MURINE HARDERIAN GLAND TUMORS AND *IN VITRO* CHROMOSOME ABERRATIONS INDUCED BY EXPOSURE TO MIXED BEAMS WITH SOME HIGH-LET COMPONENTS: SYNERGY THEORY

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We discuss recent synergy results on murine Harderian gland (HG) tumors and chromosome aberrations (CA) induced by exposure to 1-ion or mixed beams at the NASA Space Radiation Laboratory (NSRL). All CA data used has been published [1]. Synergy theory compares observed mixture dose-effect relations (DERs) to baseline no-synergy/antagonism DERs obtained by mathematical manipulations of mixture components' DERs. The simple effect additivity (SEA) baseline is the sum of the components' effects. It has been known for almost a century that this apparently obvious SEA approach is unreliable [2]. Indeed SEA is not even self consistent (reviewed in [3,4]). Many different replacements for SEA are now used in biology and each is potentially useful in radiobiology.

Our calculations use incremental effect additivity (IEA), a recently introduced replacement [4]. IEA has advantages; for example, a mixture of mixtures theorem says IEA (unlike SEA and most SEA replacements) is appropriate even when nominally 1-ion beams are actually mixtures at their target due to, e.g., mouse self-shielding. Fig. 1 compares SEA and IEA results for an illustrative mixture whose individual components' DERs, calibrated from published 1-ion NSRL data [4], take into account non-targeted effect (NTE) dominance at very low doses. All ions in the data set are high charge and high energy (HZE).

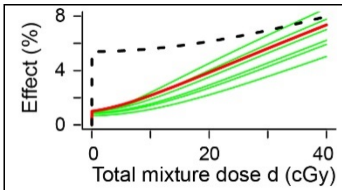

Fig. 1. SEA gives an unreliable baseline. The figure shows CA prevalence in a cell line that presents strong evidence for NTE. The apparent vertical jump and kink all curves show at $d = 0$ are actually smooth. They model NTE using DERs having large slope and high concavity. The figure is for a hypothetical mixture of all 6 ions in the data set, with each ion carrying 1/6 of the total mixture dose. It shows a typical case of SEA unreliability. Each green line shows the DER for one of the 6 mixture components, i.e. the effect that would occur if that HZE ion contributed all of the dose instead of only 1/6. The black dashed and solid red lines are, respectively, the SEA and IEA DERs that define no-synergy/antagonism. Both are calculated from the one-ion DERs. It is seen that for most of the dose range SEA synergy theory absurdly states that an effect larger than any one ion could produce by itself is not evidence for synergy but rather defines absence of synergy. This example confirms SEA unreliability for analyzing some NSRL experiments that use ions in the galactic cosmic ray (GCR) spectrum. When conducting synergy analyses of mixed beam data we therefore ignored SEA.

We felt that synergy among GCR components was unlikely since there appear to be no consistent patterns of synergy for many different endpoints or convincing biophysical arguments that track structure superpositions should induce synergy. However, results of one recent NSRL mixed-beam HG experiment were a disquieting surprise.

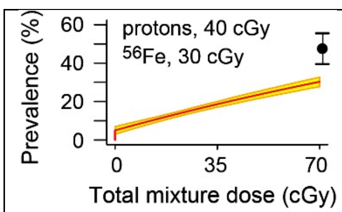

Fig. 2. Substantial synergy between protons and ^{56}Fe. The figure presents HG tumor prevalence 16 months after acute exposure to protons followed in < 2 min by acute exposure to an HZE ion. The red line is the IEA baseline. The yellow ribbon around the red line shows vertical intervals for 95% confidence intervals (CI), calculated by Monte Carlo sampling from a variance-covariance matrix rather than using an unduly pessimistic CI estimate which neglects adjustable parameter correlations. The black dot shows the experimental outcome ± 1 SE. It is seen that the prevalence lies well above the yellow ribbon, i.e. substantial synergy was present. Other recent HG mixture experiments have shown less or no synergy. It was calculated that the yellow ribbon is less than half the height that would have been found had adjustable parameters correlations unrealistically been neglected.

We concluded the following:
(A) Synergy in the induction of murine HG tumorigenesis after exposure to rapidly sequential ions has been demonstrated in one case. (B) Experiments are needed to rule out the possibility of major synergy. Synergy among HZE ions would be especially worrisome in view of the high RBEs HZE often show for various endpoints.

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