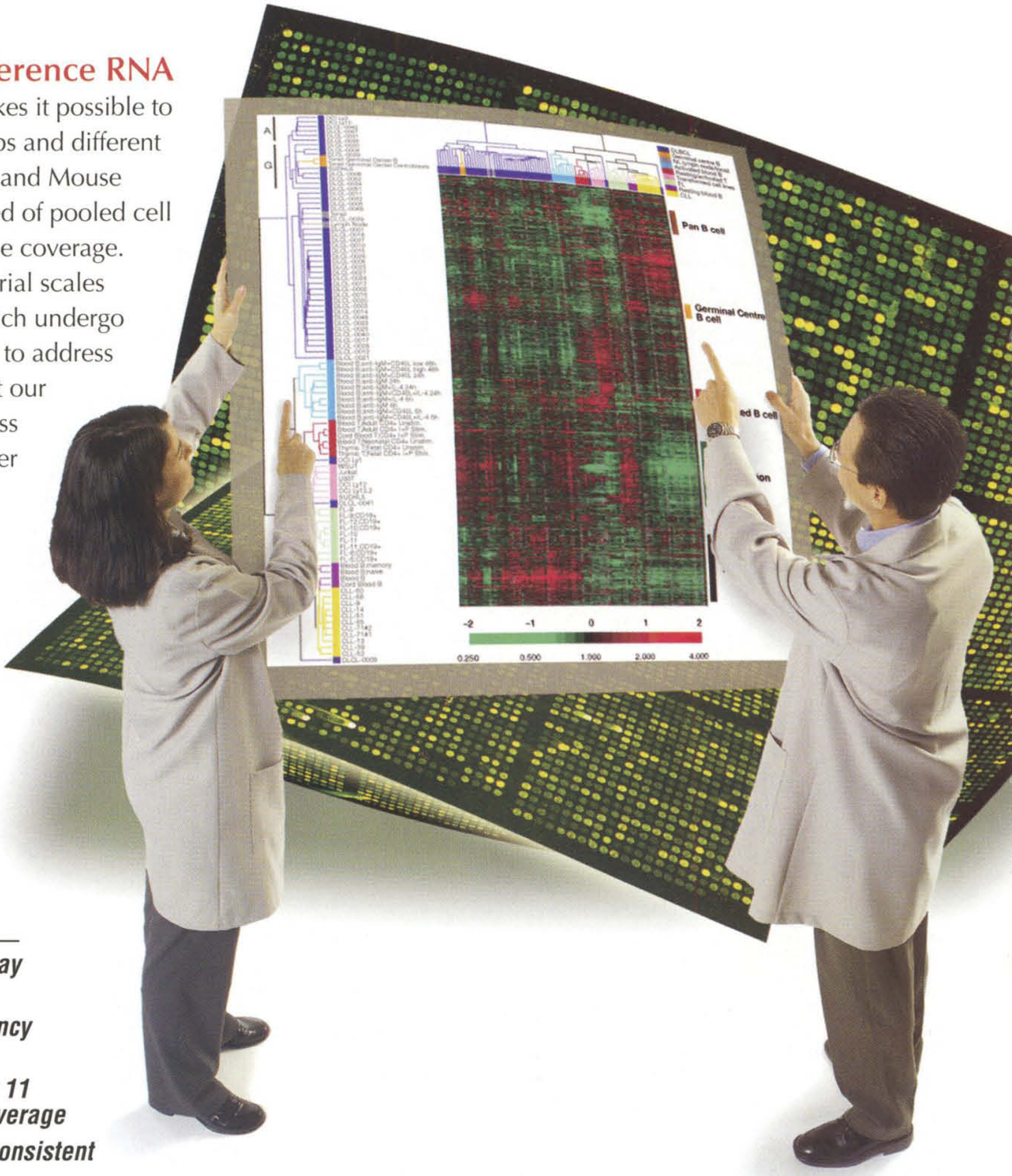
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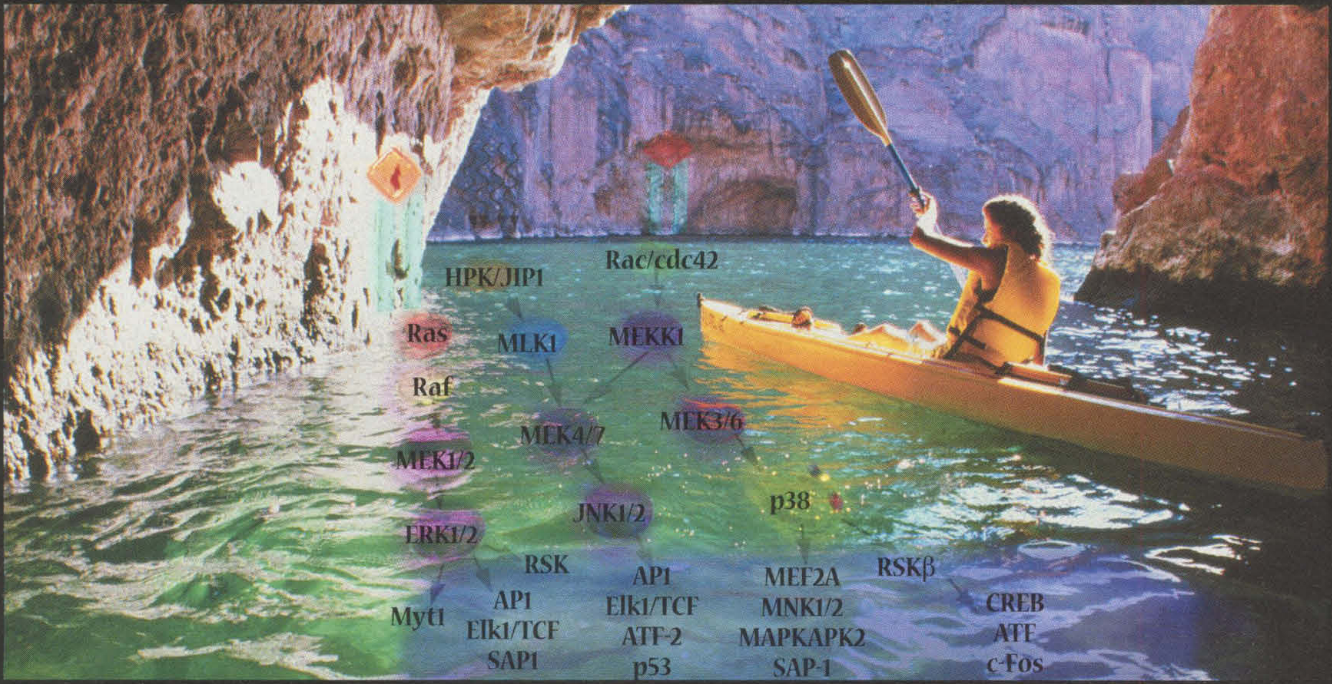

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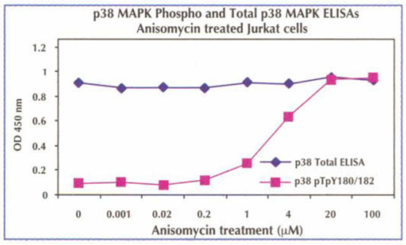
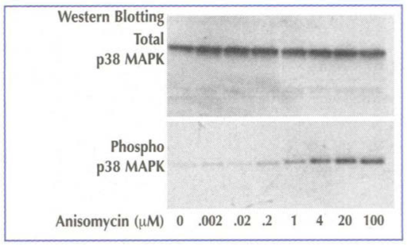


Solid Results



Cell lysates from Jurkat cells treated with various concentrations of anisomycin were tested with Total p38 MAPK ELISA (Cat.#KHO0061), phospho p38 MAPK ELISA (Cat.#KHO0071) and Western blotting. The data show excellent correlation between ELISA and Western blotting.

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Science

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Verdict in Bell Labs case **30**

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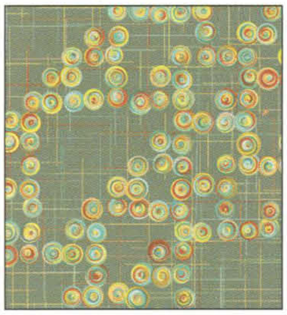

HISTORICAL ESSAY

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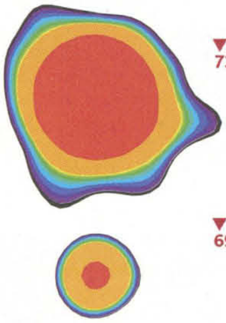

BREVIA

REPORTS

THE MOSQUITO GENOME: *ANOPHELES GAMBIAE*

VIEWPOINT

NEWS

VIEWPOINTS

The eyes of a killer. This special issue presents the complete sequence of the genome of *Anopheles gambiae*, the mosquito that is the major vector of malaria. A wall chart, Research Articles, Reports, Viewpoints, and News features present the implications of this new information for tropical medicine and arthropod research. [Image: Jim Gathany/CDC Photo Services]

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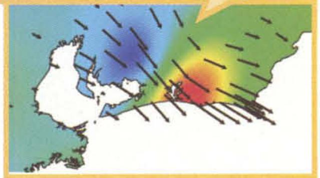
RESEARCH ARTICLES

REPORTS

See also Editorial on p. 13; News story on p. 33; Perspective on p. 74; Reports on pp. 210, 213, and 216; and Science Express *Report by Coluzzi* et al. *at www.sciencemag.org/cgi/content/abstract/1077769v1.*

New on *Science Express* **Aseismic slip rattles Japan**



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The *Anopheles* Genome. FREE. **Register at www.sciencemag.org for free access until 31 October 2002.**

CONTENT HIGHLIGHTS AS OF 4 OCTOBER 2002

science magazine www.sciencemag.org

SCIENCE EXPRESS www.sciencexpress.org

Detection and Monitoring of Ongoing Aseismic Slip in the Tokai Region, Central Japan S. Ozawa *et al.*

Aseismic slip detected about 200 kilometers south of Tokyo is changing the seismic hazards of this earthquake-prone area.

A Polytene Chromosome Analysis of the *Anopheles gambiae* Species Complex M. Coluzzi, A. Sabatini, A. della Torre, M. A. Di Deco, V. Petrarca

Analysis of chromosome inversions in the mosquito *Anopheles gambiae* links evolution to ecology in ways that will shed light on patterns of disease transmission.

53BP1, a Mediator of the DNA Damage Checkpoint B. Wang, S. Matsuoka, P. B. Carpenter, S. J. Elledge

Small interfering RNAs reveal a central role for a DNA damage checkpoint protein.

TECHNICAL COMMENTS

Early Deglaciation in the Tropical Andes

Comparing sedimentological data from lakes in the tropical Andes with records from high northern latitudes, Seltzer *et al.* (Reports, 31 May 2002, p. 1685) argued that deglaciation in the tropical Andes after the Last Glacial Maximum (LGM) preceded post-LGM warming in the Northern Hemisphere by as much as 5000 years. Clark comments that differences in the sedimentary environments of the southern and northern lakes studied by Seltzer *et al.* make comparisons between them inappropriate and that other deglaciation dates in the Northern Hemisphere show that early post-LGM deglaciation "was not unique to the tropical Andes." Seltzer *et al.*, in their response, acknowledge the differences in sedimentology between the northern and southern lake systems, but assert that additional Northern Hemisphere data support the notion that deglaciation in the tropical Andes significantly led deglaciation in northern high latitudes.

The full text of these comments can be seen at www.sciencemag.org/cgi/content/full/298/5591/7a

SPECIAL FEATURE

Science Functional Genomics

Links to online resources on the genomics of *Anopheles* and *Plasmodium* can be found at www.sciencegenomics.org/resources/res_malaria.shtml.

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science's next wave www.nextwave.org

career resources for scientists

GLOBAL: Investing in Science Edited by R. Weibl

Careers combining business acumen and scientific expertise are a big draw.

EUROPE: Filling the Swedish Recruitment Gap I. Björck

Replacing all the academics expected to retire in the next decade is going to be a challenge.

US: Career Choices—What Can You Expect from a Career Counselor? K. Sindt

Your career counselor won't write your resume or find you the perfect job. So what will they do?

UK: The Casualization of Science—A 21st Century Malaise? A. Williams

The upsurge in short-term contract research is damaging UK science.

NETHERLANDS: Transitions, Part 5—Imaginary Careers S. Oomes

A would-be entrepreneur gets by on a string of part-time careers.

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PERSPECTIVE: Setting a Trap for Aging-Related Genes in *Drosophila* J. Tower

Jumping gene zeroes in on potential biomarkers of aging.

NOTEWORTHY THIS WEEK: RAINing on the RANK Parade R. J. Davenport

Newly identified protein blocks bone destruction.

science's stke www.stke.org

signal transduction knowledge environment

PERSPECTIVE: Phosphorylation-Independent Desensitization of G Protein–Coupled Receptors? C. S. Pao and J. L. Benovic

The many possible mechanisms for GRK desensitization of GPCR signaling.

PROTOCOL: In-Gel Kinase Assay as a Method to Identify Kinase Substrates M. W. Wooten

A biochemical method to detect kinases and their substrates.

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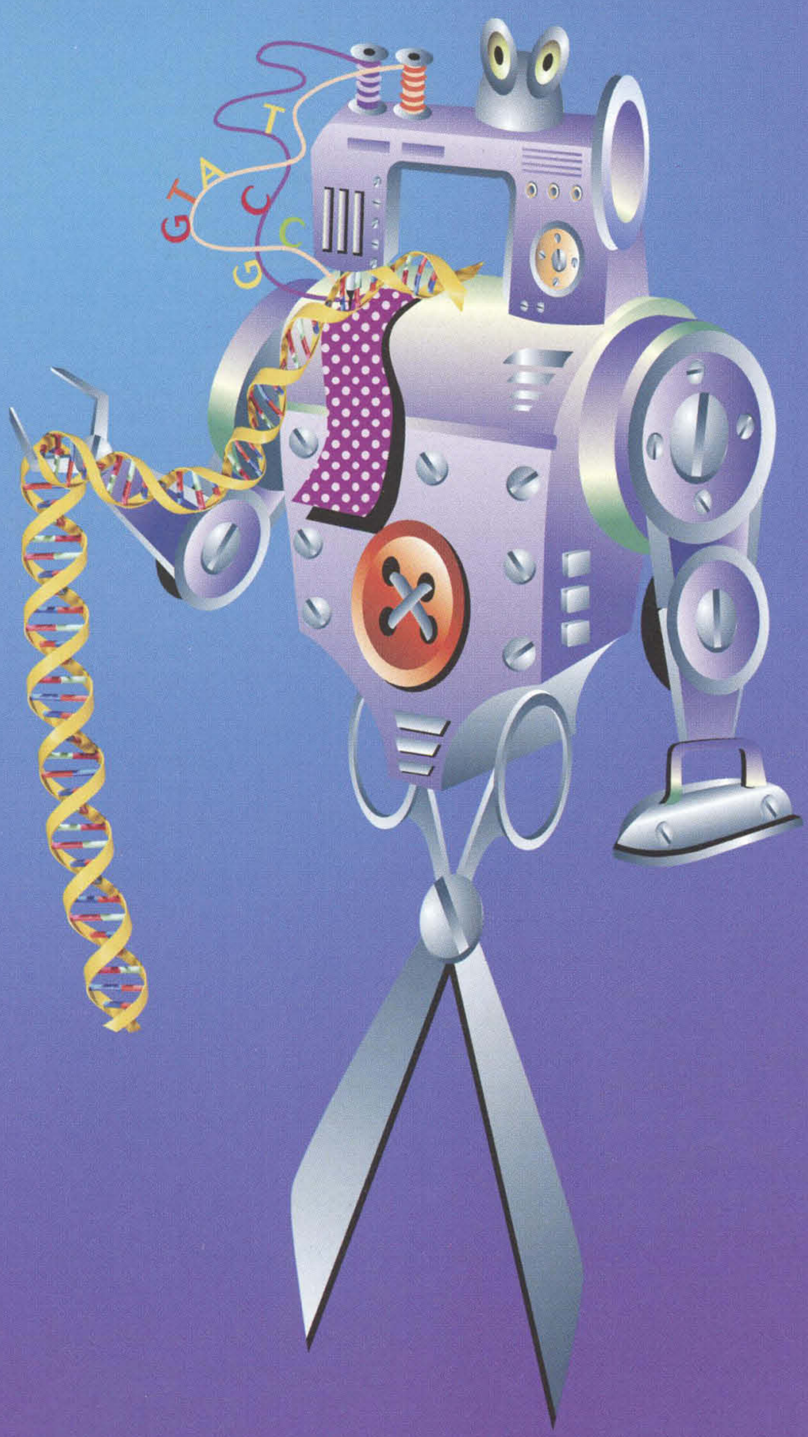

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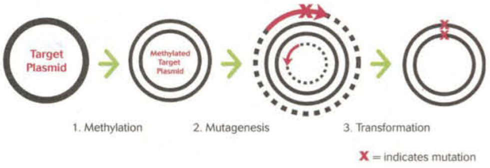

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THIS WEEK IN Science

edited by Phil Szuromi

Jets Caught in the Act

Relativistic jets of collimated plasma are produced by black holes and neutron stars. Exquisite observations of the 4-year evolution from the microquasar XTE J1550–564 synthesized by Corbel *et al.* (p. 196; see the Perspective by Rupen) show that two jets are directly related to ejecta from the black hole that was observed as an intense flare event in 1998. The knots seen in x-ray and radio wavelengths are produced by shock waves that accelerate particles to extremely high energies by synchrotron emission.

▼ 129

Genome Sequence of the *Anopheles gambiae*

The enormous worldwide death rate from malaria has prompted an international consortium to sequence the genome of the principle vector, the mosquito *Anopheles gambiae*. Holt *et al.* (p. 129) present the results of the shotgun sequencing effort, which generated a sequence of 278 megabases that represents 91% of the genome. An initial functional annotation of the identified open reading frames is presented, and the authors estimate that there are 14,000 protein-encoding transcripts for which they have multiple types of evidence. The authors also performed an expressed sequence tag analysis of genes whose expression changes after the mosquito feeds.

And in Brevia ...

A Lower Cambrian fossil (~520 million years old) described by Chen and Huang (p. 187) as a chaetognath, or arrow worm, adds to the sparse fossil record for a phylum that has survived in the oceans until the present.

Modeling Plate Motions

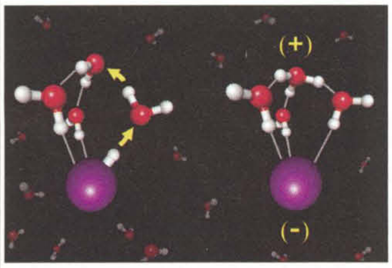
The motions of plates on Earth's surface are believed to be coupled to convection in the mantle. Conrad and Lithgow-Bertelloni (p. 207) consider two subducted slab mechanisms, slab pull in the upper mantle, where the subducted slab is attached to the plate and pulls the subducting plate faster than normal toward the subduction zone, and slab suction in the lower mantle, where the subducted slab is detached from the plate and sucks the plate toward the subduction zone by enhanced mantle flow. A plate tectonic simulation with suction and pull reproduces the observed plate tectonic motions and resolves some of the difficulties in understanding the coupling of crust to mantle.

Optical Hot Spots

Radio hot spots are concentrated regions of intense radio emission in the lobes of radio galaxies. The detailed structure of these hot spots is revealed in optical images obtained from the Very Large Telescope by Prieto *et al.* (p. 193). The bright optical emission is caused by synchrotron radiation from relativistic electrons produced by the impact of jet plasma from the galaxy with the intergalactic medium in the bow-shock region.

Polariton Condensation in a Semiconductor

Polaritons, composite particles consisting of an electron-hole pair tied to a photon mode in a cavity, have long been sought as a semiconductor-based system for the realization of Bose-Einstein condensation. In most cases, the polaritons decay before they can thermalize into the ground state. Using 12 quantum wells to ensure a sufficient supply of excitons and a high-quality cavity to tie them to photon modes with an extended lifetime, Deng *et al.* (p. 199) report on the observation of a quantum phase transition indicative of a Bose-Einstein condensed state.



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Adding Water to Acid

How many water molecules are needed to dissolve an acid such as HBr so that the separated H^+ and Br^- ions form? Pump-probe spectroscopic studies by Hurley *et al.* (p. 202; see the Perspective by Robertson and Johnson) of gas-phase HBr-water clusters of increasing size show that the transition to the ion-pair state occurs at five water molecules. In smaller clusters, the ion pair can be created through electronic excitation.

Bypassing Silicone By-Products

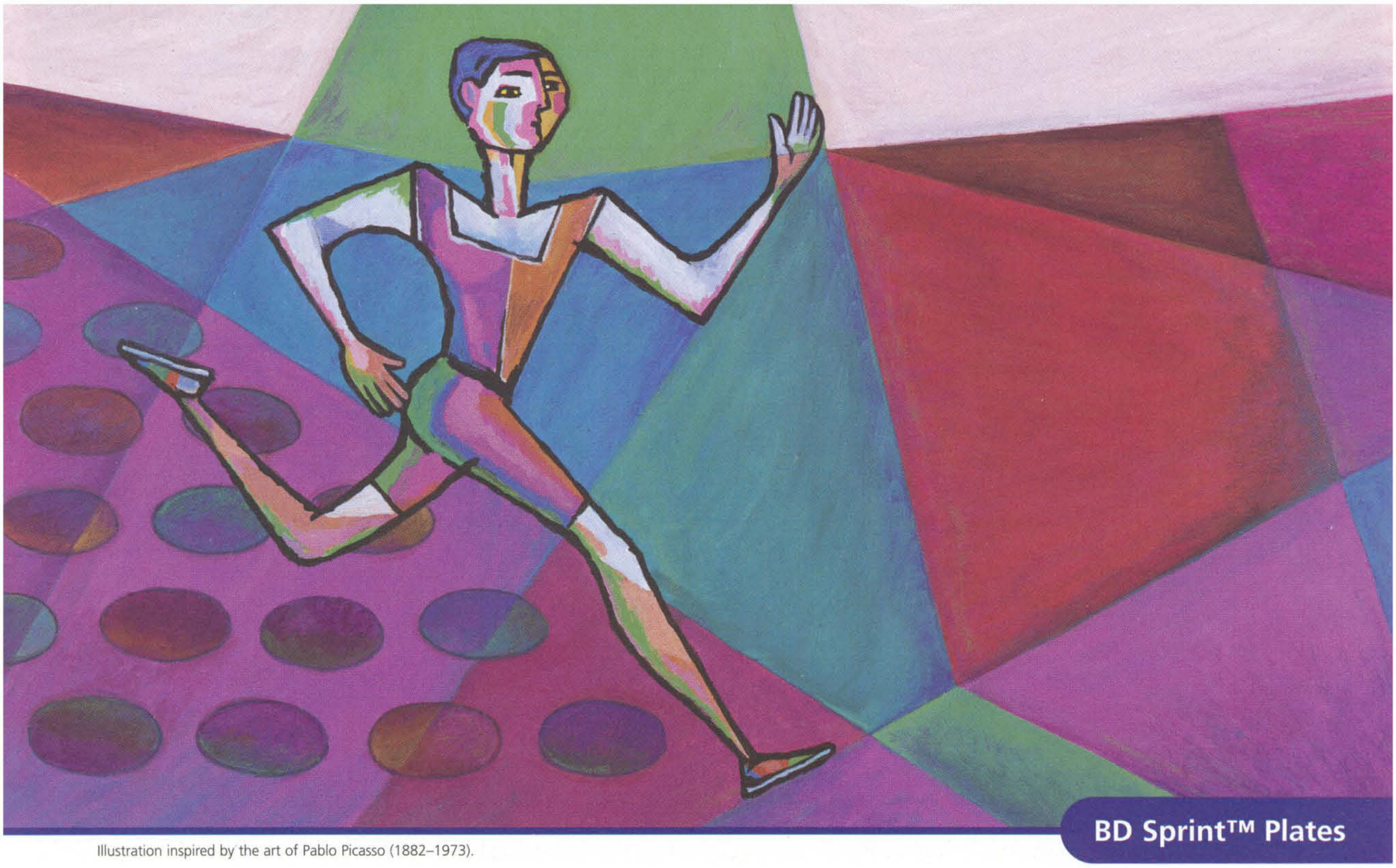
A key reaction in the synthesis of silicone polymers is the addition of a silicon compound containing a Si–H group to a C=C double bond. The main industrial catalysts for these reactions are Pt compounds that suffer from the formation of various by-products, as well as deactivation of the catalysts to form colloidal Pt that discolors the final products. Markó *et al.* (p. 204) now report on a highly active and selective Pt-carbene catalyst that suppresses both of these unwanted effects.

Comparative Genomics for *Anopheles gambiae*

The fruit fly *Drosophila melanogaster* and the mosquito *Anopheles gambiae* are separated by approximately 250 million years of evolution. An initial comparison of these genomes by Zdobnov *et al.* (p. 149) indicate that insects evolved more quickly than vertebrates; the extent of similarity between these two insects was approximately equal to that between humans and pufferfish, which diverged approximately 450 million years ago. Reorganization of significant portions of the chromosome arms has occurred between the two species, and there appears to be a reduction on noncoding regions in *Drosophila* relative to *Anopheles*. Differences in the genomes should lead to a better understanding of phenotypic controls, host-seeking preferences, and parasite susceptibility.

Christophides *et al.* (p. 159) have studied gene families and gene sets involved in innate immunity. Comparisons with *Drosophila* suggest that adaptive demands on the immune system are reflected in a lack of orthologs and an increase in species-specific gene expansions. Riehle *et al.* (p. 172) have used genomic comparisons to identify orthologous genes in the malaria mosquito that are thought to

CONTINUED ON PAGE 11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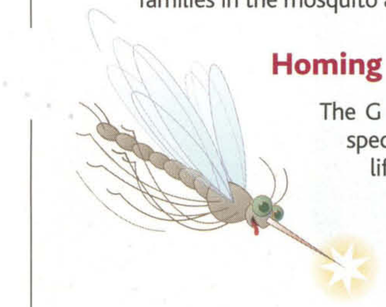
regulate the complex physiologies of parasite-host interactions, development, molting, reproduction, and the osmotic challenges of blood feeding. One potential control tactic the authors suggest is to interfere in the insulin-signaling pathway used by *Anopheles* and the *Plasmodium* malaria parasite, whereby the life-span of the mosquito is shortened to prevent the development and transmission of the parasite.

Genetic mapping studies have previously identified insecticide resistance–associated loci along the mosquito chromosomes. Ranson *et al.* (p. 179) used the genome of *A. gambiae* to pinpoint genes coinciding with these loci and to examine the three major gene families involved in insecticide detoxification, the carboxylesterases, glutathione transferases, and cytochrome P450. A comparison with *Drosophila* reveals the expansion of certain families in the mosquito as a result of local duplications.



Homing In on Us

The G protein–coupled receptors (GPCRs) in *A. gambiae* are of special interest because of their importance to the mosquito's life cycle and because odorant and gustatory receptors are likely to contribute to the extraordinary success of this mosquito as a human disease vector. Hill *et al.* (p. 176) present an initial survey of GPCRs found in the *A. gambiae* genome sequence and characterized 79 possible odorant receptors for tissue expression.

Mosquito Gene Shuffling

A comparative study of *Anopheles gambiae* and *A. funestus*, important vectors of malaria in tropical Africa, by Sharakov *et al.* (p. 182) shows that synteny (the occurrence of genes on the same chromosome) is well preserved, but that the rates of gene shuffling resulting from inversions and synonymous substitutions have been exceptionally high. More than 70 chromosomal inversions are fixed between the two species, a rate that exceeds even that observed in *Drosophila*. Chromosome 2R specifically seems to harbor a hot spot of inversion fixation. The rapid rate of chromosome evolution reflects a similarly high rate of evolution at the sequence level. This study also suggests that positional cloning and microarray experiments may be successful only for very closely related species of mosquito.

Clues into Chloroquine Resistance

Global resistance has made chloroquine, the traditional malaria drug, almost useless. Sidhu *et al.* (p. 210; see the Perspective by Hastings *et al.*) have investigated the correlation between chloroquine resistance among parasites and the occurrence of multiple point mutations in a gene called *pfcrt*, which encodes a membrane-spanning protein. Using allelic exchange, they transferred alleles of *pfcrt* from chloroquine-resistant parasites into a chloroquine-sensitive strain of *Plasmodium falciparum*. Clones of the engineered parasites displayed similar chloroquine resistance to those of the original without having had any prior exposure to the drug. The point mutations appear to confer quite specific structural recognition to chloroquine, so amodiaquine, a new antimalarial with a similar structure to chloroquine, is still effective against chloroquine-resistant parasites.

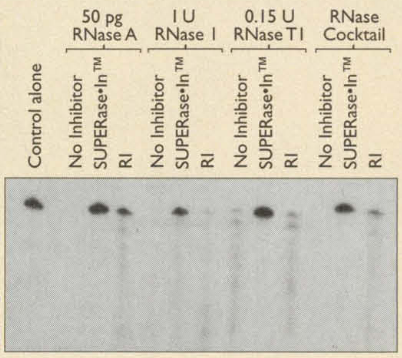
Mosquito Resistance to Malaria

Anopheline mosquitoes are naturally resistant to *Plasmodium falciparum*. Niaré *et al.* (p. 213) take an initial step toward describing the genetics of resistance and the molecular mechanisms underlying natural refractoriness in outbred populations of mosquitoes. They identified two loci on chromosome 2, *Pfin1* and *Pfin2*, associated with resistance.

Plasmodium Population Dynamics

The approach to studying the population dynamics of the malaria parasite *Plasmodium falciparum* is described by Volkman *et al.* (p. 216), who used a microarray of chromosome 2 to search for sequence polymorphisms between different parasite isolates. Most of the variation is concentrated at the chromosome ends and in few internal genes. This technology offers a rapid route to tracking the origins of infections and of new mutations involved in drug resistance and immunity.

ILLUSTRATION: TERRY SMITH



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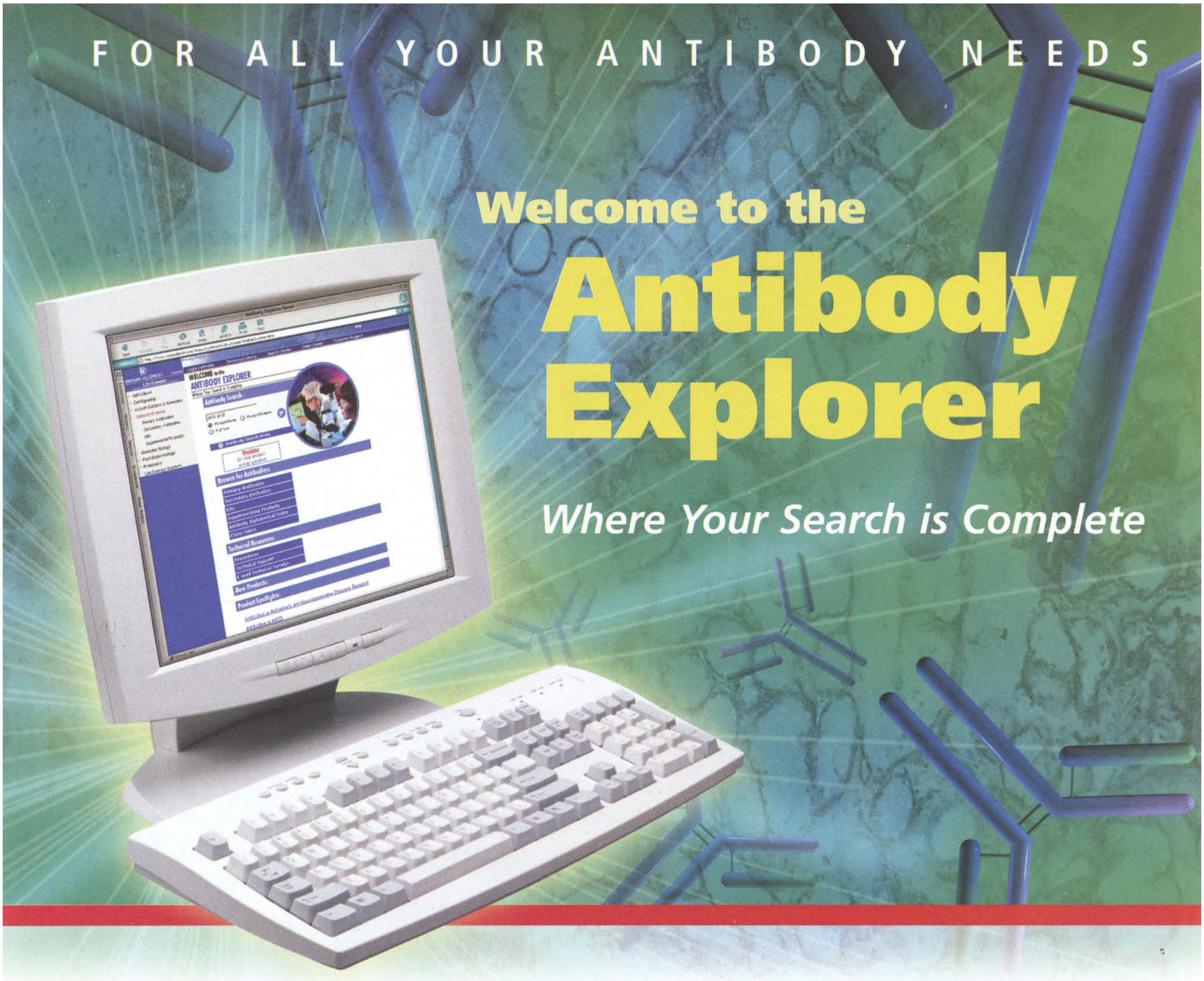
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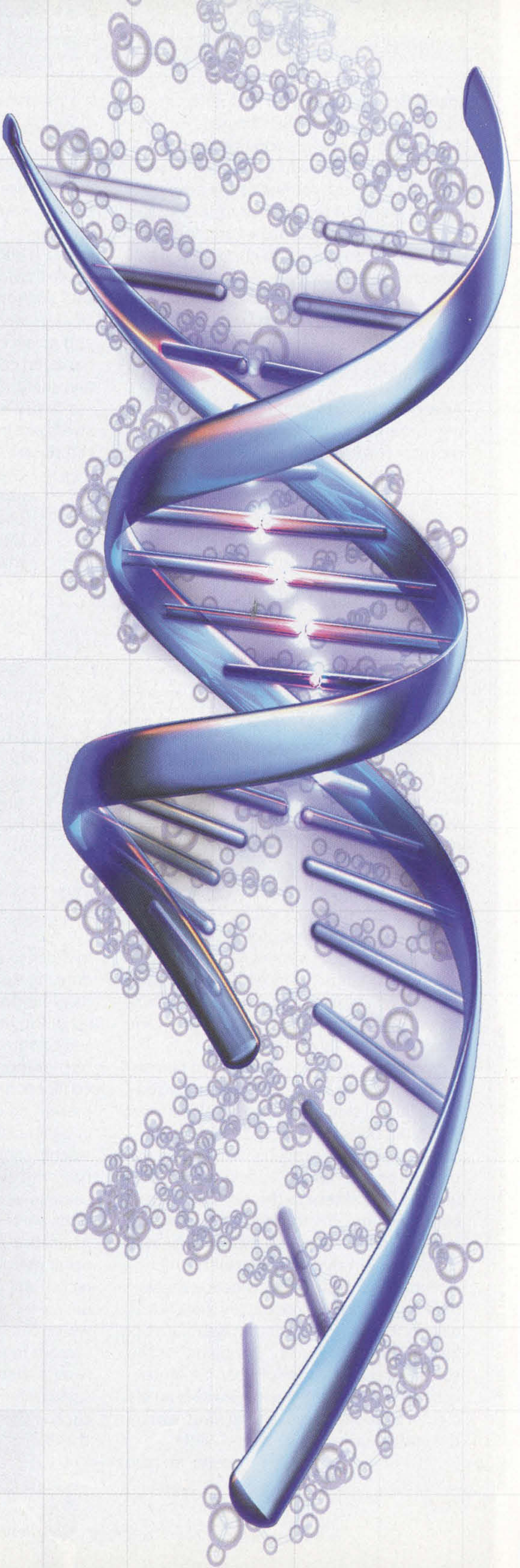

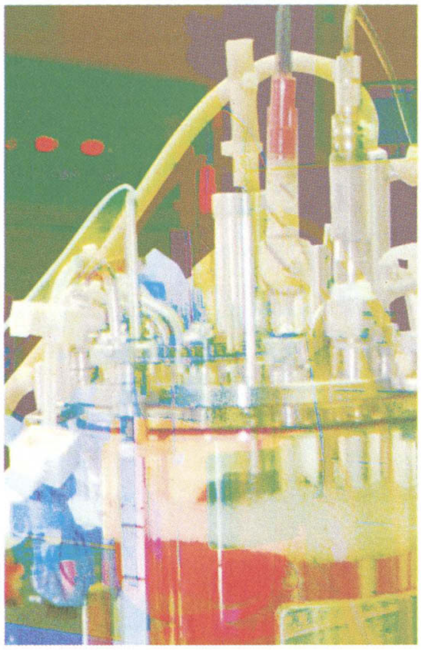

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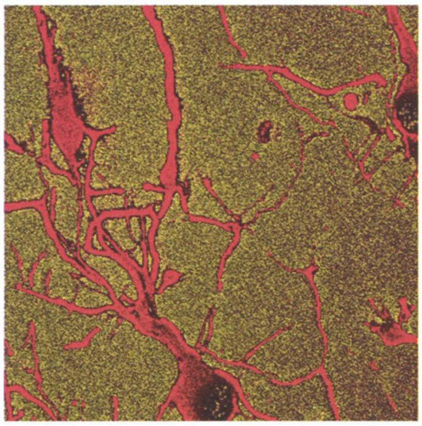

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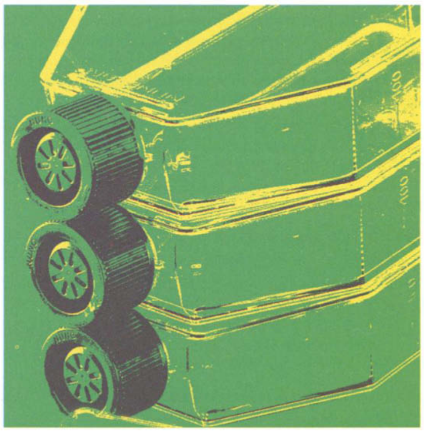

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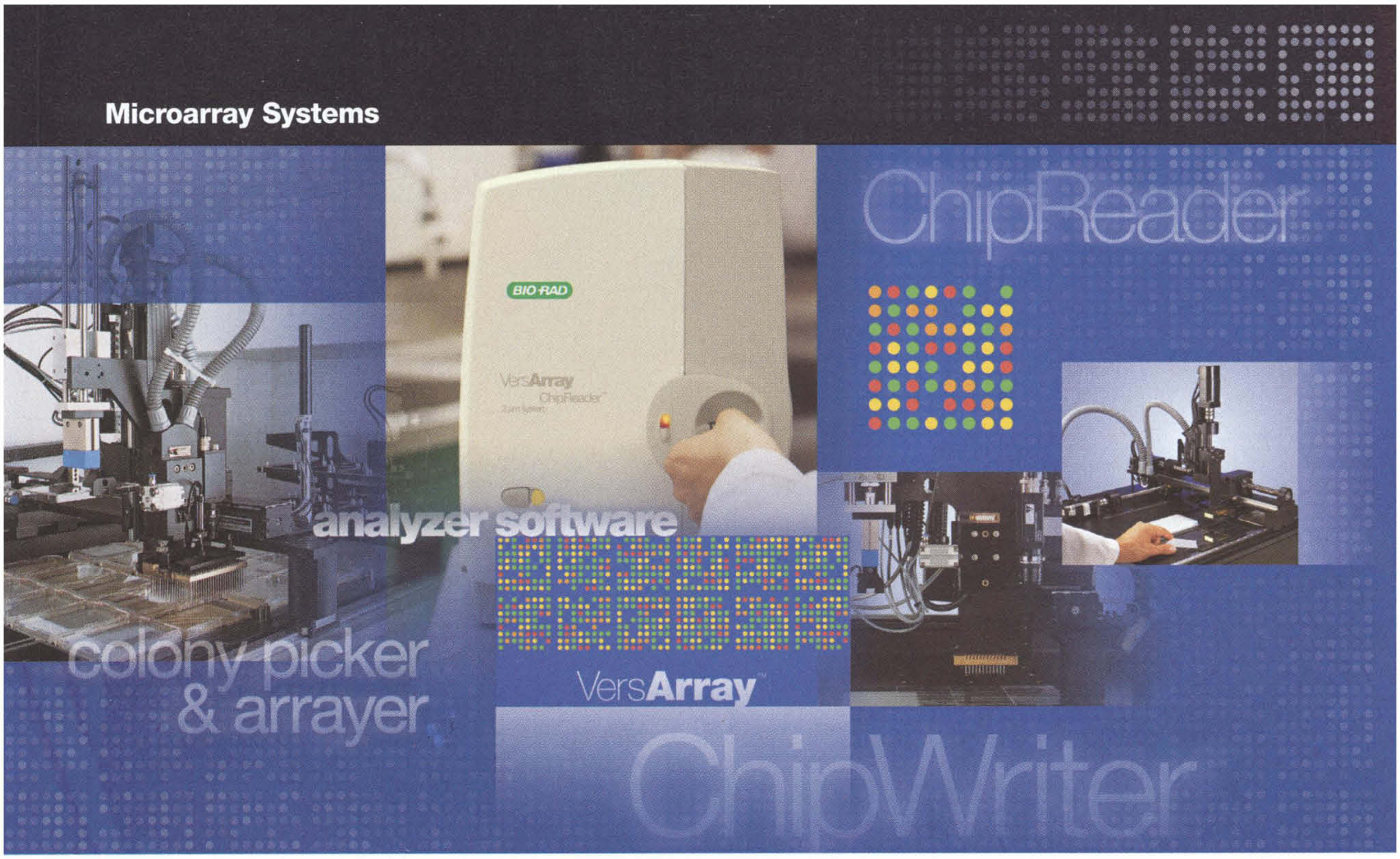

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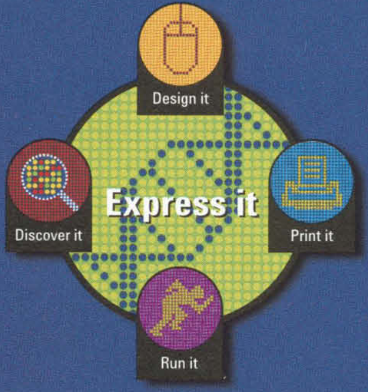

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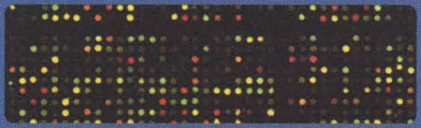

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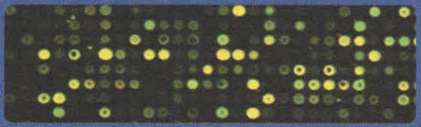

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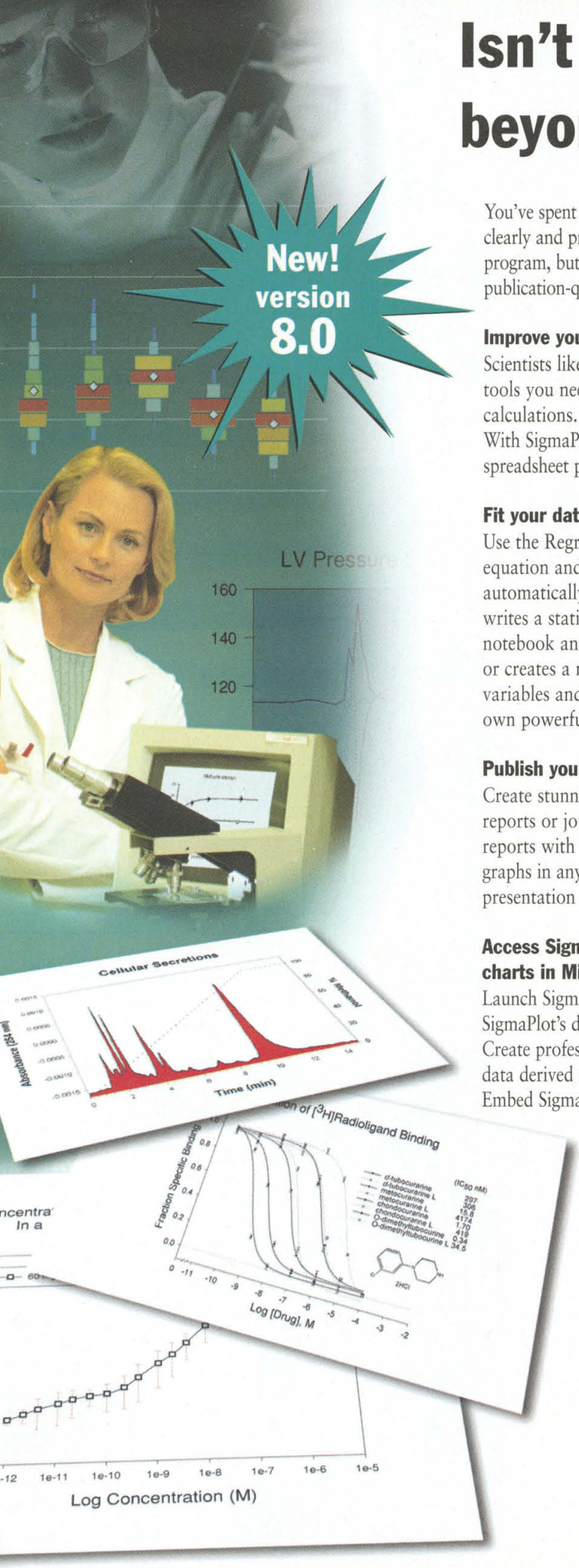
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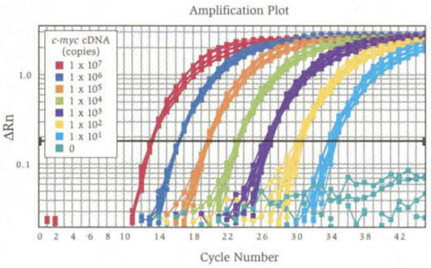
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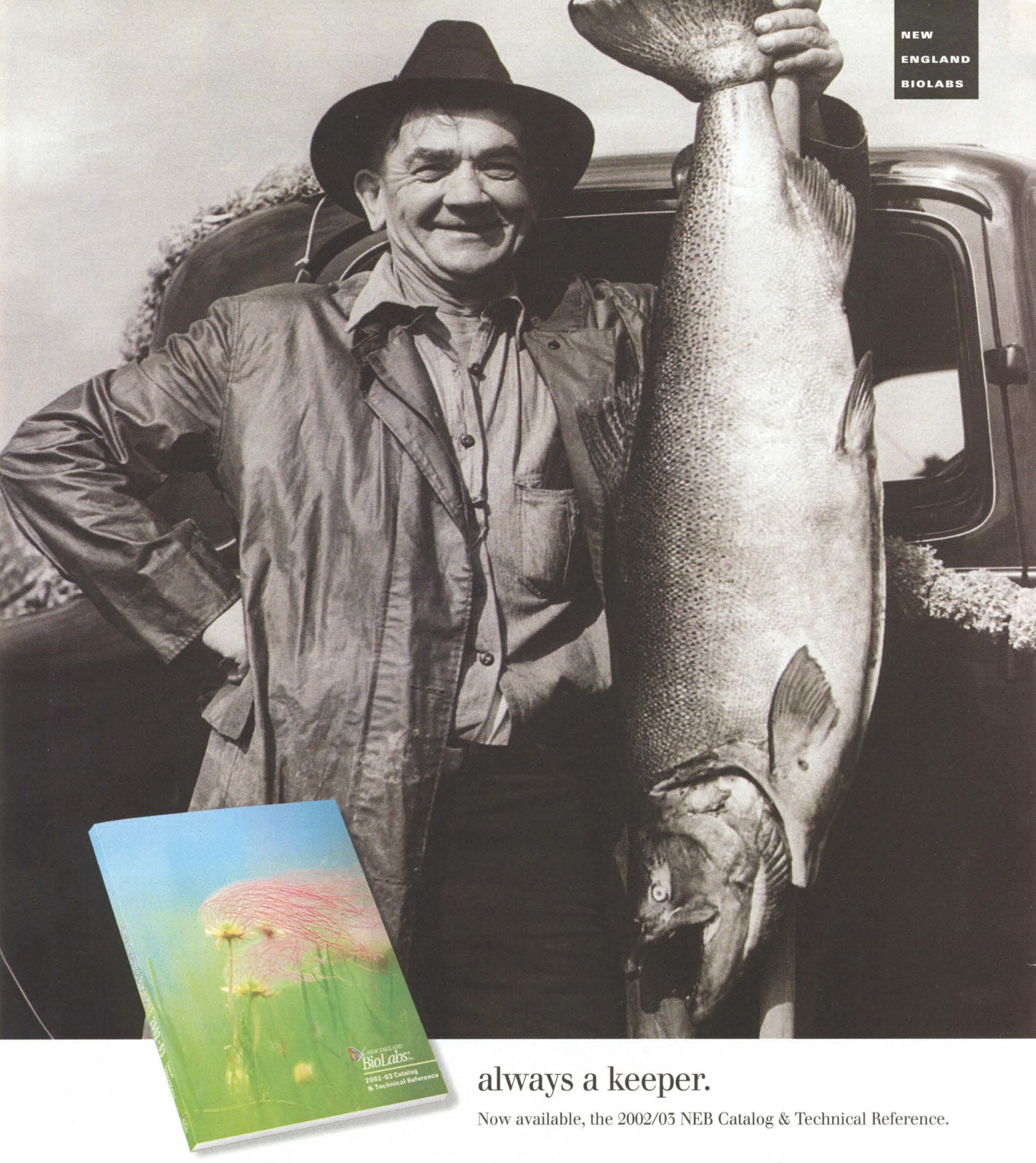
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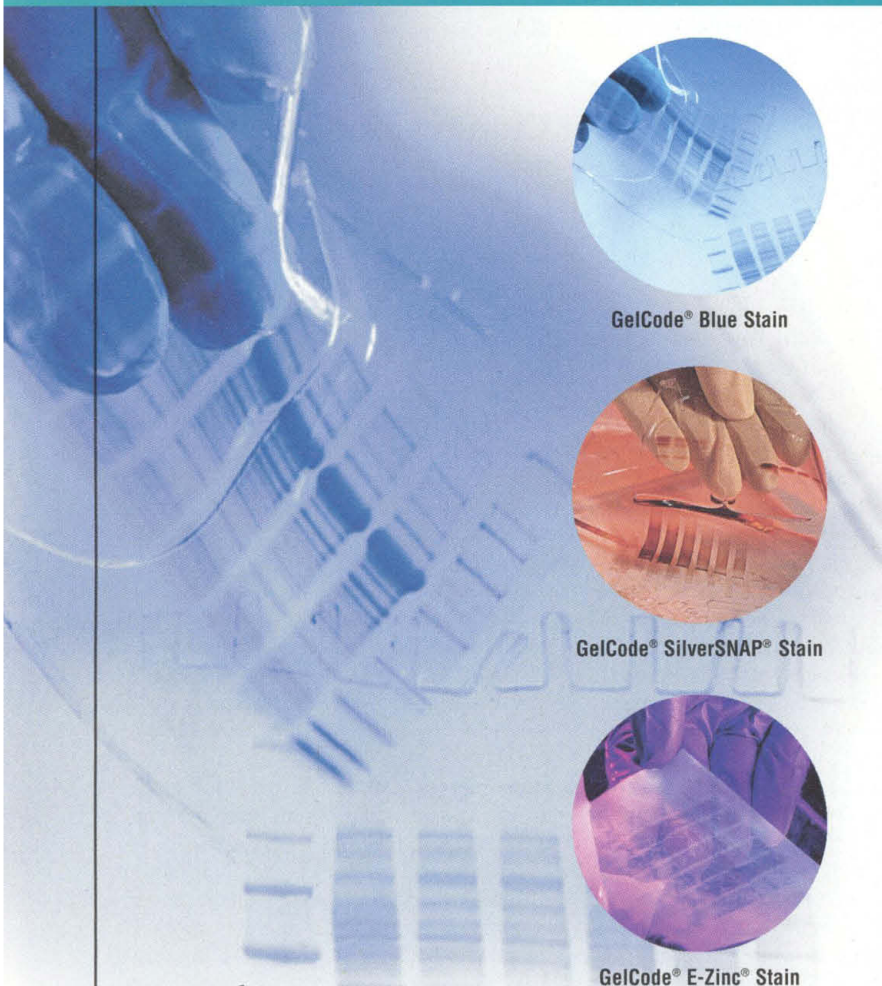

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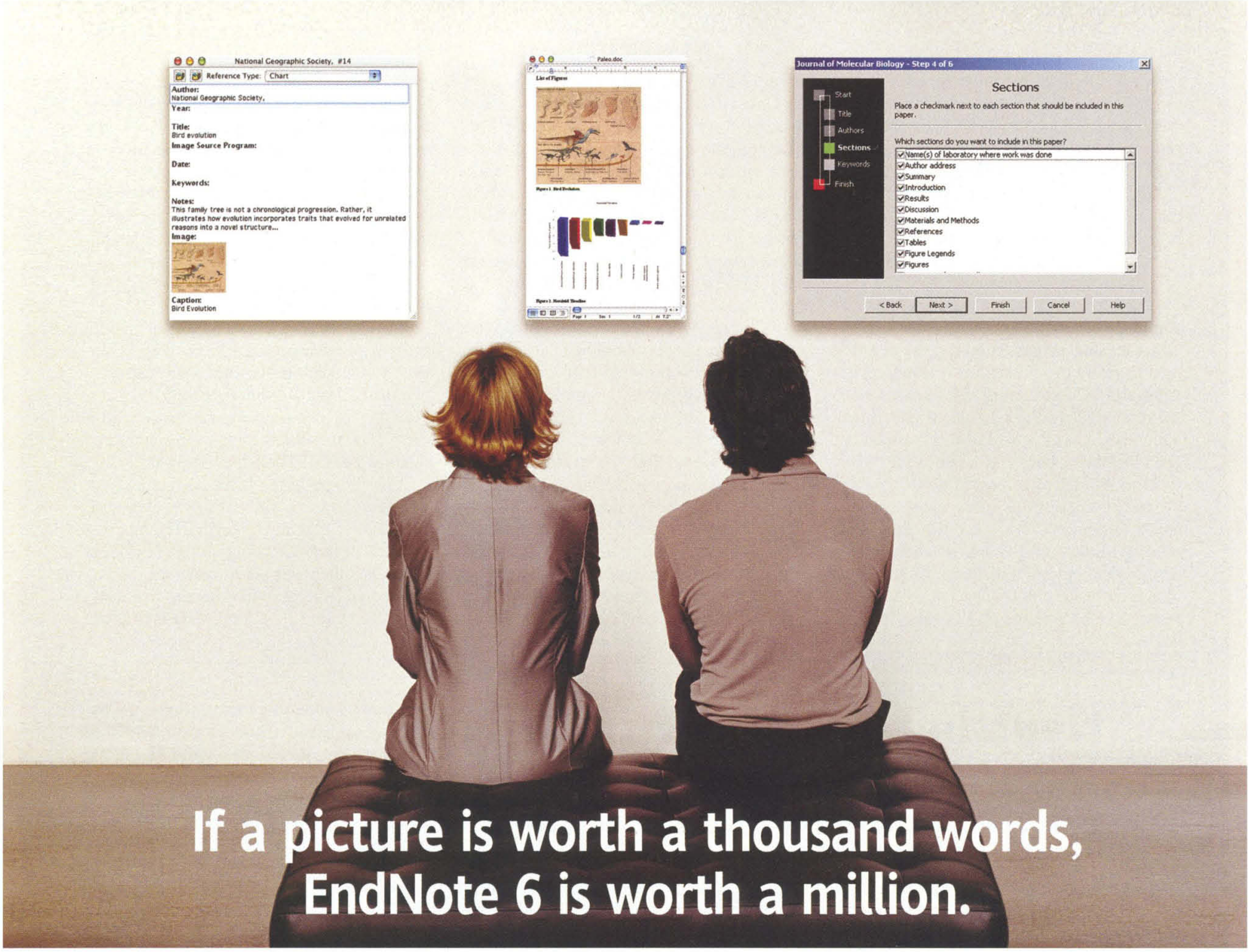

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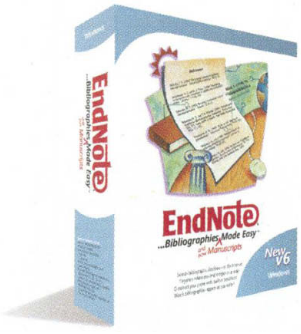

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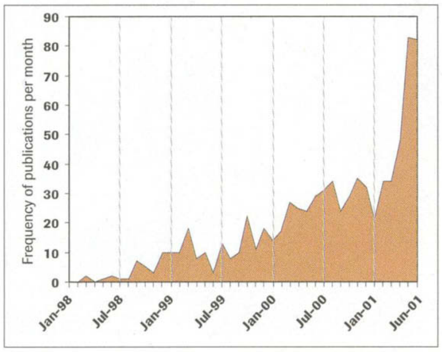

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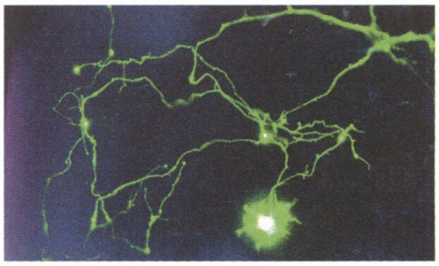

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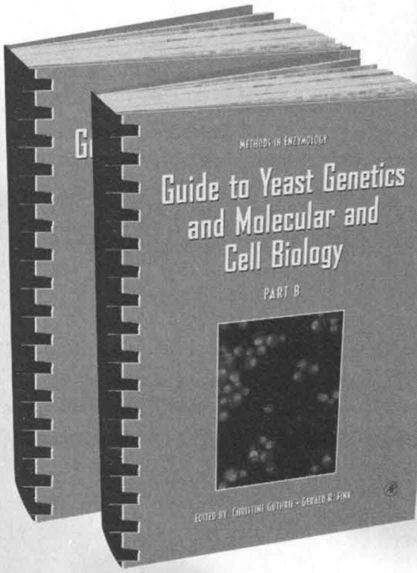

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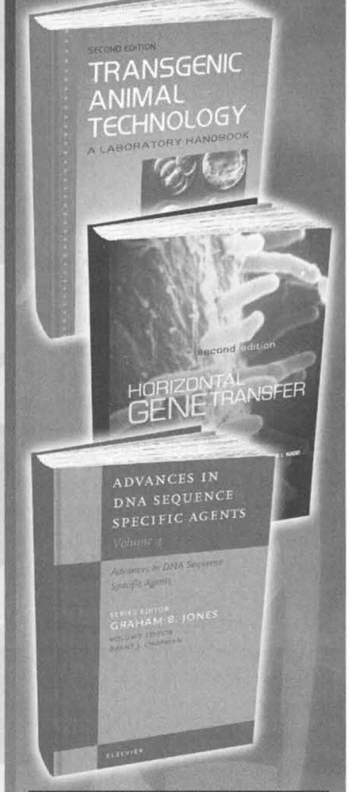

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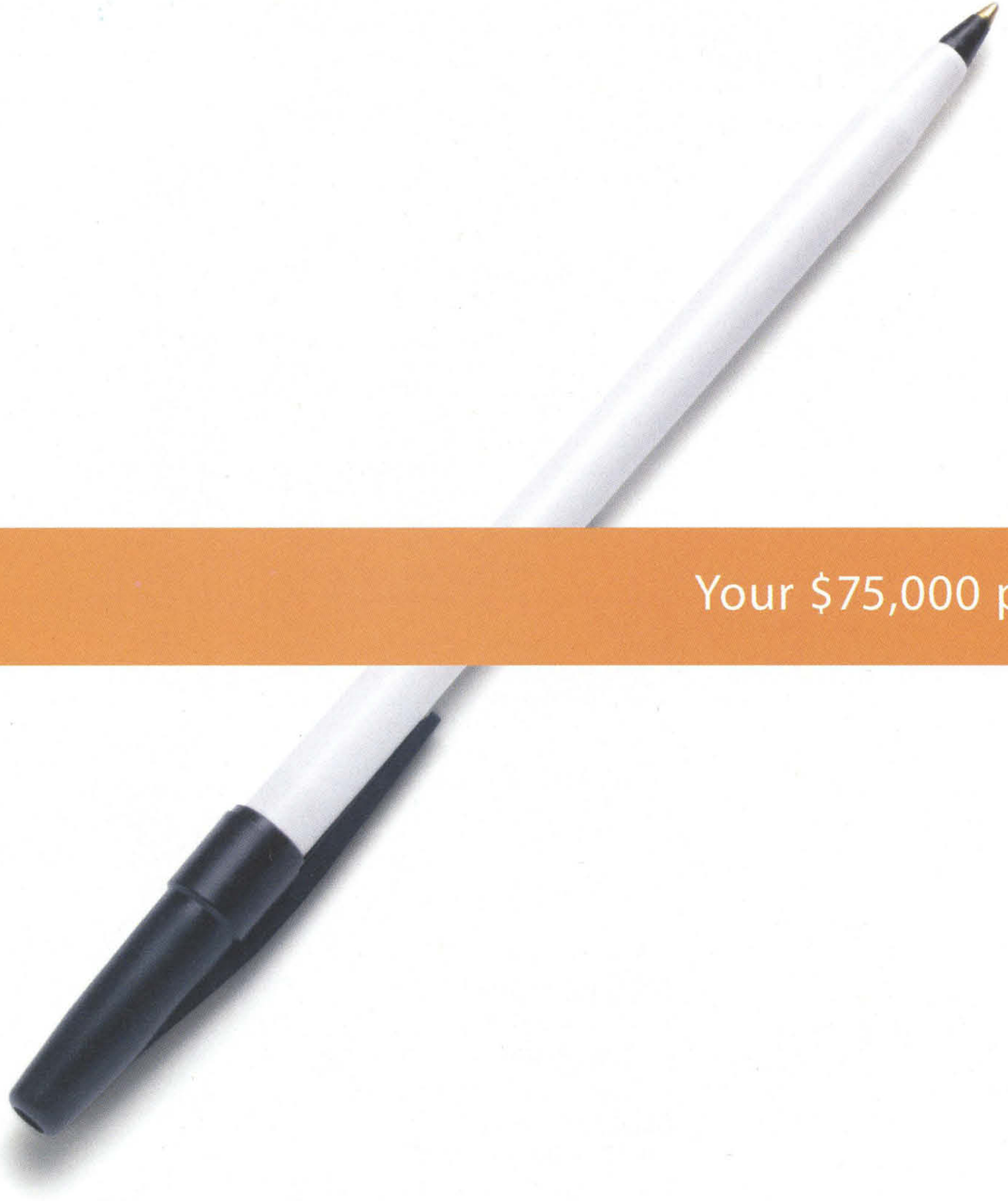

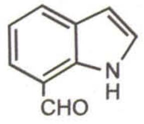
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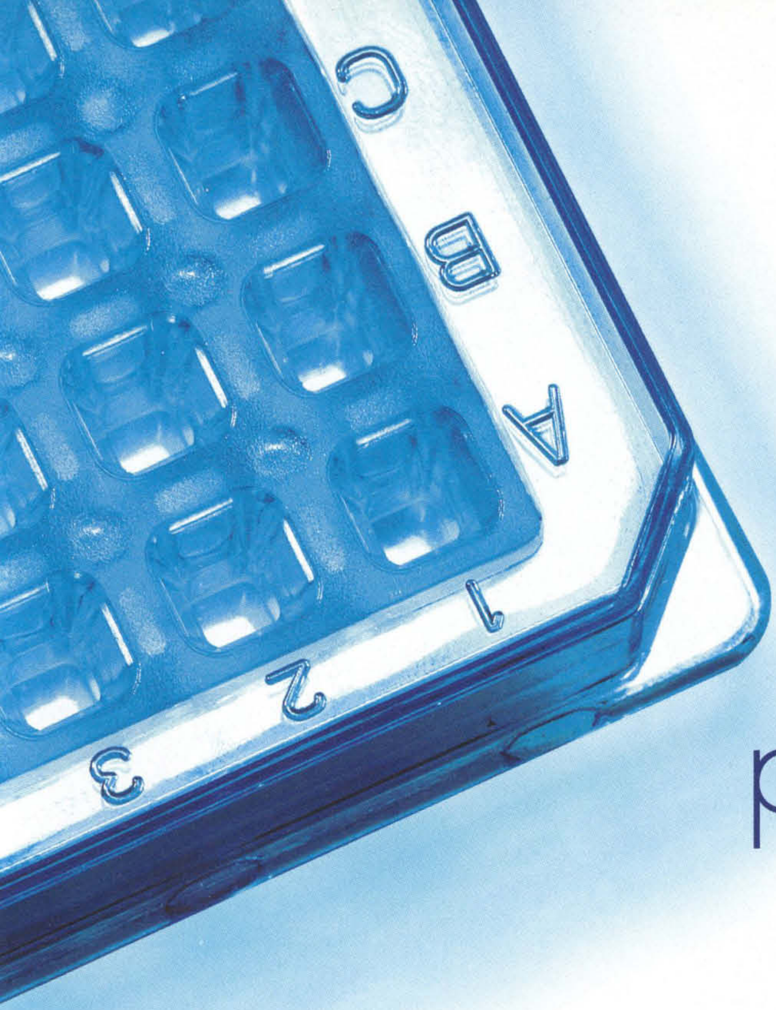

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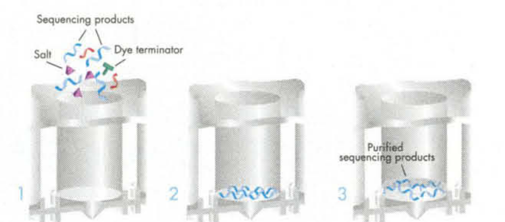

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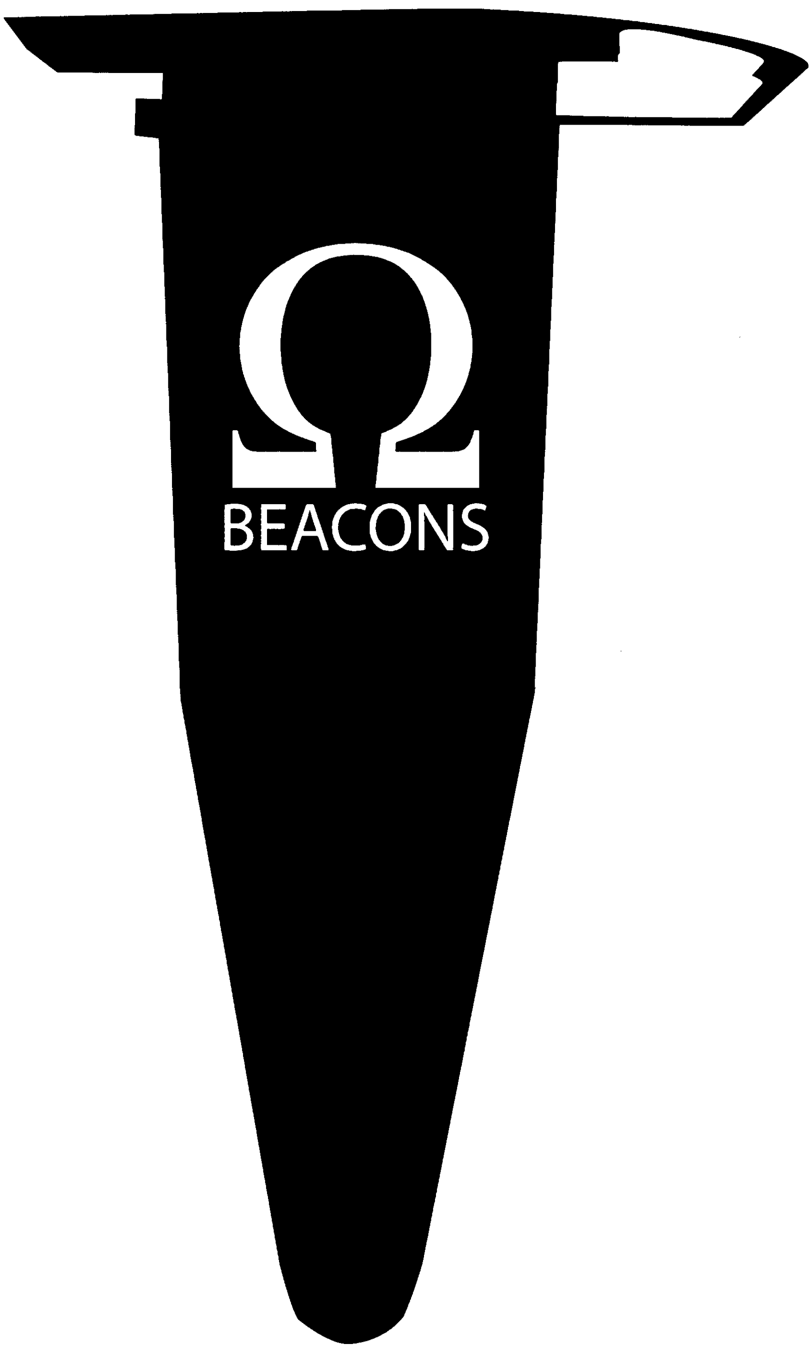
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MOSQUITO

Anopheles gambiae

Science

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Special Programme for Research and Training in Tropical Diseases (TDR)

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

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Malaria vector genomics and public health

Future directions

Better genetic characterization of vectors; elucidation of molecular mechanisms of insecticide resistance; new generation of insecticides based on genomics; new genome-based approaches to malaria control.

2002

International consortium publishes *Anopheles gambiae* genome sequence.

2002

Development of transgenic *Anopheles stephensi* unable to sustain *Plasmodium berghei* development and transmission.

2001

Germline transformation of *Anopheles gambiae*.

2001

Institut Pasteur and TDR convene *Anopheles gambiae* Genome Sequencing Summit meeting in Paris (France) which establishes international network of researchers and partners from the private and public sectors.

2000

Stable germline transformation of the malaria vector *Anopheles stephensi* demonstrated by insertion of Enhanced Green Fluorescent Protein (EGFP) gene.

1999

TDR convenes meeting of insect geneticists, genome researchers and funders to agree on a strategy for a genome project on *Anopheles gambiae*, the main vector of malaria in Africa.

1994

TDR establishes Molecular Entomology Steering Committee. Multipurpose workplan aims to produce refractory mosquito by 2005.

1991

MacArthur Foundation, TDR and Wellcome Trust organize meeting of global interdisciplinary specialists in Tucson (Arizona, USA) which devises plan to create *Anopheles gambiae* mosquitoes that are unable to host and/or transmit *Plasmodium* parasites.

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www.who.int/tdr

Discovery • Development • Production • Implementation

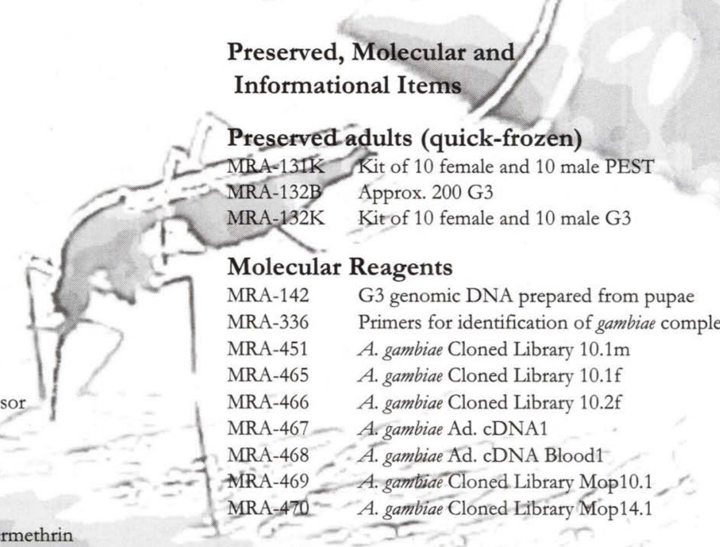
MALARIA RESEARCH & REFERENCE REAGENT RESOURCE CENTER

History & Purpose

The Malaria Research and Reference Reagent Resource Center (MR4) was established by The National Institute of Allergy and Infectious Diseases (NIAID) in 1998. Managed by the American Type Culture Collection and the Centers for Disease Control and Prevention (CDC) Foundation, MR4 provides over 450 well-characterized parasite and *Anopheles* vector reagents and protocols to registered researchers worldwide. The MR4 also conducts workshops, training programs, and disseminates information. A major goal of the MR4 is to increase technology transfer to scientists in malaria-endemic areas through free or nominal-cost distribution of reagents, and through collaborations, and training.

Anopheles Materials

The MR4 vector activity, based at the CDC in Atlanta, Georgia USA, provides both living and preserved *Anopheles* mosquitoes to qualified registrants. Shipments of living *Anopheles* vectors are reviewed by an MR4 committee. Purified genomic DNAs, libraries, and primer sets for species identification are also available. Information on mosquito culture and materials, distribution, and chromosome images are available at the MR4 web site. A list of *Anopheles gambiae* items follows. (Visit the website for a catalog of other *Anopheles* items and acquisitions.)



Living *A. gambiae*

Item	Description
MRA-105	M2 white mutant
MRA-106	M5 white mutant
MRA-108	CHR marker
MRA-109	DARK1 X marker
MRA-110	BLACK1 chr 2 markers
MRA-111	RMOSPW PEV mutation
MRA-112	G3 wild strain
MRA-186	ASEMB01 wild strain
MRA-113	P5CR marker
MRA-114	L3-5 *Plasmodium* encapsulation
MRA-121	4ARR *Plasmodium* normal
MRA-115	IN22C+ chr. 2 recomb. suppressor
MRA-116	P+DLRC+R+ marker
MRA-118	P+DLRC marker
MRA-119	PWDLRC+ marker
MRA-120	HOM1C marker
MRA-334	RSP reduced susceptibility to permethrin
MRA-335	PBAC-0 piggyBac GFP transformed strain

Preserved, Molecular and Informational Items

Preserved adults (quick-frozen)

MRA-131K	Kit of 10 female and 10 male PEST
MRA-132B	Approx. 200 G3
MRA-132K	Kit of 10 female and 10 male G3

Molecular Reagents

MRA-142	G3 genomic DNA prepared from pupae
MRA-336	Primers for identification of *gambiae* complex by PCR
MRA-451	*A. gambiae* Cloned Library 10.1m
MRA-465	*A. gambiae* Cloned Library 10.1f
MRA-466	*A. gambiae* Cloned Library 10.2f
MRA-467	*A. gambiae* Ad. cDNA1
MRA-468	*A. gambiae* Ad. cDNA Blood1
MRA-469	*A. gambiae* Cloned Library Mop10.1
MRA-470	*A. gambiae* Cloned Library Mop14.1

Identification and Biology Information

MRA-337	CD – The *Anopheles* of the Afro-tropical region
MRA-338	CD – The Mosquitoes of Mediterranean Africa

Registration & Donations

Registration by principal investigators is required to obtain reagents from the Repository and remains effective for 5 years. Forms are available at the MR4 web site. The MR4 welcomes acquisition suggestions and reagent donations. These include living *Anopheles,* genomic and cDNA libraries and informational materials. Please contact the MR4 to discuss suitability of specific items.

www.malaria.mr4.org

Knowledge • Science • People

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Special Programme for Research and Training in Tropical Diseases

What is TDR?

TDR is an independent, UN-based programme of international scientific collaboration. For over 25 years, TDR has been addressing the challenge of generating and organising knowledge, scientific and technological progress and human endeavour in the fight against a portfolio of diseases which primarily affect the world's poor, disadvantaged and socially excluded.

What does TDR do?

Using funds provided by a committed donor group, drawing on expertise from the global scientific community and operating via integrated networks of worldwide partners from the public and private sectors, TDR helps leverage funds and focus investments on the production of disease control tools, improvement of infrastructure and human resources in disease-endemic countries, and development and implementation of global public goods.

Key Achievements (1975-2002):

- 9,300 projects involving 7,000 scientists
- 6,100 R&D projects in 129 nations
- 3,200 Research Capacity Strengthening projects
- 1,200 disease-endemic country scientists trained
- 253 institutions supported
- 35 disease control tools
  (produced in collaboration with our partners).

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