



COLUMBIA UNIVERSITY
MEDICAL CENTER

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College of Dental Medicine
Mailman School of Public Health
School of Nursing*

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Dear John,

It is with pleasure that I write to support the creation of a new Department of Systems Biology at Columbia University College of Physicians and Surgeons. Systems Biology is a relatively new discipline that combines biological experimental data and advanced computational techniques to analyze massive amounts of genetic and other biological data. These data can then be integrated to understand complex cellular regulatory functions in health and disease, as well as to understand genetic and epigenetic influences that drive gene expression. This powerful analytic approach allows characterization of the molecular interactions that determine the behavior of normal and abnormal biologic systems.

Systems Biology is by its nature multidisciplinary, integrating the work of experimental scientists and computational scientists, and thus unites scientists from across the university. Examples of the kinds of work done by Systems Biologists are:

- Reconstruction of cell regulatory networks at the molecular level.
- Use of computational models to predict how genomic and epigenomic diversity is processed by such regulatory networks resulting in physiologic and pathologic phenotypes.
- Experimental validation of the biologic predictions that are derived from computational models.

Systems Biology at P&S has applications in immunology, cancer biology, infectious diseases, neurobiology, and metabolomics. Because of the importance of this new discipline, the Center for Computation Biology and Biomedical Informatics was created in 2003 to provide a base for those multidisciplinary scientists involved in this work. In early 2010, the Columbia Initiative in Systems Biology was developed to coordinate activities of the Center for Computational Biology, and the J.P. Sulzberger Genome Center. The Columbia Initiative in Systems Biology supports research in computational biophysics and structural biology, as well as the modeling of regulatory, signaling and metabolic networks, pattern discovery and recognition, machine learning, and functional genomics. It also supports active research programs in disease related areas such as cancer, human genetics, infectious diseases, metabolic disorders, and neurodegenerative and psychiatric disease, as well as stem cell and regenerative medicine.

Because of the rapid and remarkable growth at Columbia University in research at the interface of computational and basic biological sciences, the faculty of the Center for Computational Biology, as well as the Columbia Initiative in Systems Biology have been highly successful winning research funding

awards from the NIH. The Initiative in Systems Biology has produced over 300 publications in the last five years, with over one-third published in high impact journals.

In the context of the importance of this new scientific discipline, the extraordinary cross disciplinary faculty strength, and the success of the Columbia Initiative in Systems Biology in grant awards and published contributions, the creation of a Department of Systems Biology is a logical and important evolutionary step in becoming a leader in this field.

I am, therefore, highly supportive of the creation of the Department of Systems Biology. Attached is a detailed proposal describing the rationale for creation of the Department of Systems Biology submitted by Drs. Andrea Califano and Barry Honig.

With best personal regards,

Sincerely yours,

A handwritten signature in black ink, appearing to read "Lee", with a large, stylized flourish below it.

Lee Goldman, M.D.

**Proposal to Create a
Department of Systems Biology
at Columbia University Medical Center**

**Submitted by Andrea Califano and Barry Honig
May 17, 2012**

The golden age of many scientific disciplines has coincided with the development of quantitative, analytical, and predictive models. From chemistry, to physics, to economics such models have complemented the disciplines' original empirical foundations by providing new tools for the rapid generation and testing of relevant hypotheses. In many disciplines an additional period of expansion occurred when computers made it possible to numerically solve complex problems that could not be addressed at the analytical level.

In biology and medicine, the use of quantitative predictive models is a recent development. In the last decade, the widespread availability of novel genome-scale experimental techniques and the ubiquity of large-scale computing platforms have made it possible to generate and analyze massive amounts of data, enabling the development of quantitative models. These developments have heralded a new age for predictive biology and personalized/precision medicine.

The new discipline emerging at the intersection of the experimental and computational biomedical sciences is called systems biology. It has become one of the most effective frameworks for accelerating scientific discovery in both basic and translational research. A number of leading institutions around the country including Harvard University, Stanford University, MD Anderson Cancer Center, and Mt. Sinai School of Medicine have capitalized on the promise of the new discipline by creating departments of systems biology and systems pharmacology. These departments have addressed pressing needs in education and training and have become catalysts for the recruitment of outstanding faculty and students.

Over the past decade, through the combined efforts of the Center for Computational Biology and Bioinformatics and the JP Sulzberger Columbia Genome Center, Columbia University has emerged as a leader in systems biology in terms of systems biology-related National Institutes of Health (NIH) funding, publications, and program size. This academic achievement has been strongly complemented by the development of a remarkable onsite technological infrastructure, including one of the world's largest supercomputers dedicated to biological and medical research as well as state-of-the-art genomic, high-throughput screening, and high-content imaging equipment.

In response to this extraordinary growth, as well as to competitive recruitment pressure from peer institutions, a new Columbia Initiative in Systems Biology was created and funded in 2010. This enabled the recruitment of four outstanding new faculty members — bringing the total

number of affiliated systems biology faculty at Columbia (spanning both campuses) to 22 — with four to five additional recruits slated in the next two years.

This expansion has laid the groundwork for the proposed formation of a Department of Systems Biology, to be located primarily at the Columbia University Medical Center, but with joint appointees on the Morningside campus as well. Our proposal is motivated by critical opportunities and institutional priorities, including recruitment, education, fundraising, and interdisciplinary collaborations.

Historically, recruiting outstanding faculty with specialized training in systems biology has been virtually impossible. This was primarily because the candidates' research focus was not generally compatible with the more traditional objectives of existing university departments. In contrast, our recent recruitment successes have been possible because of the creation of the Initiative in Systems Biology and the expectation that it will attain departmental status.

Similarly, in terms of education and training, most of the students who apply to systems biology programs at Harvard, Stanford, and MIT fail to apply to Columbia because this discipline is not formally represented at our university. Offering a departmental home and a focused curriculum in systems biology would have an enormous impact on our ability to attract the best students.

In addition, the liaison between the basic and clinical sciences created by systems approaches creates unique opportunities to raise philanthropic support, such as has been achieved by the Lewis-Sigler Institute at Princeton, the Broad Institute, and the Department of Systems Biology at MD Anderson Cancer Center.

Finally, the creation of a Department of Systems Biology will open countless opportunities for new types of interdisciplinary and intercampus collaborations at Columbia. The department will become a resource for the entire university and will support the major genomic platforms — such as next-generation sequencing and high-throughput screening — that have become indispensable tools for performing cutting-edge research.

This document explains the importance of creating a Department of Systems Biology at Columbia, outlines its strategic goals, and describes how it will be implemented.

1. What Is Systems Biology?

Since the completion of the Human Genome Project in 2003 it has become increasingly clear that most phenotypes — observable traits in an organism — do not usually result from single genes or isolated events. Rather, they emerge from the interaction of thousands of molecular components under the control of a complex cell regulatory logic. These components, including genes, proteins, metabolites, and small molecules, all work together to produce specific phenotypes. If a regulatory mechanism is dysregulated — for example, through a gene mutation, overexpression of a particular protein, or through environmental exposures that affect

the organism's physiology — a cascade of events may ensue that results in a disease-related phenotype.

The challenge facing biologists, then, is to understand how interactions among the cell's regulatory logic, evolution at the genetic level, and epigenetic influences that affect gene expression all work together to produce physiologic and pathologic events. Addressing this challenge requires the in-depth characterization of the molecular interactions that determine the behavior of normal cells, tissues, and ultimately organisms, as well as those involved in their dysregulation in disease.

Systems biology is a rapidly evolving new discipline within the biomedical sciences that seeks to understand biology explicitly at this unprecedented level of complexity. Through experimentation and sophisticated computational approaches, multidisciplinary teams of investigators work together to:

- reconstruct cell regulatory networks at the molecular level
- use computational models to predict how genomic and epigenomic diversity processed by these networks can manifest either physiologic or pathologic phenotypes.
- experimentally validate the computational predictions that are derived from these models

At Columbia this work is complemented by analysis of the macromolecular structures that mediate regulatory interactions – including protein-protein, protein-DNA, protein-RNA and other interactions – using computational structural biology methods that elucidate these interactions at the atomic level. Integration with structural biology is a unique aspect of systems biology research at Columbia.

This new approach to biology has become possible over the last decade with the arrival of several revolutionary new technologies. For instance, high-throughput sequencing has dramatically changed our ability to quickly and economically generate accurate profiles of RNA abundance and DNA variability. For the first time, these profiles allow the comparative analysis of genomes of many individuals within a population, enabling researchers to identify differences at the systems level that are causally, not just statistically, associated with distinct phenotypes. Similarly, new high-throughput technologies for elucidating macromolecular structures, as well as for generating metabolomic, phosphoproteomic, and epigenomic profiles are already playing important roles in systems biology. The field would not have emerged, however, without the ability to analyze these data modalities using powerful computational algorithms running on large supercomputers.

Systems biology today is having major impact on the dissection of both physiologic and pathologic phenotypes, from the study of the immune system and of development, to the study of cancer, infectious diseases, neurodegenerative diseases, and metabolic syndromes. Its latest area of application is in the study of small-molecule interactions with cellular systems and organisms, an area also known as chemical systems biology, which promises to have far

ranging implications for the development of novel therapeutic strategies for the treatment of human disease.

2. Development of Systems Biology as a Discipline

In the last few years, systems biology has evolved from an embryonic science that mostly addressed theoretical aspects of gene regulation into a mature discipline that is producing exciting new biological discoveries and technologies with strong translational potential. By developing genome-wide models, systems biologists can now make precise predictions about the role of specific genes in generating particular phenotypes, and then test these predictions experimentally. At Columbia, for example, dissection and interrogation of cell regulatory networks have led to the discovery of key genes involved in tumorigenesis, tumor progression, and drug sensitivity. They have also helped elucidate genes that are crucial for the life cycle of molecular pathogens. These discoveries suggest new potential targets for drugs capable of disrupting the regulatory pathways that are involved in disease initiation.^{1,2}

Both in academia and industry, demand for researchers trained in systems biology is already extremely high and growing.^{3,4} Many scientists now recognize the importance of systems-level thinking about biological and physiological problems, and have either taken up systems approaches themselves or have begun to develop collaborations with systems biologists to bring new insights to the problems they are trying to solve. Graduates with specific training in systems biology are currently in high demand due to the specialized skill set they possess and to the increasing importance of the systems-level perspective to the future of basic science and translational research. Indeed, there are far more job openings in this area than qualified individuals to fill them.

An increasing number of universities and research institutes around the United States now offer programs organized around systems biology. Institutions including Harvard University, Stanford University, Massachusetts Institute of Technology, Princeton University, Yale University, the University of California San Francisco, Johns Hopkins University, MD Anderson Cancer Center, Mt. Sinai Medical Center, and Albert Einstein Medical Center are concentrating resources in this area. Meanwhile, industry has also incorporated systems biology into its drug discovery programs.

Funding support for research that uses interdisciplinary, systems approaches has also grown at agencies within the National Institutes of Health. Institutes including the National Institute for General Medical Sciences, National Human Genome Research Institute, Integrative Cancer Biology Project and Centers for Cancer Systems Biology at the National Cancer Institute, ENCODE (Encyclopedia of DNA Elements) Project, and the new National Cancer Informatics Program (NCIP) are particularly interested in supporting large centers that have the capacity to address challenging problems in genomics and genomics-driven medicine. Recent calls for proposals have focused on cancer, infectious diseases, neurodegenerative diseases, and other human diseases for which systems approaches hold promise in advancing science and the

search for new therapies. All of these developments point to a trend in which systems biology will become increasingly central to the practice of biomedical science in the coming years.

3. Systems Biology at the Columbia University Medical Center

The seeds of systems biology at Columbia were planted with the founding of the JP Sulzberger Columbia Genome Center in March 2000. Initiated by Isidore Edelman, former Chair of the Department of Biochemistry and Molecular Biophysics, and made possible by a major grant from Judith Sulzberger, the Genome Center is an interdisciplinary center whose goal is to expedite the adoption of novel genomics technologies throughout the Medical Center and to enable discoveries in biological and biomedical science. The Genome Center was the beginning of Columbia's efforts in gene sequencing, and as it grew, experts in bioinformatics were hired to analyze the data that were being generated.

In parallel, a separate department was established to develop applications of computational techniques within a clinical setting. The Department of Biomedical Informatics (DBMI) arose out of the Center for Medical Informatics, and in 1994 became a formal department and began training graduate students. Although the focus of DBMI is not systems biology — rather, investigators in the department develop new computational approaches for managing and extracting information from electronic medical data — it helped attract faculty with computational interests to the Medical Center.

A third factor in the development of systems biology at Columbia can be traced to Gerald Fischbach, who as Dean of the Medical Center became interested in computational biology and supported the hiring of a number of investigators in the field. At the beginning, computational biology at Columbia focused primarily on using computational methods to simulate biological processes. This contributed to the emergence of a significant community of investigators who use computational approaches in their work.

Founded by Barry Honig and Andrea Califano in 2003, the Center for Computational Biology and Bioinformatics (C2B2) was created to support this growing community. C2B2 grew from the bioinformatics program at the Genome Center, but has been administered as a separate entity. It has been involved in hiring faculty within DBMI and the Department of Biochemistry and Molecular Biophysics at the Medical Center and the Departments of Biology and Computer Science on the Morningside campus. With the development of a weekly seminar series and annual retreats, C2B2 has fostered communication and collaboration among the growing community of researchers with computational interests at Columbia. In 2005 C2B2 was given research space on the 8th and 9th floors of the new Irving Cancer Research Center, solidifying its existence and giving it a physical home and its own supercomputing infrastructure.

Recent investments in the emerging field of chemical biology on the Morningside campus further add to Columbia's strength in systems biology. Chemical biology creates high-throughput tools for manipulating and reading out biological systems, exploiting our growing understanding of systems-level behavior to devise entirely new approaches to therapeutics.

Columbia's presence in chemical biology was cemented in 2011 by the co-localization of Brent Stockwell (Department of Biological Sciences) and Virginia Cornish (Department of Chemistry) on the 12th floor of the Northwest Corner Interdisciplinary Science Building. Formalized as the Interdisciplinary Biosciences (iBIO) group, faculty across departments with interest in the interface between the biological sciences, physical sciences, and engineering have organized around regular seminar series, student training, multi-PI initiatives, and faculty recruiting. The iBIO initiative aligns naturally with the growing systems biology community at Columbia.

Finally, since its creation in 2010 with the support of Dean Lee Goldman, the Columbia Initiative in Systems Biology (CISB) now coordinates the activities of C2B2, the Genome Center and, increasingly, research in chemical biology. CISB supports basic science research in computational biophysics and structural biology, as well as the modeling of regulatory, signaling and metabolic networks, pattern discovery and recognition, machine learning, and functional genomics. It also supports active research programs in disease-related areas such as human genetics, cancer, infectious diseases, metabolic disorders, and neurodegenerative and psychiatric disease, as well as stem cell and regenerative medicine. These research areas are increasingly dependent on the analysis of massive amounts of data emerging from high-throughput biological technologies, such as next-generation sequencing and rapid screening using chemical biology approaches.

4. Accomplishments

The past decade has seen a remarkable growth at Columbia in research taking place at the interface of computation and basic biological science. National Institutes of Health funding for C2B2 alone has jumped from \$500,000 in 2003 to almost \$10 million today. In 2010, eight of the 11 grants submitted to the NIH were approved for funding and a similar percent was funded last year. CISB has been awarded eight distinct Center of Excellence grants in systems biology, seven of which are NIH funded. This accomplishment reflects not only the relevance of the science being conducted at CISB but also the uniquely collaborative and interdisciplinary nature of our program.

Columbia has assembled a robust level of talent in disciplines related to systems biology. The university is now home to nearly two dozen faculty members who pursue research in topics related to systems biology (see appendix 2), making Columbia one of the largest centers in systems biology in the country. The scientific output by CISB faculty has resulted in over 300 publications over the last five years. About one-third were published in journals with impact factor higher than 13, reserved for the top 10% of scientific journals.

Among publications by Columbia faculty are several seminal contributions within the field of systems biology. For example, just to name a few accomplishments, Columbia investigators assembled the first regulatory networks for human cancer cells that were experimentally validated⁵⁻⁸, identified a previously unknown layer of post-transcriptional regulation involving microRNAs¹, found a functional gene network associated with autism⁹, and demonstrated that nucleotide sequence determines the width of the DNA minor groove, which then determines the

ways in which Hox transcription factors bind to DNA^{10,11}. This last result, for instance, suggests new ways to integrate insights from structural biology into the practice of systems biology.

Columbia investigators have developed many algorithms and software tools for predicting the function of regulatory networks. Through a platform called geWorkbench, these tools are freely available and have been widely adopted within the research community. Our faculty have also played an important role in promoting the exchange of ideas within the global systems biology community by organizing key conferences and meetings that have attracted hundreds of investigators each year. These include a) the DREAM (Dialogue for Reverse Engineering Assessments and Methods) conferences, which are designed to establish criteria for evaluating the effectiveness of reverse engineering algorithms, b) the RECOMB Systems Biology conference, and c) the New York Academy of Sciences Systems Biology and Chemical Biology Discussion Groups. Columbia investigators have also led efforts to spotlight recent advances in cancer systems biology by co-chairing the 2011 Annual Meeting of the American Association for Cancer Research (AACR) and the 2011 AACR Conference on Cancer Systems Biology.

With the support of a planning grant from the National Institutes of Health, Columbia is also home to the Center for the Multiscale Analysis of Genomic and Cellular Networks (MAGNet), one of 7 National Centers for Biomedical Computing and one of 12 interdisciplinary Centers for Cancer Systems Biology. MAGNet's mission is to develop novel structural biology and systems biology tools, algorithms, and databases for dissecting molecular interactions in the cell and elucidating cellular phenotypes.

5. Technical Infrastructure

Through the Center for Computational Biology and Bioinformatics, Columbia is home to a world-class computational infrastructure (the Titan cluster), which comprises one of the largest academic computing environments devoted to molecular and systems biology. Titan was ranked in 79th position — among the fastest supercomputers in the world — when originally assembled in 2008. Columbia's analytical capabilities include microarray data analysis and storage, sequence and pathway analysis, and a range of tools for systems and structural biology developed under the auspices of MAGNet. The equipment is housed in several modern data centers spanning a 30,000 square-foot area in the Herbert Irving Comprehensive Cancer Center (HICCC) and the Russ Berrie Medical Science Pavilion.

The Genome Center contains the recently renovated Next-Generation Sequencing Facility, which is currently capable of sequencing several full human genomes per week at a cost of only \$3,500 per genome; this cost is expected to go down to about \$1,000 by the end of 2012. Over the last year, under CISB tutelage, the Next-Generation Sequencing Facility has roughly doubled its genomic output every quarter and constantly increased the number of Columbia faculty using the facility. It is now reaching full capacity and is projected to achieve break-even financials at the end of the next two quarters. The Next-Generation Sequencing Facility is now used routinely and successfully by a large number of Columbia investigators and has been touted by Illumina, a

major manufacturer of advanced genomics technologies, as the best run genomic facility in New York City.

The Genome Center also runs the High-Throughput Discovery and Microscopy Facility , which allows Columbia investigators to perturb biological systems with a variety of biochemical probes, including RNA interference molecules (RNAi), small molecules, and cDNA libraries to silence, express, or modulate specific genes and molecular pathways. These capabilities have been instrumental in our being selected as the screening facility for the entire New York stem cell community, funded by the NYSTEM foundation. The facility is run jointly by the Columbia Stem Cell Initiative and CISB and is expected to initiate full-scale operation in 2012.

As part of this NYSTEM grant, Brent Stockwell has established the Columbia NYSTEM Chemical Probe Synthesis Facility in the Northwest Corner Building. This facility assists researchers in designing and synthesizing chemical probes of biological processes, especially those related to stem cells. It has the capability work with researchers to perform computational chemistry, virtual screening, medicinal chemistry, metabolite profiling, drug metabolism, and pharmacokinetic studies. These resources will aid researchers in systems and chemical biology in interrogating and manipulating biological systems.

These remarkable facilities give a key competitive advantage for faculty within CISB when performing their research and applying for grants. They also provide a service to Columbia faculty outside of CISB who need powerful genomics and computational environments that would be impossible to maintain by their independent labs.

6. Reasons to Start a Department of Systems Biology

Our proposal to create a Department of Systems Biology at Columbia builds on these accomplishments, and is a strategic response to the rapidly evolving importance of systems biology to the future of the biomedical sciences. Focusing resources in this area offers six key advantages:

6.1 – Advancing Science

The Columbia University Medical Center governing board has identified systems biology as a major direction for scientific development in the coming years. Creating a Department of Systems Biology that focuses expertise in this area is a bold move to leverage the power of this new approach to achieve new discoveries.

Faculty within the Department of Systems Biology will use advanced computational and experimental methods to examine a wide range of biological phenomena that include pathogen interactions, cancer initiation and progression, stem cell programming, autoimmunity, and neurodegenerative diseases, just to mention a few. Other key areas of research include:

- Prediction of protein structure, function, and localization
- Study of protein-protein and protein-DNA interactions
- Gene expression analysis and prediction of regulatory network structure
- Study of complex inherited traits
- Reconstruction and analysis of metabolic networks
- Dynamic simulations of cellular networks
- Image analysis and interpretation
- Evidence integration

Establishing a Department of Systems Biology will enable Columbia to take a leadership role in developing the tools and making the discoveries that will push science and medical research forward, not only in systems biology but also in a range of related disciplines.

6.2 – Improving Education

In recent years systems biology programs have been attracting the very best graduate students. While other universities have already developed training programs to meet this need, Columbia is currently failing to attract these top students because it is not projecting a coherent vision for the discipline. We have outstanding faculty, funding, and facilities, but have not yet developed an integrated, standardized curriculum and training program that would make Columbia as competitive as possible in its ability to attract top graduate students.

We propose to create a fully accredited, degree-granting Department of Systems Biology that offers a highly focused curriculum emphasizing both computational analysis and biological experimentation. Attracting gifted students and early-career postdoctoral research fellows will benefit the university as a whole, as it will eventually produce a pool of junior researchers with the skills to help implement new kinds experiments and to develop advanced analytics techniques throughout the institution. As the Department of Systems Biology grows, the goal will be to graduate students in many scientific departments who have training in systems biology.

Developing a training program in systems biology will also address a pressing market need. At present, the demand for investigators trained in this area is massively unmet in both academic and industry settings. Many laboratories seek well-trained systems biologists who can use sophisticated quantitative tools to analyze large datasets. Creating a prestigious program in systems biology will help to ensure that Columbia plays a central role in meeting this need.

6.3 – Promoting Columbia’s Leadership and Prestige

Columbia University is already one of the top institutions in the country in terms of faculty and research productivity in systems biology. However, since we lack a shared institutional identity for the discipline, our strengths are not as visible as they might be, both in the greater scientific community and within Columbia.

Creating a Department of Systems Biology will make a strong statement that the university embraces and supports this cutting-edge approach to science. For potential faculty and students, creating a Department of Systems Biology will also make Columbia more recognizable as a desirable location for pursuing advanced research and education in this field, as well as in related fields that will benefit from collaborative research efforts with Systems Biology faculty and resources.

6.4 – Enhancing Competitiveness

Currently, Columbia has limitations in its ability to recruit the caliber of talent that will enable the Medical Center to fully leverage the power of systems biology. Existing departmental structures require new faculty hires to take primary appointments in departments around the institution, necessitating responsibilities that may not be central to their research in systems biology. This can make other institutions with more focused systems biology programs more attractive, and has proved to be a hurdle on several recent occasions, when opportunities to recruit highly regarded investigators in systems biology did not succeed.

Assuming a leadership role at the frontlines of the revolution that research in systems biology promises will require that Columbia become more successful in recruiting these highly trained faculty. Creating a Department of Systems Biology will make a clear statement that opportunities for research in this area are expanding. It will offer new recruits access to a program with the technological and intellectual resources to support their work, as well as a departmental structure that will enable them to focus more specifically on topics related to systems biology. Already in the past year, following preliminary discussions to create a new Department of Systems Biology, the Columbia Initiative in Systems Biology has had a number of successes in recruiting both senior and junior faculty, including Saeed Tavazoie (Princeton) as a full professor and Sagi Shapira (Broad Institute of Harvard and MIT), Peter Sims (Harvard), and Yufeng Shen (Columbia) as assistant professors. These achievements augur well for the continued growth of the Department of Systems Biology.

6.5 – Creating New Synergies

The Department of Systems Biology will become a valuable resource for investigators throughout Columbia University Medical Center. *and university* Systems Biology faculty will bring a high level of expertise in developing innovative applications of high-throughput genome sequencing, high-throughput genotyping, high-throughput chemical screening, systems-level engineering, computational analysis, and other technologies, offering researchers throughout the institution opportunities to develop new kinds of experiments that use the lens of systems biology.

Already faculty from top departments and centers in the Medical School — such as the Department of Biochemistry and Molecular Biophysics, the Herbert Irving Comprehensive Cancer Center, the Department of Pathology, Department of Biomedical Informatics, the Stem Cell Initiative, and the Motor Neuron Center — have voiced support for expanding Columbia's strength in systems biology. The integration of multiple disciplines, methodologies, and

collaboration across centers of excellence will have a huge impact on Columbia's success and distinguish it as a leader in the field.

We also anticipate that systems biology laboratories will share postdoctoral fellows and graduate students with other departments, promoting the exchange of ideas.

6.6 – Generating Revenue

Creating a Department of Systems Biology will open significant new opportunities for generating revenue. Funding for research that uses interdisciplinary, systems approaches has grown in recent years at several agencies within the National Institutes of Health. Institutes that support this type of research include the National Institute for General Medical Sciences, National Human Genome Research Institute, the Integrative Cancer Biology Project and Centers for Cancer Systems Biology at the National Cancer Institute, the ENCODE (Encyclopedia of DNA Elements) Project, and the Cancer Biomedical Informatics Grid (caBIG).

NIH is particularly interested in supporting large centers that can use systems biology to address complicated scientific problems, particularly those related to pressing issues in public health. Recent calls for proposals have focused on cancer, AIDS, diabetes, neurodegenerative diseases, and other human diseases for which systems approaches hold promise in identifying new potential drug targets.

Over the past eight years, Columbia has been very successful in attracting funding from the NIH and other sources. C2B2 now receives almost \$10 million annually from the NIH alone. These accomplishments bode well for our ability to attract additional funding in systems biology as the department grows. This in turn will impact researchers and departments throughout the university who will collaborate with Systems Biology faculty, opening up additional funding opportunities.

Creating a Department of Systems Biology also opens new opportunities for fundraising in the context of philanthropy and institutional development. A new department poised to take a leadership role at the cutting edge of scientific research should prove to be an attractive project for potential donors. Additionally, the department would increase collaborations with clinical researchers, thus increasing Columbia's presence in the translational systems biology arena and further enhancing opportunities to present to donors interested in medical applications.

7. Organization of the Department of Systems Biology

A further benefit of creating a new Department of Systems Biology will be to create a more manageable and efficient administrative structure. The new department will draw upon and consolidate resources from the Columbia Initiative in Systems Biology, the Genome Center, and the Center for Computational Biology and Bioinformatics.

7.1 - Leadership and Membership

Leadership of the Department of Systems Biology will build on the current leadership of the Center for Computational Biology and Bioinformatics. Andrea Califano will assume the position of director and chair of the Department of Systems Biology. Dr. Califano is currently director of the Columbia Initiative in Systems Biology, director of the Center for Multiscale Analysis of Genetic Networks (MAGNet), director of the JP Sulzberger Columbia Genome Center, and associate director of Bioinformatics at Columbia University's Irving Cancer Research Center. Barry Honig, who has served as director of the Center for Computational Biology and Bioinformatics will become co-director of the new Department of Systems Biology. (For more detailed biographies of Drs. Califano and Honig, please see Appendix 1.)

The faculty for the Department of Systems Biology will comprise current C2B2, CISB, and Genome Center faculty. Individuals will continue to hold joint appointments with other departments around the institution, including Biological Sciences, Biomedical Informatics, Chemistry, Computer Science, Microbiology and Immunology, Pathology, Cell Biology, Clinical Pharmacology and Experimental Therapeutics, Biochemistry and Molecular Biophysics, and Applied Physics and Applied Mathematics, as well as the Irving Cancer Research Center. (Please see Appendix 2 for a list of faculty who will be affiliated with the Department of Systems Biology.)

7.2 - Relationship between the Department of Systems Biology and the Genome Center

The JP Sulzberger Columbia Genome Center is currently closely intertwined with the Columbia Initiative in Systems Biology and the Center for Computational Biology and Bioinformatics. It is home to Columbia's High-Throughput Screening Facility and Next-Generation Sequencing Facility. Andrea Califano currently serves as the director of the Genome Center in addition to leading CISB and C2B2, and a number of faculty are members of both the Initiative in Systems Biology and the Genome Center.

Because of this overlap, the Genome Center will be subsumed into the Department of Systems Biology. This union serves an important scientific purpose, providing a clear mission for the Genome Center and offering important opportunities that are not present at most other institutions. The merger will relieve the confusion within and outside the university about the activities and goals of each of these programs as currently designed. Coordinating Columbia's computational capabilities with expertise at the Genome Center also place it at an advantage over other centers for next-generation sequencing and high-throughput screening in terms of its ability to support researchers in analyzing the huge amounts of data that result from these new technologies.

The Genome Center will also continue to function as a core facility for the the Columbia research community, supplying services including next-generation sequencing, high-throughput screening, and high-throughput high-content microscopy at a price point that is very cost-effective.

7.3 - Relationship between the Department of Systems Biology and C2B2

The Center for Computational Biology and Bioinformatics will continue to exist, but will become a unit within the new Department of Systems Biology, which will administer its budget, charges for space, and other administrative costs.

As is the case currently, the faculty of C2B2 will be drawn from throughout the University. C2B2 will include members of the Department of Systems Biology as well as faculty from other departments — both at the Medical Center and at Columbia's main campus — whose research involves computation, genomics, or systems biology. It may be possible for certain faculty to have appointments in the Department of Systems Biology without being a part of C2B2.

Retaining C2B2 as a specialized center within the Department of Systems Biology will be important because it has attained a visibility both within the university and in the wider community of computational biologists. C2B2 will also maintain ongoing grants and continue to foster interdisciplinary computational work between the Department of Systems Biology and other departments in the university.

7.4 - Relationships with Other Departments

Because systems biology is by its nature an interdisciplinary field, the new Department of Systems Biology will work closely with many other departments in the university in research, training, and the recruitment of new faculty. Departments including the Taub Institute, Motor Neuron Center, Irving Cancer Research Center, Department of Pathology, and Department of Biochemistry and Biophysics have already expressed interest in working closely with the Department of Systems Biology to help identify new recruits who use the tools of systems biology to study specific diseases. These new recruits, working in a multidisciplinary way in the context of both basic and translational research, will advance the integration of systems biology into the wider Columbia community.

7.5 - Location and Facilities

The central administration for the Department of Systems Biology will be located on the 8th and 9th floors of the Irving Cancer Research Center, which is currently home to the Center for Computational Biology and Bioinformatics. The Irving Center is also home to the C2B2 supercomputing facility, which will also now be administered by the Department of Systems Biology.

Genome Center facilities and other laboratories will continue to be housed in the Russ Berrie Medical Science Pavilion. These facilities include the Next-Generation Sequencing Facility and the High-Throughput Screening Facility. The Department of Systems Biology will also continue to provide bioinformatics analysis services through Biomedical Informatics Shared Resource.

7.6 - Plans for Expansion

A search is already underway to recruit additional junior and senior faculty in different areas of systems biology. One area of focus is proteomics, which can provide the equivalent of a snapshot of the complete set of proteins within individual cells, including post-translational modifications (for example, phosphorylation and ubiquitination) that cannot be detected using genomics alone. We are currently searching for a leading researcher in this area and, in parallel, will acquire the instrumentation required to create a world-class, comprehensive proteomics program. High-throughput proteomics has been identified as a key weakness at Columbia, in part due to the absence of an appropriate department and necessary infrastructure required to attract the kind of scientist we wish to recruit. The creation of a Department of Systems Biology will remove such barriers and enable our expansion into this exciting field.

8. Education and Training

Currently, graduate education in computational biology takes place under the auspices of several different but overlapping programs, including the Department of Biomedical Informatics, the C2B2 track within the Integrated Program in Cellular, Molecular, and Biophysical Studies, and other departmental programs that allow students to take courses on topics in computational biology. This variety of options can be confusing for students, and does not offer a consistent, clearly defined curriculum for those interested in pursuing focused training in systems biology.

For these reasons, once it is formed, the Department of Systems Biology will initiate applications to the Columbia University Senate and the New York Department of Education for accreditation to grant academic degrees in systems biology. The purpose of this effort will be to create an integrated educational program that specifically emphasizes expertise in the most essential concepts and skills that every student of systems biology should know.

9. Seed Funding

Seed money in the amount of \$20 million has been willed to Columbia University Medical Center to create a new Department of Systems Biology through a generous gift by Judith Sulzberger. An additional \$5 million has been pledged by other departments in the university — including the Taub Institute, Motor Neuron Center, Irving Cancer Research Center, and Department of Pathology and Cell Biology — to support the hiring of new faculty. Dean Lee Goldman has pledged another \$20 million in fundraising over the next 3 years. These significant resources will be sufficient to launch the new department and to begin to grow its intellectual and technological resources.

10. Conclusion

Columbia's investments in computational biology, next-generation sequencing, high-throughput screening, and high-throughput microscopy have placed it in an extremely advantageous

position within the growing field of systems biology. Over the past decade, the university has cultivated one of the most accomplished faculties in disciplines related to this new field, and has created an exceptionally powerful technical infrastructure for performing computational and high-throughput biological research.

At the same time, however, systems biology at Columbia has an identity problem that has made it difficult to administer and coordinate research in this area, recruit top scientists, attract the most gifted students and postdoctoral researchers, and integrate the tools that systems biology offers into diverse research areas, both at the Medical Center and on the Morningside campus. Creating a Department of Systems Biology will bring a new focus to systems biology at Columbia. It will open countless opportunities for new types of interdisciplinary collaborations throughout the university, leading to discoveries and innovations in both basic and translational research.

Creating a Department of Systems Biology will also make Columbia more competitive in its ability to recruit innovative faculty, postdocs, graduate students, and research technicians. For junior and senior scientists, Columbia will become a more attractive center for pursuing research. For students, creating a Department of Systems Biology will enable us to offer a coherent, focused, and standardized educational curriculum that stresses the concepts and skills that will drive progress in the biomedical sciences for many years to come.

As the Department of Systems Biology grows as a resource for investigators throughout the university, it will also enable researchers to pursue new avenues in raising funds through grants and philanthropic support. Post-genomic, multidisciplinary research that employs advanced technology has received a great deal of funding from NIH and other sources in recent years, offering opportunities in a wide range of fields. Making a strong statement of support for research at the frontiers of science will also present new opportunities for philanthropy.

Although it is still a young discipline, systems biology is one of the most exciting fields in biomedical science to have emerged in the past decade. By consolidating resources and creating a focused agenda in this area, Columbia can take a leadership role in conducting cutting-edge, innovative research that holds incredible potential to advance science and improve human health.

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APPENDIX 1
Department of Systems Biology Leadership

Andrea Califano, Dr.

Andrea Califano is director of the Columbia University Initiative in Systems Biology, director of the JP Sulzberger Columbia Genome Center, director of the Center for Multiscale Analysis of Genetic Networks (MAGNet), and associate director of Bioinformatics at Columbia University's Irving Cancer Research Center. He also currently serves as a member of the Board of Scientific Advisors of the National Cancer Institute.

After completing a doctoral thesis in physics at the University of Florence on the behavior of high-dimensional dynamical systems, Dr. Califano worked at the IBM TJ Watson Research Center, where he became involved in computational biology in 1990. In 1997 he became program director of the IBM Computational Biology Center. In 2000 he co-founded First Genetic Trust, Inc. to pursue translational genomics research and infrastructure-related activities to support large-scale patient studies with genetic components.

Dr. Califano joined Columbia University in 2003 as Professor of Biomedical Informatics, with appointments in the Department of Biomedical Informatics and the Institute for Cancer Genetics. The Califano Lab uses a combination of *in silico* reverse engineering methods and high-throughput experimental assays to characterize gene regulatory networks that determine pathophysiological behavior in cells.

His lab has developed algorithms to dissect transcriptional, post-transcriptional, and post-translational regulatory interactions in mammalian cells and to identify master regulators of aberrant cellular events. His lab has also developed methods to elucidate the mechanisms of action of drugs and to identify genetic alterations that contribute to the aberrant activity of master regulators.

In collaboration with colleagues in the Columbia scientific community, the Califano Lab was the first to publish fully context-specific molecular interaction networks (interactomes) for normal and tumor cells in humans, including neoplastic malignancies of lymphoma and glioma subtypes. Ongoing projects in the lab aim to define the regulatory networks for neoplastic states of the breast, ovary, prostate, germ cell, colon, and lung; for the study of pluripotency and lineage differentiation in stem cells; and for the mechanisms associated with the onset and progression of neurodegenerative diseases.

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Barry Honig, PhD

Barry Honig has been a professor of Biochemistry and Molecular Biophysics at Columbia University College of Physicians and Surgeons since 1981 and is director of the Center for Computational Biology and Bioinformatics (C2B2). He is a member of the National Academy of Sciences and the American Academy of Arts and Sciences, and is a Howard Hughes Medical Institute (HHMI) Investigator.

The guiding hypothesis of Dr. Honig's work is that combining information about protein sequence with biophysical analysis can reveal how biological specificity is encoded on protein structures. His laboratory uses methods from biophysics and bioinformatics to study the structure and function of proteins, nucleic acids, and membranes. His work includes fundamental theoretical research, the development of software tools, and applications to problems of biological importance.

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APPENDIX 2

Department of Systems Biology Founding Faculty

Cory Abate-Shen, PhD

Cory Abate-Shen is a professor in the Department of Urology and Department of Pathology and Cell Biology, the Michael and Stella Chernow Chair of Urological Oncology, and an associate director of the Herbert Irving Cancer Center. She is investigating the molecular mechanisms of homeobox genes in development and cancer. Her laboratory has provided groundbreaking insights on the molecular bases of how homeoproteins achieve target gene recognition *in vivo*. She has also developed mouse models of prostate cancer that have been widely used to investigate the molecular bases of prostate tumorigenesis and as preclinical models for intervention and therapy. She has been the recipient of several awards, including a Sinsheimer Scholar Award, an NSF Young Investigator Award, and the Women in Cell Biology Junior Award from the American Society for Cell Biology. She is currently the principal investigator on five federal grants including an NCI consortium grant on Mouse Models of Human Cancer. In addition, she has received funding from several other sources including the March of Dimes, the New Jersey Commission on Cancer Research and the Gustave and Louise Pfeiffer Research Foundation. She has recently been named an American Association of Cancer Research Professor.

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Dimitris Anastassiou, PhD

Dimitris Anastassiou is Charles Batchelor Professor and director of the Genomic Information Systems Laboratory at the Department of Electrical Engineering, and a member of the Center for Computational Biology and Bioinformatics and the Center for the Multiscale Analysis of Genomic and Cellular Networks (MAGNet). He is an IEEE Fellow, the recipient of an IBM Outstanding Innovation Award, a National Science Foundation Presidential Young Investigator Award, and a Great Teacher Award from the Society of Columbia Graduates. His current research in systems biology focuses on the systems-based analysis of genomic data, and has investigated problems related to diabetes, cancer metastasis, and the identification of biomarkers. Before becoming interested in systems biology, he conducted research in the area of video technology and authored several patents that have been essential for the implementation of international video standards.

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Harmen Bussemaker, PhD

Harmen Bussemaker is an associate professor in the Department of Biological Sciences. His credentials include a Lenfest Distinguished Columbia Faculty Award and a John Simon Guggenheim Foundation Fellowship. Dr. Bussemaker is known for his pioneering efforts to understand gene regulatory networks by integrating information about genome sequence, transcription factor binding, and gene expression data. Using high-throughput sequencing and affinity-based selection, the Bussemaker lab aims to quantify the DNA binding specificity of transcription factors at unprecedented resolution. He is also using biophysical models to infer cell-state specific changes in the regulatory activity of transcription factors from genomewide mRNA expression levels. Other efforts include using natural genetic variation to dissect complex cis-regulatory logic, and understanding how local chromatin context modulates the influence of transcription factors on its target genes.

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Virginia Cornish, PhD

Virginia Cornish is the Helena Rubinstein Professor in the Department of Chemistry. Her laboratory brings together modern methods in organic chemistry and DNA technology to expand the synthetic capabilities of living cells. Their interests include harnessing the ribosome for unnatural oligomer synthesis using synthetic amino acid building blocks, and engineering yeast to enable directed evolution of molecules and pathways directly in a living cell. They then exploit these synthetic methods for applications in bioimaging, diagnostics, and therapeutics. Dr. Cornish is the author of over 60 publications and patents and her research is supported by multiple grants from the National Institutes of Health, National Science Foundation, and private foundations. Her research has been recognized with numerous awards including an NSF Career Award, a Sloan Foundation Fellowship, the Protein Society Irving Sigal Young Investigator Award, and the American Chemical Society Pfizer Award in Enzyme Chemistry.

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Adolfo Ferrando, PhD

Adolfo Ferrando is an assistant professor at the Institute for Cancer Genetics. Using a combination of genomic technologies, biochemical testing, and genetic analysis, his group seeks to understand the molecular mechanisms that promote and sustain the malignant proliferation and survival of leukemic cells. He is engaged in a number of projects analyzing the functions of specific oncogenes and their role in the pathogenesis of childhood leukemia, especially T-cell lymphoblastic leukemia, an aggressive form of the disease. His goal is to uncover the mechanisms at work in leukemic cells and to translate this understanding into the identification of therapeutic targets for the design of new, molecularly tailored antileukemic drugs.

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Aris Floratos, PhD

Aris Floratos is an assistant professor in the Department of Biomedical Informatics and executive research director at the Center for Computational Biology and Bioinformatics. His lab develops collaborative bioinformatics software to support the analysis and visualization of genomic data from a wide range of domains (gene expression, sequence, protein structure, and systems biology). This software leverages standards-based middleware technologies to provide seamless access to remote data, annotation, and computational servers, enabling researchers with limited local resources to benefit from public infrastructure. The Floratos Lab is also developing innovative, systems biology-driven methodologies that offer improved power to detect the contribution of low-risk genetic factors to drug-induced serious adverse events (SAEs). In collaboration with an international network of investigators, the lab is leading the analysis of genome-wide genotyping and exome sequencing data for drug-induced disorders including serious skin rash, liver injury, cardiac arrhythmias, and osteonecrosis of the jaw. Finally, the Floratos Lab has developed motif discovery algorithms that have been used to study the underlying evolutionary architecture of genomic sequences.

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Dana Pe'er, PhD

Dana Pe'er is an assistant professor in the Departments of Biological Sciences and Computer Science. Her lab endeavors to understand the organization, function, and evolution of molecular networks, particularly how variation in DNA sequence alters regulatory networks and leads to the vivid phenotypic diversity of life. Her team develops computational methods that integrate diverse high-throughput data to provide a holistic, systems-level view of molecular networks. She is particularly interested in exploring how systems biology can be used to personalize care for people with cancer. By developing models that can predict how individual tumors will respond to certain drugs and drug combinations, her goal is to develop ways to determine the best drug regime for each patient. Her interest is not only in understanding which molecular components go wrong in cancer cells, but also in using this information to improve cancer therapeutics.

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Itsik Pe'er, PhD

Itsik Pe'er is an associate professor in the Department of Computer Science. His laboratory develops and applies computational methods for the analysis of high-throughput data in germline human genetics. Specifically, he has a strong interest in isolated populations such as Pacific Islanders and Ashkenazi Jews. The Pe'er Lab has developed methodology to identify hidden relatives — primarily in such isolated populations — that involves inferring their past demography, detecting associations between phenotypes and genetic segments co-inherited from the joint ancestors of hidden relatives, and establishing the exceptional utility of whole-genome sequencing in population genetics. With the arrival of high-throughput sequencing methods, Pe'er has focused on characterizing genetic variation that is unique to isolated populations, including the effects of such variation on phenotype.

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Raul Rabadan, PhD

Raul Rabadan is an assistant professor in the Department of Biomedical Informatics and the Center for Computational Biology and Bioinformatics. He leads an interdisciplinary team that develops and implements mathematical and computational tools to extract biologically and clinically relevant information from large data sets, with interests in infectious diseases and cancer. The Rabadan Lab is developing tools to analyze genomic data to improve understanding of the molecular biology, population genetics, evolution, and epidemiology of viruses, particularly influenza viruses. He is also using next-generation sequencing technologies to identify somatic mutations that contribute to the development of cancerous tumors. Studies to date have focused on liquid tumors including B-cell lymphomas and lymphoblastic leukemias.

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Sagi Shapira, PhD

Sagi Shapira was recruited to Columbia in 2011 as an assistant professor in the Columbia Initiative in Systems Biology and the Department of Microbiology and Immunology. His laboratory is working to decipher the genetic and molecular circuitry at the interface of host–pathogen interactions. His laboratory studies how this circuitry controls cellular responses to infection, imparts selective pressure on viruses, and affects disease progression. Using animal models of infectious disease, molecular biology, and genomic and computational methods, he seeks to generate mechanistic models of the dynamic interactions between host and pathogen. The efforts are aimed at developing general strategies for the study of host–pathogen dynamics. A mechanistic understanding of these relationships provides important insights into cellular machinery that control basic cell biology and has broad implications in human translational immunology and infectious disease research.

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Lawrence Shapiro, PhD

Lawrence Shapiro is an associate professor in the Department of Biochemistry and Molecular Biophysics as well as the Jules and Doris Stein Professor of Research to Prevent Blindness, at the Edward S. Harness Eye Institute. He is also a member of the Motor Neuron Center and the Naomi Berrie Diabetes Center. His laboratory uses methods from structural biology to understand protein structure and binding dynamics. His work focuses on two areas: 1) the structural biology and protein biochemistry of cadherins, a family of cell surface proteins that mediate adhesive binding between cells in both vertebrates and invertebrates, and 2) the protein chemistry and structural biology of proteins involved in energy homeostasis, particularly AMP-activated protein kinase (AMPK). His laboratory also participates in the Protein Structure Initiative (PSI), a federal, university, and industry effort aimed at reducing the costs and

lessening the time it takes to determine a three-dimensional protein structure by predicting structure from DNA sequences.

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Michael Shen, PhD

Michael Shen is a professor in the Department of Medicine and the Department of Genetics and Development. His laboratory pursues basic and translational research in the areas of mammalian embryogenesis and stem cell differentiation, as well as development of the prostate gland and molecular mechanisms of prostate carcinogenesis. These studies primarily utilize experimental approaches involving genetically engineered mice, but also employ cell culture and biochemical approaches to investigate molecular pathways.

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Yufeng Shen, PhD

Yufeng Shen is an assistant professor in the Columbia Initiative in Systems Biology and the Department of Biomedical Informatics. After completing his PhD in computational biology in 2007 at the Human Genome Sequencing Center at Baylor College of Medicine, he led the analysis of the first personal genome produced by next-generation sequencing (that of Dr. James D. Watson). In 2008 he joined Columbia University as a postdoctoral fellow, working in computational genomics and genetics of drug adverse reactions, and then joined the faculty in July 2011. Dr. Shen is interested in developing and applying computational methods to study human genetics and diseases. The research in his group is at the interface of biology, statistics, and computer science. Specifically, his group is working in four areas, including genome sequencing and assembly, mapping of disease genes, the role of the major histocompatibility complex (MHC) in autoimmunity, and pharmacogenomics.

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Jose Silva, PhD

Jose Silva is an assistant professor at the Institute for Cancer Genetics. His laboratory has pioneered experimental techniques that use RNA interference (RNAi) to perform genome-wide

loss of function studies in mammalian systems. He is now using these tools to understand molecular mechanisms that promote the development of breast cancer, with the ultimate goal of identifying novel targets for personalized therapies. In recent work done in collaboration with other members of the Columbia Initiative in Systems Biology, these RNAi approaches were used to validate computational predictions of master regulators of breast carcinogenesis, paving the way for high-throughput chemical screening to identify compounds that could inhibit the activity of these targets. In other work, he has used RNAi screens to identify genes that, when silenced, induce tumor-associated characteristics; he is now working to discover how they suppress tumor development. He is also interested in understanding genetic and genomic factors that lead to inflammatory breast cancer (a particularly lethal form of the disease).

1. Sumazin P, Yang X, Chiu HS, Chung WJ, Iyer A, Llobet-Navas D, Rajbhandari P, Bansal M, Guarnieri P, Silva J, Califano A. **An extensive microRNA-mediated network of RNA-RNA interactions regulates established oncogenic pathways in glioblastoma.** Cell. 2011 Oct 14;147(2):370-81.
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Peter Sims, PhD

Peter Sims joined Columbia in 2012 as an assistant professor in the Department of Biochemistry and Molecular Biophysics. Researchers in his laboratory are working to improve single-cell approaches to systems biology. These approaches are crucial because individual cells respond in different ways to identical chemical and genetic perturbations, and because clinical samples are often limited to small numbers of cells. Translating new and existing techniques for genome-wide analysis to the single cell level will facilitate their application to biomedicine. The Sims Lab develops new tools for single-cell analysis, applying cutting-edge microscopy, next-generation sequencing, and microfabrication to enable unbiased, system-wide measurements of biological samples. He and his colleagues focus on single-cell transcriptomics and sequencing technology along with novel approaches to proteomics, where current tools lag far behind those available for nucleic acid analysis.

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5. Nan X, Sims PA, Xie XS. **Organelle tracking in a living cell with microsecond time resolution and nanometer spatial precision**. *Chemphyschem*. 2008 Apr 4;9(5):707-12.

Brent Stockwell, PhD

Brent Stockwell is an associate professor in the Departments of Biological Sciences and Chemistry. He is also a Howard Hughes Medical Institute Investigator. His research group, which works at the interface of chemistry and biology, uses small organic molecules in a systematic way to perturb cellular processes and discover their underlying mechanisms. Stockwell's approach is interdisciplinary, combining chemical design and synthesis with genomics, computational chemistry, biochemistry, and cell biology, with the ultimate goal of revealing new basic biological mechanisms and disease pathophysiology. The small organic molecules he uses are complementary to genetic tools, because such compounds act rapidly and conditionally, can target multiple paralogous proteins simultaneously, and can be readily combined for multi-dimensional manipulations of biochemical networks. His laboratory is particularly interested in understanding cell death mechanisms in mammalian systems, and how they intersect with disease mechanisms in cancer and neurodegeneration.

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Milan Stojanovic, PhD

Milan Stojanovic is an associate professor in the Division of Experimental Therapeutics and the Departments of Medicine and Biomedical Engineering. Some of his research interests include developing self-operating molecular automata, programmed to process information and respond in therapeutically useful ways; sensor arrays for high-resolution analysis and classification of samples of bodily fluids; and molecules that walk and self-organize through well-defined sets of local interactions.

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Saeed Tavazoie, PhD

Saeed Tavazoie is a professor in the Department of Biochemistry and Molecular Biophysics. He was a professor in the Department of Molecular Biology and the Institute for Integrative Genomics at Princeton before joining the faculty at Columbia in 2011. His research is focused on revealing the general principles that govern the organization, function, and evolution of biological networks. Over the years, his laboratory has addressed fundamental challenges in decoding the regulatory genome and revealing how networks of interacting genes implement complex phenotypes. His research group has made significant headway in tackling these problems through the development of experimental and computational methods that both generate and utilize high-dimensional genomic and phenotypic observations. The long-term

goal of his research is to achieve a predictive understanding of biological behavior in terms of the structural and dynamical properties of the underlying molecular networks. Professor Tavazoie is the recipient of the 2008 NIH Director's Pioneer Award.

1. Goodarzi H, Elemento O, Tavazoie S. **Revealing global regulatory perturbations across human cancers.** *Mol Cell.* 2009 Dec 11;36(5):900-11.
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5. Beer MA, Tavazoie S. **Predicting gene expression from sequence.** *Cell.* 2004 Apr 16;117(2):185-98.

Dennis Vitkup, PhD

Dennis Vitkup is an associate professor in the Center for Computational Biology and Bioinformatics and the Department of Biomedical Informatics. His laboratory develops and applies novel probabilistic techniques to analyze cellular networks. Their work involves developing methods that connect network structure to function to phenotypes, and can be used to make experimentally verifiable predictions. Research in the Vitkup Lab focuses on three main topics: 1) the global probabilistic reconstruction and analysis of metabolic networks based on completely sequenced genomes, 2) the development of methods to identify new human disease genes and genetic disease modules using probabilistic functional networks, and 3) the development of methods to combine mechanistic and probabilistic approaches for the dynamic simulation of biological pathways. The Vitkup Lab developed GLOBUS, a global probabilistic method for reconstructing cellular metabolic networks, and applied it to design new drugs for malaria and understand cancer metabolism. They also created NETBAG, a novel method for considering genetic mutations in the context of molecular networks, and used it to identify networks that are perturbed in autism and schizophrenia.

1. Gilman SR, Iossifov I, Levy D, Ronemus M, Wigler M, Vitkup D. Rare de novo variants associated with autism implicate a large functional network of genes involved in formation and function of synapses. *Neuron.* 2011 Jun 9;70(5):898-907.
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3. de Hoon MJ, Eichenberger P, Vitkup D. Hierarchical evolution of the bacterial sporulation network. *Curr Biol.* 2010 Sep 14;20(17):R735-45.

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5. Feldman I, Rzhetsky A, Vitkup D. **Network properties of genes harboring inherited disease mutations.** Proc Natl Acad Sci U S A. 2008 Mar 18;105(11):4323-8.

Chris Wiggins, PhD

Chris Wiggins is an applied mathematician with a PhD in theoretical physics who develops machine learning applications for the study biological problems. His areas of focus include analysis of microarray data, comparative genomics and population genetics, design of computer vision applications for microscopy and microscopic time-lapse data, statistical inference in single-molecule biophysics, and biological network inference and analysis. Additional research interests in systems biology include the stochastic modeling of transcriptional regulatory networks and the identification of relationships between the topology of biological networks and their realizable information-processing functions. Wiggins has been a faculty member in the Department of Applied Physics and Applied Mathematics since 2001 and is also a member of the Center for Computational Biology and Bioinformatics.

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