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# Insights from an academic endeavor into central nervous system drug discovery

**Lieve van Veggel, An M. Voets, Tim Vanmierlo[*,#], Rudy Schreiber[*,#]**



Historically, "big pharma" did most central nervous system drug discovery R&D in-house. Yet, in modern times their "*management reductionism*" resulted in disappointing pipelines and pharma resided to (late) development, regulatory approval, and marketing (Thong, 2015). This had significant consequences for financing and executing research, resulting in a larger role for funding by governments and patient-organizations and a shift of research to academia (Mazzucato, 2013). Factors that make academia an attractive partner in drug discovery include: (1) their excellence in science; a sine qua non for successful drug discovery; (2) availability of open resources and incubators; (3) increasing interest in translational research, and (4) new educational programs to train drug researchers (Verkman, 2004; Shamas-Din and Schimmer, 2015; Schreiber et al., 2021). But drug discovery at academia remains a tall order and we will describe the lessons learned from an ambitious project on multiple sclerosis (MS). Our lab has extensive experience in the MS field and a strong valorization mind-set (Schepers et al., 2023; Tiane et al., 2023). It is crucial to keep searching for novel targets to treat MS, especially progressive MS and myelin repair, for which no cure nor appropriate treatment is currently on the market (Hauser and Cree, 2020). We investigated a novel molecular target: the excitatory amino acid transporter 3 (EAAT3).

**Our approach:** Like in industry (Verkman, 2004), we started our project with target identification and selection (**Figure 1**). There is a scientific rationale for our target for a variety of indications, including obsessive compulsive disorder, schizophrenia, and MS, due to EAAT3's role in counteracting glutamate excitotoxicity, as well as promoting glutathione synthesis (Bjørn-Yoshimoto and Underhill, 2016). EAAT3 contains a distinct expression profile in oligodendrocytes and neurons, the cells of interest in the context of demyelinating disorders. Together with our expertise, this funneled our focus to MS. We confirmed cellular expression profiles and modulation of EAAT3-affected oligodendrocytes, which are the key players in progressive MS. Few compounds targeting EAAT3 have been described (Shimamoto et al., 2004) and none of these are positive allosteric modulators (PAMs). Therefore, we chose EAAT3 PAMs as a highly innovative approach to treat MS.

Next, we had to secure funding and a project proposal was written. This was based on the typical steps in the early stages of the drug discovery process: target validation; *in vitro* and *in vivo* studies; and identification of PAMs ("hits"). Appropriate *in vitro* models to study myelination in MS were available for target validation, whereas hit identification required setting up partnerships with academic groups experienced in medicinal chemistry, as well as, in silico hit finding. Funding agencies liked our idea, especially the clear valorization potential and the highly innovative approach, and funding was granted for a fully paid PhD student for 4 years.

**Lessons learned – advantages:** Executing a drug discovery project in academia can provide researchers with several advantages.

First, it fosters a translational and valorization mind-set. Like their colleagues in the industry, academic researchers also have the patient in mind, meaning that a profound understanding of how results from a research project will translate to treatments that impact the life of a patient is highly beneficial. In our experience, this helps guide researchers through deciding which experiments are key to moving a project forward; for example, by focusing on behavioral measures with a good translational potential. This is what we did by using visual evoked potentials: a test that can be performed in both rodents and humans (Schepers et al., 2023). Academic research is primarily funded by government resources, as well as disease foundations funded by the public (such as the Fondation Charcot Stichting for MS research). Such research funding provides researchers with a duty to give back to society, especially as valorization is of increasing importance to funding organizations as well (Munari and Toschi, 2021). They will often ask researchers to explain the importance of the outcomes to a project for the general public. If this can be explained in detail and the importance is eminent, we have experienced that this can increase funding chances.

Second, since drug discovery requires a multidisciplinary approach, there is a need to set up appropriate, well-functioning collaborations/consortia. Setting up a drug discovery project is simply not possible without the help of external people and can therefore only strengthen a group's collaboration efforts with other institutes and, maybe more importantly, other disciplines. In our case, more than 5 new collaborations were set up, both national and international. All of them generated something tangible for the project, albeit not always with the expected outcome. These collaborations were fruitful nonetheless and good relationships were established, providing a great basis for potential future projects. It allowed researchers to broaden their skillset by research visits and learning new techniques that were not available at their home institutions. This contributes to further breaking down the barriers and limitations researchers face at home. Often, collaborators are more than happy to accommodate visiting researchers if they are independent and well-trained.

Third, novelty should be at the forefront of the project. This ties in with the first advantage where valorization should be always kept in mind and, as a consequence, the project needs to deliver something novel which is patentable. This requires researchers to sometimes think outside the box, to carefully follow the research field and competition, and to act quickly when needed. They also may need to pivot more frequently, in addition to clearly selecting the experiments, which provide the required novelty. In our experience, this will enhance the quality and translational value of the research, as well as push researchers to excel at aspects otherwise not encounter in a fundamental research setting.

All in all, looking at academic projects through a drug discovery lens has the ability to guide academic minds towards a more valorization-oriented approach, as well as to increase open collaborations and push for novelty.

**Lessons learned – pitfalls:** One reason that the preclinical drug discovery process takes only about 3 years in industry is the availability of sufficient budget. Although a project with a strong valorization focus is a good candidate for funding, opportunities remain limited. Especially when a project has been funded, perhaps even multiple times, at a certain point the so-called valley of death is reached. This means that the only way for a project to move forward, for example to human testing, is to partner with industry or create a spin-off. Big undertakings that have reduced the length of the drug discovery timeline such as high throughput screening, remain largely inaccessible to academia due to high costs. In addition, in academia experiments are often performed sequentially instead of in parallel, in order to reduce costs. This increases timelines. For example, it takes about 4 weeks to investigate target modulation in an *in vitro* model of myelination (primary mouse oligodendrocytes). If such an experiment, which involves sensitive primary cells, fails, it is often not known until the results are analyzed. Initiating several approaches to investigate target validation, such as viral transduction, CRISPR-Cas9, and pharmacological intervention, in parallel would save months. Unfortunately, the academic setting does not lend itself to this approach due to a lack of manpower, funding, and sometimes an inappropriate infrastructure.

In addition to budget, the nature of academia, often meaning completing a PhD trajectory, can also hinder drug discovery projects. A PhD project typically has a duration of 4 years and certain requirements need to be met in order to complete a thesis (e.g., a certain number of published papers) (Saqib et al., 2024). These factors, which often dominate at the end of the project, restrict the timeline even further and interfere with reaching the determined deliverables. Moreover, if during target validation the research indicates something contradictory, perhaps even making it necessary to switch disease areas, this is often not possible due to a lack of expertise or interest in the academic group. For example, in our project, we failed to identify an EAAT3 PAM and we would have therefore potentially benefitted from switching to an indication for which inhibition of the target might prove beneficial, such as obsessive compulsive disorder or schizophrenia. This proved unpractical and unachievable in the remaining time of the project.

Lastly, collaborations increase dependency on partners from outside of the organization. Of course, these dependencies do not only exist in academia, however, academics are more affected by this due to limited resources and less flexibility.

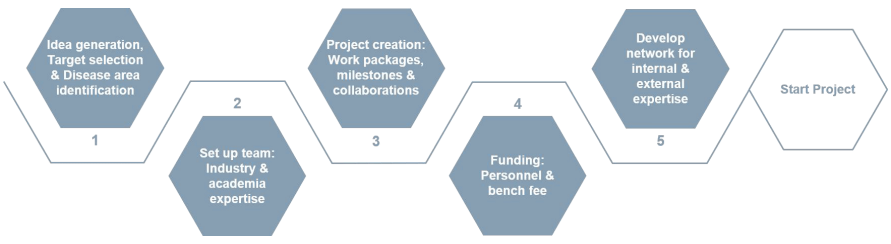


**Figure 1** | **General workflow for the setup of our academic drug discovery project.**
Created with Microsoft PowerPoint.

This can lead to unforeseen delays and the risk of people not delivering what they initially promised. Due to the often-hierarchical nature of academia, it can be difficult for a PhD student to get things arranged quickly since often this requires contact between Principal Investigators or more senior staff, who may experience a high work load. Dependencies and high work load contribute to the slower pace observed in academia, which might lead to a domino effect if any of the other pitfalls come into play. In our case, we had to pivot numerous times when it came to our *in vivo* model. Our determination to put the most accurate and translational model in place (e.g. getting caught up in details), eventually cost us valuable time. We wanted to create overexpression of our target, EAAT3, specifically in our cells of interest, oligodendrocytes. This should be very feasible in light of recent progress in the generation of animal models. However, our ideal transgenic mouse was located on the other site of the globe, with our collaborators in Chile. Together with a global pandemic that halted global transportation, it was impossible to obtain this model in our lab. Reiterating the fact that communication is sometimes slow in an academic setting, it took us many months to pivot to a different animal model.

Taken together, drug discovery in an academic setting should be addressed carefully to avoid unnecessary failure and a waste of resources due to a lack of funds, time pressure, or complicated dependencies between academic partners. In **Figure 2**, a general overview of the strengths, weaknesses, opportunities, and threats is depicted for academic drug discovery projects.

**Set up for success:** In our experience, the requirements to make a drug discovery project a success require a solid scientific basis; the right team; and access to appropriate techniques. Importantly, success should be measured by the completion of the desired work packages while performing "good science," and not only by, for example, end deliverables, such as the number of hit compounds identified. A solid scientific basis is essential and in drug discovery, this often means that target identification needs to be established before projects start. The indication does not necessarily need to be nailed down. It might even be an advantage to investigate the target in a broader context. Furthermore, it proved crucial to bring together the right expertise early on in the project. This requires thinking ahead to have the right expertise available at the right time. This is absolutely not trivial in the academic world and calls for the development of good relationships where all partners are honest about their capabilities and will benefit from the project. Of course, a part of research is thinking on your feet and tackling problems when they arise, meaning that collaborations might need to be sought out at an instant. Nonetheless, preparation and planning might help with this since it increases the network and thus opportunities. The final requirement is that the techniques used in the project need to be validated and robust, either at the home institute or with collaborators. Science should be cutting edge whenever possible, though getting techniques up and running and optimization takes time, which is already valuable in a drug discovery project. Carefully choosing which techniques to use to reach the desired deliverables in a project, are vital in setting up for success.

Overall, drug discovery in academia is a challenge. But despite this challenge, it is also necessary for patients and researchers. Patients should be at the forefront of every research project, no matter how fundamental. In turn, researchers can develop a more diverse skillset when drug discovery is part of their scientific journey. Sharing our experiences in this perspective hopefully provides insights that will be valuable for drug discovery projects in academia, since it is an excellent way to learn for all parties involved and helps to add to the valorization potential of academic groups and institutes.

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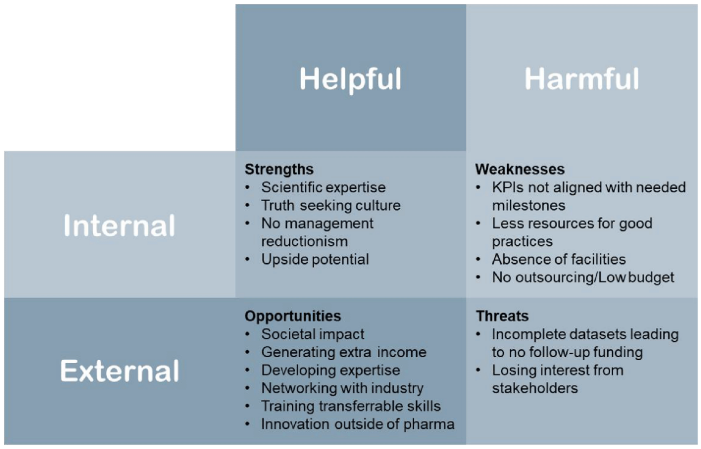


**Figure 2** | **SWOT analysis of the drug discovery in academia project indicating strengths, weaknesses, opportunities and threats.**
Created with Microsoft PowerPoint. KPIs: Key Performance Indicators; SWOT: Strengths, Weaknesses, Opportunities, Threats.

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