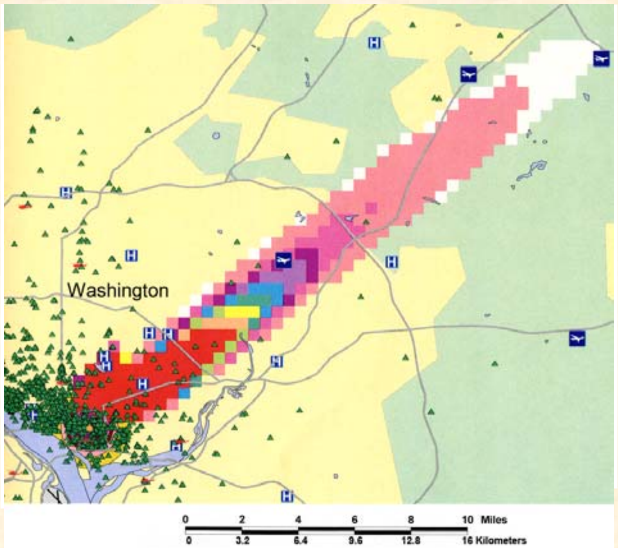
# *Biodosimetry Tools to Support Long-Term Health Monitoring After a Large-Scale Radiological Event*

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# The Scope of the Problem

## A 20 kT ground burst IND in New York City

| Dose range (Gy) | # Exposed | # Surviving Assuming conventional medical care, $LD_{50}$=6 Gy | # Surviving Assuming enhanced mitigators available ($LD_{50}$= 8 Gy) |
|---|---|---|---|
| 2 – 3.2 | 910,000 | 900,000 | 910,000 |
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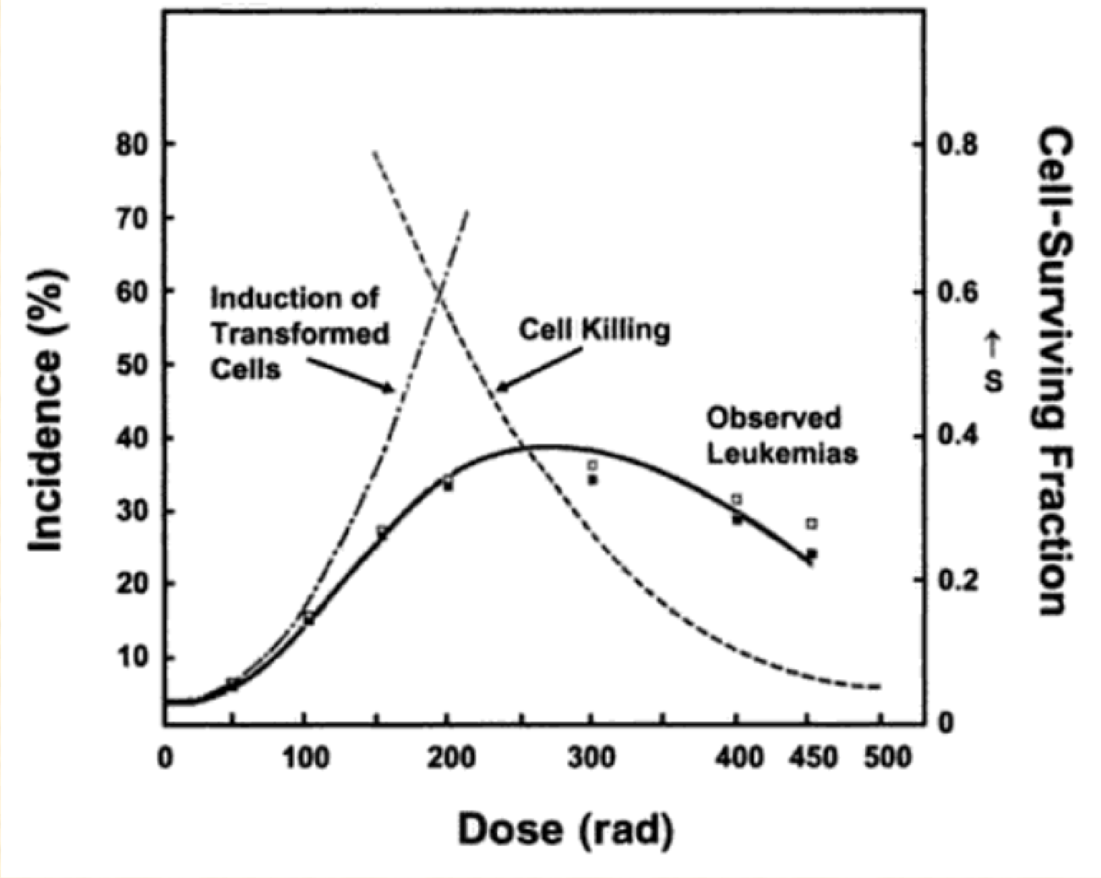
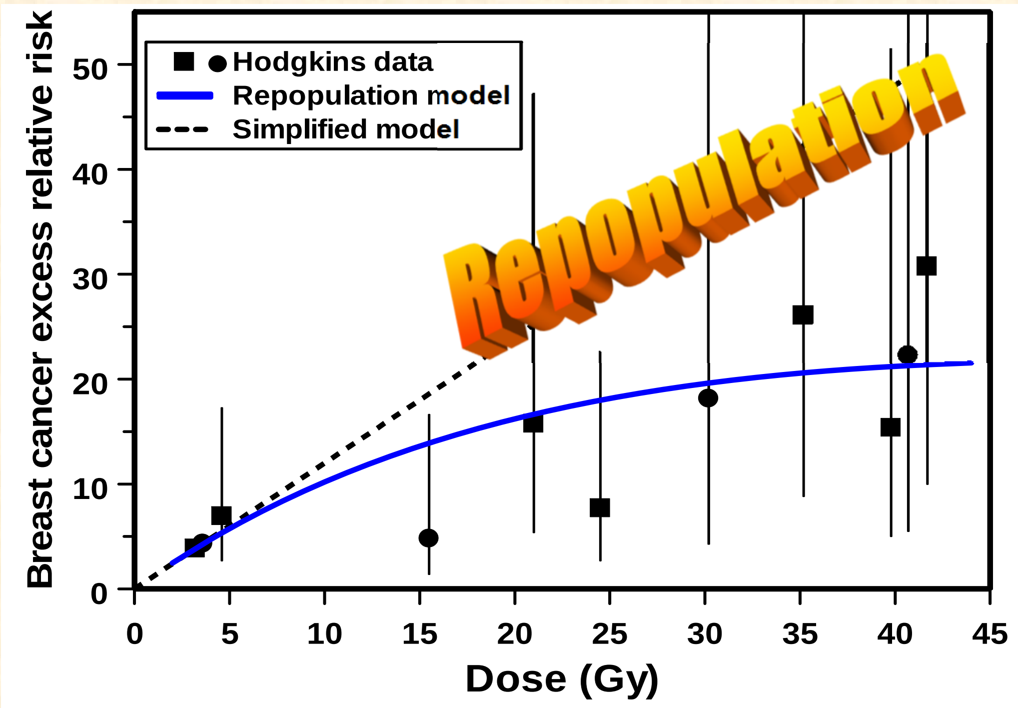
- **Doses from CATS-JACE simulation**
- **$LD_{50}$ data from Anno *et al* (2003)**
- **Deaths due to thermal effects and blast not included**

# Should we be particularly worried about the long term health of survivors who received very high doses?

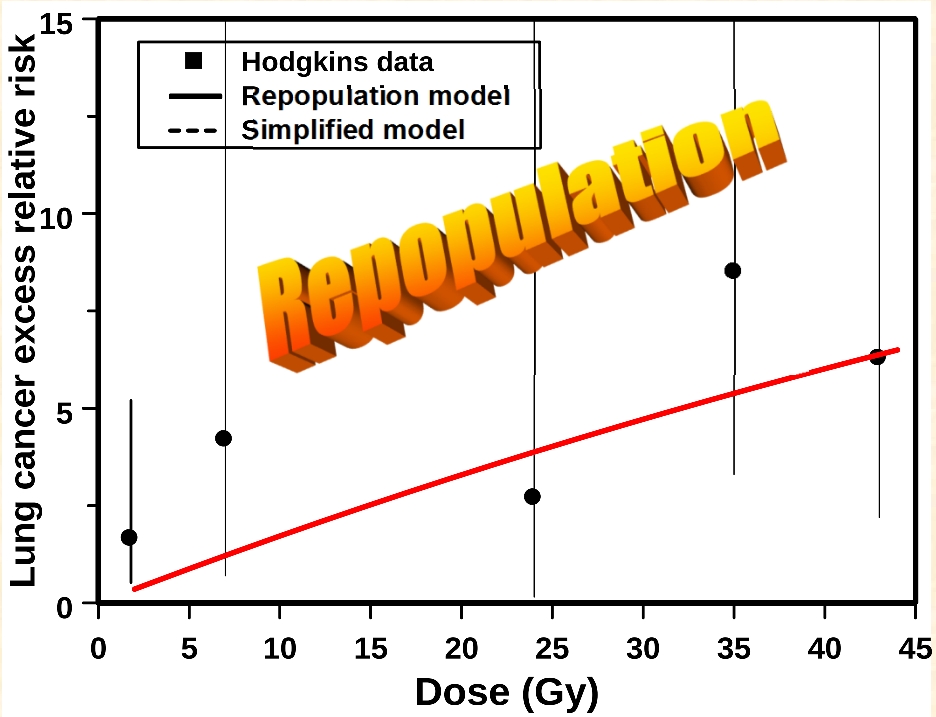


# Recent epidemiology suggests that cancer risks are not small at large doses

## Radiation-induced breast cancer




## Radiation-induced lung cancer



# The Scope of the Problem

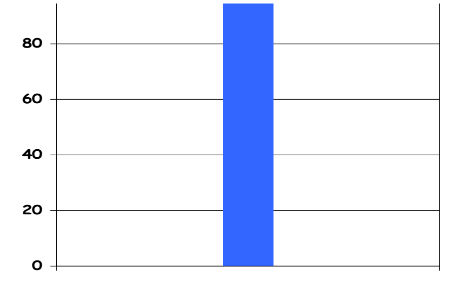
**After a large-scale IND we would want to estimate the individual doses to ~1 million people, with relevant doses between 2 and 10 Gy**

# Biodosimetry

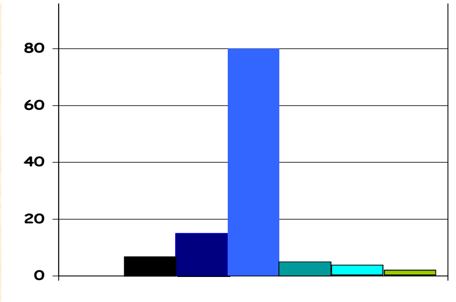
**The use of radiation-induced biomarkers in biological material to assess past personal radiation exposure**

# Biodosimetry takes into account individual radiation sensitivity

DISTRIBUTION OF PHYSICALLY- BASED RESPONSES

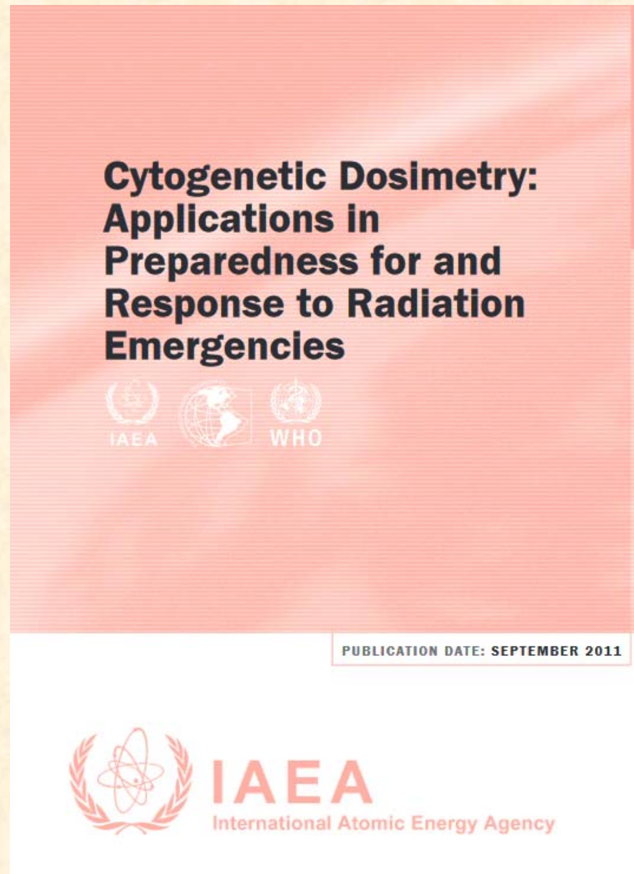



DISTRIBUTION OF BIOLOGICALLY- BASED RESPONSES



# Radiation Biodosimetry: What do we measure?

- DNA damage
- “omic” changes
  - Transcriptomics
  - Proteomics
  - Metabolomics
- EPR, OSL



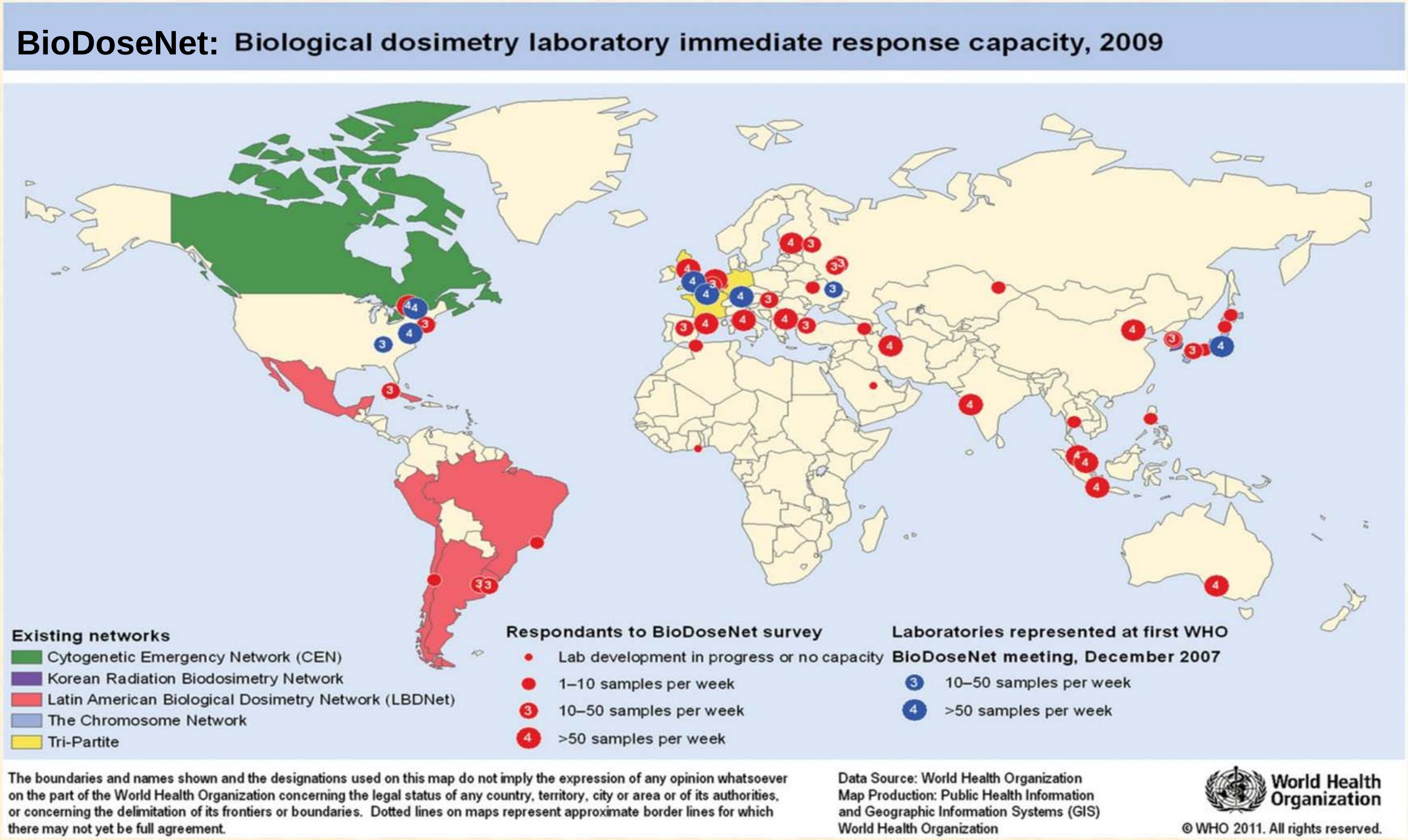
# Radiation biodosimetry is a well established technique…

**But….**

- **These cytogenetic assays are quite labor intensive, so throughput is an issue**

- **The assays generally don't work at doses above ~5 Gy**

# National / International Biodosimetry Networks



# WHO BioDoseNet

- 57 laboratories worldwide
- Total international capacity close to 10,000 per month

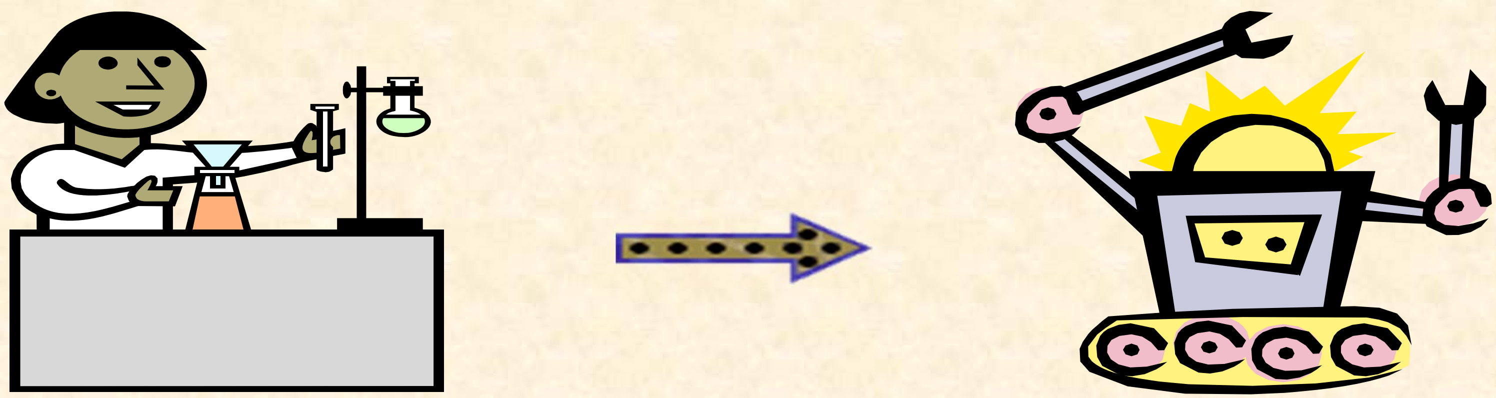
"Obviously, this capacity is nowhere near the throughput that would be required in a large mass-casualty radiological event, but it would definitely cover the needs for all the accidents that have happened up to now"

Maznyk *et al* 2012

# High Throughput: *Automation*

***Converting manually-based radiation biodosimetry assays to high throughput:***

- ***Automated sample preparation***
- ***Automated sample readout***



# RABiT:
# Rapid Automated Biodosimetry Tool

- **Fully-automated high-speed robotic biodosimetry workstation**
  - ***Use of commercial robotic cell handling systems***
- **Automated sample prep and automated imaging**
- **Automates well-established assays such as micronucleus and dicentric**
- **Single fingerstick of blood**
- **No further human intervention after samples put into the RABiT**

***The main technical innovations are:***

1) **Complete full automation of biological assay, with *in-situ* imaging in multi-well plates**
2) **Fully automated imaging**

✓ **Current throughput: 6,000 samples/day**

# Radiation biodosimetry is a well established technique...

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TABLE 1. COMPARISON OF CYTOGENETIC ABERRATION ASSAYS USED FOR DOSE ASSESSMENT[a]

| | Cytogenetic Aberration Assays | | | |
|---|---|---|---|---|
| | Premature chromosome condensation (PCC) | Dicentric (and ring) (DCA) | Fluorescent *in situ* hybridization (FISH) | Cytokinesis-block micronucleus (CBMN) |
| Typical aberrations scored for biological dosimetry applications | excess chromosome fragments; dicentrics[b] and rings<br>translocations[b] | dicentrics[b] (and rings) | dicentrics[b] (and rings)<br>translocations[b] | micronuclei<br>nucleoplasmic bridges |
| Typical radiation scenario applications | acute<br>recent exposure | acute<br>protracted<br>recent exposure | acute<br>protracted<br>old exposure | acute<br>protracted<br>recent exposure |
| Photon equivalent, acute dose range (Gy) for whole-body dose assessment | 0.2 to 20 | 0.1 to 5 | 0.25 to 4 | 0.3 to 4 |

IAEA 2011

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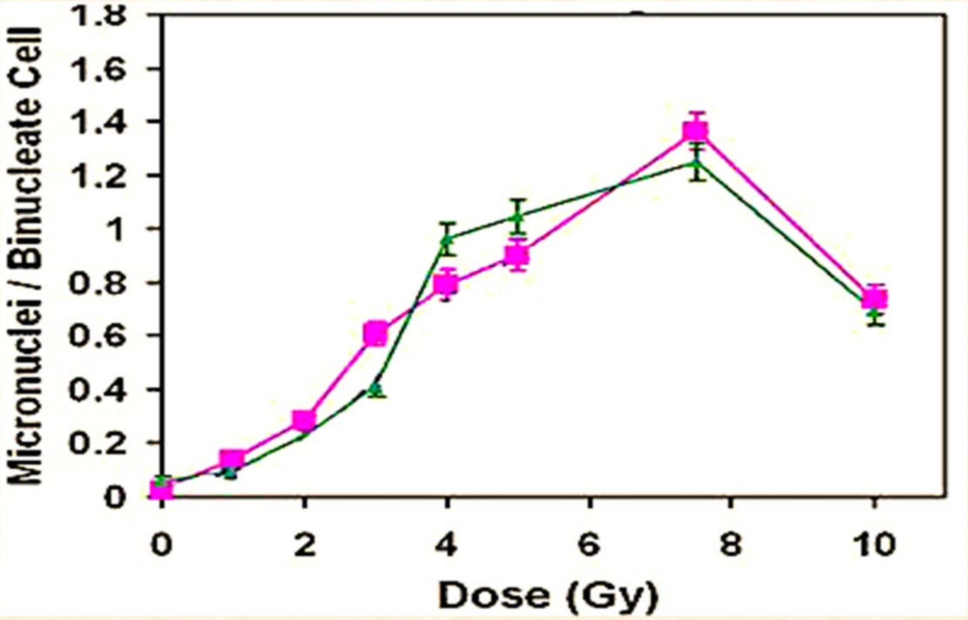
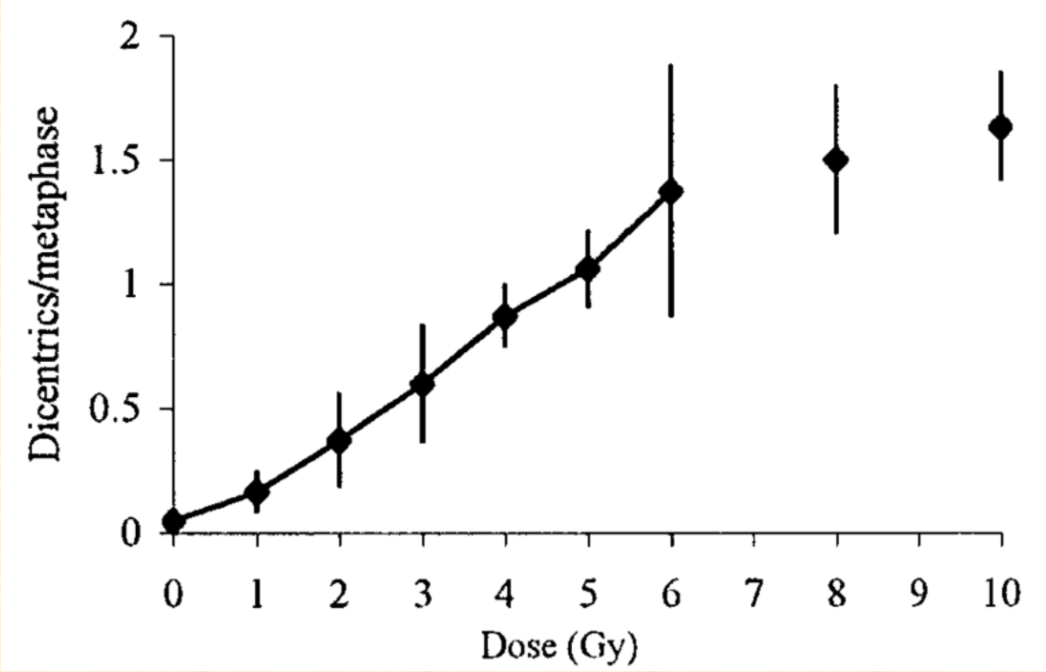
Center for High-Throughput Minimally-Invasive Biodosimetry

# The standard assays are useful up to about 5 Gy...



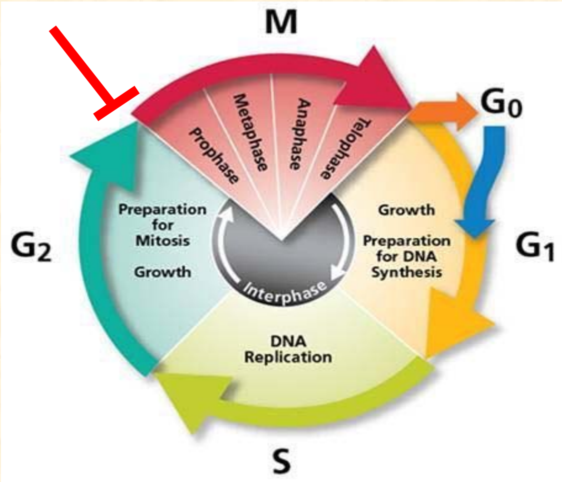




Micronuclei (Columbia, unpublished)

Dicentrics, Quina et al 2000

# Why don't these cytogenetic assays work above ~5 Gy?

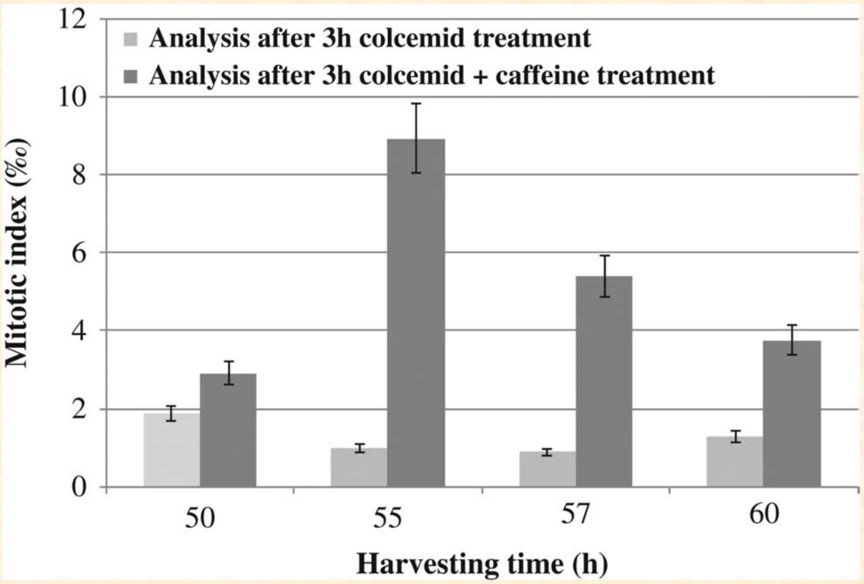
## The G2 checkpoint



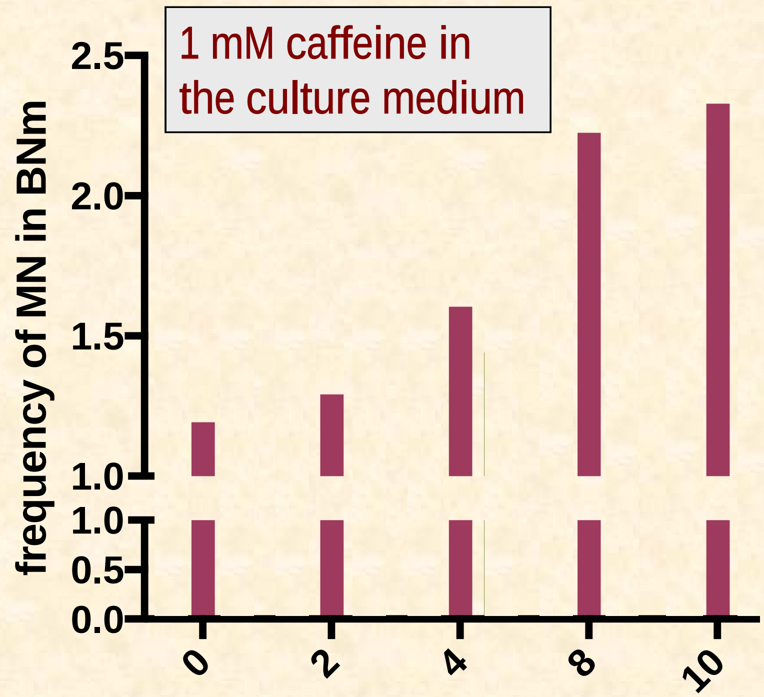

- Checks for DNA damage
- Prevents highly radiation-damaged cells from moving though to mitotic cell division

# Caffeine releases lymphocytes from the G2 checkpoint

Blood irradiated with 8 Gy




Karachristou *et al* 2016




Pujol *et al* 2018,
Columbia unpublished

# The Future of Radiation Biodosimetry

## "Beyond Dose"

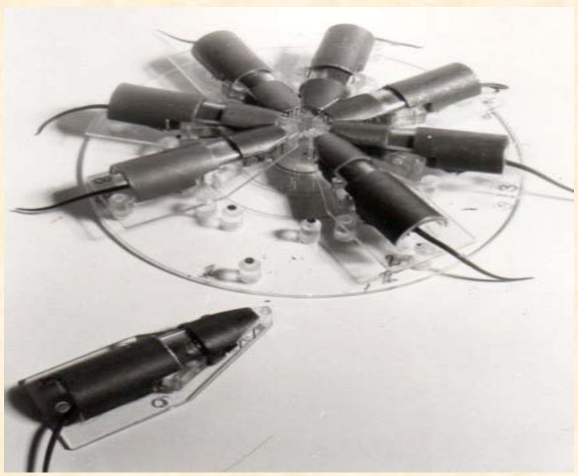
**Can we provide high-throughput biomarker-based methodologies to identify individuals who are particularly sensitive to**

1) acute radiation syndromes, or
2) long-term radiation health effects

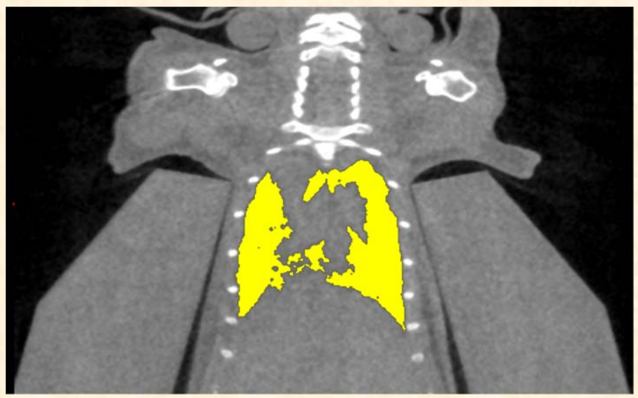
# Individualized radiation biomarkers predictive of future long-term radiation-induced disease

*e.g. Can gene expression predict future pneumonitis?*

- **Thoracic radiation dose to mice where half will die from pneumonitis and half will recover**
- **Profile gene expression in blood at intervals before and during manifestation of disease**



Mouse lung irradiation



CT imaging to monitor lung disease progression

***Gene expression***

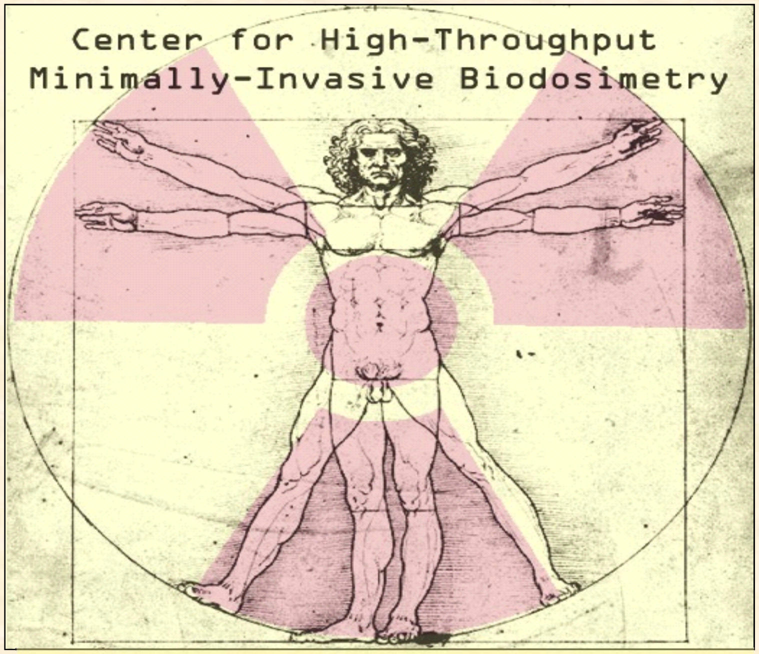
**Disease progression** ↔ **Gene expression** ↔ **Predicted outcome**

# Columbia Center for High-Throughput Minimally-Invasive Radiation Biodosimetry

NIAID

Center for Radiological Research
100 years
1916 - 2016

Georgetown University




www.cmcr.columbia.edu

The University of Arizona

tgen

Texas A&M University

# Issues for a Useful
# High-Throughput Radiation Biodosimetry System

- Processing throughput
- Sensitivity /  specificity
- Precision / accuracy
- Processing time
- Signal stability
- Internal emitter exposure
- Partial body exposure
- Neutron sensitivity

# Errors in individual dose estimates make a major difference to the downstream epidemiology