Monitoring performances and ensuring quality in drug discovery alliances

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As the trend towards mergers, alliances and take-overs in the pharmaceutical industry grows, monitoring the performance of outsourced programmes is increasingly under the spotlight. For a small company, management of partnership programmes is a key contributor to business success. This article outlines some of the chief parameters and milestones for small companies, which are crucial to maintenance of the effective research alliances that are the life-blood of their business.

The pharmaceutical industry today is under increasing pressure to discover new drug leads more quickly and efficiently than ever before. The opportunities for outsourcing new drug discovery activities are increasing (Figure 1), and large multinational companies often see these as a chance to tap into the innovation and scientific creativity of smaller organizations.

For such small companies, monitoring performances and ensuring quality in research alliances is crucial. Management of all stages of the alliance from the first contact, through establishment of the business agreement, programme initiation and operation, to ensuring outputs and maintaining project progression, is the key to success. Xenova's experiences in conducting these activities to establish alliances in natural products drug discovery will be described.

Establishing the technical basis for collaboration

When negotiating drug discovery partnerships it is important that both parties are working toward mutual objectives and focusing on the synergies and complementarities between their organizations, which will ultimately lead to success. The small company has to understand the key needs of its prospective partner and should provide high-quality, flexible technical and business proposals to fulfil these needs while not losing the focus that has hitherto enabled it to succeed.

Once the companies have established the mutual benefits of working together, the all-important budget negotiations begin. In this phase of the business discussions smaller companies need to be aware of the decision-making processes within large companies, and should ensure that contact is maintained with key influencers so that any last-minute clarification can be provided rapidly. It is wise to be aware of prospective pitfalls in both the technical and budget proposal, where possible, and to have a broad understanding of financial and other constraints under which the larger partner may be operating. In the final analysis, the partnership proposal must represent a win–win opportunity for both partners if an alliance is to succeed in the long term.

This phase of an alliance can take months, or perhaps even years to conclude, and the small company must be prepared for personnel or business strategy changes within the larger organization and respond quickly to these. As the technical and business proposal will establish the nature of an alliance that may last for several years, the small company must also be prepared to contribute its own ideas for evolution of its processes and technologies, and to demonstrate

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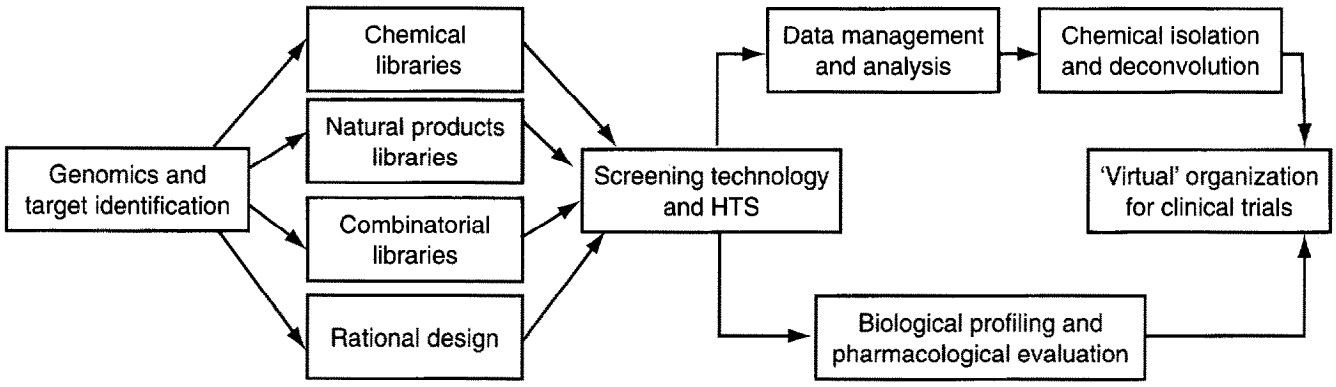

Figure 1. *Opportunities for outsourcing drug discovery functions.*

to its prospective partner how it too can benefit from these. In such cases, the small company must emphasize how rapidly smaller organizations can respond to a changing external environment to remain competitive for the mid- to long-term future.

Partnership agreement

Once the small company has secured an intent to collaborate from the large company, a partnership agreement is required. This agreement should cover a number of areas in detail, and where possible, the small company should ensure that the needs of the large company in terms of productivity measurement and milestone management are met.

The partnership agreement should cover agreed research protocols and establish parameters for exchange of research results and information. Areas such as establishment of confidentiality, product development, intellectual property and licensing of proprietary information and technology for the relationship should all be addressed.

One key area that should be included in this part of the agreement is how the programme will operate and be measured for quality and success. In Xenova's alliances, effective management of our drug discovery partnerships has been achieved by appointing experienced programme managers in both companies to act as key contact points between the two organizations. The programme managers then appoint project leaders to drive the outputs from individual targets and ensure effective establishment of communication networks both internally and with the partner. In natural products drug discovery experienced, multidisciplinary project teams are required that use all of the tools at their disposal to discover new molecules that fulfil the agreed criteria. To ensure effective teamwork, such teams are established by the programme manager and the project leader and include people with relevant expertise from microbiology, phytochemistry, biology and natural products chemistry groups.

Criteria for success must be established when drawing up the partnership agreement. These may be defined by two key parameters: the achievement of certain milestones in the discovery process that may trigger payments (i.e. the inputs), and measurement of productivity from the programme (i.e. outputs). Agreement and measurement of milestones is usually straightforward and is used as an indicator of the small company's ability to operate in accordance with contract specifications (Figure 2). Measuring productivity or outputs of the programme can be more difficult, so where possible criteria for definition of success should be agreed before a programme begins. For example, in the case of a natural products drug discovery alliance, the initial objective is the discovery of lead compounds. It is therefore wise to define what both parties would require of such a compound before a programme begins. This definition should address chemical novelty, potency and specificity against a disease-relevant biological target. If the target is unknown at this stage of the partnership, the definition of a lead should be addressed in general terms to form the basis for later discussions.

The final stages of the agreement should cover the expected duration of the proposed programme, and establish conditions for its termination should this be necessary for either company.

Programme initiation and management

At the beginning of a partnership programme the expectations of both partners are high. The programme managers

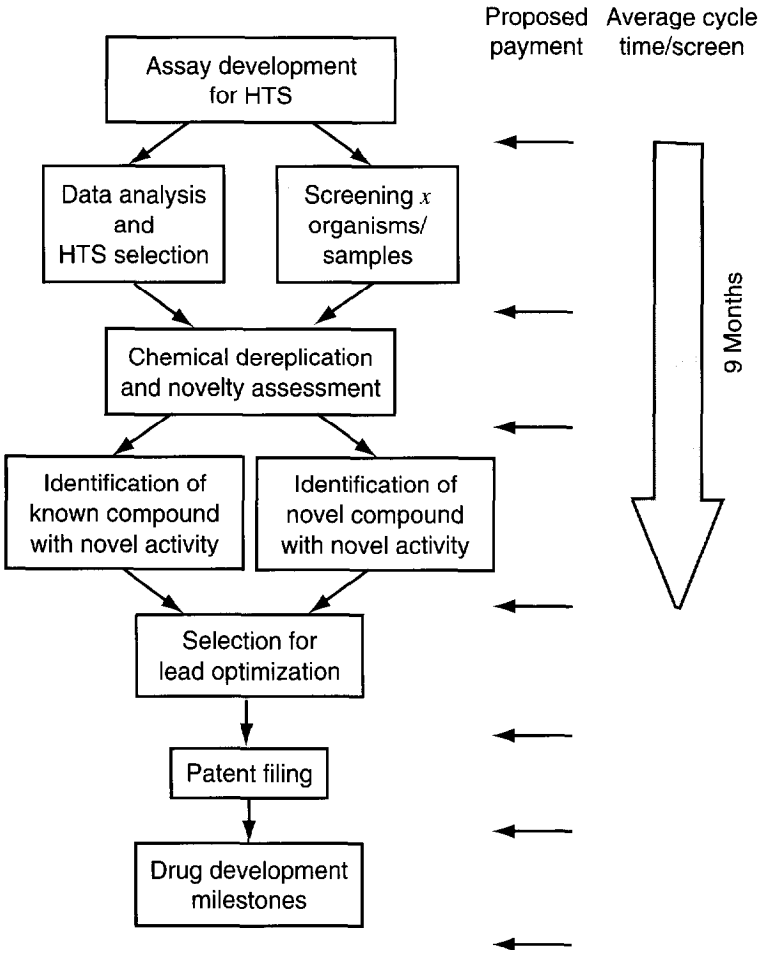

Figure 2. *Paradigm for milestone management in partnership agreements.*

in both companies are committed to its success and the project leaders are highly motivated to drive their project teams hard towards achieving the agreed outputs. With the additional enthusiasm that is generated by the prospect of drug hunting for a new target, management of resources and costs can be easily overlooked. It is therefore the function of the small company programme manager and project leaders to manage their internal resources within budget and in a cost-effective manner, while achieving agreed payment milestones and maintaining the quality of the inputs to, and outputs from, the programme.

To ensure that this remains a part of the focus of the small company's efforts, and to monitor the performance of the programme as a whole, regular contact between the programme managers by telephone, fax and e-mail, and the establishment of a communications network between other interested parties is essential. However, to ensure that the flow of information is consistent, all contacts should be reported to the programme manager (Figure 3). Regular programme meetings, which should be held at least every six months and at alternate locations, provide a great impetus for focusing both partners on the task in hand and ensuring that their resources are appropriately aligned. These meetings should address scientific matters, costs, quality assurance and project timelines, and address inputs and outputs with respect to the partnership agreement. They also provide an effective medium for negotiating and adjusting research protocols and payments if this is required.

Defining and managing success

With all partnership programmes it is possible to define success in a number of ways, and in drug discovery the early definition of the requirements of a lead compound is often difficult and therefore not captured by the contractual agreement. As the knowledge of biological targets is expanded during a programme, and the success of screening alternative libraries or perhaps even designing inhibitors becomes more measurable, the early definitions of a lead can change. For example, if a number of libraries are tested against a biological target and the best 'hit' identified has an IC_{50} of 30 μM and a relevant biological profile, this may be worthy of evaluation as a potential lead molecule. Also, if an interesting molecule is discovered using a cell-based signal transduction assay and the molecular target is poorly defined, a number of additional steps may be required before verification of its lead compound status.

Aside from these considerations there is also the possibility of staff in the large company suffering from the 'not invented here' (NIH) syndrome, i.e. there is a reluctance to invest additional time and resource on outsourced projects. The small company may then find itself in the position where it needs to add value to its products – in this case compounds – to encourage the large company to pursue them further.

Managing this stage of a relationship is crucial and reference should be made to the pathway for compound selection and progression in the original partnership agreement.

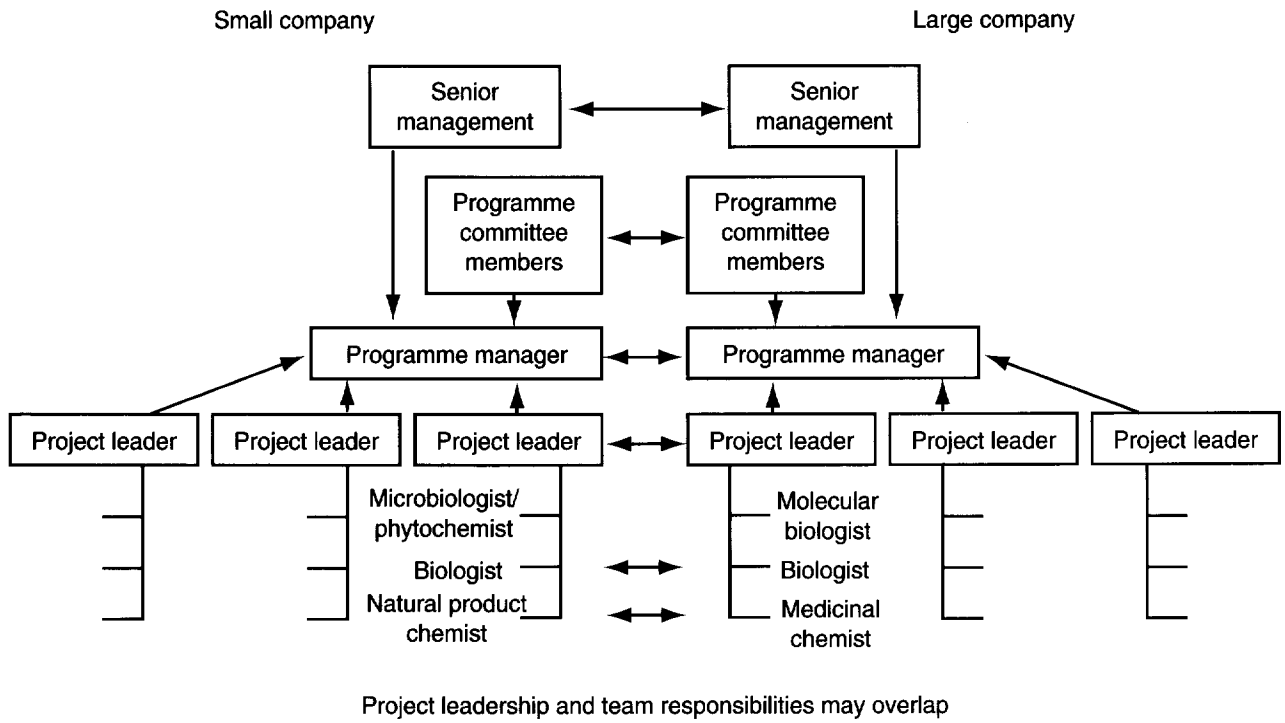

Figure 3. *Typical communications network for a natural products drug discovery partnership.*

At this stage, such projects need champions, both in the small company and the large company, and these champions should be totally committed to pursuing the project to the mutual benefit of the partners. The extensive network and establishment of relationships at the earlier stages of the alliance now come into play. In such a situation, the small company needs to ensure that while it retains its intellectual commitment to the programme, it does not fall into the trap of incurring extensive costs in its attempts to win over the large company. Key players in the large company who understand the situation of the small company then need to use their influence at all levels to ensure success and obtain the buy-in of appropriate personnel to ensure that compounds are progressed in accordance with original commitments.

Win–win situation

Once a drug lead has been accepted for further evaluation and development, the development milestones agreed in the original proposal (Figure 4) should be interrogated to ensure that criteria for success at each stage are relevant to the compound(s) identified. The alliance partners should establish parameters to maximize the chances of success of the programme, but at this stage it is likely that the majority of costs for this work will be borne by the larger partner.

The initial studies in this phase should address the chemistry, pharmacokinetics and efficacy of the lead. It may also be desirable for both companies to evaluate synthetic intermediates generated in a broad range of screens. This has the dual benefit of determining whether any new compound series are of value against other targets, and also continues to interrogate the specificity and selectivity of new leads. This stage of the programme may involve the use of traditional medicinal chemistry or combinatorial chemistry techniques and animal models, which could again be outsourced to a third party. In this case appropriate agreements will need to be established, as previously described.

Once the agreed milestones have been reached, the joint programme committee, which may by now comprise teams with different expertise, should be responsible for selection of a candidate with suitable characteristics for entry into Phase I clinical trials.

From this point on, the large company will be largely responsible for carrying out and monitoring the work, and the small company should be kept informed of progress so that drug development milestones and revenues can be

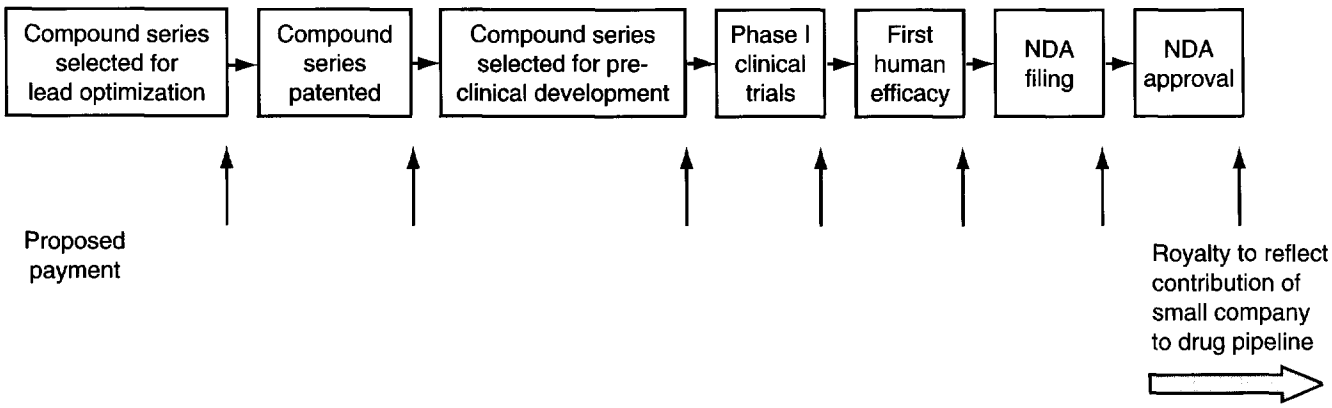

Figure 4. *Possible milestones for lead and drug development.*

projected and captured to the satisfaction of both parties. At this point the companies will benefit from the attention devoted to drug discovery pipelines and new drug launches in the pharmaceutical press. Once the new drug has been launched the alliance partners will have achieved the ultimate win–win situation and the benefits of outsourcing drug discovery activities will be reaped.

Conclusions

Research alliances are undoubtedly an attractive opportunity for companies with complementary skills and technologies to pursue new routes to drug discovery. The key to the success of such alliances is establishment of mutual understanding and fulfilment of needs, a well thought-out partnership agreement, and firm management of programmes at all levels. If these criteria are met, using such research alliances will fulfil the needs of large pharmaceutical companies to reduce the time and cost of discovery of new drug leads, enhance their drug discovery pipelines, and allow them to invest more resource in the increasingly expensive process of drug development and launch.