kinase inhibitor for cancer [5], has come out of subset screening rather than full HTS, making the use of HTS capacity a moot point. Unfortunately, we can not go back to the world of pure rational design because we need more leads than the old paradigm alone can provide. So, like addicts, we can no longer live without HTS, but we can not afford to live with it in its current form.

The question is, to be more successful does HTS need to be scheduled and more integrated into discovery processes? I suggest the effort is better spent in applying historically successful concepts of rational drug design to HTS, and worry about capacity and integration issues at a later stage. So, the idea is to do the right projects correctly, to concentrate on the science, and the ailing big pharma patient will soon be back in glowing health. That is, if you trust the doctor!

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## Targeting structured nucleic acids with antisense agents

During the past 20 years, the development of novel gene-targeting antisense agents have almost exclusively been evaluated on the basis of thermal denaturation measurements for $T_m$ determination of hybrids (duplexes) with short RNA or, more often, DNA targets. This is despite the fact that many biological targets might adopt secondary and tertiary structures and a simple $T_m$ determination does not necessarily reflect the thermodynamic (and kinetic) situation at a physiologically relevant temperature (37°C). Undoubtedly, this situation reflects the ease by which $T_m$ values could be obtained and the much more elaborate studies that are required for a thermodynamic/kinetic description of the system.

The importance of investing the effort in thermodynamic/kinetic evaluations is convincingly demonstrated by recent work on peptide nucleic acids (PNAs), as reviewed by Armitage in a recent issue of *Drug Discovery Today* [1].

The most illustrative example is probably the efficient hybridization of a PNA oligomer to a DNA hairpin despite the fact that the thermal stability ($T_m$) of the hairpin is dramatically higher (>50°C) than the $T_m$ of the resulting PNA–DNA duplex. Obviously, this is only possible because of the vastly different temperature dependence of $\Delta G$ (e.g. via different $\Delta S$ terms) stressing the need for actually determining these parameters.

Why not just avoid structured targets in biological targeting? Because structured targets, such as quadruplexes in DNA and hairpins and pseudoknots in RNA, are often biological recognition elements or switches, and the disruption of these structures could indeed elicit warranted biological and/or therapeutic effects. The Tat-binding Tar-element in HIV RNA is a notable example of a medicinally relevant RNA hairpin that has been successfully targeted by a variety of oligonucleotide derivatives. However, in this case, a thorough thermodynamic/kinetic analysis that could help to understand the results and thus to design better agents is lacking.

It is, therefore, most welcome and highly overdue that much more focus is put on detailed studies and understanding of the interactions of gene targeting 'oligonucleotide' agents with well-defined, structured DNA and RNA targets and the biological consequences of such targeting. The studies reviewed by Armitage are the first small steps along this road, and many more are encouraged.

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