

**Bio-Photonic Ventures
Selected Shorts**

Brown Forum for Enterprise

April, 2005

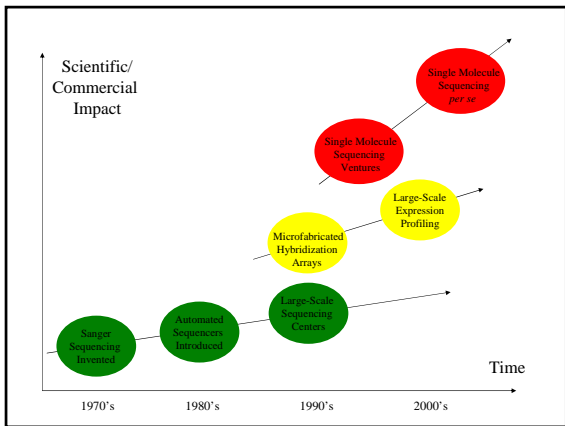
Single Molecule Sequencing Ventures

SEQ/Praelux
founded in 1987, first funded by R. F. Johnston in 1992 with \$1 mm seed funding;
initially focused on single molecule sequencing by base-at-a-time degradation
and fluorescence spectroscopy of native nucleotides

US Genomics
founded in 1997, first funded in 1999 by CB Health *et al* with ~ \$2 mm seed funding;
initially focused on single molecule sequencing based upon various schemes
described in series of patents/patent applications

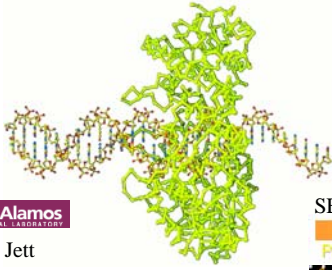
Solexa/Lynx
founded in 1998, first funded by Abingworth in 2000 with \$3.4 mm seed funding;
initially focused on single molecule sequencing by base-at-a-time synthesis
and fluorescence spectroscopy of dye-tagged nucleotides

Helicos Biosciences
founded in 2003, first funded by Flagship *et al* in 2004 with \$27 mm Series A;
initially focused on single molecule sequencing by base-at-a-time synthesis
and fluorescence spectroscopy of dye-tagged nucleotides



Single-Molecule Sequencing

- *via base-at-a-time degradation, using processive exonuclease*



Jim Jett
Dick Keller

SEQ LTD



Single-Molecule Sequencing

- *via base-at-a-time synthesis, using polymerase*



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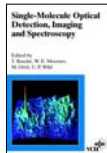



CALIFORNIA INSTITUTE OF TECHNOLOGY
CALTECH



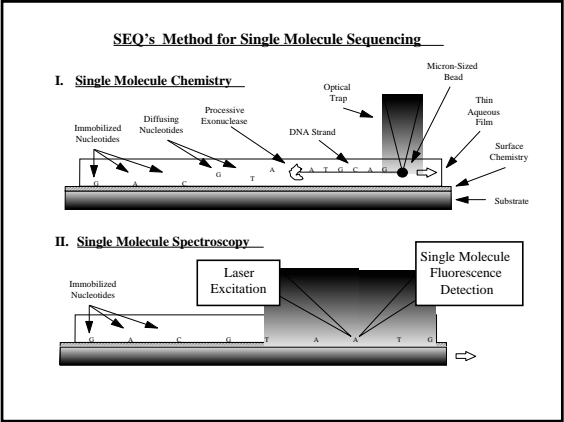
Single-Molecule Sequencing

- *in both cases, dependent upon single molecule detection*





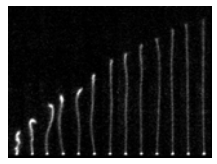


- Founded in 1987, SEQ LTD was the first dedicated genomics company; the goal was to develop a *breakthrough technology for sequencing DNA*
- Based upon inventions and ideas of Kevin M. Ulmer, Ph.D.
- Built by team of scientists led by Jay K. Trautman, Ph.D. and Timothy D. Harris, Ph.D., mostly recruited out of AT&T/Bell Labs
- Backed initially by Robert F. Johnston and funded by Allen & Company, Bristol-Myers Squibb Company, Astra-Zeneca Pharmaceuticals and the National Center for Human Genome Research (NCHGR)
- After 5 years of basic research, the Company re-directed its R&D to high performance cellular imaging, changed its name to Praelux Inc., and ultimately sold out to GE/Amersham



SEQ LTD

- Single DNA molecule manipulation
 - Steven Chu - Bell Labs; Stanford; LBNL
 - Optical Trapping
 - Nobel Prize in Physics, 1997

SEQ LTD

- Digestion of Single Molecules of DNA via processive exonuclease

Cytometry 1999 Jul 1;36(3):163-8

Single-molecule DNA digestion by lambda-exonuclease.

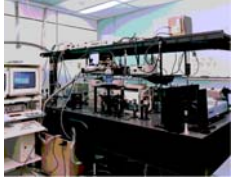
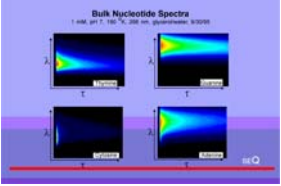

Dapprich J.

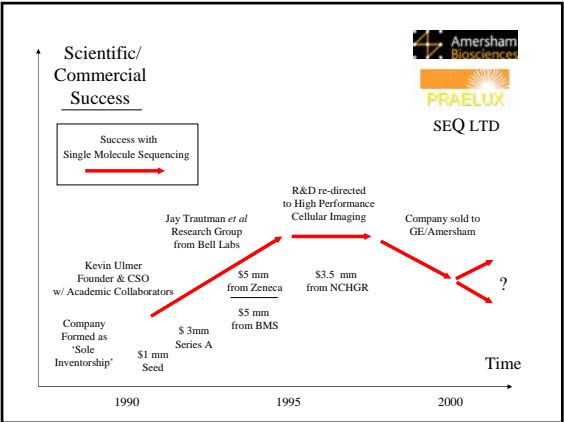
Praelux, Inc., Lawrenceville, New Jersey, USA. jdapprich@orchidbio.com


We used a bead displacement sensor to determine the enzymatic shortening of individual molecules of unstained lambda-DNA attached to optically trapped beads. The setup has been described previously (Dapprich and Nicklaus: *Bioimaging* 6:25-32, 1998) and works by observing the change in position of a trapped bead depending on its viscous drag force during motion.

SEQ LTD

- Fluorescence Detection of Native Nucleotides
 - Jay Trautman *et al* - Cornell; Bell Labs
 - Single Molecule Detection






- U.S. Genomics is pioneering tools to enable single molecule biology for the life sciences industry
- The company develops and manufactures instruments and reagents for researchers in academia, pharmaceutical and biotech companies
- The company's Trilogy™ platform is the first commercially available technology to enable the direct detection and analysis of individual molecules of DNA, RNA and proteins without the need for amplification.
- Founded in 1997 and based in Woburn, Massachusetts, U.S. Genomics has raised a total of \$50 million from HealthCare Ventures, CB Health Ventures, Still River Fund, Fidelity Biosciences Group, Zero Stage Capital and others. In addition, the company has been awarded a \$7.5 million Phase I contract by the Department of Homeland Security Advanced Research Project Agency
- Since inception, the Company has built a substantial IP position with patents and filings across a broad range of discoveries and technologies

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Issued Patents:

U.S. Patent 6,790,671 (pdf, 1.7mb)
 Optically characterizing polymers; Issued September 14, 2004

U.S. Patent 6,772,070 (pdf, 2.3mb)
 Methods of analyzing polymers using a special network of fluorophores and fluorescence resonance energy transfer; Issued August 3, 2004

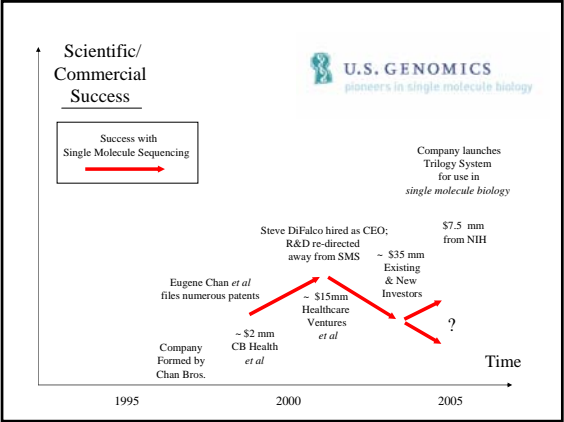
U.S. Patent 6,762,059 (pdf, 3.8mb)
 Methods and apparatuses for characterization of single polymers; Issued July 13, 2004


U.S. Patent 6,696,022 (pdf, 3.7mb)
 Methods and apparatuses for stretching polymers; Issued February 24, 2004

U.S. Patent 6,403,211 (pdf, 2.92mb)
 Methods of analyzing polymers using ordered label strategies; Issued June 11, 2002

U.S. Patent 6,355,420 (pdf, 6.9mb)
 Methods and products for analyzing polymers; Issued March 12, 2002

U.S. Patent 6,263,286 (pdf, 2.4mb)
 Methods and analysis using a spatial network of fluorophores for fluorescence energy resonance transfer; Issued July 17 2001





- Solexa is developing systems for the comprehensive and economical analysis of individual genomes
- Founded in 1998 on technology originating in the Department of Chemistry at Cambridge (UK); located outside Cambridge, England
- Backed initially by Abingworth Management, Solexa raised an aggregate of \$25 mm, prior to its merger with Lynx Therapeutics, from investors including Abingworth, Schroeders, Oxford BioScience Partners and others
- In March 2005, merged with Lynx Therapeutics to become a public company, hired John West as CEO from Applied BioSystems Inc. (ABI) and re-located headquarters to Hayward, CA

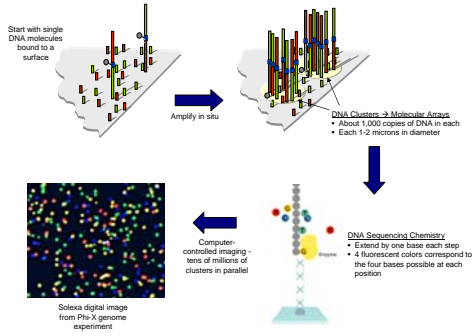
Solexa Sequencing Chemistry

- Sequencing by Synthesis (SBS)
- Reversible terminators
- Removable fluorescence
- Four-colour / four-channel strategy

DNA Sequencing Chemistry
 • Extend by one base each step
 • 4 fluorescent colors correspond to the four bases possible at each position



SBS on DNA Cluster Molecular Arrays

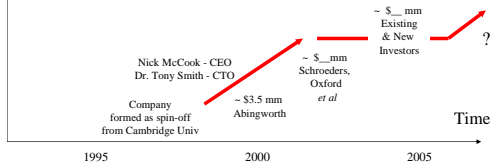



Scientific/
 Commercial
 Success

Success with
 Single Molecule Sequencing




Company merges with Lynx;
 acquires technology from Manteia
 John West hired as CEO;
 HQ re-located to Lynx in CA






CALTECH



- Founded in May 2003, Helicos BioSciences is a life-science company committed to developing instruments and reagents for the high speed sequencing of single DNA and RNA molecules
- Our technology is based on the work of Stephen Quake, PhD, as described in his paper published in the Proceedings of the National Academy of Sciences (PNAS, January 2003)



Stanley N. Lapidus, President and CEO

Mr. Lapidus is an experienced life-science entrepreneur. Helicos is his third life-science start-up.

In February 1995 he founded EXACT Sciences Corporation (NASDAQ: EXAS), an applied genomics company that develops and markets non-invasive, DNA-based methods for early detection of colorectal and other common cancers. He is currently Chairman of EXACT Sciences' Board of Directors.

Prior to EXACT, Mr. Lapidus founded Cytoc Corporation (NASDAQ:CYTC) and was President and CEO from 1987 through 1994.

In addition to his entrepreneurial activities, Mr. Lapidus holds academic appointments in the Pathology Department at Tufts University Medical School, as well as MIT's Sloan School of Management. He earned a BSEE from Cooper Union where he is also a Trustee.

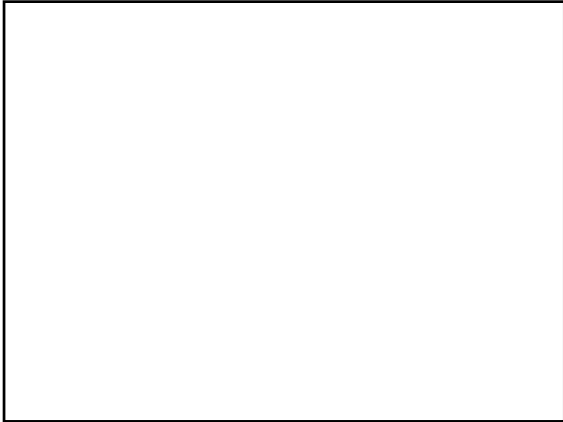
Timothy D. Harris, PhD, Director of Sequencing Technology

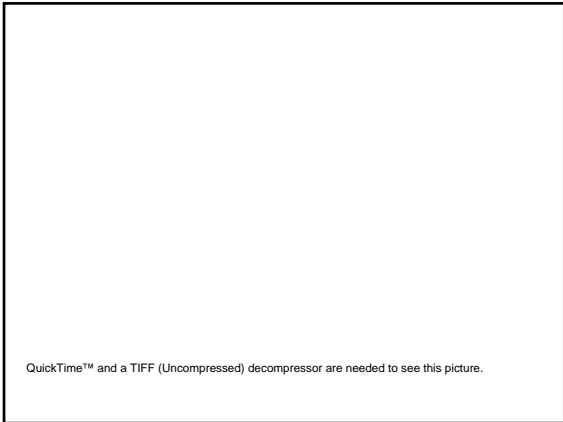
Prior to joining Helicos in January 2004, Dr. Harris was Director of Research at Praelux (formerly SEQ LTD), a wholly owned subsidiary of GE/Amersham, where his work involved single molecule DNA sequencing technology. Dr. Harris originated the design and led the development for the Amersham IN Cell Analyzer.

From 1978 to 1996, Dr. Harris worked for Bell Labs where his work led to the first report of single molecule imaging spectroscopy and lifetimes. His work resulted in more than 80 publications, 100 invited talks, the IR award in 1982 for the development of an intracavity laser spectrometer, and the 1992 Williams-Wright Award for contributions of an industrial scientist to vibrational spectroscopy.

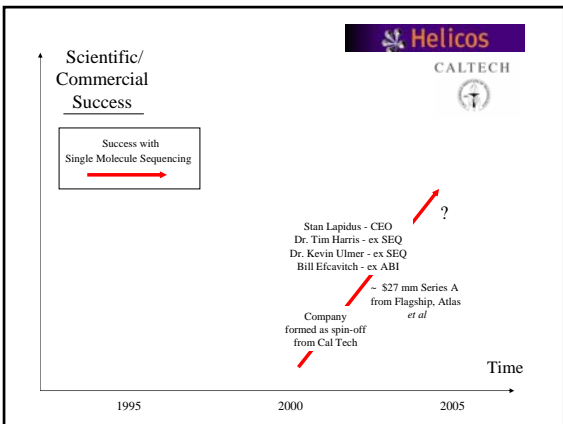
Dr. Harris received his BS in Chemistry with honors from California Polytechnic State University, and his PhD in Analytical Chemistry from Purdue University.

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Slater Technology Fund

Statement of Purpose

The Slater Technology Fund supports the development of emerging industries with potential for significant long-term growth within the State of Rhode Island.

Slater focuses its resources on the *support of entrepreneurs* who have the vision, leadership and commitment to build substantial commercial enterprises.

Slater typically invests at the inception stage in the development of a new venture, often based upon ideas and technologies originating in academic institutions and/or government research laboratories located within the region. In most cases, investments are premised upon the possibility of raising substantial follow-on financing, be it from venture capital investors or from strategic partners, the rationale being that such external funding will accelerate the process of generating a significant number of high value, high wage jobs over the intermediate to longer-term.

Slater Technology Fund

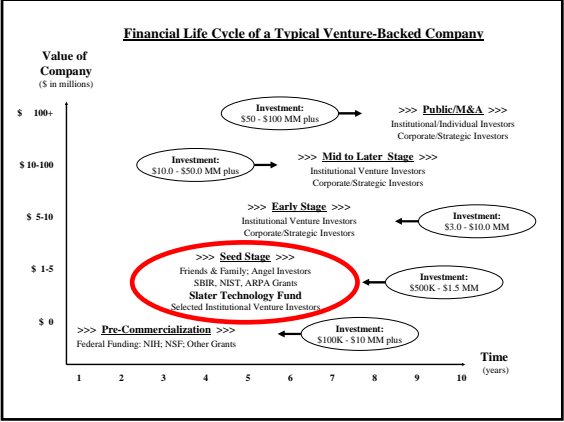
What are Slater's Objectives?

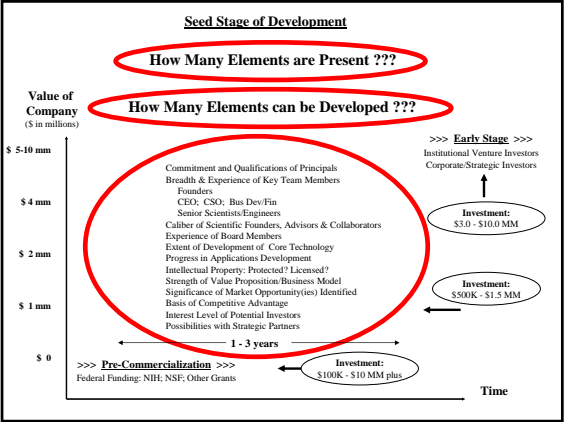
- **Mining/Direct Investment:** identifying and investing in entrepreneurs, ideas and opportunities for creating new ventures which contribute to the development of an innovation-based economy in Rhode Island
- **Mentoring/Venture Support:** working with entrepreneurs in building teams, developing business plans and raising capital to grow substantial enterprises
- **Incubator Facilities:** establishing facilities where new ventures can co-locate and achieve economies in their seed phase of development
- **Capital Formation:** developing additional sources of venture capital and corporate financing to leverage Slater's investments

Slater Technology Fund

What is Slater's Strategic Focus?

- **Sector Specific Focus:** Slater focuses on specific sectors deemed to be particularly well-suited to developing an innovation-based economy here in RI, including:
 - > Biomedical Technologies
 - > Interactive Technologies
 - > Marine & Environmental
 - > Design & Manufacturing
- **Seed Stage Investing:** Slater focuses on seed stage investment, positioned between grant support and other forms of non-profit funding on the one hand, and venture capital, private equity and corporate partnership funding on the other
- **Hybrid Return Model:** Slater aims to realize returns as measured in at least two different dimensions, including:
 - > Economic Development (industry clusters; high value jobs)
 - > Return on Investment (recovery and redeployment of capital)
- **Leveraging Other Capital:** In virtually all cases, Slater's investment is premised upon raising additional capital; in general, two different financing models are pursued, including:
 - > Venture-backed companies
 - > Private equity and/or corporate partnership-based strategies





Slater Technology Fund

Types of Direct Investment: Stages, Structures, Use of Proceeds

- Catalytic Stage:** up to \$100,000 in funding
- Inception Stage:** up to \$250,000 in funding
(of which \$100,000 may have been Catalytic)
- Fully Seed Stage:** up to \$500,000 in funding
(of which \$250,000 may have been Catalytic/Inception)

>>> investment could occur in successively-staged commitments, e.g. initially catalytic, followed by inception stage, followed by seed stage, aggregating up to \$500,000

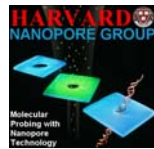
>>> alternatively, investment could occur in one-time commitments, e.g. \$100,000 catalytic, \$250,000 inception stage, or \$500,000 seed stage investment, *assuming criteria are met for respective stage of investment*

Slater Technology Fund

What is Slater Really All About ?

- *Entrepreneurship* as the strategy of choice for economic development
- Belief that *big ideas* most often *start small*
- Principle that *commitment of key people* is the foundation on which all else is built

Harvard University



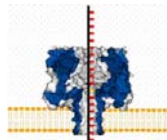
Research:

Nanopore Technology:

A novel technology for probing, and eventually sequencing, individual DNA molecules using single-channel recording techniques has been conceived.

Single molecules of DNA are drawn through a small channel or nanopore that functions as a sensitive detector. The detection schemes being developed will transduce the different chemical and physical properties of each base into a characteristic electronic signal.

Nanopore sequencing has the potential of reading very long stretches of DNA at rates exceeding 1 base per millisecond.



Molecular Biophysics: Nanopore DNA Sequencing

In this project, we seek to understand the mechanisms of electric-field driven transport of biomolecules through a nanopore, and develop solid-state and soft nanopores for single-molecule biology and physics experiments.

This work is supported by an NSF-NIRT (Nanoscale Interdisciplinary Research Team) grant.

NIRT Team: [Sean Ling \(PI\)](#), [Amit Meller](#), [David Nelson](#), [Joanne Yeh](#), and no-cost participant [Cees Dekker](#).
