REPLY

Gleave, M. and Monia, B. P.

We state many of the things in our review that are raised in the letter by Schlingensiepen *et al*. We state that our coverage is not exhaustive; that there are other trials and discovery programmes underway that go beyond the scope of the review. The main point emphasized in their letter is that it is not chemistry but rather target selection that matters most in whether or not a drug is successful in achieving sufficient activity in the clinic to prove efficacious. However, we never said that it is the chemistry that has caused the current failures and we do say that target selection is a very important consideration in an antisense development programmme. We offer advanced chemistries as a possible way to overcome past failures; we do not state that it is a proven solution. Furthermore, the recommendation by Schlingensiepen *et al.* to carry out chemical structure–activity relationships studies in humans in which different chemistries are evaluated against the same target is naive — the cost of such experiments would be prohibitive.

Although we agree that the target is important, it is not necessarily the most important. The corresponding letter by Schlingensiepen *et al.* emphasizes TGF-β and their own TGF-β oligonucleotide, which is one of a plethora of relevant therapeutic targets with documented anticancer pre-clinical proof-of-principle. You pick your targets the best way you can and use the best available chemistry that you have. A good target supported by an inferior small molecule, antibody or antisense chemistry is less likely to be clinically efficacious. Clinical development remains an equally critical step along with target selection and chemistry, as we state in our concluding remarks. Identifying optimal biological dose based on safety and tolerability, serum/tissue pharmacokinetics, and target regulation data, as well as optimal combination regimen and a target population are also crucial steps in the process.

The letter by Schlingensiepen *et al.* includes other statements that we would like to comment on. First, to say that Genasense produced a marked improvement in progression-free survival is an overstatement. If that were true, it would be approved. Genasense might yet prove efficacious, but it would have to be on the basis of new data emanating from longer follow-up studies. Second, we never said that the failures to date are due to chemistry. We stated that this could be one explanation. Third, to say that PKCα is part of a redundant pathway is unsubstantiated. If that were the case, why do tumours in xenografts shrink?

Target, chemistry, optimal biological dose, target population, clinical trial design and regulatory issues form the intricate matrix for successful drug development; weakness in any one, or over-emphasis of any one, will compromise both efficacy and approval.