Spinning off success

Bringing basic research from lab bench to market

John Maroney (seated, right) discusses a new technology transfer opportunity with colleagues Jason Wen and Vlad Drozdoff (standing).

Scientists at Cold Spring Harbor Laboratory have a long history of producing groundbreaking discoveries and technological innovations that have revolutionized entire fields of science. Most of this research appears within highly cited publications. Some of it has captured public acclaim and high honors, including eight Nobel Prizes. And some of it has also served as the springboard for commercial ventures that have turned fundamental discoveries into products, jobs and most importantly, advances in human health.

Since the 1980s, research done at CSHL has been, in part or in whole, the founding basis of many biotechnology startup companies. The "technology transfer" income from these, along with technology licensing activity and corporate partnerships, is an important source of support for the always productive basic science research engine at CSHL.

Regional economic development studies often tout the following as the key ingredients that academic institutions need to achieve startup success: large departments in engineering, math and other physical sciences; and geographical proximity to and symbiotic existence with hi-tech industrial hubs. CSHL has found its strength in other virtues.

"What we do have is an influx of scientific talent from all over the world, which has made CSHL rich in intellectual capital," says John Maroney, Vice President and Director of CSHL's Office of Technology Transfer, which has helped CSHL-related startups to take root all over the nation. "The ability of CSHL scientists to create technology that is highly regarded by the world's research community and also valued by the biomedical industry has helped launch commercial endeavors."

The Laboratory's efforts in technology transfer began in the 1980s with the growing realization that others were reaping the financial benefits of CSHL technology without providing any of the support needed to create and develop those technologies. For example, a company that commercialized enzyme purification technology developed in the 1970s by then CSHL scientist and Nobelist Rich Roberts had grown into the hugely successful Massachusetts-based New England Biolabs. But none of the revenue benefitted the CSHL research programs that had led to the company's commercial success.

That's when Maroney, with the support of the Laboratory's leadership and scientists began to establish agreements with commercial organizations that would complement both basic academic research at CSHL as well as the commercial application of its results for public good. CSHL scientists have kept him and his team busy ever since in securing intellectual property rights, developing patents, licensing technologies and launching startups [see timeline].

As it gained experience in tech transfer, the Laboratory achieved several early successes, including the launch of Oncogene Science in 1983. Inspired by the discovery of the first human cancer gene, the oncogene *Ras*, by CSHL scientist Mike Wigler, OSI Pharmaceuticals, as it eventually became known, became a huge success. Responsible for creating hundreds of high paying jobs on Long Island, it gained fame internationally after it developed the drug Tarceva® to treat lung, pancreatic and other types of cancer. A genetic screening platform developed by Wigler helped launch another startup in 1983 called Icos Corp., which used this technology to identify the enzyme inhibitor that would gain worldwide fame as the drug Cialis®.

In the following decade, a stream of innovations from Wigler's group rapidly lengthened the lineup of CSHL's spin-offs: a gene co-amplification method that helped produce vast quantities of blood clotting factors and other biological products; a technique to accelerate the design, testing and analysis of small synthetic peptides for use as inhibitors of biomolecules (Pharmacopeia, Inc.); and a method called Representational Difference Analysis (RDA) to identify oncogenes and tumor suppressor genes by comparing cancer cell DNA to a normal cell's DNA. This last technology was the founding basis of Amplicon Corp., a startup that was acquired by Tularik Inc. (which was later purchased by biotech giant Amgen). "That's how Mike and CSHL contributed to the creation of the biotech industry," says Maroney.

CSHL had emerged as a genome sequencing powerhouse in the late '90s and early 2000s as a result of its key role in international collaborations that sequenced various species, including humans. In a bid to sequence

Startups based on CSHL innovations

1981 Protein Databases Inc.
Based on software developed by Jim Garrells to analyze patterns in 2-dimensional gel electrophoresis arrays of cellular proteins; acquired by Bio-Rad Laboratories.

1983 Oncogene Science (OSI) Initiated after breakthrough discovery of *Ras* oncogene by Mike Wigler; developed cancer drug Tarceva®.

1990 ICOS Corp.
Highly successful spin-off that developed the blockbuster drug Cialis® based on gene cloning technology patented by Mike Wigler.

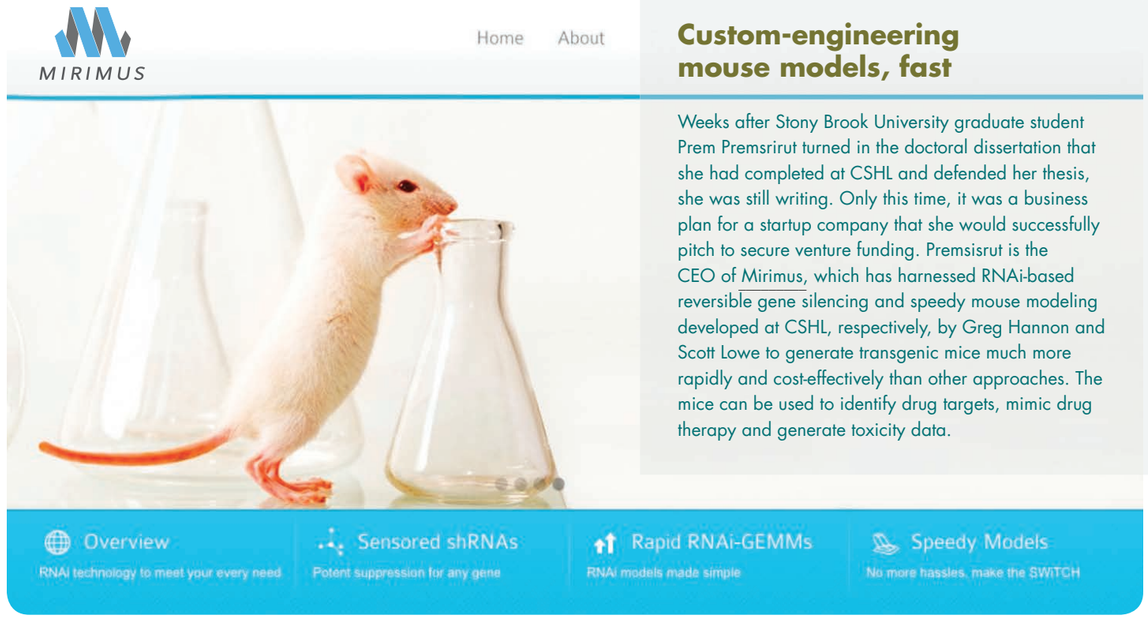
1991 Pathogenesis Corp.
Infectious disease drug development using Mike Wigler's representational difference analysis (RDA) technology; acquired by Chiron Corp.

1992 Geron Corp.
Partly based on Nobelist Carol Greider's breakthrough research on telomerase; develops cancer- and geriatrics-related therapies.

1992 Mitotix, Inc.
Developed cancer diagnostics and therapies based on David Beach's work on cyclins — proteins involved in the cell cycle; bought by German company GPC Biotech.

1993 Pharmacopeia, Inc.
Based on a successful collaboration between Mike Wigler and scientists at Columbia University in encoded combinatorial libraries for high-throughput drug screening.

1994 Amplicon Corp.
Licensed Mike Wigler's RDA technology to look for genes associated with cancer and other diseases before being acquired by Tularik Inc.



Custom-engineering mouse models, fast

Weeks after Stony Brook University graduate student Prem Premsrirut turned in the doctoral dissertation that she had completed at CSHL and defended her thesis, she was still writing. Only this time, it was a business plan for a startup company that she would successfully pitch to secure venture funding. Premsisrut is the CEO of Mirimus, which has harnessed RNAi-based reversible gene silencing and speedy mouse modeling developed at CSHL, respectively, by Greg Hannon and Scott Lowe to generate transgenic mice much more rapidly and cost-effectively than other approaches. The mice can be used to identify drug targets, mimic drug therapy and generate toxicity data.

the large genomes of crops like rice and corn, Rob Martienssen and W. Richard McCombie developed a technique called methylation filtration to capture and sequence only the gene-rich regions in the genome. This became the basis of a startup called Orion Genomics, LLC., one of the first companies in a niche that has since become one of the hottest growth sectors within the biotech industry.

The Laboratory's other technological *tour de force* in recent years has been the development of RNA-based tools to silence gene expression by Gregory Hannon, a pioneer in the field of RNA interference (RNAi). The RNAi libraries, as these tools are known, are key to investigating the functions of individual genes and developing new therapies to target those genes that cause disease when they malfunction. In addition to being available to all basic science researchers, Hannon's creations, which have received several patents, have provided the foundations of several commercial ventures, including the recently launched startup, Mirimus, which generates customized mouse models that serve as superior preclinical test subjects in the drug discovery process [see "Custom-engineering mouse models, fast"].

"The system that is in place at the Laboratory to commercialize discovery makes it very easy for people like me," says neuroscientist and Associate Professor Pavel Osten, who won venture capital funding last year to launch Certerra Inc., a startup that also aims to make an important contribution to improving drug discovery. "I'm walking down a well-trodden path."

The company is based on a groundbreaking technology developed by Osten and collaborators at TissueVision Inc. and MIT called Serial Two-photon Tomography. It involves a novel high-throughput microscopy platform that produces speedy, automated image maps of a whole brain at cell-level resolution. Osten's goal is to use this technology to investigate brain circuits in mouse models of brain disorders and map drug-activated brain circuits for preclinical screening of new drugs for the pharmaceutical industry.

Drug companies currently spend up to $1 billion to find out whether a drug compound that worked well in animal testing also works well in human clinical trials. However, the probability of success — the chance that a drug will eventually make it into the market — is low; for drugs targeting the brain, it is a dismal 5%. Osten's approach could help improve the ability of drug developers to predict the outcome of clinical trials before embarking on this long and expensive process [See "'Pharmacomapping' the brain"].

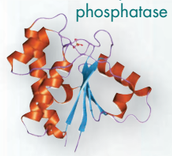
"As we learn more about how neuronal activity patterns change in our mouse models of disorders such as autism and bipolar disorder, and build up a drug-specific pharmacomap database at Certerra Inc., we may eventually be able to make predictions about which drug would be a good bet to reverse the changes that we see in the disease models," says Osten. With most pharma companies cutting their neuroscience and other research programs and lacking fresh ideas for a better drug screening process, Osten's approach, which grew out of a need for better brain visualization techniques, as well as Mirimus's strategy, offer new hope for developing effective drugs faster through a more economically viable pipeline.

'Pharmacomapping' the brain

Here's one scenario of how Certerra's technology might help reduce the failure rate of drugs in clinical trials: Because a drug's effects in the brain are largely determined by which neurons it activates, treating a mouse with an existing drug, say for depression, and mapping subsequent brain activity will generate a 'pharmacomap' for the drug. Simply comparing this map to that generated by new candidate drugs for depression will help pharma companies sift out the duds and focus only on those compounds that work on par or better than the existing benchmark.

At a time when more than 12 million Americans are out of work, investing in basic research might at times provoke a reaction along the lines of "What's in it for me?" The answer is that basic research breakthroughs have defined and driven whole new industries in the last 50 years. Imagine a world without the internet or the semiconductor, robotics and the biotech industries, all sparked by innovations in academic labs.

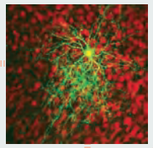
Surveys by The Association of University Technology Managers show that academia-spawned companies continue to crop up at a brisk pace, with 651 created in 2010 alone, up 15% since 2007, emphasizing the potential that academic startups have to continue expanding the job market while introducing innovative and transformative new technologies. It's entirely conceivable that sprouting today within one of CSHL's 50 labs is a scientific or technological breakthrough that will seed the next high-growth company and many new high-paying jobs. **Hema Bashyam**



1995 Charybdis Corp.
Formed to develop and commercialize new classes of small-molecule pharmaceuticals in type 2 diabetes, obesity and oncology, based on protein tyrosine phosphatase discoveries by Nick Tonks.

1996 Genomica Corp.
Licensed a genome scanning technology developed by Tom Marr for genomics-based drug discovery; acquired by Exelixis, Inc.

1997 deVGen
Belgian company based in part on Michael Hentgartner's discoveries of novel cell death-regulating proteins in worms.

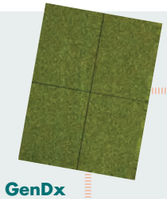


1997 Helicon Therapeutics
Launched by Tim Tully to develop drugs for Alzheimer's, age- and trauma-related memory impairment.

1998 Genetica
Started by David Beach and Gregory Hannon to apply their research on RNAi in the development of high-throughput tools for drug target validation and their work on retrovirus vectors for antibody production.

1998 Orion Genomics, LLC.
Used filtered shotgun sequencing technique invented by Rob Martienssen and Dick McCombie to sequence and analyze plant genomes; now developing diagnostics for multiple cancer types.

2002 Juventis, Inc.
Based on Grigori Enikolopov's discovery of the role of nitric oxide in controlling the regeneration of stem cells in the brain.



2007 GenDx
Based on Mike Wigler's ROMA (representational oligonucleotide microarray analysis) technology to develop DNA diagnostics for breast cancer.

2011 Mirimus
Rapidly customizes mouse models for drug development based on advances in RNAi and mouse modeling by Gregory Hannon and Scott Lowe.

2011 Certerra Inc.
Based on novel platform co-developed by Pavel Osten to quantitatively map drug activity in mouse brains and improve drug discovery in neuroscience.