CHICAGO BIOMEDICAL CONSORTIUM

The University of Chicago
University of Illinois at Chicago
Northwestern University

2012 Perspectives

The CBC is funded by the Searle Funds at The Chicago Community Trust

Cover

Images of fluorescently-labeled cells overlaid on a Google earth (©2012 Google) image of the Chicago area. CBC-affiliated researchers contributed the cell images.

North: *Drosophila melanogaster* (fruit fly) imaginal disk. Richard Carthew, Northwestern University, Evanston campus

East: Interneurons. John Kessler, Northwestern University, Chicago campus

West: Accumulation of Quantum Dot protein conjugates in the perinuclear region of fibroblasts. Brenda Russell, University of Illinois at Chicago

South: Two-stage *Caenorhabditis elegans* (roundworm) embryo. Michael Glotzer, The University of Chicago

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The Searle Funds at The Chicago Community Trust began funding the Chicago Biomedical Consortium (CBC) at the level of $5 million per year in 2006. To date, $35 million has been invested in the CBC. As a result:

- Northwestern University, The University of Chicago, and the University of Illinois at Chicago (UIC) have come together and undertaken unprecedented joint activities.
- CBC-funded research has generated $214 million of further funding. This is a six-fold return on investment in six years.
- According to standard economic models, research activity stimulated by the CBC has provided an economic impact of $605 million for Chicago.
- At least 170 jobs have been directly supported by CBC funding, CBC awards have helped attract eight new faculty members to Chicago, and literally thousands of researchers have benefitted from CBC programs.
- Breakthrough scientific discoveries have been reported in 576 peer-reviewed publications.
- Effective programs to foster Biotech entrepreneurs have been implemented.
- CBC is investing in the future with educational programs for the next generation of researchers.
- CBC is capturing national recognition as an innovative, successful, collaborative venture.

As summarized by Paula Allen-Meares, Chancellor of UIC: "The CBC has become an important engine for economic growth and job creation, combining the resources of the city's great research universities to help Chicago compete for the large collaborative projects that are at the heart of 21st-century science."

NORTHWESTERN UNIVERSITY

THE UNIVERSITY OF CHICAGO

UIC UNIVERSITY OF ILLINOIS AT CHICAGO

CBC History

John G. Searle led the Skokie-based pharmaceutical company G.D. Searle from the 1930s to 1966, transforming it from a producer of traditional medicines to a research-based company that introduced a variety of unique new products, including the first oral contraceptive. The company's motto was "Research in the Service of Mankind." When John Searle died in 1978, he established a large fund at The Chicago Community Trust, stating in his will that when making grants from the Searle funds, "emphasis be placed, so far as feasible, on **research in medicine, chemistry, and the biological sciences."**

John G. Searle 1901-1978

The CBC began in December 2001, when the late Dan Searle, John Searle's son, challenged faculty members at Northwestern, The University of Chicago, and UIC to think of ways to foster scientific collaboration. The paramount goal was to design a plan that pulled faculty researchers from across the city into a connected intellectual community, reducing rivalries and encouraging cooperation. A complementary goal was to raise Chicago's profile on the national scene, both fostering and drawing attention to the breadth and depth of local research accomplishments. In 2002, with a Planning Grant from The Chicago Community Trust, work began to turn a concept into reality. Each university sent representatives to form a citywide Strategic Planning Group.

This was quite visionary and innovative. Sylvia Manning, then the Chancellor at UIC, described the concept as "revolutionary" and "irresistible." Terry Mazany, President and CEO of The Chicago Community Trust, applauded the effort to "knit together three world-class institutions in a way where the whole is greater than the sum of its parts."

In 2003, the CBC submitted a proposal to The Chicago Community Trust for an ambitious Demonstration Project. Upon its successful completion, in 2006 The Searle Funds at The Chicago Community Trust granted the CBC $5 million per year for operating funds for 2006 through 2010. The grant to the CBC was renewed in late 2010, providing operating support from 2011 through 2015.

THE CHICAGO COMMUNITY TRUST AND AFFILIATES

While the CBC operates with the much-appreciated guidance and support of the university Provosts, it remains a grass-roots-style organization. The three Scientific Directors (one from each university) collaboratively provide leadership for the overall enterprise. Advisory Boards provide the peer review that assures the merit of funded projects. Members of the Searle family, civic leaders, and three prominent out-of-town scientists serve on the CBC's External Advisory Board, which meets yearly.

Not long before he passed away, Dan Searle spoke about his enthusiasm for the CBC: "It is something that John Searle would have been proud of. It is something he would have been engaged in. It's innovative – nobody else is doing this – and **I honestly believe CBC is going to be one of the greatest legacies of John Searle**." All who are involved in the CBC are proud to be part of this important enterprise, and proud to honor the Searle legacy.

Celebrating the Legacy of John G. Searle

Members of the Searle family; the leaders of Northwestern, UIC, and The University of Chicago; and leaders of the CBC at the official launch of the Chicago Biomedical Consortium at the Chicago Cultural Center, December 11, 2006. (Photo Credit: Dan Dry)

CBC Mission

The mission of the Chicago Biomedical Consortium is to stimulate collaboration among scientists at Northwestern University, the University of Chicago, and the University of Illinois at Chicago that will transform research at the frontiers of biomedicine. The CBC works to:

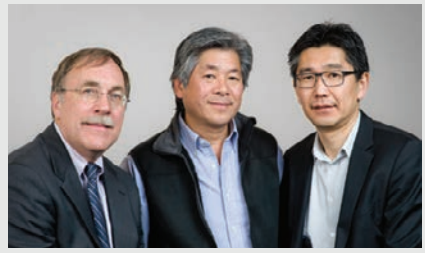
- Stimulate research and education that bridge institutional boundaries.
- Enable collaborative and interdisciplinary research that is beyond the range of a single institution.
- Recruit and retain a strong cadre of biomedical leaders and researchers in Chicago.
- Promote the development of the biomedical industry in Chicago.
- Execute a plan capable of improving the health of citizens of Chicago and beyond.

CBC Programs

- **Catalyst Awards** fund new high-risk/high-reward collaborative projects involving researchers from at least two of the CBC universities.
- **Lever Awards** provide up to $2.5 million to match collaborative large-scale federal awards for National Centers.
- **Spark Awards** have supported seven innovative investigations, ranging from the structure of cellular nuclei to ways to improve Magnetic Resonance Imaging (MRI) in human brain disease.
- **Recruitment Awards** provide $1 million for each university to hire an outstanding senior faculty member. In addition, junior faculty recruitment awards have allowed each university to bring on board two outstanding assistant professors.
- The CBC supports numerous **educational programs**, including the annual Symposia and the CBC Scholars program for advanced graduate students. The CBC also has initiatives to encourage the growth of the local biotechnology industry.

Three Universities, Shared Goals

The CBC is a collaborative enterprise, which directs funding received from the Searle Funds at The Chicago Community Trust. Funding decisions are made by boards of researchers, who evaluate the scientific merit of applications. The overall direction of the CBC is set by three Scientific Directors *(pictured below)* who regularly consult with a cross-section of biomedical faculty members, as well as the Provosts of the universities.



Brian Kay, PhD *(left)*
Professor and Head
Department of Biological Sciences
University of Illinois at Chicago

Shohei Koide, PhD *(right)*
Professor
Biochemistry and Molecular Biology
The University of Chicago

Richard Morimoto, PhD *(center)*
Bill and Gayle Cook Professor of Biology
Director, Rice Institute for Biomedical Research
Department of Molecular Biosciences
Northwestern University

Measures of Impact

The CBC has become a central part of the fabric of Chicago's biomedical research community. Encouraged by the CBC, inter-university and interdisciplinary collaboration has become common, creating many new scientific teams doing cutting-edge research. This expansive approach to doing science has had profound impacts not only on the three CBC universities but also on the city of Chicago.

Strengthening the City

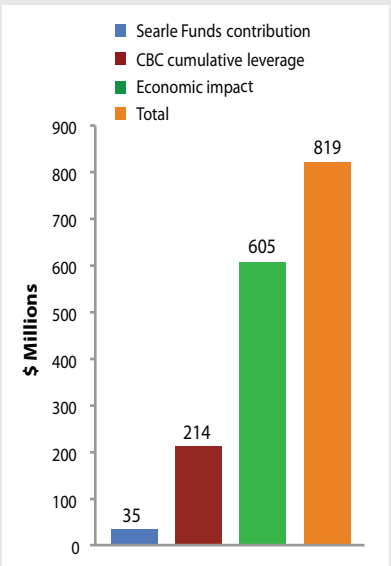
In addition to its impact on health and technology development, biomedical research has **general economic benefits** that are often underappreciated.

- The $35 million in funding received between 2006 - 2012 by CBC from the Searle Funds at The Chicago Community Trust (SFCCT) has **launched research projects that have gone on to garner an additional $214 million in further support**, primarily from the National Institute of Health (NIH). That represents a 6-fold leverage of the funds contributed by the SFCCT.

- Studies by economists have shown that **for every dollar awarded by the NIH in Illinois, total business activity increases by $2.43**[1,2]. Thus, the $35 million in funding that CBC has received from the SFCCT, plus the $214 million from the NIH, has yielded an **economic impact of over $600 million**. Added all together, the Searle Funds contribution to the CBC has injected over $800 million into the Chicago economy since 2006 *(see graph below)*.

- A basic research lab operates like a small business, with a yearly budget of $250,000 to $1 million. The CBC has provided **support to over 110 research laboratories**.

- **CBC funding has helped support more than 170 research workers**, including 22 graduate students and 60 post-doctoral fellows. In addition, economists have calculated that the "jobs multiplier" for each $1 million in NIH funding is 17 [1,2], which means that **the $214 million in follow-on NIH funding has supported some 3600 jobs in research labs in Chicago.**



CBC Economic Impact on Chicago

From 2006 to 2012, the Searle Funds at The Chicago Community Trust (SFCCT) provided $35 million in funding to CBC *(blue bar)*. The research projects supported with CBC funding have received an additional $214 million* *(red bar)* from external sources, primarily the NIH. Since each dollar awarded in Illinois by the NIH increases business activity by $2.43[1,2], the economic impact of the combined SFCCT and NIH funding exceeds $600 million *(green bar)* and the total dollar amount injected into the Chicago economy during 2006-2012 that can be attributed to the CBC activities amounts to over $800 million *(orange bar)*.

*As of July 31, 2012

Featured in

The New York Times

The recruitment of Kevin P. White to The University of Chicago is an example of how CBC-supported science can have a wide-ranging impact. A $1 million CBC Recruitment Award helped convince White to move to Chicago, where he took leadership of the newly-established Institute for Genomics & Systems Biology (IGSB) in August 2006. The University of Chicago committed $40 million to White's recruitment, including start-up funding for his lab, funding to bring in additional faculty, and endowment for the IGSB. By August 2012, with the help of Lever matching funds from the CBC, IGSB has grown to employ approximately 70 persons, about 50 of whom moved into the Chicago area from elsewhere. Among the newcomers are three faculty members, each with an active lab. Dr. White and his colleagues at IGSB have received upwards of $50 million in funding from external sources. Truly ground-breaking science is taking place in Chicago at the IGSB – such as the **ENCODE** research project that was featured on the front page of ***The New York Times*** on September 6, 2012.

Kevin P. White (Photo Credit: Dan Dry)

World's Most Influential Cities

Chicago was ranked #6 in A.T. Kearney's 2010 Global Cities Index[3] behind New York, London, Tokyo, Paris, and Hong Kong and ahead of Los Angeles, Singapore, and San Francisco. A key component of this ranking is Chicago's "Human Capital," defined as "…educational achievement, and quality of universities." (Image Credit: National Geographic, November 2011)

Strengthening the Universities

The University of Chicago, UIC, and Northwestern are vibrant institutions with international reputations, playing key roles in the intellectual infrastructure of Chicago. **Chicago was ranked #6 in A.T. Kearney's 2010 Global Cities Index**[3]. A key component of this ranking is Chicago's "Human Capital," defined as "…educational achievement, and quality of universities." The CBC universities thus are crucial for the city's standing in the rapidly globalizing world, and the CBC has strengthened the universities, and Chicago's human capital, in numerous ways.

- The benefits and activities of the CBC have become a powerful recruiting tool, helping universities attract new faculty, fellows, and students. CBC funds have helped bring **two senior and six junior faculty members** to Chicago.

- CBC awards have helped talented young faculty to succeed and provided an incentive for all faculty to try **risky, potentially high-impact research** projects.

- The CBC actively works to bring the members of the three university communities together. The CBC Annual Symposium has become a signature event, and every year there are additional events, including technical workshops, focused forums, and small brainstorming meetings. **CBC programs have reached at least 3,000 members of the research community.**

- Inspired and supported by the CBC, the directors of each university's office of shared research facilities (i.e. core facilities, such as DNA sequencing facilities) have formed the **Inter-Institutional Core Advisory Committee**. This group has begun developing a *Memorandum of Understanding* to enable open access to core facilities across universities, and ideally will allow larger-scale coordination and redundancy avoidance among these important units.

- The CBC website (www.chicagobiomedicalconsortium.org) has become an important asset, providing central listings of citywide seminars, news, core facilities, and links to a variety of resources. To date, over 3500 citywide events relevant to biomedical research have been publicized on the CBC website. In 2012, the CBC launched a centralized platform containing links to online tools to help researchers find a collaborator in Chicago and thus become eligible for CBC Awards. Reflecting the utility of these improvements, traffic to the CBC website is strong – in fact, **over 25,000 unique users visited the CBC website between July 2009 - June 2012, viewing a total of close to 150,000 webpages**.

- The CBC Scholars program has established **a 'salon' for outstanding graduate students**, who have embraced various leadership opportunities, ranging from organizing seminars to community service.

3rd Annual CBC Scholars Scientific Exchange

The 3rd Annual CBC Scholars Scientific Exchange took place on March 27, 2012, at the University of Chicago Gleacher Center in downtown Chicago. Seventeen scholars presented talks describing their thesis research. Established in 2010, the CBC Scholars Program is a leadership forum for students from the CBC universities, advancing the CBC mission of fostering collaboration and excellence. Twenty-six CBC Scholars have been named to date.

Strengthening Science

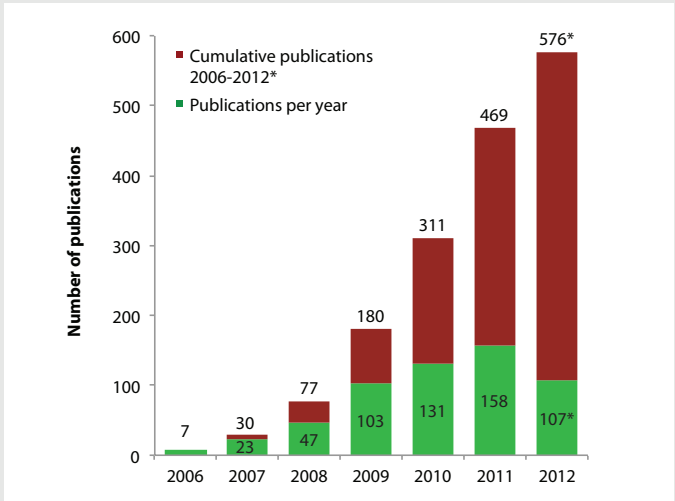
At its core, the mission of the CBC is to "transform research at the frontiers of biomedicine." There have been many notable achievements in pursuit of that mission.

- As of July 31, 2012, **CBC-funded research has produced 576 peer-reviewed publications** *(graph below)*. The great majority of the publications have been in high-impact journals.

- **47 collaborative teams have been funded** – frequently joining junior and senior researchers, and almost always interdisciplinary. Many of the teams have continued to work together, even when CBC funding has ended.

- **CBC-funded researchers have developed new techniques for reading the genetic code, new ways of viewing the functions of living cells, and new technologies for replacing monoclonal antibodies**. These discoveries, and the teams behind them, are described later in this report.

CBC supports risky, but potentially highly-rewarding projects that are not eligible for other types of support. As expected with this type of "venture funding," some projects have not worked out. But some have been extremely productive and have moved scientific understanding forward dramatically. As an example, a Catalyst Award in 2007 launched the **Chicago Consortium in Diabetes and Obesity Genetics**[4].



CBC-funded Publications 2006-2012

A total of 576 publications have been attributed to CBC-funded research from 2006 through July 31, 2012. Cumulative publications are graphed in red and yearly publications in green.

*As of July 31, 2012

Nissim Hay

Nissim Hay, Professor in the Department of Biochemistry and Molecular Genetics, UIC, is a co-recipient of the CBC Catalyst Award, "Chicago Consortium in Diabetes and Obesity Genetics"[4] and a Spark Award[5]. (Photo Credit: Kathryn Marchetti, Copyright The University of Illinois Board of Trustees)

This group has maintained a highly prolific collaboration investigating the complex interplay of factors (including sleep) that impact obesity and diabetes. To date, the group attributes 63 publications and over $20 million in outside grant funding to work springing from their Catalyst award. In 2011, the group received a CBC Spark Award[5] to test a potential paradigm shift that could change the treatment of metabolic syndrome (a constellation of abnormalities associated with increased risk for the development of type 2 diabetes and heart disease). Given that metabolic syndrome affects 44% of the U.S. population over age 50, the need for innovative thinking is clear, and the potential impact of a breakthrough is profound. Nissim Hay *(pictured above)*, UIC collaborator on both CBC Catalyst and Spark Awards, had this to say about the scientific partnership: "Collectively, our groups have formed a *'de facto'* scientific family that continues to spawn new ideas and new opportunities for research growth in Chicago."

"Collectively, our groups have formed a *'de facto'* scientific family that continues to spawn new ideas and new opportunities for research growth in Chicago," Hay said.

Currently, **12 CBC Catalyst teams are in the midst of pioneering projects** studying, for example:

- a new way to address the pressing question of **how to manage antibiotic resistance**[6],

- a new way **to identify the warning signs for the development of leukemia**[7],

- a new biochemical approach that could **improve the efficacy of CPR (cardiopulmonary resuscitation)**[8].

It's not yet clear if any or all of these projects will be successful, but a breakthrough could profoundly impact human health as well as scientific understanding.

CBC Lever Awards were conceived as a way to bring more large research centers to the city and in this, the program has succeeded spectacularly. According to Kevin White *(see p. 6)*, "The NIH program staff have commented on the importance of the CBC support in their decision to fund our proposal" (the CCSB, *see below*). Thanks in part to the CBC, five National Research Centers are now located in Chicago, bringing teams of researchers from all three CBC universities together to produce pathbreaking discoveries in an array of scientific fields.

- The **Chicago Center for Systems Biology** (CCSB), led by Kevin White, is an interdisciplinary group that combines experimental and computational tools to study the behavior of gene networks in cells, tissues, and organisms. Researchers affiliated with the CCSB have published 102 publications to date, many of which are in top biomedical journals such as *Cell*, *Science* and *Nature*, and have contributed to the massive ENCODE project that recently mapped at least 4 million gene regulatory switches in what used to be considered "junk" human DNA. The CBC Lever Award, to White, Richard Morimoto, and Robert Grossman, established specialized, high-end facilities that are available to the CBC community.

- The **Chicago Tri-institutional Center for Methods and Library Development** (CTCMLD), led by Sergey Kozmin, Karl Scheidt, and Jie Liang, has used innovative methods of high-throughput organic synthesis to generate large libraries of unique chemical compounds that are available to screen for potential drug candidates or for other biological activities. The leaders of the CTCMLD have recently applied for additional NIH funding to establish a Center for Accelerated Innovation, with the express purpose of identifying new drugs and moving them to market.

According to Kevin White, "The NIH program staff have commented on the importance of the CBC support in their decision to fund our proposal."

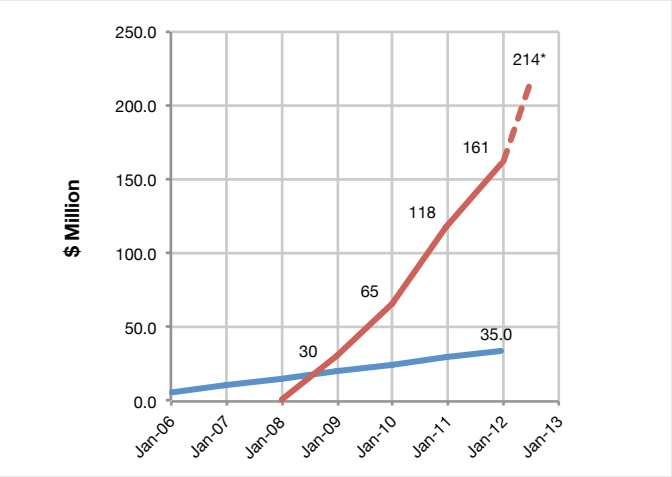
- The **Chicago Center for Nanomaterials for Cancer Diagnostics and Therapeutics**, led by Chad Mirkin, Milan Mrksich, David Eddington, and Joel Collier, develops, fabricates, and disseminates advanced materials for culturing cancer cells. Numerous CBC researchers are making use of these custom-designed materials.

- The **Silvio O. Conte Center on the Computational Systems Genomics of Psychiatric Disorders**, led by Andrey Rzhetsky, Richard Morimoto, and Edwin Cook, will design and validate a battery of novel analytical tools to find relationships among human genetic variations and environmental factors that can lead to psychiatric disorders such as autism and schizophrenia. This research is on the cutting edge of both genetics and informatics, and CBC researchers will be able to submit proposals for use of the computational and experimental resources.

9th Annual CBC Symposium
Engineering Biology: From tools to insights

The 9th Annual Symposium took place on Friday, October 21, 2011, at the UIC Forum and was attended by over 200 participants. In addition to attendees from CBC universities, participants came from the University of Illinois at Urbana-Champaign, Rush University Medical Center, Baxter, Agilent Technologies, Illinois Institute of Technology, Children's Memorial Hospital of Chicago, Iowa State University, DePaul University, Argonne National Laboratory, Tel Aviv University and Wollenterprises.

- The **Synthetic Antibody Consortium**, led by Anthony Kossiakoff, Geoffrey Greene, Brian Kay, and Jason Brickner, will use revolutionary methodologies to generate synthetic antibodies against a variety of proteins and functional RNAs. Synthetic antibodies are less expensive and more effective than standard antibodies, and have unique capabilities. CBC researchers will have special access to these antibodies, which promise to open major new avenues of research.



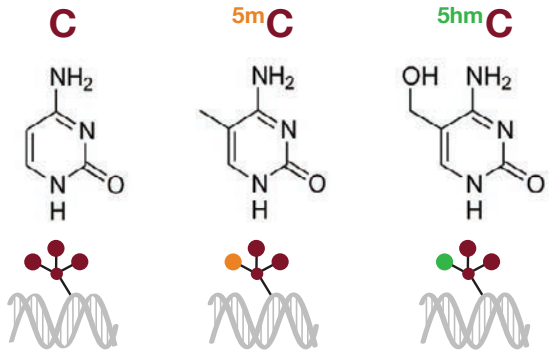
CBC Cumulative Leverage

During 2006-2012 the Searle Funds at The Chicago Community Trust generously provided $35million in funding to CBC *(blue line)*. Each year the CBC leveraged this funding with additional funding from external sources, primarily from the NIH. By July 31, 2012*, the total leveraged by the CBC amounted to $214 million *(red line; dashed line indicates January 1 - July 31, 2012)*.

CBC Catalyst:

Unveiling Hidden DNA Code

"Imagine reading an entire book, but then realizing that your glasses did not allow you to distinguish "g" from "q." What details did you miss?"[9] The discovery that there are two modifications of cytosine (one of the four bases that make up the DNA code; *see right*) has made researchers wonder what they have been missing. The two forms of cytosine have different functions, but until recently, there was no way to detect precisely where each modification is found in particular tissues and cell types. In June 2012, a team of researchers including Chuan He from The University of Chicago and Jung-Hyun Min from UIC published in *Cell* a new technique to accurately map each modified cytosine[10]. It turns out that these previously-hidden molecules play crucial roles in the lives of cells.



Cytosine and its Modified Forms

Cytosine, one of the building blocks of DNA, can exist in three different forms. The simple form (C, left) is most common. 5-methylcytosine (5mC, center) and 5-*hydroxy*methyl-cytosine (5hmC, right), the so-called 'modified cytosines,' are also found in DNA. The distribution patterns of the modified cytosines turn out to play critical roles in gene expression and may even shape the development of the human brain[10].

Jung-Hyun Min came to UIC in 2010 as an Assistant Professor of Chemistry. Her expertise is in using the "MultiBac" system to make highly purified, highly active multicomponent proteins. Her research goal is to understand the structure and function of the complicated "molecular machines" that are responsible for repairing damaged DNA. Min *(pictured below)* remembers that when she was interviewing at UIC, faculty members talked about the CBC as a special advantage of coming to Chicago. So when she needed a collaborator, someone who specialized in cross-linking biological molecules, she looked first at CBC institutions and found Chuan He.

Chuan He, a Professor of Chemistry, welcomed the opportunity to work with Min, and they immediately focused on perfecting a breakthrough technique to map modified cytosine in DNA. This project has provided new information about the distribution and pattern of modifications in various types of cells (for example, stem cells and brain cells), and it has revealed that these DNA modifications have a broad impact on fundamental life processes and diseases such as cancer. Their *Cell*[10] paper describes a method called TAB-Seq and presents the first map of the precise location of 5-hydoxymethylcytosine (5-hmC, the modified DNA base; *see top right*) throughout the entire genome.

A patent is pending on this invention, and Chicago-based Wisegene is marketing the technology, which is expected to quickly become widely adopted for studies of gene expression.

A patent is pending on this invention, and Wisegene (www.wisegeneusa.com), a new start-up company based in Chicago, is marketing the technology, which is expected to quickly become widely adopted for studies of gene expression.

Min and He received a CBC Catalyst Award in January 2012 for the project "Capturing Kinetically Labile Protein Assemblies on DNA.[11]" The Catalyst project aims to determine the structure of previously intractable protein-DNA complexes, focusing on detailed characterization of binding events – work made possible by joining Min's expertise in producing active proteins with He's expertise in stabilizing unstable structures. Min says that the Catalyst project is going well. They are finishing up structural studies of the protein assemblies and have some intriguing results.

The Catalyst was Min's first grant, and she says that thanks to her collaboration with He, she was able to start a new collaboration with Professor Anjum Ansari, a physicist at UIC. Their work recently won a UIC Chancellor's Discovery Fund award for multi-disciplinary research. In addition, Min and He are co-principal investigators on a National Science Foundation (NSF) proposal and envision applying for NIH funding.

Jung-Hyun Min at Work

"Personally, the CBC award has given me a lot of momentum. Chuan He is a very good collaborator and has been extremely supportive. His post-doc regularly comes to work in my lab," said Min. According to He, "We really benefit from having access to the highly active enzyme that Jung-Hyun's lab can produce. Working with Jung-Hyun has been huge."

Jung-Hyun Min is an Assistant Professor of Chemistry at UIC and a co-recipient of the CBC Catalyst Award: "Capturing Kinetically Labile Protein Assemblies on DNA.[11]"

CBC Catalyst:

TULIPs Come into Bloom

Many organisms have the capacity to respond to light. Light striking our retinas induces biochemical changes that enable us to see. Likewise plants and microbes sense light in order to orient their growth or movement. The field of optogenetics began in 2002, when investigators began to exploit naturally occurring, light-responsive proteins to make specific neurons respond to light. In 2010, *Nature Methods* chose optogenetics as the "Method of the Year" across all areas of science and engineering. Recently, the CBC Catalyst Award team of Tobin Sosnick, Eric Weiss, and Michael Glotzer published their contribution to this important new field. Their 2009 Catalyst project[12] developed innovative and broadly applicable tools called TULIPs[13] (TUnable, Light-controlled Interacting Protein tags) that use light to directly manipulate the formation of protein complexes. This technology makes it possible to answer many important questions for the first time.

The project sprang from Devin Strickland's Ph.D. thesis in the Sosnick lab, which showed that a small part, or "domain," of a photosensitive protein could be used to modulate other protein domains with light. "We realized that many interesting biological processes could be studied from a novel angle if we could regulate a whole host of different proteins with light," recalled Glotzer. Strickland *(pictured below)* joined the Glotzer lab to take on the challenge.

Making many individual proteins light-regulated would require a lot of protein engineering. "We decided to go around this problem and figure out a way to make the interaction between two small proteins light-regulated and then attach other proteins of interest to these two proteins. Formation of light-regulated dimers (the two small proteins) could then be used to control the localization of specific proteins or the formation of specific protein complexes," explained Glotzer.

Sosnick and Glotzer applied for an NIH Eureka grant to fund this high-risk/high-reward project. Then they realized that the project could benefit from interactions with Eric Weiss at Northwestern, who studies yeast and is experienced in high-throughput screening.

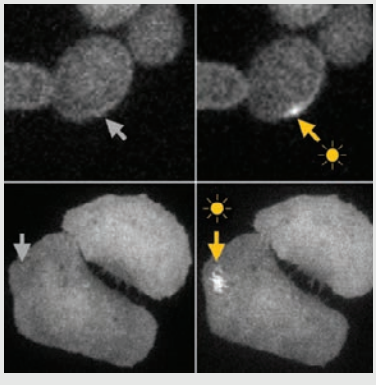
Weiss was excited to participate and the three Principal Investigators submitted a CBC Catalyst application to incorporate the Weiss lab's expertise into the project. "We were fortunate to get both proposals funded," said Glotzer. "The collaboration worked very smoothly. All of us were excited to see if we could make it work."

As it turned out, the project worked beyond expectations. The TULIPs technology was mostly developed in the Glotzer lab, and the collaboration with Weiss facilitated the use of budding yeast to screen many variants quickly. The yeast system allowed the team to determine which variants worked inside living cells and to demonstrate that this system could control cell growth and polarity. The Sosnick biophysics lab provided an understanding of how the light-sensitive protein domain changed its shape in response to light exposure – which led to improvements in the design of the TULIPs system.

"The CBC's goal of bringing the Chicagoland institutions together was very successful," Sosnick summarized.

"The CBC project allowed us to take risks that we normally would have taken a pass on, and ended up getting us a tool that will let us do entirely new things," remarked Weiss. "As an added benefit, it also established a collaborative team that works well together and has begun spinning off even more new ideas." Indeed, all three labs still meet frequently and exchange ideas. "We are now using these advances to study new aspects of biology and develop second generation strategies to study cells with light," concluded Glotzer. In particular, Glotzer's lab is employing TULIPs to dissect the mechanisms by which cells become polarized and divide, two processes that go awry in diseases such as cancer.

As Sosnick summarized: "The CBC's goal of bringing the Chicagoland institutions together was very successful. It motivated us to expand the University of Chicago collaboration to include Eric at Northwestern. Eric brought a new, critical component which helped with the success and direction of our multi-disciplinary project, and will undoubtedly lead to more Chicagoland optogenetic studies."



TULIPs System in Action

The TULIPs "system" is a technology that uses light to study protein-protein interactions. One of the interacting proteins is made light-responsive – it requires light to be active. Once activated, this protein begins interacting with the second protein, whose function then can be studied in live cells at the exact location dictated by the precise positioning of the beam of laser light. Shown here (left) are the photos of yeast cells (top) and cultured human (HeLa) cells (bottom) expressing light-responsive protein and its interacting partner (fluorescently-tagged). In the dark, these two proteins do not interact (left panels; grey arrows mark the location where the laser light will point). After a brief laser pulse (right panels), the light-responsive proteins are activated and recruit the fluorescently-tagged proteins to the activation site (bright spots). (Image Credit: Elizabeth Wagner and Devin Strickland *(right)*/Glotzer lab)

SCIENTIFIC VIGNETTE

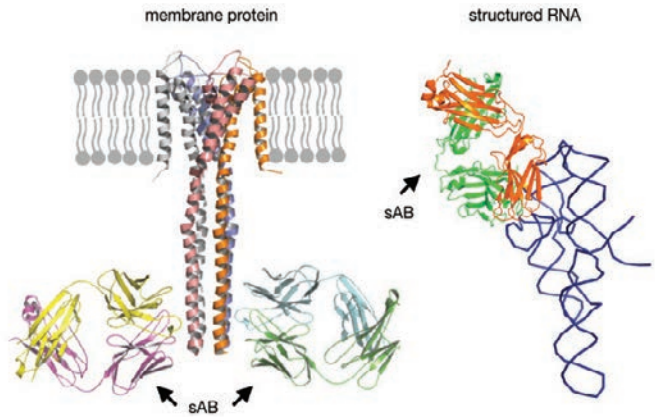
Lever Award:

Designer Antibodies to the Rescue

Engineers are envious of many accomplishments of biological systems. For instance, the immune system can generate powerful and specific antibodies to a vast range of molecules – typically to fight off infections. The development of monoclonal antibodies (MAb), first reported in the 1970s, was an important step towards engineering antibodies, and they were welcomed as "magic bullets." For the past 30 years, MAbs have been important tools in biochemistry and cell biology. Modified MAbs also have become successful drugs for the treatment of cancer and autoimmune diseases, with the breast cancer drug Herceptin as a prime example.

However, there are significant drawbacks to the current antibodies available for research. They are challenging and time-consuming to find, and expensive to produce. It has not been possible to make MAbs to many important types of molecules (e.g. RNA). And more than 50% of the time, commercial antibodies just don't work like they are supposed to. Antibodies are used in virtually all branches of biological research, and their quality is often the determining factor for what systems can be studied and how credible the results are. Thus there is a continuing need to improve the "engineering" of antibodies.

Anthony Kossiakoff, Professor of Biochemistry and Molecular Biophysics at The University of Chicago, and his colleagues have studied and built molecular recognition systems, using antibodies as a model system. Over the past decade, sophisticated methods have been developed for constructing antibody fragments that can be "engineered" to bind to specific targets. These "synthetic antibodies (sAB)" have been designed and built from the ground up, and they have many advantages over standard monoclonal antibodies. For example, sABs can be generated in a fraction of the time and at 10% of the cost required to generate MAbs. Importantly, sABs bind their targets in a tight and highly specific manner. And sAB technology has produced the first-ever antibody to RNA.



Crystal Structures of Synthetic Antibody–Target Complexes

Synthetic antibodies (sAB, arrows) can interact with a variety of cellular targets, such as proteins (left) and RNA molecules (right). (Image Credit: Shohei Koide and Anthony Kossiakoff)

A 2009 CBC Spark Award[14] to Kossiakoff and Northwestern collaborators Charles Clevenger and Vladimir Gelfand, expanded the use of sABs into cell biology. A system was developed to deliver sABs to the interior of living cells, which opens broad new avenues for studying intracellular events, since standard MAbs are too large to enter living cells. Shohei Koide, one of the developers of sAB technology, used them to detect breast cancer cells in animal imaging. One of his goals is to take advantage of the highly specific and tight sAB binding to deliver toxins or drugs directly to the cancer cells. Spark funds were also used to develop a high-throughput technology platform to efficiently produce customized sABs.

As Koide remarked: "In the beginning, people were skeptical of the potential of the synthetic antibody technology. The CBC funding was instrumental in getting the project off the ground and producing data to convince colleagues and funding agencies."

Based in part on advances made with Spark support, Kossiakoff and colleagues applied to a major NIH initiative to develop the next generation of affinity reagents. The CBC promised a Lever Award of $2.3 million if the NIH application was successful. Indeed, the "Recombinant Antibody Network" was awarded $12 million from the NIH in the fall of 2011. While the NIH grant supports production of sABs for a particular class of human proteins, the Lever[15] funding makes this revolutionary technology available to CBC researchers who are investigating a variety of biological questions. Lever funds are supporting a protein production core facility at Northwestern, a facility at UIC that focuses on technology development, and the high-throughput sAB production pipeline at the University of Chicago. In addition, Lever funding will be used to support numerous pilot projects to develop sABs to targets of high biomedical interest.

Kossiakoff Discusses Synthetic Antibodies at Northwestern

CBC Lever Award recipient Tony Kossiakoff (left) and CBC Catalyst Award recipient Keith Tyo pose after Kossiakoff's seminar at Northwestern about the Synthetic Antibodies CBC Lever project[15] on September 27, 2012.

Strengthening the Environment for Biotech Entrepreneurs

One of the long-term goals of the CBC is to promote the development of the biomedical industry in Chicago. A number of initiatives are underway in this arena.

- Building on the example of the CBC, the Technology Transfer Offices at the three universities have launched several collaborative activities. The most far-reaching is the **Chicago Innovation Mentors** (CIM) program, modeled on a program developed at Massachusetts Institute of Technology (MIT). CIM matches faculty entrepreneurs with business-savvy mentors and, thanks in part to an award from the CBC, CIM has grown rapidly. Currently 118 mentors are working with 51 active ventures. Two to four new mentors are recruited each month, and CIM meetings have become a prime networking venue for the Chicago biotech community.

- From 2008-2011, **CBC sponsored a Business Plan Competition focused on biomedically-related companies**, which was open to students at the Northwestern, University of Chicago, and UIC business schools. Agile Diagnosis, the 2011 winner, was founded by students at the University of Chicago's Booth School of Business and faculty from the University's Pritzker School of Medicine. The product, which is an iPhone App guiding diagnostic decision-making, is now being beta tested by 11,000 users. Agile Diagnosis recently 'graduated' from CIM when it received $2.6 million in seed funding from venture investors.

- Modern drug development typically begins by testing a large number of chemical compounds – so-called small molecules – for a desired biological activity. In July 2012, CBC organized and presented "Tech Day: Small Molecule Discovery in Academia," which highlighted the **impressive drug discovery resources available at the three universities**. Close to 170 people learned about the multi-step process of identifying biologically-active and potentially therapeutic compounds. Automated High-Throughput Screening (HTS) is a key component of the search for new drugs, and CBC Tech Day brought together, for the first time, the directors of the HTS facilities at the three universities. The HTS directors are now considering ways they can cooperate and potentially coordinate activities.

- After Tech Day, the HTS directors reported an immediate up-tick in inquiries about potential screening experiments. To help assure that the most meritorious of these projects move forward, the CBC is developing a **matching grant program to enable researchers with promising systems to initiate pilot projects to search for potential drugs**.

- In September 2012, the CBC made its 14th Lever pledge to the team of Karl Scheidt (Northwestern), Gregory Thatcher (UIC), and Sergey Kozmin (The University of Chicago) for the "Tri-institutional Center for Accelerated Translation (TCAT)." The Lever pledge promises $2.5 million in matching funds if the team is successful in securing a $24 million U54 grant from the National Heart, Lung, and Blood Institute (NHLBI) for a Center for Accelerated Innovation (CAI). The CAI award explicitly **funds the development of early stage academic discoveries to a level that attracts investor and industry partners**. The CAI grant would support an impressive infrastructure focused on moving treatments for heart, lung, and blood diseases "down the development pipeline." The CBC Lever award would provide access to this infrastructure, and would fund pilot projects addressing a range of diseases.

CBC Tech Day: Small Molecule Discovery in Academia

CBC Tech Day: Small Molecule Discovery in Academia took place on Monday, July 9, 2012, at Prentice Women's Hospital Conference Center in downtown Chicago. Close to 170 people learned about the practical steps of using high-throughput screening to identify biologically-active molecules. The meeting included panel discussions and posters describing the cutting-edge technology, knowledgeable staff, and extensive small molecule libraries that are available at Northwestern's High Throughput Analysis (HTA) Lab, the University of Chicago's Cellular Screening Center (CSC) and UIC's new High Throughput Screening (HTS) facility.

Above, poster session at the CBC Tech Day 2012.

Capturing National Recognition

The CBC is an innovative and unusual enterprise, and its activities have been noted by the scientific community beyond Chicago.

Seeds of Collaboration

Paul Smaglik began his 2009 article in *Nature*[16] this way: "Chicago, popularly known for its gangsters, sports fans and deep-dish pizza, also has a cluster of impressive research institutions that often get overshadowed by the elite universities on both US coasts. But now, the city's biggest research players are beginning to team up, combining their time, talent and collective strengths to earn serious federal funding."

The article goes on to say: "Northwestern, the University of Chicago, and UIC have historically done well in securing federal research funding. But recent successes in landing large collaborative grants … have come about very much by design. In 2002, a philanthropic fund set up by the **Searle family,** which built its fortune on pharmaceuticals such as the first oral contraceptive and the anti-inflammatory drug Celebrex, saw an opportunity to turn rival institutions into collaborators. The family formed the **Chicago Biomedical Consortium (CBC) … and mandated funding partnerships.**" … "The CBC has caused a cultural shift in Chicago's research landscape," said (then) CBC scientific director Jonathan Silverstein."

Smaglik concludes with this: "All the new collaborative grants should collectively bring hundreds of new researchers into the area. And **the team approach – fostered by the CBC – is changing the way these groups interact with each other.** "The old philosophy was 'Oh my God! The other guy is beating us'," says (Donald) Levy (vice president of research at the University of Chicago). The new one turns former competitors into cheerleaders. "You look upon the other guy's success as your success," Levy says."

(Photo Credit: J. Fuste Raga/Corbis)

NIH Cites CBC as a Role Model

In a Policy Commentary "Core Facilities: Maximizing the Return on Investment" published in *Science Translational Medicine*[17] (August 10, 2011), Gregory Farber (National Center for Research Resources) and Linda Weiss (National Cancer Institute) say, in a section headlined "Uniting Neighbors" "… Also being explored are core facility centralization and sharing activities that reach beyond a single institution. For example, the **Chicago Biomedical Consortium, ... provides core facilities to researchers at three Chicago-based universities**. This idea could certainly be expanded to other metropolitan areas that have multiple research-intensive institutions."

CBC Model Going Viral

In an article "Rowan or Rutgers: No need to change names to win grants" published March 12, 2012 in the *Philadelphia Inquirer*[18], the CBC is highlighted as a consortium role model that, if followed, could "leverage the existing strengths of four institutions and transform southern New Jersey into a hot spot for life-science and biomedical research in the region and the state." The article goes on to state: "**The consortium model has been implemented with great success elsewhere, including the Chicago Biomedical Consortium** (Northwestern University, University of Chicago, and University of Illinois at Chicago); the Broad Institute (MIT, Harvard, and affiliated teaching hospitals); and the Research Triangle Park (Duke University, North Carolina State, and University of North Carolina at Chapel Hill)."

Citywide Shared Research Facilities

The CBC has supported many research facilities that house cutting-edge technologies. CBC-supported facilities are available to the city-wide research community, and outreach workshops are a common way to educate potential users. Shown here are participants in a workshop at the Cellular Screening Center. Other CBC-supported facilities include: Advanced Imaging Core, BAC-Recombineering Core, Center for Advanced Molecular Imaging, CCSB Computation Core, Hitachi HD-2300A Scanning Transmission Electron Microscope (STEM), Mass Spectrometry Metabolomics and Proteomics Facility, Microenvironmental Control Foundry, and the Proteomics Center of Excellence.

Promoting Chicago as a Leading Center of Excellence for Biomedical Research and Training

As summarized in this report, the CBC has a demonstrated record of impact – on science, on the CBC universities, and on the city of Chicago. The investment by the Searle Funds at The Chicago Community Trust has already earned substantial, measurable returns, and **there is a clear pattern of accelerating growth in the return on investment**. And this is only the beginning. Ongoing benefits will accrue from the new research areas that are opened, the productive scientific careers that are launched, the critical mass of local research talent that expands, the new biomedical companies that are started, and the improved health that will be the ultimate result of discoveries made possible by the CBC.

The CBC has well-established programs that are highly effective, and they continue their strong rate of growth and productivity. At the same time, the CBC has introduced new initiatives, continuing to expand its impact. **Thanks to the tremendous power of private philanthropy coupled to local control, the CBC can be nimble in adjusting programs to fit evolving realities and needs.**

By bringing together the universities and the community of biomedical researchers, CBC has reinforced the fact that **the Chicago biomedical research enterprise is an important regional strength** – a strength that can be leveraged into the future.

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Credits

Images and photos: John G. Searle, courtesy of the website of The Chicago Community Trust; Northwestern Arch, courtesy of the website of Northwestern Kellogg School of Management; CBC Staff and Leadership, Richard F. Gaber; Chicago skyline *(this page)*, Justin Kern; otherwise CBC or as indicated in figure legends.
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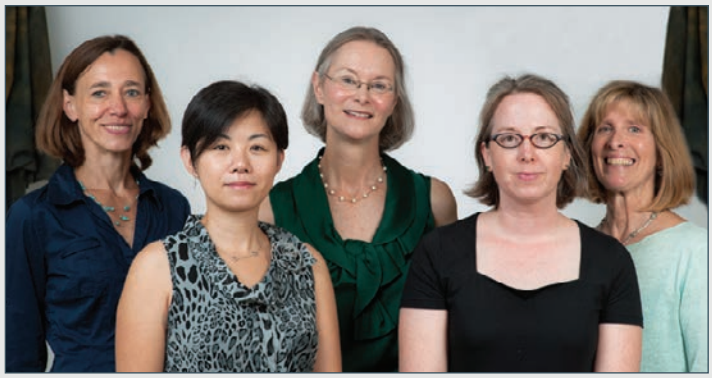
Professional Staff

A strong central staff is critical to maintaining large-scale collaboration. Located at the various member institutions, the CBC Core Staff are charged with connecting people, managing projects, communications and finances in a multi-institutional matrix organization.



Northwestern University Office:
2205 Tech Drive, Hogan 2-100, Evanston, IL 60208

Kathryn Stallcup, PhD *(center)*
Executive Director
Phone: 847-467-0389 / Fax: 847-467-0382
Email: k-stallcup@northwestern.edu

Karen Snapp, DDS, PhD *(far right)*
Associate Director
Phone: 847-467-0633 / Fax: 847-467-0382
Email: ksnapp@northwestern.edu

Kimberly Corn *(second right)*
Business Administrator
Phone: 847-467-0357 / Fax: 847-467-0382
Email: k-corn@northwestern.edu

The University of Chicago Office:
Cummings Life Science Center, Room 161 D
920 East 58th Street, Chicago, IL 60637

Jola Glotzer, MD *(far left)*
Program Manager
Phone: 773-834-5132 / Fax: 773-702-3172
Email: jolaglotzer@uchicago.edu

University of Illinois at Chicago (UIC) Office:
Molecular Biology Research Building, Room 4070
900 South Ashland Avenue, Chicago, IL 60607

Corinna Kitcharoen, MBA *(second left)*
Program Coordinator
Phone: 312-996-1311 / Fax: 312-413-2691
Email: ckitch1@uic.edu