ESTIMATING RADIATION QUALITY DEPENDENCIES FOR GCR-INDUCED TARGETED VS. NON-TARGETED HEALTH EFFECTS

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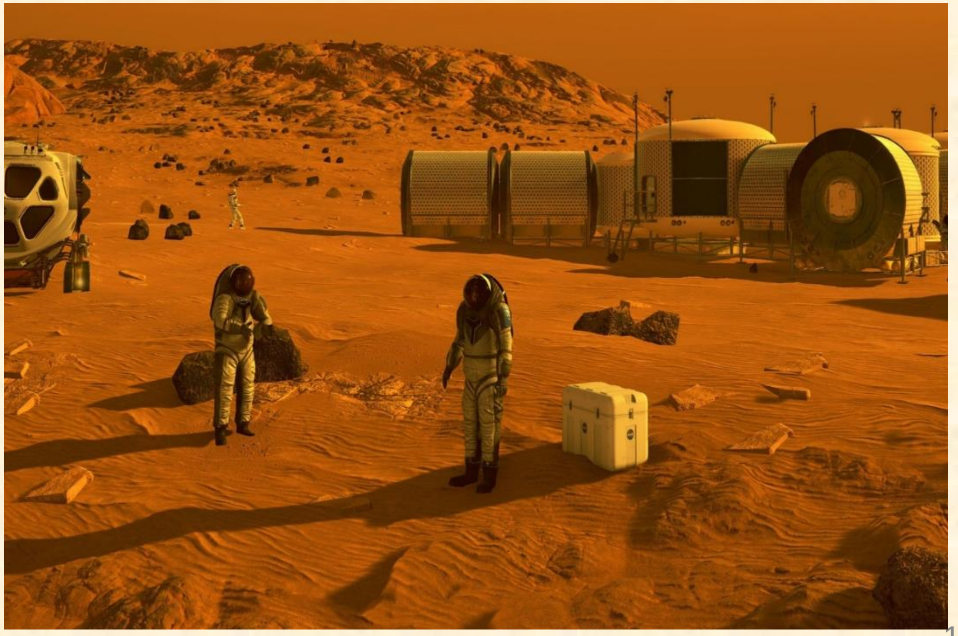
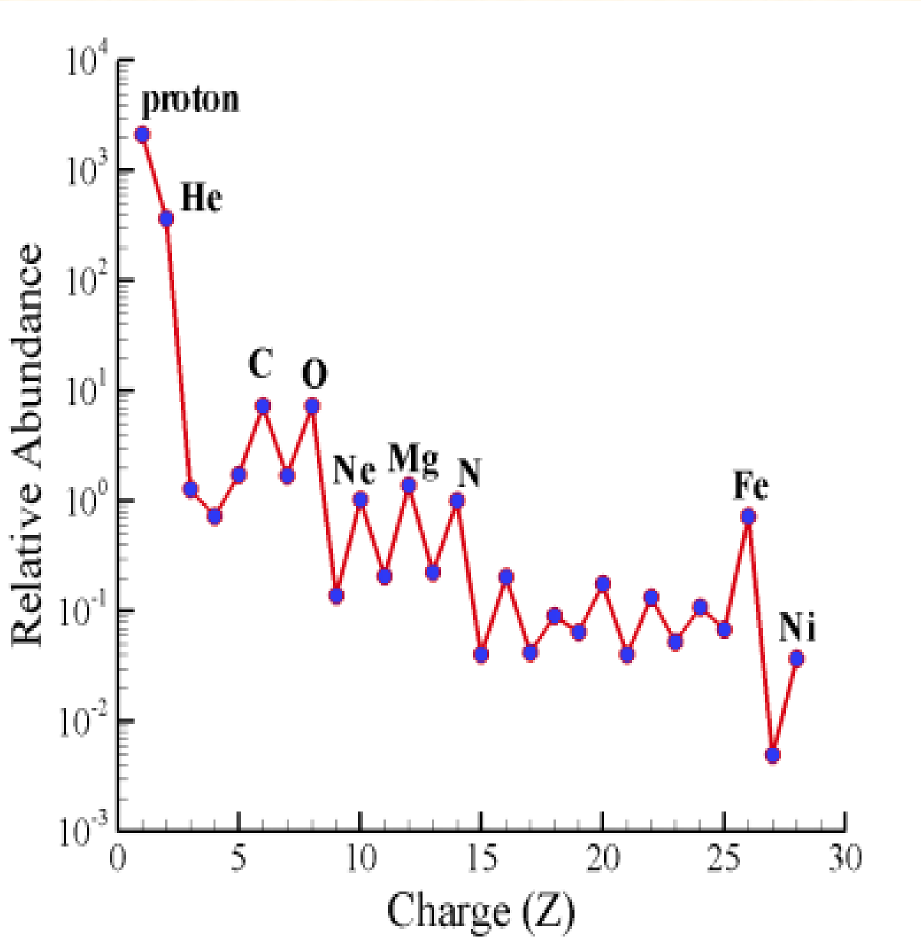
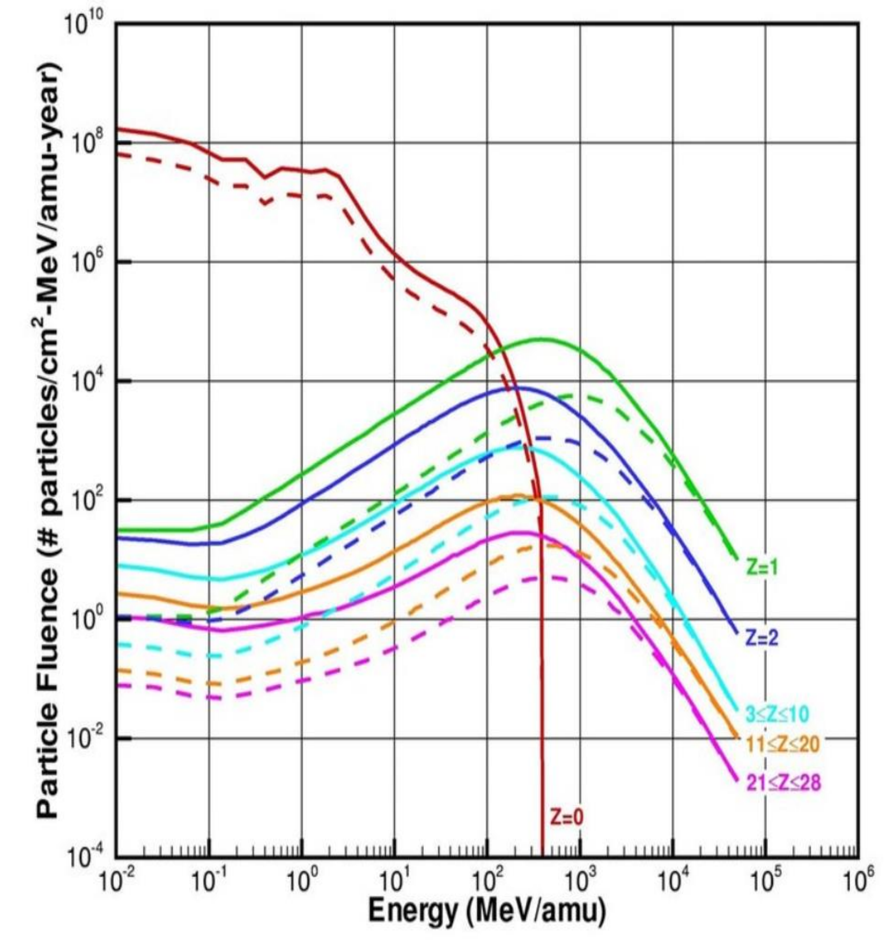


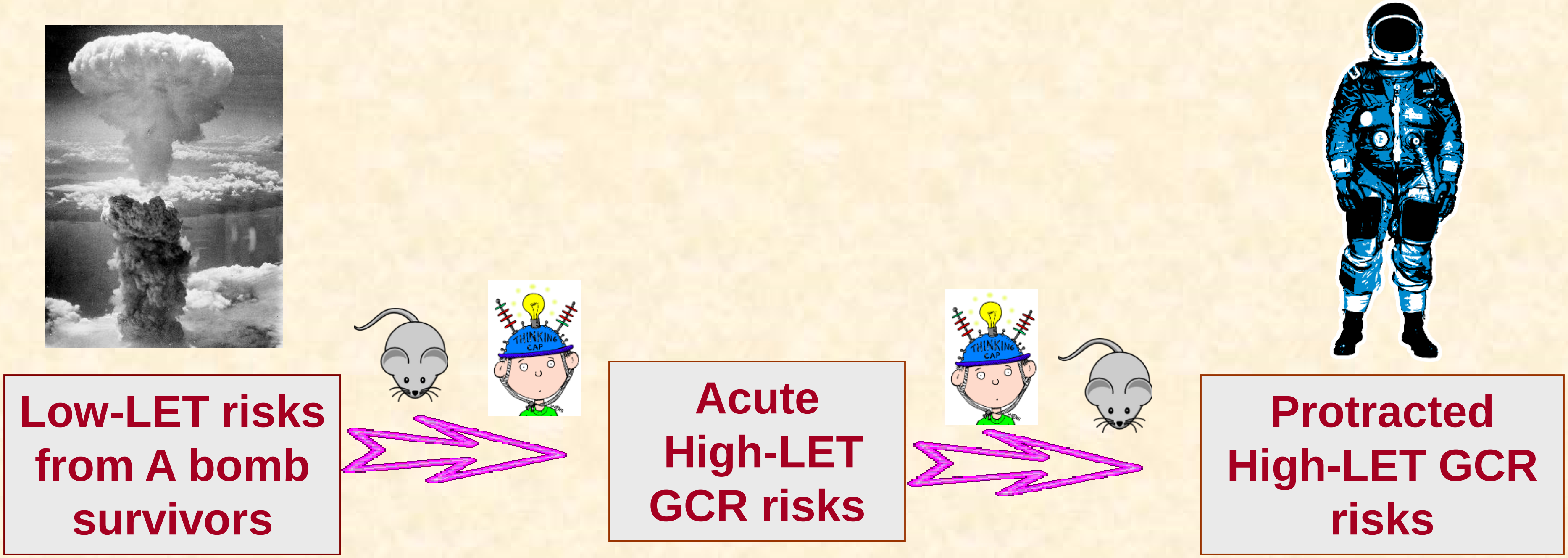
Mars mission astronauts will be exposed to complex mixed radiation fields both in flight and on Mars





O’Neill et al 2015,
Tripathi et al 2001

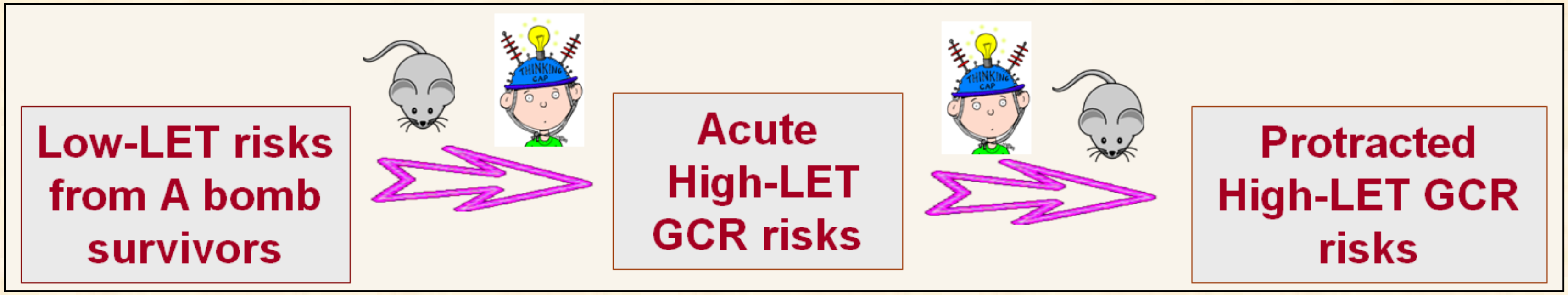
The NASA Radiation Risk Model



Low-LET risks from A bomb survivors

Acute High-LET GCR risks

Protracted High-LET GCR risks



Low-LET risks from A bomb survivors

Acute High-LET GCR risks

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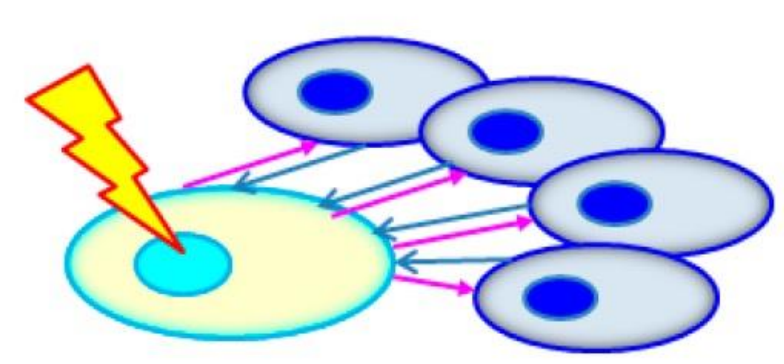
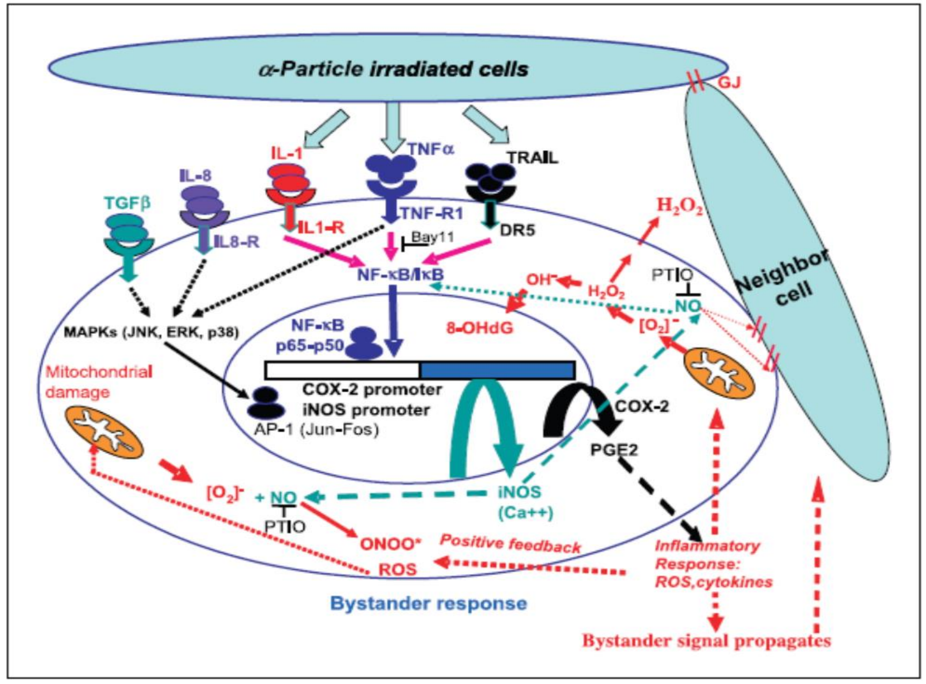
Our current major problem

- **Low doses of densely-ionizing GCR radiation appear to produce biological damage largely through different (*non-targeted*) mechanisms as compared to high doses of GCR radiation**



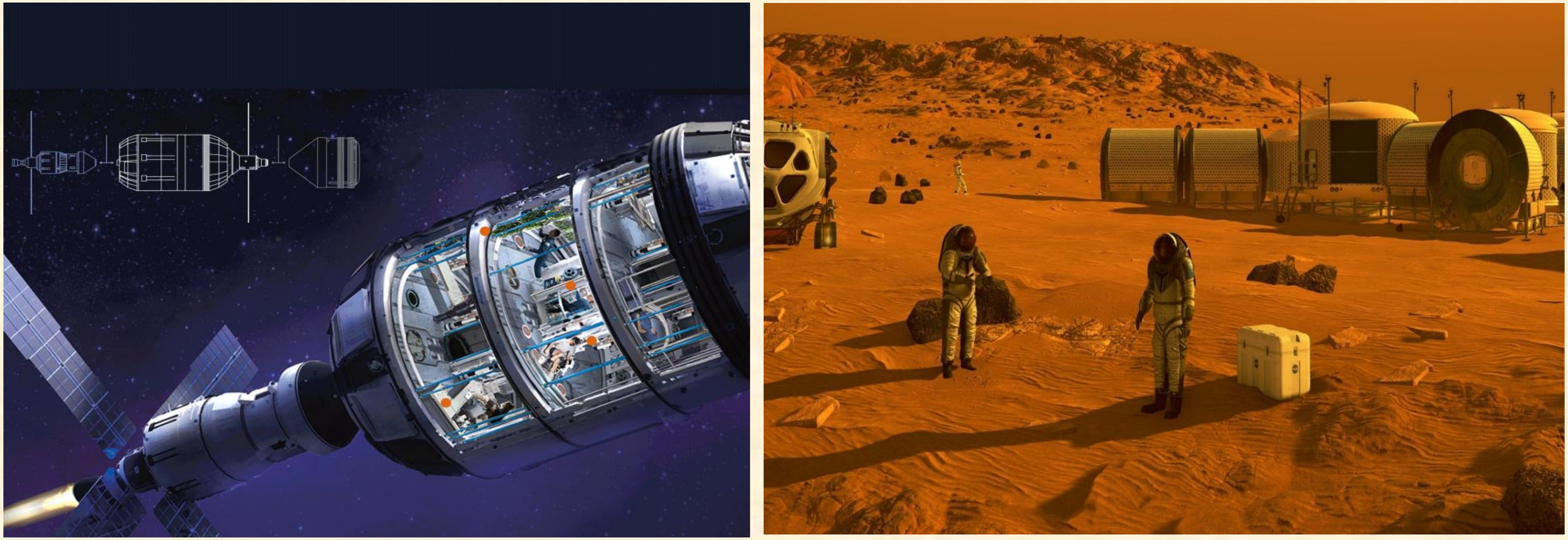
Non-Targeted Effects (NTE)

- ☑ **Also called “bystander effects”**
- ☑ **Unirradiated cells respond to signals emitted by nearby irradiated cells**
- ☑ **First noted by Nagasawa & Little (1992): Exposed cells to low doses of alpha particles, about 1% of cells were hit, but 30% of cells showed increased chromosomal aberrations**
- ☑ **NTE reported for most endpoints, mainly after low doses of high-LET radiation**
- ☑ **Many signaling pathways and reactive oxygen species (ROS) appear to be involved, shifting cells into an “activated” stressed state**

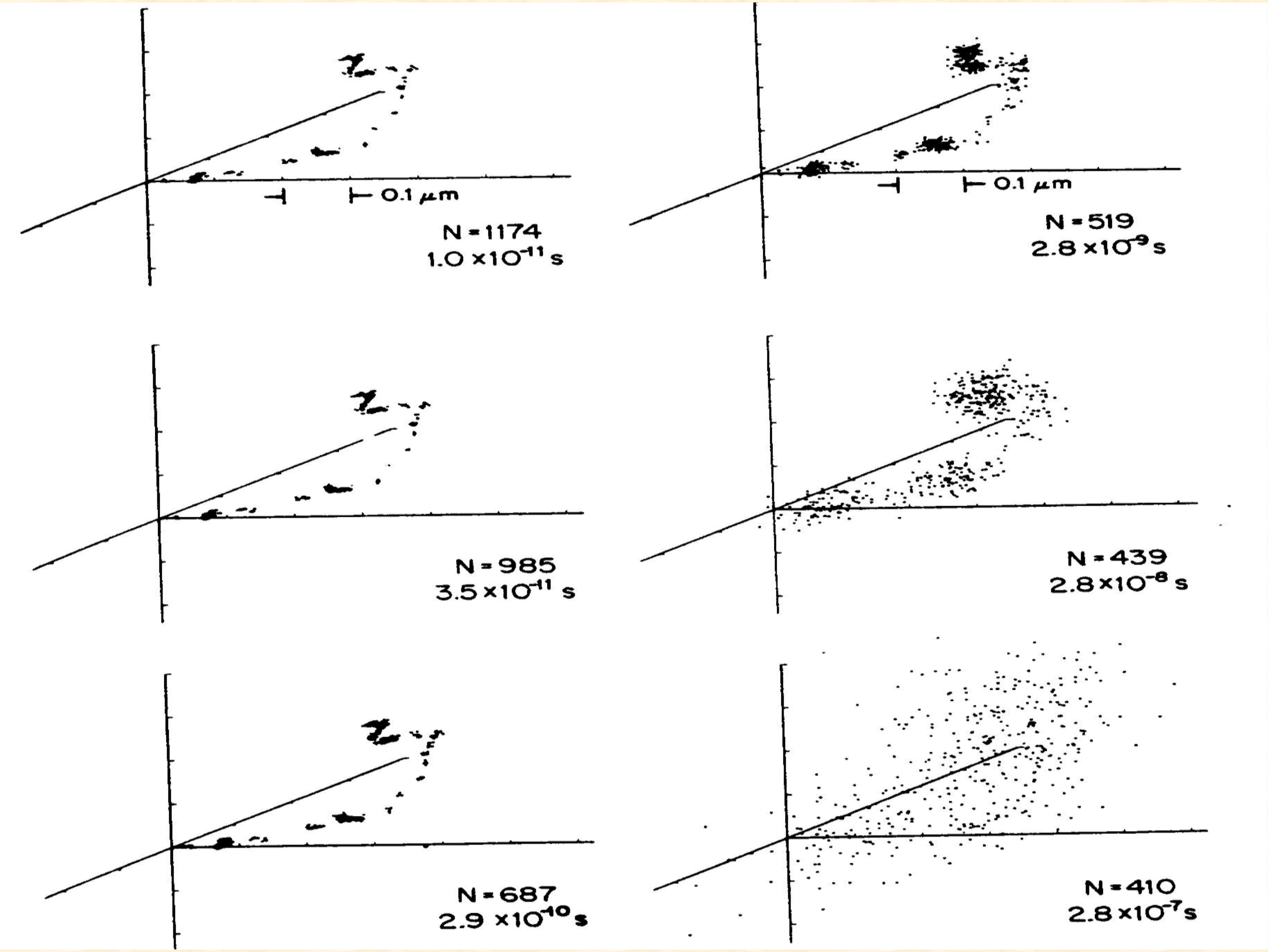


Zhou et al. *Cancer Res*, 2008

To establish radiation weighting factors for targeted effects (TE) and non-targeted effects (NTE), and to develop a practical approach for their use in complex and time-varying space radiation fields



Relative effects of different radiation qualities must be due to the initial track structure



Wright 1982

Track Structure Models

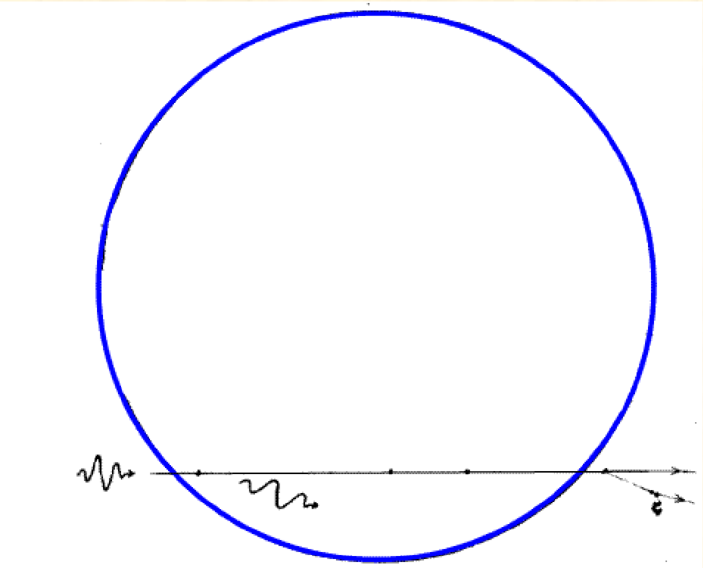
1. Katz Model

- Phenomenological biophysically-based model, initially of cell killing, developed by analogy to radiation effects in nuclear emulsions
    - Model input can’t be directly measured
    - Needs large amount of nuclear data to calculate model input for every radiation field

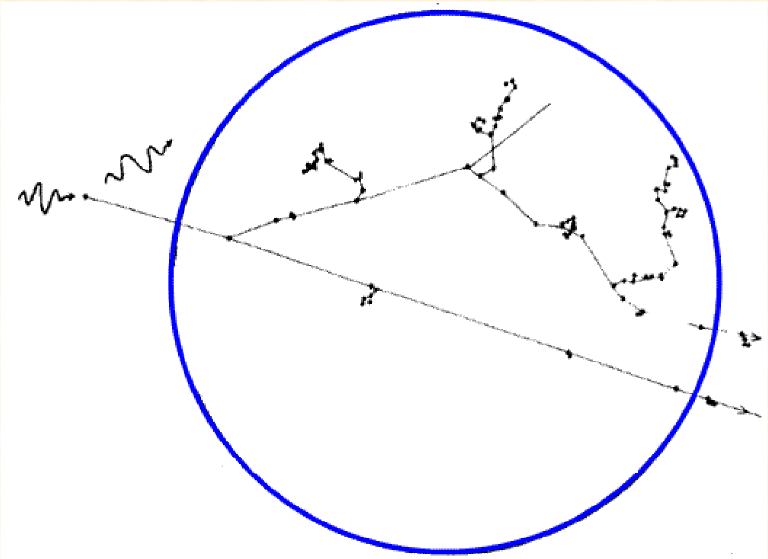
Track Structure Models:

2. Microdosimetry

- ***Microdosimetry*: Study of the distribution of deposited energy in cell-nucleus sized microscopic volumes**



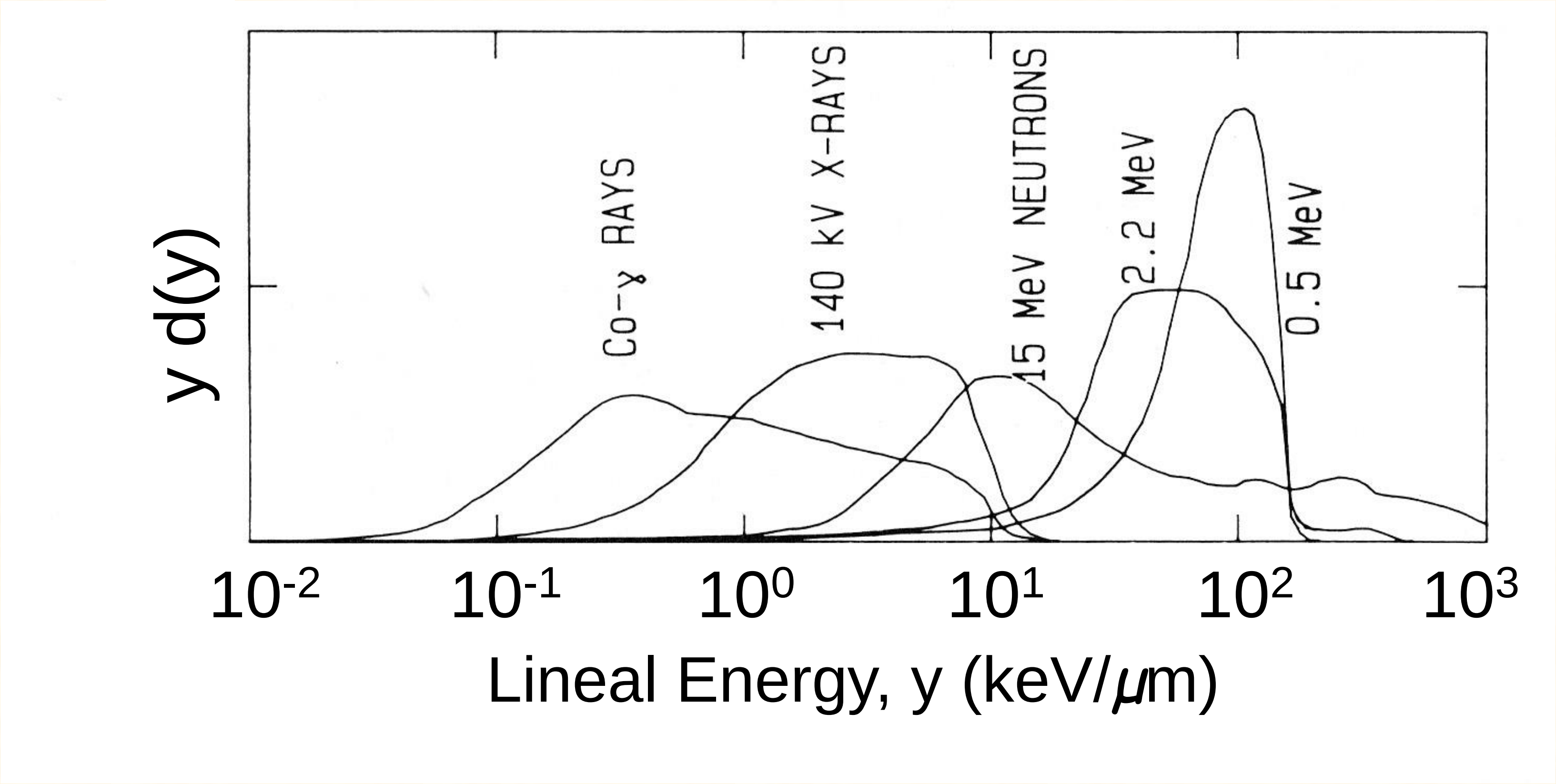
Simulation of single gamma ray passing through cell nucleus



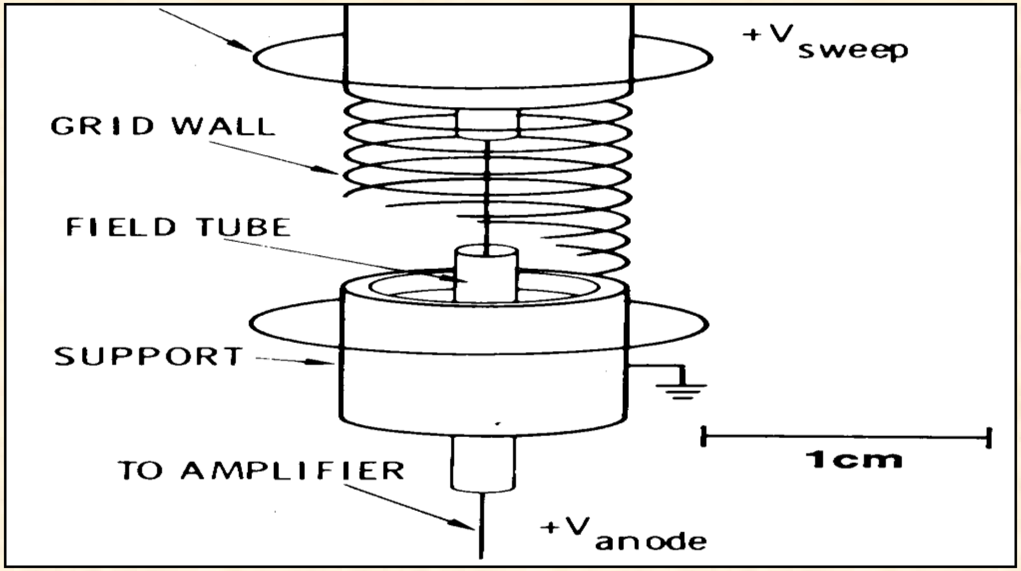
Simulation of single gamma ray passing through cell nucleus

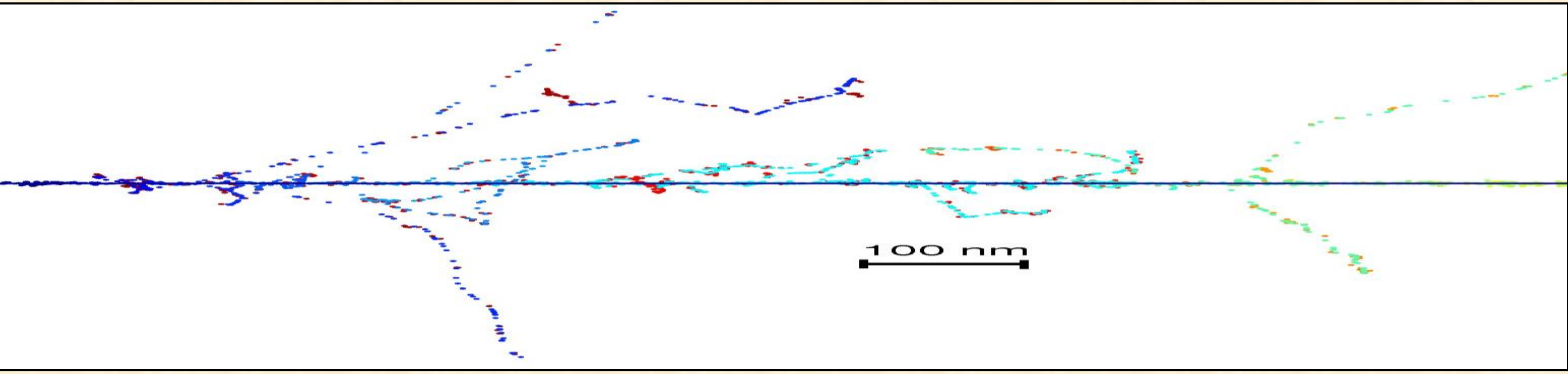
Microdosimetric Distributions:

Distributions of energy depositions, y, in microscopic site sizes

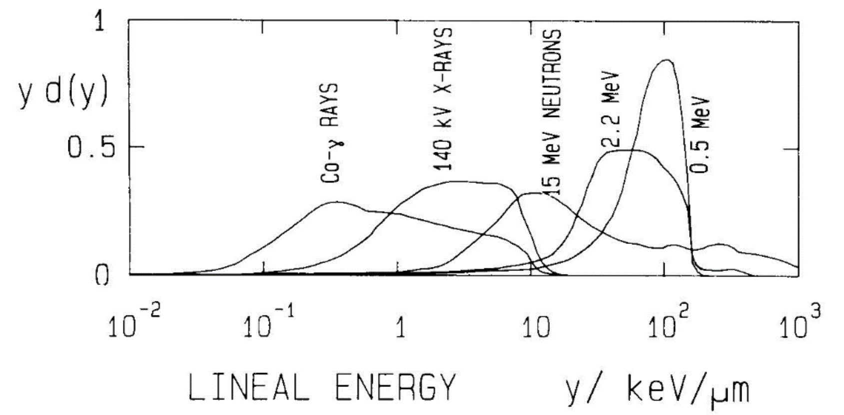


Microdosimetric distributions can be directly measured or calculated





From microdosimetric distributions to relative biological response



$$\textbf{Response} \propto \int \mathbf{d(y)} \times \mathbf{Q(y)} \, \mathbf{dy}$$

Microdosimetric distribution

Biological response function

Track structure

Biological endpoint

How do we estimate Q(y), the Biological Response Function?

Imagine a set of experiments with biological endpoint ε in which *i* different radiation types were used:

$$\boxed{\varepsilon_i \quad \propto \quad \int d_i(y)\, Q_\varepsilon(y)\, dy}$$

These are a series of *i* Fredholm equations, and given the experimental results, ε_i and the microdosimetric spectra, $d_i(y)$, they can be numerically unfolded to produce an estimate of $Q_\varepsilon(y)$

Quantifying TE vs NTE responses for densely-ionizing GCR at low doses

- **Fornace *et al.* measured tumors in APC$^{1638N/+}$ mice exposed at NSRL to:**
  - **Protons (50 to 120 cGy; 1.3 keV/μm)**
  - **^{4}He (5 to 50 cGy; 2 keV/μm)**
  - **^{12}C (10 to 200 cGy; 13 keV/μm)**
  - **^{16}O (5 to 50 cGy; 22 keV/μm)**
  - **^{28}Si (5 to 140 cGy; 69 keV/μm)**
  - **^{56}Fe (5 to 160 cGy; 148 keV/μm)**
  - γ rays (5-200 cGy)
- **20-39 mice / radiation type / dose, including zero dose**

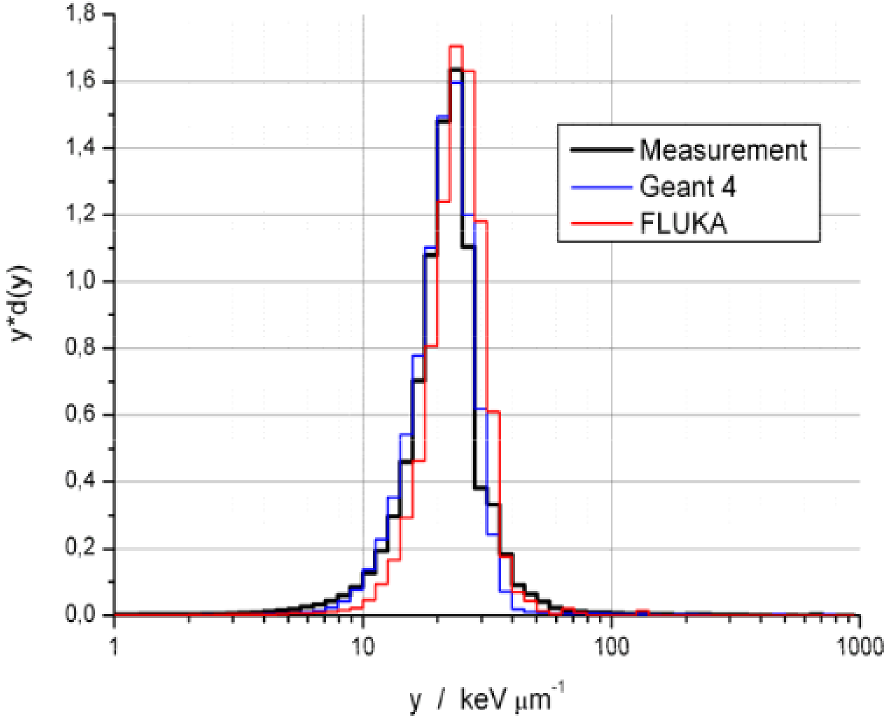
Best-Fit Model Parameters for NTE and TE

	LET (keV/µm)	**NTE parameter**	**TE parameter (Gy^{-1})**
Gamma	0.3	**0.79** [0.18, 16.5]	**2.88** [0.00, 3.80]
Protons	1.26	**0.94** [0.00, 1.77]	**2.88** [0.00, 4.30]
He ions	2	**1.29** [0.83, 1.76]	**2.88** [0.00, 4.20]
C ions	13	**2.64** [1.43, 4.69]	**3.47** [2.05, 5.04]
O ions	22	**2.72** [1.99, 3.71]	**2.88** [0.00, 5.52]
Si ions	69	**4.53** [3.15, 6.85]	**10.12** [7.68, 12.8]
Fe ions	148	**3.94** [2.61, 6.49]	**5.06** [2.67, 6.83]

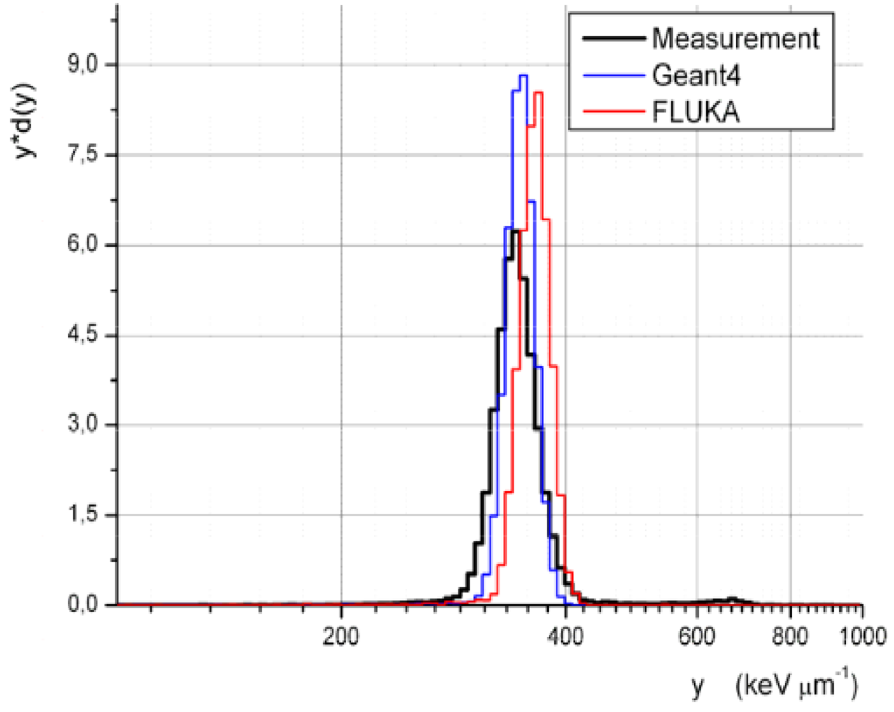
Calculated vs. experimental microdosimetric spectra

Based on FLUKA or GEANT4 (Beck 2006)

Oxygen 400 MeV/u



Iron 300 MeV/u



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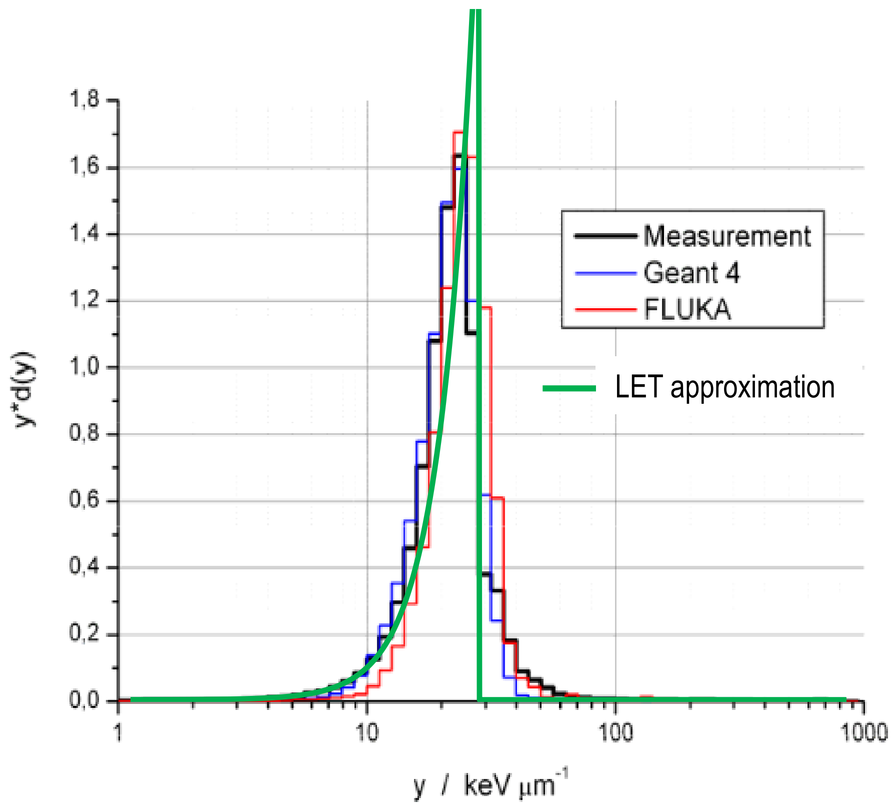

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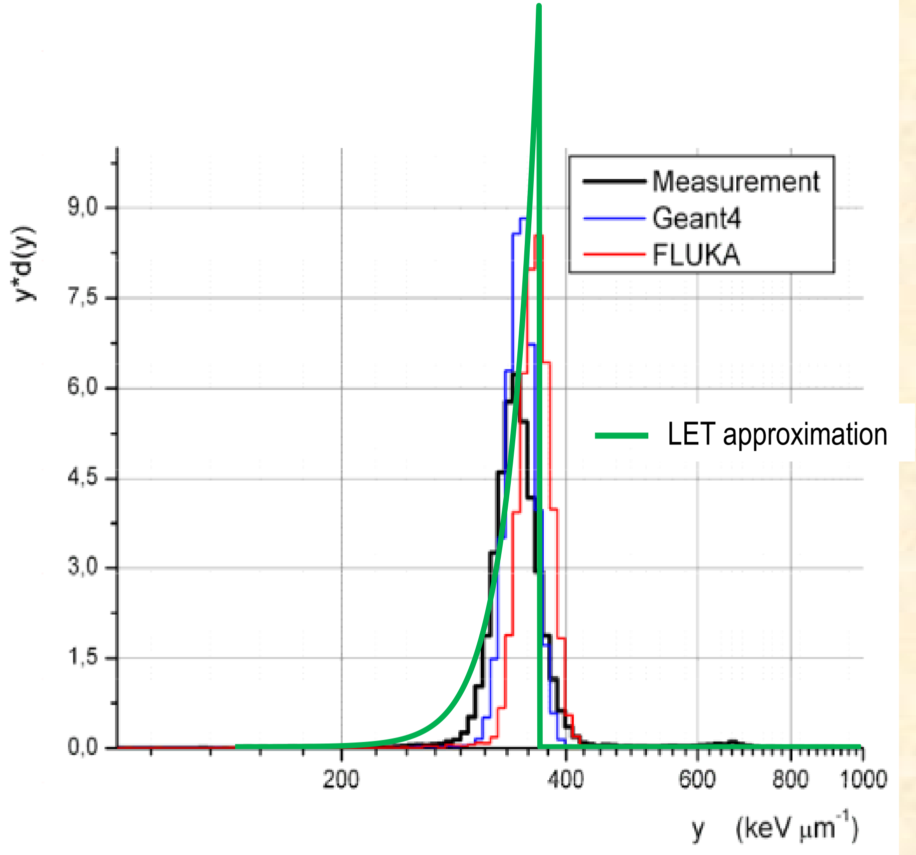

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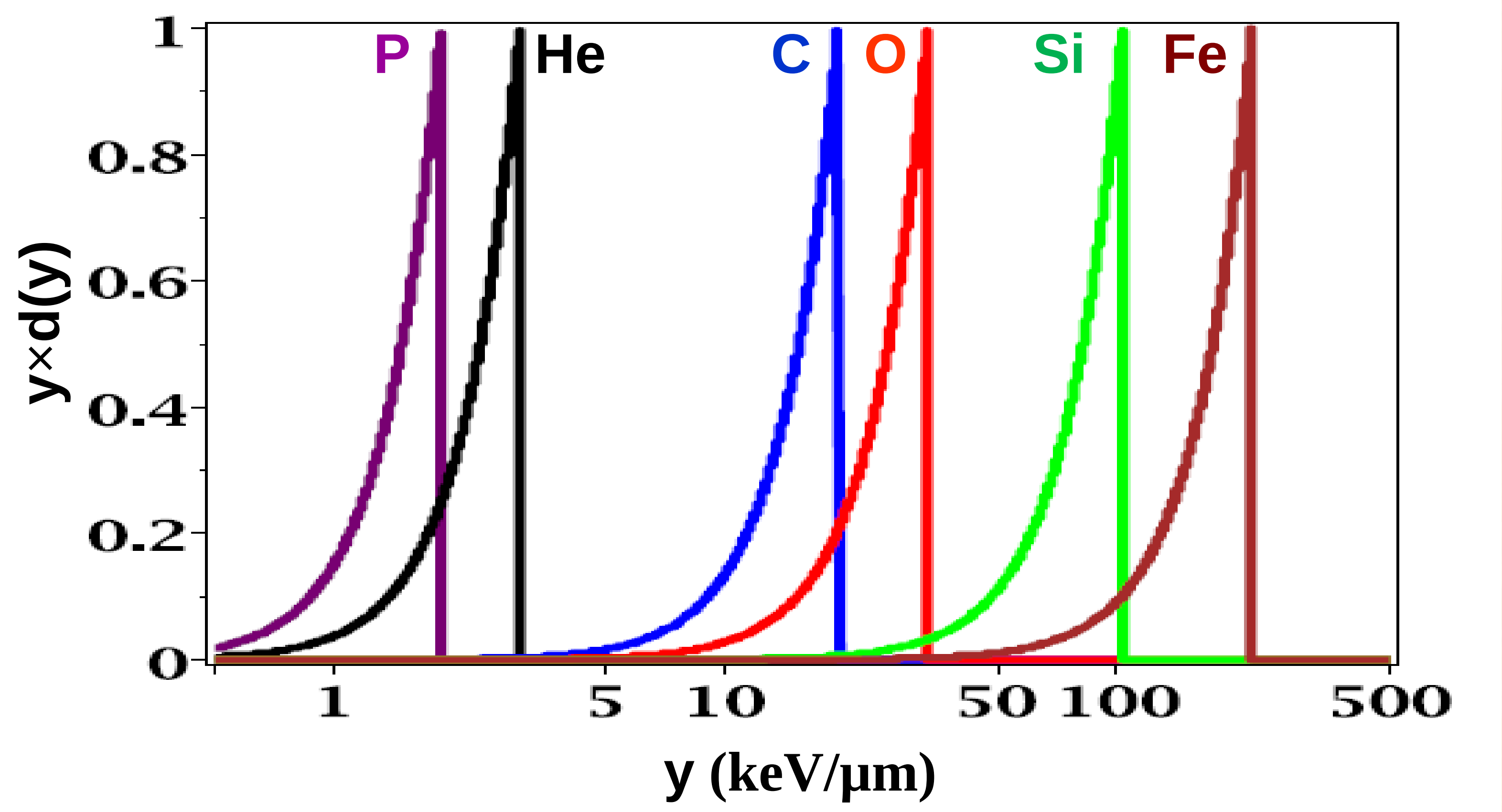

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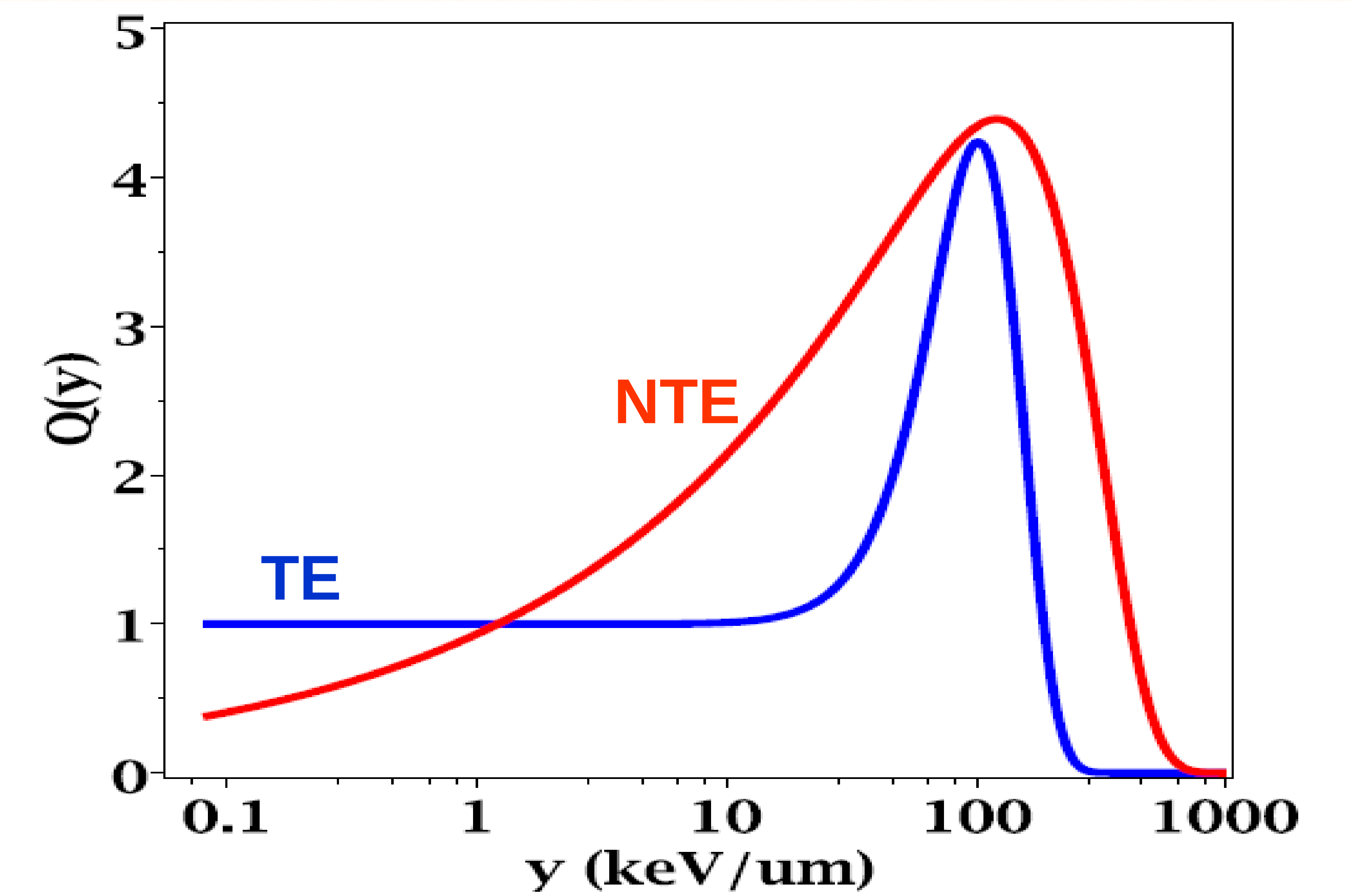
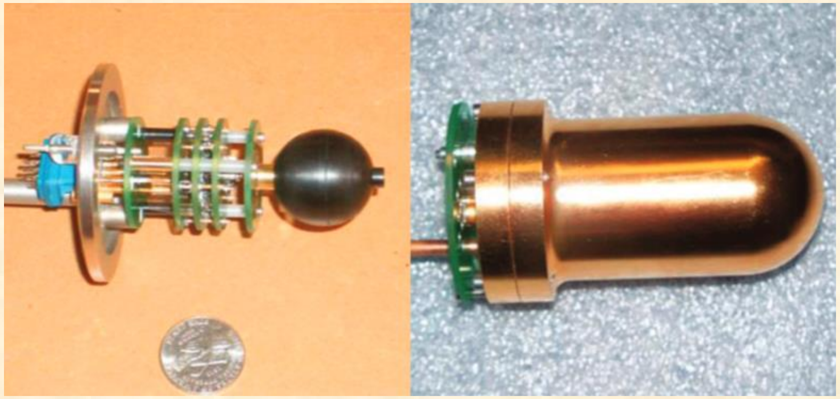
Preliminary Best-Fit Results: $Q_\varepsilon(y)$ shapes for mouse GI tumor endpoint



Ongoing…..

1. **Generate more detailed d(y) microdosimetric spectra (Geant 4+ RITRACKS) and redo this preliminary analysis**
2. **Generate $Q_\varepsilon(y)$ functions for a variety of different endpoints ε, both for cancer and non-cancer endpoints**
3. **Generate consensus Q(y) function(s)**
4. **Assess in-flight d(y) measurement tools, to allow in-flight assessments of Q**

TE gas microdosimeter. Straume et al 2015



Silicon microdosimeter. Rosenfeld et al 2014