Response to 'Interaction-altered cancer prevention by antioxidants'

Karen Brown*, Alessandro Rufini and Andreas Gescher

Cancer Chemoprevention Group, Department of Cancer Studies, Cancer Research UK Leicester Centre, University of Leicester, Leicester, LE2 7LX, U.K.

*Corresponding author. E-mail: kb20@le.ac.uk

The letter by Guerra *et al*. (*1*) questions the findings reported in our recent manuscript entitled 'Cancer chemoprevention: Evidence of a nonlinear dose response for the protective effects of resveratrol in humans and mice' (*2*) as interaction effects. They claim that 'resveratrol itself had opposite outcomes on intestinal tumorigenesis'. This is factually incorrect, since we did not observe opposing activity in Apc^{Min} mice, rather, we saw either a complete lack of effect on adenoma development, or efficacy, as measured by a significant reduction in tumor number and/or burden. Furthermore, they failed to recognise that the low, dietary achievable dose of resveratrol had no effect on adenoma development when given along with a standard fat diet but reduced adenoma number by ~40% and decreased the overall tumor burden by ~52% relative to control animals, when given with a high fat diet. We maintain that this is undoubted evidence of an interaction between resveratrol and dietary fat, although we acknowledge that the underlying mechanisms remain to be elucidated.

In our manuscript we urged investigators to examine the effects of low, dietary achievable doses/concentrations of candidate cancer chemopreventive agents in their experimental models. However, we did not in any way state that we expect all compounds will display efficacy at these levels, we just consider it important to have a comprehensive understanding of dose-response relationships and to work with concentrations that can be attained in human plasma/target tissues, to maximise the chances of successful translation of laboratory data to the clinic.

In their letter, Guerra *et al*. provide data on the chemopreventive effects of lipoic acid (LA) in Apc^{Min} mice. They state that 'LA and resveratrol appear to have a similar, linear-dose chemopreventive activity, suggesting a similar mechanism of action.' This claim is somewhat surprising as there is absolutely no scientific basis to draw such conclusions; even if two compounds exhibited an identical dose-response relationship it certainly does not mean that the underlying mechanisms of action are the same. Most, if not all dietary-derived compounds with anti-cancer activity are multi-targeted and impact on numerous molecular pathways, for example, at least 20 proteins have been identified as directly binding with resveratrol (*3*). To simply describe those with redox activity as antioxidants, as Guerra *et al*. have in their letter, risks trivialising the complexity of these compounds and the possibility of failing to recognise other key mechanisms of action in humans. It is likely that a variety of factors, including dose, metabolic status and target tissue will influence the relative contribution of different mechanisms to any cancer chemopreventive efficacy, and it represents a challenging but essential task to unravel these connections.

Finally, we agree with the sentiments of Guerra *et al*. that better knowledge is needed of the interactions between diet-derived compounds used for cancer prevention and metabolic, hormonal, lifestyle and environmental factors; this will only come from an improved

mechanistic understanding, gained by conducting high quality studies using clinically-relevant models and clinically achievable doses.

References

1. E. Guerra, M. Piantelli, S. Alberti, Interaction-altered cancer prevention by antioxidants. *Sci. Transl. Med.* **xxxxx** (2015).
2. H. Cai, E. Scott, A. Kholghi, C. Andreadi, A. Rufini, A. Karmokar, R. G. Britton, E. Horner-Glister, P. Greaves, D. Jawad, M. James, L. Howells, T. Ognibene, M. Malfatti, C. Goldring, N. Kitteringham, J. Walsh, M. Viskaduraki, K. West, A. Miller, D. Hemingway, W. P. Steward, A. J. Gescher, K. Brown, Less is more for cancer chemoprevention: evidence of a non-linear dose response for the protective effects of resveratrol in humans and mice. *Sci. Transl. Med.* **7,** 298ra117 (2015).
3. R. G. Britton, C. Kovoor, K. Brown, Direct molecular targets of resveratrol: Identifying key interactions to unlock complex mechanisms *Ann. N. Y. Acad. Sci.* **1348**, 124-133 (2015).