editorial

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French/European academic compound library initiative

Since the year 2000, French academic medicinal chemists took the initiative to collect molecules and natural extracts produced in their labs over the past years to catalyse scientific partnerships with biologists through virtual and experimental screening. This formatted collection was named 'Chimiothèque Nationale' (National Compound Library). After eight years of existence, the outcome in terms of development of collaborations at the chemistry–biology interface, as well as in terms of scientific and therapeutic innovation, has been very significant and demonstrates the relevance of this low-cost and modest 'bottom-up' initiative.

The scientific context and the project genesis

As early as 1997, chemists and biologists from the Illkirch campus anticipated that the deciphering of the human genome would change the research paradigm and lead to a new important challenge: understand the relationship between genes, the proteins they code for, the physiological functions of these proteins and their involvement in pathologies. In these early days of what will be called 'Chemical Biology', we and others [1] reasoned that small molecules would represent very valuable tools to explore this relationship and more particularly novel proteins functions in isolated systems, in whole cells, in tissues and *in vivo* in various species and conditions. These tools might also represent interesting lead compounds for drug design. Chemists and biologists decided then to set up an academic high-throughput screening (HTS) facility to accelerate the discovery of molecular probes that would catalyse novel or existing collaborations between biologists and medicinal chemists (PCBIS Screening Platform, see: http://ifr85.u-strasbg.fr/rubriques/PF/IntroPCBIS.htm). They knew that HTS would, at best, provide hits in their test system and that these hits would necessarily have to be optimised through a one to five year collaboration before reaching a sufficient level of efficacy, specificity and bioavailability. This led to the decision to screen compounds coming from academic medicinal chemistry laboratories rather than commercially available compounds or combinatorial libraries. Commercial compounds, or libraries coming from pure chemistry laboratories, present several advantages: their access is easy, the purity of the compounds is generally good and warranted, high amounts of compounds are usually available and they do not generate intellectual and industrial property problems. It will, however, usually be very difficult for a biologist to get a medicinal chemist involved in his project to analyse the hit list, to select the most promising templates and to optimise them into useful probes or leads. In contrast, a medicinal chemist will be very eager to enter into a scientific collaboration and to initiate a hit-to-lead optimisation around hits coming from his laboratory, in his field of expertise. In our minds, to be successful, academic screening should be a joint venture between two highly motivated scientists: usually a biologist working on 'his' targets and a medicinal chemist working on 'his' hits. We anticipated that this would be a key factor for success. We thus decided, in 1997, to create our laboratory compound library. Actually, we had no idea of the number and quality of the compounds that could be found in a typical academic medicinal chemistry laboratory like ours. We opened the drawers and the cupboards and we were able to find

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about 7000 flasks containing products prepared over 40 years by generations of scientists. About 1000 compounds could not be identified or were clearly decomposed. Another 1000 could not be used, because of intellectual and industrial property issues. Finally, 5000 compounds were identified, found in quantities greater than 30 mg, with a reasonable purity (statistically >70% on average). Despite the fact that this collection was structurally diverse and drug-like, it seemed too limited to provide hits in most screening campaigns. This prompted us to extend the initiative to other academic chemistry and medicinal chemistry laboratories in France, towards an academic National Compound Library.

From a laboratory to a National Academic Library

Several other collections existed in France, most of them sleeping in labs whereas a few others were already exploited through modelling-assisted mining (S Rault collection in Caen [2]), bio-guided fractionation (natural substances collection, ICSN, Gif sur Yvette [3]) or low-throughput screening (e.g. on kinases, L Meijer, in Roscoff [4]). Most contacted teams adhered to the strategy and an informal network of 20 different laboratories belonging to 17 French universities or institutions was informally created in 2000 and later formalised as a research consortium named Chimiothèque Nationale, sponsored by CNRS. The main missions of this consortium were the following:

- to network the French academic laboratories willing to create their compound library in a standardised format, compatible with HTS requirements;
- to promote the biological screening of these compounds via scientific partnership;
- to promote the optimisation of hits into useful pharmacological tools and/or preclinical candidates; and
- to manage the intellectual and industrial property issues.

The strategic and technical implementation developed as follows:

- The National Compound Library is a federation of local libraries. Indeed, we found it initially psychologically and technically difficult to centralise the different compounds since the chemists and their institutions have a strong ownership feeling with respect to their molecules.
- Molecules or plant extracts are stored in 96 well microtitreplates with 80 substances per plate, in DMSO, at a concentration of 10 mg/mL.
- The structures of the molecules or the origin of the plant extracts are available in a single, open database. The access to these data is managed via a central information system (see http://chimiotheque-nationale.enscm.fr/).
- Substances can be selected and requested by biologists via this portal. They will also have to describe briefly their project and the screening protocol. Their request is then transmitted to the chemists contributing to the library who will evaluate the scientific interest of the project and the degree of miniaturisation of the screening to avoid wasting compounds. They will generally accept to enter into a partnership and to provide their molecules or extracts but they might sometimes refuse depending on the spirit, objectives and terms of the collaboration.
- Compounds are free but the partners will have to cover the conditioning and expedition costs of the library.
- Before compound transfer, a generic material transfer agreement will have to be signed based on the general principle that biologists and chemists agree to share the intellectual property of any discovery issuing from the partnership.
- Once compounds have been screened, the results are shared and discussed by biologists and chemists who decide together of the future of the collaboration (publications, patents and licensing). In particular, the chemist has a right of first refusal on the hit optimisation process.

After eight years of maturation and practice, the whole process works satisfactorily. The National Compound Library currently contains 40,000 molecules and 11,000 plant extracts coming from 20 French academic laboratories. It is freely accessible online and most processes have been improved, based on experience. The objective is to reach 100,000 compounds within the next three years, in France. In terms of quality, statistics on about 20% of the molecules indicate that most compounds are indeed what they are supposed to be, with an average purity of 70% (LC–MS). We found very little degradation with time in the mother plates. It is also very interesting to note the excellent diversity and drug-likeness ratios over the number of molecules [5,6]. This was, in fact, expected from substances collected in several medicinal chemistry laboratories working around very different pharmacophores for many years. Most importantly, the scientific outcome of the activity around the Chimiothèque Nationale is very significant. As expected, more than hundred scientific collaborations between chemists, biologists and molecular modelling groups emerged around screening projects, bridging these disciplines. Hits often represent the seed of long-term partnerships going much beyond the simple screening phase. The first successes catalysed the development of several academic screening platforms in the country and the large-scale chemical biology is now fully integrated into research strategies. The balance sheet in summer 2005 recorded 150 screening campaigns, validated hits on 95 different projects, 6 participations in large European projects, 20 publications, 13 patents, creation of 9 start-up companies (e.g. Prestwick Chemicals, Domain Therapeutics, Phytodia and so on) and one compound in the clinic. These screenings led to the development of novel technologies (such as the FRET-based screening of fluorescent libraries for receptor deorphanisation [7a and 7b]), to the discovery of novel scientific concepts (such as functional allosteric switches [8] or splicing modulators [9]) or to the discovery of novel therapeutic agents such as Minozac, currently in Phase 2 clinical trials for Alzheimer disease in partnership with Chicago University [10].

From a French to a European compound library

We have recently undertaken to extend the French library to the European level to further increase the size and diversity of the library as well as the network of scientific partnerships with European biologists. Around Sylvain Rault as coordinator, medicinal chemists from 12 European countries have agreed to join the network. The project was selected by the European Integrated Infrastructure Initiative (I3) Committee, but not funded. The European academic libraries have now another opportunity to emerge, merge and grow within the EU-Openscreen project recently labelled in the European Strategy Forum on Research Infrastructures (ESFRI) 2008 Roadmap (coordination: Walter Rosenthal, Ronald Frank).

Bottom-up versus top-down

In conclusion, the French compound library was born in 1997–2000 at the initiative of a few medicinal chemists who believed in Chemical Biology and in the scientific interest of HTS in an academic environment. With extremely limited financial support from the institutions (40,000 €/year for the whole network. . .) but with a strong and durable commitment of the chemistry and biology laboratories, this very modest bottom-up initiative proved to be efficient and cost-effective in terms of research networking, scientific production and technology transfer. Although on a very different scale, it would be interesting to put this outcome in regards of the NIH Molecular Libraries Initiative.

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