BIODOS - *Biodosimetry application in emergency preparedness*
BIOPEX - *Emergency preparedness exercise for biological dosimetry*

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Mass casualty scenarios in radiological accidents and biological dose assessment

- large number of exposed individuals with wide range of doses
- rapid and reliable dose assessment required

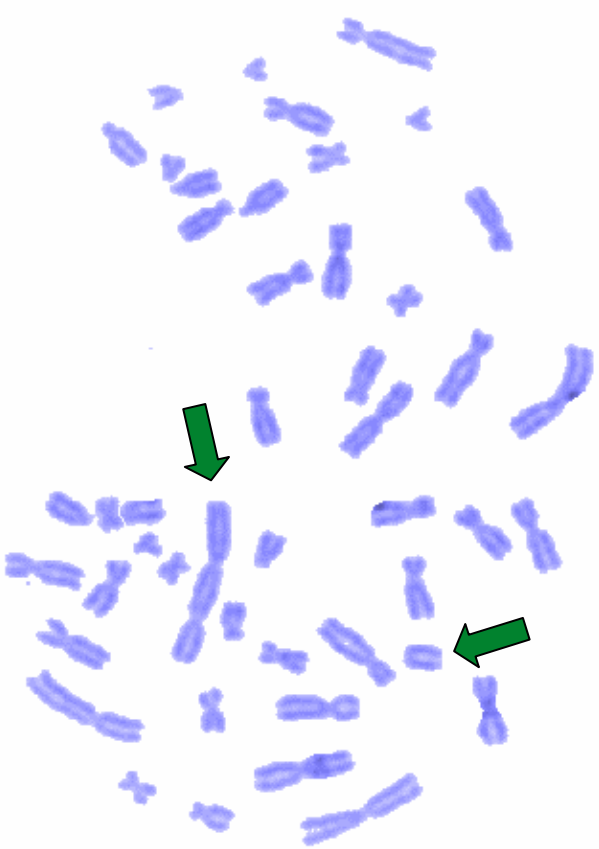
- physical dosimetry and clinical analysis (blood cell counts) may not give sufficient support for medical decision making
- identification of individuals with no or low exposure

- capacity of small biodosimetry laboratories exceeds easily: collaboration and networking are key issues

Classic chromosome aberration assay

- based on dicentric chromosomes observed in blood lymphocytes
- sensitive: 100-200 mGy (low-LET); 10-20 mGy (high LET), with

- demanding, analysis requires excessive training
- upper dose limit 6-8 Gy
- dependent on mitogen sensitive cells (T-lymphocytes) reaching mitosis (high doses may block cell cycle)

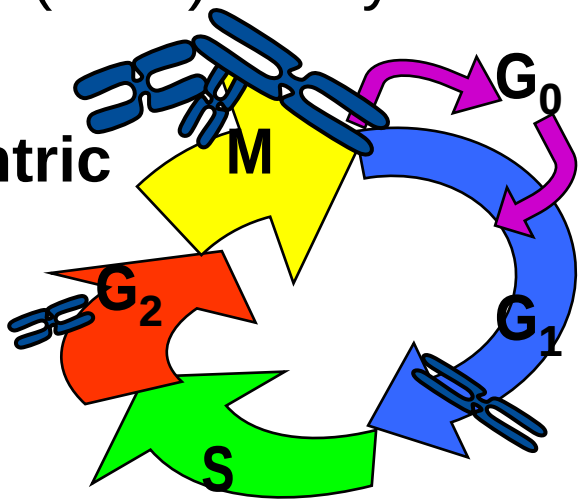


NKS-project 2006-2007: Biodosimetry application in emergency preparedness (BIODOS)

- **prematurely condensed chromosome** (PCC) assay

Advantage of PCC with respect to dicentric assay

- scoring of radiation-induced damage in pre-mitotic cell cycle stages
- ability to estimate very high doses
- potential for more rapid scoring



Cell cycle

Chemically induced PCC and analysis methods

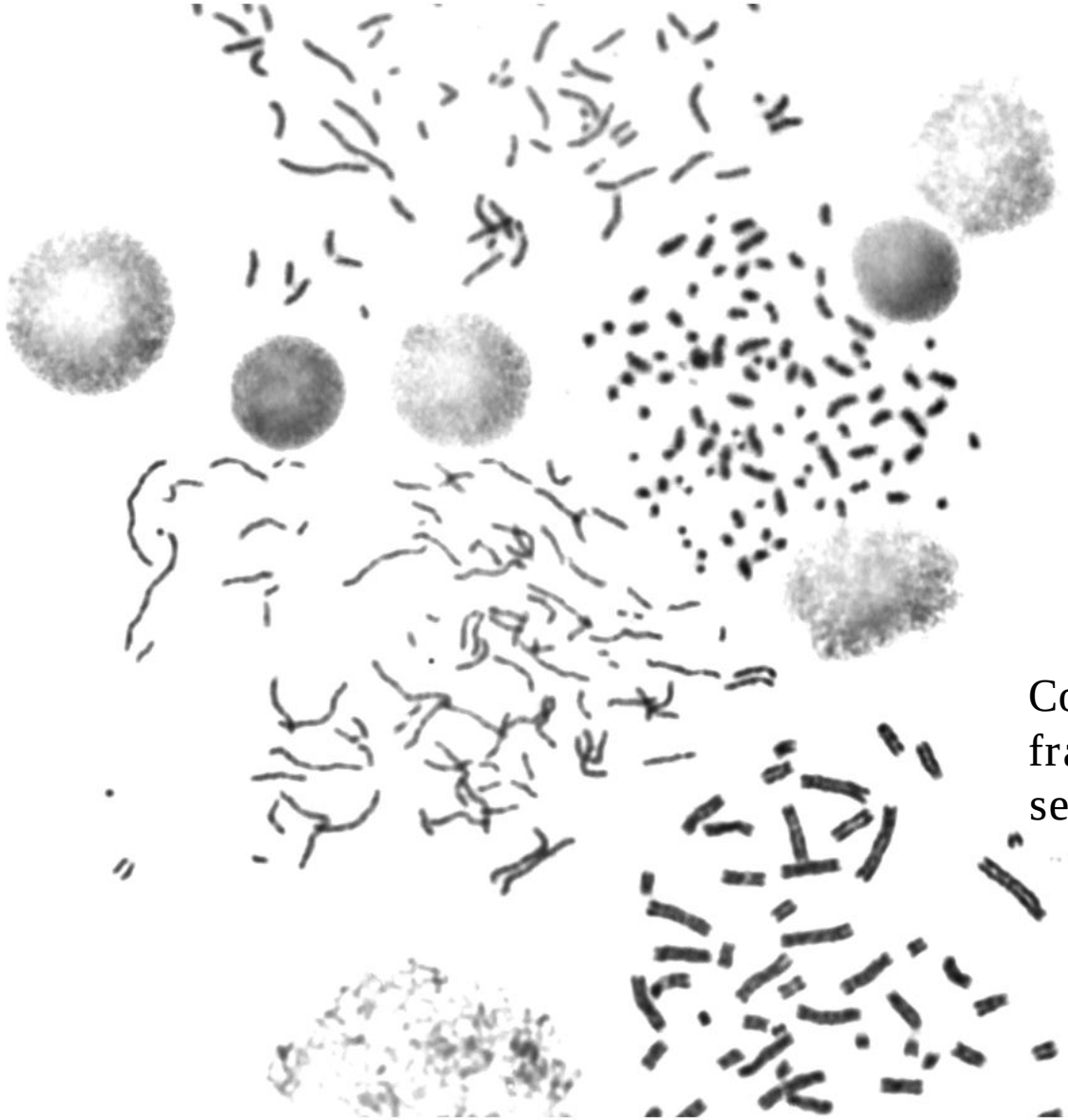
Okadaic acid and Calyculin A

- Giemsa-staining
  - excess fragments
  - ring chromosomes
- Fluorescence in situ hybridization (FISH) with chromosome probes
  - exchange type aberrations

Protein kinase/Cyclin B + OA or CalA

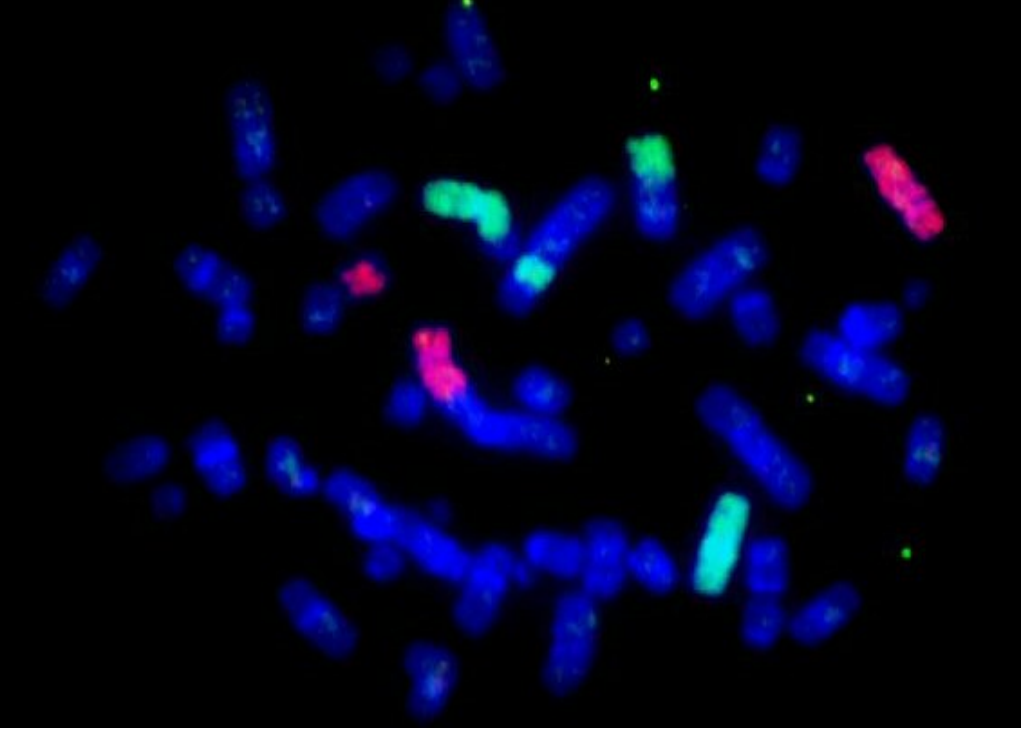
- FISH
  - evaluation of painted chromosome “areas”

Analysis Approach	Consideration
Excess fragments	Reliability and accuracy
Ring chromosomes	Time required for analysis
Aberrations detected by FISH	
“Spot” technique (FISH)	Technical characteristics

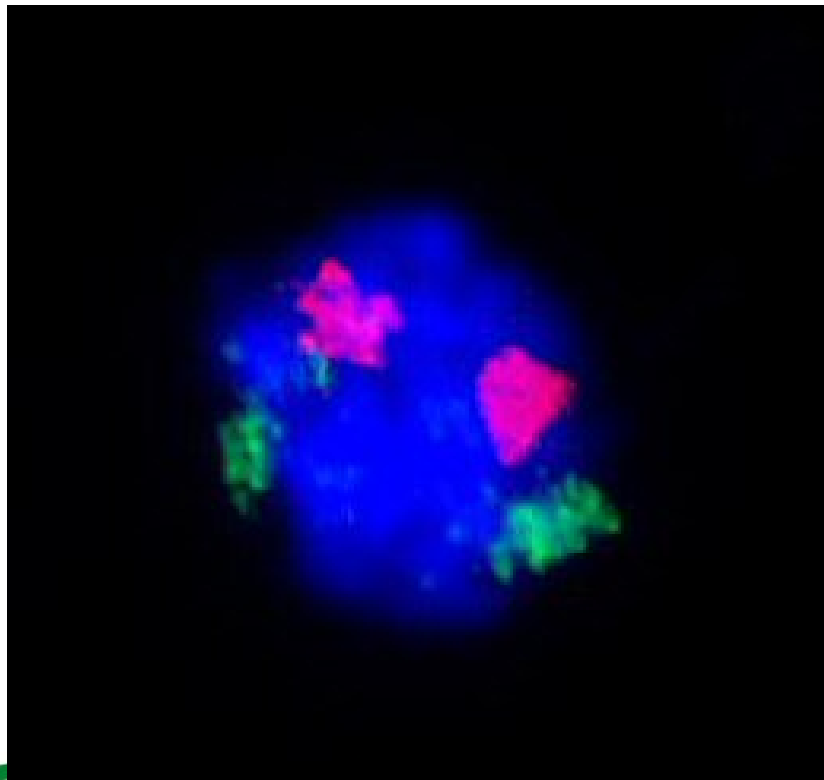


Okadaic acid induced PCC in cells in different cell cycle stages

Counting of excess fragments (>46 elements seen)

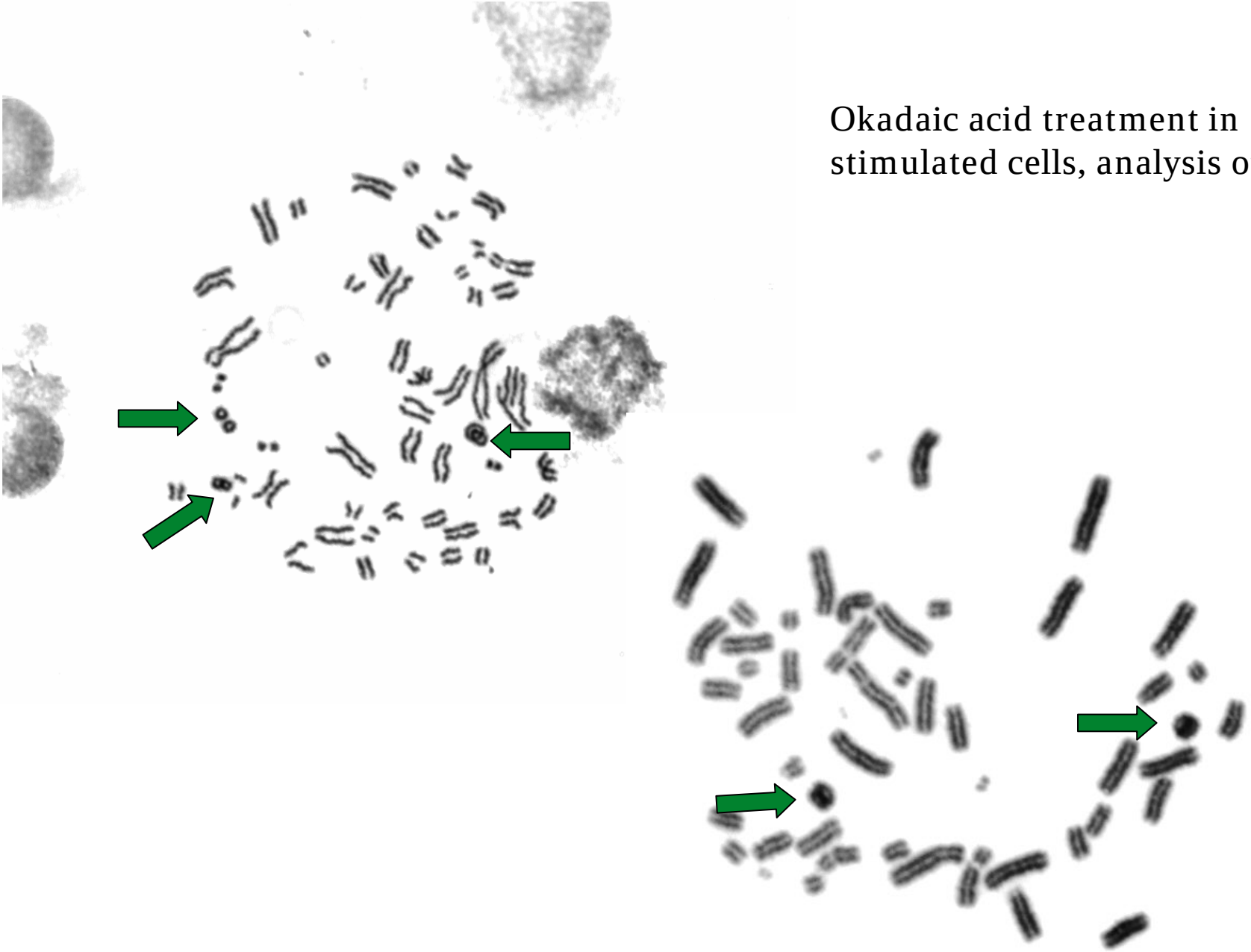


Chromosome aberration analysis in FISH painted stimulated cells



”Spot analysis” after FISH painting in cyclin B kinase + CalA treated unstimulated cells

Okadaic acid treatment in stimulated cells, analysis of rings



Curve calibration of the PCC ring data

- Data best described by linear relationship:

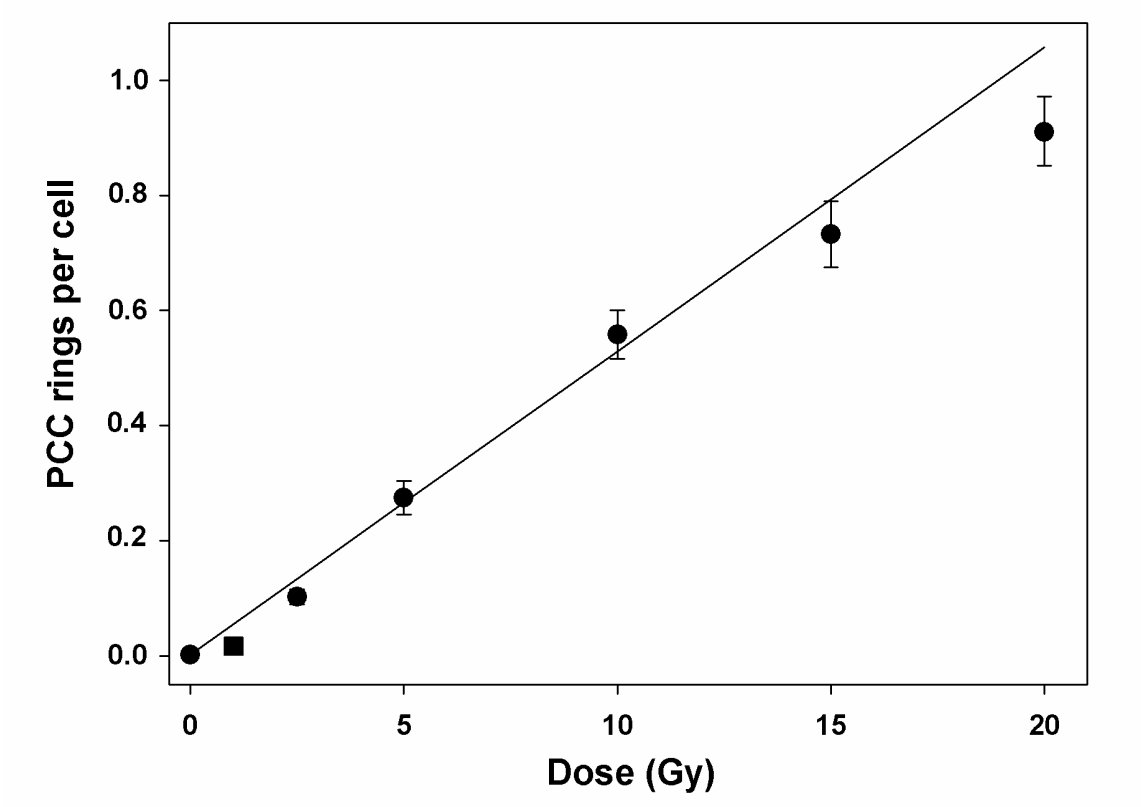
  $Y=C + \alpha \bullet D$
- where:

  Y = freq. of PCC rings

  C = 0,002 (±0,002)

  α = 0,049 (±0,006)

  D = dose (Gy)



Conclusions from BIODOS

- Okadaic acid treatment of lymphocyte cultures gives best quality of PCC
- Evaluation of ring chromosomes
- Linear fit of data 0 - 20 Gy
- The PCC assay may be most applicable at doses above 5 Gy
- For emergency preparedness applications, the dicentric assay and PCC assay cultures could be run in parallel and evaluated in triage mode
- PCC ring assay is somewhat faster and requires less training than the classical dicentric assay

Emergency preparedness exercise for biological dosimetry (BIOPEX) NKS 2008

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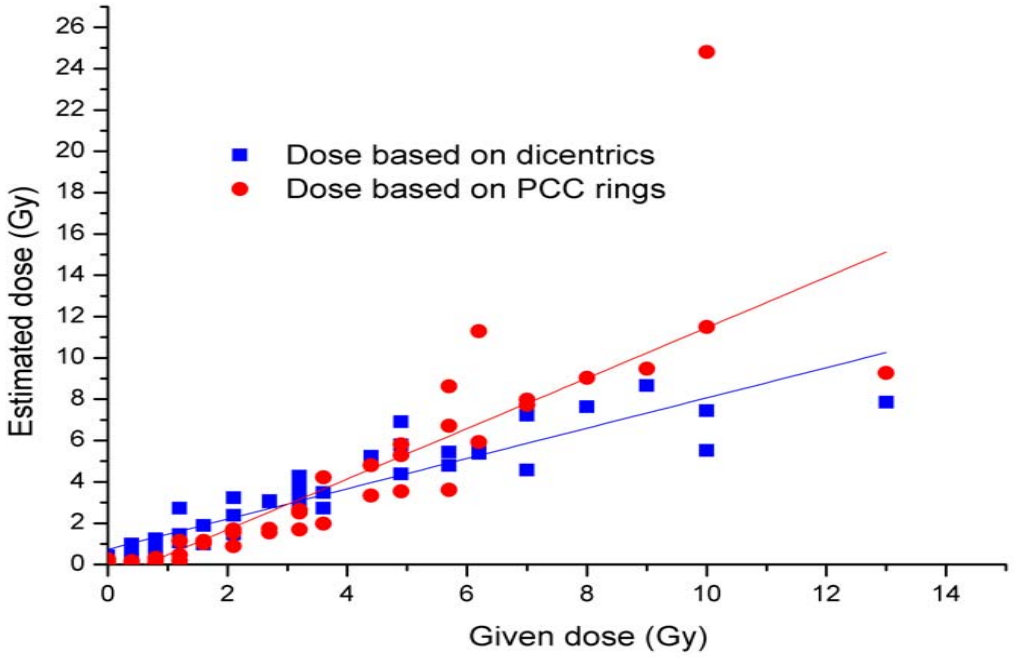
- In mass casualty, rapid decisions to be made concerning which of the victims need hospital care and at which level
- Aim
  - to evaluate the applicability of the PCC ring and the dicentric assays side by side
  - to assess whether estimated dose fitted into crude dose categories

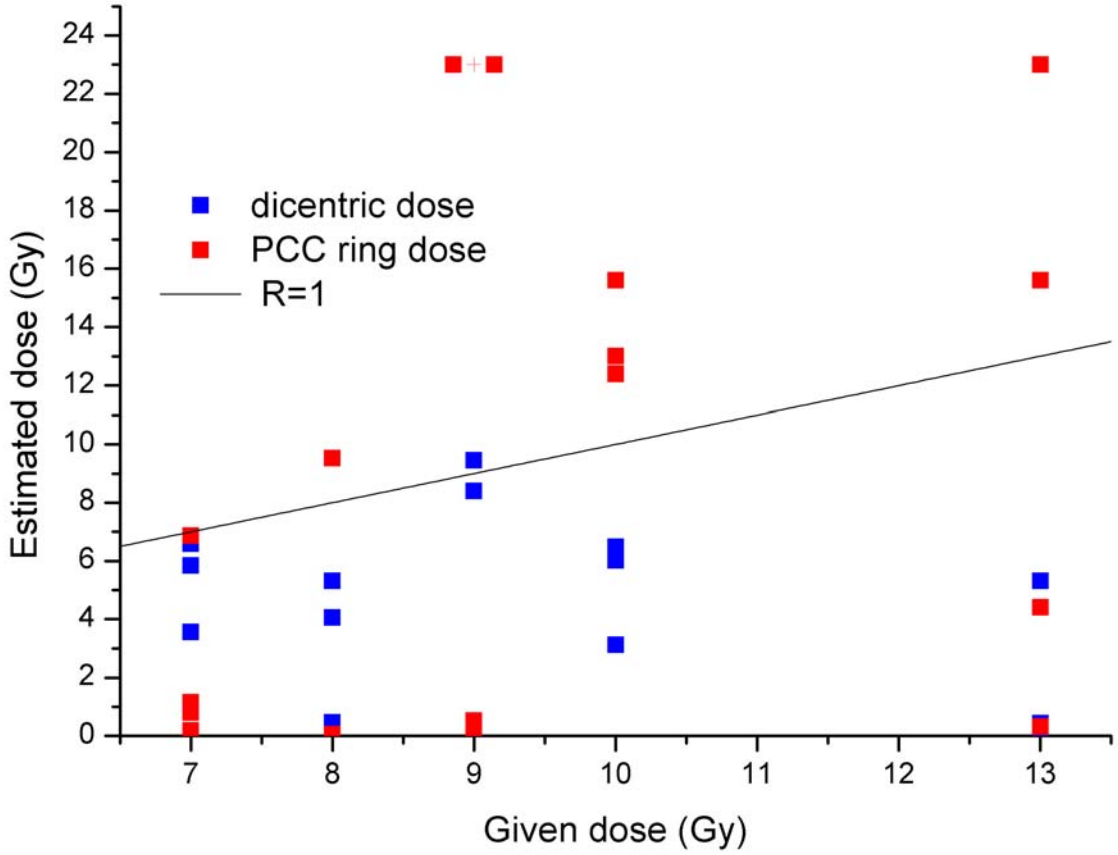
- Possible scenario which the study was based on:
  - Very strong gamma source hidden in a public transport vehicle, giving rise to a dose rate of 20 Gy/h close to the source and 2 Gy/h at 5 m distance.
  - Close to the source, because of partial shielding it would be possible to get a high dose to only part of the body
  - 62 persons with clinical symptoms and potential exposure to be evaluated with both assays

- 62 simulated casualties = 62 blood samples
- *In vitro* exposure with ^{60}Co; 0.3 Gy/min
  - wide range of doses: 0 - 13 Gy
  - uniform exposure: 44 samples
  - non-uniform exposures: 18 samples (10-40% of cells exposed)
- PCC ring and dicentric assays run in parallel
- analysis in triage mode: 50 cells in dicentric assay; 300 PCC cells
- Dose estimation using the new PCC ring curve (BioDos) and routinely used dicentric curve in each laboratory

Simulated mass casualty: dose estimates for whole body exposures (44 cases) based on dicentrics or PCC rings



Simulated mass casualty: partial-body exposures (18 cases)



Level of hospital care needed, based on early estimation of acute whole body dose

Estimated dose	Decision
Less than 2 Gy	Follow up in general hospital or on outpatient basis
2 – 4 Gy	Transfer to hematological department
4 – 6 Gy	Transfer to well equipped hematological department within two days. Early initiation of cytokine therapy
6 – 8 Gy	Early transfer to hematological department with capacity for reverse isolation and allogenic stem cell transplantation
More than 8 Gy	Palliative care if resources are strained. Otherwise as above. Prognosis for long term survival is bad.

Rate of whole-body exposed cases in correct dose categories or given dose within estimated confidence limits

Dose category (Level of hospital care needed)	Estimated dose in correct dose category		Given dose within estimated 95% confidence limits	
	Dicentrics	PCC rings	Dicentrics	PCC rings
Non-exposed	6 / 7	5 / 7	6 / 7	5 / 7
>0 to < 2 Gy	9/10	9/10	8/10	6/10
2 to < 4 Gy	9 /10	2/10	7/10	5/10
4 to < 6 Gy	7 / 8	3 / 8	7 / 8	5 / 8
6 to 8 Gy	1 / 5	3 / 5	4 / 5	4 / 5
> 8 Gy	1 / 4	4 / 4	1 / 4	3 / 4
All	34 /44 (77%)	26 /44 (59%)	32 /44 (73%)	28 / 44 (64%)

Conclusions from BIOPEX

- Both triage assays were capable of discerning non-exposed (control level) cases.
- Uniform exposures: dicentrics scoring resulted in more accurate estimates at 5 Gy and below
- High doses: better dose estimates with PCC
- Categories based on level of hospital care needed (dose >0 Gy) : generally, dicentric assay more efficient (27 cases of 37 correct) than PCC ring scoring (21 out of 37)
- Non-uniform irradiations: neither assay gave satisfactory results in identifying or estimating partial body doses
  - due to low number of scored cells

PCC ring assay

- Somewhat faster than the dicentric assay
- Scoring of rings relatively easy to adopt
- Suitable method for estimating doses in an accident involving a large number of exposed casualties
- Especially applicable for estimation of high doses