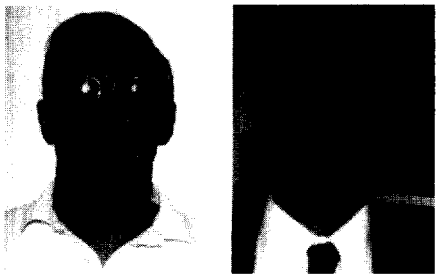
Combinatorial chemistry consortia for cost-effective drug discovery



Is collective cost sharing the way forward?

Combinatorial chemistry technology is an important component in the drug discovery process. The founders of Systems Integration Drug Discovery Company (SIDDCO) recognize that many pharmaceutical and biotechnology companies do not have sufficient resources to mount a combinatorial chemistry program or to recruit the talented chemists needed to run such a program. SIDDCO's Combinatorial Chemistry Consortium spares the resources of its consortium partners and was conceived with a vision about how drug discovery technology might be advanced and transferred in a form that would satisfy the combinatorial chemistry needs of several pharmaceutical companies. The consortium comprises companies with a common purpose and has no outside controlling capital interests. While pursuing this novel funding paradigm, the company has financed its operations entirely through its collaboration contracts and the equity sold to consortium partners.

The consortium rationale

A consortium is a group of companies that collectively share the cost and development of a technology product. In SIDDCO's Combinatorial Chemistry Consortium, each member shares the development costs and the resulting combinatorial chemistry know-how. A consortium arrangement is ideal for this particular technology niche because the rate-limiting step in a combinatorial chemistry program is the development of new chemical reactions and the validation of building blocks that are suitable for library construction. An individual chemist may need anywhere from several months to 1 year to explore and validate a chemical reaction that is suitable for combinatorial exploitation. The application of many chemists to the development process gives some assurance that a reasonable number of chemistries will be advanced and become available for combinatorial library synthesis. The consortium development team achieves this 'critical mass'. This team is collectively funded by the consortium and is able to satisfy the long-term development needs of each partner. Each consortium partner can utilize all of the reactions developed by this large group of chemists. Because each reaction is developed by an individual chemist, of which there are several per consortium partner, each partner can focus on its production needs while leaving the longer-term development needs to be satisfied by the work of the rest of the development team. The partner is thereby free to focus attention on its immediate synthetic needs by employing specific chemical reactions obtained from the group effort. The consortium thus satisfies both the immediate and long-term chemistry development goals of its members. Furthermore, the consortium eliminates the need for member companies to mount an internal combinatorial development effort and thereby allows them to focus on producing applied combinatorial chemistry libraries.

The technology being developed and transferred to each consortium partner includes a searchable reaction database of the optimized reaction conditions and validated building blocks. Methodologies for classifying library diversity, searching and designing libraries, automating synthesis, quality control and structural analysis are also a shared valuable resource. A single validated chemical reaction scheme can be used to synthesize hundreds to millions of possible compounds. The medicinal chemist can choose the specific building blocks to produce a manageable sized library of compounds of greatest potential application for a specific drug discovery target. Separating applied and optimization chemistry from development chemistry focuses management attention and increases productivity. The separation of activities enables the consortium partners to concentrate their efforts on the applied synthesis of libraries and the optimization of compounds for specific target programs rather than on the development of chemical reactions, automation and other

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shared know-how of the combinatorial chemistry process. Through the consortium, each partner accesses a pool of medicinal chemists dedicated to the drug discovery process and a dedicated project team that works only with that partner under complete confidentiality.

Managing confidentiality

As part of the consortium arrangement, SIDDCO supplies each consortium partner with the confidential services of a small team of medicinal chemists dedicated to designing and synthesizing libraries for that partner. Thus, the consortium partners do not have to expose any confidential information relative to the structure of compounds or drug discovery targets to other consortium partners. The medicinal chemists working on the applied projects of a particular consortium partner collaborate solely with that partner and are able to maintain confidentiality of structures and target information.

Ownership of compounds

Each partner owns the libraries and active compounds contained within the libraries synthesized for them. Any compound with commercial development potential is patented by the consortium partner and can be taken to the marketplace without any contingency milestone or royalty payment. The cost of consortium membership is fixed, does not escalate and is not burdened with downstream payments.

Consortium management

Consortium management is shared equally by the company and its consortium partners at both the executive and the scientific level. Each partner elects a member to the Consortium Executive Committee. In addition, each partner participates in oversight and direct management of the shared combinatorial chemistry database development and, with SIDDCO, manages a dedicated team of chemists responsible for the confidential design and production of partner-exclusive libraries for screening and lead optimization. Each partner can increase the size of its dedicated team to match its own strategic purpose. The consortium dedicated team can be used to supplement an internal chemistry team or to avoid hiring a team of chemists. At any time, the consortium partner can establish its own chemical team by utilizing the routinely transferred technology or through the technology training program.

SIDDCO is successful in attracting experienced medicinal chemists with combinatorial chemistry experience because it offers chemists the opportunity to be part of a large chemistry department in a small company entrepreneurial environment. The company itself is a consortium partner and has the same business development objectives as its partners. As a consortium partner, it depends upon the productivity of the shared development team in the same way as any of its contracted partners. Thus, each partner is assured that SIDDCO management attention is focused on the combinatorial chemistry objectives and on producing the best possible product. This arrangement assures that there are no hidden agendas. Each consortium partner knows, approves and evaluates the objectives and performance of the individual SIDDCO scientist on its dedicated chemistry team. Collectively, all of the consortium partners approve and track the performance of these chemists on the technology development team. Thus, direct performance accountability is achieved.

Sharing technology

By pooling the resources of each consortium partner to fund the common development effort, each partner obtains a sevenfold gain in technology development. Each partner pays for the activity of three people on the development team and gains the collective productivity of its 21 members. This resource enables consortium members to avoid the need for an internal combinatorial technology development program and instead to focus on building an applied combinatorial chemistry drug discovery team. Furthermore, SIDDCO takes on the capital risk of technology development and validation of hardware for synthesis and analysis, and the software for diversity analysis and computational chemistry. The transfer of combinatorial chemistry technology to partners is also facilitated through a visiting scientist program. Each consortium partner can build an internal chemistry dept by harnessing the technology being transferred to them.

Sharing libraries

The Combinatorial Chemistry Consortium provides a mechanism for the sharing of libraries. This library archive provides an additional pooling or leverage of the resources and assets of the consortium that partners can take advantage of if they choose to do so. SIDDCO maintains and resynthesizes archived libraries as requested by any consortium partner on a proportional quid pro quo basis.

Summary

The consortium approach has many advantages. Pooling of resources is a very cost-effective way to achieve the common objective of developing combinatorial chemistry know-how. Each partner receives a financial leverage of its research funding and the combined funding enables a critical mass of talented scientists to be hired and made available to its partners. Partners also gain by sharing libraries and by dramatically reducing the cost of compounds synthesized for drug discovery. Partners have direct management participation in the consortium at both the executive and scientific management level. In addition to sharing resources, the consortium provides its partners with several exclusive services, including the synthesis of libraries of new compounds and their optimization into clinical candidates. The synthesized libraries of compounds and any biologically active compounds identified by the consortium partners are owned by that partner and are not subject to contingency or royalty payments.

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