

## Systems Biologists Seek Fuller Integration of Systems Biology Approaches in New Cancer Research Programs

Olaf Wolkenhauer<sup>1</sup>, Charles Auffray<sup>2</sup>, Simone Baltrusch<sup>1</sup>, Nils Blüthgen<sup>3</sup>, Helen Byrne<sup>4</sup>, Marta Cascante<sup>5</sup>, Andrea Ciliberto<sup>6</sup>, Trevor Dale<sup>7</sup>, Dirk Drasdo<sup>8</sup>, David Fell<sup>9</sup>, James E. Ferrell, Jr.<sup>10</sup>, Daniel Gallahan<sup>11</sup>, Robert Gatenby<sup>12</sup>, Ulrich Günther<sup>13</sup>, Brian D. Harms<sup>14</sup>, Hanspeter Herzel<sup>15</sup>, Christian Junghans<sup>1</sup>, Manfred Kunz<sup>16</sup>, Ingeborg van Leeuwen<sup>17</sup>, Philippe Lenormand<sup>18</sup>, Francis Levi<sup>19</sup>, Michael Linnebacher<sup>1</sup>, John Lowengrub<sup>20</sup>, Philip K. Maini<sup>21</sup>, Arif Malik<sup>22</sup>, Katja Rateitschak<sup>1</sup>, Owen Sansom<sup>23</sup>, Reinhold Schäfer<sup>3</sup>, Karsten Schürle<sup>24</sup>, Christine Sers<sup>3</sup>, Santiago Schnell<sup>25</sup>, Darryl Shibata<sup>26</sup>, John Tyson<sup>27</sup>, Julio Vera<sup>1</sup>, Michael White<sup>28</sup>, Boris Zhivotovskiy<sup>17</sup>, and Robert Jaster<sup>1</sup>

### Abstract

Systems biology takes an interdisciplinary approach to the systematic study of complex interactions in biological systems. This approach seeks to decipher the emergent behaviors of complex systems rather than focusing only on their constituent properties. As an increasing number of examples illustrate the value of systems biology approaches to understand the initiation, progression, and treatment of cancer, systems biologists from across Europe and the United States hope for changes in the way their field is currently perceived among cancer researchers. In a recent EU-US workshop, supported by the European Commission, the German Federal Ministry for Education and Research, and the National Cancer Institute of the NIH, the participants discussed the strengths, weaknesses, hurdles, and opportunities in cancer systems biology.

*Cancer Res*; 70(1); 12–3. ©2010 AACR.

### Defining Cancer Systems Biology

Aiming at understanding the dynamic interactions among components of a cell, among cells and their interaction with the environment, cancer systems biology is an approach by

which biomedical questions are addressed through integrating experiments in iterative cycles with mathematical modeling, simulation, and theory. Modeling is not the final goal, but is a tool to increase understanding of the system, to develop more directed experiments, and finally to enable predictions. This definition of cancer systems biology matches closely the definition of the EraSysBio consortium of 16 European ministries, funding bodies, and project management agencies from 13 countries.<sup>29</sup>

The most popular definitions of systems biology refer to “dynamics,” “mechanisms,” “principles,” and “behaviors.” The complexity of biological systems and/or functions arises from the interaction of a myriad of nonlinear spatio-temporal phenomena and components. The fact that most cellular processes, such as cell-cycle control, cell differentiation, and apoptosis, are inherently dynamical highlights the need for integrating mathematical modeling into life science and clinical research. A systems biology approach can help identify and analyze the principles, laws, and mechanisms underlying the behavior of biological systems.

The participants of the strategic workshop concluded that advancing biomedical applications through systems biology approaches requires the development of new theoretical methodologies, such as novel techniques for data-based system identification, theoretical concepts for the design of experiments, good methods for hypothesis testing, theoretical frameworks to couple processes occurring at (and across) different spatial and temporal scales, and

**Authors' Affiliations:** <sup>1</sup>University of Rostock, Rostock, Germany; <sup>2</sup>CNRS, Villejuif, France; <sup>3</sup>Charité, Berlin, Germany; <sup>4</sup>University of Nottingham, Nottingham, United Kingdom; <sup>5</sup>University of Barcelona, Barcelona, Spain; <sup>6</sup>FOM-IEO, Milan, Italy; <sup>7</sup>Cardiff School of Biosciences, Cardiff, United Kingdom; <sup>8</sup>INRIA, Le Chesnay, France; <sup>9</sup>Brookes University, Oxford, United Kingdom; <sup>10</sup>Stanford University School of Medicine, Stanford, California; <sup>11</sup>National Cancer Institute, Bethesda, Maryland; <sup>12</sup>Moffitt Cancer Center, Tampa, Florida; <sup>13</sup>University of Birmingham, Birmingham, United Kingdom; <sup>14</sup>Merrimack Pharmaceuticals, Cambridge, Massachusetts; <sup>15</sup>Humboldt University, Berlin, Germany; <sup>16</sup>University of Lübeck, Lübeck, Germany; <sup>17</sup>Karolinska Institute, Stockholm, Sweden; <sup>18</sup>Centre Antoine Lacassagne, Nice, France; <sup>19</sup>Hospital Paul-Brousse, Villejuif, France; <sup>20</sup>University of California, Irvine, Irvine, California; <sup>21</sup>University of Oxford, Oxford, United Kingdom; <sup>22</sup>Microdiscovery, Berlin, Germany; <sup>23</sup>Beatson Institute for Cancer Research, Glasgow, United Kingdom; <sup>24</sup>DECHEMA, Frankfurt, Germany; <sup>25</sup>University of Michigan Medical School, Ann Arbor, Michigan; <sup>26</sup>University of Southern California, Los Angeles, Los Angeles, California; <sup>27</sup>Virginia Polytechnic Institute & State University, Blacksburg, Virginia; and <sup>28</sup>University of Liverpool, Liverpool, United Kingdom

**Note:** Supplementary data for this article are available at Cancer Research Online (<http://cancerres.aacrjournals.org/>).

Cancer Systems Biology: Molecular Mechanisms and Mathematical Modelling was held June 7–10, 2009, in Rostock-Warnemuende, Germany ([www.sbi.uni-rostock.de/casysbio/](http://www.sbi.uni-rostock.de/casysbio/)). A list of speakers and participants is provided as supplementary information.

**Corresponding Author:** Olaf Wolkenhauer, University of Rostock, Ulmenstrasse 69, Rostock 18051, Germany. Phone: 49-0-381-498-7570; Fax: 49-0-381-498-7572; E-mail: [olaf.wolkenhauer@uni-rostock.de](mailto:olaf.wolkenhauer@uni-rostock.de).

doi: 10.1158/0008-5472.CAN-09-2676

©2010 American Association for Cancer Research.

<sup>29</sup> <http://www.erasysbio.net>, strategy paper, page 6.

effective algorithms to solve problems of computational complexity.

### Approaching Tumor Complexity by Integrating Experiments with Mathematical Modeling

In order for systems biology to succeed in cancer research, and ultimately become an integrated part of it, rather than a separate discipline, it has to overcome significant barriers to the acceptance of mathematical modeling in the life sciences. Such models are necessary because of the dynamic nature of many biological processes involved in the initiation and progression of cancer. In order to allow the formulation and calibration of mathematical models, quantitative data have to be generated.

Because the systems approach is, above all, a different way of thinking about the organization and behavior of dynamical systems, the impact of systems biology approaches is more difficult to measure. This situation is further confounded by the fact that all models are abstractions of reality, because all the hypotheses on which they are based will eventually prove to be incomplete in one way or another, and science progresses by uncovering these shortcomings and looking for models that are improved (if never perfect).

Mathematical models, however, have the advantage of being quantitative and interactive rather than solely descriptive. The process by which models are formulated, and which may include the representation of genetic, epigenetic, cellular, and tissue effects across the various physical and temporal scales during tumorigenesis, helps to articulate hypotheses and thereby supports the design of appropriate experiments to test them. Consequently, models cannot be regarded as “deliverables” or “final products” that unambiguously mark the success of a systems biology project.

The role of mathematical modeling is to provide a conceptual framework for the formulation and quantitative testing of hypotheses. However, the initial purpose is not prediction but to enhance our “understanding” of a biological system. Generating predictions is one way to test whether this understanding is consistent with the behavior of the system of interest.

### An Unlikely End to a New Discipline

Rather than defining systems biology as a separate discipline, the workshop participants' recommendation is to encourage the incorporation of “systems biology approaches” across new research programs, particularly those of medical relevance to cancer. Systems biology emphasizes the integration and coordination between theoretical and experimental efforts. If systems biology approaches were widely adopted in the life sciences as a powerful tool for hypothesis testing, there would be no need to consider systems biology as a separate discipline. However, considering the skepticism that exists toward mathematical modeling in the life sciences, it remains important to emphasize and show its value in dealing with biological complexity.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

### Acknowledgments

The organizers of the workshop would like to thank Dr. Frederick Marcus and Prof. Frank Laplace from the BMBF for their support, advice, and encouragement. We are grateful for the organizational support of the event by Petra Gefken, Ulf Schmitz, Peter Raasch, Peggy Sterling, and their team.

### Grant Support

The transatlantic strategic workshop took place in Rostock-Warnemünde, Germany, June 7–10, 2009 and was funded by the National Cancer Institute (NCI) of the National Institutes of Health (NIH), the German Federal Ministry for Education and Research (BMBF), and the European Commission through the Specific Support Action (SSA) SysBioMed (Systems Biology for Medical Applications). SysBioMed was managed by Dr. Frederick Marcus, Principal Scientific Officer, European Commission, Directorate F, Unit F.4.

Received 7/29/09; revised 10/17/09; accepted 11/3/09; published OnlineFirst 12/22/09.