High Throughput Screening

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Preface

Science is changing. As new methods evolve to generate data and create knowledge from it, the pace of discovery increases on an ever-steeper slope. One of the most fundamental changes is our ability and desire to approach the scientific method on a grander scale. Scientists can no longer afford to carefully isolate a single hypothesis and test it exhaustively before moving on to the next experiment. Now we must intellectually grasp an entire system, design experiments to test its many variables, and then probe them in a single multivariate experiment. Fortunately, innumerable new tools are being developed to facilitate this change.

The field we address in *High Throughput Screening* (HTS) has evolved in the midst of these changes and, I like to think, been instrumental in the creation of many of the enabling tools and methodologies. On the simplest level, HTS is the testing of large numbers of candidate molecules in a biological assay. However, when one considers that, at the time of this writing, large is generally accepted to entail over 500,000 samples in a period of only a few weeks or days, and that those numbers have doubled every two years for the past decade, the perspective changes.

High throughput screening requires the successful integration of four diverse scientific disciplines. The Biological sciences, including Pharmacology, Genomics, Molecular Biology, Enzymology, and Biochemistry, yield the targets and screens. A mastery of Chemistry is required to produce diverse libraries of compounds for testing as well as to optimize the lead compounds. Because of the level of industrialization of HTS, Engineering obviously plays an increasingly important role. Finally, the millions of data points produced must be mined for meaningful knowledge, so Information Technology becomes a lynchpin in the operation. Underlying all these is a need for logistical management and above all, a hunger for speed!

Arguably, the first high throughput screen took place in 1948–1949 when Charles Pfizer and Company organized a team of 56 scientists who examined 100,000 soil samples for antibiotic activity over an 18 month period *(1)*. This effort resulted in the discovery of Terramycin, which eventually captured half of the broad-spectrum antibiotic market—and the race was on. Pharmaceutical, chemical, and agricultural companies amassed collections (libraries) of chemical compounds from their efforts that were then reused in other discovery efforts. With the advent of laboratory robotics in the 1990s, it became

feasible to test these libraries in their entirety in screening targets and the field of HTS came into its own.

Although HTS has become an integral part of nearly every discovery operation, there is not a clear career path into the field or an associated body of literature. Until recently, nearly every scientist working in HTS had a unique story detailing precisely how they had arrived there. All that is changing. Training programs are beginning to appear and the techniques created in HTS are being used more and more frequently in laboratories outside the field. By providing both background material and real-use cases of HTS technology, I hope this manual will serve as an introduction for those seeking a greater understanding of HTS, as well as provide enough detail to be useful for scientists in established lead generation laboratories. Each author was asked to submit the chapter they wished they had been provided at the time they started in HTS. I hope that their efforts will be of use to you.

I would like to thank Celestine Pulliam, LouAnn Mitchell, and Wendy Spencer for their assistance in the preparation of this volume.

William P. Janzen

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