p53 and chemosensitivity

To the editor — Wahl *et al.*[1] found that loss of wild-type p53-sensitized mammalian cells to Taxol cytotoxicity. They demonstrated that normal primary human lung fibroblasts, mouse embryo fibroblasts and human foreskin fibroblasts became more sensitive to Taxol if they lacked p53, either through targeted disruption of the p53 gene, targeted degradation using HPV16 E6 or functional inactivation using SV40 large T-antigen. Increased sensitivity to Taxol correlated with increased G2/M cell-cycle arrest and apoptosis induction in cells lacking functional p53.

We have been studying the role of p53 in determining the chemosensitivity of human cancer cells from different tissues to the clinically useful agents adriamycin, carboplatinum, cytoxan, and etoposide[2]. We found that endogenous p53 status predicted *in vitro* chemosensitivity in only a minority of cancer cell lines (ovarian and some Burkitt's lymphoma cells, but not in leukemia or lung cancer cells). We used HPV16 E6 to target degradation of p53, in wild-type p53-expressing H460 human lung cancer cells, via ubiquitin-mediated proteolysis. The H460 lung cancer cells did not become more resistant to adriamycin or etoposide when their p53 was degraded[2].

We have since engineered PA-1 human ovarian teratocarcinoma cells to express HPV16 E6 protein, since our initial observations suggested that, in these cells, p53 status may in fact be an important determinant of chemosensitivity. Fig. 1 shows that p53 protein was undetectable either before or after chemotherapy in two independent PA-1/E6 clones, and that induction of $p21^{WAF1/CIP1}$, the cell-cycle inhibitor, by chemotherapy was also lost in the E6-transfected cells as compared with either parental cells or a neo-clone. As previously demonstrated with H460-E6 cells[2], the E6-transfected ovarian carcinoma clones also displayed a deficiency in cell-cycle arrest following exposure to etoposide (data not shown), thus confirming loss of p53-checkpoint function. We confirmed that p53 mRNA was produced at similar levels in

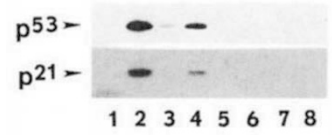

Fig. 1 Disruption of p53 function in human ovarian teratocarcinoma (PA-1) cells. Western blot analysis of p53 (upper panel) and p21 (lower panel) protein expression in PA-1 cells (lanes 1, 2), a G418-resistant clone (PA-1/Neo; lanes 3, 4) and two HPV16 E6-transfected clones (PA-1/E6-5, lanes 5, 6; and PA-1/E6-10, lanes 7, 8) is shown either untreated (lanes 1, 3, 5, 7) or treated (lanes 2, 4, 6, 8) with 0.2 μg/ml adriamycin as previously described[2]. p53 and p21 protein bands are indicated by arrows.

The true Western diet

To the editor — While being satisfied that Frederich *et al.* have validly proven the point expressed in their title (Leptin levels reflect body lipid content in mice: Evidence for diet-induced resistance to leptin action. *Nature Med.* **1**, 1311–1314; 1995), I confess to being somewhat disturbed by some implications and imprecisions in the paper itself.

First, they give the name "Western" to the experimental diet they fed their mice. Of course, Messrs. Teklad are free to call their wares by whatever name they chose, but the obvious, and possibly misleading, implication is that this mouse diet has something to do with anything typically consumed by humans in Western countries.

Yet the diet fed to these mice misses the mark by a wide margin. Admittedly, the French use butter freely (as other Western nations use olive oil or animal fat), but the proportion of fat (21% wt/wt) in the experimental diet reminds one of the regimen of the Inuits, who are Western only because they are so far east. More important, in my opinion, is the fact that, of the nearly 50% (wt/wt) of carbohydrates in the diet, 70% was sucrose, whereas in Western Europe the bulk of carbohydrates is provided by starch, under the guise of bread, pasta or potatoes: more accurately than "high fat," the diet fed the experimental mice should be called "high sucrose." Finally, cellulose appears to be absent from the mouse diet, whereas, as vegetables, it is an important constituent of meals eaten in Western Europe.

The above considerations reflect on a possible "Western is bad" indiscriminate interpretation of the Frederich *et al.* results by the general public. More relevant to their scientific interpretation might be the following. The experiments were performed under an *ad libitum* protocol. Ingested quantities would be central in the interpretation of results. (In fact, the authors only indicate quantities ingested in the final week of the experiment and these are not significantly different between groups.) The data provided do not afford the elements that could be used to falsify an alternative hypothesis to the "high-fat diet" one. Sucrose, being more rewarding a food than is standard Mouse Chow, induces, when given immediately after weaning, a feeding behavior leading to obesity. Increased body fat then induces increased serum leptin levels, which reduces food intake to normal, but is insufficient to reduce body fat. This interpretation, instead of being static, is a sequential one. It would fit data, too numerous to be cited, that show that "normal" obese humans have a normal or quasi-normal food intake, and that weight reduction necessitates a drastic reduction of food intake to below normal.

Of course, I am writing all this because I have been fed by my mother and then by my wife a perfect "Western" diet, complete with Roti Sauce Béarnaise and Sauerkraut Garni and Homard à l'Américaine and Pasta Fagioli, washed down with appropriate quantities of French wines, without ever any idea of "dieting." I am 67 years old, 1.72 m tall and weigh 64 kg, and am in apparently perfect health. Are genes everything, as suggested by my svelte parents who lived respectively to ages 91 and 89, and *a contrario* by the UCP-DTA transgenic mice? Or do I owe a good response to leptin action to the fact that my mother never fed me sweets?

J.-F. FONCIN
Laboratoire de Neurohistologie
Laboratoire Montyon – La Salpêtrière
47 Boulevard de l'Hôpital
75651 Paris, Cedex 13, France