

UNIK Center for Synthetic Biology

University of Copenhagen

Scientific Advisory Board Report on the UNIK Synthetic Biology Initiative

It is a pleasure to see how the funding of the UNIK initiative has enabled the establishment of a coherent center of excellence with world leading competences and potential within synthetic biology, being both a novel area of expertise at UCPH and furthermore a large-scale cross-disciplinary endeavor. Within the first four years, tremendous progress has been made scientifically and educationally as well as in terms of establishing a supportive and dynamic scientific working environment for both senior and young investigators, building industrial relations, attracting funding and focusing on the ethical and communicative aspects of synthetic biology. The initially broad research program has been trimmed in a timely fashion resulting in strong emphasis on areas where seminal advantages are made. This serves to exemplify the power of strong academic leadership and successful engagement of the staff in multidisciplinary research projects.

Overall the progress is excellent, projects are on track and several have been advanced ahead of stipulated goals. The strong focus and increased support to highly successful elements and promising approaches are highly commendable and has resulted in the establishment of a truly unique research center.

The annual report presents an excellent update of the accomplishments. We provide a few additional comments to each of the highlighted areas in the following.

1: The research initiatives to develop light driven cell factories

This research area was introduced in the original proposal based on previous work on photosystem I but with no detailed outline of the experimental approach. Now the partial integration of the photosystem I complex and cytochrome P450s into a functional supramolecular enzyme complex has been achieved. This is excellent basic research and wonderful progress. The work represents a major step forward in developing efficient solar energy based production systems for production of fine and complex chemicals. The work has recently been published in ACS Synthetic Biology and is the fourth most downloaded paper in the ACS journals this spring. Furthermore, a podcast of the results is being planned by the journal. This work demonstrates the potential of original approaches within synthetic biology.

2: Combinatorial biochemistry offering new-to-nature diterpenoids

The idea of combinatorial synthesis of new-to-nature diterpenoids is a creative idea directly based on the not yet fully exploited biosynthetic potential residing in plants. The different diterpenoid core structures obtained by combining Type II and Type I terpenoids synthases from different medicinal plants are impressive and the decoration of these core structures with the hydroxylation potential of P450s is going to provide key and entirely new lead compounds for novel drugs. This project is another example of the center's excellent work combining strong knowledge within

natural product biochemistry with visionary ideas. Furthermore, these results and their enablement for future goals were not a part of the initial UNIK outline, but enabled due to UNIK-discoveries in this program. Importantly has been the multi-disciplinary backgrounds present in this highly collaborative group which has enabled discover and follow-through on potent candidate knowledge by the Center's Steering Group, thus demonstrating its ability to identify and harvest results dynamically.

3: The research initiatives on the interaction of nanostructures with biological systems

The ultimate goal of this effort is to develop sensitive *in vivo* sensors to assess and monitor the metabolic status and disease related disorders at the cellular level, major goal of personalized medicine. Development of robust sensing systems constitutes a major challenge. The researchers involved have managed to develop nano-wire arrays which provide unprecedented reproducibility and signal-to-noise ratios. Advantage has been gained by having other research groups in the center providing isolated membrane proteins. New approaches to achieve increased biocompatibility by covering the nano-wires with peptide are proving promising. The interfacing of nano-electronics and living cells holds great promise for basic and applied studies within cell biology, and the detailed understanding and characterization of the nanowire based sensing systems achieved represent important breakthroughs in the advancement of their future uses. Furthermore, the possibility of connecting this to solar cells represents an additional benefit. The progress made has been supported by a state-of-the-art infrastructure partly funded by the UNIK center.

4: Research initiatives focusing on fundamental research on receptors and membrane transporters as well as scaffolding and signaling proteins.

The center has to be congratulated on the numerous research accomplishments made within this area. Fascinating advantages have been made within all the systems studied: GPCRs, signalosomes involved in neural signal transduction and the proteins involved in complex cellular transport as isolated from both plants and animals. Major breakthroughs in understanding the intricate role of scaffolding proteins in clustering and recycling rates have been made. In highly cross-disciplinary collaborations within the center, the studies have been taken to the single-molecule level. This area holds great promise for the future, revealing the precise mechanisms of complex cellular machines that are involved in health and disease as well as critical environmental reactions.

5: Single molecule studies

The center is praised for its ability to advance the use of single molecule studies. State-of-the art microscopes have been acquired based on prioritized UNIK investments. Studies of additional membrane proteins at the single molecule level have commenced, for example the study of several cytochrome P450 oxidoreductase which are based on cross-group collaborations. Rapid screening modalities have used a novel electron acceptor that becomes highly fluorescent upon reduction. The single molecule studies are approaching the state where conformational changes observed in a single molecule can be associated with its detailed catalytic activity. We foresee that the future studies within this area, taking advantage of the analytical tools that have now been established at the center, are going to set entirely new standards with respect to our understanding of the function of membrane proteins.

6: Research initiatives on advanced application of biophysical methods to study and characterize key components of interesting biomolecular systems in a near-natural environment

The technology platforms stipulated in the original proposal to drive the research initiative have been successfully implemented as documented in the publication list of the UNIK center. This includes the nanodisc technology platform, reconstitution in nanocontainers, protein dynamic studies by fluorescent techniques, solution small angle and X-ray scattering and structural analysis of Nanodiscs containing proteins at the air-water or solid-liquid interphases. Free-flow electrophoresis constitutes a new add-on to these platforms and has proved valuable in obtaining monodisperse Nanodisc preparations. Recently, the isolation of labile membrane enzyme complexes has been achieved using a styrene-maleic acid polymer based technology. This again sets the stage for remarkable new advances in the center. The availability of this versatile toolbox has proven its importance in enabling the researchers in the UNIK center to gain easy access to “in-center” technologies offering solutions to experimental problems they were facing. One example is the initial set-back in the use of scattering technologies to study the structure of membrane proteins inserted into Nanodiscs.. Use of free-flow electrophoresis has now been implemented to obtain the size homogeneity and monodispersivity needed for precise analysis. Continued financial support to the center is required to maintain and develop these state-of-the-art platforms.

Scientific leadership and management of the Center

It is obvious that the leadership and coordination of the center is excellent. The center is headed by a highly dedicated and ambitious Head with strong academic credentials (recently awarded ERC Advanced Grant) and guided by a well-functioning steering committee. Projects are evaluated continuously and continuation based on state-of-the-art research. Some projects like the ‘Toxin Terminator’ and the development of a “Nano-scale Synthetic Fuel Cell” have been discontinued as a result of this input. The working environment of the scientists has high priority and structures to ensure good collaborations are enforced with special attention to the young scientists. The leadership at the center responds actively and positively to the arising needs which are demanding and often also costly to meet in a new and at the same time converging and diverging research area like Synthetic Biology. The most eminent young scientist are clearly being nurtured and trained to understand the essential elements of science as well as its demands both in terms of advancing knowledge production and dedication. The center’s instigation of the Network of Young Synbio Investigators is an excellent way to support the young student group in a way that enhances relations-building and interactions, and provides an ‘open space’ for dialogue both among themselves and with external parties. Combining this with poster sessions open to local faculty and departments would increase the students’ communication skills even more.

Industrial collaborations and societal acceptance

The center has great focus on industrial collaborations both directly in call-collaborations and strategically. Strong collaboration has been established with Danish and international pharmaceutical companies, food ingredient companies and producers of industrial enzymes. In this respect the center profits from the presence of strong world-leading companies based in Denmark. We advise that the UNIK center further explores the option of filing joint applications with additional universities and industries, enlarging the community and co-directing the direction of synthetic biology in Europe and with additional focus on the development in US, South Korea and China. Implementation of Synthetic Biology to the benefit to society demands

extensive efforts in public dialogue. This dialogue must be carried out in a focused manner. It is a pleasure to see, that the center has already adopted a strategy of always presenting Synthetic Biology in connection to societal benefits and bio-economy, and has managed to fully integrate the research interests of a philosopher in the center. This demonstrates that the UNIK Center takes the public reservations seriously, while not undermining scientific progress. The collaboration with the DIY community should be further strengthened to pave a path for greater public understanding.

Continuation of funding for the Center

The University is commended on having prioritized the establishment of the UNIK Center for Synthetic Biology. The research projects of the center are unique and trend-setting. The fundamental research carried out is excellent. The use of the "share-your-parts-principle" of synthetic biology is being fully exploited in designing the research projects and has already given rise to great discoveries. Furthermore, the center set-up favors the future development of "plug-and-play" production platforms that are based on renewable resources. The UNIK center serves as an excellent example to illustrate how skills from entirely different research environments may be successfully merged into new successful research ventures. The center has focused on active communication with politicians, industry and the general public. We commend the center on those activities since previous attempts to introduce new production systems or to market products derived based on such technologies have been controversial and met with a lot of resistance in Europe as well as resulting in decreased interest of European industries to invest. To avoid a similar situation with respect to the implementation of synthetic biology, the dissemination and communication activities of the UNIK center have to be maintained at the current high level. Direct center interaction with do-it-yourself citizen scientists provides an additional route of communication, engagement and hands-on experience for both innovative students as well as lay-people.

When launching a highly ambitious initiative within a novel area and with the excellent advances made by the UNIK center so far, it is our clear advice that the University of Copenhagen must provide substantial continued funding to keep momentum and continue this excellent research initiative. It would be very sad to see this fall apart because of the key researchers reverting to their "old and easier to run pet projects". Furthermore, although the publication record of the center is already highly impressive, the University must recognize that cross-disciplinary initiatives have a longer lack-phase than traditional, disciplinary initiatives. However, they hold the promise of larger scale and faster results once the experimental systems are fully developed and used in the cross-group collaborations nurtured by the center. Reaching this important synergetic turning-point is a major achievement that we expect the center to reach within the next five-year period. These challenges with which the center is now confronted must be recognized and dealt with by the University.

We strongly recommend that the University leadership ascertains that the center structure is maintained and that the University provides the center with at least 2/3 of the amount of funding currently provided by the UNIK grant. The leadership of the UNIK center is excellent. They know how to operate and develop an entire new research area based on their strong research standing and well developed personal skills. Accordingly, to further advance the success of the UNIK

center, the continued University funding should be fully flexible enabling the leadership of the center to operate and make new recruitments and to continue the build-up a state-of-the-art infrastructure. 4-5 years from now, the initiative will be fully able to be funded externally with an excellent return-on-investment for the University in sight. With the intended new extensive building plans at the University that are to include the UNIK Center, the option exists to develop the University as the central European hub for synthetic biology. It would be sad not to see this unique opportunity being fully exploited due to lack of gap funding.

Unfortunately Provost Bertil Andersson did not have time to attend annual meetings and to comment on the annual reports from the center. Accordingly, Professor Anderson has neither contributed to nor approved our report.

Date May 26th

Best regards

A handwritten signature in black ink, appearing to read "SgSligar". The signature is fluid and cursive, with the first letters of the first and last names being capitalized and prominent.

Professor, Director Stephen G. Sligar,
University of Illinois, Urbana, IL, USA

Professor Brian K. Kobilka,
Stanford University, Stanford, CA, USA

Professor Mark A. Reed,
Yale University, New Haven, CT, USA

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