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Strategic alliance management: lessons learned from the Bayer–Millennium collaboration

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Alliances play increasingly important roles in drug discovery and development – both complementing the companies' internal technology and competencies, as well as providing partners with access to pipeline products and capital. The purpose of this feature article is to share our experience in managing the research collaboration between Millennium Pharmaceuticals (http://www.mlnm.com) and Bayer HealthCare AG (http://www.bayerhealthcare.com), one of the largest pharma/biotech alliances.

We describe the set-up of the collaboration and outline key success factors. These include complementary core competencies, continuous involvement of key executives from both parties, a dedicated and collaborative leadership, a close collaboration between scientists, research management, business development and patent and legal people, and a commitment to adapt the partnership to changes in the scientific environment.

For decades the entire pharma industry has focused on a limited number – about 500 – of drug targets [1]. Owing to advances in molecular biology and genome technology at the beginning of the 1990s, it was, for the first time, feasible to discover a large number of novel genes from the human genome and to establish an intellectual property position (IP) on the use of those genes as drug targets or for diagnostic purposes. Both public and private initiatives were established to provide access to all human genes. The publicly funded Human Genome Project (HUGO; http://www.gene.ucl.ac.uk/hugo) was started in 1990 with the goal of completing the whole sequence by 2005 [2]. A competitive, privately funded genome project aimed at completion of the sequence as early as 2001 [3]. In 1994, the initial estimate of the number of genes in the human genome was between 50,000 and 100,000 [4,5]. Later estimates in 2000 ranged from 30,000 to 140,000 [6–8]. Whereas in 1980 only three gene-sequence patents were published, in 1995 the number had increased to 435 [9]. Companies rushed to patent DNA sequences [10] and the first patent on Expressed Sequence Tags was issued in 1997 [11]. As a result, having access to intellectual property on genes as potential drug targets was considered to be crucial for every company involved in drug discovery, including Bayer.

Strategic considerations at Bayer that lead to the deal

Bayer was founded in 1863 as a chemical company and has a track record of pharmaceutical discoveries dating back 100 years. Traditionally, Bayer's focus was on medicinal chemistry and pharmacology, but by the mid 1990s Bayer wanted to take part in technological developments involved with the human genome and boost its investment in pharmaceutical research to increase productivity. Bayer had developed an HTS platform that enabled it to screen compounds against a large number of novel disease targets and invested heavily in enhancement of its compound library. Research leadership at Bayer perceived that significant synergies might be created by combining Bayer's internal strength in small-molecule discovery and development with access to novel disease targets that were derived from the application of genomics technologies. Furthermore, Bayer identified access to intellectual property from the human genome as a strategic priority.

Bayer decided to 'buy' rather than 'build' genomics technologies, because it wanted to have immediate access and believed that a big pharma company is not necessarily the best organization to manage fast emerging and changing technologies, such as HTS or array filter production. Such technologies are historically better developed and implemented by special biotech companies, whose business model is more aligned with development and implementation of technology services. In addition, Bayer wished to keep its focus on 'compound-related' technologies, such as HTS, medicinal chemistry and pharmacology. Consequently, Bayer developed a series of criteria for evaluation of prospective target discovery partners. These were:

- A proven experience and a competitive position in various genomics technologies;

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Table 1. Overview of the Bayer–Millennium alliance

Program term	**5 years (1998–2003)**
Objective	Identification of 225 therapeutically relevant, proprietary drug targets; Immediate access to and transfer of genomics technologies
Disease areas	Cardiovascular diseases, hematology, liver fibrosis, pain, cancer, osteoporosis, virology
Targets classes	Receptors, enzymes, ion channels
Investment	Up to US$465 million including 14% equity investment in Millennium

- A validated and fully integrated technology platform (including the ability to incorporate emerging technologies);
- Breadth of disease area expertise, and;
- An experienced management team with a track record of working successfully with big pharma.

After extensive due diligence, Bayer selected Millennium Pharmaceuticals, of Cambridge, MA, USA, as the partner that best met these selection criteria.

Strategic considerations at Millennium that lead to the deal

By 1998, Millennium Pharmaceuticals had established itself as a premier biotech organization with a track record of delivering on ambitious goals. The company had built an integrated target discovery and early-stage drug discovery technology platform that was unique within the industry in its depth and breadth. Moreover, Millennium had created an entrepreneurial culture that embraced change and believed strongly that innovation in drug discovery would be driven by leadership in disease biology and facilitated by the industrialization of genomics-related technologies. Collaborating with Bayer provided Millennium with an opportunity to maximize value creation from its technology platform and disease biology infrastructure that was already largely in place, while at the same time providing an opportunity for the company (which was developing its drug discovery capabilities) to participate directly and indirectly in early-stage drug discovery on a large scale.

The ambition of the collaboration – industrializing drug discovery

The goal of the 5-year Bayer–Millennium collaboration was to identify in multiple disease areas 225 novel, IP-protected drug targets, that were exclusive to Bayer and could be subjected to HTS for drug discovery (see Table 1 for an overview). If a target could not be successfully configured into a high-throughput screen, it was replaced by another target. Based on probabilities of success for downstream drug discovery processes available at that time, 225 high-throughput screens were predicted to result in 30 preclinical development candidates. In contrast to previous biotech/pharma alliances, the goal of the collaboration was not only to discover exciting disease biology, but also to generate – in a predictable and industrialized manner – drug targets that could be advanced immediately into the drug discovery process, similar to supply chains in other industries. Therefore, the collaboration focused on a 'Target by Class Drug Discovery Approach', whose primary objective was to provide a pipeline of novel (by disease annotation and possibly also by sequence) targets belonging to protein classes for which there were precedents for successful drug discovery efforts. Specifically, G-protein coupled receptors, ion channels, nuclear hormone receptors and selected enzyme classes were given highest priority, although there was some flexibility for considering additional target classes if particular members showed promise. Novel disease annotations for these sequence-novel genes, as well as for known genes falling within 'Targets by Class' priority categories, were driven by a combination of tissue/cell-specific expression and abnormal expression in diseased human or animal tissue, and were linked by a disease hypothesis to the known or predicted mechanistic properties of each candidate target.

The collaboration's initial assumption was that to arrive at 225 targets (proteins falling within 'Targets by Class' priority categories with plausible disease hypotheses and corresponding IP position), about 10 times that number of genes (i.e. ~2200) would need to be analyzed. This required the industrialization (i.e. adapted to high throughput and with production-style, rigorous quality control standardization) of a suite of technologies, such as cDNA library production, mRNA expression profiling, quantitative PCR and *in situ* hybridization. In addition, clear responsibilities and quantitative deliverables for each step of the process needed to be defined. Fixed timelines were established for almost every step, from gene identification to preclinical candidate presentation, and if these were not met, the particular gene/project was terminated. In addition to the demands that these throughput and quality-control requirements placed upon Millennium's technology experts, disease area scientists had to quickly adapt to parallel evaluation of data sets for many more candidate genes than their prior academic training or industrial experience had exposed them to. In other words, the ambition was to have both a high throughput approach and a strict focus on successful projects.

A new approach to target discovery – changing mindsets and culture

Another major challenge for the collaboration was to ensure that the biotech culture of Millennium was aligned with Bayer's big pharma culture. Millennium's ambition was to 'Transcend the limits of medicine' by using genetic and genomics approaches and to provide the right patient with the right drug at the right time. Furthermore, Millennium, in its short history, had already completed several collaborations and a successful IPO, securing hundred of millions US dollars in funding. Bayer scientists, by contrast, had decades of experience in medicinal chemistry and pharmacology and were rather skeptical about the utility of the new genomics technologies. To cope with these challenges, regular (at least quarterly) face-to-face meetings between Millennium and Bayer scientists were essential and helped to convince the Bayer scientist how the new technologies could help them in finding new medicines. Inclusion of external expert advisory panels for each of the collaboration's disease indications helped to provide an outside view both from a scientific as well as a clinical perspective. In addition, joint technology development teams were established to facilitate mutual learning from each company. To facilitate communication, data analysis and candidate target evaluation, a team of Bayer scientists (one for each of the collaboration's disease areas) worked onsite at Millennium. This co-location and cross staffing ensured successful technology transfer from Millennium to Bayer and directly benefited the visiting Bayer scientists themselves. Furthermore, the presence of these scientists from Bayer benefited Millennium in understanding how an established pharma organization brings its past drug discovery experience to influence future target selection.

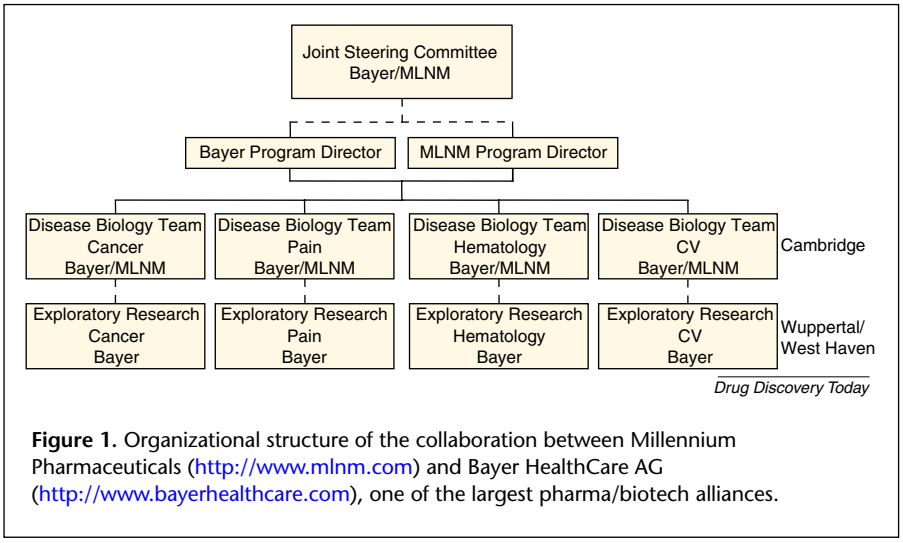

Figure 1. Organizational structure of the collaboration between Millennium Pharmaceuticals (http://www.mlnm.com) and Bayer HealthCare AG (http://www.bayerhealthcare.com), one of the largest pharma/biotech alliances.

The deal structure

The collaboration was structured in such a way that each party was responsible for those aspects of the drug discovery and development process that matched with their core competence. Millennium was solely responsible for the discovery of drug targets. Assay development activities for HTS were shared between the parties, while Bayer was responsible for all subsequent components of drug discovery – HTS, lead discovery, lead optimization, development and marketing. Under the terms of the deal, Millennium is entitled to receive up to about US$368 million consisting of guaranteed funding and performance fees. First, Millennium received license fees for Bayer accessing and transferring its genomic technology and know-how. Second, Millennium received annual payments to build and maintain the infrastructure required to identify a large number of targets. Third, Millennium received performance fees for delivered drug targets and configured assays for HTS. In addition, Millennium will receive royalties on all products that originated from the program. Bayer received from Millennium an exclusive license on Millennium know-how and patent rights to use the identified targets in drug discovery and to develop and commercialize derived compounds in one or more indications. If a target failed after successful assay development, Millennium had an option for a non-exclusive right on know-how and patent rights generated by Bayer on this particular target including chemical matter, if available.

Independently, Bayer made an equity investment of about US$97 million to participate in the development of Millennium.

Management of the alliance

The alliance involved approximately 200 people from each company that needed to be aligned to deliver on the challenging goals. The alliance was managed by two program directors, one from each organization. The main responsibility of the program directors was to ensure delivery on goals and to manage the collaboration in such a way so as to achieve maximal value from the collaboration to both companies. The program directors reported directly to a Joint Steering Committee (JSC; see Figure 1), comprising three members of senior management from each company, to whom they provided quarterly status updates and strategic recommendations. JSC-approved strategies were subsequently implemented by the program directors who worked in close collaboration with disease area and

technology line management within their respective organizations. Such a small group of senior managers supported fast and collaborative decision making. During the collaboration, staff learned that it was crucial to have the program directors spend sufficient face-to-face time (one week a month) to establish a trusting relationship and joint ownership of the collaboration. Although decision-making was generally undertaken jointly between these two individuals, the Bayer program director had the final approval as to which targets should be accepted into the program.

To implement target discovery and nomination within the collaboration's disease areas, corresponding biology teams were established. Each disease biology team was headed by a lead scientist from each company, who together were held jointly responsible by the program directors for the successful achievement of goals within their specific area of the collaboration. The lead scientist from Bayer was also responsible for integrating the disease biology program into the exploratory research program for the different indications at the different Bayer Research sites. Supporting these lead biologists was a multi-functional team of biologists and technologists (representing functions such as molecular pathology, transcriptional profiling, high throughput sequencing and bioinformatics) from Millennium. Data were shared among and between teams through an extensive, web-based environment that enabled facile navigation between internal and external sites.

Evolution of the alliance

The contract between the parties stated clear quantitative and qualitative goals that were associated with financial figures. Both Bayer and Millennium accepted the speculative and ambitious nature of the collaboration and there was an understanding from its initiation that the collaboration's goals, strategy and tactics would need to evolve in the light of joint experience and external scientific developments. For example, Bayer and Millennium jointly predicted that the sequence of the Human Genome would not be completed before 2005, whereas this was actually achieved in 2001 [12,13], which marked the end of opportunities for new sequence discovery. In response to this important development, the parties agreed to focus their collaboration on patentable disease annotations. During the course of the collaboration, various techniques evolved from being used in selected labs to widespread, robust technologies. Examples include quantitative PCR, transcriptional profiling, *in situ* hybridization and RNA interference. These technologies were immediately incorporated – even if the exact language of the initial contract did not include or cover it. Another challenge was to accommodate changes in indication areas as the paradigms became exhausted or the parties became interested in additional disease areas.

Given the breath of the collaboration, it was possible to identify synergies and enhance the collaboration. For example, several dorsal root ganglion-expressed proteins originally implicated in the role of pain sensation subsequently were shown to have relevance in the control of bladder function. Subsequent pharmacological intervention created opportunities for the treatment of urinary incontinence.

The novelty of the targets and the complexity of the diseases targeted presented another challenge. On the one hand, the novel sequence or disease annotation was crucial in establishing an IP position, but on the other hand establishing meaningful screening cascades and moving the projects further downstream proved to be more difficult than originally anticipated. For example, while for drug targets derived from literature functional recombinant expression is usually known when a project is started, for many of the genome-derived targets functional recombinant expression was not feasible or appropriate substrates or ligands were not available or could not be identified. To arrive at 225 drug targets that can be subjected to HTS and to replace the higher than anticipated number of failures in assay development, processes and throughput were adapted to identify a much higher number of targets.

Furthermore, we learned that the complex patho-physiology of disease make it difficult to discriminate, on the basis of gene expression data alone, targets that directly contribute to a disease state from genes whose expression changes in response to a pathological phenotype. However, it is very encouraging that for a significant number of the genes identified through the collaboration, evidence from the literature is emerging that supports our disease hypothesis.

Accomplishments

When Bayer formed the collaboration, it had three major strategic objectives: (1) To obtain immediate access to state-of-the-art genomics technologies. This was successful and several of these technologies have since been established and implemented in-house. (2) To create an IP estate for genes of the most important target classes in all indications of interest. This was also successful – when the collaboration ended in October 2003, Millennium identified and delivered to Bayer more than 450 drug targets having a novel sequence or novel disease annotation using transcriptional profiling and gene expression studies. Bayer had advanced 180 of these targets into later stages of drug discovery when the collaboration ended. (3) To create a pipeline of 30 pre-clinical development candidates. This has been partly successful and, to date, two preclinical development candidates have been identified and more are expected. One compound is expected to enter clinical development in the near future.

Considerable work was done to identify such a large number of targets. More than 6000 genes were bioinformatically analyzed, more than 1700 clinical and pharmacological samples were analyzed by transcriptional profiling, more than 3000 genes were profiled by Taqman and more than 60,000 *in situ* hybridization slides were evaluated. The mass discovery of such a significant number of targets is unprecedented in the industry and demonstrates that the collaboration has been able to industrialize target discovery and exhaustively explore druggable targets in the indications of interest.

How to integrate science and business

One of the major challenges in a collaboration involving cutting-edge technology is to provide a contractual framework that covers all eventualities to the satisfaction of both parties. Once both parties agree in principle, lengthy negotiations about the exact legal language are extremely challenging. Critical to a successful collaboration is engaging several disciplines early on in the business development discussion, particularly the scientists, who need to understand the legal issues relevant to their work. Furthermore, in an area of fast-developing technology it is important that both parties commit to constantly adapt and evolve the contractual framework to include and reflect the advances in science and technology. The collaboration agreement between the Bayer and Millennium was amended six times and finally amended and restated.

Conclusion of the alliance

Due to the comprehensive approach and the smaller than expected genome, the disease paradigms were exhaustively explored after five years and the collaboration was concluded on 31 October 2003, as planned. At that time, Bayer had progressed more than 180 targets into various stages of assay configuration and drug discovery.

However, as mentioned previously, a large number of targets have not been configured into assays for technical reasons. To continue to generate value from those targets, the companies have amended the agreement to provide Bayer with extended exclusive access for up to seven years to this large pool of proprietary targets. If information emerges from the public domain on how a particular target can be successfully configured into an assay, Bayer can choose this target from the available pool of targets and initiate assay development. Millennium can also select a certain number of targets. At the end of the seven-year period, the targets remaining in the pool will be returned to Millennium.

Lessons learned for alliance management

During the collaboration several key lessons were learned: (1) An alliance is truly successful if the core competencies of the partners are complementary and the alliance is created in a way that each partner can contribute unique know-how. The know-how, technology and 'cultural' transfer was facilitated greatly by Bayer scientists working onsite at Millennium. (2) The concept of an exclusive, but time-limited license motivated partners to deliver rapidly. The agreement, as it was structured, compelled Millennium to present a sufficient number of targets, and Bayer to successfully progress those targets in drug discovery. (3) It was important that key executives and a collaborative and dedicated leadership who were committed to maximizing value for both partners were involved rather than trying to get the most out of the collaboration for each party. (4) It was crucial that there was a close collaboration between scientists, research management, business development, patent and legal people ('get everybody involved'; both in cross-functional as well as cross-company teams). (5) Finally, both parties must commit to continuously update the contractual framework to reflect the scientific progress and change in strategy of both companies.

Conclusion

In summary, the Bayer–Millennium collaboration has shown that genomics enables industrialized target identification and assay development and, that genomics technologies played a key role in obtaining biological IP. It has also shown that translating this into novel development compounds has proven to be more difficult and will take longer than originally anticipated. The next step will be to continue to validate the patho-physiological relevance of those targets and to generate pharmacological tools and lead compounds.

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