An investigation of the response of the radiochromic dosimeter PRESAGETM to irradiation by 62 MeV protons

Shamsa Al Nowais1, Andrzej Kacperek2, John N H Brunt2, John Adamovics3, Andrew Nisbet1,4 and Simon J Doran1,5

1 Department of Physics, University of Surrey, Guildford, Surrey, UK
2 Douglas Cyclotron, Clatterbridge Centre for Oncology NHS Trust, Wirral, UK
3 Heuris Pharma, Skillman, NJ, USA
4 Royal Surrey County Hospital, Guildford, Surrey, UK
5 CRUK and EPSRC Cancer Imaging Centre, Institute of Cancer Research, Sutton, Surrey, UK

Abstract. Measurements of the 62 MeV proton beam at the Clatterbridge Centre for Oncology using the radiosensitive plastic PRESAGETM have previously shown a dependence of the dosimeter sensitivity (dose-response slope) on the linear energy transfer (LET) of the ionising particles. This work focuses on a possible explanation in terms of track structure theory (TST). Experimental measurements of highly irradiated PRESAGETM samples established the $D_{37}$ parameter of the theory to be of the order of 1000 Gy. Initial attempts at applying the theory showed good agreement of the theoretical and experimental values of relative effectiveness, but more work is needed to verify the model and understand its different parameters.

1. Introduction
Preliminary results — previously reported in abstract form [1-2] — have shown that optical CT of PRESAGETM dosimeters is an extremely suitable method for obtaining high resolution isotropic 3-D maps of dose from a proton beam. However, that initial work raised concerns that the dosimeter under-responded significantly in the high-LET region of the Bragg peak.

Previous authors have established a theoretical framework known as track structure theory, based on a part-theoretical / part-empirical model initially introduced by Katz in the late 1960s [3-6]. The work was later corrected by Zhang et al. [7] and a semi-empirical formula was proposed by Waligórski et al. [8] to account for dosimeter under-response. The framework was applied to polymer gel dosimetry by Jirasek and Duzenli [9], where it explained a number of key features of the gel under-response. Our aim was to extend this work and assess the degree to which the theory explains the observed effects for PRESAGETM.

2. Application of track structure theory to PRESAGETM
The δ-ray theory of track structure (TST) is attractive because it is a general-purpose radiological model that requires very few explicit details of the interactions by which dose deposition causes
changes in any given detector. It is based on the statistical properties (Poisson distribution) of a single- or multiple-hit interaction of absorbed radiation with the detector, and predicts the effectiveness of high-LET radiation for most physical detectors, once a few parameters obtained from low-LET irradiations are known.

Building on the target theory of Lea [10], the basic assumption is that any radiation detector consists of radiation sensitive elements, often referred to as “targets”. The target size is characteristic of the individual detector, which, in the case PRESAGE™, is the leuco dye molecule. These sensitive elements have two states “non-activated” / “activated”: for PRESAGE™, this would correspond to “non-absorbing” / “absorbing” or “light green” / “dark green”. The targets are converted between the two states by a radiation “hit” (or in more complex models multiple hits). They are embedded in a more or less passive matrix acting as an energy transfer medium. We further assume that the targets are bathed with a locally uniform field of secondary electrons following x- or γ- irradiation and that the probability of a hit can be calculated from standard Poisson statistics. The resultant response of the detector as a whole is obtained by (i) calculating the radial dose distribution around the path of the penetrating ion, which leads to an inhomogeneous distribution of radiation effects; (ii) integrating over the whole irradiated volume to find the average response of the medium; (iii) calculating the response after a specified fluence of particles.

The reason that high-LET radiation leads to an under-response in chemical detection systems is that the dose immediately surrounding the particle track is extremely high (~10^5 Gy at a distance of 1 nm from the path of a proton). Some of this dose is “wasted”, as all the targets in the vicinity are activated by a much smaller dose. By contrast for the low-LET radiation, the given dose is “spread out” over a larger number of elements.

The relative effectiveness, \( RE \), is the ratio of sensitivities of the dosimeter for the two radiations being compared [11], in this case, x-rays (\( k_\gamma \), low-LET) and protons (\( k_p \), high-LET). To apply track structure theory, two detector parameters are required: (a) \( D_{37} \) is the experimentally-measured dose at which \( e^{-1} \) (~37%) of the elements remain inactivated when the sample is irradiated with x-rays. It can be shown that \( k_\gamma = 1/D_{37} \). (b) \( a_0 \) is the size of the sensitive element and can be estimated either based on known physical characteristics of the detector (e.g., the diameter of the leuco-dye molecule) or from track structure theory itself. Using these inputs, \( RE \) can be calculated theoretically according to:

\[
RE = \frac{k_p}{k_\gamma} = \frac{D_{37}}{\sigma \text{LET}}
\]

where \( \text{LET} \) is the average energy deposited per unit path length in a unit density material, as obtained from the collision stopping power of the moving ion, which is equal to \( \text{LET}_{\text{e}} \), and \( \sigma \) is the relevant interaction cross-section, calculated using track structure theory (see [9] for details). \( RE \) can also be measured experimentally at different points along the depth-dose curve (i.e., at different LET values), using the data from [1]. The purpose of this study is therefore to compare the theoretical and empirical values of \( RE \), to determine whether track structure theory is applicable for the case of PRESAGE™. It is hoped that a better understanding of the PRESAGE™ response to protons will allow an improved dosimeter to be created that shows less of an under-response in the high-LET regions.

### 3. Materials and methods

#### 3.1 Determination of \( k_\gamma = 1/D_{37} \)

As is well known, PRESAGE™ has a very wide dynamic range and previous experiments [12] had shown that irradiation of standard cuvettes with a 10 mm path length led to samples that were too dark to be measured using standard techniques. Furthermore, it was not feasible to use a standard hospital linac to irradiate samples to the high levels (several thousand Gy) required to determine saturation.
Figure 1: (a) Relationship between dose and optical density for the 15 cuvettes irradiated at ESRF, as measured at three different wavelengths. Inset is the complete spectrum for a representative set of cuvettes. Note how the intense coloration of the PRESAGE™ causes the spectrophotometer to saturate at the normal measurement wavelength of 632 nm. Using the data for 700 nm, we are able to fit a curve to the ideal single-hit detector model. (b) Enlarged version of the low-dose behaviour showing an excellent linear relationship between dose and OD_{632}, but with OD_{690} and OD_{700} too insensitive to dose to make any effective measurement at low dose. (Note: it was difficult to make reliable estimates of the experimental error and so error bars have not been included for this figure.)
Thus, ultra-micro UV cuvettes (Eppendorf UVette®) with 2 mm optical path-length were filled with PRESAGETM ($C_{270}H_{460}N_{19}O_{68}Br$, $z_{eff} \approx 9.6$, $1.08 \text{ g/cm}^3$) and irradiated at the ID17 Microbeam Radiation Therapy (MRT) beamline at the European Synchrotron Radiation Facility (ESRF) in Grenoble, France. Operating in filtered broad-beam mode, with a spectrum ranging from ~35 to 350 keV, the dose delivery rate by the beam can be up to $16 \text{ kGy s}^{-1}$. Each cuvette was placed individually on a stand and irradiated, and the sequence yielding the following nominal doses over the 15 cuvettes: 1, 2, 5, 8, 12, 20, 30, 50, 80, 140, 200, 300, 500, 2000 and 5000 Gy. Two unirradiated control samples were measured to establish a base-line. The optical absorbance spectra of the samples were measured using a CARY 5000 UV-Vis-NIR spectrophotometer (Varian, Inc.). Despite the low optical path length, the highly irradiated samples were still almost completely opaque at the normal measurement wavelength of 632 nm, with $OD_{632} >> 2$, and could not be measured by our apparatus. To obtain a value of $D_{37}$, we assumed that the x-ray dose-response of PRESAGETM measured at 700 nm would scale linearly with that at 632 nm, whilst leaving the optical absorbance still within the dynamic range of the spectrophotometer. Future measurements on thin PRESAGETM films might remove the need for this.

3.2 Determination of $a_0$

For a physico-chemical detector the approximate size of the sensitive element $a_0$ may simply be the size of the sensitive molecule. For leuco malachite green, this is approximately 0.65 nm, from tabulated values [13]. However, it is also possible to derive a value of “effective radius” from target theory itself, which suggests that $a_0$ may be ~10 nm, larger than the physical size of the molecule.

3.3 Determination of relative effectiveness

The LET for protons in PRESAGETM in MeVcm$^2$/mg was calculated using an Energy-LET-Range converter software application [14], by entering the elemental target densities weighted by their relative stoichiometry. A MathCad spreadsheet was used to implement the track structure theory calculations. The experimental value of $RE$ was estimated by making the initial approximation that the absolute efficiencies of the protons at the entrance channel and x-rays are similar (both are considered to be “low-LET” radiations). The ratio of the optical and ion chamber results was then found for all depths and then multiplied by a calibration value obtained from the entrance dose. Although the ion chamber measurements were made in a water phantom, depths have been converted to equivalent depths in PRESAGETM simply by dividing the ratio of densities.
4. Results
The results of the spectrophotometer analysis are displayed in Figure 1. Applying a standard Poisson model to the single-hit target, yields $OD \propto 1 - \exp(-D/D_{37})$ and a fit to this model gave a value of 1070 Gy for the $D_{37}$ parameter. Previously reported results [1-2] for the 62 MeV proton beam are repeated for convenience in Figure 2(a), where the Bragg curve imaged with our CCD-based optical CT scanner is compared with relative dose measurements made with a PTW/Markus (parallel-plate) ionization chamber. The corresponding relative effectiveness values are shown in Figure 2(b). Notice that the size of the targets is a free parameter in the theory and clearly has a big influence on the results. Further verification of the correctness of our model is necessary.

5. Conclusions
Track structure theory provides a good basis for an explanation of the variation with proton LET of the dose-response of PRESAGETM. The under-response at the Bragg peak is attributed to the large doses deposited by delta rays close to the track of a proton, which causes detector elements to saturate. The theory does not specify the nature of the sensitive element, though the size of the element is an important parameter for the model. The experimental and theoretical values of relative effectiveness of PRESAGETM show similar trends. However, more work is needed to understand the model fully.

6. References
[1] Doran, S.J., et al., True-3D scans using PRESAGETM and Optical-CT: A case study in proton therapy J Phys Conf Ser, 2006. 56 p. 231–234.
[2] Al-Nowais, S., et al., A preliminary analysis of LET effects in the dosimetry of proton beams using PRESAGETM and optical CT. Applied Radiation and Isotopes, 2009. 67(3): p. 415-418.
[3] Butts, J.J. and R. Katz, Theory of RBE for heavy ion bombardment of dry enzymes and viruses. Radiation Research, 1967. 30(4).
[4] Katz, R., Track structure theory in radiobiology and in radiation detection. Nuclear Track Detection, 1978. 2(1): p. 1-28.
[5] Katz, R., S.C. Sharma, and M. Homayoonfar, The structure of particle tracks, in Topics in radiation dosimetry, F.H. Attix, Editor. 1972, Academic press: New York. p. 317-383.
[6] Kobetich, E.J. and R. Katz, Width of heavy ion tracks in emulsion. Bulletin of the American Physical Society, 1968. 13(1): p. 130-&.
[7] Zhang, C.X., D.E. Dunn, and R. Katz, Radial-distribution of dose and cross-sections for the inactivation of dry enzymes and viruses. Radiation Protection Dosimetry, 1985. 13(1-4): p. 215-218.
[8] Waligorski, M.P.R., R.N. Hamm, and R. Katz, The radial-distribution of dose around the path of a heavy-ion in liquid water. Nuclear Tracks and Radiation Measurements, 1986. 11(6): p. 309-319.
[9] Jirasek, A. and C. Duzenli, Relative effectiveness of polyacrylamide gel dosimeters applied to proton beams: Fourier transform Raman observations and track structure calculations. Medical Physics, 2002. 29(4): p. 569-577.
[10] Lea, D.E., Actions of radiations on living cells. Second ed. 1962, New York: Cambridge University Press.
[11] Hansen, J.W., Experimental investigation of the suitability of the track structure theory in describing the relative effectiveness of High-LET irradiation of physical radiation detectors. 1984, Riso National Laboratory, DK-4000 Roskilde, Denmark.
[12] Al-Nowais, S., et al., An attempt to determine the saturation dose for PRESAGETM. J Phys. Conf. Ser., 2009. 164: p. 012043.
[13] Koltuniewicz, A.B. and E. Drioli, Membranes in Clean Technologies: Theory and Practice. Vol. 1. 2008: John Wiley and Sons Ltd.
[14] Zajic, V., Energy vs. LET vs. Range calculator, http://tvdg10.phy.bnl.gov/LETCalc.html.