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DNA Microarrays: Past, Present and Future

P. D. Hoeprich

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Ventura, CA, United States
January 14, 2007 through January 19, 2007

Chemical & Biological Terrorism Defense

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Integrating Biodefense, Homeland Security and Basic Science

Gordon Research Conference
January 14-19, 2007

DNA Microarrays: Past, Present & Future

Dr. Paul D. Hoeprich, Jr.

Lawrence Livermore National Laboratory

code UCRL

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This evening's outline:

Short Introduction	**P. Hoeprich**
Advances in Maskless Microarray Technology	**T. Albert**
Translating Pathogen's Genome Information into Microarray Tools For Discovery and Diagnostics in Biodefense	**L. Brizuela**
Multi-pathogen Detection Using High-density Oligonucleotide Arrays	**G. Kennedy**
Appraoches to Field-based Pan-pathogen Detection with Array Technologies and Electrochemical Detection	**A. McShea**

The Past or "in the Beginning…"

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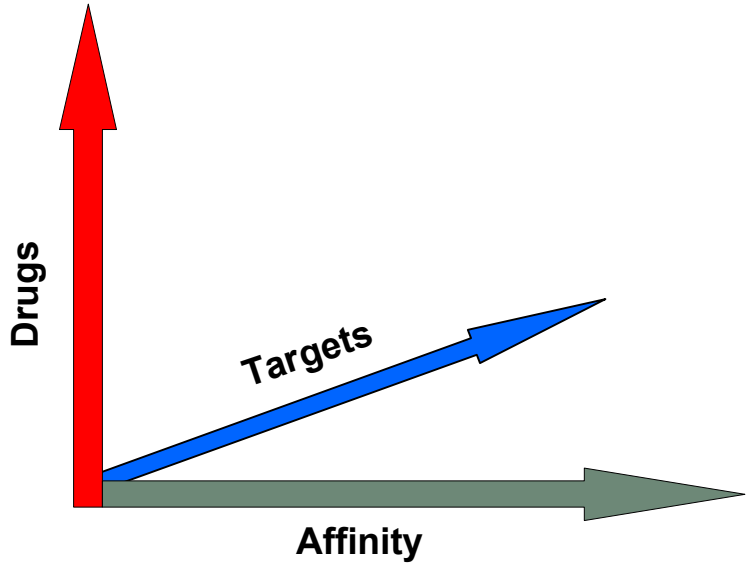
Affymax NV, 1988 → A. Zaffaroni, P. Schultz, M. Pirrung, L. Read, L. Stryer

"Affinity Matrix" concept – circa 1988



Affymax NV → Integrated Solutions

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Parallel Processing

Simultaneous processing of multiple compounds, samples or data in the workflow of Drug Discovery

For example:

- Peptides → all possible pentapeptides = $5^{18} = 3.8 \times 10^{12}$!!
  → 8 amino acids = $5^8 = 390{,}625$ ← **that's possible**

- DNA → only 4 bases!

All possible 25mers = $25^4 = 390{,}625$!!
All possible 40mers = $40^4 = 2{,}560{,}000$

Bill Dower

code

OK, the numbers make sense – but how?

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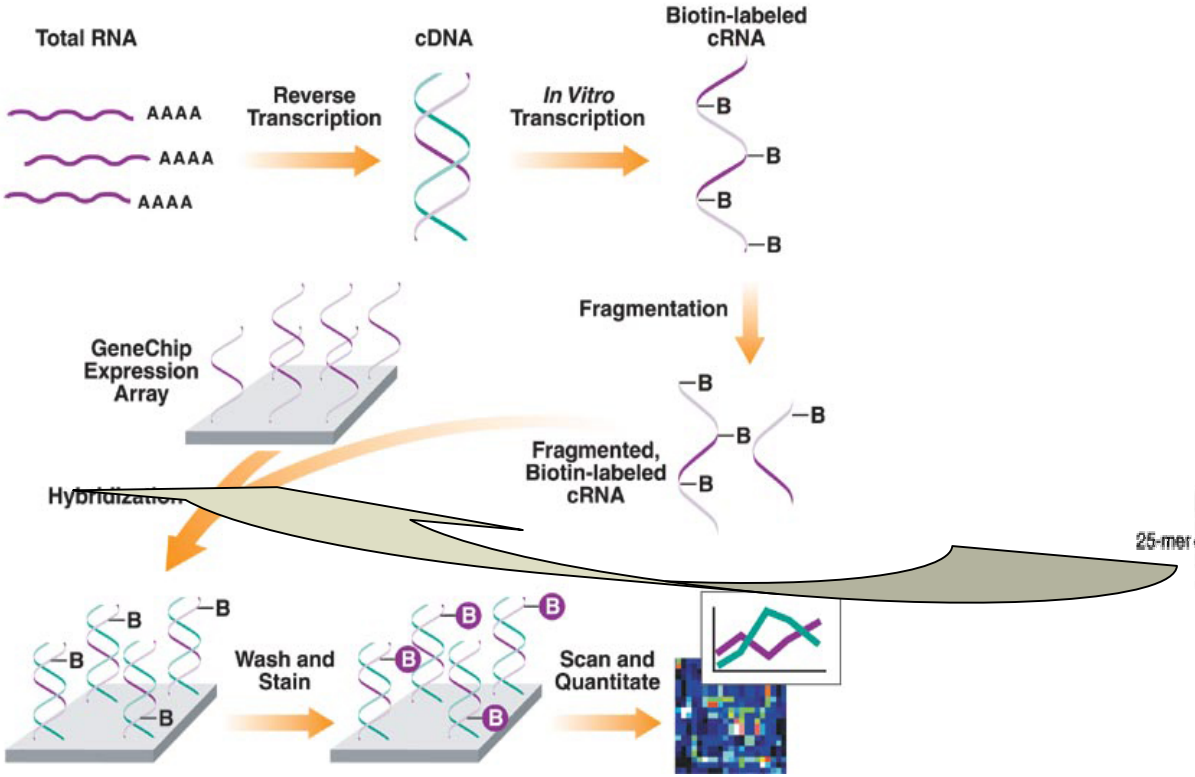
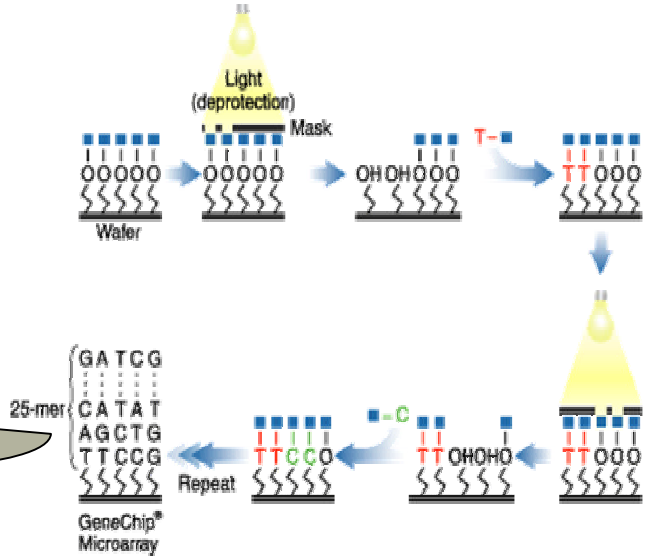
Answer – Hey, we're in Silicon Valley – VLSI

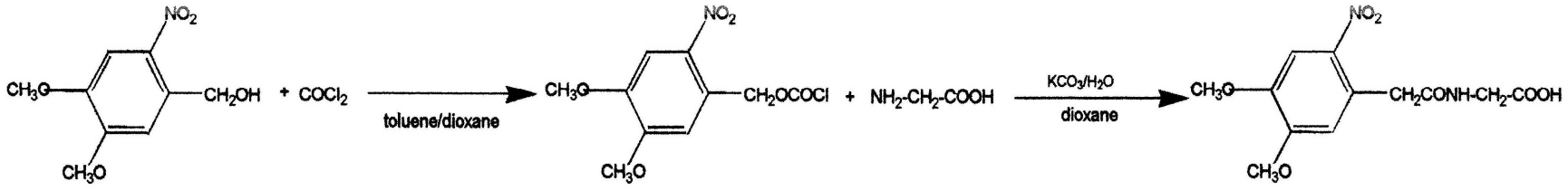
Very **L**arge **S**cale **I**ntegration →**V**ery **L**arge **S**cale **I**mmobilized **P**olymer **S**ynthesis **(VLSIPS)**



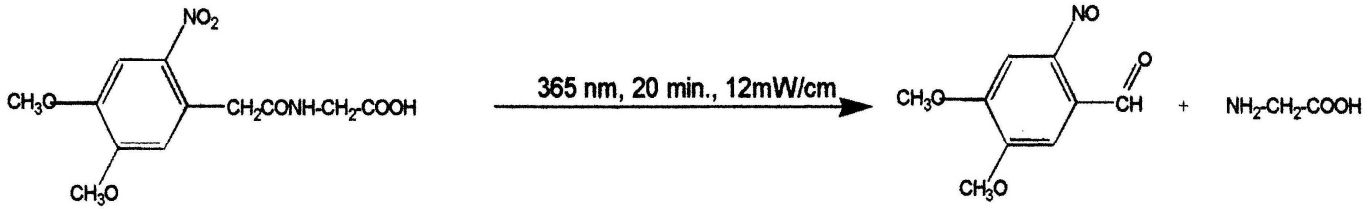


Photoresist??

NVOC Chemistry



6-nitroveratryl alcohol phosgene carbonyl chloride glycine NVOC-glycine



NVOC-glycine nitroso-aldehyde glycine

Original Ideas and Early Thoughts

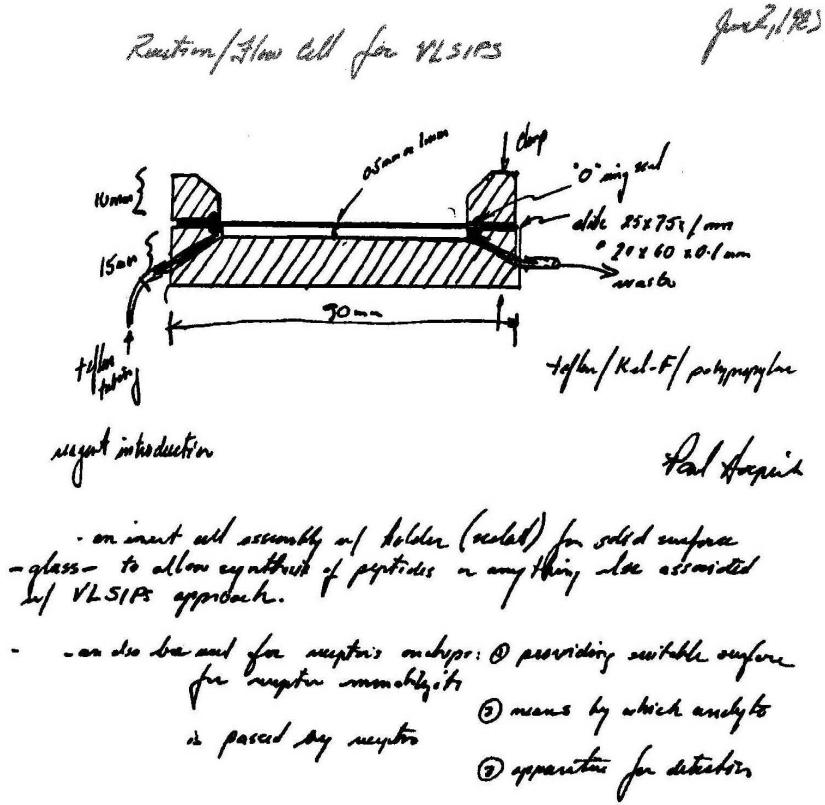


Figure 27. Original sketch, dated June 2, 1989, made by Paul Hoeprich of the flow through reactor used in the Affymax photolithographic method.

Some early ideas – we were young and excited!!

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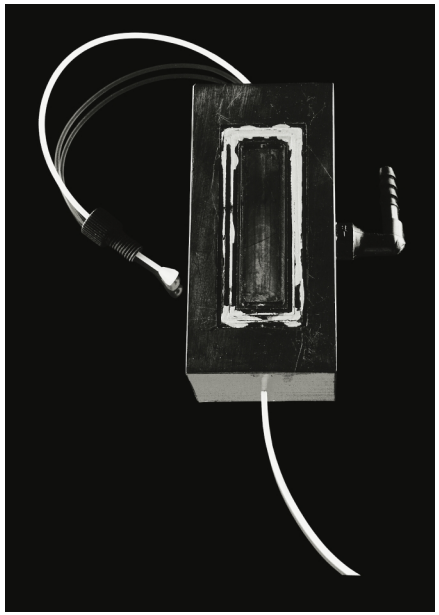
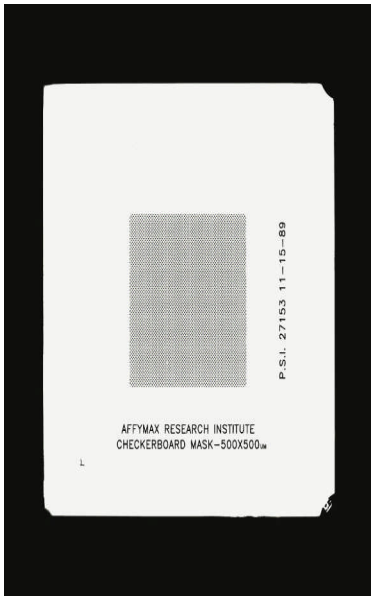
Parallel Processing

Simultaneous processing of multiple compounds, create workflow for Drug Discovery





Obligatory Intellectual Property

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US006506558B1

(12) **United States Patent**
Fodor et al.

(10) Patent No.: **US 6,506,558 B1**
(45) Date of Patent: ***Jan. 14, 2003**

(54) **VERY LARGE SCALE IMMOBILIZED POLYMER SYNTHESIS**

(75) Inventors: **Stephen P. A. Fodor**, Palo Alto, CA (US); **Lubert Stryer**, Stanford, CA (US); **Michael C. Pirrung**, Mesquite, TX (US); **J. Leighton Read**, Palo Alto, CA (US); **Paul D. Hoeprich, Jr.**, Danville, CA (US)

(73) Assignee: **Affymetrix Inc.**, Santa Clara, CA (US)

(*) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **08/563,759**

(22) Filed: **Nov. 29, 1995**

Related U.S. Application Data

(63) Continuation of application No. 08/348,471, filed on Nov. 30, 1994, which is a continuation of application No. 07/805,727, filed on Dec. 6, 1991, now Pat. No. 5,424,186, which is a continuation-in-part of application No. 07/624,120, filed on Dec. 6, 1990, now abandoned, which is a continuation-in-part of application No. 07/492,462, filed on Mar. 7, 1990, now Pat. No. 5,143,854.

(51) **Int. Cl.**[7] **C12Q 1/68**; A61K 38/00; C07H 21/00

(52) **U.S. Cl.** **435/6**; 435/7.2; 435/DIG. 1; 435/DIG. 35; 435/DIG. 37; 435/DIG. 46; 435/DIG. 49; 530/334; 536/25.3

(58) **Field of Search** ..... 435/28, 7.2, 6, 435/5, DIG. 1, DIG. 34, DIG. 35, DIG. 37, DIG. 46, DIG. 49; 436/518, 5.3; 530/334; 536/23.1, 25.3, 25.31

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"A Sequencing Reality Check," *Science*, 242:1245 (1988).
"Affymax raises $25 million to develop high–speed drug discovery system," *Biotechnology News*, 10(3):7–8 (1990).
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Adams et al., "Photolabile Chelators That "Cage" Calcium with Improved Speed of Release and Pre–Photolysis Affinity," *J. Gen. Physiol.*, p. 9a (12/86).
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Primary Examiner—Padmashri Ponnaluri
(74) *Attorney, Agent, or Firm*—Townsend and Townsend and Crew LLP

(57) **ABSTRACT**

A synthetic strategy for the creation of large scale chemical diversity. Solid-phase chemistry, photolabile protecting groups, and photolithography are used to achieve light-directed spatially-addressable parallel chemical synthesis. Binary masking techniques are utilized in one embodiment. A reactor system, photoremovable protecting groups, and improved data collection and handling techniques are also disclosed. A technique for screening linker molecules is also provided.

9 Claims, 42 Drawing Sheets

So, what have we become?

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Applied Biosystems

AFFYMETRIX

NimbleGen SYSTEMS, INC.

Agilent Technologies

COMBIMATRIX

illumina making sense out of life

febit biotech gmbh
Innovative Microarray Technologies
GENIOM – The Instrument !

CLONDIAG chip technologies

ect

…and many more.

Finally, where to now St. Peter?

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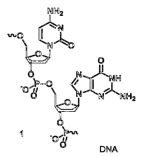
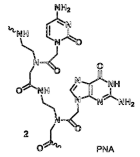
- **New polymers**

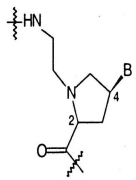


deoxyribose phosphate



N-(2-aminoethyl) glycine

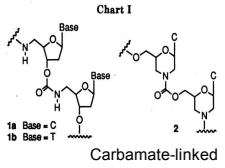
Egholm et al. 1992
JACS **114**, 1895



Aminoethylprolyl – (aep)

*aep*PNA (2*S*/*R*,4*S*)
B = A,G,C,T

Ganesh et al. 2001
Org. Letters **3**,1281



Carbamate-linked

Weller et al. 1991
J. Org. Chem **56**, 6000

- **New substrates**
  - **Glass to plastics?** **Cyclo-olefin Co-polymers (COP)**

  - **CNT mesh/networks**

- **Higher numbers & smaller features?**

- **2,000,000 probes?**
- **<1 um^2 feature size?**
- **Scanning/Scanners?**

That's a Wrap, folks!

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"So long and thanks for all the fish."

- Douglas Adams

Questions/Discussion

Who is John Galt?

code