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

David Brenner
Center for Radiological Research
Columbia University
djb3@columbia.edu
The Scope of the Problem

A 20 kT ground burst IND in New York City

<table>
<thead>
<tr>
<th>Dose range (Gy)</th>
<th># Exposed</th>
<th># Surviving Assuming conventional medical care, LD$_{50}$=6 Gy</th>
<th># Surviving Assuming enhanced mitigators available (LD$_{50}$= 8 Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 – 3.2</td>
<td>910,000</td>
<td>900,000</td>
<td>910,000</td>
</tr>
<tr>
<td>3.2 – 4.8</td>
<td>500,000</td>
<td>450,000</td>
<td>495,000</td>
</tr>
<tr>
<td>4.8 – 7.2</td>
<td>200,000</td>
<td>100,000</td>
<td>170,000</td>
</tr>
<tr>
<td>&gt; 7.2</td>
<td>600,000</td>
<td>120,000</td>
<td>300,000</td>
</tr>
<tr>
<td>Any dose &gt;3.2 Gy</td>
<td>1,300,000</td>
<td>670,000</td>
<td>965,000</td>
</tr>
</tbody>
</table>

- 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
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
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

**BioDoseNet:** Biological dosimetry laboratory immediate response capacity, 2009

The map illustrates the distribution of biodosimetry networks globally, with a focus on the capacity and response rates of laboratories. The map includes existing networks and indicates the number of samples they can process per week. The map contains symbols representing the number of samples per week, with categories ranging from lab development in progress or no capacity to >50 samples per week. The boundaries and names shown in the map do not imply the expression of any opinion concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dot lines on maps represent approximate border lines for which there may not yet be full agreement.
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...

But....

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

- The assays generally don’t work at doses above ~5 Gy.

<table>
<thead>
<tr>
<th>Typical aberrations scored for biological dosimetry applications</th>
<th>Premature chromosome condensation (PCC)</th>
<th>Dicentric (and ring) (DCA)</th>
<th>Fluorescent in situ hybridization (FISH)</th>
<th>Cytokinesis-block micronuclei (CBMN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excess chromosome fragments; dicentrics (and rings)</td>
<td>Dicentrics (and rings)</td>
<td>Micronuclei</td>
<td>Nucleoplasmic bridges</td>
<td></td>
</tr>
<tr>
<td>Translocations</td>
<td>Translocations</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Typical radiation scenario applications</th>
<th>Acute</th>
<th>Acute protracted</th>
<th>Acute protracted</th>
<th>Acute protracted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute exposure</td>
<td>Recent exposure</td>
<td>Recent exposure</td>
<td>Recent exposure</td>
<td></td>
</tr>
</tbody>
</table>

| 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
The Scope of the Problem

A 20 kT ground burst IND in New York City

<table>
<thead>
<tr>
<th>Dose range (Gy)</th>
<th># Exposed</th>
<th># Surviving Assuming conventional medical care, LD50=6 Gy</th>
<th># Surviving Assuming enhanced mitigators available (LD50= 8 Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 – 3.2</td>
<td>910,000</td>
<td>900,000</td>
<td>910,000</td>
</tr>
<tr>
<td>3.2 – 4.8</td>
<td>500,000</td>
<td>450,000</td>
<td>495,000</td>
</tr>
<tr>
<td>4.8 – 7.2</td>
<td>200,000</td>
<td>100,000</td>
<td>170,000</td>
</tr>
<tr>
<td>&gt; 7.2</td>
<td>600,000</td>
<td>120,000</td>
<td>300,000</td>
</tr>
<tr>
<td>Any dose &gt;3.2 Gy</td>
<td>1,300,000</td>
<td>670,000</td>
<td>965,000</td>
</tr>
</tbody>
</table>
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 through to mitotic cell division
Caffeine releases lymphocytes from the G2 checkpoint

**Blood irradiated with 8 Gy**

- Analysis after 3h colcemid treatment
- Analysis after 3h colcemid + caffeine treatment

Karachristou *et al* 2016

Pujol *et al* 2018, Columbia unpublished

Frequency of MN in BNm

1 mM caffeine in the culture medium
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
Columbia Center for High-Throughput Minimally-Invasive Radiation Biodosimetry

www.cmcr.columbia.edu
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.