NICPB Science Advisory Board Report

1. Overview

The Science Advisory Board met over a period of two days from June 26-27, 2012 in Tallinn to evaluate the scientific program of the National Institute of Chemical Physics and Biophysics (NICPB). The SAB members present were Professors Peter Littlewood (Chairman), Robert Kaptein, Tapio Niinikoski, Mart Saarma, Hanna Tähti and Marten Wikström. The members missing were Prof. Dmitri Basov and Prof. Carlos Ibáñez, all of whom, however, provided written input. Evaluation involved an in depth review of the main research programs, tours of the facilities and laboratories, discussions with younger researchers and potential leaders, and a panel discussion on new initiatives and strategy.

The Institute is sound and well run, with a good relationship between the Staff and the Director. Over the last few years, the NICPB is evolving a strategy and direction that will be beneficial for the Institute and for Estonia as a whole, and despite some structural and financial impediments, is performing well scientifically. There are many high quality science programs, of international calibre, across the disciplines but including high energy physics, quantum condensed matter physics, NMR spectroscopies, toxicology, and bio-energetics. These programs increasingly make interdisciplinary links within the Institute, and some also support substantial national and international collaborations. The committee believes that there are considerable opportunities to increase the role and impact of the Institute as a major national laboratory of Estonia, as long as major strategic decisions are swiftly taken and executed.

2. Key Recommendations

A vision for a National Science and Engineering Laboratory is naturally constructed around several features:

- the ability to operate at scale, supporting facilities, infrastructure and competences that are too large for the academic sector, and/or too early for the commercial one;
- the ability to bring together multidisciplinary teams to address complex problems of national importance;
- the ability to showcase research activities of international prominence and thereby attract top international scientists and engineers.

The Institute is continuing to evolve in this direction.

A number of junior researchers are joining the institution, but that number should be radically increased to match expected retirements, and those younger researchers should rapidly be brought into PI status and then leadership roles in the Institute. Bringing in independent young researchers will require the allocation of start-up resources and salaries outside the currently funded programs, and is necessary in order to maintain the intellectual foundation and ensure a flow of new ideas and programs. A partial remedy, that will also beneficially increase the flow of students and postdocs, is to pursue joint appointments with universities. In turn, strong programs at NICPB will benefit the universities, providing better interdisciplinary links to the naturally discipline-based institutions. It is important that NICPB set up rules how to promote scientists.

The SAB had presentations from the emerging leaders Angela Ivask (Toxicology group) and Mario Kadastik (High Energy Physics group) and considered them both highly suitable to take leadership roles in the institute. Both are already playing important roles in their respective collaborations.

The Institute has considerable autonomy, but in the current form operates as an entirely soft-money organisation dependent on short-term funding via external grant income, which is not a tenable situation for a national laboratory that aspires to intellectual leadership as well as supporting permanent facilities for the benefit of the nation. There needs to be developed a different financial model that allows for seed funding of new activities, long-term support of excellence, and support of large-scale facilities for the university and commercial sector.

We consider that there are considerable opportunities, especially given the physical location of the Institute, for better interaction and integration with both commercial institutions and start-ups, and with the Tallinn University of Technology. The ability of a national lab to do pre-competitive engineering and scale-up places it in an enviable position in an entrepreneurial economy. It is also important that the Institute establishes good working practices toward intellectual property protection in order to support industry collaborations.

We encourage a discussion between the Institute and Government over the establishment of national priorities, considering the opportunities available. Without wishing to endorse any particular amongst the following we noted that:

- a strong position in the science of environmental and nanotoxicology could be readily parlayed into a centre for medium-throughput assaying, with applications from mining to testing of consumer products;
- the established links to CERN, and the participation in a centre of excellence in high energy physics, are a strong opportunity for high profile science investment, which brings benefits in technology applications as well as public appreciation of science;
- the "big data" applications of a CERN tier 2 centre have already played out into national grid infrastructure and this could be amplified in different disciplines;
- the strong fundamental condensed matter program could be complemented by an applied materials effort that connected to applications and the emerging industry of "materials for energy applications" - such an effort could interact well with University programs in materials and chemical engineering;
- the established and internationally prominent programs in advanced NMR techniques provide a possible entry for an Estonian Magnet Lab to be one of the five pillars of the European Magnet Lab - this could bring sophisticated users from across the EU and beyond;
- applied materials and NMR - both probe- and magnet-development - produce natural synergies;
- the current financial disarray in some EU countries generates an opportunity to attract creative junior scientists into a well run and creative institution that is proud of its open borders - these are people who will be the engines of the economy in the future.

To accept these opportunities requires a number of changes. The first, already mentioned, is long term investment. In parallel a strategic vision that looks outward into the societal implications of the research activity. And lastly, ambition on the part of national funding agencies and universities to support the continuing transformation.

3. Reports on research programs

Main research programs of targeted financing

The panel recommends that on an annual basis the research programs provide an informational report on their activities, which might include:

- number of doctoral and postdoctoral students, and other research personnel;
- research grants;
- publication activity;
- research collaborations with national universities, international partners and with industry.

High Energy and Theoretical Physics (Kadastik/Raidal)

NICPB is the coordinator of the CERN-Estonia Cooperation Agreement that was recently signed for extension by the Minister of Education and Research. NICPB therefore has a national mandate to oversee the relations with CERN and its experiments. The participation of Estonia in CERN, and specifically in the CMS experiment, was one of the items in the Estonian Research Infrastructures Roadmap 2010.

HEP and Computational Physics Laboratory NICPB houses a Tier 2 cluster of the CMS Computing Grid. The architecture of the cluster, evolving with the advances in the hardware, was designed by Dr. Mario Kadastik. An imminent ambitious upgrade will raise the performance of the Tier 2 cluster close to that of an average Tier 1 center. NICPB is also member of Estonian Scientific Computing Infrastructure (ETAIS), another item in the Estonian Research Infrastructures Roadmap 2010. This will be managed by the Estonian Educational and Research Network (EENet), which also represents Estonia in pan-European Grid projects, of which the LHC Grid is most important.

The CMS experiment at CERN The High Energy Physics team of NICPB is highly appreciated in the CMS collaboration. The leader of the Estonian group in CMS is Martti Raidal, a well known theorist whose activities include Supersymmetric Grand Unification and its implications in Dark Matter and LHC data analysis. The group contributes notably in the data validation, in which Mario Kadastik is leader, and which is vital to CMS because it not only ensures the quality of the data used for the final analysis and selection steps, but also provides key information for the operation and future upgrades of the detector. The group also focuses on the searches of doubly charged Higgs bosons in CMS data, in which they are leaders.

Two of the above NICPB items are already in the present Roadmap, and their importance will likely be highlighted by the discoveries of CMS and ATLAS that will be disclosed on 4 July 2012. The SAB therefore recommends strongly to continue and support these activities and to help them flourish and grow in their national and pan-European frameworks.

Chemical Energy Technology (Lippmaa)

This program contains a set of diverse and creative activities which are linked by the skill and energy of the leader, who has given a great deal to the Institute and continues to be active.

This includes the participation of NICPB in the TOTEM experiment at CERN**.** Endel Lippmaa initiated the cooperation with CERN and CMS (the above program) but later moved first to the proposed (but unapproved) experiment FELIX, and then to its successor TOTEM. NICPB has contributed to the development of the so-called Roman pot detectors in TOTEM, but this and other possible hardware contributions were not specified in the short talk by Lippmaa. TOTEM has the goal to measure accurately the total cross section in proton-proton collisions, which is important for the calibration of the luminosity measurement during the operation of the collider. The accurate knowledge of the luminosity is required for the determination of the production cross sections for existing and new particles, and this becomes particularly vital once new particles have been discovered. TOTEM was also recently approved for the measurement of diffractive processes together with CMS.

This program also includes research on argillite shales, which has established benchmarks for mineral composition in Baltic rocks, providing important data for possible mining interests. There is interesting work on the important problem of proton hopping in zeolites, and a computational approach to acidity in solvation.

The Institute needs to select a path forward for the leadership of this program in the medium to longer term.

Spectroscopy of Functional Materials (Rõõm)

This is a strong fundamental condensed matter science program built around expertise in THz and optical spectroscopy under conditions of high magnetic fields and low temperatures. This group is truly world-leading in the application of these methods, and expansion of the THz work to milliKelvin temperatures and 12T fields will continue this. The committee was shown strong work on multiferroic materials, hidden order in a heavy fermion compound, and endohedral small molecule fullerenes. The group has many international collaborations, beyond those necessary to acquire samples. It links well to solid-state NMR techniques at the Institute. Future work on 2-photon spectroscopy (Rebane) and in particular interactions with incoming young scientists Huvonen and Tsirlin in the area of quantum magnetism will further enhance the intellectual strength of this area, and provide links to theory, and to neutron scattering.

New Developments and Applications of NMR Techniques (Heinmaa)

Traditionally, NMR plays a central role at NICPB as many groups use the technique in research projects ranging from materials research to structural biology. In particular the special MAS probes developed at the institute attract many outside users from Estonia and abroad, which leads to many collaborations. A range of NMR spectrometers up to 800 MHz is available for solid state and high-resolution NMR.

NICPB has been in the forefront of the development of the Magic Angle Spinning (MAS) NMR spectroscopy that enables the high-resolution measurement of NMR signals in solids, even in spin species with $I > ½$ that may have a large broadening due to electric quadrupole interactions. Therefore it is not surprising that the Estonian Magnet Laboratory (EML) has been chosen among the Roadmap 2010 items. The MAS probe development provides an important advantage to the experimenters who wish to push the limits to new temperature regions in materials with unique and unexplored capabilities. The THz spectroscopy fills an important gap between the microwave and infrared frequencies, employs some of the magnet infrastructures, and has unique cryogenics for extending the temperature range down to about 100 millikelvin. The MAS NMR cannot be replaced by spin manipulation technologies based on multiple pulses and accurate control of the frequency and phase of the rf source.

The research efforts of the group are partly devoted to the development of high-speed MAS probes and partly to NMR applications. The construction of CryoMAS probes for sample tubes with outer diameters of 1.8 and 1.0 mm that can operate at temperatures down to 6-10 K at spinning rates of 10-15 kHz was an extraordinary accomplishment (see also section on NMR probe development).

These probes were used in solid state NMR studies of inorganic magnetic materials, H2 trapped in fullerenes, and various organic compounds. Similarly, the high temperature MAS probes (going up to 1100 K) were used in studies of ionic conductivity and the structure of fuel cells.

The quality of the NMR research program is very good. The international visibility could become even larger by focusing on a few themes of high interest, for instance, magnetic materials and solid oxide fuel cells, where the unique MAS probes can be exploited. The development of novel hyperpolarization or dynamic nuclear polarization techniques is encouraged. The SAB recommends strong support to the continued development of the MAS probes in the framework of the Estonian Magnet Laboratory planned in NICPB, and encourages the materials physics programmes that use the unique equipment, knowhow and infrastructure available in NICPB. Protection of the IP rights by patenting is also encouraged.

NMR probehead development at NICPB and MAS Systems Ltd (Reinhold)

The NMR development group at NICPB has built a strong international reputation in the development of probes and methodology for solid state NMR. They pioneered the construction of magic angle spinning (MAS) probes with extremely high spinning rates (now up to 120 kHz). Also, the development of double axis rotation probes was very challenging. Recently, the focus is on MAS probes that can be operated at very low and very high temperatures. At present a large range from 6 K to 1100 K can be covered, which opens new possibilities for solid state NMR studies in material science. This development work is of very high technical quality and has led to the establishment of the company MAS Systems Ltd in 2006.

Mechanisms of regulation of integrated energy metabolism in muscle cells (Käämbre/Saks)

The Saks laboratory reports on several new concepts relating to the control of the rate of aerobic energy production, mainly in heart myocytes and heart muscle mitochondria. Modulation of the Michaelis constant for ADP is related to ADP transport across the outer mitochondrial membrane VDAC pores and its proposed control by tubulin. A reversed Warburg effect is reported for breast cancer, where the density of mitochondria is shown to be enhanced relative to control tissue. This interesting finding is in accord with the heterogeneity of catabolism in different malignant tumours, only some of which seem to conform to Warburg's original hypothesis. Research in the Saks group continues at the international forefront of studies of catabolic control, even though some of the current proposals still seem hypothetical and will require adequate controls before acceptance.

Phosphorous NMR studies of the creatine phosphate system on the *in vivo* level in collaboration with the Institute's NMR lab are recommended as a future development, and the SAB recommends continuing support for this group.

Mechanisms and interactions in toxicology and toxinology: *in vitro* models (Kahru)

In vitro ecotoxicology has been intensively developed in NICPB. Especially during the last few years the extension of the toxicological studies into the evaluation of toxicity of nanoparticles has created high level research with many international contacts e.g. in the form of EU-funded research projects. The team of Dr Kahru includes both doctoral and postdoctoral students and has active research contacts to national universities.

The development of *in vitro* test methods is urgently needed, since, according to the chemical legislation in EU (REACH, Registration, Evaluation and Authorisation of Chemicals) the safety of more than 30 000 chemicals should be evaluated in a very short time frame (before 2018). To implement this task, the *in vitro* methods are in a central position. Also the new directive on the use of experimental animals in EU (2010/63/EU) favours the use of *in vitro* methods instead of experimental animals whenever possible.

The research of NICPB's nanoecotoxicology team has excellent research projects on a topical area in toxicology, because the safety of nanoparticles is not known. The knowledge on the toxic mechanisms and effects of synthetic NPs is scarce, and their role as an environmental hazard is unknown.

The most important goal of the team of Dr Kahru has been the evaluation of the toxicity of chemicals/nanomaterials and the detection of the mechanisms of their toxic actions. Especially the role of reactive oxygen species and genotoxic effects has been studied in different low organisms: bacteria, protozoa and crustaceans. Based on the research on toxic mechanisms the most sensitive targets of the toxic action have been elucidated. Determination of the physicochemical properties of NPs (Zn, Cd, Ag, Cu, etc.) is part of the studies, as well as evaluation of the biological availability of the particles. The goal of a new EU funded project of the group NanoBioPredict is to seek new scientific knowledge on the translation of novel structural properties of synthetic nanoparticles/nanomaterials into their biological properties.

The SAB strongly recommends support for the group to continue research on the present lines. After the mechanistic phase of studies, optimisation and validation of the tests are possible for a wider use e.g. in industry. Automation can be applied to these *in vitro* studies, and thus high throughput low-cost tests for industrial use will be possible. The future of this research is promising and should be further developed in NICPB.

Environmentally Friendly Utilization Strategy of Oil Shale Processing Solid Wastes (Kirso)

Undoubtedly the challenges posed by processing, disposal and use of solid wastes from oil shales are important for society, and this research program has contributed to measurements and analysis of bioavailable concentrations of pollutants. Apparently the work has migrated from estimations of the environmental impact toward strategies for waste utilization. However, the presentation and our evaluation of the published work, left the committee unclear both as to the impact of the current work and to its technical direction in the future.

Other research programs

SOFC Development (Subbi)

This program is balanced between applied and basic science of fuel cell materials. This includes applied analysis and electrochemical testing of prototype solid oxide fuel cells provided by an industrial partner, where the goal is to advise on optimisation of the device design. The basic science explores high-temperature NMR measurements of ion transport which reveals mechanisms of activated transport up to very high temperatures, and solid solubility of different phases. The high temperature NMR is an outstanding and effective tool. This is a strong program that could benefit from more links to a very active commercial community.

This technology is used mainly in space applications, and its exploitation in automotive applications is likely to grow with the evolution in the cost, taxes and emission control of petrol-based fuels used in explosion engines. The team of Juhan Subbi collaborates with local industry active in this field, and complements in a highly useful manner the competences of the firm with their scientific knowledge and access to the state-of-art NMR equipment of NICPB. The high-temperature NMR probe is a unique tool in this application.

The SAB recommends to support strongly the SOFC development, and to encourage the close collaboration with the NMR group. It is also recommended to refine the policy of NICPB in the protection of Intellectual Property rights by encouraging patenting, either alone or together with the firm.

Quantum Magnets (Tsirlin)

This is a new proposal by A Tsirlin that will bring both theory and experiment on quantum magnets to the Institute, and is a very good fit to other research in fundamental condensed matter physics. This will provide significant strength in theory and new materials that complements other measurements and spectroscopies, and is an excellent addition to the Institute. The SAB recommend support for this new activity.

Alzheimer disease and Bio-NMR (Jarvet)

Dr. Jarvet's research involves structural studies of peptides and proteins using high-resolution NMR and other biophysical techniques. Recently, he has focused on the aggregation properties of Alzheimer β (Aβ) peptide. In particular, the oligomeric form of Aβ, which is an intermediate in the formation of fibrils, is believed to be the toxic species that leads to Alzheimer's disease (AD).

The Aβ peptide can occur in a wide variety of secondary structures and these were all characterized by circular dichroism (CD) spectroscopy. Recently, Dr. Jarvet was able to find conditions that stabilize the oligomeric form of Aβ, which is a very important result. It will allow the structure determination of Aβ oligomer by NMR and possibly the development of vaccines against AD in future work.

This research is of high quality and Dr. Jarvet is in an excellent position to exploit his finding and produce a major break-through in this very competitive field of research; this is very worthy of support by the Institute.

Snakes and drug design (Siigur)

This research mainly concerns the various protein components of the venom from the viper *V. lebetina*, many of which have been identified by the group, including cloning of the corresponding genes. The snake venom is extremely rich in interesting enzymes and other proteins, such as "disintegrins" and nerve growth factor (NGF). Several venom proteins affect specific components of the complicated blood coagulation cascade, and might therefore in the future be utilised in diagnostic assays of such coagulation factors. Interesting initial results were reported on the effect of "disintegrins" on the viability of cancerous cells, where the effects appeared quite specific for some forms of cancer. Such specificity is potentially very important and may well lead to development of specific anti-cancer treatments. The SAB recommends that the group should focus on this and other aspects of possible future use of snake venom components in diagnostics and cancer therapy, and considers this group well worthy of continued support.

Peter Littlewood, as chair of the Scientific Advisory Board

28th July 2012