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Grants4Targets – an innovative approach to translate ideas from basic research into novel drugs

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Collaborations between industry and academia are steadily gaining importance. To combine expertises Bayer Healthcare has set up a novel open innovation approach called Grants4Targets. Ideas on novel drug targets can easily be submitted to http://www.grants4targets.com. After a review process, grants are provided to perform focused experiments to further validate the proposed targets. In addition to financial support specific know-how on target validation and drug discovery is provided. Experienced scientists are nominated as project partners and, depending on the project, tools or specific models are provided. Around 280 applications have been received and 41 projects granted. According to our experience, this type of bridging fund combined with joint efforts provides a valuable tool to foster drug discovery collaborations.

Introduction

The pharmaceutical industry is currently undergoing major changes. The old 'blockbuster' model seems to be out of date and several major acquisitions have taken place in recent years. A key driving force behind the acquisitions is the repopulation of dwindling pipelines based on patent expiry of blockbuster medication as well as a lack of innovative new products [1]. Although acquisitions lead to an enriched pipeline in the short term, a long-term focus on innovation is required to develop a sustainable pipeline providing the basis for corporate growth and future business. Whereas large pharmaceutical companies have the know-how, the technology and the power to develop novel drugs, innovative ideas for novel treatment approaches are often bred in smaller, more specialized units such as universities, biotech companies or research centers [2]. Successful translation of this know-how existing in universities, research institutes or biotech companies into innovative drugs via collaborations and alliances between academia, biotech and the pharmaceutical industry will be key levers for future success for both the pharmaceutical industry and society.

Recent investigations by Lessl and Douglas [3] have revealed increasing 'needs' to collaborate on both sides, academia and industry. Whereas scientists in public institutions are more and more interested in field-testing and validating their hypotheses (e.g. those generated from the – omics area), industry (because of the productivity gap) needs to foster innovation and broaden expertise in an efficient and flexible manner. Furthermore, governments are pushing publicly funded research organizations to translate their know-how into products to generate a return on investment for the society as a whole. By joining forces and complementing expertise, benefits for both partners can be realized [4]. But the challenging question of how this can best be achieved remains. What models are suitable to successfully translate ideas from academia into novel drugs and generate value for both partners? As part of a holistic strategic approach dealing with external innovation sourcing and interaction with partners in academia and biotech companies, we developed a novel type of collaborative model focusing on the very beginning of the drug discovery process, namely the identification of novel drug targets.

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On the one hand, the identification of novel molecular targets, representing pathophysiologically relevant key molecular switches, forms a major challenge in drug discovery. On the other hand, many scientists all over the world are engaged in unraveling signal transduction pathways related to disease processes and key regulators of metabolic or signaling processes representing potential novel and innovative targets [5]. This results in the situation that academia has several ideas on potential regulators, whereas industry has the know-how about how to validate these potential drug targets with relevant *in silico*, *in vitro* and *in vivo* methods [6] and how to set up and perform a screening process after successful validation. This confronted us with the challenging question of how the existing knowledge of novel targets could be transferred to industry so that the many ideas could be evaluated and synergies be leveraged. To achieve this we started a new initiative called 'Grants4Targets' as a 'controlled experiment'. The basic idea of this initiative is to provide bridging grants as well as drug discovery know-how to academia to support the evaluation and validation of novel drug targets. The grants – depending on the results – are seen as a first step toward further joint efforts with the academic partner.

BOX 1

Grant types Grants4Target program

Support Grants (€5,000–10,000) to further advance research on targets that are at a very early stage of discovery; fixed grant approval letter; IP rights remain with the applicant.
Focus Grants (€10,000–125,000) for more mature ideas, for example, to address specific aspects of a target as a first step towards transferring it to the drug-discovery process; fixed grant approval letter; IP rights remain with the applicant.
Collaborative Grants (€50,000–250,000) to move the target into the drug discovery process in a substantial joint effort; terms have to be negotiated.

The G4T approach

Easy access to grant scheme

A grant scheme has been established to further advance target ideas by providing funding for focused experiments to validate the proposed molecular target. The grants are provided for a period of one year. Three types of grants have been set up, which are described in Box 1. In case of the support and the focus grant, all Intellectual Property (IP) remains with the applicant within the funding period. This increases the attractiveness and allows a fast processing of the grants. The terms of the collaborative grant have to be negotiated on an individual basis. To allow easy access to the initiative from all over the world, an internet portal has been established allowing academic groups or young start-up biotech companies to submit their ideas on novel targets. In addition, announcements were made in selected scientific journals, at conferences or via emails to scientific groups.

Fast throughput of proposals and clear definition of needs

To distinguish the G4T initiative from other grant schemes, a fast processing of the proposals, low bureaucratic hurdles as well as a clear description of the specific target needs were identified as key success factors. Therefore, a stringent review and decision process flow has been established, allowing the applicants to get feedback at the latest 8 weeks after the closing of the submission deadline (Fig. 1). Furthermore, the application process was set up in a user-friendly manner, allowing for filing a grant application in a reasonably short timeframe. In addition, a detailed list of the disease areas, the indications as well as the therapeutic principles we are interested in and that the targets should match has been provided on the internet to ensure a strategic fit on both sides. This has been acknowledged by the scientific community: *'There are two advantages in the G4T program. First being the speed with which the grant is funded. The second being the potential of further collaboration in the future to advance common research interests.' Prof. Jean Wang, University of California San Diego, Cancer Center La Jolla.*

Combine expertise of both partners to advance targets

A key aspect of the initiative is to leverage the specific expertise of both partners – academia and industry – to bring forward innovative target ideas and to generate value for both partners. Benefits for both partners are summarized in Table 1. To meet this goal, senior scientists within the company are nominated for every granted project as key contact persons. These project partners provide their drug discovery expertise, explain requirements to be fulfilled in each step

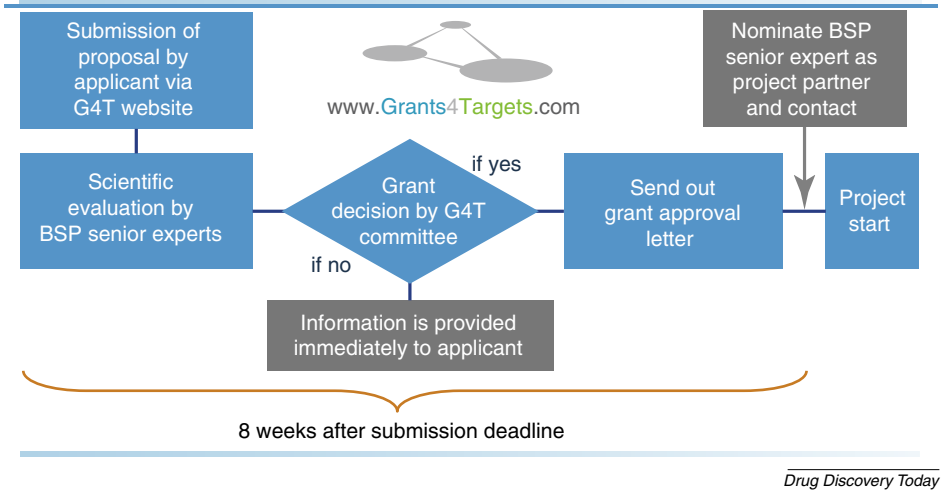

FIGURE 1

The grant application process: From submission to project start. A fast and efficient processing of grants is seen as a key success factor of the initiative. To allow a close interaction, senior experts from Bayer Healthcare are nominated as project partners for every granted project.

TABLE 1

The G4T program delivers benefits for both partners – industry and academia

Academia	Industry
Gain access to bridging funds to field-test novel target ideas and take the next step to translate discoveries into therapeutics	Gain access to novel drug target ideas and leading academic groups
Gain access to specific tools such as compounds and modern *in silico*, *in vitro* or *in vivo* drug discovery methodologies to validate novel targets	Gain access to specific tools, assays, and animal models supporting target validation and compound characterization
Obtain specific know-how about drug discovery such as target validation criteria and plans, screening	Get information on disease-specific know-how such as signal transduction pathways
Low bureaucratic burden for grant application and fast response	Clear communication ensures high strategic fit of applications
Possibility to further advance target in a joint collaborative project after successful target validation	Leverage complementary expertise to develop novel drugs

of the development process, help to generate the target validation plan and support projects with relevant tools (such as compounds) if required. In some cases also (around 1/3 of the projects) parts of the projects are performed within the company (such as specific animal models, biochemical assays or extensive gene expression array analyses). Furthermore, we have implemented measures to ensure efficient collaboration management for the benefit of both partners. Here we follow the RESOLVE Model that has been developed at Bayer Healthcare [3], summarizing key success factors for collaborations. These are successful **RE**lationship management, high **S**trategic fit of partner's interests, professional **O**perational management of collaboration, openness to **L**earn new things, **V**alue communication and ensure **E**nthusiasm and commitment at all levels. In addition, to foster required competencies in our own organization, relevant training courses such as relationship management, negotiating and cross-cultural communication have been implemented.

The G4T approach generated novel ideas for drug targets in areas of joint strategic interest

One year after the kick-off of the program, three rounds of applications have successfully been accomplished. In total we received approximately 280 submissions for grant applications. As mentioned above the initiative was started as a 'controlled experiment', not knowing whether we would receive thousands of applications or none. The goal was to obtain a manageable number of applications meeting the target needs and allowing a fast and efficient way to process the applications. Interestingly, only 12% of the applications did not match the target criteria described on the G4T website. This can be rated as a fairly low number of mismatches, further substantiating our approach of clearly and openly defining the key target requirements (Box 2). Applications were sent in from all over the world, with the highest percentage of proposals from Germany (35%). This was expected as the initiative was most prominently advertised in Germany as a first step (Fig. 2a). We received applications in all our four target focus areas, which are oncology, cardiology, women's health (gynecological diseases) and molecular imaging (Fig. 2b). The highest percentage of applications received was in the area of oncology (50%), the lowest in the areas of women's health (8%) and molecular imaging (3%). This is in accordance with the amount of public funding available for those research fields. This accentuates another goal of our initiative, which is to foster research in areas of our strategic interest where public funding is limited.

Whether or not we would obtain ideas on really novel targets was another key question we asked ourselves during the set-up of the initiative. Interestingly, the data obtained from the applications so far clearly indicate that approximately 60% of the target ideas are novel to us (Fig. 2c) for a certain indication or within a therapeutic area. Also ideas on ongoing projects were of interest, as some of them provided important tools (such as assays) for ongoing projects. This underscores the high potential of the approach of fostering innovation by bringing in ideas from different avenues. As intended, most of the applications received were from academic research institutes (94%) and 6% from young start-up companies. Most of the applications were in the area of target validation (as intended), in some cases novel target discovery approaches, extensions of indications for existing compounds or novel compounds or models were proposed.

We neither received nor expected any applications that contained a fully *validated target* fulfilling all our internal criteria for starting a lead identification process. This further underscores the need for a complementary approach bringing together the expertise of both partners – industry and academia. Specific know-how about how to validate a target such that it meets the internal, stringent target criteria is required to further develop the proposed candidates. This specific knowledge on drug discovery has to be

BOX 2

Target definition and criteria for G4T submissions

Drugable target: Is a gene which codes for a protein whose activity can be modulated by drug. The drug can be a small-molecular-weight chemical compound addressing an enzymatic activity or a protein–protein interaction or a biological, such as an antibody or a recombinant protein.

Validated target: Is a target which has been shown to be mechanistically involved in the disease by relevant *in vitro* or *in vivo* models. Mechanistic interference can be demonstrated *in vitro* either by siRNA or shRNA knockdown experiments, by over-expression of wildtype or mutant variants of the enzyme or with a tool compound or an antibody. Relevant *in vitro* read-outs could be, for example, effects on proliferation, apoptosis, migration, angiogenesis, fibrosis or immunological parameters. Appropriate *in vivo* models can be either specific disease models, knock-out, or transgenic mouse models, or – in case of oncology – xenograft, or syngeneic models.

Criteria for target/project submission:

1) Strategic fit to the 4 key research areas of Bayer Healthcare (Oncology, Gynecology, Cardiology, and Molecular Imaging) and to the treatment paradigms indicated on the website.
2) Drugability of the target suggested.
3) Scientific rationale for target proposal (why is this a relevant target to treat a specific disease).

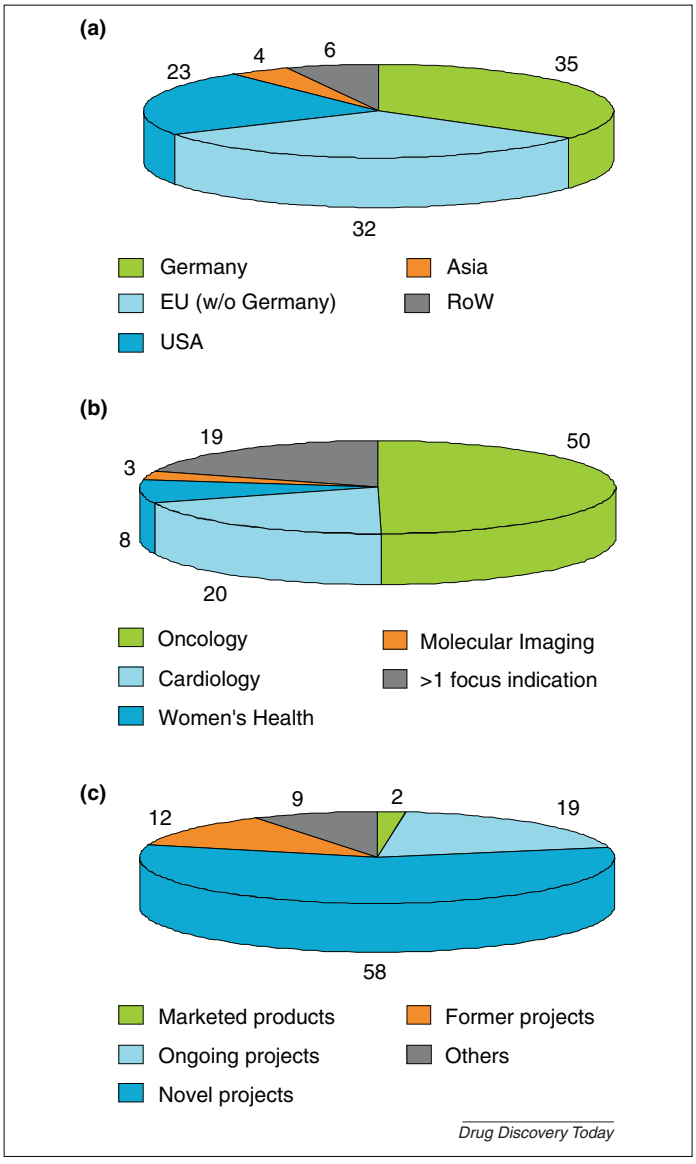

FIGURE 2

Results of three rounds of G4T applications. All data are given in % and are related to target ideas that matched our target criteria: **(a)** national distribution of applications received, (RoW, Rest of the World), **(b)** applications received per therapeutic area, **(c)** % of target ideas relating to targets of marketed compounds, projects currently pursued (ongoing) in-house, former projects, novel project ideas and others (such as projects related to identification of novel targets). Novel targets are defined as targets that have not been addressed previously for a particular therapeutic area or indication.

further promoted in academia, which can best be achieved in a close collaboration between industry and academic scientists, as done in the granted G4T projects. So far we approved 41 grants across all our strategic indications, resulting in an application success rate of approximately 15%. The main type of grant provided so far is the focus grant. In addition to ideas on novel targets, contacts with distinguished scientists in our key research areas were established, providing further insights into disease processes, and the initiative gained access to novel assays, tool antibodies or animal models with implications for ongoing internal projects.

As the program has delivered encouraging results so far, we aim to continue it with two annual deadlines (September 30 and March 31) and extend the international reach of the initiative. Furthermore, we are planning to extend the program and are in the process of establishing an additional similar initiative providing grants for novel lead compounds.

Concluding remarks

The Grants4Targets initiative provides a novel way of translating early drug target ideas into novel drugs. It is an open innovation approach following the idea of Chesbrough [7] to combine internal and external ideas to generate innovation. In our opinion, permeable boundaries and transparency in the communication of needs and strategic interests are essential prerequisites to enable open innovation. However, approaches like this can only be successful if they are part of an overall strategy on dealing with external innovation. Therefore, we have set up a holistic strategy process for sourcing innovation from the outside and generating value for both partners. Without real internal commitment and resources, the G4T initiative and any other collaborative effort cannot be successful. In our experience, a fast and efficient processing of the requests, a low bureaucratic burden for generating and granting the proposals and intensive personal direct contacts with the scientists in the academic institutes after the grant approval are key prerequisites for success. This is strengthened by the fact that know-how about drug development is limited in academia and an intensive exchange is required to generate awareness and understanding of the whole process.

The Grants4Targets initiative is an open innovation approach in line with a more general trend in the pharmaceutical industry [8,9] as well as academia to leverage the know-how of the 'crowd' to answer specific questions. Other programs following this trend are the 'Call for targets' program of MRC Technology (http://www.callfortargets.org) in the UK, the Phenotypic Drug Discovery Scheme of Eli Lilly (http://www.pd2.lilly.com) or the Pharma in Partnership Program (P*i*P, http://www.pharmainpartnership.gsk.com) of GSK. Another remarkable initiative in this direction is the Innovative Medicine Initiative, fostering know-how on drug development via an EU education and training program (http://www.imi.europa.eu) [10] by setting up respective master studies and programs.

Crowd sourcing is a powerful instrument to promote innovation if it is used appropriately. In general, the partnering model chosen has to match the question which the partnership is intended to address. Other interesting collaborative approaches are alliances with institutions or clusters, such as the partnership between Sanofi-Aventis and AVIEASAN, a network of French elite research institutes, which aims to foster new research areas such as ageing, immuno-inflammatory diseases, infectious diseases and regenerative medicine [11]. The advantage of this type of partnership is that it enables complex questions and novel, emerging research fields to be evaluated. By contrast, the size and complexity of such partnerships make

them challenging to manage, and this aspect requires adequate resources. The Incubator concept pursued by Pfizer and Biogen Idec (http://www.thepfizerincubator.com; http://www/bi3.biogenidec.com) is another interesting model which provides young start-ups with financial, infrastructural and strategic support while preserving the independence of the companies to maintain their entrepreneurial and innovative spirit. Virtual pharma discovery organizations such as the Center of Excellence for External Drug Discovery (http://www.ceedd.com) at GlaxoSmithKline are another way to promote drug discovery through external innovation. An established network with preferred partners from biotech companies and academia is a prerequisite for an undertaking of this kind, as is a high level of expertise in collaboration and alliance management. Furthermore, the links to the *in-house* R&D organization have to be managed well to promote the uptake of assets generated by this 'external drug development center' at a later stage of development (usually after proof of concept).

There is no 'one size fits all' solution for translating ideas from the university or start-up setting into novel drugs and for sourcing external innovation. The most suitable partnership model has to be chosen for the question to be addressed and the organizations involved. In addition, excellent alliance management and commitment in terms of resources, know-how and enthusiasm are key in generating value out of the partnership for both partners.

With roughly 280 applications from all over the world and 41 granted projects, the G4T program has delivered encouraging results so far. We therefore aim to continue the initiative with two annual deadlines (September 30 and March 31) and extend the international reach of the initiative. The feedback we received from academia further strengthened our positive evaluation and supported the view that such funds are required as bridging funds to bring forward ideas from research to the clinical stage.

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