

Case Study – Cyclofluidic Ltd

In just under 3 years since commencing laboratory operations, [Cyclofluidic](#) have created an automated platform for iterative hit to lead SAR generation, achieving in 90 minutes, unattended, what typically takes 1 or more weeks in the more traditional pharma/biotech company.

On 1st February 2012, they put out a press release announcing that their platform has been used to design, make and screen potential drug molecules active against a specific target.

The Background

There is always pressure to lower both the cost and/or the time to market of a new drug. Research suggests that around 20 hit to lead programs are required for each drug that reaches the end of the process, costing on average \$166M. More than 50% of the attrition rate is due to characteristics of the molecule itself (pharmacokinetics, toxicity for example). It has been shown that drug structures are closely related to their leads and these leads to the hit series from which they were optimised, indicating that much of the success or failure of a potential drug molecule is laid down at this very early point in the drug discovery process.

In a typical hit to lead project, an iterative cycle (each comprising of designing the molecule, chemical synthesis, analysis and biological assay) is carried out to build a structure activity relationship. Each of these iterations can take from one to a number of weeks with the quality of the output dependent on the number of iterations that can be performed in the available time.

A system for significantly speeding this process and hence capable of performing many more iterations in a rapid, automated fashion, would therefore offer not only a time saving but also the real potential for improvement in the attrition rate.

This is what Cyclofluidic set out to achieve.

The Company

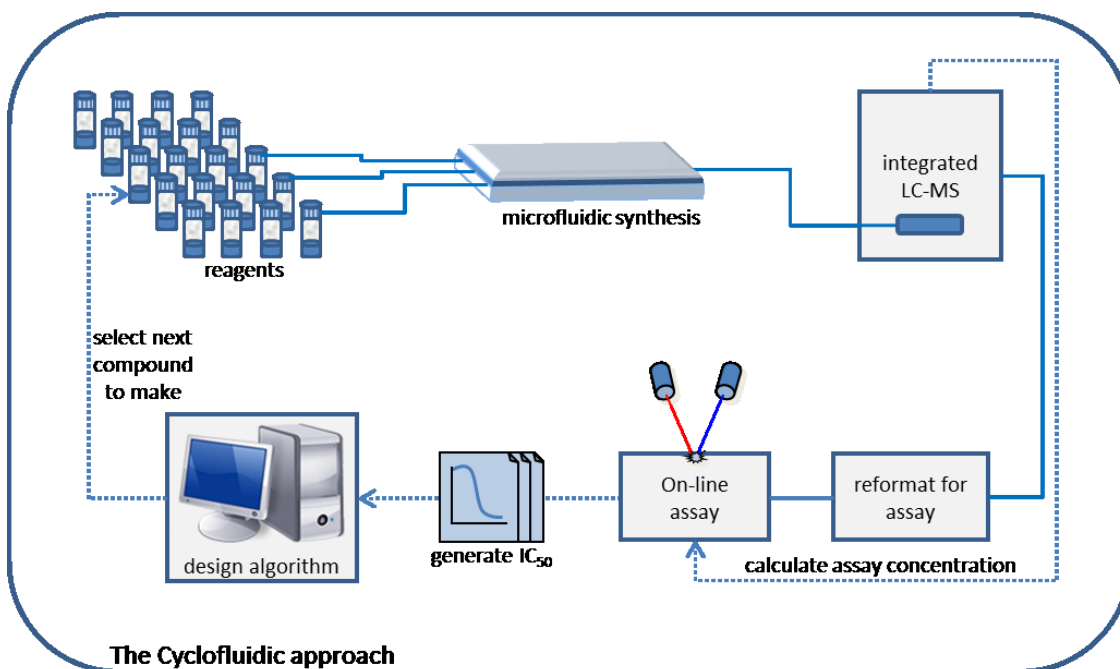
Cyclofluidic was formed in 2008 receiving the first tranche of funding on 1st December of that year. It has two equal shareholders, UCB Pharma and Pfizer, with additional support by a Micro and Nano Technology Capital Fund grant from the UK Technology Strategy Board (TSB). One of the stipulations of the TSB funding is that Cyclofluidic is open access, i.e. its capabilities are available to all and not constrained just to its owners.

In three years the company has come a very long way, addressing numerous technical challenges en route, and has recently announced the successful completion of their first fully automated experiment, generating drug like molecules active against thrombin, a target associated with stroke.

As Chief Operating Officer Dave Parry puts it “We got where we expected to be by now (in fact we’re ahead of schedule)”. But when asked which, if any of the technical steps along the way proved more difficult than expected, he laughs. “Most of them”.

The Approach

In essence, the Cyclofluidic approach is to create an automated iterative system which can synthesise candidate molecules, test against a biological assay and then, via a suitable algorithm, decide what molecule to synthesise next to get closer to the optimum.



The resulting platform consists of

- An automated reactant store giving access to 1 million potential molecules
- a [Vapourtec R Series](#) Flow Chemistry system
- HPLC purification
- Mass Spec Driven Collection

- ELSD for quantification
- A microfluidic chemistry biology interface module
- Biological activity determination using the online assay
- An integral design algorithm to determine the next molecule that should be made
- A master control program to control and schedule the various platform components, including the selection of synthesis and analysis conditions.

Typically the entire cycle time is 60 – 90 minutes with the flow chemistry reactions taking 10 – 30 minutes, the remainder for purification, analysis and the biological assay.

At the time of writing, Cyclofluidic have two such platforms, one a production platform that is run almost continuously for the generation of medicinal chemistry SAR data and a second used for continuing development work.

The longest completely unattended run that had been performed at the time of writing was 62 hrs having initiated the platform on a Friday afternoon and returned to the laboratory on the Monday morning to the continuing experiment.

Because the equipment platform is now readily scaleable, the long term throughput bottleneck is the availability of the experienced staff who can prepare a project for running on the system. And as you might expect, Cyclofluidic are currently recruiting.

Why Vapourtec ?

The choice to go for a Vapourtec R Series flow chemistry system was based on 3 criteria. .

Firstly, the decision to go for an off the shelf system. An in house “built from scratch” flow system would have theoretically given Cyclofluidic total freedom to define the entire performance envelope, but there would be a quantity of wheel re-inventing to be done, and it was important that there was already plenty of evidence of the effectiveness of the flow platform. With such a large (more than 120) installation base and a significant number (>50 at the time) of publications it was clear that the Vapourtec platform had been widely shown to be effective.

Secondly, the system needed to be flexible. The ability to easily reconfigure up to 4 reactors in any combination of temperature range, homogeneous or heterogeneous etc, meant that the Vapourtec system would be able to adapt to the different needs that may arise.

The other key consideration was the ease of software integration. Vapourtec's [automation API](#) enabled Cyclofluidic to develop an overall supervisory application in Matlab and interface directly to the [FlowCommander™](#) control program, setting parameters and controlling overall functionality at a fairly high level while leaving FlowCommander™ to deal with all of the low level implications of running the reaction.

A Typical Collaboration

The company is now at the point where the technology has been shown to be viable, and will be undertaking the first collaborations later in the current year.

Typically Cyclofluidic will start with one or more early hits at a target (some prior knowledge about the structure activity relationships at the target), would undertake the required preparatory work to validate the chemistry and ensure the assay was in a form compatible with the system, before initiating the platform run. This is where it gets interesting, with a rapidly evolving SAR landscape developing almost in real time and the ability of medicinal chemists either to review results or to influence the design and selection of the molecules to be made.

The Future

Improvements and enhancements to the system are of course continuously being worked on.

One area of focus is the expansion of the biological assay repertoire that can be achieved on the Cyclofluidic platform. To date the majority of the work has been with isolated proteins however drug discovery space is much broader than this. Cyclofluidic are currently exploring additional approaches including biophysical techniques such as SPR alongside planning activities to enable cell based screening assays on the platform. The latter represents a considerable and exciting technical and scientific avenue that the team hope to be able to address in the coming years.

And over the next year, it is expected that a number of collaborations will be setup, leading inevitably to growth of the company.

But as Dave Parry points out

“We already have plenty to do for the next year as it is !”