The role of transforming growth factor-β in carcinogenesis
Comment

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In their review, Gleave and Monia[1] gave an overview of the current status and future directions of selected antisense compounds in clinical development for systemic cancer therapy. We would like to add some points to the discussion, as to the clinical potential of first-generation phosphorothioate oligodeoxynucleotides (PS-ODNs).

Taking Genta's Genasense as an example, evidence of effectiveness, indicated by a marked increase in progression-free survival and responses in melanoma, was demonstrated[2]. The criticism of the Food and Drug Administration (FDA) during the Oncology Drugs Advisory Committee (ODAC) meeting was directed at study design deficiencies, not to the nature of the compound. Nevertheless, Genasense is still in advanced clinical trials and has recently shown activity for non-Hodgkin lymphoma[3]. Failure to meet the primary endpoint in melanoma could have several causes; the chemical nature of the compound is just one suggested reason. If the chemical modification was the reason for the lack of efficacy of antisense compounds in recent clinical trials as cited in the review, the logical consequence would be to target molecules such as protein kinase C α (PKCα) or BCL2 with second-generation ODNs. Instead, the compounds in current clinical development that were suggested as promising by the authors are directed against other targets. Consequently, the change in targets makes the comparison between the ODN-generations regarding anti-tumour efficacy impossible.

In our opinion, the choice of target is most important for successful antisense therapy. The ideal drug candidate should drive tumour progression and should not, as is the case for PKCα, have redundant pathways. The crucial role in cancer of transforming growth factor β (TGFβ) has recently been the topic of numerous publications[4–10] and conferences devoted to the TGFβ superfamily (American Association for Cancer Research, 2003, Keystone Symposium, 2005 and Federation of American Societies for Experimental Biology, 2005).

So, we chose a target with pleiotropic effects — TGFβ overexpression in advanced tumours has been shown to correlate with tumour-induced immunosuppression, invasiveness and angiogenesis, and is associated with malignant progression. Blocking TGFβ therefore constitutes a multimodal anti-tumour approach. AP 12009 is a PS-ODN, referred to in the review as a first-generation PS-ODN, for the targeted downregulation of TGFβ2. Although the authors argue that the first-generation ODNs were the reason for current lack of clinical success, including insufficient potency, low stability and increased side effects compared to second-generation ODNs, we could show an excellent safety profile of this first-generation drug in both animal systemic toxicological studies[11] and phase I/II studies in high-grade glioma patients with local application to circumvent the blood–brain barrier[12–14] (P. Hau and K.J., personal communication). Furthermore, anti-tumour activity in phase I/II studies demonstrated TGFβ2 suppression with AP 12009 to be a promising therapeutic approach. A phase I/II study for the intravenous treatment of patients with other solid tumours is ongoing.

The future therapeutic success of antisense compounds will depend, as is the case with any targeted therapy, on the careful selection of optimal targets, dosing, schedules and clinical trial design. A comparison of clinical efficacy of antisense compounds with different chemical modifications for the same target is neither given nor suggested for future studies in the review. So, the judgment on the therapeutic usefulness of different chemical modifications of antisense compounds as implied in the review cannot be made based on comparing the results of one chemical modification with a particular sequence against a particular target (for example ISIS 3521/Affinitak against PKCα) with the results of another chemistry with a different sequence against a different target gene (for example OGX-011 against clusterin).

Comment

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