The RIKEN Center for Molecular Imaging Science (CMIS)

The CMIS Advisory Council (AC) meeting on May 10-13, 2011-05-11 in Kobe

CMIS-AC 2011: prof Hideo Saji, prof Norihiro Sadato, Dr Noburo Yumoto, Dr Joanna Fowler,Dr Mats Bergström, prof Koichi Tanaka and prof Bengt Långström (chairman)

Background: On the 10th of May the CMIS-AC met and was briefed and updated on RIKEN business by Executive Director Dr Maki Kawai who also covered some of the vision statements made by President Ryoji Noyori. The AC went through the prepared program and made some minor adjustments and this program was adopted and followed.
The recommendations from president Noyori given to the RAC to discuss were as follows

1. Evaluate RIKEN's response to the recommendations made by the 7th RAC report entitled "RIKEN, Laying the foundation for creative advancement"
2. Under the 5 year plan from April 2013-March 2018, RIKEN will continue its mission as a creative scientific research institute contribute to the gathering of knowledge for humanity's continued existence. The AC is asked to advise on the governance, strategies, research system and management policies.
3. Evaluate RIKEN's cross boundary research among Centres, Institutes both national and international as well as with universities, industry etc. and recommend on how to maximize RIKEN's collective strength.

President Noyori furthermore directed the following points to the AC to consider

- Does CMIS have achievements of major significance and social impact?
- Does CMIS have a PDCA cycle especially mechanisms for reorganizing, improving or closing down if not efficient?
- Are personal management practices (hiring employment) world class? A special concern of president Noyori to determine whether the diversity of researchers is maintained at a high level.
- Evaluate the CMIS collaborative activities within and outside RIKEN and the efforts to create international collaborations.

On the 11-13 of May the meeting started with a review of Dr Watanabe where he also responded to the comments made the previous AC and clarified actions that CMIS had been taken. Some of the responses were then discussed.
After Dr. Watanabe's review, the presentations from the PI's were given. The AC was

pleased with this and other materials like the white book sent out in advance and the collected publications produced the last years. The AC was also pleased with the arrangement to meet the younger scientists in smaller group sessions to listen to their presentations and discuss with them their future perspective. With this information, the AC felt sufficiently informed to make comments on the CMIS's performance over the 2.5 years since the last AC meeting.

Summary of the CMIS-AC's internal discussions
We decided to base our responses on a SWOT analysis and then to propose some future actions

Strengths
CMIS has an impressive set up of instrumentation, experienced PIs with an international reputation and an experienced and qualified staff.

Access to several non-anesthetized animal models is a great asset for molecular imaging (MI) research and here CMIS has created a facility and organization with international excellence. The inclusion of both anesthetized and non anesthestized primates and rodents makes it possible to keep animals for long time thus facilitating longitudinal studies with repetitive investigations, even at short time intervals, in the same animal subject. This further reinforces the strength and value for CMIS in their future research program where notably the inclusion behaviour in relation to brain physiology is an exciting scope.

This will become even more valuable with the anticipated integration of genetics, proteonomics and other x-omics information.

The central position of synthetic chemistry and radiolabeling is in the process of being solidified. The establishment of a large number of radiotracers in short time is indeed impressive. There are some interesting developments of new labelling technologies and techniques, which might be valuable in the future.

The centre has been involved in a strong line of drug distribution studies based on good external collaborations, good chemistry for labelling drugs and the access to imaging in preclinical species and followed by an expansion into humans through transfer of chemistry to external collaborators in hospitals. Preparation for the GMP requirement is well underway.

The Microdosing concept facilitates early clinical trials and that should make CMIS an attractive partner for pharmaceutical companies promoting biodistribution studies as one part of drug development also supporting academic drug discovery.

To belong to RIKEN is an important strength for CMIS, because molecular imaging research is in "an interdisciplinary field that melds various branches of research, including synthetic chemistry, radiochemistry, biochemistry, applied physics, molecular biology, cell physiology, pharmacology, clinical medicine, mechanical engineering, electrical engineering and computer engineering".

Within RIKEN, collaborations with the advanced science institute like Centre for Developmental Biology, Brain Science Institute, SPring-8 Centre, Bio Resource Centre, Systems and Structural Biology Centre, and Research Centre for Allergy and Immunology is in progress and maybe of significant value.

RIKEN covers the majority of these fields except for clinical medicine. CMIS is, however, placed in a medical cluster in Kobe, enabling close and mutual collaboration with the clinical medicine. Collaboration with Institute of Biomedical Research and Innovation (IBRI) regarding translational research is an example (White paper P61). This link with the medical cluster in Kobe makes CMIS unique among the research centres of RIKEN.

CMIS has a strong position in the molecular imaging community of Japan and works nicely collaboratively with the other centres in Japan as exemplified by a large number of guest researches.

Potential scientific heights

Based on the strengths of CMIS, the energetic and enthusiastic researchers, the AC is expecting the organization to accomplish high level of scientific achievements on an international level. Some projects hold the promise of forming the basis for a high-level world-wide hub for specific cellular molecular imaging.
CMIS seems to take responsibility to attract future scientists to the field of Molecular imaging by setting up a PET academia and doing outreach to the community by open house/ activities.

Weaknesses

The AC thinks that to end translational research without a stronger connection to phase 0/1 clinical trials in man misses a major component of gathering knowledge for the improvement of the human condition. We hope the opportunity to attach a clinical site directly to CMIS

will be fulfilled, but also realize that such undertaking will impose organizational and scientific challenges.

CMIS has still limited experience in imaging in drug development especially as PD marker for optimization for dosing and scheduling. Furthermore, the tools for supporting patient selection is still in its infancy and therefore CMIS can, as of today, only play a limited role in drug development. The excellent examples of drug distribution shown by the site, includes also a weakness in the sense that such studies is only requested to a limited extent by pharma.

CMIS is under-resourced for the "planned missions" (alternatively CMIS needs to focus on increasing their visibility).

In relation to the scientific excellence, CMIS has comparably a few international collaborations and few grants from international bodies.

In the interest to label new compounds and old drugs and perform biodistribution studies,CMIS has sometimes lacked in the depth of validation and exploration of the complexity of biological processes underlying this in vivo distribution.

More emphasis needs to be placed on understanding and characterizing of the biological processes which influence the distribution and kinetics of labelled compounds in vivo. Careful validation is even more important when a promising labelled compound is translated to humans, and back-translation into the mechanistic pre-clinical studies are necessary.

Opportunities

Use the chemistry, the radiochemistry and the animal models strengths of the CMIS for the evaluation of PK/PD relations in order to bring new knowledge to the field of drug development.

Inclusion of PK/PD modelling already in the pre-clinical animal studies would make a nice translational path towards modelling in Phase 0/1 human studies. Association with Computational Biology is here a great opportunity.

One of the contributions to drug development where CMIS could be of value is to further speed-up the decision process in the early phase of drug development where PET is unique in enabling the assessment of specificity and bioavailability.

With the right guidance and further collaborations with pharmaceutical companies CMIS can be expected to make an impact in drug development.

This could be achieved by the combination of the labelling chemistry, animal models and PET imaging systems that have been established within CMIS. The full potential of these resources will be realized with the future development of the infrastructure for human studies.

Access to knowledge and distribution of various molecules through research collaboration with pharma and the establishment of the clinical network will be valuable.

Collaboration with several national and international research institutes has been established and will be important.

RIKEN / CMIS has no formal education responsibility: however CMIS/RIKEN should lead in a future mission of communicating/discussing with regulatory bodies and society institutes regarding safety/risk benefit analysis and foster a new generation of health service researchers in the hurdles and benefits of molecular imaging. This is important for the future of MI and will have a positive societal impact. That mission should also be taken on with regard to an international responsibility.

Bring in people with a deeper understanding to some areas of human physiology and who can bring in the important questions and knowledge gaps around the clinical needs. This is a key point and closely connected to the need of establishing a first time in man possibility for new molecular entities.
The combination of labelling chemistry and PET imaging systems especially when applied in various experimental designs is a powerful scientific tool allowing new ways to explore physiology and pathophysiology. This is an area where CMIS and it's collaborators can make significant contributions to new knowledge.

To work on eminent research target, which has significant societal impact would be important. An example is chronic fatigue syndrome, which has been continuously investigated by Dr Watanabe et al and might be such a target area since it holds many challenging elements fitting into the field of molecular imaging.

Use the strengths to get visibility and recognition by high impact publications.

The possibility to collaborate with the new Quantitative Biology centre can also be beneficial.

The establishment of a network for promotion of clinical studies may become a very strong link, which needs to be recognized.

Threats

Working with pharma requires a high degree of structure and compliance to their formalities, which can be missed by a research oriented organization and which may also be difficult to appropriately integrate in a research structure.

Not being able to clarify the area where CMIS would have a unique niche and where it should and can contribute to.

Sub-critical resources may drive CMIS to become a service organization.

Missing the opportunity to inform researchers in- and outside CMIS about the directions of the research conducted because of the interdisciplinary functions of CMIS.

Not continuously keeping a self critical attitude and performing reality checks.
For the sustainability it is necessary to foster the next generation of leaders.

The CMIS-AC has also responded to Director Watanabe's suggested topics:

- Recommendations on CMIS's future research policies and the management structure to promote research, such as organization of teams, etc. for RIKEN's next Mid-term Plan (third 5-year plan from April 2013 to March 2018)
- Evaluation of Principal Investigators (excluding head of Drug Discovery Chemistry Platform Unit and Drug Discovery Imaging Platform Unit.)

AC acknowledges the CMIS roadmap, the new organizational plan and its underlying strategic emphasis on health science with focus on fatigue and pain. Rearrangement of the roadmaps according to the future plan would clarify the research strategy.

A plan has been submitted for funding for the development and construction of a Collaborative Research Centre for Molecular Imaging for first-in-man evaluation of potential new radiotracers. The AC strongly supports this initiative for evaluating promising new tracers in humans including the development of kinetic modelling strategies for the quantification of molecular targets directly in humans. This initiative will result in new knowledge, which is anticipated to have broad public impact.

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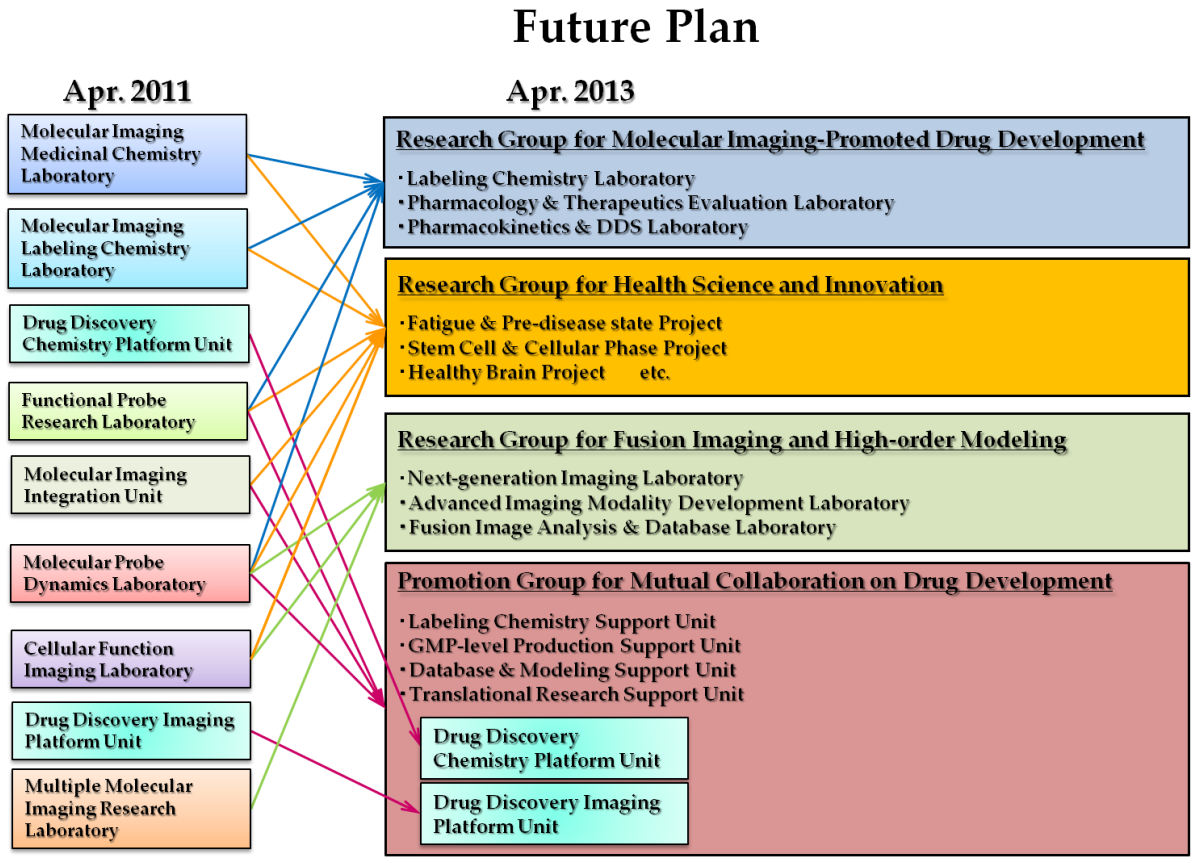
To facilitate the development of a human imaging program, the AC recommends the recruitment of a physician scientist to work across groups in the CMIS to build up this part of the program and to integrate across projects. Along this line the AC recommends adding another box called *Human Studies*to cover First-in man studies (radiotracer quantification, dosimetry and radiation protection, protocol development, institutional approval, subject care and safety, documentation and medical records etc) to the diagram (below) as described in Dr Watanabe's future vision.



The AC has been pleased with meeting the younger scientists in smaller groups in order to carry out discussions. These meetings were very stimulating and confirmed that the CMIS has created a stimulating scientific environment. The AC found this very encouraging. However a comment is that there is still a need of improvements in speaking and understanding the English language, even if it continuously is improving. The AC would ask if CMIS could arrange that there is a possibility to obtain professional internal language training and to foster an internal climate of use of English.

As a comment with regard to the language the chairman of AC acknowledge, that for the first time he had been attending a Takeda symposium organised by RIKEN collaborators and the whole meeting was performed in English.

Another issue which was briefly has been discussed before within the AC was the gender aspects of CMIS and the results is presented below is not indicating any change. However, Dr Doi mentioned that in radio-chemist group, there is now equal male female ratio (50: 50).

2008.10.01	Male		Female		Total
Lab Head	6	100%	0	0%	6
Research Scientist	19	83%	4	17%	23
Research Associate & Technical Staff	9	39%	14	61%	23
Visiting Fellow	70	82%	15	18%	85
Graduate Student	15	94%	1	6%	16
Support Sraff & Assistant	5	33%	10	67%	15
Total	124	74%	44	26%	168

2011.3.31	Male		Female		Total
Lab Head	8	100%	0	0%	8
Research Scientist	30	88%	4	12%	34
Research Associate & Technical Staff	11	29%	27	71%	38
Visiting Fellow	103	87%	16	13%	119
Graduate Student	35	81%	8	19%	43
Support Sraff & Assistant	8	35%	15	65%	23
Total	195	74%	70	26%	265

GREI

The achievement of novel imaging instrument (Gamma-ray Emission Imaging devices) is excellent at the scientific level. Development of multi-molecular simultaneous imaging technology is an important issue to be solved in this field, but the contribution of this group to the activity of CMIS is limited at this moment. For example, regarding the research direction, it is not clear what is the merit for the PI to combine the development of GREI cameras and tracer development. Divided labour might be better. The cost for development of GREI system is another concern. The scientific /clinical merit of multi-tracer imaging, and target biological question to which the multi-tracer technology will be fruitfully applied, should be clarified, in relation to the development cost.

In the future development within CMIS the use of the excellent research animal models will play an important role in the translation of biological knowledge into applications in man. A common denominator in human biology and physiology is the endogenous compounds and the radio-labelling and assessment of such agent's distribution in vivo is hitherto

undervalued.

To further extend the chemistry competence there is a need to reserve cyclotron time and hotlab space in order to perform basic radiochemical research and have time for the necessary (appropriate) technology development. These points may be very important if CMIS is going to be a leader in forming a promotion committee for the clinical consortium.

The Clinical consortium with its promotion committee will be important in many aspects of translational molecular imaging as well as a resource for obtaining extramural funding.

Proposal to actions / recommendations:

● To increase budget by seeking International funding of joint programs

● To stimulate collaborations and other relationships with university & external partners.

One of the remote research goals of CMIS is to obtain Proof of Concept (POC) of the pathophysiology of diseases such as dementia and refractory cancer, in the frame-work of neuro-immuno-endocrino interaction to open the field of 'live-science'.

CMIS has strong background of synthetic chemistry and radio-labelling, with access to several non-anesthetized animal models with solid imaging capability. These competences are critical to achieve the goals. However, the number of PIs in the medical field or young researchers with medical backgrounds, who are indispensable, is still small.

To pursue the goal, therefore, AC expects CMIS
(1) to recruit PIs of MD/PhD in the field of medical research with imaging capability and interest in pathophysiology of diseases, and
(2) to accept MD/PhD students from medical schools using consigned PhD student system.