

CNS Drug Discovery in Academia: Where Basic Research Meets Innovation

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The involvement of academic research in drug discovery is consistently growing. However, academic projects seldom advance to clinical trials. Here, we assess the landscape of drug discovery within the National Centre of Competence in Research (NCCR) TransCure launched by the Swiss National Science Foundation to foster basic research and early-stage drug discovery on membrane transporters. This included transporters in central nervous system (CNS) disorders, which represent a huge unmet medical need. While idea championship, sustainable funding, collaborations between disciplines at the interface of academia and industry are important for translational research, Popperian falsifiability, strong intellectual property and a motivated startup team are key elements for

1. Introduction

Drug discovery is widely discussed as a possible asset of academic research as drug development in the pharma industry is facing an innovation crisis, especially for neuropsychiatric disorders.[1–3] One reason for this crisis that has already been discussed extensively is the so-called "low hanging fruit" or "mining out" problem.^[4-5] It states that the comparably straightforward scientific questions have been solved and only the more complex disease targets are left which are not entirely understood yet and more difficult to investigate.^[4] Another reason is the lack of reproducibility of research data, hampering successful translation.^[5] The latter is related to the overstated emphasis on data from model organisms like inbred mouse lines and of artificial disease models used in preclinical research. Nevertheless, molecular genome-altering technologies such as CRISPR/Cas9 allowing for relatively fast introduction of genetic mutations into the germ line of mice, recent developments of

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innovation. This is exemplified by the NCCR TransCure spin-off company Synendos Therapeutics, a clinical stage biotech company developing the first selective endocannabinoid reuptake inhibitors (SERIs) as novel treatment for neuropsychiatric disorders. We provide a perspective on the challenges related to entering an uncharted druggable space and bridging the often mentioned "valley of death". The high attrition rate of drug discovery projects in the CNS field within academia is often due to the lack of meaningful animal models that can provide pharmacological proof-of-concept for potentially disruptive technologies at the earliest stages, and the absence of solid intellectual property.

somatic transgenesis using viral vectors, "humanization" of animal disease models, developments in neuroimaging, as well as manipulations of gene expression using shRNA and antisense oligonucleotides now enable an in-depth validation of new drug targets relatively easily.^[6-8] However, promising data from preclinical studies are not always recapitulated in clinical trials. Thus, innovation remains limited when it comes to translation of knowledge from basic research, causing massive development costs of drugs.^[9] Gaudilliere provided a comprehensive economic analysis of the debates on innovation in the drug sector.^[10] Because curiosity is the driving force in basic research, even the remotest drug discovery hypotheses can be refuted or confirmed experimentally. Consequently, new drug discovery concepts from academia, where research focuses on biochemical mechanisms that can be targeted by small molecules or biologics, have generated potential and actual opportunities for translational research. Despite the discussed innovation crisis, pharmaceutical innovation has significantly increased over the last several decades and so called "Pioneers", which are new molecular entities whose chemical scaffolds were not used in any previously FDA-approved drugs, are emerging widely as new therapies.[11–13] The design of ligands, either small molecules or proteins is easier than ever and can be achieved through services and the increasing number of high-resolution structures of macromolecules from cryoEM or AlphaFold3 in public databases provide new opportunities to target hitherto unknown functional motifs.^[14-15] Thanks to the accessibility of purchasable compound libraries (e.g. found in ZINC20 or Pubchem) and advances in synthetic chemistry, novel tools or drug prototypes can be developed relatively easily and enable the exploration of yet unknown biochemical systems. Moreover, public databases reporting "omics data" from healthy and diseased patients help to validate drug discovery ideas.[16]

Accordingly, the argument of drug discovery, besides the general disease context of the life sciences, is heavily used in grant proposals, research papers, as well as to encourage young researchers to engage in an academic career path. Drug discovery targeting the central nervous system (CNS) is particularly challenging $[17]$ because it requires the combined skills of neuroscience and basic pharmacology, the latter often being neglected in academia. Major factors responsible for the failures in CNS drug development are a) the lack of understanding of the basic principles of CNS physiology and disease, b) the overemphasis on data from rodent models, c) unpredicted CNS side effects, and d) the inability of drugs to efficiently penetrate the blood-brain barrier (BBB). Regrettably, neuropsychological disease states in primates are rarely recapitulated in rodents due to fundamental differences like types of human astrocytes not found in rodent brain and more extensive arborisation of dendritic fields associated with dendritic action potentials in human neocortex than in rats or mice.[18] A decade ago, a number of late stage failures in development, particularly in Alzheimers Disease (AD), coupled with the high costs associated with testing new molecules in humans, resulted in several pharmaceutical companies significantly scaling back or halting drug development for psychiatric and other CNS disorders. This trend has reversed in recent years as a result of successful progress with AD treatments and in psychiatric disorders among biotech companies. Innovation in drug discovery is increasingly outsourced and pharma companies acquire innovative and successful clinical stage phase 2 biotechs.^[19] A good example is the successful phase 3 programme for KarXT in schizophrenia from Karuna which resulted in its acquisition by Bristol Myers Squibb for USD 14 billion in December 2023.

2. The NCCR TransCure (2010–2022)

Membrane proteins are iconic drug targets and Sriram and Insel^[20] estimated that \sim 700 approved drugs act on GPCRs, implying that approximately 35% of approved drugs target GPCRs. Ion channels have been recognized to yield a still insufficiently explored biochemical space of feasible drug targets. It has been estimated that 10–20% of small molecule drug targets are voltage- or ligand-gated ion channels, resulting in numerous potential new drug candidates.^[21] In the case of membrane transporters such as solute carriers, given their emerging roles in diseases, the space for drug discovery remains largely unexplored.^[22-23] This gave the impetus for the argument of reinforcing basic research and drug discovery on transporters. In 2010, the NCCR (National Centre of Competence in Research) TransCure^[24] was funded by the Swiss Government also based on one of its promises related to transporter research "from genes to drugs", hence the name TransCure (TRANSporter and CURE). A key idea of the NCCR TransCure was the generation of new transporter ligands that could act as novel tool compounds and/or drug leads. For that reason, in many projects synthetic chemistry played an important role. Together with structural biology and physiology, chemistry platform on which fundamental research and drug discovery were executed. A knowledge and technology transfer (KTT) committee was established to encourage meaningful collaborations with pharma industry and to create an awareness that drug discovery can be feasible within NCCR TransCure. For instance, the collaboration with the Novartis Institutes for BioMedical Research (NIBR) encompassed several aspects, such as the scale-up of physical high-throughput screening (HTS) assays on specific transporters (vide infra) and education. Within the framework of the project on the amino acid transporter SLC7A5 (LAT1) LAT1,^[25] TRPM4^[26] and iron transport,^[27] we could sign agreements for the use of the FASTLab facilities at the NIBR Basel, to execute HTS on chemically diverse public domain libraries offered by Novartis. Realizing that innovation is a culture that needs continuous inspiration, NCCR TransCure also engaged in the startup events Swiss Company Maker and later Bench2biz.^[28] The pre-seed workshops for aspiring entrepreneurs have been a major activity to support young scientists with a bold vision for translation, hence from bench to the market. These workshops targeted researchers with premature to early-stage marketable ideas who wanted to enter the Swiss startup ecosystem.^[29] The KTT committee soon realized that a solid understanding of patents is a key element in translational research. We therefore initiated a cooperation with the Swiss Federal Institute of Intellectual Property (IPI) and we agreed that solid IP is key for any technology transfer endeavour.

formed the "trias" and constituted the pillars that supported the

Because of the limited resources in synthetic chemistry within NCCR TransCure, in silico methodologies, in particular ligand shape and pharmacophore similarity, became quickly instrumental for identifying purchasable molecules for initial screening.^[30] This powerful technology worked very successfully in different projects and enabled a fast identification of new small organic molecules with low micromolar potency (generally inhibitors), providing feasible starting points for further synthetic development of bioactive chemical scaffolds.^[30] In several projects some degree of synthetic optimization and medicinal chemistry was implemented, and more potent inhibitors could be developed based on structure-activity relationship (SAR) studies. However, in most projects the SAR data did not reach the depth of a pharma drug discovery project and data were published prematurely (Figure 1). As shown in a decision tree analysis (Figure 2), a major bottle neck was the generation of IP which proved to be instrumental for translation (vide infra). Even though NCCR TransCure successfully developed different tool compounds, including potent inhibitors of for the ion channels transient receptor potential cation channel subfamily V member 6 (TRPV6)^[31] and TRPM4,^[26] LAT1,^[25] ATP-binding cassette super-family G member 2 $(ABCG2)$,^[32] endosomal Na + /H + exchangers $(NHEs)$,^[33] calciumsensing receptor (CaSR),^[34] targeting astrocyte-specific vesicular monoamine transporter VMAT2 via astrocytic SLC01 C1 (OATPC1) transporters, and selective endocannabinoid cellular uptake,[35] performing groundbreaking research in structure biology and physiology, $[36-38]$ translation towards drug discovery remained sluggish. There were substantial problems related to the development of drug-like molecules and IP generation. As

Figure 1. The process of drug discovery and development in four stages. Innovative projects aiming at developing new drugs invest considerable efforts at stage 3 to obtain pharmacological and genetic proof of concept in mice, full toxicological assessment in different animals, knowledge on drug administration, distribution, metabolism and excretion (ADME), as well as pharmacodynamics (PD). In basic academic research, stage 3 is usually omitted, and new concepts are published prematurely without challenging or refuting the technology (hope sign). To move drug discovery projects beyond stage 2, the protection of technologies and IP rights is fundamental to enable translation at stage 4. Evidence-based medicine requires a series of clinical assessments in which the drug safety and efficacy is challenged and often refuted (death sign) in randomized placebo-controlled clinical trials.

Figure 2. Decision tree analysis of the drug discovery process in NCCR TransCure. The numerical probabilities of chance nodes are shown as decimals (rounded to one digit) and illustrate the bottlenecks for innovation in academia. After medchem, IP (patents) were critical for successful startups. MTS, medium-throughput screening, SAR, structure-activity relationship, POC, proof of concept, PK, pharmacokinetics, PD, pharmacodynamics, NDF, non-dilutive funding. The tress is represented by lines (branches), squares (decision nodes), circles (chance nodes) and triangles (end nodes).

illustrated in Figure 1, the journey from making new molecules to obtaining experimental evidence of their efficacy in vivo and successfully obtain IP is long and cumbersome and requires pragmatic entrepreneurial skills not established at universities. This led to a strong bias towards publishing over patenting.

3. How to Select the Right Seedlings for the Flourishing Drug Discovery Startup Ecosystem: The Power of Falsifiability

Creativity is thinking up new things. Innovation is doing new things. Theodore Levitt.

Based on the analysis of NCCR TransCure drug discovery, we tried to analyze the more fundamental problems in drug discovery attempts relating to entrepreneurial spirit rather than technological shortcomings. Undoubtedly, rodent experiments do not fully predict the bioavailability and central effects in humans and informal human testing could be instrumental to understand whether the technology works in principle. The analysis indicates that within the NCCR TransCure basic pharmacology was neglected. Unlike in industry, where it is prohibited to perform self-experimentation, universities do not generally prohibit it. Although debated as ethically questionable, informed self-experimentation by experts is scientifically legitimate and ethically sound.^[39] The transition from bench to bedside is exceedingly complex and lengthy, and the number of drug withdrawals has increased to historic highs, especially also in the CNS domain.^[40-41] Few scientists completely object to the possibility that their research could lead to innovative technologies, or even inspire the foundation of startup companies. Nevertheless, some scientists still see a conflict regarding translation and believe that drug discovery should stay within the pharma industry. Basic research is often seen as an unbiased enterprise at liberty that should be protected from economic interests and thus freely investigates how biology works without a priori expectations to be useful or profitable. We believe that this view is mistaken because a) the financial sources that fund research ultimately come from capitalistic societies through foundations or taxpayers (including profitoriented companies) and b) because translational research makes scientific concepts stronger and helps to accelerate the development of drugs that not only benefit industry but also humanity, which is the goal of medicine and life sciences. Research is a curiosity-driven process, based on the principles of science (reproducibility) and knowledge acquisition (understanding causalities). Analyses on the impact of academic research in cancer treatment and infectious diseases provided constructive evidence that taxpayer-supported research can successfully address public health needs.^[42] As discussed by Kinch et al., the optimistic view on the role of academia in drug discovery is consistent with the prominence of entrepreneurial ventures supported by academic intellectual property as a sustaining force for the biotechnology revolution, which began in the 1970.^[42] Let us imagine that there is a connection between knowledge, experimental observation, creativity, and innovation. Knowledge is continuously changing based on new insights that are generated through research. We perform experiments to either prove or falsify hypotheses that sustain broader theories. Yet, often the so called "negative data", which do not support the common theories or paradigms, are ignored, or put aside as "not understood". Negative data cannot be ignored in science and translation because they provide the

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foundation for groundbreaking new ideas that can lead to disruptive technologies. The famous science philosopher Karl Popper (1902–1994) stressed throughout his work the importance of falsifiability.[43] In drug discovery and translational research, falsifiability is one of the most important gateways to abandon ideas that do not work. Fixed ideas, by definition, are persistent, and hard to abandon, and they flourish in academia. Steve Fuller in his "The Knowledge Book" provides an excellent historical account of the nature of knowledge and social epistemology that also influence technologies and industries.^[44] This goes along with big or small paradigm shifts described in Kuhn's 1962 landmark book "The structure of scientific revolutions".^[45] In current drug discovery, in addition to the recent mRNA technologies, 3D biology and artificial intelligence (AI), promises regarding a change in thinking (i. e. paradigm shift) could be systems therapeutics, i.e. moving away from the 'one-size-fits-many' approaches and adopting a 'precision medicines' approach, for which entirely different models for therapeutic interventions apply^[46] or rational network pharmacology.^[47] The recently introduced approach of ligandomics, which relates to disease-selective drug target identification, could further accelerate drug discovery,^[48] but the biggest impact could be related to empowering AI-driven algorithms in data analysis^[49] and the return to academic selfexperimentation.^[39]

Possibilities and hopes are sold most expensively, or as Thucydides put it "hope is an expensive commodity". While universities foster creativity and knowledge creation, they may be less demanding when it comes to innovation, (i. e. doing new things) which paradoxically is both the university's strength and weakness. The selection of the right projects for successful translation, e.g., via startups, licensing out IP to companies, or to engage in meaningful industry collaborations depends on many factors. These include the potentially disruptive nature of the technology, the IP situation, the economic case for development, and the dedicated research team aiming at developing the technology. Once we realized that the NCCR TransCure lacks preclinical pharmacological expertise, we expanded the Screening, Profiling and Analytical Facility (SPAF) to include LC-ESI-MS/MS analytics.^[50] This allowed for early PK characterization of drug leads *in vivo*, thus supporting or refuting their potential for IP. As illustrated in Figure 2, the selection of projects that may successfully lead to academic startups directly depends on their IP situation and, of course, the entrepreneurial team behind the development of the technology. Since drug development is costly, only defendable technologies that can be protected through granted patents or trade secrets have a chance to be successful for translation. To promote strong patents, the NCCR TransCure KTT board established the "4 N rule" to be considered for composition of matter IP applications with small molecules:

- 1 New: The molecule(s) should be new (e.g. not be found in SciFinder) and relate to a new group of molecules that can be protected by a Markush formula.
- 2 Not yet published anywhere (also no mention of the molecule on the internet).
- 3 Not a pan-assay interference compound (must have drug-like properties and reasonable potency).
- 4 Novel biological effect that can be associated to a therapeutic or diagnostic value.

Not surprisingly, throughout the NCCR TransCure emphasis was put on publishing papers and not on IP generation, which directly hindered translation of potentially innovative technologies. What went wrong? During the time as KTT delegate, the first author was confronted with the opinion that the purpose of scientists is to "create knowledge" and not to be innovative, which ultimately infers different motivations. We believe that the problem was a lack of entrepreneurial spirit and the missing examples of successful pharma startups within the research network. It needs a startup biotope to grow new startups. The entire startup ecosystem in Switzerland, also driven by academia, has been growing steadily over the last decade and is now worth a total \$149 Billion, thus three times more since 2016, with significant value driven by the country's leading health and biotech startups, and university spinouts.^[51] According to dealroom.co, Switzerland, despite being a small country by population, is particularly entrepreneurial, with more startups per capita than its bigger neighbours. It has also created more unicorn startups (a private startup company with a value of over \$1 Billion) per capita than anywhere else in Europe but Sweden.^[52-53] A frequently asked question is how one can reach a development stage at university to attract sufficient funding to have a functional startup that can progress fast enough without getting trapped in the "valley of death" (vide infra). We believe that it is crucial to generate strong pharmacological data as early as possible. When it comes to drug discovery with small molecules, one problem is that biological assays used in academia often generate highly potent inhibitors in vitro under highly artificial conditions and the potency is not repeated in high-content assays or in vivo. There are two kinds of proof-ofconcept studies that are important in drug discovery. First, target validation in vivo and second, ligand validation in vivo. The NCCR TransCure SPAF, was established to provide workforce, expertise and equipment required to develop and validate screening assays for diverse transporter targets and for preclinical pharmacology. The SPAF assisted PIs from the individual projects in upscaling their assays for screening of small molecules in a typical medium-throughput screening (MTS) format (*<*6'000 compounds), and if required for selectivity studies. Compounds were typically provided by the chemistry groups either as targeted libraries selected by virtual screening, from CROs, or as series of focused synthetic compounds generated in house or in collaboration with industry partners. A focus of the SPAF was to engage more in translational research and help early decisions on the metabolic stability and proof of concept studies in vivo. The collaboration with clinics for reverse pharmacology and biomarker discovery projects further accelerated translation.

4. Translating Basic Science Into Drug Development: Synendos Therapeutics

The endocannabinoid transport project was considered a highrisk project within NCCR TransCure for several years as the exact molecular target responsible for endocannabinoid membrane transport remained elusive until recently^[54] (scientific publication in preparation). Unlike other projects that followed a target-based approach, this project embarked on a phenotypebased strategy to develop a new class of modulators in endocannabinoid system (ECS) pharmacology named selective endocannabinoid reuptake inhibitors (SERIs).^[35]

The ECS is a lipid biochemical system comprised of two Gprotein couple receptors, named cannabinoid receptors type-1 (CB1R) and type-2 (CB2R), a class of N-arachidonoyl derived ligands called endocannabinoids (i. e. 2-arachidonoly glycerol, 2-AG and N-arachidonolyethanolamine, AEA), a series of biosynthetic (e.g. NAPE-PLD, DAGL) and degrading (fatty acid amide hydrolase, FAAH and monoacyl glycerol lipase, MAGL) enzymes and a class of endocannabinoid carrier proteins (e.g. fatty acid binding proteins (FABPs), heat shock protein 70 (HSP70), albumin).^[55] The ECS responds to different forms of stress and plays a fundamental role for homeostasis.^[56-58] Endocannabinoids modulate (attenuate) chemical neurotransmission at synapses in the brain.^[59-60] They are biosynthetically generated from arachidonic acid-containing phospholipids and thus connect neurotransmission with inflammatory processes through an intriguing and yet poorly understood endocannabinoid-prostaglandin axis. The ECS is fundamental to maintaining balance in our brain. Several neurological and neuropsychiatric disorders show an altered or even deficient ECS.^[61-65] From the beginning of the NCCR TransCure, we were convinced that the plasma membrane transport of endocannabinoids was worth investigating as it had a significant translational potential. It was already clear that if we could selectively block endocannabinoid cellular reuptake in neurons by using small molecules that enter the brain, this would be a potential new mode of action for drug discovery and development in this field.

The reason why the endocannabinoid transport project endured in the NCCR TransCure was mainly due to the very robust pharmacological and cellular data strongly suggesting that a druggable membrane protein exists (i.e. the putative transporter) that facilitates the diffusion of endocannabinoids across the cell membrane.^[35,55,66] Strong proof of concept was obtained both in vitro and in vivo using the tool compound WOBE437, the prototype of first-generation SERIs.^[35,67-69] Considering that the idea was conceived around 2011/2012 and Synendos Therapeutics was founded in 2019 (Figure 3), one can easily understand that it was a long journey. The success of the project was rooted in the collaborative research within the network, the serendipitous discovery of a novel biochemical mechanism that controls the levels of endocannabinoids at the cannabinoid receptors in the brain, and a critical knowledge of comparative pharmacology within the ECS. The success story is also closely related to a fruitful collaboration between scientists and IP experts. Indeed, IP protection of inventions is crucial for

Figure 3. History of the development of selective endocannabinoid reuptake inhibitors (SERIs): From the idea to a clinical-stage biotech company.

translational projects in drug development. Related to this, it was also fundamental that researchers engaged in the overall iterative process of questioning or refuting old technologies and inventing new ones. Synendos was founded to ensure that the results of the scientific research could be translated into a commercial entity able to explore the therapeutic potential of this new mode of action in patients with mental illness. To prevent being trapped in the "valley of death", referring to the challenging period that many new companies face between their initial formation and the point at which they start generating sufficient investments or revenue to sustain their operations, Synendos acquired significant non-dilutive funding (*>*4 Million CHF) and counted on the startup mentoring from BaseLaunch, an incubator focused on launching and growing the next generation of biotech companies. In addition to the grants obtained by our research group at the University of Bern (e.g., EIN Roche), Synendos Therapeutics has obtained several other grants from public and non-profit institutions in Switzerland and in Europe to support initial development of the project. The EIN Roche grant obtained early in the project allowed us to make an important step towards drug discovery and development and to design second generation drug-like SERIs, in collaboration with a specialized medicinal chemistry service provider. Five years after incorporation, Synendos Therapeutics has completed non-clinical development of the SERI drug candidate SYT-510 and has initiated Phase 1 clinical development in healthy volunteers, marking the significant transition into a clinical stage biotech company. The mission of Synendos is to develop breakthrough safe and effective therapies for neurological and neuropsychiatric disorders through modulation of the ECS with SERIs to enable restoration of the natural functioning of the brain. Synendos continues to successfully collaborate with the University of Bern on basic and translational research in the field of endocannabinoid membrane transport. The aim is to capitalise on the scientific expertise in the field of ECS biology and pharmacology to expand the portfolio of drug candidates acting with novel modes of action to tackle unmet needs in human medicine. This symbiotic relationship is key to ensuring the dissemination and understanding of the data supporting the SERI technology among the scientific community.

A strength of the project is the novel ECS modulation of SERIs. The pharmaceutical industry is looking for patent protected disruptive technologies with the potential to be "game changers" in the field, addressing unmet medical needs. While basic research does not routinely yield such technologies,opportunities for drug discovery in academia are substantial. The risk of failure of clinical drug development is more than 90% which creates huge costs.^[64] Clinical drug candidates are therefore carefully selected based on criteria often unknown to academia, which is a major problem. Translational research is more than "from bench to bedside" as it is a two-way street. It's a loop between non-clinical and clinical stakeholders, a continuous cycle, with one research result inspiring another. In drug discovery this process definitively starts with the clinical development.

5. Conclusions

The journey of drug development from bench to bedside is a long hurdle race that suffers from a high attrition rate, especially at early stages of development. Academia represents an optimal ecosystem to combine basic research and drug discovery. The complexity to recapitulate human disease in nonclinical models (especially in the CNS space), the difficulty to validate novel drug targets and the limited medicinal chemistry and translational pharmacology expertise represent some of the challenges faced in basic academic research. Nonetheless, academia offers a unique environment to enable multidisciplinary collaborative efforts to translate promising findings into valuable drug discovery programmes. In this context, falsifiability exerts a critical gatekeeper function to enable abandoning ineffective ideas while paving the way for potential disruptive technologies. The flexibility to change paradigms and follow new intuitions is an intrinsic feature of basic research that empowers academia to a leading role in innovation. The endocannabinoid transport project within NCCR TransCure exemplifies the challenges and strengths of academic research in the pursuit of innovation. Starting as highrisk endeavour, this drug discovery project diverged from a more conventional target-based approach to adopt a better suited phenotype-based strategy which culminated in the development of SERIs, a novel class of endocannabinoid system modulators. The lead candidate of SERIs has reached clinical development and represents a new therapeutic approach for CNS disorders. We believe it is the fine balance between optimism and scepticism combined with a problem-solving attitude, curiosity and a rigorous scientific approach that puts academia in the driving seat to spark innovation towards developing disruptive technologies to improve human health.

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Conflict of Interests

AC and JG are co-founder of Synendos Therapeutics. JG serves on the scientific advisory board of Synendos Therapeutics. AC is an employee of Synendos Therapeutics.

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- [1] U. Laermann-Nguyen, M. Backfisch, SN Business & Economics 2021, 1, 164. <https://doi.org/10.1007/s43546-021-00163-5>.
- [2] M. D. Tricklebank, T. W. Robbins, C. Simmons, E. H. F. Wong *Psychopharmacology (Berl).* **2021**, *238*, 2045, doi: [10.1007/s00213-021-05859-y](https://doi.org/10.1007/s00213-021-05859-y).
- [3] I. Cockburn (2006) Is the pharmaceutical industry in a productivity crisis? Innov Policy Econ 7 :1–32. [https://doi.org/10.1086/ipe.7.](https://doi.org/10.1086/ipe.7.25056188) [25056188](https://doi.org/10.1086/ipe.7.25056188).
- [4] P. Danzon, E. Keuffel, (2014) Regulation of the Pharmaceutical-Biotechnology Industry. In: Rose N (ed) Economic Regulation and Its Reform: What Have We Learned? University of Chicago Press, Chicago, 2014, pp 407–484.
- [5] S. V. Frye, M. R. Arkin, C. H. Arrowsmith, P. J. Conn, M. A. Glicksman, E. A. Hull-Ryde, B. S. Slusher, *Nat. Rev. Drug Discovery* **2015**, *14*, 733. doi: [10.1038/nrd4737.](https://doi.org/10.1038/nrd4737)
- [6] H. Li, Y. Yang, W. Hong, M. Huang, M. Wu, X. Zhao, *Signal Transduct Target Ther.* **2020**, *5*(1), 1. doi: [10.1038/s41392-019-0089-y.](https://doi.org/10.1038/s41392-019-0089-y)
- [7] A. Zuberi, C. Lutz, *ILAR J.* **2016**, *57*(2), 178–185.
- [8] The role of machine learning in neuroimaging for drug discovery and development. O. M. Doyle, M. A. Mehta, M. J. Brammer, *Psychopharmacology* **2015**, *232(21-22)*, 4179–89.
- [9] S. Andrew, Khalil, Rudolf Jaenisch, David J. Mooney, *Adv. Drug Delivery Rev.* **2020**; *158*, 116–139. doi: [10.1016/j.addr.2020.09.012](https://doi.org/10.1016/j.addr.2020.09.012).
- [10] Jean-Paul Gaudilliere, *BioSocieties* **2021**, *16*, 411–432.
- [11] J. R. Everett, *Expert Opin. Drug Discovery* **2015**, *10*(9), 937–44.
- [12] T. J. Wills, A. H. Lipkus, *ACS Med. Chem. Lett.* **2020**, *11*(11), 2114–2119. doi: [10.1021/acsmedchemlett.0c00319.](https://doi.org/10.1021/acsmedchemlett.0c00319)
- [13] S. L. Schreiber, J. D. Kotz, M. Li, J. Aubé, C. P. Austin, J. C. Reed, H. Rosen, E. L. White, L. A. Sklar, C. W. Lindsley, B. R. Alexander, J. A. Bittker, P. A. Clemons, A. de Souza, M. A. Foley, M. Palmer, A. F. Shamji, M. J. Wawer, O. McManus, M. Wu, B. Zou, H. Yu, J. E. Golden, F. J. Schoenen, A. Simeonov, A. Jadhav, M. R. Jackson, A. B. Pinkerton, T. D. Chung, P. R. Griffin, B. F. Cravatt, P. S. Hodder, W. R. Roush, E. Roberts, D. H. Chung, C. B. Jonsson, J. W. Noah, W. E. Severson, S. Ananthan, B. Edwards, T. I. Oprea, P. J. Conn, C. R. Hopkins, M. R. Wood, S. R. Stauffer, K. A. Emmitte, *Cell.* **2015**, *161*(6), 1252–65. doi: [10.1016/j.cell.2015.05.023](https://doi.org/10.1016/j.cell.2015.05.023).
- [14] M. J. Robertson, J. G. Meyerowitz, G. Skiniotis, *Trends Biochem. Sci.* **2022**, *47*(2), 124–135.
- [15] S. Agajanian, M. Alshahrani, F. Bai, P. Tao, G. M. Verkhivker, *J. Chem. Inf. Model.* **2023**, *63*(5), 1413–1428.
- [16] M. A. Trapotsi, L. Hosseini-Gerami, A. Bender, *RSC Chem Biol.* **2021**, *3*(2), 170–200.
- [17] C. M. Hempel, C. A. Werley, G. T. Dempsey, D. J. Gerber *Drug Discovery Today Technol.* **2017**, *23*, 17–25.
- [18] M. Dragunow, *Trends Pharmacol. Sci.* **2020**, *41*(11), 777–792.
- [19] [https://www.harriswilliams.com/our-insights/hcls-return-on-innovation](https://www.harriswilliams.com/our-insights/hcls-return-on-innovation-part-8-investing-in-drug-discovery)[part-8-investing-in-drug-discovery](https://www.harriswilliams.com/our-insights/hcls-return-on-innovation-part-8-investing-in-drug-discovery).
- [20] K. Sriram, P. A. Insel, *Mol. Pharmacol.* **2018**, *93*(4), 251–258. doi: [10.1124/](https://doi.org/10.1124/mol.117.111062) [mol.117.111062](https://doi.org/10.1124/mol.117.111062).
- [21] S. K. Bagal, A. D. Brown, P. J. Cox, K. Omoto, R. M. Owen, D. C. Pryde, B. Sidders, S. E. Skerratt, E. B. Stevens, R. I. Storer, N. A. Swain, *J. Med. Chem.* **2013**, *56*(3), 593–624. doi: [10.1021/jm3011433.](https://doi.org/10.1021/jm3011433)
- [22] The International Transporter Consortium. *Nat Rev Drug Discov* **2010**, *9*, 215–236. doi: 10.1038/nrd3028.
- [23] A. César-Razquin, B. Snijder, T. Frappier-Brinton, R. Isserlin, G. Gyimesi, X. Bai, R. A. Reithmeier, D. Hepworth, M. A. Hediger, A. M. Edwards, G. Superti-Furga, *Cell.* **2015**, *162*(3), 478–87. doi: [10.1016/j.cell.2015.07.022.](https://doi.org/10.1016/j.cell.2015.07.022)
- [24] NCCR TransCure Excellence in Membrane Transport Research from **2010** until **2022**. H. Abriel, J. L. Reymond, *Chimia (Aarau).* **2022**, *76*(12), 989.

- [25] Structure, Function and Pharmacology of SLC7 Family Members and Homologues. J. M. Jeckelmann, J. Zaugg, V. Morozova, J. Müller, S. Kantipudi, M. Schroeder, J. Graff, C. Albrecht, K. H. Altmann, J. Gertsch, D. Fotiadis, *Chimia (Aarau).* **2022**, *76*(12), 1011–1018.
- [26] Targeting Ion Channel TRPM4. B. Preti, J. S. Rougier, I. Papapostolou, F. Bochen, C. E. Gerber, H. Abriel, M. Lochner, C. Peinelt, *Chimia (Aarau).* **2022**, *76*(12), 1039–1044.
- [27] The Structural Basis for Metal Ion Transport in the SLC11/NRAMP Family. C. Manatschal, R. Dutzler, *Chimia (Aarau).* **2022**, *76*(12), 1005–1010.
- [28] [https://bench2biz.ch/.](https://bench2biz.ch/)
- [29] <http://www.neworks.biz/index.html>.
- [30] J. L. Reymond, *Chimia (Aarau).* **2022**, *76*(12), 1045–1051.
- [31] C. Simonin, M. Awale, M. Brand, R. van Deursen, J. Schwartz, M. Fine, G. Kovacs, P. Häfliger, G. Gyimesi, A. Sithampari, R. P. Charles, M. A. Hediger, J. L. Reymond, *Angew. Chem. Int. Ed. Engl.* **2015**, *54*(49), 14748– 52.
- [32] S. M. Jackson, I. Manolaridis, J. Kowal, M. Zechner, N. M. I. Taylor, M. Bause, S. Bauer, R. Bartholomaeus, G. Bernhardt, B. Koenig, A. Buschauer, H. Stahlberg, K. H. Altmann, K. P. Locher, *Nat. Struct. Mol. Biol.* **2018**, *25*(4), 333–340.
- [33] T. M. Ho, S. Berger, P. Müller, C. Simonin, J. L. Reymond, C. Von Ballmoos, D. G. Fuster, *Chimia (Aarau).* **2022**, *76*(12), 1019–1024.
- [34] Daniel Bátora, Jérôme P. Fischer, Reto M. Kaderli, Máté Varga, Martin Lochner, Jürg Gertsch, *ACS Pharmacol Transl. Sci*, ahead of print.
- [35] A. Chicca, S. Nicolussi, R. Bartholomäus, M. Blunder, Rey A. Aparisi, V. Petrucci, I. D. C. Reynoso-Moreno, J. M. Viveros-Paredes, M. Dalghi Gens, B. Lutz, H. B. Schiöth, M. Soeberdt, C. Abels, R. P. Charles, K. H. Altmann, J. Gertsch, *Proc. Natl. Acad. Sci. USA* **2017**, *114*(25), E5006–E5015.
- [36] C. Manatschal, J. Pujol-Giménez, M. Poirier, J. L. Reymond, M. A. Hediger, R. Dutzler, *Elife.* **2019**, *8*, e51913. doi: [10.7554/eLife.51913.](https://doi.org/10.7554/eLife.51913)
- [37] N. M. I. Taylor, I. Manolaridis, S. M. Jackson, J. Kowal, H. Stahlberg, K. P. Locher, *Nature.* **2017**, *546*(7659), 504–509.
- [38] F. Petrelli, G. Dallérac, L. Pucci, C. Calì, T. Zehnder, S. Sultan, S. Lecca, A. Chicca, A. Ivanov, C. S. Asensio, V. Gundersen, N. Toni, G. W. Knott, F. Magara, J. Gertsch, F. Kirchhoff, N. Déglon, B. Giros, R. H. Edwards, J. P. Mothet, P. Bezzi, *Mol. Psychiatry* **2020**, *25*(4), 732–749.
- [39] B. P. Hanley, W. Bains, G. Church, *Rejuvenation Res.* **2019**, *22*(1), 31–42.
- [40] M. J. Waring, J. Arrowsmith, A. R. Leach, P. D. Leeson, S. Mandrell, R. M. Owen, G. Pairaudeau, W. D. Pennie, S. D. Pickett, J. Wang, O. Wallace, A. Weir, *Nat. Rev. Drug Discovery* **2015**, *14*(7), 475–86. doi: [10.1038/](https://doi.org/10.1038/nrd4609) [nrd4609.](https://doi.org/10.1038/nrd4609)
- [41] Jonathan J. Danon, Tristan A. Reekie, Michael Kassiou. *Trends in Chemistry*, Published: May 23, 2019. DOI: 10.1016/j.trechm.2019.04.009.
- [42] M. S. Kinch, C. Horn, Z. Kraft, T. Schwartz, *ACS Pharmacol Transl Sci.* **2020**, *3*(6), 1427–1429.
- [43] K. Popper, **1963**. *Conjectures and Refutations: The Growth of Scientific Knowledge*, Routledge & K. Paul.
- [44] Knowledge. The Philosophical Quest in History, by Steve Fuller Steve Fuller, The Knowledge Book: Key Concepts in Philosophy, Science, and Culture. Montreal and Kingston: McGill-Queen's University Press, 2007, 240 pp.
- [45] Thomas S Kuhn. The structure of scientific revolutions. University of Chicago Press, 1962.
- [46] M. Danhof, K. Klein, P. Stolk, M. Aitken, H. Leufkens, *Drug Discovery Today* **2018**, *23*(12), 1990–1995.
- [47] A. L. Hopkins, *Nat. Chem. Biol.* **2008**, *4*(11), 682–90.
- [48] P. Waduge, H. Tian, K. A. Webster, W. Li, *Drug Discovery Today* **2023**, *28*(3), 103430.
- [49] A. V. Katritch, *Nature.* **2023**, *616*(7958), 673–685.
- [50] [https://www.ibmm.unibe.ch/services/spaf/index_eng.html.](https://www.ibmm.unibe.ch/services/spaf/index_eng.html)
- [51] [https://dealroom.co/blog/the-swiss-startup-ecosystem-in-numbers.](https://dealroom.co/blog/the-swiss-startup-ecosystem-in-numbers)
- [52] *SN Business & Economics* volume **1**, Article number: 164 (**2021**).
- [53] <https://www.ddnz.uzh.ch/en.html>.
- [54] [https://www.grc.org/cannabinoid-function-in-the-cns-conference/2023/.](https://www.grc.org/cannabinoid-function-in-the-cns-conference/2023/) [55] M. Maccarrone, V. Di Marzo, J. Gertsch, U. Grether, A. C. Howlett, T. Hua, A. Makriyannis, D. Piomelli, N. Ueda, M. van der Stelt, *Pharmacol. Rev.* **2023**, *75*(5), 885–958. doi: [10.1124/pharmrev.122.000600.](https://doi.org/10.1124/pharmrev.122.000600) Epub **2023** May 10. Erratum in: Pharmacol Rev. **2023** Dec 15; **76**(1):194. PMID: 37164640; PMCID: PMC10441647.
- [56] I. Katona, T. F. Freund, *Annu. Rev. Neurosci.* **2012**, *35*, 529–58. doi: [10.1146/annurev-neuro-062111-150420](https://doi.org/10.1146/annurev-neuro-062111-150420). Epub **2012** Apr 17. PMID: 22524785; PMCID: PMC4273654.
- [57] B. Lutz, G. Marsicano, R. Maldonado, C. J. Hillard, *Nat. Rev. Neurosci.* **2015**, *16*(12), 705–18. doi: [10.1038/nrn4036.](https://doi.org/10.1038/nrn4036) PMID: 26585799; PMCID: PMC5871913.
- [58] G. Bedse, M. N. Hill, S. Patel, *Biol. Psychiatry* **2020**, *88*(7), 520–530. doi: [10.1016/j.biopsych.2020.01.015.](https://doi.org/10.1016/j.biopsych.2020.01.015) Epub **2020** Mar 17. PMID: 32197779; PMCID: PMC7486996.
- [59] R. I. Wilson, R. A. Nicoll, *Nature.* **2001**, *410*(6828), 588–92. doi: [10.1038/](https://doi.org/10.1038/35069076) [35069076](https://doi.org/10.1038/35069076). Erratum in: Nature **2001** Jun 21; **411**(6840):974. PMID: 11279497.
- [60] B. Dudok, L. Z. Fan, J. S. Farrell, S. Malhotra, J. Homidan, D. K. Kim, C. Wenardy, C. Ramakrishnan, Y. Li, K. Deisseroth, I. Soltesz, *Science* **2024**, *383*(6686), 967–970. doi: [10.1126/science.adk3863.](https://doi.org/10.1126/science.adk3863) Epub **2024** Feb 29. PMID: 38422134; PMCID: PMC10921710.
- [61] G. N. Petrie, A. S. Nastase, R. J. Aukema, M. N. Hill, *Neuropharmacology.* **2021**, *195*, 108626. doi: [10.1016/j.neuropharm.2021.108626](https://doi.org/10.1016/j.neuropharm.2021.108626). Epub **2021** Jun 8. PMID: 34116110.
- [62] L. M. Mayo, C. A. Rabinak, M. N. Hill, M. Heilig, *Biol. Psychiatry* **2022**, *91*(3), 262–272. doi: [10.1016/j.biopsych.2021.07.019.](https://doi.org/10.1016/j.biopsych.2021.07.019) Epub **2021** Jul 24. PMID: 34598785.
- [63] A. Scheyer, F. Yasmin, S. Naskar, S. Patel, *Neuropsychopharmacology.* **2023**, *48*(1), 37–53. doi: [10.1038/s41386-022-01438-7](https://doi.org/10.1038/s41386-022-01438-7). Epub **2022** Sep 13. PMID: 36100658; PMCID: PMC9700791.
- [64] F. Bellia, A. Girella, E. Annunzi, B. Benatti, M. Vismara, A. Priori, F. Festucci, F. Fanti, D. Compagnone, W. Adriani, B. Dell'Osso, C. D'Addario, *Transl Psychiatry.* **2024**, *14*(1), 118. doi: [10.1038/s41398-024-02829-8.](https://doi.org/10.1038/s41398-024-02829-8)
- [65] L. E. Rosas-Vidal, S. Naskar, L. M. Mayo, I. Perini, M. Altemus, H. Engelbrektsson, P. Jagasia, M. Heilig, S. Patel, *bioRxiv* [Preprint]. **2024** *30*, 2024.01.30.577847. doi: [10.1101/2024.01.30.577847.](https://doi.org/10.1101/2024.01.30.577847)
- [66] A. Chicca, J. Marazzi, S. Nicolussi, J. Gertsch, *J. Biol. Chem.* **2012**, *287*(41), 34660–82. doi: [10.1074/jbc.M112.373241](https://doi.org/10.1074/jbc.M112.373241). Epub **2012** Aug 9. PMID: 22879589; PMCID: PMC3464571.
- [67] I. Reynoso-Moreno, S. Tietz, E. Vallini, B. Engelhardt, J. Gertsch, A. Chicca, *ACS Pharmacol Transl Sci.* **2021**, *4*(2), 765–779. doi: [10.1021/acspts](https://doi.org/10.1021/acsptsci.0c00214)[ci.0c00214.](https://doi.org/10.1021/acsptsci.0c00214)
- [68] I. Reynoso-Moreno, A. Chicca, M. E. Flores-Soto, J. M. Viveros-Paredes, J. Gertsch, *Front Mol Neurosci.* **2018**, *11*, 180. doi: [10.3389/](https://doi.org/10.3389/fnmol.2018.00180) [fnmol.2018.00180.](https://doi.org/10.3389/fnmol.2018.00180)
- [69] P. Mäder, R. Bartholomäus, S. Nicolussi, A. Baumann, M. Weis, A. Chicca, M. Rau, A. C. Simão, J. Gertsch, K. H. Altmann, *ChemMedChem.* **2021**, *16*(1), 145–154. doi: [10.1002/cmdc.202000153.](https://doi.org/10.1002/cmdc.202000153) Epub **2020** May 26. PMID: 32369259.

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PERSPECTIVE

Drug discovery in academia provides both challenges and opportunities as shown by an in-depth analysis of drug discovery projects in the Swiss National Centre of Competence in Research TransCure (2010–2022). A successful translational project related to selective endocannabinoid reuptake inhibitors is discussed providing a showcase of how innovative research in academia can inspire drug discovery.

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