





Discovering new drugs and diagnostics from 300 trillion points of data

Atul Butte, MD, PhD abutte@stanford.edu
Chief, Division of Systems Medicine,
Department of Pediatrics,
Department of Medicine, and, by courtesy,
Computer Science

Center for Pediatric Bioinformatics, LPCH Stanford University



Disclosures

- Scientific founder and advisory board membership
 - Genstruct
 - NuMedii
 - Personalis
 - Carmenta
- Past or present consultancy
 - Lilly
 - Johnson and Johnson
 - Roche
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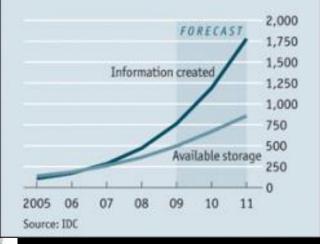
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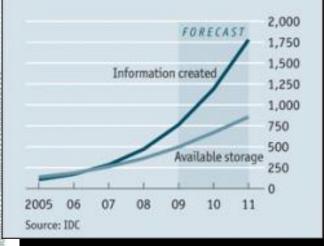
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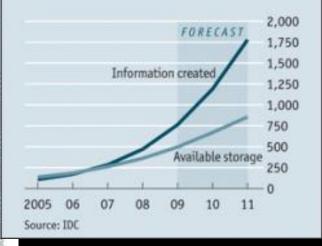
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SCIENCE : DISCOVERIES

The End of Theory: The Data Deluge Makes the Scientific Method Obsolete

By Chris Anderson ≥ 06.23.08

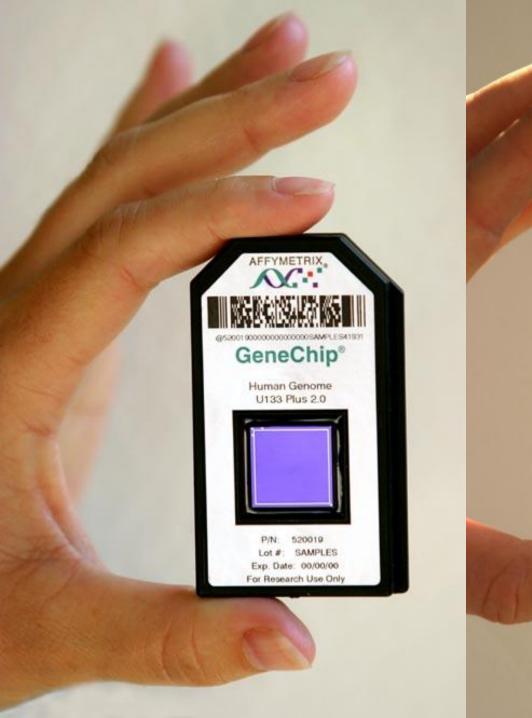


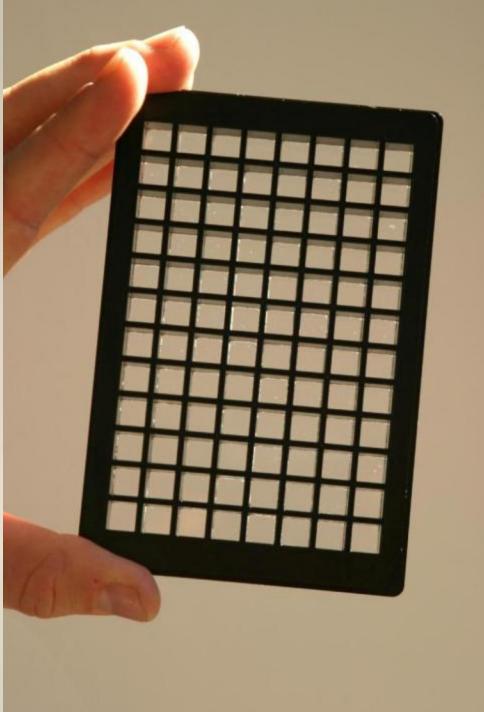
THE PETABYTE AGE:

Sensors everywhere. Infinite storage.
Clouds of processors. Our ability to capture,
warehouse, and understand massive
amounts of data is changing science,
medicine, business, and technology. As our
collection of facts and figures grows, so will

"All models are wrong, but some are useful."

So proclaimed statistician George Box 30 years ago, and he was right. But what choice did we have? Only models, from cosmological equations to theories of human behavior, seemed to be able to consistently, if imperfectly, explain the world around us. Until now







DNA microarrays allow researchers to analyse the expression of a huge number of genes simultaneously.

GENOMICS

Gene data to hit milestone

With close to one million gene -expression data sets now in publi The number of gene-expression data sets in researchers can identify disease trends without ever having to en nearly one million over the past decade.

BY MONYA BAKER

urvesh Khatri sits in front of an oversized computer screen, trawling for treasure in a sea of genetic data. Entering the search term 'breast cancer' into a public repository called the Gene Expression Omnibus (GEO), the postdoctoral researcher retrieves a list of 1,170 experiments, representing nearly 33,000 samples and a hoard of gene-expression data that could reveal previously unseen patterns.

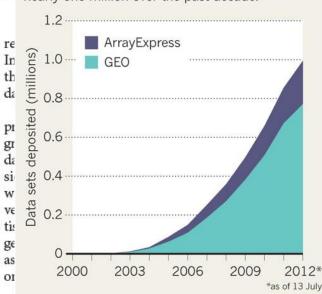
That is exactly the kind of search that led Khatri's boss, Atul Butte, a bioinformatician at the Stanford School of Medicine in California, to identify a new drug target for diabetes. After downloading data from 130 gene-expression

for discovery," he says. Those are for validating hypotheses. The beauty of analysing data from multiple experiments is that biases and artefacts should cancel out between data sets, helping true relationships to stand out, Butte says. "There is safety in numbers."

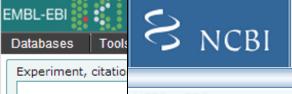
And those numbers are rising rapidly. Since 2002, many scientific journals have required that data from gene-expression studies be deposited in public databases such as GEO, which is maintained by the National Center for Biotechnology Information in Bethesda, Maryland, and ArrayExpress, a large gene-expression

DATA DUMP

publicly available databases has climbed to



DATA DUMP

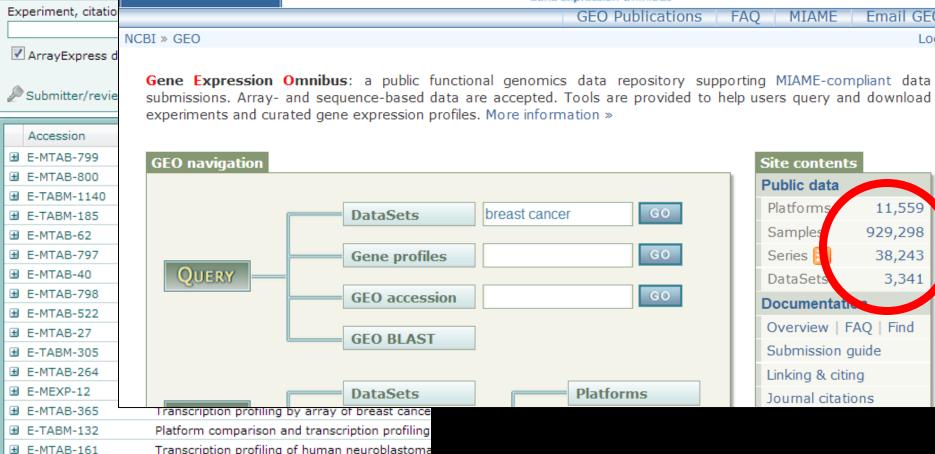


■ E-MTAB-145

■ E-TABM-927

■ E-TABM-913





Platform comparison and transcription profiling
Transcription profiling of human neuroblastoma
Transcription profiling of human separated leuk
Transcriptomics for Cancer Cell Line Project
Chromatin immunoprecipitation genome wide le
Transcription profiling of mouse metaanalysis s
Gene expression analysis of 789 cancer cell lin
Transcription profiling of mouse samples - re-a
Genotypia or numeral suphoblastoid cell lines
Kinasi activity profiling of human locally advan
Gent project of human cancer cell lines
6338 experiments, 228417 assays Displaying experi

Total 1.2 million microarrays available

Doubles every 2-3 years

Butte AJ. Translational Bioinformatics: coming of age. *JAMIA*, 2008.



Sign in to NCBI

GEO DataSets

GEO DataSets V

breast cancer

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Display Settings: Summary, 20 per page, Sorted by Default order

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Results: 1 to 20 of 39372

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of 1969 Next >

Last >>

Platforms (34)

All (39372)

Samples (37742)

Series (1455)

Leukemia inhibitory factor effect on Sin3a-silenced MCF7 breast cancer cell

line

Analysis of SIN3 transcription regulator homolog A (Sin3a)-depleted MCF7 cells stimulated with LIF cytokine to activate signal transducer and activator of transcription 3 (STAT3). STAT3 transcription factor is a potent oncogene. Results provide insight into role of Sin3a in mediating STAT3 activity.

Organism: Homo sapiens

Type: Expression profiling by array, transformed count, 2 agent, 2 genotype/variation sets

Platform: GPL570 Series: GSE35696 11 Samples

Download data: GEO (CEL)

DataSet Accession: GDS4388 ID: 4388

PubMed Full text in PMC **GEO Profiles** Analyze DataSet Similar studies

▼ Top Organisms [Tree]

Homo sapiens (36547)

Mus musculus (2686)

Rattus norvegicus (182)

Canis lupus familiaris (31)

Human herpesvirus 8 (5)

More...

Co-expression of tyrosine kinase receptors HER2 and HER3 in mammary epithelial cells MCF10A grown in three-dimensional cultures

Analysis of MCF10A mammary epithelial cells expressing HER2, HER3, or HER2/HER3 heterodimer. Co-expression of HER2 and HER3 induced migration and invasion of MCF10A cells. Results provide insight into the role of HER2 and HER3 in breast cancer.

Organism: Homo sapiens

Type: Expression profiling by array, transformed count, 4 genotype/variation sets

Find related data

Database: Select



GEO DataSets V breast cancer



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All (39372)

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Type: Expression profiling by array, transformed count, 2 agent, 2 genotype/variation sets

Platform: GPL570 Series: GSE35696 11 Samples

Download data: GEO (CEL)

DataSet PubMed

Intel and Siemens Competition finalist

Andrew Liu (2010)

Intel Science Talent Search semi-finalists

- Rohan Chakicherla (2009)
- Denzil Sikka (2009)
- Tony Ho (2010)
- Irving Hsu (2011)

epithelia

Analysis o heterodim MCF10A

Co-expre

cancer.

Organism:

Type: Expi



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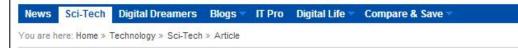
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8:44AM



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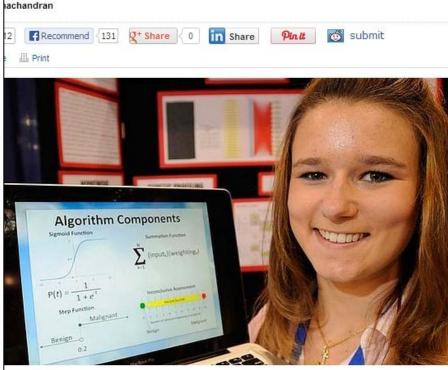
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A high school junior has created a computer brain that can diagnose breast cancer with 99 percent sensitivity.

Seventeen-year-old Brittany Wenger of Sarasota, Fla., wrote a breast cancer-diagnosing app based on an artificial neural network, basically a computer program whose structure is inspired by the way brain cells connect with one another. She won grand prize at the Google Science Fair for her invention in ceremony held in Palo Alto, Calif. last night (July 23).

Like other artificial intelligence programs, artificial neural networks "learn" what



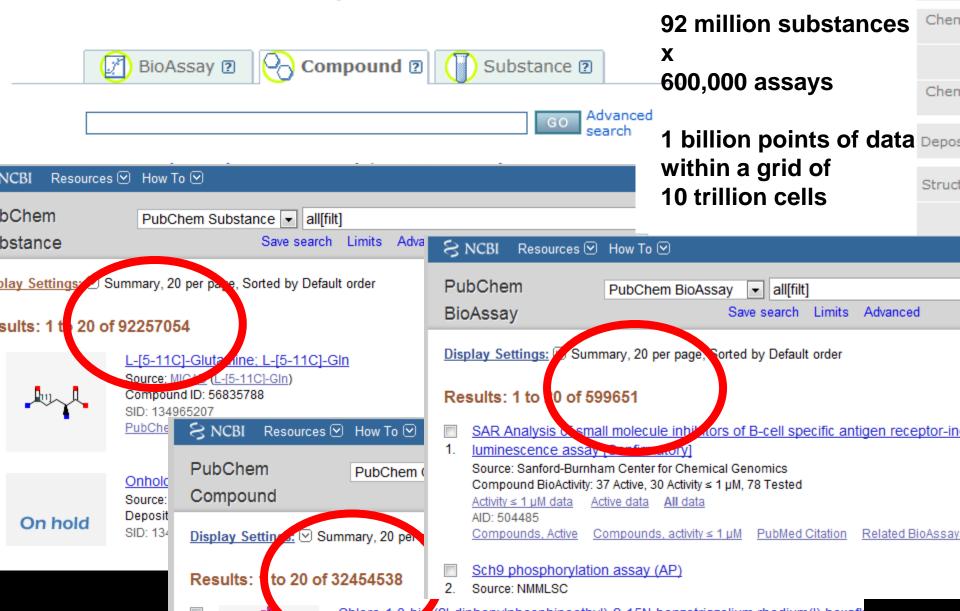
rove that the infrastructure I built could work with multiple diseases": Brittany Wenger. Photo: Intel

ras originally published on Mashable.

enger isn't your average high-school student: she taught a computer how to diagnose

most amazing part about science is you can answer stions and really revolutionise the world and our





stru



Revolutionizing human genome discovery

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Sample Sequence Data

Complete Genomics has recently made several complete human genome data sets available. The genomes were sequenced at the Complete Genomics commercial genome sequencing center in Mountain View, California as part our Complete Genomics Analysis Service (CGA™ Service). These data are largely consistent with the quality and attributes of other data provided to Complete Genomics customers.

When using these data in your research please cite the Complete Genomics website and our publication "Human Genome Sequencing Using Unchained Base Reads on Self-assembling DNA Nanoarrays." Science 1 January 2010 Vol. 227. no. 5961, pp. 78 - 81 DOI: 10.1126/science.1181498

69 Genome Data Set

Documentation

Swarvie

Complete Genomics is releasing a set of public genome sequences on its FTP server

(ftp2.completegenomics.com). There are four sets of data: a Yoruba trio; a Puerto Rican trio; a 17-member 3-generation pedigree; and a diversity panel representing 9 different populations. The CEPH samples within



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Anemia

Idiopathic Pulmonary Fibrosis

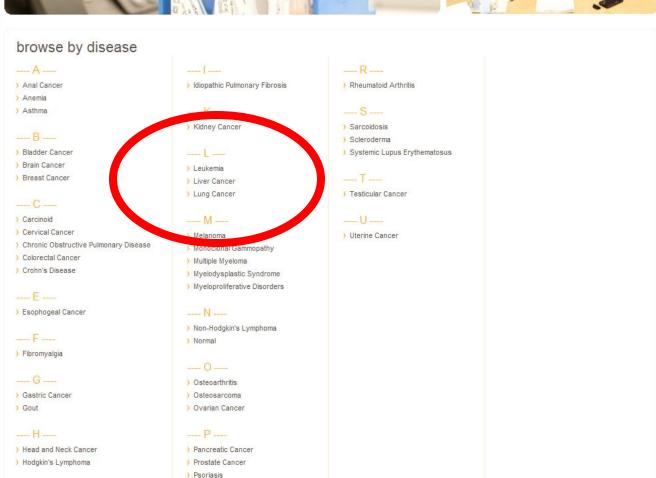


Rheumatoid Arthritis









Search Results Leukemia You've Selected: View as: 21 Items Previous 1 2 Next Disease: Leukemia (X) 15 Items Per Page • • Sort By .. Clear All Selections Category Bone Marrow | B Cells, CD19 | Bone Marrow | B Cells, Negative Products (21) Selection | Leukemia Leukemia SKU: BMA-BCE-LE SKU: BMA-CD19-LE Tissue \$500.00 \$500.00 Bone Marrow (9) Peripheral Blood (12) Cell Type B Cells CD19 (2) Bone Marrow | T Cells, CD3 | Leukemia Bone Marrow | CD45 | Leukemia B Cells Negative Selection (2) SKU: BMA-CD3-LE SKU: BMA-CD45-LE Buffy Coat (1) \$500.00 \$500.00 CD45 (2) Fresh (2) Mononuclear Cells (2) Plasma (1) Serum (1) Bone Marrow | Fresh | Leukemia Bone Marrow | Mononuclear Cells | Special Processing (2) SKU: BMA-FRE-LE Leukemia T Cells CD3 (2) SKU: BMA-MON-LE T Cells Negative Selection (2) \$2,500.00 Viable Plated Cells (2) \$750.00 0.3mL (1) 0.5 million cells (10) Bone Marrow | Special Processing | Bone Marrow | T Cells, Negative 0.5mL (2) Leukemia Selection | Leukemia 1 unit (2) SKU: BMA-SPE-LE SKU: BMA-TCE-LE 5.0 million cells (2) \$500.00 \$500.00 Price \$0.00 - \$1,000.00 (17) \$1,000.00 - \$2,000.00 (2) \$2,000.00 - \$3,000.00 (2) Bone Marrow | Viable Plated Cells | Peripheral Blood | B Cells, Negative Selection | Leukemia Leukemia Relevant Esoteric Tests SKU: PBL-BCE-LE SKU: BMA-VPC-LE ABL1 (21) \$2,750.00 \$600.00 ATM (21) CDKN2A (21) **CEBPA** (21) FLT3 (21) Peripheral Blood | Buffy Coat | Leukemia Peripheral Blood | B Cells, CD19 | NPM1 (21) Leukemia NRAS (21) SKU: PBL-BUF-LE SKU: PBL-CD19-LE TP53 (21) \$50.00 \$500.00 Relevant Cell Markers

Search Results

You've Selected:

Disease: Leukemia (X)

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Category

Products (21)

Tissue

Bone Marrow (9)

Peripheral Blood (12)

Cell Type

B Cells CD19 (2)

B Cells Negative Selection (2)

Buffy Coat (1)

CD45 (2)

Fresh (2)

Mononuclear Cells (2)

Plasma (1)

Serum (1)

Special Processing (2)

T Cells CD3 (2)

T Cells Negative Selection (2)

Viable Plated Cells (2)

Units

0.3mL (1)

0.5 million cells (10)

0.5mL (2)

1 unit (2)

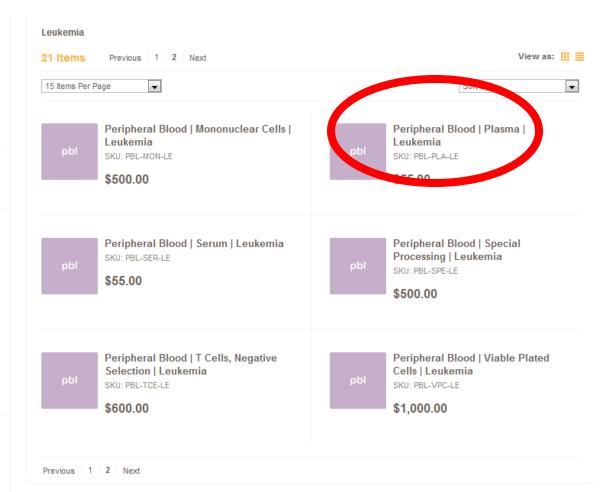
5.0 million cells (2)

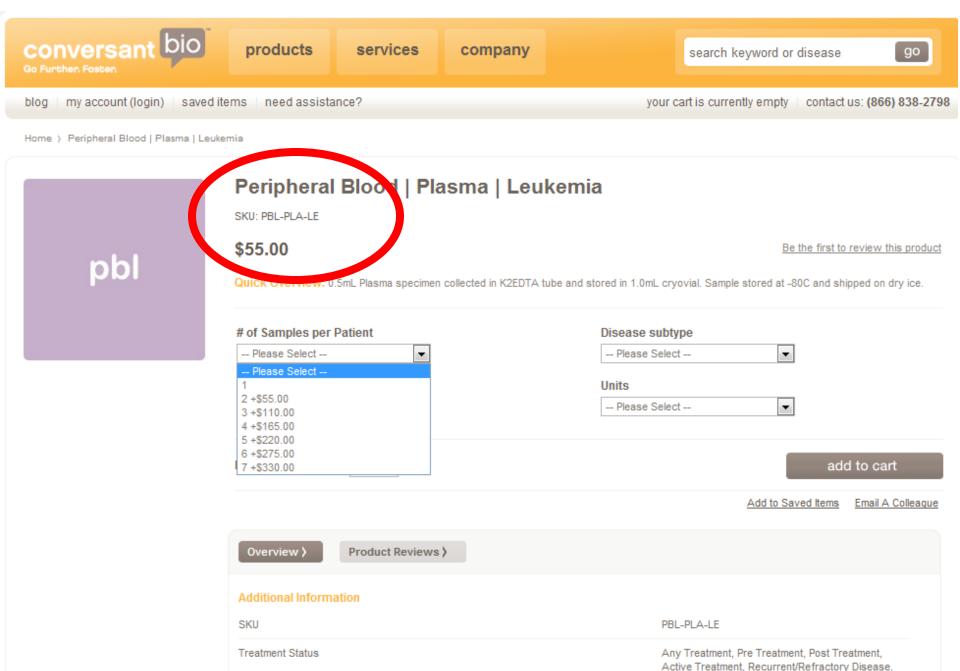
Price

\$0.00 - \$1,000.00 (17)

\$1,000.00 - \$2,000.00 (2)

\$2,000.00 - \$3,000.00 (2)





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Wound Healing

Diabetes Models

BB/W Rats

Food Intake

Goto-Kakizaki Rats

Non Obese Diabetic Mice

-1 ---

Obese Mice

Primate Diabetes

Streptozotocin Mice

Streptozotocin Rats

More...

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Ascaris Lung Allergy Cough



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toxicology

Home » Pharmacology » Diabetes and Obesity » Obese Mice

ob/ob Diabetes Model - 16 Mice

Service Description

Provider: Links Biosciences is a US company with laboratories in Hangzhou, China. The laboratory has been offering exploratory (non-GLP) pharmacology services to US and Chinese biopharma since 2004.

Background: The obese mutant mouse model was first reported by Ingalls A *et al* from the Jackson Laboratory in 1951 (Obese, a New Mutation in the House Mouse [164 KB]). The obese mouse resulted from a spontaneous mutation in a gene that was named *ob* in the V stock. Mice homozygous for the obese spontaneous mutation, (Lep^ob^; commonly referred to as *ob* or *ob/ob*), are first recognizable at about 4 weeks of age. Homozygous mutant mice gain weight rapidly and may reach three times the weight of wild-type controls. In addition to obesity, mutant mice exhibit hyperphagia, a diabetes-like syndrome of hyperglycemia, glucose intolerance, elevated plasma insulin, subfertility, impaired wound healing, and an increase in hormone production from both pituitary and adrenal glands. Friedman J *et al* reported leptin in 1994, and demonstrated that leptin, the product of the *ob* gene, was produced in white adipose tissue and served as the peripheral signal to the central nervous system of nutritional status.

Service Details: This service offers a 28 day db/db mouse model of T2DM and obesity. Customer has various options that are conveved to Links Biosciences using a Service Order Form. Customer assigns up to 16 mice to



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Validation methods are increasingly commoditized

Scroll down to browse a list of available research models for Type I and Type II diabetes, hyperglycemia, insulin resistance, diet-induced obesity and related diseases. Use the filters on the left to refine the list and then click on any listing to view technical information or to ask a question.

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BB/W Rats Food Intake Goto-Kakizaki Rats Non Obese Diabetic Mice Obese Mice Obese Primates Primate Diabetes Streptozotocin Mice Streptozotocin Rats db/db Diabetic Mice

Certifications

fa/fa Zucker Diabetic Rats

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FDA (5)

USDA (4)

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Locations

United Ctates (64)

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133 results get help

♠ Univ. of Maryland School of Medicine Obesity and Diabetes Research Center

University of Maryland School of Medicine Obesity and Diabetes Research Center focuses on research of obesity, diabetes, and aging in nonhuman primates.

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vendor info

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♠ Transgenic Rabbit Models

Transgenic Rabbit Models offers transgenic rabbit models for the study of atherosclerosis, ophtalmology, hypertrophic myopathies, diabetes, obesity, hemostasis, respiratory diseases, AIDS, and cancer.

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215-369-0965 cjacklin@assaydepot.com

♠ Ophthy-DS

Ophthy-DS offers ophthalmic model services for macular degeneration, diabetes, uveitis, and dry eye.

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♠ PharmaNess

PharmaNess offers pharmacokinetics, pharmacodynamics, formulations, behavioral assay, in vivo screening, ex vivo screening, microscopy, stereology and histology staining services.

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Search PubMed

Search PubMed for "Diabetes and Obesity" using BioWizard.

Selected Vendors

♠ Wisconsin National Primate Research Center

Wisconsin National Primate Research Center focuses on research of regenerative medicine, reproduction, immunology, virology, aging, and metabolic diseases.

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Diabetes and Obesity

BB/W Rats Food Intake Goto-Kakizaki Rats Non Obese Diabetic Mice Obese Mice Obese Primates Primate Diabetes Streptozotocin Mice Streptozotocin Rats db/db Diabetic Mice

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fa/fa Zucker Diabetic Rats

GLP (48) AAALAC (28) GMP (20) ISO 9001 (7) GCP (7) FDA (5)

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n Univ. of Maryland School of Medicine **Obesity and Diabetes Research Center**

University of Maryland School of Medicine Obesity and Diabetes Research Center focuses on research of obesity, diabetes, and aging in nonhuman primates.

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Search PubMed

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Selected Vendors

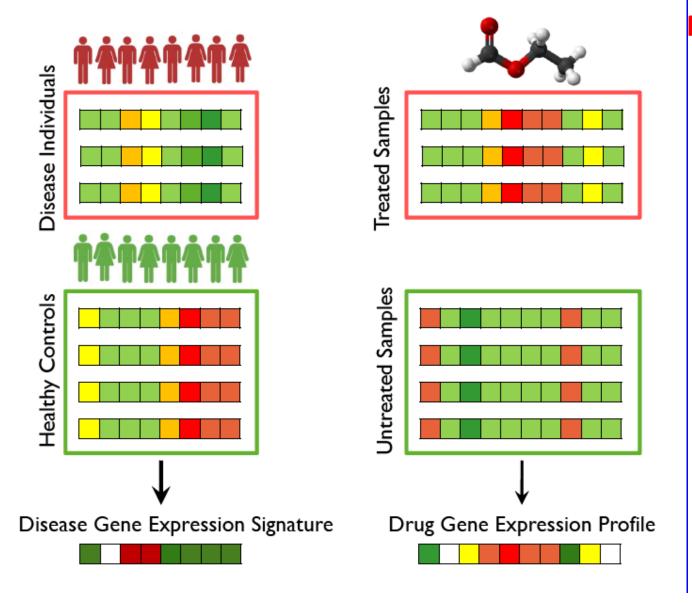
Misconsin National Primate Research Center

Wisconsin National Primate Research Center focuses on research of regenerative medicine, reproduction, immunology, virology, aging, and metabolic diseases.

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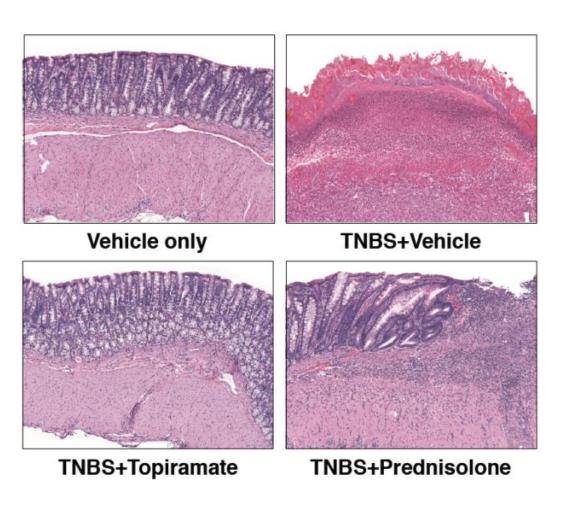
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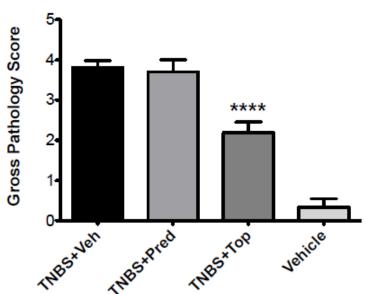


Marina Sirota Joel Dudley

Lamb J, ..., Golub TR. Science, 2006. Sirota M, Dudley JT, ..., Sweet-Cordero A, Sage J, Butte AJ. Science Translational Medicine, 2011.

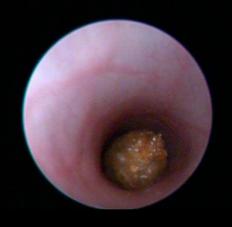
Anti-seizure drug works against a rat model of inflammatory bowel disease





Marina Sirota
Joel Dudley
Mohan M Shenoy
Jay Pasricha

Anti-seizure drug works against a rat model of inflammatory bowel disease





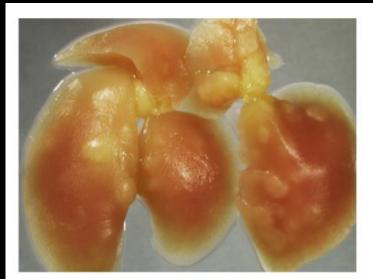


Rat colonoscopy

Rat with Inflammatory Bowel Disease

Inflammatory
Bowel Disease
After
Anti-seizure Drug

Drug X Shows Significant Activity Against Small Cell Lung Cancer





p53/Rb/p130 triple knockout model of SCLC





Mice dosed after tumor formation

Joel Dudley Nadine Jahchan Julien Sage Alejandro Sweet-Cordero

Vehicle control

Drug X

NuMedii

We are used to kids starting computer, mobile, and Internet companies in garages and dorm rooms...

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Maybe kids today need to start "garage pharma companies" and "dorm room biotechs"?



Take Home Points



 Big Data is out there: molecular, clinical, individual, epidemiological.
 Deciding what to do is the hard (and fun) part.



 We can use big data to understand why diseases occur and what we can do about treating them.



 We need new scientists (even kids) to ask questions of big data, not just tool builders.

Lessons Learned on the Way

- We are only as junior as we want to be
- Train as much as you can afford
- Set the level of your peers as high as you can
- You determine your future, not NIH
- Enable yourself first, and the world will be enabled
 - What are you going to do with the tools you build?
- Innovate beyond your university
- There is no difference between launching a startup and launching a lab
 - Writing a grant = writing a business plan
 - Convince folks with money to give some to you, to change the world
 - Impact doesn't end at a publication
- Shoot for changing the world

Collaborators

- Jeff Wiser, Patrick Dunn, Mike Atassi / Northrop Grumman
- Ashley Xia and Quan Chen / NIAID
- Takashi Kadowaki, Momoko Horikoshi, Kazuo Hara, Hiroshi Ohtsu / U Tokyo
- Kyoko Toda, Satoru Yamada, Junichiro Irie / Kitasato Univ and Hospital
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- Mark Davis, C. Garrison Fathman / Immunology
- Russ Altman, Steve Quake / Bioengineering
- Euan Ashley, Joseph Wu, Tom Quertermous / Cardiology
- Mike Snyder, Carlos Bustamante, Anne Brunet / Genetics
- Jay Pasricha / Gastroenterology
- Rob Tibshirani, Brad Efron / Statistics
- Hannah Valantine, Kiran Khush/ Cardiology
- Ken Weinberg / Pediatric Stem Cell Therapeutics
- Mark Musen, Nigam Shah / National Center for Biomedical Ontology
- Minnie Sarwal / Nephrology
- David Miklos / Oncology



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