

## **White Paper: The International Receptor Tyrosine Kinase Networks Consortium Executive Committee**

*Editor's Note: In February, The Scientist's editor, Richard Gallagher, wrote in an editorial[1] that we would soon be publishing "the manifesto of [a] bottom-up, big science group:"*

*"The organization will be low-key, with no central management and no massive block funding. It will be organized around the traditional approach of small, independent research teams chipping away at pet problems. Science will remain a personal pursuit, with scientists maintaining control of their own research. But the team's efforts will be integrated and designed as a virtuous circle of modeling of the system driving experiments that will in turn tune the model, generating more experiments."*

*The purpose, he wrote, would "be important contributions to a broader agenda, bringing a fuller understanding to a complex and vital area of biology. At least as important will be what I anticipate is the proof of principle of this important strategy." We are pleased to present the white paper of that group, the International Receptor Tyrosine Kinase Networks Consortium.*

By the members of the Executive Committee of the Receptor Tyrosine Kinase Networks Consortium

### **Background**

Biology is undergoing a fundamental shift from a descriptive to a quantitative and ultimately predictive science. This transition is being driven by the development of computer-based models of complex biological processes that can both capture and recapitulate the central metabolic and information processing networks of cells.

Receptor tyrosine kinases (RTKs) are central components of cell signaling networks and play crucial roles in normal physiological processes, such as embryogenesis, cell proliferation, and cell death (apoptosis). RTK networks function to detect, amplify, filter, and process a variety of environmental and intercellular cues. Although these networks have been intensively studied for the last 20 years, only since the completion of the Human Genome Project has the breadth and scope of their regulatory function been apparent.

RTK networks regulate human development, embryogenesis, and aging. Malfunction of RTK networks is a leading cause of major human diseases, such as developmental defects, cancer and diabetes. Moreover, several innovative drugs that target various RTKs (e.g., Herceptin, Cetuximab, Iressa, and Gleevec) have been approved by regulatory agencies in the last few years. These new drugs can be very potent and exert minimal adverse clinical effects in a well-defined group of patients, indicating the great therapeutic potential of RTK targeting.

Nevertheless, there is a lack of in-depth understanding of RTK networks because of their enormous complexity and multiplicity. This is a major obstacle for designing improved and more targeted therapies. The application of systems biology is a promising approach for improving our understanding of RTK networks. However, it requires developing very sophisticated

mathematical models and acquiring large amounts of appropriate quantitative experimental data. These data must be acquired using cellular systems that are relevant for human disease and are under conditions that are highly controlled and reproducible.

The technological resources needed to create a systems-level model of RTK signaling networks with significant predictive power are well beyond the research capability of any single institute or nation. To address this daunting, yet critical goal, scientific groups at the forefront of experimental, clinical, and computational molecular cell biology met in Yokohama in January 2005 to launch the International RTK Consortium.

## **Vision**

The vision of the Consortium is to facilitate and coordinate international efforts to understand RTK signaling and its relationship to human pathologies. Experimental data derived from various diseases and tissue settings, as well as high-throughput experiments will be combined into a shared database. The database will be used to build a constantly improving and expanding global model that will be supervised by the Consortium. Understanding mechanisms underlying RTK network function will provide breakthroughs in the diagnosis and treatment of major human diseases, lead to the design of new therapeutic drugs, and decrease the attrition rate of new drugs in development.

Because of the complexity of RTK networks, they can only be understood by rigorous and extensive experimental analyses of a limited number of well-defined experimental systems and equally rigorous and extensive mathematical analyses. The required mathematical and experimental expertise for understanding RTK networks cannot be found in any single laboratory or even country. Thus, the Consortium is dedicated to a strategy in which individual research groups can focus on their own area of excellence, and the data and models can be integrated at the community level. This requires a community infrastructure that can support distributed research. The Consortium will provide the standards that will allow multiple labs across the world to work together productively.

## **Mission**

The RTK Consortium is organized from a systems biology perspective to develop the framework necessary to understand RTK signaling networks central to major human pathologies and therapies. Systems biology is the study of living organisms in terms of their underlying network structure rather than simply their individual molecular components.

The Consortium will

1. Produce and consolidate new and existing sets of unified experimental data relevant to building a systems-level model of RTK networks
2. Establish a universal computational framework for the collection, dissemination, and analysis of both data sets and models of RTK signaling networks.

The Consortium will foster cooperation between academia and industry to create predictive, systems-level models that can be used to develop therapies for human malignancies including cancer, immune-based disorders, inflammation, and diabetes. The Consortium will develop standards to 1) facilitate the comparison and integration of experimental data and modeling results between labs and industry groups worldwide, and 2) apply the most appropriate mathematical analyses to well-defined applications.

## **Organization**

The Consortium has been founded by premier modeling and experimental research groups from the USA, Japan, and Europe and will operate globally. These groups have voluntarily committed to form a research consortium, share experimental data and emerging concepts in a timely way, and to make a substantive commitment to its success. Within the Consortium there will be an exchange of experimental data and mathematical models, as well as extensive sharing of human capital, protocols, reagents, and technologies. Large-scale experiments will be designed by both the computational and experimental groups. We expect that the mathematical analyses will be motivated by experimental and clinical groups with the aim of producing clinically relevant answers.

The Consortium will be managed by an executive committee and be assisted by an international advisory board. The ultimate control will be held by a council, which consists of the research leads of all participating groups.

## **Activities**

The activities of the Consortium will include the following:

- Define a set of appropriate experimental model systems to be used by the Consortium to study various aspects of RTK signaling, including various disease contexts, dynamic properties, spatial regulation and effect of drugs and therapeutic modalities
- Collect, integrate, and improve computational models and analytical methods necessary to study RTK signaling networks
- Create and maintain a distributed database that allows data and model sharing among Consortium members
- Produce and collect the large amounts of high-quality data necessary for modeling and standardize technology and methods needed for data production
- Host a web site for disseminating Consortium results to the general scientific community and providing information on Consortium activities
- Hold workshops in which computational and experimental scientists work together to determine activities necessary to further improve RTK network models
- Hold workshops where scientists and clinicians design research programs that could improve therapies
- Provide cross-disciplinary training courses to improve communication between experimental and mathematical participants and to facilitate their productive interactions

- Communicate with relevant research and advocacy groups such as pharmaceutical industry clinicians and patients to increase their involvement with the Consortium's research program
- Provide an integrated computational platform to the Consortium members for representation, simulation and data handling
- Define the most critical technologies that need to be developed and data that need to be collected
- Promote and coordinate grant applications of members to enhance synergy and complementation, reduce duplication of effort and increase accessibility to expensive core facilities
- Educate a new generation of researchers in the systems biology of RTK signaling and gene networks.

### **Outreach and Public Relations**

The Consortium will have regular communication with the general public, in particular with relevant patient groups to educate and to increase their involvement with the Consortium's research program.

### **Membership**

The Consortium will welcome the participation of outstanding research groups that will significantly contribute to its mission. Decisions on admission to the Consortium will be made by the executive committee with input from the international advisory committee.

### **Contact information**

Web: <http://receptorkinase.gsc.riken.jp> and [www.systembiology.net](http://www.systembiology.net)

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### **Executive Committee**

Yoshiyuki Sakaki (president), RIKEN Genomic Sciences Center, Japan

Boris N. Kholodenko (chair), Thomas Jefferson University, USA

Hiroaki Kitano (systems biology), Sony Computer Science Laboratories, Japan

Walter Kolch (Biological knowledge environment for RTK networks molecular mechanisms), The Beatson Institute for Cancer Research, UK

Pierre De Meyts (partnerships with industry), Hagedorn Research Institute, Denmark

Yosef Yarden (partnership with clinical institutions), Weizmann Institute of Science, Israel

Hans V. Westerhoff (general secretary, secretariat Europe), Vrije University, The Netherlands

H. Steven Wiley (communication, data and model management, secretariat Americas), Pacific Northwest National Laboratory, USA

Mariko Hatakeyama (information, data and model management, secretariat Asia-Pacific), RIKEN Genomic Sciences Center, Japan

## **International advisory committee**

Joseph Schlessinger (chair), Yale University School of Medicine, USA  
(Others invited)

## **Members**

The founding members were present at the first RTK Consortium meeting, January 17-19, 2005, RIKEN, Yokohama. The participant list can be found at: <http://receptorkinase.gsc.riken.jp>  
1. R. Gallagher, "Come together," *The Scientist*, February 14, 2005 19[6]:3.