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Editorial Comment

Science and serendipity in cancer research

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In our quest for more selective and more effective treatments of cancer, how likely is it that our human intellectual creativeness can do better than the processes of nature itself? Where is the balance between scientific hypothesis and serendipitous findings in drug discovery? Recent announcements about the human genome project have aroused great excitement throughout the scientific community, not least amongst cancer researchers. There is credibility in the belief that the potential now exists for making real progress in understanding the genetic make-up that leaves some people more prone than others to carcinogenic risks. New opportunities now present themselves for understanding why some patients respond to radiation and chemotherapy, where others are resistant. Particularly through micro-array technology, we can now ask literally thousands of questions in the same experiment — potentially saving years of traditional investigation. Enormously exciting, enormously expensive and enormously challenging. For those involved in funding research — academia and industry — the human genome project poses at least as many questions as it is potentially capable of providing answers. A key question is whether this 'new knowledge' will lead to new cancer treatments? Cancer researchers, by natural selection, have to be optimists, but intelligence (hopefully a co-variable) cautions about the timescale for seeing truly novel results. There is no quick fix! Funders and regulatory authorities beware, be warned and be patient.

We assume that greater scientific insight will lead to hypothesis-led progress — but in parallel with such enquiry, nature continues to offer us new leads serendipitously. Amongst the most significant developments in chemotherapy over the past decade have been the emergence of taxanes and topoisomerase I inhibitors. The origin of these new drugs is based in nature — the Yew tree for paclitaxel (taxol) and the Tree of Joy (*camptotheca acuminata*) for topotecan. Having identified activity through screening, science can then be applied to refine activity and (partially) understand mechanisms for such activity. Such is the case for a new group of marine-derived alkaloids, the first of which, ET-743, is the subject of a paper by M. D'Incalci's group in this issue of the journal [1] (pp. 97–105). ET-743 is a tetrahydroisoquinoline alkaloid isolated from *Ecteinascidia turbinata*, a tunicate that grows on the roots of mangroves found in the Caribbean Sea. At very low concentrations, ET-743 has been shown to have a wide spectrum of activity against human tumour cell lines, and the rapid phase I and phase II clinical trial programme has shown some most interesting results in refractory cancers, such as soft tissue sarcoma, osteosarcoma and melanoma [2]. In their paper, Erba and colleagues demonstrate some unexpected results from cell cycle and DNA repair experiments. ET-743 has exquisite sensitivity to cells in G1, but is relatively inactive in cells deficient in nucleotide excision repair (7–8 times less active than in control cells). Whilst the complete mode of action of ET-743 is not yet resolved, it is clear that this is, if not unique most unusual, and as such correlates with the interesting and unusual clinical results produced to-date. It is likely that the development of micro-array technology and information from the human genome project will allow us to further understand how the products of nature can be harnessed as useful anticancer medicines. Since naturally occurring products can be refined to produce cleaner medications, the competition to see whether or not man's creative abilities can prove superior to nature's own experiments, remains as keen as ever. Darwin would have loved it.

References

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2. Delaloge S, Yovine A, Taamma A, *et al.* Preliminary evidence of activity of Ecteinascidin (ET743) in heavily pre-treated patients (Pts) with bone and soft tissue sarcomas (STS). *Proc Am Soc Clin Oncol* 2000, **19**, 554a.

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