

RTK Consortium Members Meeting
October 23, 2005
Harvard Medical Conference Center
Boston, Massachusetts

Attendees

RTK Consortium Executive Committee

Yoshiyuki Sakaki, RIKEN Genomic Sciences Center, Japan
Boris N. Kholodenko, Thomas Jefferson University, USA
Hiroaki Kitano, Sony Computer Science Laboratories, Japan
H. Steven Wiley, Pacific Northwest National Laboratory, USA
Mariko Hatakeyama, RIKEN Genomic Sciences Center, Japan

RTK Consortium Members and Others

Jan Hoek, Thomas Jefferson University, USA
Alexander Sorkin, University of Colorado Health Science Center, USA
Haluk Resat, Pacific Northwest National Laboratory, USA
Julie Gephart, Pacific Northwest National Laboratory, USA
Marta Cascante, University of Barcelona, Spain
Pedro 'de Atauri, University of Barcelona, Spain
Shinya Kuroda, University of Tokyo, Japan
Michael Blinov, Los Alamos National Laboratory, USA
Takeshi Nagashima, RIKEN Genomic Sciences Center, Japan

The Consortium meeting convened after the very successful workshop and lunch. The purpose was to discuss where the Consortium has been and how to move forward, especially in the next year.

Progress Report

The committee has been investigating a number of organizations as models for the Consortium; for example, the Alliance for Cell Signaling and HUPO. The former has not been successful, for reasons outlined in Hiroaki Kitano's presentation at the workshop. HUPO is a good example of a successful government-sponsored entity, although it did not start out that way. It was able to attract government funding once it demonstrated that it could effectively coordinate research for the broader community.

Proposed Consortium structure. Because of extensive legal issues related to intellectual property (IP) and technology transfer, the easiest route for the Consortium to take at this time would be to form a non-profit entity—a scientific organization. Creating such a “professional” organization would allow individuals to join and provide a legal structure for the Consortium. The Consortium must have a legal structure in place to generate legal documents; for example, confidentiality and nondisclosure agreements. PNNL came up with a draft document capturing the “statement of intent” to form the RTK Consortium, a copy of which Wiley gave to the Executive Committee.

Feedback. In discussion among the group, the consensus was that pushing the RTK Consortium forward and increasing the membership is the number one priority; therefore, taking the path to become a non-profit entity is the most expedient. This will give the Consortium time to sort out legal issues, including those related to IP and technology transfer.

Industry sponsorship is necessary to continue down this path and to support other Consortium activities. The question is, what does a sponsor get in return? Kitano noted that it depends on how much is asked for, and he recommended we ask for sponsorship of specific functions rather than to the Consortium in general. It is safer to ask for, for example, \$5K to be a workshop sponsor. This avoids having strings attached, as there would be if a large amount were given to the general Consortium. It also makes the Consortium less likely to be “colored” by or associated with one specific sponsor/donor.

Wiley noted that the Consortium membership can't be restricted to research groups or laboratories. Legal entities are individuals or organizations. Laboratories have no legal standing, can't sign agreements, etc. Membership has to be at the individual level.

Sakaki asked if the Consortium could own its own IP, if it funded the research itself, through funding from each institute or laboratory. Wiley responded that this would have to be worked out institution by institution. For example, if RIKEN funded it, RIKEN owns it unless they explicitly turned over the IP to the Consortium.

Infrastructure. The website is done and operational at www.rtkconsort.org. Stacy Berg at PNNL is the webmaster, and items can be sent directly to her at stacy.berg@pnl.gov or to Mariko Hatakeyama at marikoh@gsc.riken.jp

A SharePoint site (that is, a community site from which people can upload and download files—even large ones—data, images, etc., have message boards, calendars) is in the implementation stage at PNNL. This will be made it available to members, who will have to register using user name and password. Others can be given privileges as necessary.

The database is in preliminary discussions.

Test projects. At the June meeting, we talked about test projects, and the report from that meeting is on the website. However, what was decided on turns out to be hard to accomplish in the originally estimated time frame.

The initial system selected is a 15-minute stimulation of ERK by EGF (see report on website). This is still a reasonable plan. We were going to generate test datasets, but the high-throughput assays were not available. Investigators at PNNL tried to use quantitative Western blots, but these were inadequate.

Assays. Assay systems are being evaluated. An imaging assay for ERK was completed; an ELISA assay for ERK and phosphoERK has been established. The assay results will

be posted on the SharePoint site. PNNL is designing high-throughput intermediate assays for Src, Ras (funding started Oct. 1 with internal money from PNNL). One-minute assays are still ongoing.

Joint experiments. These are still in discussion. The members want to exchange cell types: HMEC from PNNL and MCF7 cells from RIKEN. It was remarked that scientists tend to stovepipe cell types and assays in certain groups because it's comfortable, but then the peculiarities of a particular system become second nature, and wrong assumptions can be made. So if we use more than one cell type, all sites will do the same cell types to ensure quality control and that we're seeing the same effects. Kholodenko noted that Thomas Jefferson University has been using Hek 293 cells, but they will likely drop the studies.

The Consortium will offer the scientific community high-quality molecular-level data. There's a series of mathematical models that involve multiple feedback loops and focus on the ErbB receptor family pathways including MAPK pathways; therefore, at least two cell types are needed for the high-quality data. The issue with the large network maps is that they represent a compilation of results from many different cell types. It is unclear whether all of the components of a given pathway are present in a given cell. The possibility of creating cell-specific pathway maps was received favorably. This could serve as the foundation for modeling efforts.

By definition, we should be able to model phenomena on two different cell types. It's very important to know all the conditions, sub-cell level, temperature, specific descriptions, etc. in the protocol so that we can reproduce accurately.

Hoek noted that we could adjust the network maps to particular cell types and potentially superimpose on that an estimate of the quantitative levels of the different proteins. This should be one of the Consortium's goals, so scientists can know what to start looking for. He suggested hepatocytes as another system to explore.

The Consortium needs a realistic five-year plan. We must ask what the significance of any system is to engage/obtain funding from the biological community. What problem will this model solve; e.g., cancer, diabetes, and/or aging? Once you choose a problem, it dictates the rest of the decisions, including who the collaborators are.

Workshops

The Consortium will hold a workshop at the 2006 ICSB in Yokohama, but another meeting is needed in the April timeframe. Several options were discussed, including having another workshop similar to this one, following a major meeting or conference to facilitate attendance at a general meeting. However, in follow-on discussions after the meeting, the Executive Committee agreed that it would be better to have a members meeting in Europe to involve the European members and to focus on progress related to the Consortium's goals.

Subsequently, Pierre De Meyts of Novo Disk has proposed to arrange the next committee meeting in Copenhagen in March. More information will be forthcoming.

Open Forum

Recruitment. The question of recruiting members came up. The group will entertain suggestions of members who can bring something to the Consortium; for example, Forest White of MIT, and the attendees from Los Alamos National Laboratory.

Kholodenko noted that he was receiving inquiries from students and postdocs about Consortium membership and/or participation, It has become clear that the Consortium needs to address this issue, as student involvement will be an important issue for new research. Following the meeting, he received a query from a graduate student about the possibility of helping organize student involvement. This will be a topic for the March meeting. Hatakeyama gave an example of the success Christopher Voight at University of California-San Francisco is having in using students' ideas to accelerate the field of synthetic biology.

Database. Hatakeyama asked about the progress on HMEC set asides, and if PNNL could make a public database. Wiley replied that metadata is the problem. PNNL has been building a database to store metadata that is nearing completion.

EGFR network map update. In response to Kitano's suggestion that the Consortium update his EGFR network map, the group agreed it was a good suggestion; however, it would be difficult to implement a framework within which changes could be made. Changes would have to be able to be followed and tracked. Determining how to provide input and in what format it is solicited from others is new territory. In similar work on databases, typically individuals are allocated portions. How would this be done for a pathway map? Does anyone have any experience?

Kholodenko remarked that it's important to know for each connection or piece what papers apply directly to it. There are a lot of people making models. The Consortium might read the paper referring to a specific part, then agree or disagree with interpretation, but this is very difficult to do for the whole picture.

Wiley suggested a "jamboree," such as those that have been held by gene annotation groups, where you take a day and go through piece by piece and do by consensus. This is effective, but it would have to be well organized, which is a lot of work and responsibility.

Michael Blinov said that you need a way to incorporate comments in model structure, and to trace a proposed connection to a specific reference. If we can take information and put in a structure database, it would be part of the Consortium's resources. We could then annotate it, maintain it and so forth. The SBML group is working on software that will allow this type of task to be done easily, so we don't have to do it. He recommended that we wait a little while and a solution would be at hand.

Shinya Kuroda asked if we would upload different portions of different models and work on them, have our own database of models.

It depends on the scope of the model. Many are very easy. Not enough yet that it's impossible. Any model with partial differential equations can be done. Stochastic and compartmental models are currently not possible. Approaches to incorporate these more sophisticated models need to be explored.

Issue to deal with: how to store models? XML community is dealing with this.

Hoek: The problem with such network maps is that they are all encompassing rather than biologically relevant. He would like half a day at our next workshop devoted to current status of maps to talk about relevance. We could weed out some of these and build confidence in the utility of the remaining maps.

Wiley: We need to be developing experiments to test models and models to test experiments. Keep scope focused on that. Keep focus more general than highly focused such as EGF map.

Next Steps. Take framework, modeling, etc. and then put timeline together for implementing data storage experiment. Define the framework to be built for Consortium, databases, etc. Then decide who will build it. Get agreement via e-mail. Until we get infrastructure in place, can't really move forward.

Goal: By the 2006 meeting in Yokohama, the Consortium will be able to give a live demonstration.

Julie Gephart will be in charge of developing a monthly summary of Consortium activities that can be sent to the membership. Send items to her at Julie.Gephart@pnl.gov.