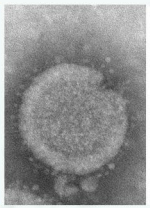
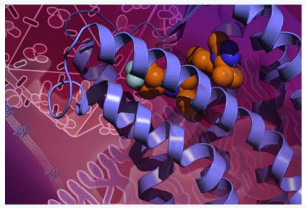
THE SCRIPPS RESEARCH INSTITUTE

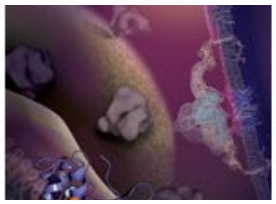

Vaccine and Global Health Initiative at The Scripps Research Institute

An Interconnected World

In today's interconnected world, people can travel from one continent to another in one plane trip—and, with them, so can a myriad of viruses and bacteria that are responsible for major human diseases.

At the same time, these organisms are constantly mutating, greatly complicating efforts to counteract them.

This scenario makes the need for new defenses against these diseases all the more pressing. Vaccines in particular continue to hold huge promise for protecting humans against current and emerging threats.



The Flu – An Unpredictable Opponent

- Influenza, or flu, is a viral infection familiar to most people, with symptoms that include coughing, sore throat, runny nose, muscle aches, fatigue and fever.
- While the flu can be relatively mild, it can also be deadly—especially for the elderly, infants and people with some chronic diseases. On average, influenza results in 3,000 to 49,000 deaths per year in the US.
- Experts estimate that the overall cost of influenza to the American economy exceeds $87 billion during an average flu season.
- Averages, however, don't represent the full threat of the flu, as the virus also harbors the potential for causing global pandemics such as the four that have struck in the last 100 years. During 1918-19, 20 to 40% of the worldwide population became ill and an estimated 50 million people died.
- While flu vaccines exist, they only protect against the strains most common in a single season, so vaccines must be re-administered every year.
- Flu vaccines tend to be less effective when given to people over about 60 years of age. Ideally, a flu vaccine would be given to infants and would last a lifetime.

HIV/AIDS – A Global Scourge

- AIDS (acquired immune deficiency syndrome), caused by HIV (human immunodeficiency virus), first exploded as a public health threat in the 1980s, when a mysterious and deadly disease was noticed spreading among gay men.
- Later, the culprit was identified as HIV, a virus that impairs immune cells crucial to the body's ability to fight disease.
- Each year, some 50,000 people in the US are newly infected with HIV through contact with bodily fluids, usually via unprotected sex, sharing of needles, transfusion, or mother-to-infant transmission. An estimated 1.1 million people in the US and 34 million worldwide currently live with HIV.
- Regimens of antiretroviral drugs now enable many patients to manage HIV as a chronic disease. However, in addition to undesirable side effects, regimens are typically expensive and are not be available to many in developing countries.

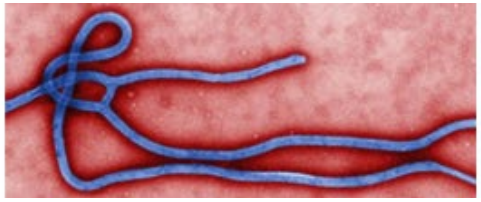
Photo by Jon Rawlinson

Hepatitis C – A Silent Killer

- Hepatitis, a general term for inflammation of the liver, can be caused by different viruses, including hepatitis A, B and C.
- Approximately 3.2 million people in the US and 170 million worldwide have chronic hepatitis C, generally thought to be the most serious hepatitis infection.
- Hepatitis C is most commonly spread through contact with infected blood, although unprotected sex and childbirth can also transmit the disease.
- Total annual healthcare costs for hepatitis C in the US have been estimated at $6.5 billion.
- While symptoms can include fatigue, nausea, fever, abdominal pain and jaundice, many people are unaware they have the disease until liver damage appears; complications include liver cancer, liver failure and permanent liver damage (cirrhosis). Viral hepatitis is the most common reason for liver transplants.
- New medications are available to treat hepatitis C and are proving very successful, but costs are likely to be high.
- While vaccines are available against hepatitis A and B, there is no vaccine against hepatitis C.

Ebola – The Deadliest of Diseases

- Ebola hemorrhagic fever, caused by the Ebola virus, is one of the most virulent diseases known to humankind.
- Ebola virus and its cousin Marburg virus are spread when people come into contact with the bodily fluids of an infected person or animal. Infection causes rapidly progressing high fever, hemorrhage and shock.
- There is no treatment aside from administering fluids; case-fatality rate can be up to 90%, depending on which strain is involved.
- Once rare, the viruses are now reemerging with increasing frequency, causing at least four outbreaks among humans in the last two years. Although the viruses are found most often in Africa, they have been unintentionally imported into the United States and Europe several times.



TB – A Threat Made Worse By Growing Drug Resistance

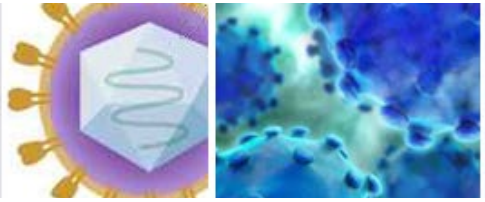
- Tuberculosis (TB), caused by the bacterium Mycobacterium tuberculosis, is a potentially fatal disease most often affecting the lungs.
- One third of the world's population is infected with TB; about 10% of these cases become active.
- In 2012, 8.6 million people fell ill with TB and 1.3 million died from the disease, making TB second only to HIV/AIDS as the greatest killer worldwide among single infectious agents.
- TB is a leading killer of people living with HIV, causing one quarter of all deaths.
- While a vaccine is available, it is not very effective; TB is usually treated with a 6- to 12-month course of antibiotics.
- Worrisome drug resistance has been observed in TB (and many other diseases); extensively drug-resistent TB has been identified in 84 countries.

The Game-Changing Potential of Vaccines

- According to the World Health Organization (WHO), current vaccines save an estimated 2.5 million lives every year.
- According to the Centers for Disease Control and Prevention, in the past two decades immunization has prevented about 20 million deaths worldwide.
- Independent experts and the WHO have shown that vaccines are far safer than therapeutic medicines.
- Research on vaccines also often points to other promising approaches to new therapies.

Issues in Vaccine Design

- An effective vaccine induces antibodies (specialized immune system molecules) against a virus prior to exposure.
- These antibodies circulate through the blood and tissues binding to viruses they encounter and preventing an infection from taking hold.
- Some viruses, however, pose special difficulties for vaccine design.
- HIV, for example, is cloaked with sugar molecules that make it difficult for antibodies to bind to the virus and thereby prevent it from entering target cells.
- Many viruses—including influenza, HIV and hepatitis C—also mutate rapidly; antibodies elicited by any vaccine must be able to sense and destroy multiple strains with different structures.

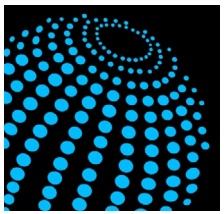


Current Research Efforts Fall Short

- Despite the huge potential of research on vaccines and other interventions to alter the course of millions of lives in the US and around the world, federal funding for basic biomedical research has been declining in real dollars.
- The research funded by the National Institutes of Health (NIH) and the National Science Foundation (NSF) tends to be incremental. What is needed to achieve scientific breakthroughs are high-risk, high-reward endeavors.
- Pharmaceutical companies rarely invest in the basic biomedical research necessary to search for breakthrough vaccines, diagnostics and therapies.

The New Initiative at TSRI Offers a Solution

- TSRI proposes an organization that enhances TSRI's world-class expertise and technology in virology, structural biology, immunology, chemistry and related fields to make the development of groundbreaking vaccines and other therapies a reality.
- The Initiative's scientists will tackle diseases that affect the health of millions around the world today and impact the course of some of the biggest health threats of tomorrow.
- The Initiative will build on current efforts at TSRI, which include:
  - Work toward an HIV vaccine, which would represent a huge leap forward in the fight against AIDS.
  - Efforts toward a "universal" flu vaccine that could ward off virtually all strains of flu and be effective for life with a single dose.
  - Endeavors to better understand viruses such as hepatitis C and Ebola to lay the foundation for new approaches to better treatment and prevention.
  - Progress against multidrug-resistant organisms, including TB.



Why TSRI?

TSRI has:

- A track record of basic discoveries translated into new therapies, including treatments for arthritis, lupus, hemophilia and cancer.
- More than 50 companies launched from TSRI discoveries.
- More than 800 patents on innovative technologies.
- 30 pharmaceuticals currently in clinical development.
- Recognition as a leader at the intersection of biology and chemistry—ranked number one in the world in chemistry, number two in microbiology (ranked by Thomson Reuters, citations per paper over a decade).
- Designation as the "top institution" in HIV/AIDS research (with Harvard), according to Thomson Reuters.

Opportunities for Synergy

TSRI has already been selected as:

- A Center for HIV/AIDS Vaccine Immunology & Immunogen Discovery (CHAVI-ID), funded by a seven-year $77 million grant from the NIH.
- A leader of three centers in the NIH Protein Structure Initiative, whose grants to TSRI total $65 million over five years.
- Home of the IAVI Neutralizing Antibody Center, supported by the International AIDS Vaccine Initiative (IAVI) and the Bill & Melinda Gates Foundation.

TSRI Scientists at the Forefront

TSRI scientists can already boast of many contributions including:

- Discovering and characterizing of antibodies that target critical sites of vulnerability on HIV, influenza and hepatitis C—antibodies capable of preventing infection by widely differing strains of these viruses in cell culture and in animal models.
- Determining the most detailed pictures yet of key surface structures on HIV, influenza, hepatitis C and Ebola viruses.
- Demonstrating that vaccines can be designed based on structural knowledge of how viral surface structures and antibodies interact, an approach central to rational vaccine design.
- Describing the mechanisms of action of important Ebola virus proteins, providing potential new targets for drugs.
- Discovering a promising new compound that attacks TB in two different ways.

Some TSRI Researchers in the Field

For faculty bios, see www.scripps.edu

- Roberto Baccala, PhD
- Dennis Burton, PhD
- Kate Carroll, PhD
- Frank Chisari, MD
- Hyeryun Choe, PhD
- Juan Carlos de la Torre, PhD
- John Elder, PhD
- Michael Farzan, PhD
- Nathalie Franc, PhD
- Kim Janda, PhD
- Corinne Lasmezas, PhD
- Mansun Law, PhD
- Richard Lerner, MD
- Vince Mauro, PhD
- Michael McHeyzer-Williams, PhD
- Kerri Mowen, PhD
- David Nemazee, PhD
- Glen Nemerow, PhD
- Michael B.A. Oldstone, MD
- James Paulson, PhD
- Vijay Reddy, PhD
- William Roush, PhD
- Erica Ollmann Saphire, PhD
- William Schief, PhD
- Anette Schneemann, PhD
- Peter Schultz, PhD
- Ryan Shenvi, PhD
- Timothy Tellinghuisen, PhD
- Luc Teyton, MD, PhD
- Susana Valente, PhD
- Andrew Ward, PhD
- Richard Wyatt, PhD
- J. Lindsay Whitton, MD, PhD
- Ian Wilson, DPhil
- Changchun Xiao, PhD
- Jiang Zhu, PhD
- Michael Zwick, PhD

A Collaborative and Focused Effort

To make progress toward high-impact vaccines, the Vaccine and Global Health Initiative at TSRI will:

- Marshal an organized and focused collaborative research effort, turning the best scientific minds loose on the problem.
- Recruit talented young investigators working in the area and support their initial efforts in research.
- Create a collaborative, interdisciplinary, synergistic environment that expands scientific thinking about vaccine development from many perspectives.
- Evaluate Initiative-funded research aggressively on an annual basis to ensure that only promising pathways are pursued.

Supporting Innovative Research

Grants

- TSRI investigators submit requests for funding for innovative research.
- Accepted projects receive funding for three years to develop new approaches that then will be competitive for National Institutes of Health/National Science Foundation funding to continue the work.

Oversight

- A scientist-director holds an endowed chair to provide administration and scientific direction.
- An internal grant committee and outside evaluators review the proposals and provide granting recommendations.
- A Scientific Advisory Board monitors the progress and research integrity of the Initiative, reviews and evaluates work in progress, and issues recommendations concerning the continuation or discontinuation of projects.

Funding

The initiative will be funded by contributions totaling $100 million.

Expenditure plan:

- $5 million – Endowed chairs for two senior investigators (including a director)
- $5 million – Upgrades to laboratories, new cutting-edge equipment
- $20 million – A ten-year term endowment to ensure resources are available to follow up on the most promising findings, for example with clinical trials
- $20 million – 10 Early Career Awards of $2 million each over two to five years to support promising scientists starting independent laboratories
- $50 million – $5 million per year over 10 years to fund high-risk, high-reward seed initiatives, chosen on the basis of merit; these studies will acquire data to lay the groundwork for future government funding

A Lasting Contribution

Contributions totaling $100 million will support world-class talent and equipment and fund innovative research projects related to vaccine design and related problems. Add to that the federal and state funding that will result from the discoveries made at TSRI due to this initiative, and this effort will change the course of world health.

Appendices

Appendix 1:
Drugs Developed from TSRI Discoveries

- **Humira®** for rheumatoid arthritis, plaque psoriasis, Crohn's disease, ulcerative colitis and other inflammatory conditions
- **Benlysta®** for lupus, a debilitating autoimmune disease
- **Leustatin®** for hairy cell leukemia, an unusual cancer of the blood
- Purification of **Factor VIII** for the bleeding disorder hemophilia
- **Vyndaqel®** for transthyretin familial amyloid polyneuropathy (TTR-FAP), a rare, progressive and fatal neurodegenerative disease
- **Surfaxin®** for infant respiratory distress syndrome, a life-threatening condition affecting pre-term infants
- **Cyramza®** for gastric and non-small cell lung cancer
- **Unituxin™** for the childhood cancer neuroblastoma

Appendix 2: Companies from TSRI Technology or Faculty

2014
- Aldabra Biosciences
- Padlock Therapeutics
- Transplant Genomics, Inc.

2013
- Blackthorn Therapeutics Inc.
- iGenomiX
- Sirenas Marine Discovery
- Zebra Biologics

2012
- Abide Therapeutics
- Cypher Genomics
- Vesper Biologics

2011
- RQx Pharmaceuticals

2010
- Ember Therapeutics
- Epic Science

2009
- Receptos Pharma
- Protix, Inc.
- Zyngenia

2008
- aTyr Pharma
- Curna
- Eyecyte, Inc.
- Fate Therapeutics
- Proteostasis Therapeutics
- Sapphire Energy

2007
- Fabrus, Inc.
- Xcovery

2006
- Affinity Pharmaceuticals
- Calmune
- Viriome LLC
- Wittycell S.A.S.

2004
- Achaogen Inc.
- Motility, Inc.
- Promosome
- Rincon Pharmaceuticals (acquired by Sapphire Energy)

2003
- Ambrx Inc.
- FoldRx Pharmaceuticals
- Prion Solutions (acquired by Chiron)

2002
- CovX Research (acquired by Pfizer)
- NanoRX (acquired by Adaptive Therapeutics)
- VAXDesign (acquired by Sanofi Pastueur)

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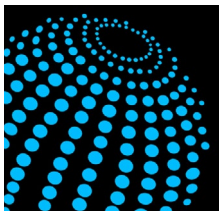


Appendix 2 - continued

2001
- Kalypsys
- Phenomix
- Syrxx (acquired by Takeda)

2000
- ActivX Biosciences (acquired by Kyorin)
- Neurome

1999
- Geneformatics (merged with Structural Bioinformatics)
- Optimer Pharmaceuticals
- Prolifaron (acquired by Alexion Pharmaceuticals)

1997
- Epicyte (acquired by Biolex Therapeutics)

1996
- Digital Gene Technologies (purchased by Neurome)
- Discovery Labs (merged with Acute Therapeutics)
- Drug Abuse Sciences
- Sangamo Biosciences

1995
- PharMore
- Thrombosys

1994
- Apovia AG (formerly EVAX Technologies, originally Immune Complex Corp.)
- Applied Molecular Evolution (formerly Lxsys; acquired by Lilly, Inc.)
- CombiChem (acquired by Dupont-Merck Pharmaceutical and merged with Bristol-Myers Squibb)

1993
- Ciphergen Biosystems (acquired by Bio-Rad Laboratories)

1992
- Sequel Therapeutics (later acquired by Cytel, which was subsequently spun-out as Epimmune)

1989
- Avanir Pharmaceuticals (formerly Lidak)
- Corvas (acquired by Dendreon Corporation)
- UNASYN

1986
- MP Biomedicals (formerly Qbiogeneand Bio101)
- NeoMPS (formerly Multiple Peptide Systems)

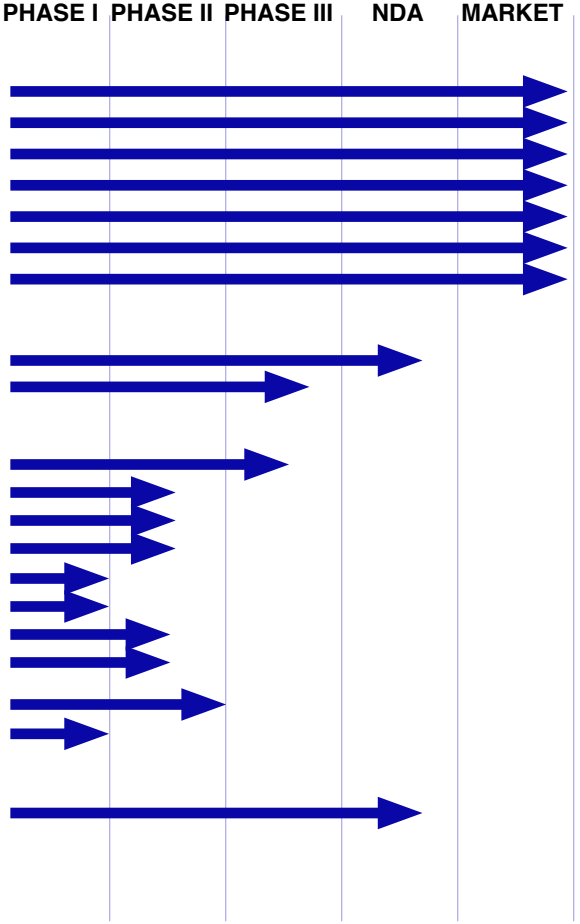
1984
- Stratagene

1982
- Synbiotics

1981
- Quidel

Appendix 3
Therapeutic Pipeline

COMPOUND	THERAPEUTIC AREA	COMPANY
MARKETED PRODUCTS		
• Humira	Autoimmune	Abbott
• Benlysta	Autoimmune	Human Genome Sciences
• Cyramza	Oncology	Lilly
• Vyndaqel	Amyloidoses	Pfizer
• Leustatin	Oncology	J&J
• Monoclate-P	Cardiovascular	Sanofi Aventis
• Surfaxin	Respiratory	Discovery Labs
• Unituxin	Oncology	United Therapies
LATE STAGE PRODUCTS		
• Solithromycin	Antibiotic	Cempra
• RPC-1063	Autoimmune	Receptos
OTHER CAT PRODUCTS		
• Tralokinumab	Respiratory	Medimmune/AstraZeneca
• CAM-3001	Inflammation	Medimmune/AstraZeneca
• Rozrolimupab	Cardiovascular	Symphogen
• GC-1008	Multiple Areas	Genzyme
• BI-505	Oncology	Bioinvent
• MT-203	Inflammation	Micromet
• Bertilimumab	Allergy	iCo Therapeutics
SANGAMO PRODUCTS		
• SB-728	HIV	Sangamo
• SB-313	Oncology	Sangamo
CLICK CHEMISTRY PRODUCTS		
• AZ-01	Autoimmune	Allozyne



Appendix 3 continued

COMPOUND	THERAPEUTIC AREA	COMPANY
AMBRYX PRODUCTS		
• ARX-201	Growth Deficiency	Ambrx
• ARX-424	Autoimmune	Ambrx
• ARX-618	Diabetes	Ambrx
• ARX-328	Lipodystrophy	Ambrx
OTHER EARLY STAGE PRODUCTS		
• IC-14	Respiratory	Implicit
• ALT-801	Oncology	Altor
• Shok-Pak	Organ Failure	InflammaGen
• RG-2833	Friedreich's Ataxia	BioMarin
• HSC-835	Oncology	Novartis
• 3K3A-APC	Cardiovascular	ZZ Biotech
• VS-4718	Oncology	Verstem
• Resokine-IV	Autoimmune	aTyr