the level of parallel processing, an approach that is considerably less expensive than investing too early in visionary new technologies.

Although continuing efforts at maximizing the efficiency of HTS are worthwhile, we must keep in mind the law of diminishing returns. If we abide by this law, we will be free to invest our efforts in the more compelling problems of drug discovery, for example, validating targets, improving times for lead optimization, increasing the rate of *in vivo* testing of optimized leads, and developing better experimental predictors of clinical safety and efficacy.

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Whither solid-phase chemistry? – Reply ▲

Initial letter: Terrett, N. (2000) *Drug Discovery Today* 6, 16

Response from Tony Baxter

I agree with much of the detail of Dr Terrett's letter. Certainly, preparing and screening mixtures of compounds is now seen as largely an outmoded concept. Improvements in synthetic methodology and, in particular, analytical techniques have ensured that the quality of single compound libraries has significantly increased and this, coupled with improvements in HTS techniques, has meant that screening mixtures is now largely redundant.

With regard to the use of solid-phase chemistry, I am not totally in agreement with Dr Terrett. Whilst solution-phase techniques have been more widely embraced within the library synthesis community (certainly at Oxford Asymmetry International, >50% of compounds are produced using solely solution-phase methods), it is still true to say that solid-phase chemistry plays a valuable role in the production of larger 'lead discovery' libraries and can have a significant impact on the speed in which certain lead optimization programmes can proceed.

The main issue with solid-phase chemistry is that it takes significant resources, training and time to build up a critical mass of knowledge and skills that can then be applied to various projects. The pharmaceutical industry, typically, does not have the time or resources available to dedicate to producing such a skill base and I suspect that it will be the larger service-based companies that will be the main users and beneficiaries of such technologies in the future. It should also be stated that solid-phase chemistry should not be seen in a competition context with solution-phase methods but more realistically as a complementary methodology in which both techniques have their place in the synthetic armoury of today's medicinal chemist.

We very much support the efforts of the academic community who are further developing new solid-phase methodologies that can be applied to industry-based synthetic problems. There is a view that such new methods and technologies represent new and better tools that can be added to the technical 'toolbox' and applied to an ever-increasing range of given problems.

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