proliferation through the activation of LHRH receptors [3]. On the basis of these findings, we propose that the inhibition of prostate cancer cell proliferation induced by Cetrorelix may emphasise the presence, in this analogue, of agonistic properties which may appear when it acts directly on prostate tumour cells. This may indicate that Cetrorelix acts as a LHRH antagonist at the level of the pituitary, and as a LHRH agonist at the level of the prostate. If this is the case, a more accurate characterisation of the pharmacological profile of Cetrorelix activity on prostate tumour cells appears necessary to clarify its precise mechanism of action.

In conclusion, it is clear that Cetrorelix directly inhibits the proliferation of androgen-independent prostate cancer cells. However, the selection of the experimental protocols seems to be crucial for detecting its antitumour activity. Finally, and most importantly, the profile of the pharmacological activity of this compound at the level of the tumour needs further clarification before definitive conclusions can be drawn.

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Response from A.V. Schally, A. Jungwirth and A.M. Comaru-Schally

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We welcome the comments of Limonta and associates [1] regarding our article [2], but we do not consider all of the viewpoints expressed by them to be either definitive or necessarily correct. Firstly, the demonstration of the inhibitory effect of the modern luteinising hormone-releasing hormone (LH-RH) antagonist Cetrorelix on the growth of human androgen-independent prostate cancers *in vivo* was made not only in the DU-145 line as reported in our paper [2], but also in the PC-3 line [3]. At least 2 weeks of administration of Cetrorelix are necessary to obtain growth inhibition and the inconsistent results of Limonta and associates *in vivo* [1] are due, as the authors indicated, to a short treatment period. Further, growth inhibition of DU-145 tumours by the LH-RH agonist Zoladex does not correspond to well-established events in clinical settings, where all hormonal therapies, including LH-RH agonists, aimed at androgen deprivation in patients with advanced prostatic cancer do not prevent an eventual relapse. The patients eventually die, apparently of androgen-independent prostate cancer [2–4].

The question of a direct effect of LH-RH analogues, both agonistic and antagonistic, on various tumours is interesting and important and has received much attention from various investigators, including Limonta, Dondi, Motta and associates [1, 4, 5]. However, most effects *in vitro* are obtained only at very high concentrations and may not be applicable under clinical conditions. Previously, the authors described stimulatory effects of an LH-RH antagonist on the growth of DU-145 cells cultured *in vitro* [5] and now their letter reports that Cetrorelix, a modern and well-characterised LH-RH antagonist, inhibits DU-145 proliferation.

The conjectures of an inhibitory LH-RH loop on prostate cancers and especially of agonistic effects of LH-RH antagonists, like Cetrorelix, on prostate cancer are difficult to accept. An LH-RH loop may exist on various tumours and it has also been postulated by others, but it is more likely to be of a stimulatory nature, since LH-RH is not an antiproliferative hormone, like somatostatin. Such a stimulatory loop could in turn be inhibited by LH-RH agonists, antagonists and antisera to LH-RH, resulting in a tumour suppressing effect.

Very extensive pharmacological investigations have already been carried out on Cetrorelix [4, 6–8], although additional studies would, of course, be welcome. The efficacy of Cetrorelix in the treatment of patients with advanced prostate cancer has already been demonstrated [4, 6–8]. The use of antagonists such as Cetrorelix appears to be particularly appropriate in order to induce immediate tumour inhibition in patients with metastatic invasion of the spinal cord or metastases to the brain and liver, in whom the flare-up in disease that is occasionally caused by the LH-RH agonists, must be avoided [6, 7]. Thus, many favourable characteristics of Cetrorelix have already been established and studies in progress should define others.

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