The term "multidrug resistance" has come to mean different things to different people. Initially, it was coined to describe the laboratory phenomenon of cross-resistance to various natural products, and this phenomenon was later found to relate to increased expression of P-glycoprotein (gp170) \((P < .0001, \text{Table 4 in (2))}\). Since then, many laboratory scientists and some clinicians have mistakenly assumed that the clinical observation of drug resistance to a wide range of cytotoxic agents has the same basis. Are the two in fact related? In this issue of the Journal, Trock et al. (2) have conducted an exhaustive review of the literature in an attempt to answer this question as it relates to breast cancer. There has been a plethora of studies with widely varying conclusions, and an attempt to distill them into a single review article is indeed praiseworthy. But there are problems.

First, and predictably, the use of meta-analysis in this field is bound to provoke criticism, and the authors acknowledge this. While clinicians have readily accepted for some years the value of meta-analysis in allowing conclusions to be reached when randomized trial data are pooled (3), using it to look for clinical associations of laboratory observations is fraught with danger. Trock et al. have meticulously drawn up criteria for judging the quality of the various studies; they proceed to point out that very few studies actually meet these criteria. An important example is the fact that 67% of the studies that were based on immunohistochemical detection of gp170, which is probably the preferred technique, used only one antibody, despite the acknowledged major problem of cross-reactivity with other proteins. Does this high level of concern about the validity of the basic data not call into question the reliability of any conclusions drawn from them?

Second, no attempt was made to analyze in detail the various criteria for "positivity," although Trock et al. did suggest that such differences probably contribute significantly to heterogeneity. Is there, for example, some threshold percentage of positively staining cells with the use of immunohistochemistry? Since, as stated by Trock et al. (2), "approximately 40% of all breast tumors express detectable levels of MDR1/gp170," it would have been helpful to have had some notion of the range of positivity involved.

Third, and most importantly, there are the tentative conclusions by Trock et al. regarding the association between clinical response and gp170 positivity. It is clear from the article by Trock et al. that exposure to cytotoxic drugs (not exclusively of the MDR1-related type) increases gp170 expression [two-sided \(P < .0001, \text{Table 6 in (2))}\]. This is entirely in keeping with laboratory observations on induction of multidrug resistance (4). Does this represent induced expression, or does it result from the selection of tumor subpopulations based on failure of response to treatment? Trock et al. favor the latter explanation, stating that gp170 is likely to have a role in conferring clinical resistance "in a significant proportion of breast tumors."

One problem in assessing this proposal is the major drawback that very few data are available on serial samples from the same patient, and Trock et al. rightly urge that such studies be done in the future. Nevertheless, there remains the intriguing observation of a highly significant association between gp170 positivity, particularly in samples taken after chemotherapy, and the lack of response to that treatment. This association is seen after chemotherapy with many drugs as well as with those restricted to the MDR1 family, with a two-sided \(P\) value on the association of \(<.0001\) [Table 6 in (2)]. On the other hand, and importantly, Trock et al. observed that gp170 positivity before chemotherapy is not significantly associated with lack of response to subsequent treatment, with a \(P\) value of .088 on the relative risk, albeit from a pooled total of only 115 case patients.

Thus, the conclusion made by Trock et al. is open to debate. Despite all the methodologic reservations expressed above, there does appear to be an association between poor clinical response and gp170 positivity in samples from treated breast cancer patients. However, this finding does not necessarily mean that the two are causally linked. The development of drug resistance is likely to lead to tumor cell populations with various molecular and genetic characteristics, for example, increased numbers of cells with mutations in the p53 gene. MDR1 gene expression is regulated by several factors; experimentally, these factors have been shown to include mutant p53, which specifically stimulates the MDR1 promoter (5). Thus, an alternative explanation for several of the observations made by Trock et al. is that gp170 positivity is an epiphenomenon and that, in poorly responsive cases of breast cancer, it is a result of other genetic changes. Such an argument is strengthened by the absence of a significant association between initial gp170 positivity and response to treatment; if there were a strong functional relationship, one

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*Correspondence to: S. B. Kaye, M.D., CRC Department of Medical Oncology, University of Glasgow, CRC Beatson Laboratories, Garscube Estate, Switchback Rd., Bearsden, Glasgow G61 1BD, U.K.

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would expect there to have been a positive conclusion, as has been observed, for example, in studies linking the clinical resistance to platinum compounds to the presence of mutant p53 sequences in primary tumor samples of ovarian cancer (6,7).

And yet much still has to be learned. There remains the tantalizing observation made by some authors of a significant association between gp170 positivity and survival in a range of tumor types. Although this association is not confirmed in the article by Trock et al., a testable hypothesis is that gp170 expression is a marker of cell behavior and has a possible role in the processes of invasion and metastasis (8). Of course, clinicians are impatient people, and they have already embarked on a number of trials of multidrug resistance modulators, based on positive experimental data. The findings from these trials have largely been disappointing, at least with regard to solid tumors, but some would say that, in many of these trials, the use of modulators with little potency is an important consideration.

Recently, enthusiasts for multidrug resistance modulation have been stimulated by the intriguing experimental observation that exposure of tumor cells in vitro to the modulating agent PSC 833 suppresses the emergence of MDR1 gene mutants, thereby inhibiting the development of drug-resistant cells, in the presence of the MDR1-related drug doxorubicin (9). This observation raises potentially important clinical issues. In particular, if one assumes that gp170 is indeed one of the factors responsible for clinical drug resistance to MDR1-related drugs, would the time to interfere with its function not best be during the initial exposure rather than later in the patient’s clinical history, as Trock et al. propose, by which stage it is even more likely that other factors will dominate the picture?

Trock et al. conclude their worthy review article by expressing their hope that further discussion will take place. This should indeed be the case, with maximum dialogue between laboratory and clinical scientists. Until then, the jury on gp170 in breast cancer and in other cancers remains firmly out.

References