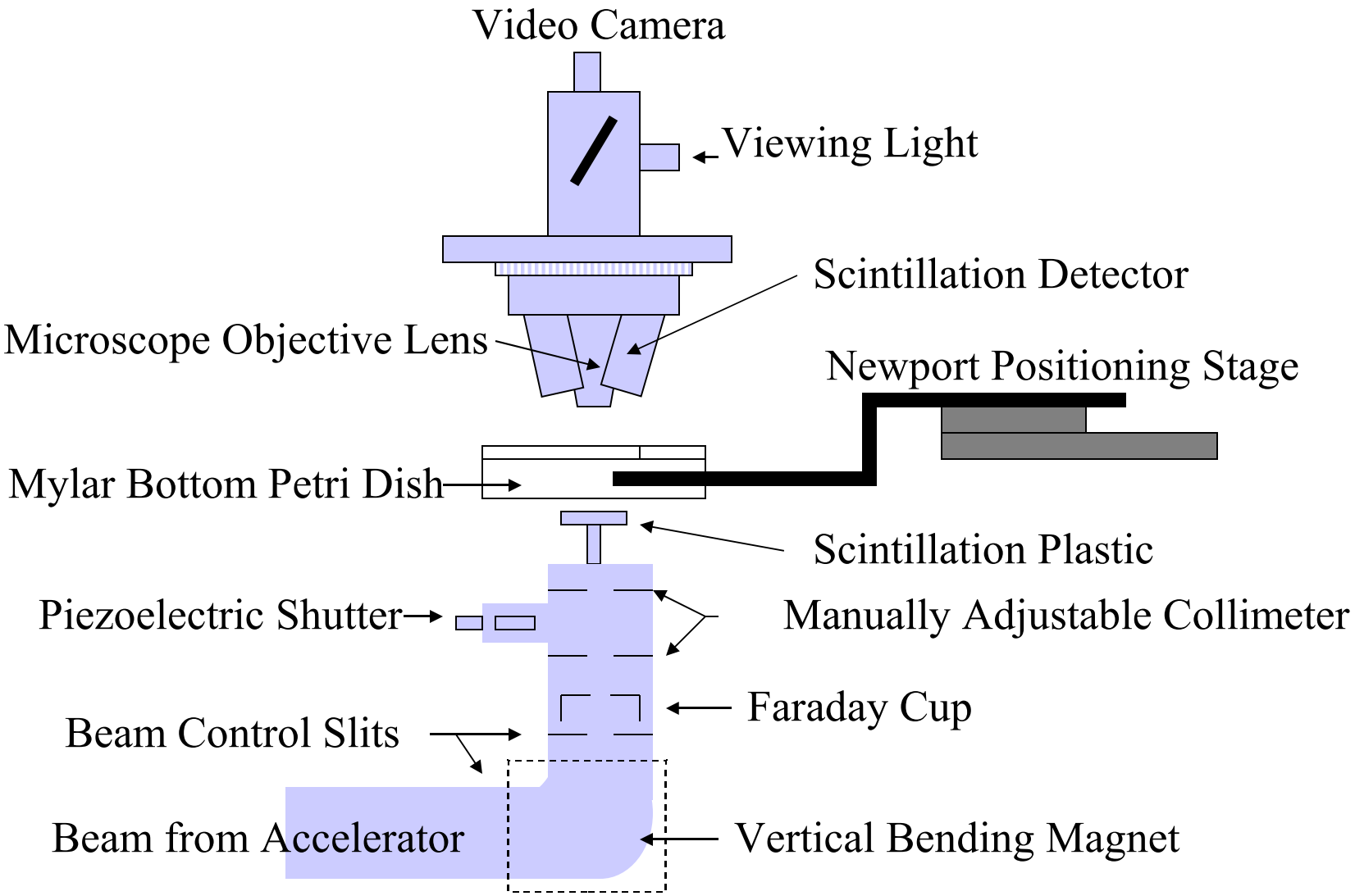

CCD
camera
lamp
epi-fluorescent
microscope
micropositioning
stage
optical
shutter
zone-plate
semblyas
electron gun
X-ray mirror
carbon
target
Gray Laboratory, England

Spatially-Resolved Electron Gun

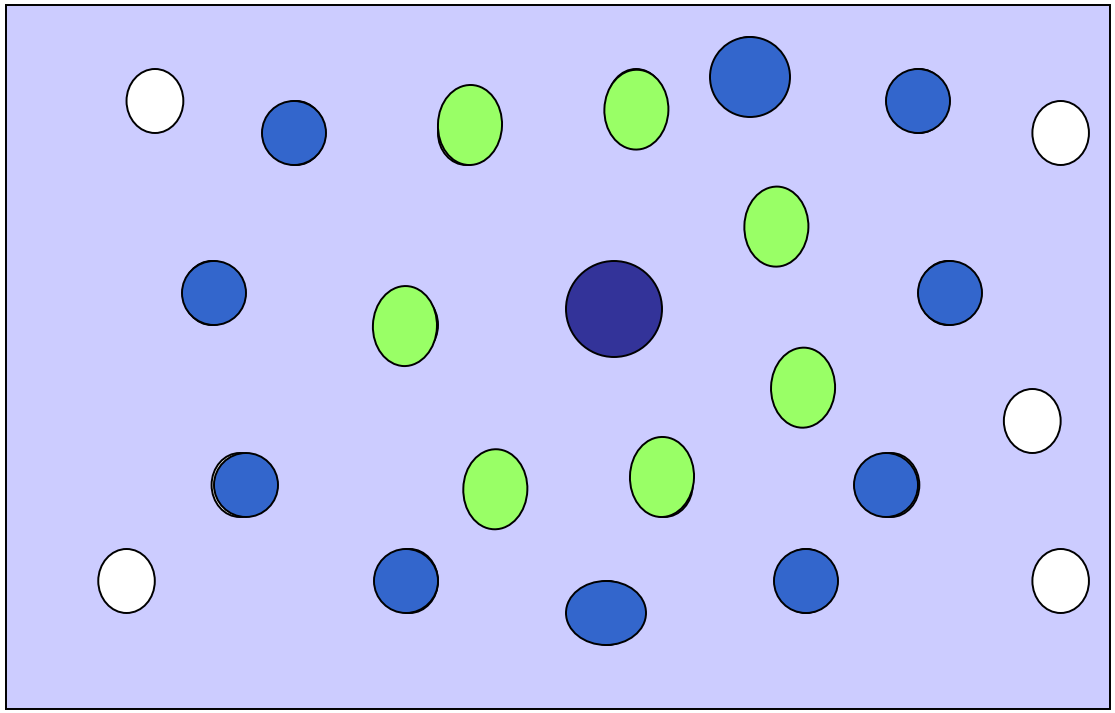


Pacific Northwest National Laboratory

Alpha-Particle Radiation System

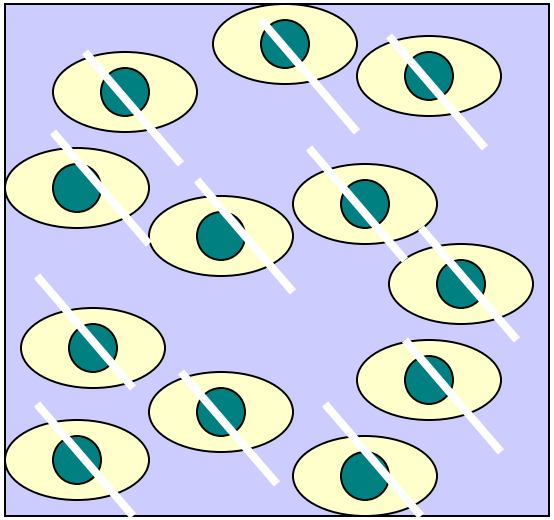


Bystander Effects

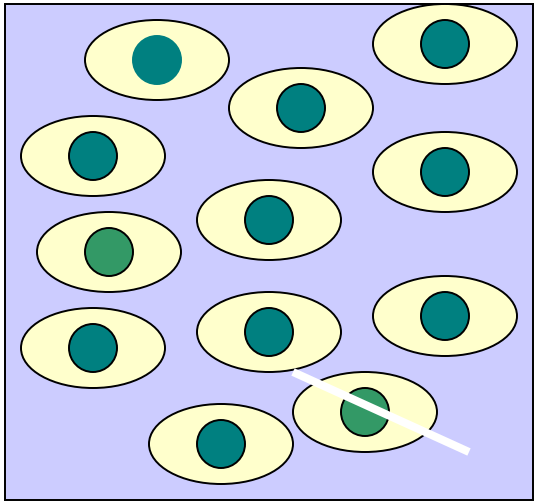


Microbeam

Each cell hit by one particle

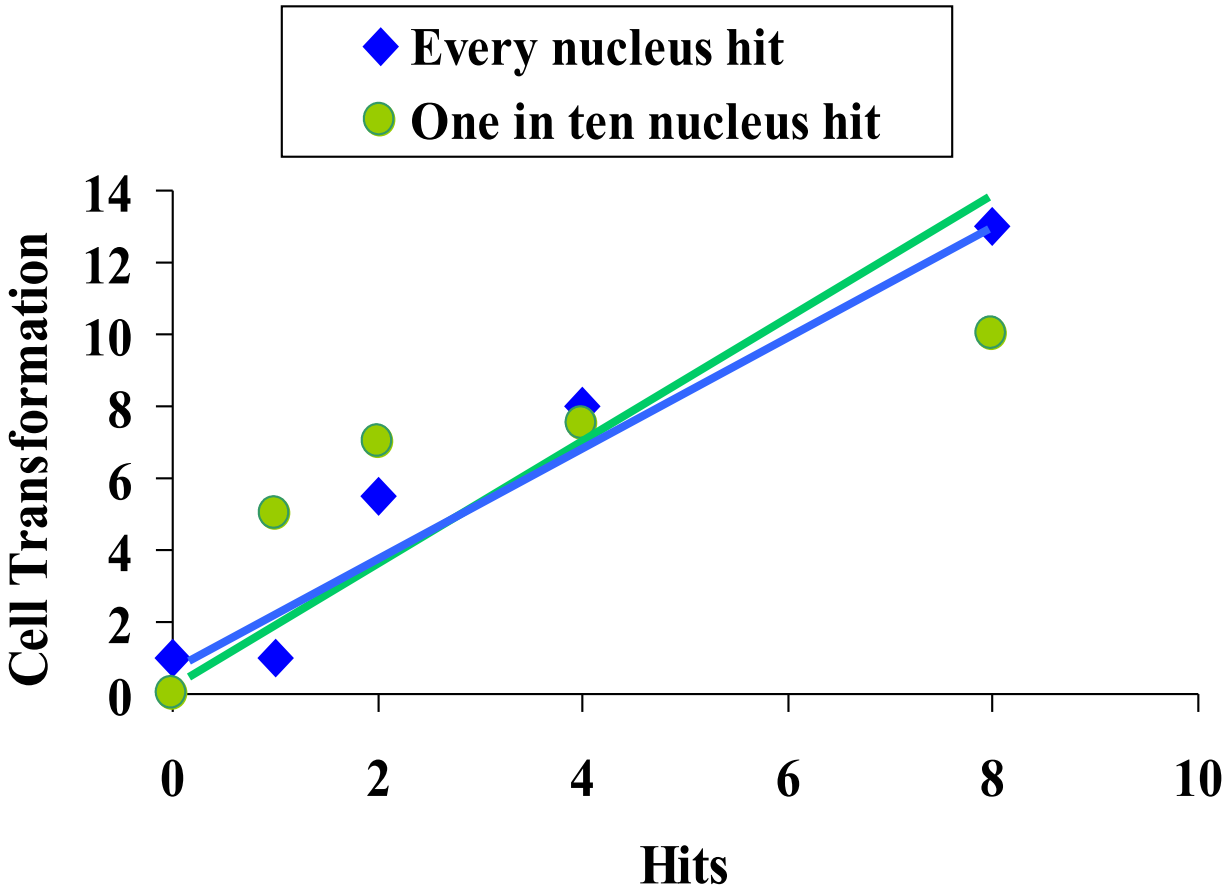


10 % of cells hit with 1 alpha particles



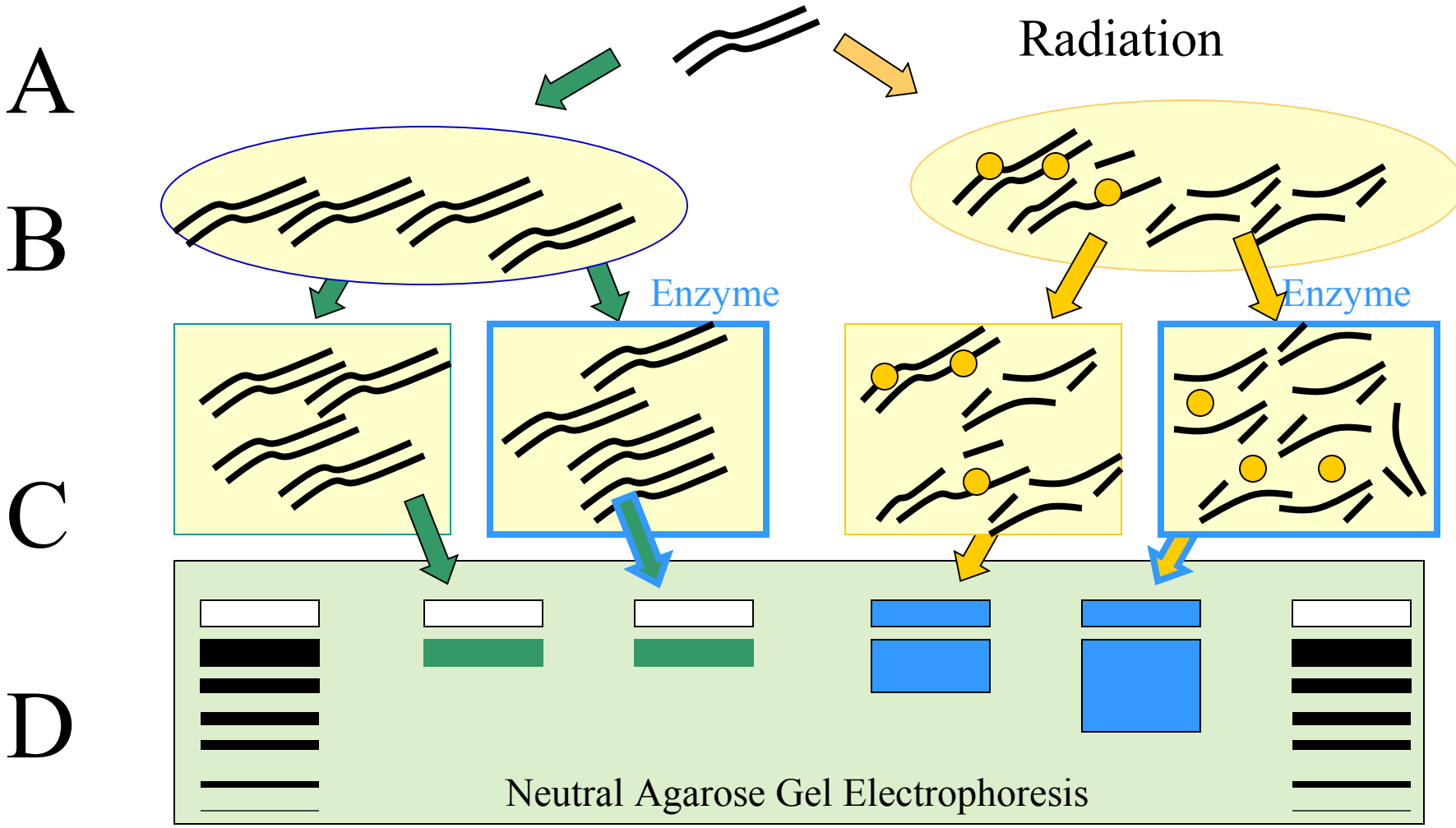
Sawant et al. 2001

Cell Transformation



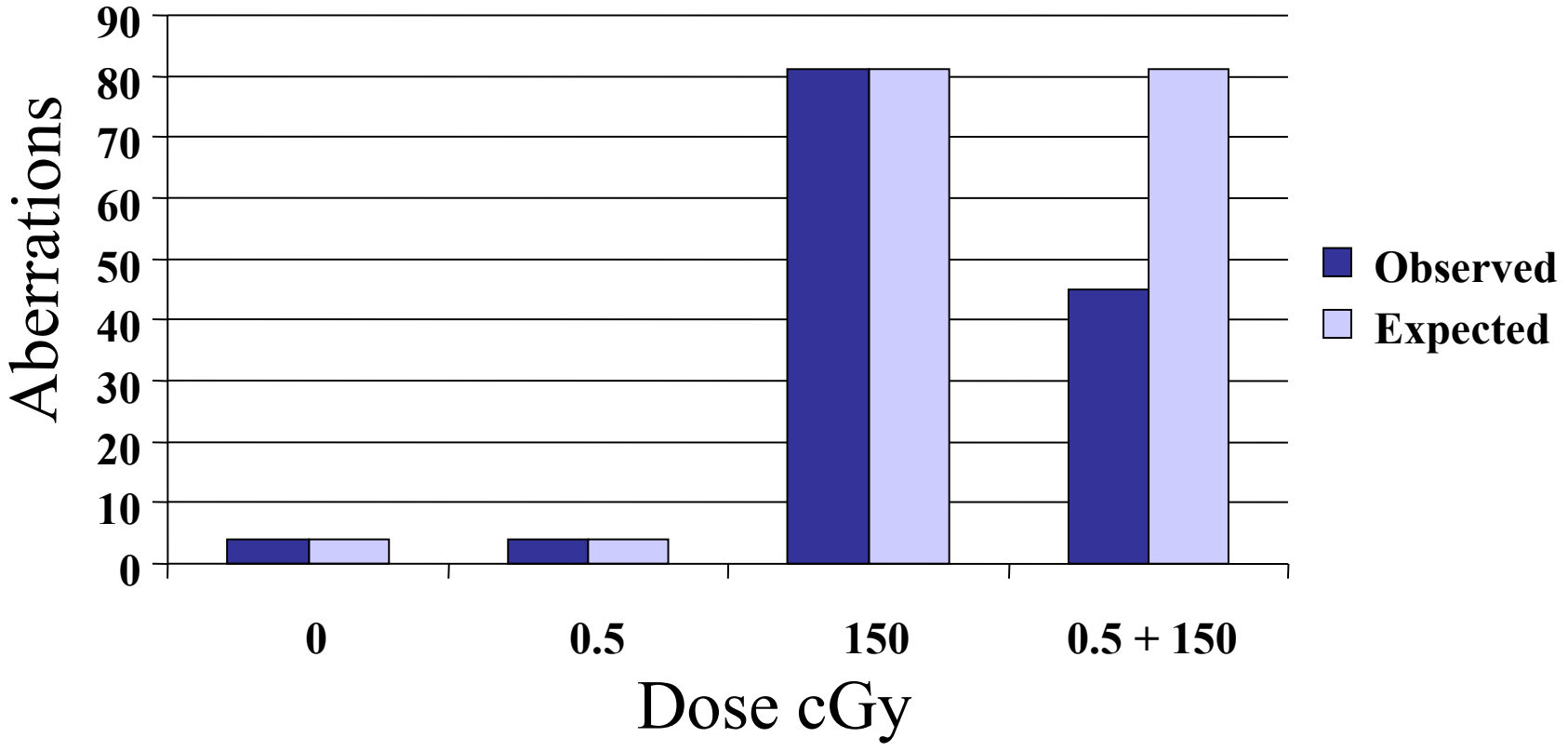
Sawant et al.2000

Clustered DNA Damages: Quantitative Gel Analysis



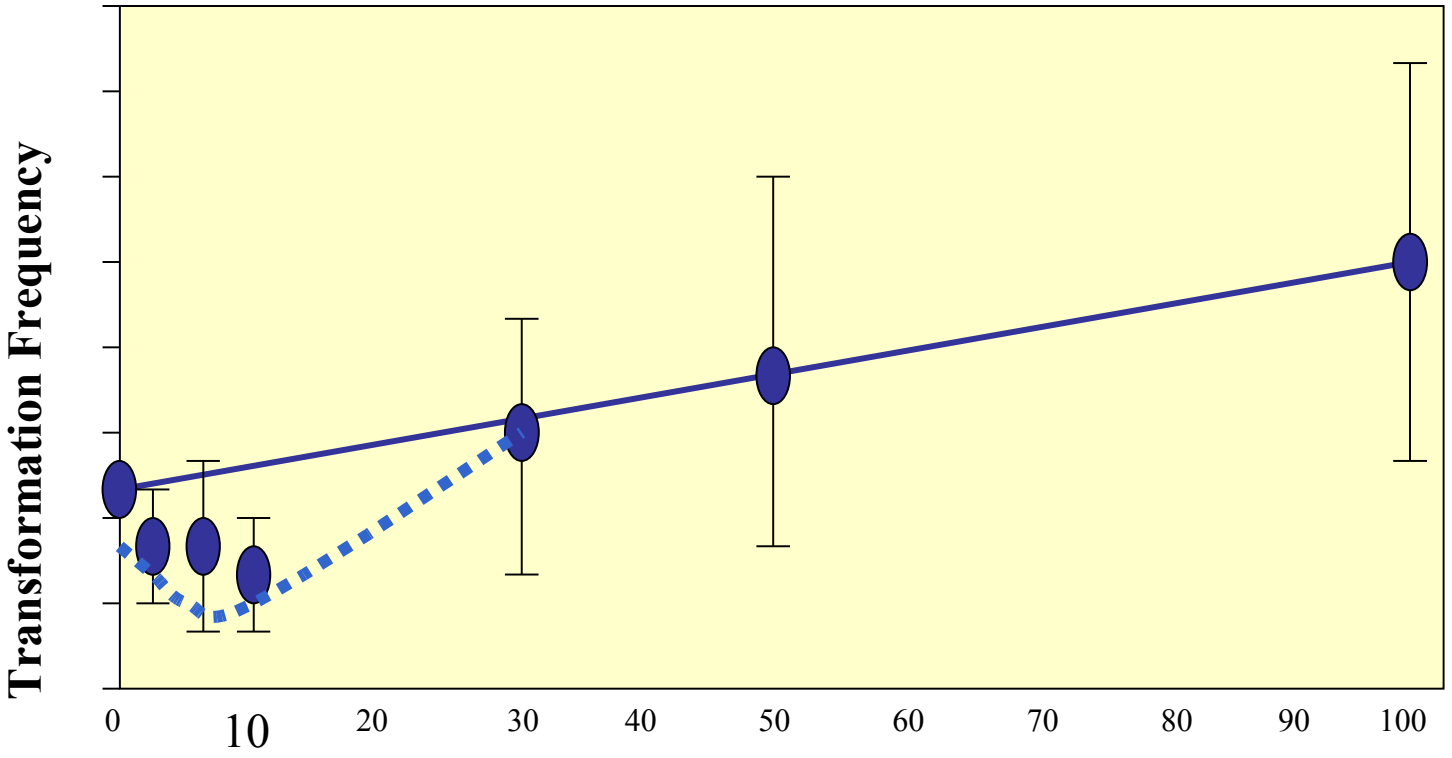
Sutherland

What Genes are Responsible for the Adaptive Response ?



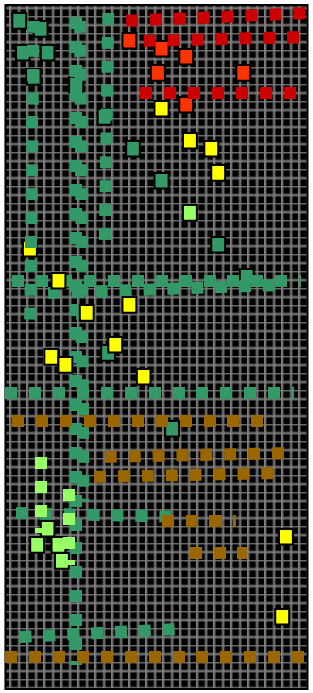
Shadley and Wolff 1987

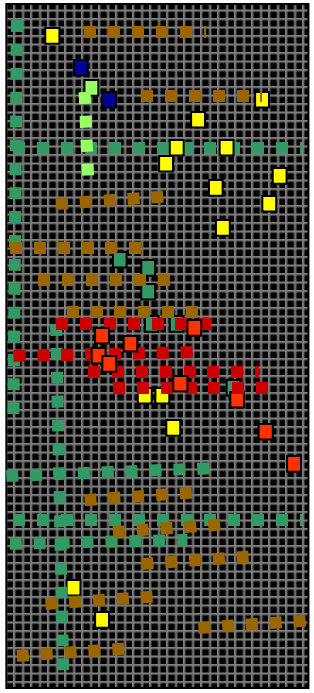
What Genes are Activated at Low Dose to Reduce Cell Transformation?



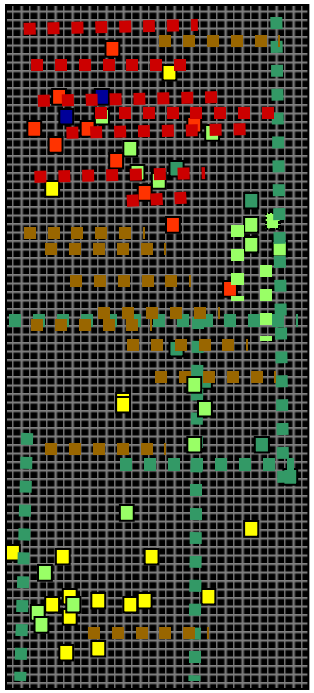
Redpath et al. 2001

Gene Expression





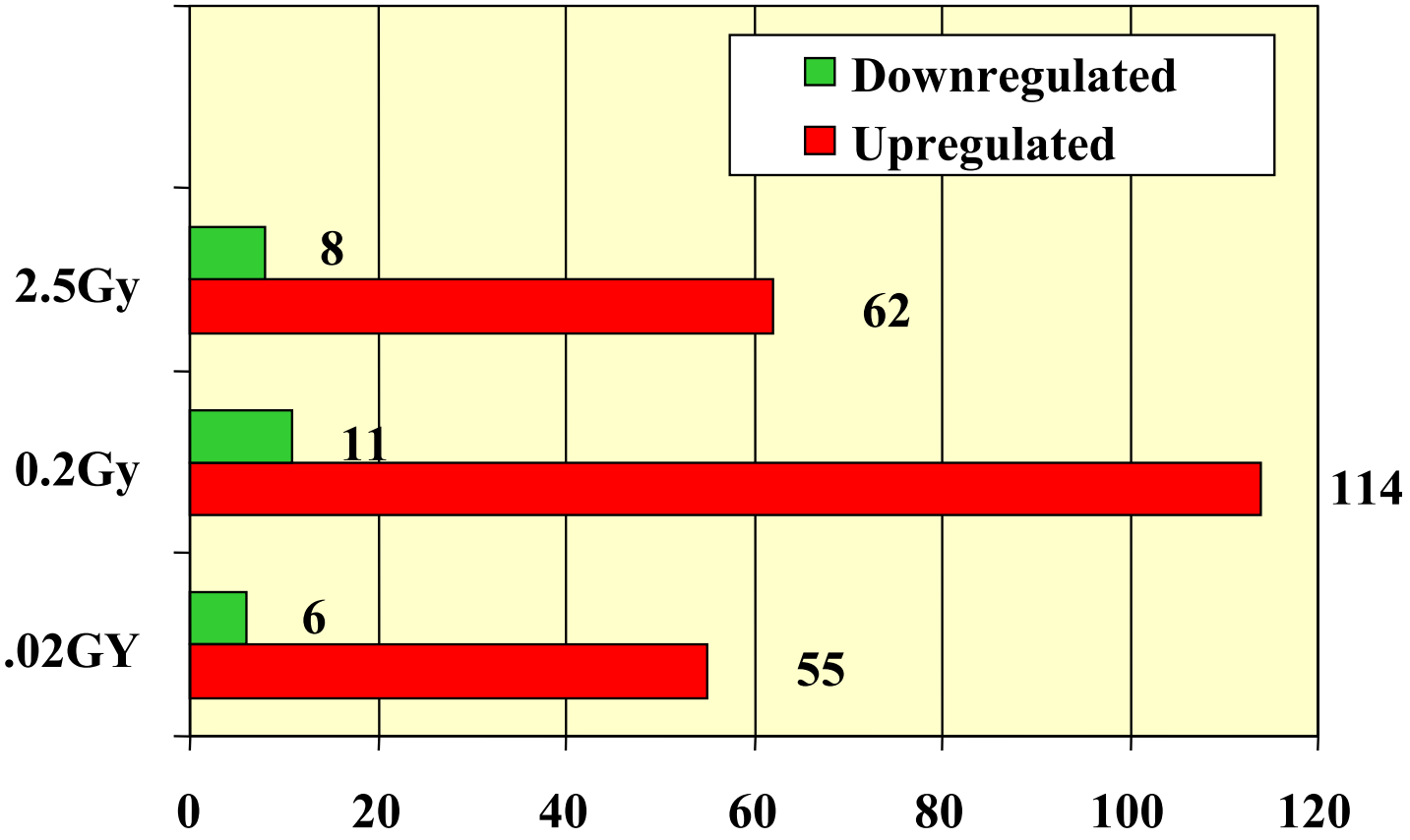
Polycyclic
CCl_4



Low
Dose
Radiatio

Results for "Stress Chip"

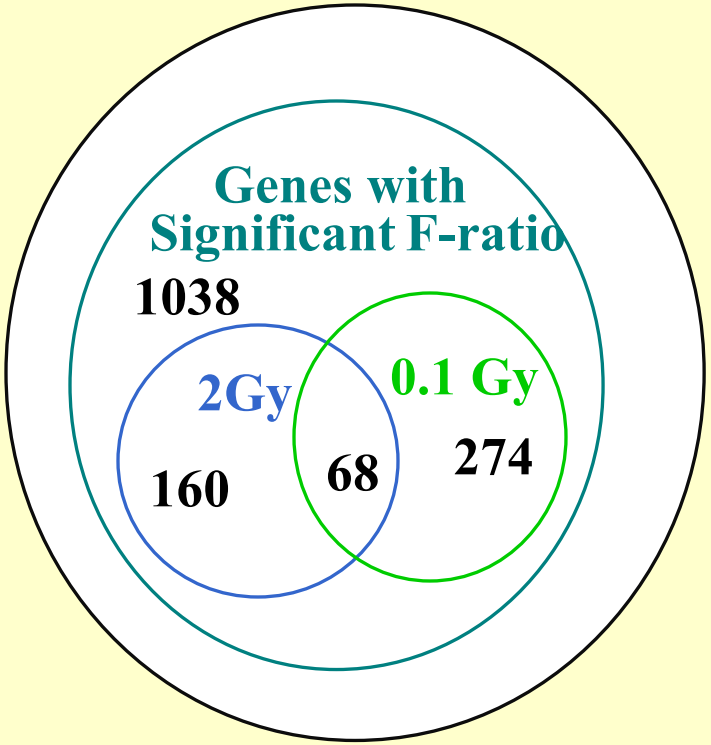
7000 genes tested 24 hours after radiation



Fornace

DIFFERENCES IN TRANSCRIPTION PROFILES BETWEEN LOW AND HIGH DOSE IRRADIATION IN HUMAN LYMPHOBLASTOID CELLS

HLB Cell Line



Total gene set contains over 12,000 genes

Numbers of Genes Differentially Regulated in HLB Cells after IR

Up-regulated at 2Gy	71
Down-regulated at 2Gy	147
Up-regulated at 0.1Gy	191
Down-regulated at 0.1Gy	141

Wyrobek

Genetic Susceptibility

Who is susceptible to radiation?

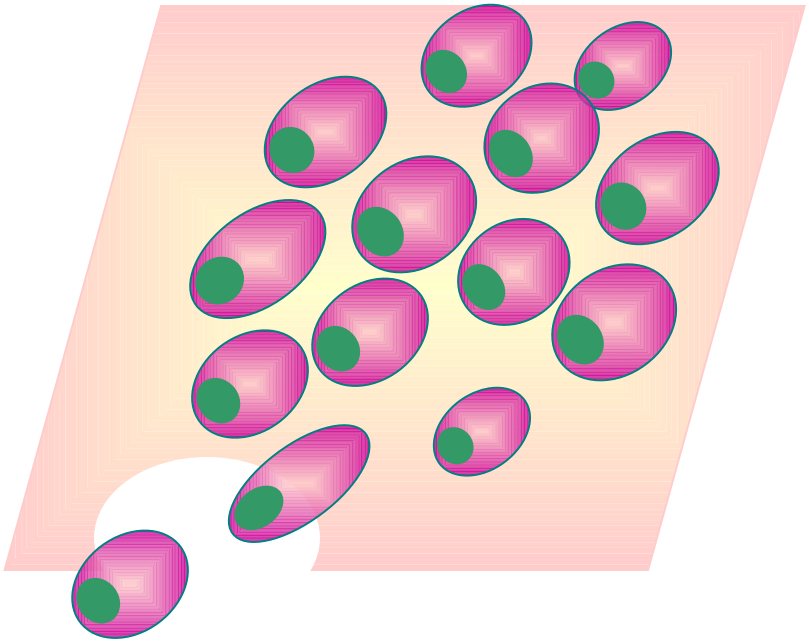
Rapid gene sequencing makes identification possible.

Genes involved in Radiation Sensitivity and Cancer Susceptibility

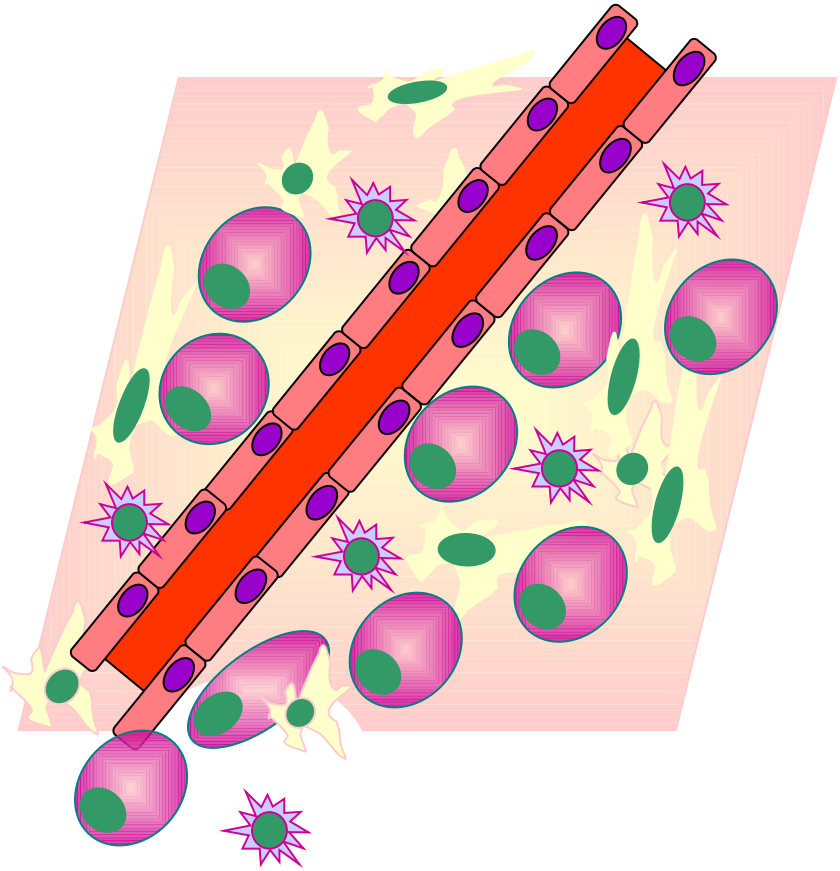
- Can we identify them?
- How many genes are there?
- How prevalent are they in the population?
- How sensitive do they make the people?

Schwartz 2002

The Reductionist View



A Heterotypic Cell Biology

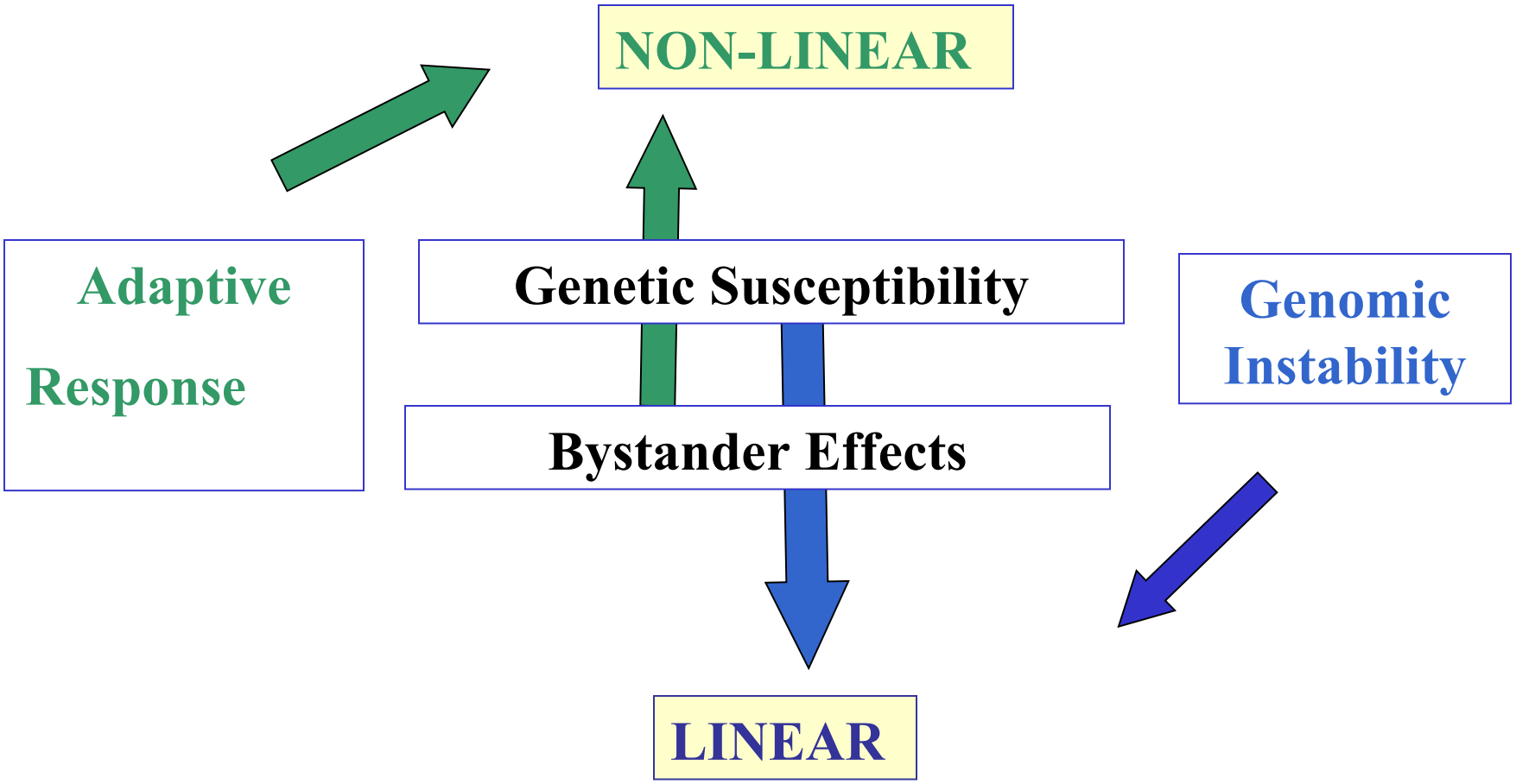


Hanahan and Weinberg 2000

Observations Suggesting Major Paradigm Shifts

- Adaptive response vs additive or synergistic effects
- Hit theory vs. bystander effects
- Mutation vs. gene induction
- Single cell vs tissue responses

How will this Research Impact Standards?



Potential Impact of Research on Public Perception

- Provide scientific outreach
- Level of understanding increased
- Risk and fear put into perspective
- Scientific basis for standards

Summary

- **Radiation risks from low levels of radiation exposure cannot be predicted with epidemiological studies alone.**
- **Combining advances in technology with those in cell and molecular biology make it possible to detect biological changes after low doses and dose-rates of radiation exposure.**
- **Understanding the role of these biological changes in cancer risk may or may not impact radiation protection standards, but will help ensure that the standards based on scientific data and are both adequate and appropriate.**