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Bright Minds Battling Dark Diseases

San Diego is home to world-class biomedical scientists focused on cutting-edge projects touted president

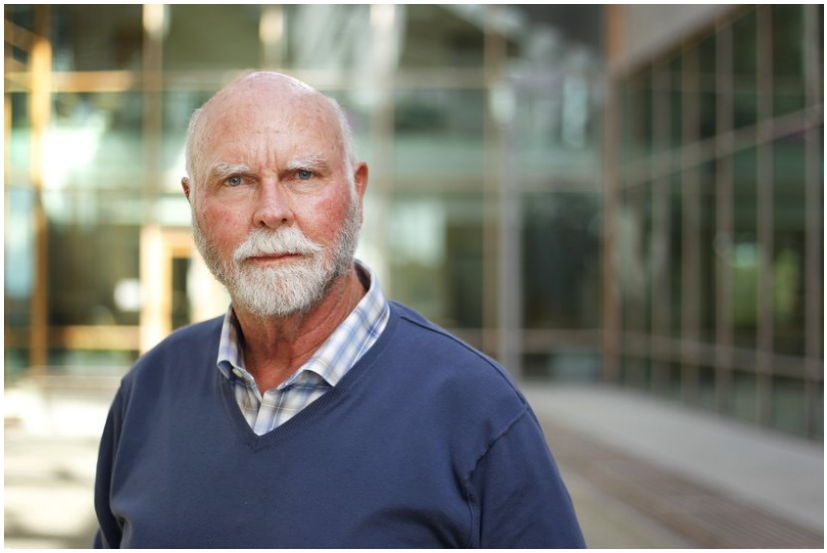
By: Gary Robbins | Saturday, June 25, 2016

You can see the brake lights a half mile away.

Every morning, traffic slows to a crawl at the Genesee exit off Interstate 5 in La Jolla, where an already large effort by scientists to prevent and treat illness and disease is growing even larger.

UC San Diego is in the midst of a multibillion-dollar expansion on both sides of the freeway. And business is crackling at nearby research institutes and biotech companies.

“We’re sequencing a human genome every 15 minutes, 24 hours a day,” said geneticist J. Craig Venter, whose company, Human Longevity, recently partnered with drug giant AstraZeneca.



Genomics pioneer J. Craig Venter. — *K.C. Alfred / San Diego Union-Tribune*

Much of the research is focused on cancer, the brain and the DNA of the trillions of microbes that live in and on your body — the so-called microbiome. The Obama administration has launched major science initiatives in all three fields in hopes of speeding up the search for ways to treat everything from dementia to leukemia to Crohn'sdisease.

The programs include the National Cancer Moonshot Initiative, which will get special attention on June 29th at the Sanford Burnham Prebys Medical Discovery Institute in La Jolla. The institute will hold a symposium on the state of cancer research.

Scientists from across San Diego are helping the government shape the initiatives. They include Rob Knight, a UC San Diego biologist who is among the world's leading experts on the microbiome, and Terry Sejnowski of the Salk Institute for Biological Studies, who's been helping guide President Barack Obama's brain initiative.

More than two dozen of these elite scholars took time to reflect on the current state of research, and where it might be going.

Physician-researcher Catriona Jamieson of the UC San Diego School of Medicine has been helping develop new drugs to battle cancer. *Courtesy of UCSD*

CANCER

Overview

Hope, fear, confusion.

You'll experience all three emotions if you explore the state of cancer.

The death rate is falling. But the number of people diagnosed with cancer is rising. And cancer is extraordinarily complex. Patients often struggle to understand the challenges they face.

The decline in mortality reflects a big drop in smoking. Patients also have benefited from new drugs, including Gleevec, a medication that arose from discoveries at the Salk Institute for Biological Studies in La Jolla. UC San Diego helped develop Imbruvica, a new treatment for a type of leukemia.

There also have been notable improvements in screening, which has contributed to a rise in cancer diagnosis. So has the simple fact that Americans are living longer. Cancer most often occurs in older people.

Progress isn't easy to come by.

More than 60 percent of the experimental cancer drugs that go into final-stage trials don't produce the desired results, and few of them make it to market.

"Eliminating cancer is the biggest scientific challenge that mankind has ever faced," said Dr. Scott Lippman, director of the Moores Cancer Center at UC San Diego.

"Not only does it require an understanding of the normal, but also the abnormal. And every cancer is abnormal in a different way."

In some areas, science has overcome that challenge.

Researchers have developed effective vaccines for human papillomavirus and hepatitis B. There are new drugs that can cure hepatitis C, a virus that can cause cancer.

And after years of setbacks, it appears that scientists will be able to tweak people's immune systems to fight some types of cancer.

The Salk Institute is working on that challenge. So is Sanford Burnham Prebys, the J. Craig Venter Institute, The Scripps Research Institute and the La Jolla Institute for Allergy and Immunology.

But the biggest player in town is UC San Diego, the nation's sixth-largest research university.

And the school is getting bigger.

UC San Diego recently opened a $269 million “translational medicine” institute, where scientists are trying to speed up the process of turning discoveries into new drugs and therapies.

The institute is 100 feet from the $943 million Jacobs Medical Center, which will open this fall. The facility will be heavily used to test therapeutic drugs.

The university is building a $140 million outpatient pavilion, which will include cancer treatment. The $120 million Center for Novel Therapeutics will be built nearby.

UC San Diego will open the Jacobs Medical Center this fall. *Courtesy of UC San Diego Health System*

Scientific challenges

Fighting cancer poses many problems. The biggest may be complexity. Lippman said, “Each cancer is made up of different parts that can change unpredictably, especially in response to treatment. We are just beginning to understand that complexity and develop effective prevention, detection and treatments ...

“In a sense, we need to look at every patient’s cancer as a separate entity, find out what makes that person’s cancer succeed, how the person’s immune system has responded, what side effects they will be susceptible to, what predisposing cancer genes they harbor, and, only then, decide what the best treatment will be.”

Treatment needs to be sharply focused for individual patients, said Geoffrey Wahl, a geneticist at the Salk Institute.

“We not only have to catch cancers early, we also have to develop the knowledge to know which patients will benefit most from therapy, and which will do just fine without it,” Wahl said.

“All therapies have side effects. So sometimes withholding therapy will do the patient more good than harm. We just don’t (know) from which patients to withhold therapy.”

Scott Lippman, director, Moores Cancer Center, UC San Diego *Courtesy of UC San Diego Health System*

Promising developments

Cancer can be caused by many things, ranging from tobacco to radiation to viruses, infections and obesity. Inherity also can be a determining factor.

The common denominator is genetics.

People’s genes frequently mutate, usually without consequence. But some mutations can change how cells grow and divide, potentially leading to cancer.

Studying such changes used to be slow and extraordinarily expensive. A decade ago, it cost $10 million to sequence one human genome. Illumina has reduced the cost to $1,000. Further cuts are likely.

These advances are leading to a seismic shift in medicine. Physicians are increasingly prescribing drugs that are tied to an individual's specific gene mutations rather than using population data.

The pharmaceutical industry is investing heavily in genomics. Financial terms weren't disclosed, but AstraZeneca recently hired Venter to sequence up to 500,000 DNA samples.

Venter also introduced Health Nucleus, a program that uses advanced imaging, gene sequencing, microbe analysis and family history to thoroughly assess a person's health. The test can cost up to $50,000.

"We have had several cases where we've discovered tumors in people who thought they were healthy," Venter said. "The tumors were removed, and they went back to work a week later."

The sequencing coincides with efforts by at least a half-dozen San Diego companies to develop liquid biopsies — tests that search for potentially harmful tumor cells or mutated DNA in the bloodstream. The test is emerging as a less-invasive alternative to tissue biopsies.

Five-year forecast

By 2021, it's likely that "genomics (will be) performed on every patient with cancer at the time of diagnosis," said Razelle Kurzrock, chief of hematology and oncology at UC San Diego's Moores Cancer Center. Kurzrock also says "liquid biopsies will be performed every two months on patients to follow their progress" and that patients will receive highly individualized treatment that includes immunotherapy.

Salk Institute neuroscientist Terry Sejnowski is helping shape the Obama administration's BRAIN initiative. *Courtesy of the Salk Institute*

THE BRAIN

Overview

The brain is capable of extraordinary things. But scientists aren't close to figuring out exactly how it works.

Researchers have a good understanding of the brain's anatomy. They know that its 100 billion nerve cells — or neurons — work together in networks. And that the networks govern every aspect of human existence, from our ability to wiggle a finger, to remember a name, to sense pain.

But scientists know comparatively little about neurons and networks — certainly not enough to clearly explain how brains are wired, and how and when that wiring changes.

That makes it hard to do things like develop an effective treatment for Alzheimer's disease.

The underlying problem largely involves vision; scientists have yet to develop imaging tools that are powerful enough to see and monitor large numbers of neurons in real-time.

"There are billions of neurons in the brain, and we can only see a few hundred at once," said Patrick Mercier, an engineering professor at UC San Diego. "That's like trying to understand New York City by looking at one intersection."

President Barack Obama leaves the stage in the East Room of the White House in Washington, Tuesday, April 2, 2013, after he spoke about the BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative. *AP Photo/Charles Dharapak*

Scientific challenges

Solving the vision problem has become a national priority largely because of a group of elite scientists that included UC San Diego's Ralph Greenspan.

During a 2011 meeting near London, the group began sketching out the Brain Activity Map, an effort to map the working brain. The plan highlighted the need to develop better tools. Greenspan and five other scientists turned the idea into a formal proposal.

To the surprise of many, the Obama administration transformed the basic idea into a national initiative in 2013, and gave it an unwieldy name: Brain Research through Advancing Innovative Neurotechnologies (BRAIN).

The plan called for the government, industry and the science community to spend about $1 billion on BRAIN over a decade. UC San Diego hustled to become part of it. So did the Salk Institute, which committed $28 million.

The projected cost of BRAIN quickly grew to $4.5 billion, which underscores how hard it will be to improve upon such technologies as magnetic resonance imaging and computed tomography, which are widely used to diagnose brain tumors.

Scientists also need to find non-invasive ways to stimulate large numbers of neurons so they can test their ideas about what the brain is doing. And they've got to come up with better ways to crunch the daunting amount of data they're producing.

Promising research
Salk neuroscienist Terry Sejnowski sees lots of reason for hope. “We are making progress on understanding how memories are consolidated during sleep by analyzing recordings from the human cortex,” said Sejnowski, who is famous for making sense of data.

He also reports progress on one of the toughest problems in science: Determining the neural basis for consciousness.

“We can now record from a large number of neurons, which is giving us a global picture of internally generated brain activity,” Sejnowski said.

Five-year forecast
There’s also some optimism at the U.S. Defense Advanced Research Projects Agency. In January, DARPA announced that it will help scientists find ways to record 1 million neurons in real-time. They want to achieve the goal by 2020.

It’s unclear whether that will happen. But Sejnowski still believes the prediction he made in 2013 when BRAIN was announced: “The new mapping tools will transform our understanding of the brain in the way that the Human Genome Project revealed the nature of DNA.”

UCSD professor Rob Knight, a world leader in the study of the microbiome and co-founder of the American Gut Project, shown here in the Biomedical Research Facility II building at the university. — *K.C. Alfred*

THE MICROBIOME

Overview

This is just an estimate, but there about 100 trillion micro-organisms living in and on your body.

Try not to be grossed out; most of the microbes are beneficial. They help you digest food, metabolize drugs, battle infections and boost your immune system.

Microbes also can make you sick, especially when it comes to your gastrointestinal system.

Scientists have known this for a long time. But they've only recently started to understand and quantify the broad importance of the microbiome — the term used to describe the collective DNA of those tiny organisms.

Researchers were helped along by Illumina, which made it quicker and cheaper to sequence microbial DNA wherever it is found, whether it's in humans, the ocean, the air or plants.

The advance helped turn the microbiome into one of the hottest fields in science. UC San Diego has become a focal point of such work because it was able to recruit a star researcher.

Computational biologist Rob Knight was lured away from the University of Colorado, where his passion and gift for studying microbes impressed editors of the respected journal Nature.

Knight "has probed the microbes that blanket various natural and man-made environments, from freshly fallen snow to computer keyboards and bathroom floors," Nature wrote. "He does all this at a restless, relentless pace."

Knight's talent also was noticed by the Obama administration, which sought his advice this year when it was creating the National Microbiome Initiative. The program — with $121 million in federal seed money — will study the global impact of microbes. UC San Diego signed on as a partner. Knight will lead the effort, which will have a strong local flavor. Venter is involved, and so are Rady Children's Hospital and the University of San Diego.

Scientific challenges

The public has reason to be confused about what's happening.

There's been a flood of scientific studies on the microbiome. But many of the studies are based on rodents, which aren't always a good model for humans. And there's no consensus on many key questions, such as whether the microbiome plays a fundamental role in autism. It's still "early days," as researchers say about emerging science.

Despite the uncertainty, publishers have been churning out health and diet books that offer conflicting viewpoints about how people should tweak their microbiome to deal with things like inflammatory bowel system, infections and depression.

Scientists are still struggling to define what a healthy microbiome looks like, and whether it greatly varies across populations of people.

Promising research
The field is benefiting from momentum.

There's a growing belief that understanding the microbiome is essential to preventing and treating a wide array of illnesses and disease. The idea is being pushed hard by people like Knight, who repeatedly notes that the microbial genes that people acquire during their lives vastly outnumber the genes they are born with.

The shift in attitude is translating into money for research, a move reflected by the Obama administration's decision to create the National Microbiome Initiative.

Five-year forecast
Knight believes that scientists will go from simply describing what the microbiome is to finding specific ways to improving human health, as well as agriculture and the environment. He also says that scientists will make great progress in characterizing healthy microbiomes. And he hopes that researchers "develop 'smart' toilets that give you a gut microbiome readout every time you flush."