



PERSPECTIVE

Collaboration for success: the value of strategic collaborations for precision medicine and biomarker discovery

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Abstract: Precision medicine aims to provide the precise treatment for the patient with the right dose at the right point of time. Biomarkers (BM) are vital for the identification of patients who would benefit the most from individualized treatment. In addition, they help to enable the prediction of prognosis, the detection of early therapeutic and adverse effects, and may serve as surrogate endpoints in clinical trials. BM are becoming essential tools to increase productivity in drug discovery and impressively enhance the way medicine is practiced. However, the identification, sufficient validation and implementation of such BM are challenging. This process requires expertise from different areas and high resource investments. Collaborations of different partners may be helpful to overcome these challenges. In the past decade, collaborations between diagnostics and pharmaceutical companies as well as industrial–academic collaborations have been increasingly pursued. Moreover, public funding may offer support and open new opportunities to form such consortia. Herein we give an overview of the different types of collaborations, their opportunities and challenges, and describe experiences in forming strategic partnerships with other companies.

Keywords: precision medicine, consortia, drug discovery, patient selection, public funding

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Introduction

Precision medicine aims to treat diseases with consideration for individual biological variability. It represents one of the most important trends in medicine^[1]. Owing to biological variability, often only a subset of patients may benefit from a particular therapy. Thereby, biomarkers (BM) are essential tools required to predict therapeutic responses as

well as to facilitate the selection of appropriate patients for treatment with certain drugs. Despite the major progress in drug discovery, the research and development costs to launch new drugs has increased dramatically over the last decade exceeding more than 1 billion € per new drug. The number of Food and Drug Administration (FDA) approved drugs per billion US dollars of research and development spending has decreased by 50% approximately every nine years

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(Figure 1). This indicates a productivity gap^[2]. It is not a sustainable process and one that ought to be further evaluated. One of the main driver costs is the high attrition rate of drugs in the early clinical development phase. This is particularly challenging as many drugs fail rather late in their development after many years of multimillion-dollar investments. Success rates in phase II studies, studies describing the first application of an investigational drug to patients, have been historically low and have further decreased to an unsustainable level (Figure 2)^[3]. Remarkably, the lack of or insufficient therapeutic effects is the main reason for failure at the present time.

It should be noted that the application of a ‘BM stratified approach’ referring to drugs that are approved for particular patients’ subgroups only, would

increase the success of clinical testing. Vice versa, applying a non-BM stratified population, the proportion of successful selected patients would decrease, since the ‘dilutive effect’ of patients not suited for a precision therapy would have resulted in a negative outcome of the study even in case of a tremendous response rate in a small subgroup. Thus BM are effective tools to reduce attrition rates and companies started to invest significant efforts and money into the development of precision medicine. Because of its use to predict prognosis and detect early therapeutic and adverse events, the impact of BM is significant. Also BM may serve as surrogate markers for clinical endpoints, shortening the product development period and saving costs. As a consequence, BM are of increasing importance in medicine and drug discovery^[1,4].

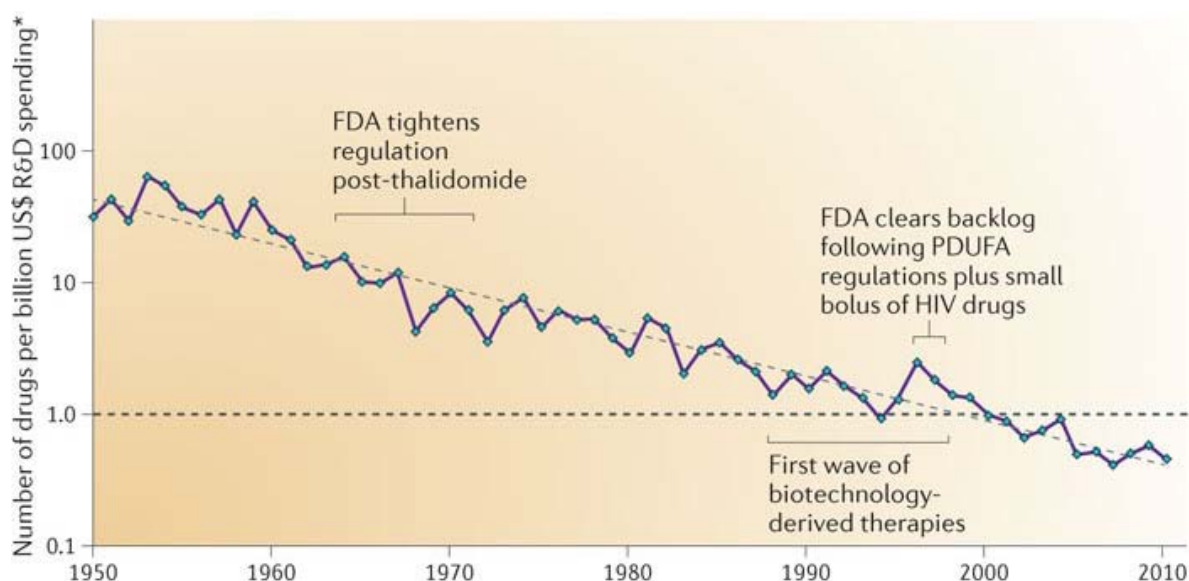


Figure 1. Decline of productivity in the pharmaceutical industry.

The number of FDA approved drugs per billion US dollars of R&D spending has halved approximately every nine years. Figure reproduced from: Scannell J W, Blanckley A, Boldon H, *et al.* 2012^[2]. Published with approval by Nature.

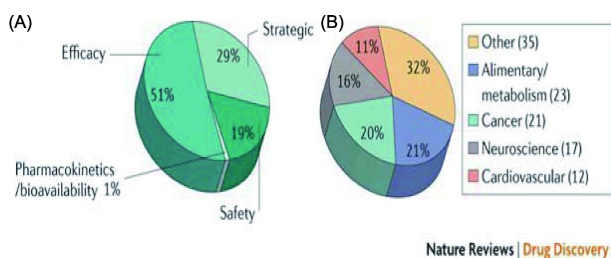


Figure 2. Increasing phase II failures.

Success rates for new development projects in phase II have fallen from 28% to 18%, with insufficient efficacy as the most frequent reason. The 108 failures are divided according to (A) reason for failure when reported (87 drugs) and (B) therapeutic area. Figure reproduced from: John Arrowsmith, 2011^[3]. Published with approval by Nature.

Need for Collaboration: Opportunities and Challenges

Developing BM is challenging and expensive. Two elements are required for the successful BM establishment:

(i) *The sufficiently validated BM.* This includes a measurable parameter and a qualified assay for its detection. Usually the required expertise exists only within dedicated groups in academia or in the pharmaceutical companies, rather than at a single institution. This is not surprising since it requires a substan-

tiated understanding of disease pathophysiology, the particular pathway targeted, and the mode of action of the compound.

(ii) *The expertise to develop and market diagnostic tests.* This is not linked to academia or to pharma companies alone. Most pharma companies separated their diagnostic business. *Roche* is probably a rare exception still running its own diagnostic business. In contrast, such knowledge is well established in the diagnostic industry which in turn lacks the other expertise described and usually does not have the capacity to establish BM on its own. This is particularly true if it is intended to be used to support a drug not yet on the market. For stratification biomarkers regulatory agencies strongly suggest it is essential that the drug and the BM are developed together from early on using a simultaneous model with the end result being a ‘companion diagnostic’. BM validation requires extensive testing of clinical samples, i.e., access to well-defined patient samples which are usually best provided by experienced clinical academic groups. Therefore it is obvious that collaboration between academia and different partners from the pharmaceutical and diagnostic industries with complementary skills may be beneficial and are needed. [Table 1](#) summarizes the strengths of the various types of partners. [Figure 3](#) shows different kinds of collaborations. *Partnerships* are well suited for competitive research

with ‘intellectual property generation’ and the short- to mid-term need for complementary competencies. *Consortia* seem to be most attractive for work in pre-competitive areas, with long-term interest which shape the environment. These two categories of collaborations are within the main scope of this review. Further ‘traditional’ well established collaborations with key opinion leaders and fee-for-service collaborations are not specifically discussed in this paper.

Since the business models of pharmaceutical and diagnostic industries are different, specific cooperation challenges are formed. Typically the pharmaceutical industry works with high risk development costs, long development duration and high rewards. For the diagnostic industry a contrasting scenario is depicted. Comparably low risk development, low costs, and short development duration, but with lower financial reward. A consequence for diagnostic companies is that it is not rewarding to invest into the development of BM on their own due to high costs caused by regulatory requirements and uncertain recapture of investments. The possibility of drug development failure is high.

It is well known that more than 90% of drug developments fail at the start of clinical investigation. If a diagnostic test is successfully developed in parallel it is more likely that the diagnostic company will end up with a viable product that can be sold with the drug.

Table 1. Strengths of partners involved into BM collaboration

Partner	Core competence and strengths
Academia	Access to well defined patient material In-depth pathophysiological understanding of target diseases and pathways Innovative ideas for novel targets, biomarkers, assays, and technologies
Pharmaceutical industry	Drug discovery skills Expert knowledge regards the development compound Regulatory expertise for drug development
Diagnostic industry	Diagnostic assay development and marketing skills Access to novel assay technologies Regulatory expertise for assay development

Consortia	Alliances/Partnerships	Fee-for-Service
<ul style="list-style-type: none"> pre-competitive long-term interest shaping the environment 	<ul style="list-style-type: none"> competitive research intellectual property generation short- to mid-term interest need for complementary competencies from partner 	<ul style="list-style-type: none"> clearly defined task no intellectual property generation short-term interest

Figure 3. Different kinds of pharmaceutical collaborations.

Key elements of the particular categories of collaborations are shown. Different collaborations can be applied and combined for particular projects.

Moreover, profits for diagnostics usually result from high volume testing. However, this does not apply to small populations such as specific types of cancer patients who are tested only once for the purpose of drug stratification. Finally, the prices for diagnostic tests are set by the technology (e.g. dependent whether its immunohistological, PCR based etc.) and not value based. This ignores the higher development costs for companion diagnostics which makes it more unappealing for diagnostic companies to invest in stratification BM on their own without additional incentives. There is a high need for common calculation, and cost and risk management between pharmaceutical and diagnostic partners. Pharmaceutical companies tend to stimulate and support BM development activities in diagnostic companies either by paying for the BM development costs or paying a premium for access to an available companion diagnostic. An advantage of working on a project-to-project basis is the given flexibility. However, for the pharmaceutical company, investment costs may rise if there is an increase in demand and competition from other pharma companies due to the possible limitations of diagnostic development capacities. Strategic partnerships create an opportunity to overcome the majority of these challenges.

The idea of a strategic partnership includes a significant commitment for the long-term, sometimes even an exclusive collaboration between two or more partners with complementary strengths. Another possible collaboration opportunity is to form large consortia. In addition to bringing together complementary expertise, it also helps to share significant costs. In the case of establishing surrogate BM many companies would stand to benefit, in contrast to individual drugs which only benefit a few. Providing public funding for consortia could be particularly interesting as this appears to be an increasingly popular new trend.

Partnerships Between Diagnostic and Pharmaceutical Companies

In the ‘biomarker arena’ partnerships between two or more pharmaceutical companies with individual di-

agnostic divisions are well established. These relationships allow for the development of companion diagnostics, which are essential for patient stratification biomarkers. In the era of precision medicine most pharma companies have decided to use the competence and expertise of the diagnostic companies rather than to build up in house-diagnostic development capabilities themselves. At the same time, guaranteed assay development slot and pricing structures are thought to be important and secured by forming such relationships. For the diagnostic companies in turn it provides stability by securing a significant number of projects leading to a more continuous and reliable workflow. For both partners the administrative workload to enter and manage the collaboration decreases over time due to the learning curve. Oftentimes academic partners do not enter such core collaborations. However, they can become crucially involved if novel technologies are necessary or a marker needs to be evaluated in larger patient populations.

The Partnership Between Bayer and Ventana

Bayer established several partnerships in order to develop companion diagnostics with experts that have proven experience with developing and commercializing companion diagnostics (Ventana and Qiagen). Bayer also established one partnership with a company that had an innovative novel technology platform (Sysmex Inostics) as shown in [Table 2](#).

Following in line with other pharmaceutical companies, Bayer has been successful at developing Antibody Drug Conjugates (ADC) against novel oncology targets. Immunohistochemical (IHC) assays are usually used to select patients that should receive the ADC. Considering that there are only three IHC diagnostic manufacturers with limited development capacities, Bayer decided to align with Ventana. The advantage of this strategic partnership was the robust prototype IHC assay that was implemented and used in the early phase I studies. It was evaluated for the use as a companion diagnostic, the test that would be required for pivotal registration trials and drug submission. Using this approach was helpful to limit the risk of failure in

Table 2. Established partnerships of Bayer to develop companion diagnostics

Partner	Technology	Portfolio relevance
Ventana	Immunohistochemistry FISH	(Over)expression necessary for drug action in multiple projects
Qiagen	Mutational Analysis Tissue	Tumor driver mutation targeted by compound or downstream of target
Sysmex/ Inostics	Blood based Mutational analysis	Tissue difficult to access/Screening for low mutation frequency

the clinical drug development program, since the antibody assay would have shown early in the development phase critical points.

The partnership was established at the phase I studies. Both teams had the opportunity to learn crucial steps needed to co-develop an IHC diagnostic assay along with the ADC. A key element for success was to align as early as possible on the diagnostic and drug development strategies. This was because regulatory agencies within different countries have different approval timelines, which can dramatically delay clinical trials and start times. Moreover, regulatory interactions require communication with different FDA departments: Center for Devices and Radiological Health (CDRH) for the medical device and Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) for Biologics License applications. The different departments have their own standards. By aligning the regulatory teams from Bayer and Ventana, regulatory data packages were more easily assembled and submitted in a timely manner.

Another important advantage was the possibility to generate antibodies according to the specifications required by Ventana to perform on formalin fixed paraffin embedded tissue. Ventana's antibody manufacturer is aligned on the process and requirements needed for a sensitive and specific IHC assay.

Collectively the streamlined processes that Ventana offers should expedite the development of appropriate IHC assays that can be further developed as companion diagnostics without delays to the commercialization and launch of the pharmaceutical companies ADC.

The Partnership Between Bayer and Qiagen

Bayer also entered a strategic relationship with Qiagen to develop clinical trials assays for several early phase clinical programs. For Bayer the advantages of this partnership comprise of global penetration, the know-how with regards to RT-PCR tests, the regulatory expertise of Qiagen with validating kits to European *CE* and US *FDA* standards, and experience in filing pre-market applications.

By engaging early and aligning clinical development programs, Bayer was able to identify rare samples needed for the verification and validation of the polymerase chain reaction (PCR) tests. When timelines in the clinical trial changed, Qiagen modified their development plans to accommodate Bayer's clinical trial demands. Bayer used only one test that

was taken to the Investigational-use-only-level and later stage bridging studies were not necessary.

The knowledge that Bayer scientists gained by developing an IHC companion diagnostic assay coupled with the lessons learned from Qiagen were helpful for subjects working in the Bayer global drug discovery division to feel more comfortable and knowledgeable on implementing companion diagnostics tests ranging from research use only assays to investigational use only assays in early and pivotal clinical trials. These experiences have been invaluable for phase I dose escalation and expansion studies that require the use of stratifications assays.

The Partnership Between Bayer and Sysmex-Inostics

Several tumors shed deoxyribonucleic acid (DNA) into the blood stream which can be measured as circulating tumor DNA (ctDNA)^[5]. The detection of ctDNA offers the possibility for minimally invasive testing and the ability to study the mutational status of a tumor. Compared to invasive biopsy sampling procedure this is associated with lower risk for patients. It allows for the testing of patients who do not have accessible tumors which can be biopsied. This also allows for the detection of resistance through continuous monitoring of the mutational status of tumors during the therapy. One may also speculate whether this method represents a more holistic readout of the mutational tumor status, especially in a metastatic setting, than a single biopsy from a potentially non-representative part of the primary neoplasia.

In order to detect minute amounts of ctDNA in blood a highly sensitive technology platform is necessary. The *BEAMing* technology platform offered by Sysmex-Inostics provides such a platform^[6]. Initially the partnership was intended to establish a regulatory pathway with the FDA and to validate the platform ready to use for prospective patient selection as there are no FDA approved companion diagnostics based on the *BEAMing* technology. The *BEAMing* technology was successfully implemented in a global prospective study to screen for patients with a certain mutational status in a tumor indication where sampling invasive biopsies would have a high risk of bleeding. Furthermore, several studies conducted with the use of *BEAMing* compared the two technologies: the ctDNA mutational status and the mutational status detected via conventional PCR methodologies in tumor tissue.

Entering into a strategic partnership with Sysmex-Inostics revealed several challenges. Some of the

challenges were the lack of regulatory experience requiring the use of external regulatory consultants at times and working through the growth and establishment process of the company respectively. Advantages of working with smaller companies are due to their higher flexibility to shape the technology implementation strategy and to match clinical development timelines and needs. Overall the partnership was successful. The FDA was shown the value through a combination of new technology coupled with clinical data which allowed them to work closely with Sysmex Inostics.

Partnerships Between Academia and Industry

Collaborations between academic institutions and the diagnostics and pharmaceutical industry are increasingly initiated and executed. It is assumed that these relationships could help to improve research and development productivity in the industry, as well as enable academic institutions to better exploit the translational potential of their research^[7].

The Partnership Between Bayer and the German Cancer Research Center

In 2009, Bayer and the German Cancer Research Center (DKFZ) joined forces in a strategic partnership along the entire drug discovery and early development value chain. Since then this partnership has resulted in 30 joint projects, mainly in the area of target discovery and validation. More than half of them have already achieved milestones on lead discovery or optimization. In 2013 both partners decided to extend their collaboration with a joint laboratory for immunotherapies at the National Center for Tumor Diseases in Heidelberg^[8]. This strategic partnership based on positive experiences has led to a better understanding of relevant pathways in a number of cancers and to novel biomarker candidates with the potential to support patient stratification in specific indication areas. Key success factors for this partnership are long-term collaboration on an equal scientific level with close interaction and exchange of expertise resulting in mutual benefit. An efficient process has been achieved with a framework of agreement enabling the quick setup of joint projects, based on a short joint decision process and without additional single project negotiations. This enables scientists involved from both sides to translate their research into application.

Science Hubs — Fostering Interactions Through Co-localization

Another approach to promote the interaction between

industry, academia and start-ups are science hubs and incubators. Bayer was the first company establishing an Innovation Center next to the University of California, San Francisco in Mission Bay. Furthermore, Bayer established an Incubator — a so-called “CoLaborator” for start-ups offering space and expertise. This model has proven to be very successful as a number of new partnerships evolved over time. The co-localization of scientists facilitates close interaction and informal exchange. Recently, this project was extended to Bayer facilities in Berlin, where young biotech start-ups are hosted.

Other Examples

Other examples for Bayer collaborative efforts are the *Grants for targets* initiative and a compound provision program, which we reviewed elsewhere^[9–11].

Consortia Supported by Public Funding

Significant public funding has become available for biomarker research in the past years. Public-private-partnerships like the *Innovative Medicines Initiative*, the *FDA-Biomarker-Consortium* and others, as shown in [Table 3](#), offer the opportunity to create critical mass consortia of excellent partners in specific areas. In most cases, multiple companies and academic institutions join forces to address an issue which would be difficult to address by only one participant alone. Recently these approaches have been reviewed^[12].

Examples include the pooling of resources to decipher the molecular basis of complex diseases such as diabetes, resulting in better safety and efficacy markers (www.imi-summit.eu). Similarly, novel approaches like systems medicine for the identification of novel biomarker patterns with potential for patient stratification may be tested. One of these successful examples is the *Innovative Medicines Initiative* project OncoTrack, where more than 200 colon cancer patients were analyzed in a novel modelling system using data from next generation sequencing and methylome analysis (www.oncotrack.eu). The recently constituted *Innovative Medicines Initiative* consortium CANCER-ID (www.cancer-id.eu) aims to evaluate the clinical utility of different technologies for enrichment, isolation and analysis of circulating tumor cells, circulating free tumor DNA, and microRNAs.

These biomarkers serve the concept of ‘liquid biopsy’ which may allow for longitudinal sampling when standard biopsies are not available or pose a significant risk to the patient. The 36 European and

Table 3. Current examples of Biomarker Consortia, supported by public funding in Europe and the United States

Name	Country / Main participants	Disease areas	Link
IMI	Several member states within the EU	Broad indication coverage, e.g. T2 Diabetes (IMIDIA, SUMMIT, DIRECT), AD (Pharma-Cog), Asthma (U-BIOPRED), Oncology (OncoTrack, Cancer-ID), Autism (EUAIMS), Drug Safety (SAFE-T, MIP-DILI, MARCAR) Vaccine Safety (BioVacSafe)	www.imi.europa.eu
HORIZON 2020	Several member states within the EU	Various programs, e.g. breast cancer	http://ec.europa.eu/programmes/horizon2020/
Dutch Biomarker Development Center	The Netherlands	COPD, Type2 Diabetes, Alzheimer's Disease	http://www.biomarkerdevelopmentcenter.nl/
EATRIS-ERIC	Several member states within the EU	Cross indication, focus on infrastructure for translational medicine	http://www.eatris.eu/
BBMRI-ERIC	Several member states within the EU	Cross indication, focus on infrastructure of bio-banks and biomolecular resources	http://bbmri-eric.eu/
Biomarker Consortium	US (FDA, industry)	Broad indication coverage	http://www.biomarkersconsortium.org/
BIQSFP	US (NCI)	Cancer: Biomarker, Imaging and Quality of Life Studies Funding Program (BIQSFP)	http://www.cancer.gov/aboutnci/organization/ccct/other-programs/biqsfp
Parkinson's Disease Biomarker Program	US (NINDS)	Parkinson's Disease	https://pdpb.ninds.nih.gov/

Modified after Asadullah K, Busch A, Gottwald G, *et al.* 2015 (supplement)^[12]. Published with approval by Nature.

US CANCER-ID partners are now working on:

- (i) defining standards for circulating tumor cell identification and counting, and
- (ii) standard operating procedures for pre-analytical sample handling and analyses.

The European consortium, Biomarker-Driven Immunosuppression, is going to implement recently identified biomarkers into the management of immunosuppression after solid organ transplantation. For the first time, in several clinical trials supported by diagnostic and pharma companies, biomarkers will be used as decision criteria to guide personalized immunosuppression. This would allow drug minimization or even weaning without harming the kidney and liver allografts. The methodical implementation of these biomarkers is finalized. As a result up to 1,000 patients will be enrolled in different multi-center trials^[12]. Other examples for successful consortia in the biomarker area are the *Biomarkers consortium*^[13], the *Predictive safety testing consortium*, and the coalition against major diseases^[14].

Concluding Remarks and Further Perspectives

Collaboration between academia, diagnostic and pharmaceutical industry, best in consortia, is essential for successful biomarker discovery, development, and implementation as it requires high resources and complementary skills^[12,14]. It can be assumed that the number of academic-industrial collaborations will further increase, partly due to the increasing availabil-

ity of public funding. The current biomarker consortia with collaborating groups from academia, pharmaceutical and diagnostic companies will probably be joined by information technology companies as 'big data', e.g. generated by whole genome analyses, needs to be analysed. Involvement of young academic groups and biotech companies may provide access to highly innovative technologies. Science hubs and incubators are providing a promising opportunity to support the activities of biotech and internet start-ups and bring them in close proximity to established pharmaceutical companies where the co-location of scientists facilitates intense interaction and informal exchange. For the exploration and clinical validation of a new biomarker candidate or a novel technology larger consortia may be appropriate^[12]. Each category of collaboration has its own needs and challenges to overcome in order to be successful. Crucial factors for complex consortia are:

- (i) a good balance between critical mass and manageable size,
- (ii) involvement of both diagnostics and pharmaceutical industry partners,
- (iii) early alignment on the joint goals between public and private partners, and
- (iv) a professional project management.

Based on our experience such consortia are essential to create the critical mass needed to achieve acceptance of surrogate biomarkers, a new technology, or to validate a stratification biomarker in a complex

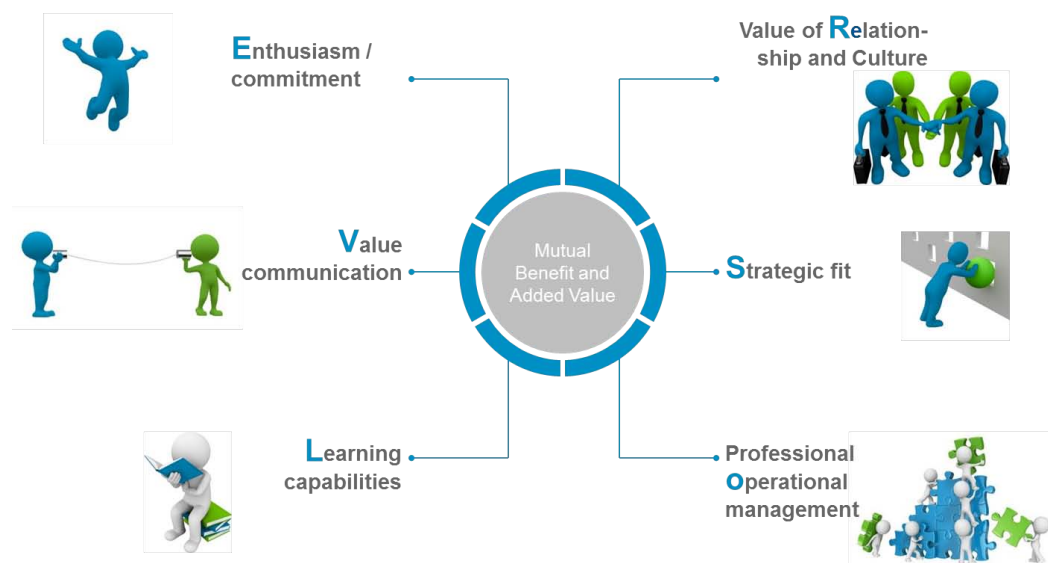


Figure 4. Key success factors for partnerships (RESOLVE MODEL).

clinical setting.

However, people will only actively engage in collaboration when the benefit they derive is greater than the effort and time it takes to collaborate. We have identified key success factors for collaborations that are summarized in the RESOLVE Model as shown in Figure 4^[15]. According to the model six key elements have to be taken into account:

- (i) good relationship management,
- (ii) clear agreement on the strategic goals of the partnership,
- (iii) transparent definition of processes and governance structures (operational excellence),
- (iv) openness to learn from each other as the differences between the partners are a key driver of the partnership,
- (v) open communication. and
- (vi) support from the bench and the senior management.

In summary, collaborations that result from strategic partnerships and consortia are key for successful biomarker discovery and establishment. The kind of collaboration needs to fit to its purpose.

Conflict of Interest and Funding

LL and PR have no conflict of interest to declare. AB, PC, MG, and KA are employees and shareholders of Bayer AG. JR is a shareholder of Bayer AG and an employee of Astra Zeneca.

References

1. Landeck L, Kneip C, Reischl J, *et al.* 2015, Biomarkers

and personalized medicine: current status and further perspectives with special focus on dermatology, in *Experimental Dermatology*. (In press)

2. Scannell J W, Blanckley A, Boldon H, *et al.* 2012, Diagnosing the decline in pharmaceutical R&D efficiency. *Nature Reviews Drug Discovery*, vol.11: 191–200.
3. Arrowsmith J, 2011, Phase II failures: 2008–2010. *Nature Reviews Drug Discovery*, vol.10: 328–329.
4. Salter H and Holland R, 2014, Biomarkers: refining diagnosis and expediting drug development — reality, aspiration and the role of open innovation. *Journal of Internal Medicine*, vol.276: 215–228.
5. Bettgowda C, Sausen M, Leary R J, *et al.* 2014, Detection of circulating tumor DNA in early- and late-stage human malignancies. *Science Translational Medicine*, vol.6: 224.
6. Diehl F, Li M, He Y, *et al.* 2006, BEAMing: single-molecule PCR on microparticles in water-in-oil emulsions. *Nature Methods*, vol.3: 551–559.
7. Lessl M, Bryans J S, Richards D, *et al.* 2011, Crowd sourcing in drug discovery. *Nature Reviews Drug Discovery*, vol.10: 241–242.
8. Wellenreuther R, Keppler D, Mumberg D, *et al.* 2012, Promoting drug discovery by collaborative innovation: A novel risk- and reward-sharing partnership between the German Cancer Research Center and Bayer HealthCare. *Drug Discovery Today*, vol.17: 1242–1248.
9. Lessl M, Schoepe S, Sommer A, *et al.* 2011, Grants-4targets — an innovative approach to translate ideas from basic research into novel drugs. *Drug Discovery Today*, vol.16: 288–292.

10. Dorsch H, Jurock A E, Schoepe S, *et al.* 2015, Grants4Targets — an open innovation initiative to foster drug discovery collaborations between academia and the pharmaceutical industry. *Nature Reviews Drug Discovery*, vol.14: 74–76.
11. Schmitz A A, Hackethal S, Schulz A, *et al.* 2015, Pharma compound sharing with academia: experiences with providing Vitamin D receptor ligands. *Nature Reviews Drug Discovery*, vol.14: 294–296.
12. Asadullah K, Busch A, Gottwald G, *et al.* 2015, Industrial–academic collaborations for biomarkers. *Nature Reviews Drug Discovery*, vol.14: 805–806.
13. Wholley D, 2014, The biomarkers consortium. *Nature Reviews Drug Discovery*, vol.13: 791–792.
14. Stephenson D, Sauer J M, 2014, The predictive safety testing consortium and the coalition against major diseases. *Nature Reviews Drug Discovery*, vol.13: 793–794.
15. Lessl M, Douglas F, 2010, From technology-transfer to know-how interchange. *Wissenschaftsmanagement*, vol.(2): 34–41.