SciLifeLab DDD Strategies

2022 and beyond

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Executive Summary

The current organization and operative model have served the Drug Discovery and Development platform (DDD) at Science for Life Laboratories (SciLifeLab) well over the last eight years. DDD has a specific governmental mission and the accompanying responsibility for *continuous improvement* to meet two core missions:

1. DDD to support academic scientists driving drug discovery programs
2. DDD to provide state-of-the-art drug discovery technologies to life science in Sweden

Over the years, SciLifeLab has added additional responsibilities for DDD:

3. offering the DDD infrastructure capability in public-public and public-private partnerships
4. initiating a systems transformation of the support systems for therapeutic entities spun out from academia
5. integrate the OligoNova Hub into DDD

Suggested actions for strategic development of SciLifeLab DDD to meet future challenges are:

A. Clarify the **scope of responsibilities** for DDD with key stakeholders

B. Restructure the project portfolio into flexible pipes based on available workforce and competence at DDD to optimize work with our **therapeutic modalities**.
- Support of 12-18 programs and four technology areas
- A full cost model gives access to additional pipes

C. Introduction of four **technology areas:**
- Drug discovery Aided by Machine Learning (DAML)
- Therapeutic Oligonucleotides (TO)
- Display & Selection (DaS)
- Proximity induced agents and protein Degraders (PD)

D. **Proactive engagement** with industry, venture capital investors and patient organizations for public-public and public-private partnerships

E. Initiate a **systems transformation** of the support systems and universities for development of drugs spun out from academy

Background

In 2013, the Swedish government took the strategic decision to establish a Drug Discovery and Development platform with earmarked funding within the Science for Life Laboratories (SciLifeLab) SciLifeLab (research and innovation bills 2012/13:30 and 2016/17:50).

The mission of DDD is to turn academic discoveries into innovations - prototype drugs - and to provide technologies and training for state-of-the-art drug discovery in Sweden. DDD has become a trustworthy, efficient, and internationally recognized professional national hub with a proven impact on Sweden´s life science strategy. Since the start, DDD has supported progress of three drug discovery programs to clinical phase 1 studies, five to international partnerships, and five to new Swedish biotech – some subsequently listed on Nasdaq First North Growth market (two during 2021). Integration of DDD within the vibrant SciLifeLab environment offers access to novel complementary technologies and expertise that seldom are available even at large pharma companies. Among the host universities for DDD (UU, KI, KTH, SU, and LU), UU is the legal proxy. In the years to come, DDD will expand operations from the current five host universities to also include early-stage therapeutic oligonucleotide drug discovery at GU and strive to take a more active role in working together with tech transfer offices around Sweden for more efficient innovation.

International evaluations of SciLifeLab in both 2019 and 2020 have pointed out the importance of DDD as a powerhouse for early-stage drug discovery. The DDD infrastructure received an overall score of 8 out of 9 possible from the international evaluators. Moreover, when Swedish universities, excluding host-universities for SciLifeLab, ranked the importance of DDD as a national infrastructure the score came out as 7.9 out of 9. Examples of quotes from the international reviewers were “Chief among the achievements” at SciLifeLab and a member of the Swedish university infrastructure committee said DDD was “The center of the SciLifeLab universe”. DDD is internationally recognized, and is engaged in several international drug discovery related initiatives, e.g. IMI, and EATRIS.

In the SciLifeLab roadmap 2020-2030, DDD was given a special role to build translational and innovation capabilities. On June 3, 2020, the national DDD steering group revised and adapted the rules of procedure to enable DDD to take on this additional role. To enable DDD to act as a hub for drug discovery research in Sweden, a consortium agreement was signed April 1st 2019 and revised January 1st, 2021, which gives Uppsala University the authority to act as a legal proxy for all host universities. The governance structure for DDD is defined in the “Terms and Conditions for funding” document, September 19th 2018” in which the DDD national steering group is given the mandate to oversee operations at DDD according to conditions stated by the SciLifeLab board and considering the special assignment from the government to DDD. The authority of the national steering group includes:

- Decide on policies for prioritization and publishing
- Give advice to the SciLifeLab management
- Decide upon strategic decisions for implementation and organization of operations
- Approve distribution of funding and bring to the national SciLifeLab board for final decision
- Approve DDD rules of procedure
- Approve operational plans

Governmental funding shall support $DDD_{PROGRAM}$- and $DDD_{SERVICE}$-projects. Up to 20% of the governmental funding can be used to support technology development. $DDD_{COLLABORATIVE}$-projects can be offered using a full cost model provided that resources required to support $DDD_{PROGRAM}$- and $DDD_{SERVICE}$-projects are not displaced.

The current organization, proposed organizational changes and technical capabilities of SciLifeLab DDD are shown in Figure 1.

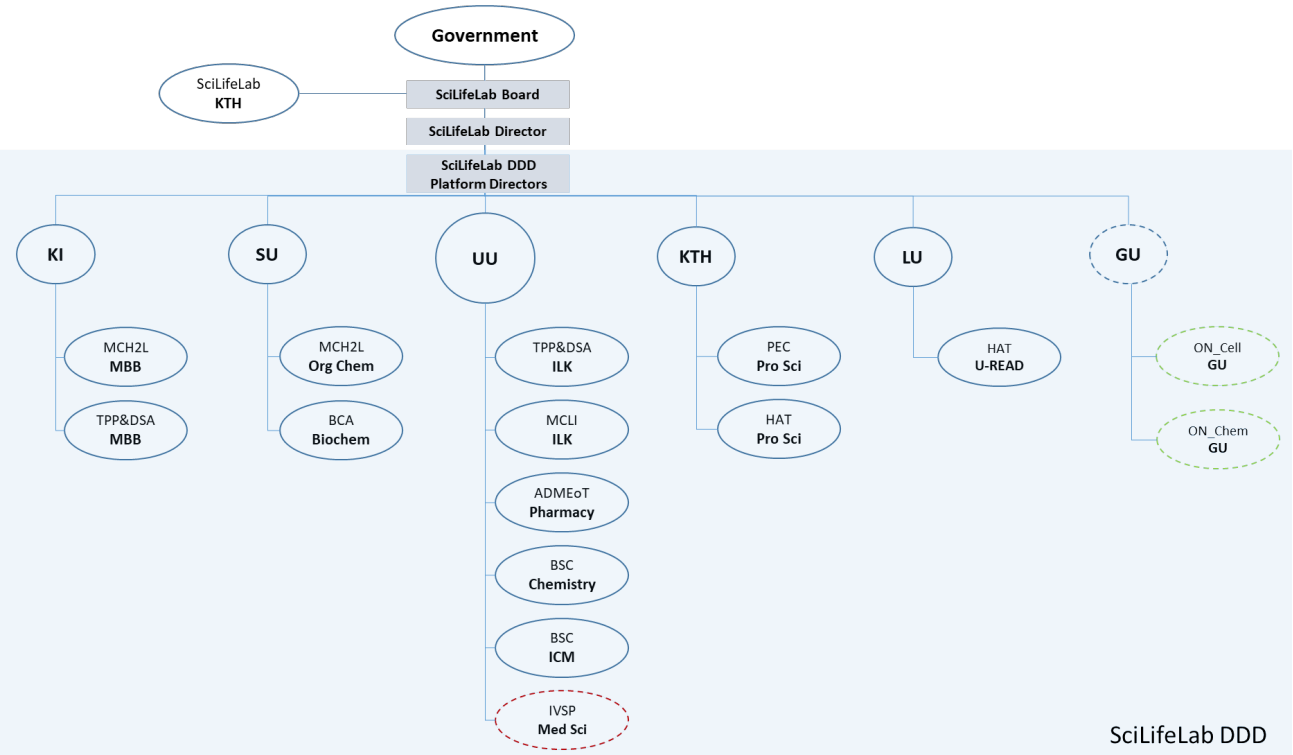

Figure 1. Overview of the SciLifeLab DDD platform, host universities and associated units. *SciLifeLab DDD (blue field) is a distributed national research infrastructure within SciLifeLab hosted by Karolinska Institutet (KI), Stockholm University (SU), Uppsala University (UU), The KTH Royal Technology Institute in Stockholm (KTH) and Lund University (LU). Gothenburg University (GU) is expected to join SciLifeLab DDD as a host university in 2022 (green dashed line).* ***UU*** *is the host of six units. TPP&DSA (co-hosted with KI) at the Dept. of Medicinal Chemistry (ILK) has the responsibility for platform and project coordination and assessment of liabilities driven by target, SM or Biologics. Support to PI's and Innovation offices. TPP&DSA_UU also hosts the SciLifeLab DDD office function. The unit Medicinal Chemistry Lead Identification (MCLI) is also located at ILK. MCLI prepare, compare and design lead molecules with a promising profile for proof-of-concept in vivo. MCLI has technologies for DNA encoded chemical libraries and access to radiochemistry and peptide chemistry. The ADME of Therapeutics (ADMEoT) unit at the Dept. of Pharmacy performs studies to determine absorption, distribution, metabolism, excretion (ADME) of putative drugs and perform pharmaceutical profiling (irrespective of therapeutic modality) using PKPD and PBPK modeling based on bioanalytical data. The unit for Biochemical Screening and Characterization (BSC) co-hosted by the Dept. of Chemistry and Dept. Cell and Molecular Biology (ICM) identify and characterize ligands, structural biology & fragment-based lead generation using methods for biophysical studies and structural analysis. The unit for In Vitro and Systems Pharmacology (IVSP) at the Dept. for Medical Sciences (Med. Sci) investigate drug mechanisms of action for product differentiation and identification of putative biomarkers. A decision has been made by the SciLifeLab Board to phase out this unit during 2022 (red dashed line).* ***SU*** *hosts two units. The unit for Medicinal Chemistry Hit to Lead (MCH2L) at the Dept. Organic Chemistry (Org Chem) prepare, compare and design lead molecules with a promising profile for proof-of-concept in vivo. The MCH2L unit is co-localized with the Chemical Biology Consortium Sweden and collaborates to manage the SciLifeLab compound collection and to distribute compounds in assay ready plates from the SciLifeLab compound collection. Operations at MCH2L are coordinated with MCLI at UU. The unit Biochemical and Cellular Assays (BCA) at the Dept. Biochemistry (Biochem) develops and runs assays required to drive chemistry and to confirm functional binding of antibodies. KTH hosts two units. The unit for Protein Expression and Characterization (PEC) at the Dept. Protein Sciences (Pro Sci) prepare, purify and*

characterize transient production of proteins from E. coli, insect and HEK cells. The unit for Human Antibody Therapeutics (HAT) at the Dept. Protein Sciences (Pro Sci) design human phage libraries, make selections and characterize therapeutic antibody candidates. Selections are also performed on DNA Encoded Chemical Libraries. ***KI*** *employs the Platform Director for SciLifeLab DDD and co-host MCH2L and TPP&DSA.* ***LU*** *co-host the HAT unit at the Dept. of Immunotechnology, unit for rapid engineered antibody development (U-READ) with design of human phage libraries, selections and characterization of therapeutic antibody candidates. Operations at U_READ are coordinated with HAT at KTH. Two new units are being established at* ***GU*** *(green dashed lines)****.*** *Starting 2022, is it expected that the OligoNova hub for cell biology (ON_Cell) performs screens for antisense oligonucleotides and siRNA to find candidates for therapeutic development. The OligoNova hub for chemistry (ON_Chem) prepare, compare and design antisense and siRNA oligonucleotides with a promising profile for proof-of-concept in vivo. ON_Chem also takes responsibility to manage the storage and distribution of oligonucleotides collection in assay ready plates.*

Problem statement and feedback from the platform advisory board

Missions

The organization and operative model has served DDD well over the last eight years. DDD has a specific governmental mission and the accompanying responsibility for *continuous improvement* to meet two core missions:

1. DDD to support academic scientists driving drug discovery programs
2. DDD to provide state-of-the-art drug discovery technologies to life science in Sweden

In addition, the SciLifeLab roadmap for 2020-2030 highlights DDD as a major driving force for building translational capabilities at SciLifeLab by:

3. offering the DDD infrastructure capability in public-public and public-private partnerships
4. initiating a systems transformation of the support systems for therapeutic entities spun out from academia

Also, a decision by the SciLifeLab board on February 3rd, 2021, was to, on top of small molecules and antibodies, add a third therapeutic modality as an integrated offering from DDD

5. integrate the OligoNova Hub into DDD

Problem statement

SciLifeLab DDD can be a national HUB for drug discovery research serving both academia and industry. However, SciLifeLab DDD needs to develop a strategy to both address the core objectives and give support to added objectives. *Sufficient funding is required to meet these missions alternatively a decision is required to prioritize between SciLifeLab DDD missions.*

Feedback from the platform advisory board

The challenges above have been discussed with various stakeholders and the SciLifeLab DDD Platform Advisory Board (PAB). PAB consists of Kjetil Taskén (University of Oslo, Norway), Fiona Marshall (Merck, USA), Justin Bryans (LifeArc, UK), Lorenz M. Mayr (Vector BioPharma AG, Switzerland) and, Lovisa Afzelius (Flagship Pioneering, USA). High level recommendations from the PAB are:

- **Make sure to fully understand expectations from key stakeholders**
- **To build life science in Sweden: protect the teacher's exemption law and take advantage of this for translational research**
- **Future therapies will increasingly be based on novel technologies, not new targets**
- **Do not spread resources too thin**

Action plan

A – Scope of responsibilities

Reference bodies like PAB, Vinnova and SSF have raised a number of questions concerning the scope of activities at DDD. These concerns include sustainability of activities, the responsibility for universities versus Vinnova in relation to “the third mission” activities and strategic decisions for the platform.

PAB points out the following:

- DDD main competitive advantage is the close alliance with Swedish academic scientists.
- The teacher’s exemption law is a very important competitive advantage for innovations emerging from Swedish academic research. Universities and innovation agencies should jointly use the teacher’s exemption law and find incentives to apply these to the DDD platform operations.
- Future therapies will increasingly be based on novel technologies, not new targets. DDD should not include disease focus within the platform, rather stay focused on technologies.
- Stay focused on a few modalities – do not spread resources too thin.
- The ability to form strategic partnerships with industry is essential.

Strategic decisions for DDD

The translational research done at SciLifeLab DDD sits between basic research and applied science. This has the possible advantage that funding could come from both areas. Unfortunately, funding to basic research and innovation is done separately meaning that translational research that sits in between is not prioritized by any part (the Swedish research Council - VR, Universities or Vinnova). Vital competence is also absent to evaluate applications focused on translational research from SciLifeLab DDD or from principal investigators seeking funding to run projects in collaboration with DDD. This is true both from a basic research perspective and for applied research. SciLifeLab DDD has an increasingly outdated instrument park and is at the same time expected to increase the services provided by inclusion of a third therapeutic development (oligonucleotides) and an increased support to the innovation system.

At an organizational level, SciLifeLab ambitions for DDD and the strategic responsibilities for the national steering group for DDD are not fully aligned when presented to the SciLifeLab board. DDD is placed within SciLifeLab and has a specific task and earmarked funding from the government. Funding from the government is distributed through KTH and additional funding is distributed through UU representing the five host universities for DDD (SciLifeLab DDD plus LU). The distribution of governmental funding is proposed by the SciLifeLab management team, approved by the SciLifeLab board on this information and finally decided by the board for KTH. The SciLifeLab DDD national steering group decides on strategies, prioritization of projects and approves on the principles for how to distribute available funds (governmental and additional funds). Two platform Directors have the operational responsibility for the platform and report both to Universities (KI and UU), the SciLifeLab Director and the national steering group. However, strategic changes for DDD can be proposed in the SciLifeLab management team and communicated to the SciLifeLab board for decision without full support from the DDD steering group. In the SciLifeLab management group, only the SciLifeLab Director and the SciLifeLab Infrastructure Director has an insight into strategic directions and related operations at DDD. Special care should therefore be

taken in communication with the SciLifeLab board in matters concerning DDD. This is especially important when additional responsibilities are added to DDD, which may dilute resources and impact on the ability to fulfil the core missions. For clarity, we propose that the platform Directors and the chair of the DDD Steering group is present when matters concerning DDD are decided at the SciLifeLab board. It would be beneficial if the board of SciLifeLab is actively supportive in interactions between DDD and stakeholders at Universities, Vinnova and research councils.

The function Target Product Profiling and Drug safety Assessment (TPP&DSA) contains the DDD Office function and management but also constitutes the point of interactions for consultation in drug discovery matters to academic scientists, innovation systems and industry. This work should be visualized as a unit within SciLifeLab DDD along other units to facilitate support to innovation systems and industry.

Drug repurposing, phenotypic screening and target deconvolution at SciLifeLab is handled by the Chemical Biology and Genome Engineering (CBGE) platform. DDD is focusing on target-based drug discovery. A close collaboration between the platforms exists, e.g. joint responsibility to maintain the SciLifeLab compound collection and efficient shunting of projects between platforms. Systems pharmacology at DDD is handled by the In Vitro and Systems Pharmacology (IVSP) unit. Financial limitations have forced the platform to phase out this unit during 2022. An inventory should be made to identify options to compensate for data that the IVSP unit is providing.

From a financial perspective, a recent substantial reduction of the fee from DDD to general SciLifeLab operations is now allowing investments in the most urgent instrument replacements. There is still a projected gap in financing of new instruments estimated to approximately additional 2 MSEK per year from 2024. Instrument deprecation is primarily handled by accrual payment in the running budget for the platform.

Action A – Scope of responsibilities

There are different viewpoints from stakeholders on the future direction of SciLifeLab DDD. The time plan below outlines actions needed to arrive in a joint understanding of the SciLifeLab DDD missions and strategies to fulfill these.

Period:

2022:	Establish new routines for reporting to the SciLifeLab board
	Explore ways to integrate support to academic innovations from DDD, innovation offices, incubators and university holding companies.
	Establish the Target Product Profiling Drug Safety Assessment (TPP&DSA) as an official unit within SciLifeLab DDD
2023-2024:	With key stakeholders, define the scope of responsibilities for SciLifeLab DDD concerning core missions and added responsibilities
	Clarify and communicate funding needs until next research and innovation bill
2025-2030:	Maintain operations, identify and communicate bottlenecks in support.

B – Optimization for therapeutic modalities

One of the present objectives for SciLifeLab DDD is to support academic scientists driving drug discovery programs. At the start of DDD was focus on a portfolio of 4-6 projects with small molecule and antibody therapeutics. Over the years, the infrastructure has maximized the use of available resources to grow the portfolio to a size of 16-20 projects and has proven capable of delivering essential innovative support to drug discovery programs that are based on other modalities, like peptide– and oligonucleotide conjugates, cell-therapies, and bi-specific antibodies. SciLifeLab DDD has also initiated technology development programs that aim to offer new technologies such as DNA encoded chemical libraries and new therapeutic modalities such as protein degraders (Protacs).

As depicted in Figure 2 below, modern drug discovery is characterized by an impressive number of novel chemical modalities under development. These new modalities are important because they open up new target landscapes and offer treatment options for diseases that are otherwise not easily targeted with conventional small molecules or antibody therapeutics.

The current model to prioritize and allocate resources to projects is very flexible and allows maximal use of resources irrespective of technical modality. The balance of projects in the portfolio is the result of requests for support from academic scientists, the scientific merits and medical need; available competence at DDD and; to lesser degree on available resources.

For more predictable use of available resources, to facilitate expansion into new therapeutic modalities and to facilitate the capability of DDD to engage in collaborative projects, we propose to organize the portfolio into flexible “pipes” based on four modalities offered by the platform (small molecule, antibodies, oligonucleotides and a “new modalities” pipe) and four technology areas (see action B below). The intention is to optimize available resources in order to provide the life science community with required technologies to develop the future drugs to come. The strategy is to work with target-based drug discovery in all pipes:

- for small molecules we have to identify and express the target protein and understand suitable binding sites for compounds and how these could be developed into prototype drugs
- for antibodies we have to identify suitable epitopes on the antigen and to produce relevant target protein(s) in the lab to select binders for further development
- for oligonucleotides we have to identify the suitable target sequence and a suitable cellular assay
- also the new modalities pipe is target focused but may encompass new approaches that does not fit into either of above modalities or run across above pipes. Examples could be cell therapies, antibody-drug-conjugates and protein degraders.

Projects in the technology areas secure that the provided modalities use frontline drug discovery technologies.

A pipe is based on the available workforce and competence at DDD with the aim to support in total 12-18 programs and four technology areas. Additional pipes may be offered at a full cost model. The current estimate is that the small molecule pipe may contain 3-6 programs, the antibody pipe 5-6 programs, the oligonucleotide pipe could contain 4-6 programs. The new modality pipe is used *ad hoc* when an opportunity emerges.

We need to adapt our selection criteria for new project applications in order to run according to our version of target-based lead generation. Of importance is to develop efficient x-SciLifeLab platform, academic and industrial collaborations.

Action B – Optimization for therapeutic modalities

Organize DDD-projects into flexible “pipes”. Each pipe is based on the available workforce and competence at DDD with the aim to support in total 12-18 programs and four technology development areas. Additional pipes may be offered at a full cost model to collaborators. The current estimate is that the small molecule pipe may contain 3-6 programs, the antibody pipe 5-6 programs and the oligonucleotide pipe could contain 4-6 programs. The new modality pipe is used *ad hoc* when an opportunity emerges.

Period:

2022:	Determine the number of projects and associated costs in the pipes. Adapt prioritization criteria and revise the platform rules of procedures accordingly. Identify suitable projects to fill the pipes
2023-2024:	Identify collaborative partners interested to invest in long term commitments of additional modalities
2025-2030	Explore possibilities to include additional offerings of modalities into pipes

C – Introduce oligonucleotides as a therapeutic modality

As depicted in figure 2, an impressive number of novel chemical modalities are under development. These new modalities are important because they open up new target landscapes and offer treatment options for diseases that are otherwise not easily targeted with conventional small molecules or antibody therapeutics. SciLifeLab DDD has already been involved in the development of bifunctional antibodies and protein degraders (Protacs) but has so far not been involved in oligonucleotide therapeutics.

In the beginning of 2021, Knut and Alice Wallenberg Foundation together with SciLifeLab committed to establishing a new capacity and competence center for oligonucleotide therapeutics at Gothenburg University – OligoNova HUB. The intention is to provide therapeutic oligonucleotides as a therapeutic modality to Swedish life science as an integrated function within SciLifeLab DDD.

PAB recommendations is to not take responsibility for drug delivery of ON (very competitive area that requires licenses). Restrict responsibility to identify active ON in translational human models (prePoC). Instead, identify areas within small interfering RNA (siRNA) and antisense oligonucleotide (ASO) technologies where it is possible to protect IP (first generation ON chemistry may be less attractive unless additional novel properties can be protected). Identify a technology key area where DDD/ON can have competitive advantage and use that to build partnerships. Consider applications of ON other than knockdown of mRNA and remember that data from cell-based assays will be key assets for future AI technologies in drug discovery – protect these assets.

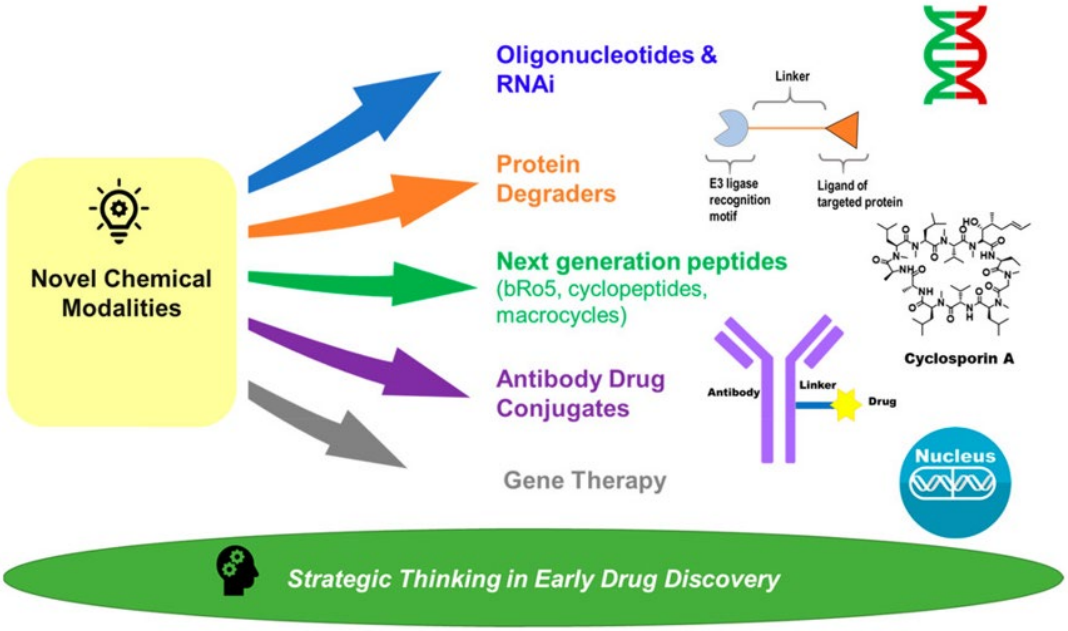

Figure 2. Examples of new chemical modalities for drug intervention (Blanco et al, 2020 *ACS M. Chem. Lett.* 2020, 11, 3, 228-231)

Action C – Oligonucleotides as a therapeutic modality

Oligonucleotide therapeutics are different from conventional medicine as they can inhibit the expression of certain genes. The development of oligonucleotide therapeutics is done through chemically modified artificial nucleic acids. Artificial oligonucleotides are being developed which have improved in vivo stability, enhanced affinity to target mRNA, homing to target organs and reduced off-target side effects. Therapeutic oligonucleotides are divided into antisense oligonucleotides (ASO), ribozymes, aptamers, miRNA, CpG/immunostimulatory and RNAi oligonucleotides. Starting in 2021/2022, the OligoNova Hub at Göteborg University will consist of two units (cell biology and chemistry) located to the BioVentureHub in Gothenburg and will be run according to the operational principles established at DDD. The focus will be on ASO and siRNA therapeutics.

Period:

2022:	Establish two new units at Gothenburg University, ON_Cell and ON_Chem. Secure competence and capacity at other SciLifeLab DDD units to support project scouting and progression of ASO/siRNA therapeutics
2023-2024:	Build a project portfolio of 4-6 ASO/siRNA projects
2025-2030:	Maintain operations and identify bottlenecks in support, including addition of additional types of therapeutic oligonucleotides

D – Technology areas

As pointed out by the PAB, will future therapies increasingly be based on novel technologies, not new targets. We have to build on abilities and competences already developed but we should not spread our resources too thin. We therefore introduce “Technology areas” which will put focus on what we believe are important areas for DDD to be competitive and attractive to academic partners also in the future drug discovery landscape.

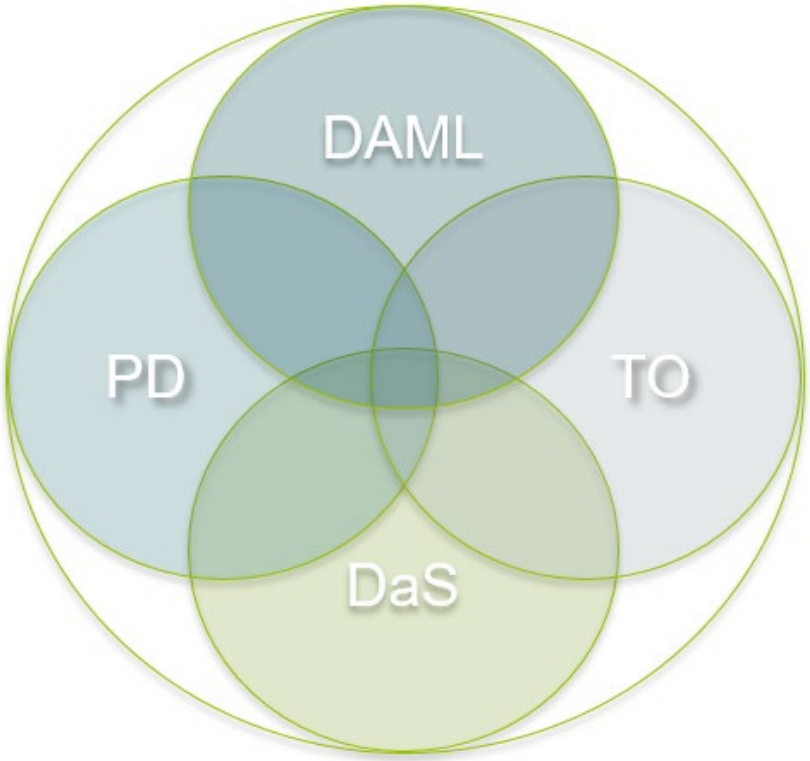

Figure 3. Technology areas Drug discovery Aided by Machine Learning (DAML), Therapeutic Oligonucleotides (TO), Display & Selection (DaS), and Proximity induced agents and protein Degraders (PD).

Proposed technology areas are:

- Drug discovery Aided by Machine Learning (DAML)
- Therapeutic Oligonucleotides (TO)
- Display & Selection (DaS)
- Proximity induced agents and protein Degraders (PD)

DDD launches projects in these areas in collaboration with external partners (academic/industrial). The intention is to integrate progress in technologies derived from these projects as offerings from the DDD platform.

Drug discovery Aided by Machine Learning (DAML)

Small molecules remain the most prominent type of therapeutics in investigational clinical trials and are the most common request for support asked by academic scientists from DDD. However, this pipe is the most resource intensive at DDD with somewhat longer timelines. There are, however, new technical breakthroughs in e.g. computational simulations and machine learning that may render drug discovery of small molecule therapeutics more efficacious. More detailed information of target protein structures and rapidly increasing possibilities for data simulations and machine learning are now driving both the discovery of ligands binding to discrete structures of the target protein as well as the design of small molecule therapeutics. However, DDD has prioritized projects where the academic scientists have provided their own tool compounds for further development, compounds that sometimes have had technical challenges for development into drugs. With a smaller portfolio of small molecule projects, DDD has to increase the throughput for these projects if the output from DDD is to be maintained. DDD therefore needs to revise criteria for prioritization of projects into the small molecule pipe. In addition, we propose to develop our understanding of how drug discovery by machine learning (DAML) can be used to our advantage. The first step in this direction has already been taken by the development of an informatics system for DNA encoded chemical libraries (DECL) adapted to machine learning (DECLIS).

Therapeutic Oligonucleotides (TO)

As described in section C above therapeutic oligonucleotides will become a third pipe and therapeutic modality for DDD. As pointed out by PAB, DDD has to develop a core strength in this area to become an attractive collaborative partner for major academic institutes and biotechs. Suggested areas for technology build up include tools for better understanding of non-target binding of oligonucleotides and novel conjugation chemistry. A technology area for therapeutic oligonucleotides should be established.

Display & Selection (DaS)

Antibody therapeutics developed by DDD rely on phage display technologies and selection from libraries developed in house (SciLifeLib 1-5). Know-how of display and selection technologies is a core strength of DDD and complementary technologies like DECL have in part been established thanks to this competence. Continuous development of display technologies, e.g. yeast display to facilitate affinity maturation of antibodies or how Alphafold-2 could be used to make selections more effective should be considered.

Proximity induced agents and protein Degraders (PD)

Proximity induced agents, using either small molecules or biologics, are rapidly opening new target landscapes. DDD needs to relate to this development and make wise investments to stay attached. A small toolbox for the development of Protacs molecules is available at DDD and has been shown to be functional. A strategy should be developed for proximity induced agents and this could be based on the skills at DDD in biophysics and conjugation chemistry.

Action D – Technology areas

To maintain support and output from DDD for small molecules we underscore the importance of prioritizing projects where conditions are good to obtain structural knowledge of the target linked to the principal scientists mechanistic understanding of why targeting this molecule, or a defined structure of the target, may have beneficial therapeutic activity. This information facilitates both identification of chemical starting points as well as how to guide design of therapeutic compounds (ideally facilitating DAML). Furthermore, a target-based approach for discovery of small molecule, antibodies and oligonucleotide therapeutics enables us to take full advantage of the opportunities of being part of SciLifeLab where there is substantial know how and resources for molecular bioscience (data driven life science initiatives, Cryo-EM, structural biology, data simulations and IT-support, sequencing etc.). However, we need to focus our resources where it can benefit our pipes. We therefore suggest to nominate four technology areas: Drug discovery Aided by Machine Learning (DAML), therapeutic oligonucleotides (TO), Display & Selection (DaS) technologies and Proximity induced agents and protein degraders (PD). If sufficiently funded, these technology areas could be resourced in national postdoc programs together with SciLifeLab and host universities. Note that current funding to DDD is not sufficient to support such a postDoc program.

Period

2022:	Define viable projects within prioritized technology areas. Develop postdoc programs and funding strategies together with SciLifeLab and universities. Consolidate investments made in DNA encoded chemical libraries and protein degraders
2023-2024:	Establish x-platform collaborations for mechanism-linked and target-based lead generation. Launch postdoc programs. Introduce technologies into DDD programs
2025-2030:	Maintain operations and identify bottlenecks in support, including addition of additional modalities

E – Proactive engagement for public-public and public-private partnerships

A natural evolution of the DDD infrastructure is to leverage the basic governmental investment to strengthen Sweden´s role in global pharmaceutical R&D. Historical examples have been individual Swedish researchers that have used the DDD infrastructure for participation in EU funded IMI programs ENABLE, ULTRA-DD, and Conception. In order to formalize DDDs engagement in such public-private partnerships, the DDD steering group proactively implemented the $DDD_{COLLABORATIVE}$ projects as a means to harbor external, fully funded programs without compromising the original objective to support academic researchers with drug discovery ideas through $DDD_{PROGRAMS}$ and $DDD_{SERVICE}$. Another prerequisite has been to secure the legal proxy agreement with Uppsala University that secures a contractual ability for the whole DDD platform. Importantly, DDD should not engage in partnerships unless motivated by the strategic direction of the platform. At some level, ongoing discussions at DDD concerning Public-Private partnerships should involve the national DDD steering group.

Action E - public-private partnerships

There is a clear interest from both private and public organizations to collaborate with DDD, e.g. KAWs requirement for funding OligoNova HUB, Cytiva and Testa center, IMI programs, charities, and other governmentally funded initiatives. In addition to making DDDs infrastructure and expertise available to more users, $DDD_{COLLABORATIVE}$ programs help maintain a critical mass of personnel and instrumentation. We aim to be more proactive in offering the DDD infrastructure to interested parties in the full-cost, non-displacing, $DDD_{COLLABORATIVE}$ model as advised by the steering group, and facilitated by the pipe-concept outlined in B above. Ongoing efforts directed to this measure are an agreement with IMI program “EUbOpen”, and DDD to be involved in the national antibiotics drug discovery effort “ENABLE2”.

Period

2022:	Identify and proactively engage with industry, venture capital investors, research funding organizations and patient organization with the intention to collaborate.
2023-2024:	Evaluate opportunities from private and public partners to buy into pipes at DDD
2025-2030:	Together with SciLifeLab MG, work for the creation of a “Swedish investment fund for pharmaceuticals” that assures return on investment for academic projects in Sweden, incl. managing financing and IPR.

F – A systems transformation of academic drug discovery

In the SciLifeLab roadmap 2020-2030, DDD was given a special role to build translational and innovation capabilities. Support to therapeutic innovations in Sweden is fragmented with a number of gaps in the support chain. This directly affects the chance for otherwise sound drug discovery projects to bridge "the valleys of death" between discovery, development and clinical studies.

In 2021, the Innovation Agency in Sweden, Vinnova, sponsored a DDD-initiative "InnoPharma" to find solutions for how to structure the national support systems (University innovation offices, University Incubators and holding companies) with efforts made by SciLifeLab DDD so that scientists, working under the teacher's exemption law, have optimal preconditions to progress their findings to clinical practice. Included in this project is also development of key performance indicators, KPIs. The InnoPharma project is scheduled to report in January 2022 but some conclusions can already be made:

1. Joint project teams should be formed with project leader support from DDD and commercialization support from the innovation systems
2. DDD could support the innovation systems with technical validation of candidate projects and the innovation systems can schedule their support aligned with ongoing work in the labs
3. The academic group led by the principal investigator should be eligible to hire an entrepreneurial postdoc with the task to communicate with the innovation systems and DDD and to take responsibility for lab work done in the academic group
4. Facilitate funding opportunities and investor insight into ongoing projects

Of fundamental importance is to lower the barrier for academic scientists to be involved in translational research. Incentives are today weak for academic scientists and universities to fully commit to translational research because it will many times have a negative impact on the scientists' academic careers and there is no clear advantage for the University.

Action F - Systems transformation

The InnoPharma project provides insight and proposes solutions that, *if funded*, could represent a systems transformation for how innovation support is offered to academic drug discovery programs, and more widely to programs supported by national life-science infrastructures like Testa Center, MaxIV, ESS, etc.

Period:

2022:	Report from InnoPharma and discussions with key stakeholders. Initiate measures to clarify options to support start-ups. Propose KPI for DDD that are aligned with more effective support to academic scientists and within the innovation systems.
2023-2024:	Bridge-funding to initiate a pilot project for selected parts of the proposed solutions from InnoPharma. Discussions with key stakeholders for prolonged basal funding and continuous support from the innovation systems and DDD
2025 -2030:	Continuous support from innovation systems and DDD, contribute to exploring options for national infrastructures to secure long-term return on investment.

Anticipated impact on DDD

Organization

- Integration of two OligoNova units (ON_cell and ON_chem) at GU will increase the national footprint of SciLifeLab DDD.
- Maintain the units for human antibody therapeutics (HAT_KTH and HAT_LU) at KTH and LU to support the antibody pipe.
- Strengthening of the unit for protein expression and characterization (PEC) at KTH to support development of oligonucleotide therapeutics and an increased attention to structure-based drug discovery of small molecules.
- Strengthening of the unit for ADMEoT to support profiling of ADME related properties of oligonucleotide and protein therapeutics.
- Strengthening of the unit for biophysical screening and characterization (BSC) at UU to support oligonucleotides and structure-based drug discovery.
- The units for Medicinal Chemistry at SU (MCH2L) and UU (MCLI) adjust work-flow accordingly to support target-based drug discovery projects, with increased use of structural information and computational methods.
- Generation of cell data for projects should be consolidated to BCA at SU and ON_cell at GU. Over time the unit for biochemical and cell assays (BCA) at SU must be strengthened. Unless additional funding can be found, the in vitro and systems pharmacology (IVSP) unit should be closed.
- Additional resources to TPP&DSA at UU should be provided to run the SciLifeLab DDD office, to give support for development of oligonucleotide therapeutics, to innovation systems with technical evaluation of targets and with design of pharmacological studies.
- Additional resources for project lead support from DDD should be available to principal investigators and innovation systems. These resources should be distributed and integrated within units at SciLifeLab DDD. Funding for this is currently not available.

Operational structure

- Introduction of tollgates and revision of checkpoints in the operative process for projects to adapt to joint project teams with the innovation systems and principal investigators.
- Establishment of new points of interactions and collaborations with SciLifeLab platforms and innovation systems.
- Depreciation costs are fully accounted for in the running budget using accrual payment.
- Introduction of pipes for collaborative projects.
- Clarify the role of DDD as infrastructure in relation to free academic research teams and external partners (e.g. start-ups) concerning aid regulations
- Proactive approach of DDD to find collaborators
- Continuous monitoring of new technologies and modalities requires that the infrastructure is made accessible for DDD sponsored postdoc programmes
- A revision of KPIs is warranted. Soft support to innovation systems and the life science community must be registered as well as transitions over checkpoints and tollgates

Deliverables

- Offering of new therapeutic modality (oligonucleotides) from DDD will lead to:
    - Increased target space
    - Possibility to approach new indications
- Together with innovation systems, built of a joint arena for drug discovery research in Sweden
- More efficacious generation of prototypes for small molecule therapeutics

Risk analysis

Implementation of the measures described above comes with a risk. The SWOT analysis in Figure 4 below highlights the most prominent strengths, weaknesses, opportunities and risks with this strategy.

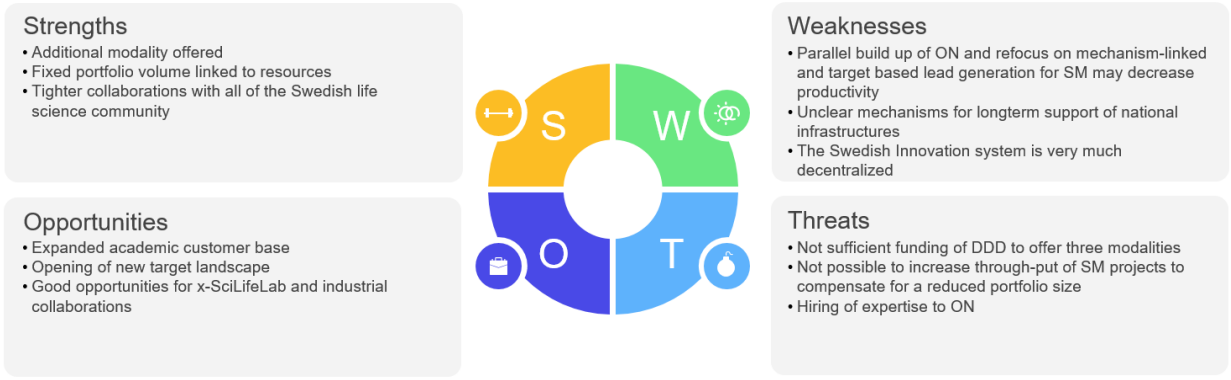

Figure 4. SWOT analysis of the proposed revised strategies for SciLifeLab DDD.