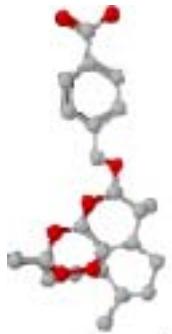
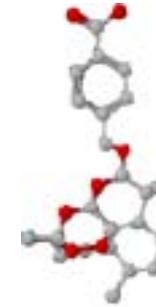
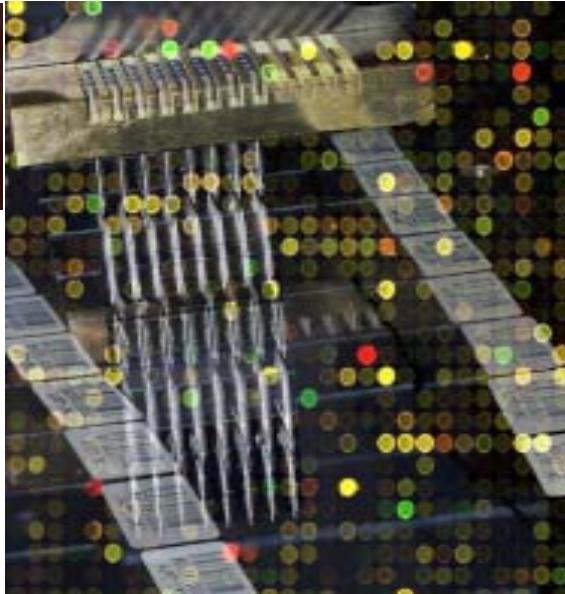


# WRAIR Antimalarial Drug Discovery and Development Program



*Major Karen M. Kopydlowski, Ph.D.*

*Department of Parasitology*

*Division of Experimental Therapeutics, WRAIR*



# *P. falciparum* Genome Sequencing Project

## I. *P. falciparum* Sequencing Project

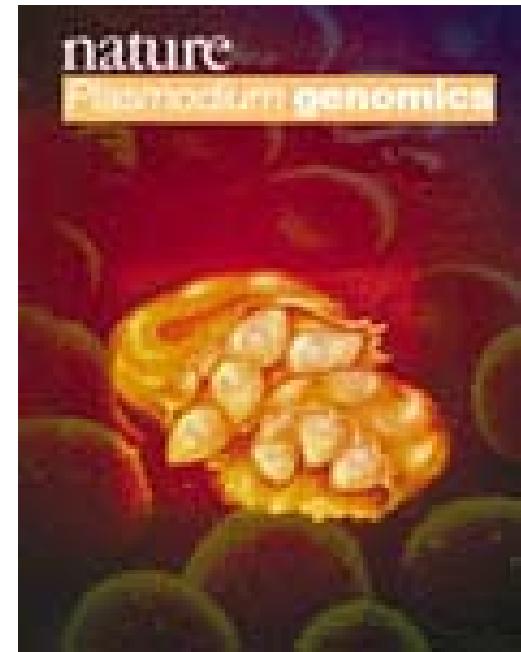
- Sequencing Centers: TIGR, Sanger, Stanford
- Published *Nature* October 2002, Vol. 419

## II. *P. falciparum* 3D7 genome:

- 14 chromosomes (23 MB)
- 80% A-T Rich

## III. We have the sequence...now what?

- Gene prediction (estimate 5,268)
- Bioinformatic tools only identified potential functionality for 40%  
∴ 60% UNKNOWN



# **Application of Microarrays for Antimalarial Drug Discovery and Development**

- I. Identify and validate new drug targets**
- II. Delineate mechanism of action and “off target” effects of current and newly developed antimalarial compounds**
- III. Elucidate mechanisms of resistance to antimalarial compounds**
- IV. Identify Predictive Patterns of Drug Toxicity**



# Overview of the Microarray Program

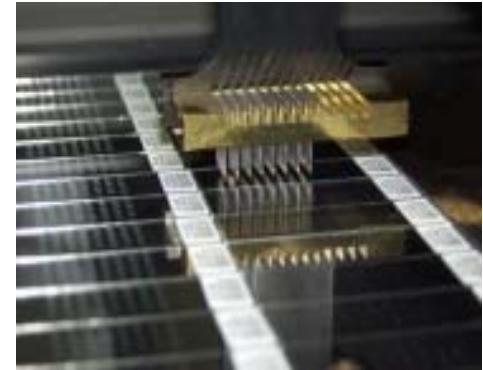
## I. *P. falciparum* Microarrays:

- Technology: spotted microarrays (oligo)
- Collaborators:
  - Dr. Sheila Peel, De Novo Array Lab, Div. Retro, WRAIR
  - 3<sup>rd</sup> Millenium, Inc. (SBIR Partner)

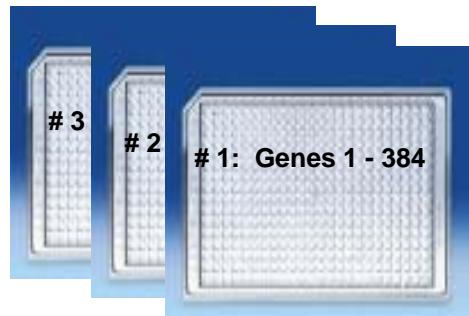


## II. Rat GeneChip: Toxicity Studies

- Technology: Rat GeneChip (Affymetrix)
- Collaborators:
  - Dr. Maryanne Vahey, Affymetrix GeneChip Facility, Div. Retro, WRAIR

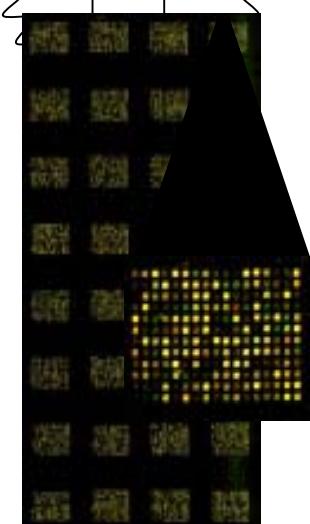
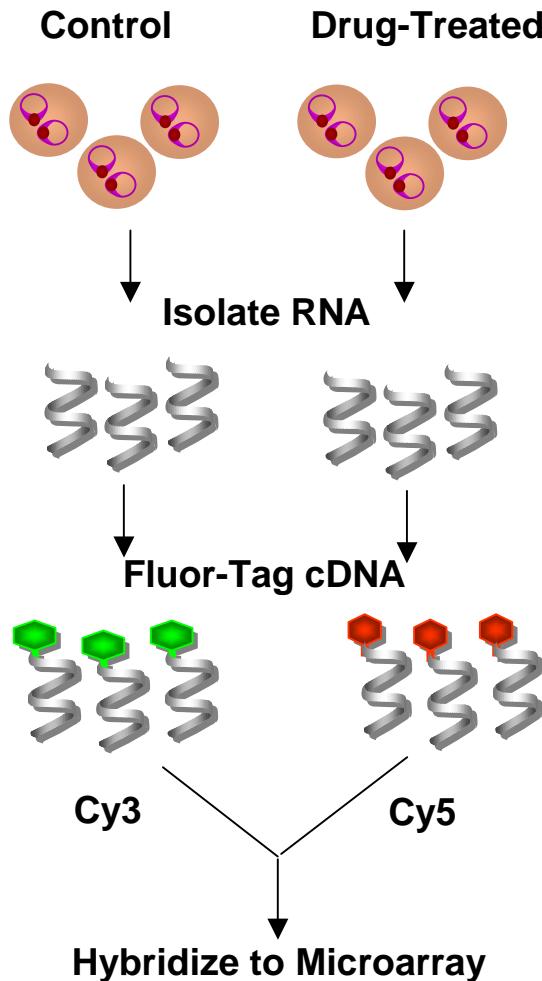
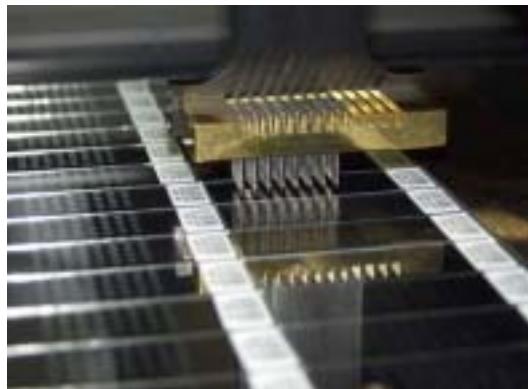


# Microarrays: Process Overview

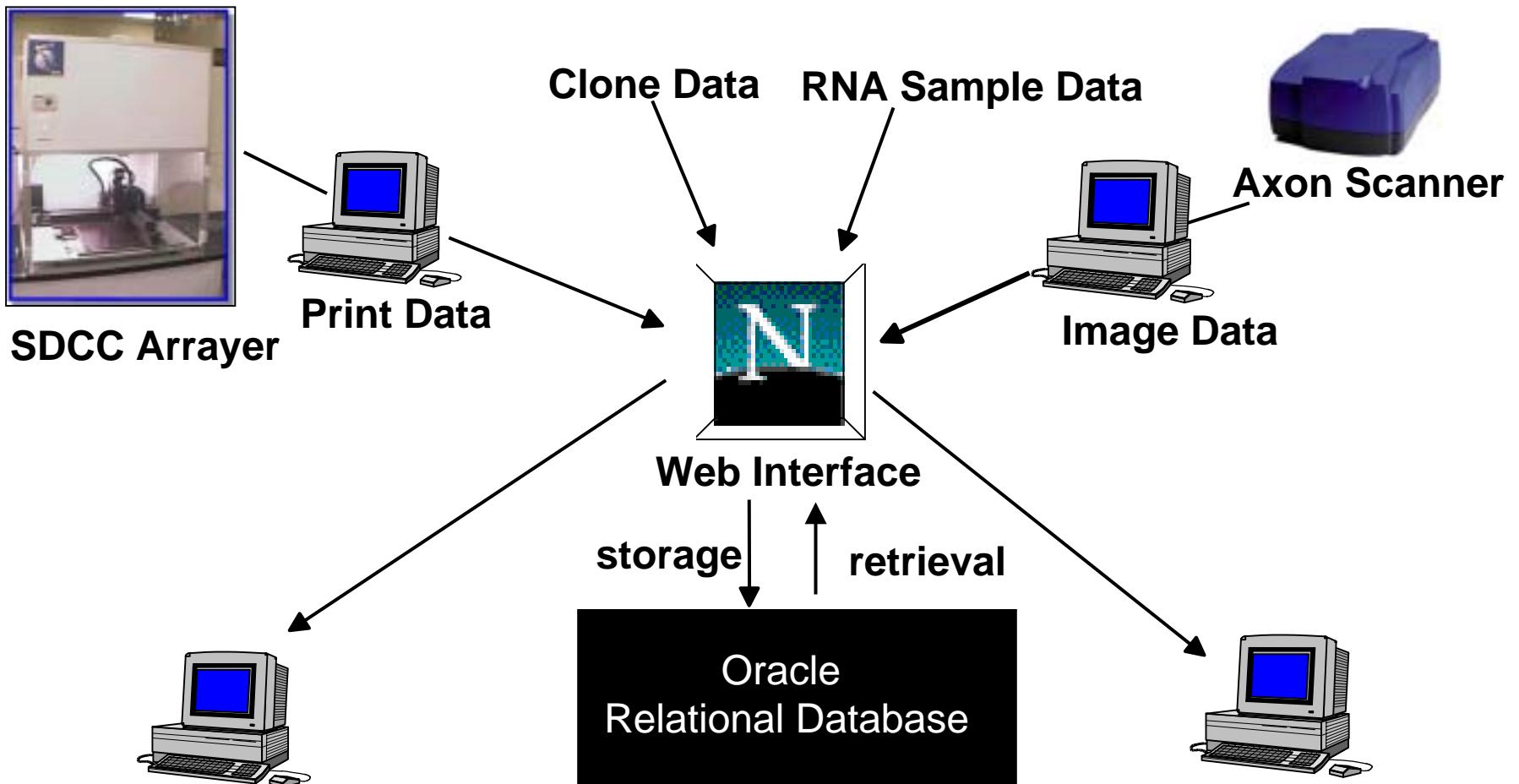


P.falciparum Oligo Library  
(6,300 70-mers)

Print DNA



# Microarray Hardware and Informatics Schema



## Image and Data Analysis

- **GenePix™**
- **GeneSpring™**
- **Partek Pro™**

## Links to external databases

- **GenbankEMBL**
- **SwissProt**
- **KEGG**

# Web-Driven Bioinformatics Platform for Microarrays

**3<sup>rd</sup> Millennium, Inc., Cambridge, MA: SBIR Partner**

- LIMS - track data generation (MIAME compliant)
- AIMS - track and manage analysis of data
  - Full repertoire of analysis tools
  - Meta-analyses across experiments
    - Search on gene expression profiles
    - Search on biological context
    - Search on gene annotation/functional groups
- Sophisticated access controls (FDA Audit Trails)
- Status:
  - Phase I: Prototype database and search engine
  - Phase II: Hardware in place for Prototype launch



# Microarray Program for Antimalarial Drug Discovery

- **Future Directions:**
  - Gene expression profiling of current antimalarials
  - Installation of relational database and bioinformatics infrastructure
  - Develop decision-making process for target selection
  - Integration of microarray data in Chemical Information System
- **Considerations**
  - Funding commitment: multi-year initiative
  - Bioinformatic support: infrastructure and personnel



# Acknowledgments

- **Division of ET, WRAIR**
  - Dr. Geoffrey Dow
  - SGT Jennifer Rotger
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  - Jill Ferlan
  - Lucia Gerena
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  - Dr. Sheila Peel
  - Alison Hege
- **Division of Retrovirology, WRAIR Affymetrix GeneChip Lab**
  - Dr. Maryanne Vahey
  - Marty Nau
- **Division of CD&I, WRAIR**
  - COL David Haynes
  - Kathy Moch
- **3<sup>rd</sup> Millenium, Inc. (SBIR partner)**
  - Dr. Jack Pollard

