

ANNUAL REPORTS IN MEDICINAL CHEMISTRY Volume 36

*Sponsored by the Division of Medicinal Chemistry
of the American Chemical Society*

Editor-in-Chief: **ANNETTE M. DOHERTY**

PFIZER GLOBAL RESEARCH & DEVELOPMENT
FRESNES LABORATORIES
FRANCE



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CORRECTION-

In Volume 35 of Annual Reports in Medicinal Chemistry, the first author was inadvertently omitted from chapter 6. We apologize for this error. The correct heading for this chapter is as follows:

Chapter 6. Recent Developments In Antitussive Therapy

Robert Aslanian, John A. Hey and Neng -Yang Shih
Schering Plough Research Institute
2015 Galloping Hill Road
Kenilworth, NJ 07033

This chapter has been updated, and appears in this Volume as Chapter 4.

PREFACE

Annual Reports in Medicinal Chemistry continues to focus on providing timely and critical reviews of important topics in medicinal chemistry together with an emphasis on emerging topics in the biological sciences that are expected to provide the basis for entirely new future therapies.

Volume 36 retains the familiar format of previous volumes, this year with 30 chapters. Sections I–IV are disease-oriented and generally report on specific medicinal agents with updates from Volume 35 on antitussive therapy, anticoagulants, antibacterials, and antiretroviral therapies. As in past volumes, annual updates have been limited to the most active areas of research in favor of specifically focused and mechanistically oriented chapters, where the objective is to provide the reader with the most important new results in a particular field.

Sections V and VI continue to emphasize important topics in medicinal chemistry, biology, and drug design as well as the critical interfaces among these disciplines. Included in Section V, Topics in Biology, are chapters on bioinformatics, protein structure prediction, proteonomics, and therapeutic antibodies. Chapters in Section VI, Topics in Drug Design and Discovery, reflect the current focus on mechanism-directed drug discovery and newer technologies. These include chapters on aspartyl protease inhibitors, ADME by computer, PET ligands for assessing receptor occupancy *in vivo*, and strategies for analytical characterization and profiling of compound libraries.

Volume 36 concludes with To Market, To Market — 2000, a chapter on NCE and NBE introductions worldwide in 2000 and chapters on new developments in animal health care and the impact of intellectual property issues on the pharmaceutical industry. In addition to the chapter reviews, a comprehensive set of indices has been included to enable the reader to easily locate topics in Volumes 1–35 of this series.

Volume 36 of *Annual Reports in Medicinal Chemistry* was assembled with the superb editorial assistance of Ms. Sylvie Duchesne, Ms. Nadège Pingray, and Ms. Lisa Bausch and I thank them for their hard work. I have continued to work with innovative and enthusiastic section editors and my sincere thanks goes to them again this year. I hope that you will enjoy and profit from reading this volume.

Annette M. Doherty
Fresnes, France
May, 2001

CONTENTS

CONTRIBUTORS	xi
PREFACE	xv

I. CENTRAL NERVOUS SYSTEM DISEASES

Section Editor: David W. Robertson, Pharmacia Corporation, Kalamazoo, Michigan

- | | |
|---|----|
| 1. Same Brain, New Decade: Challenges in CNS Drug Discovery in the Postgenomic, Proteomic Era | 1 |
| <i>Michael Williams, Northwestern University School of Medicine, Chicago, Illinois; Joseph T. Coyle, Harvard Medical School, Belmont, Massachusetts; Sanober Shaikh, Genset SA, Evry Cedex, France; Michael W. Decker, Abbott Laboratories, Abbott Park, Illinois</i> | |
| 2. Potassium Channel Modulators for Treatment of CNS Disorders | 11 |
| <i>Michael J. Coglian, Murali Gopalakrishnan and William A. Carroll, Abbott Laboratories, Abbott Park, Illinois</i> | |
| 3. New Developments in the Study of Corticotropin Releasing Factor | 21 |
| <i>John Saunders and John P. Williams, Neurocrine Biosciences, San Diego, California</i> | |

II. CARDIOVASCULAR AND PULMONARY DISEASES

Section Editor: William J. Greenlee, Schering-Plough Research Institute, Kenilworth, New Jersey

- | | |
|--|----|
| 4. Recent Developments in Antitussive Therapy | 31 |
| <i>Robert Aslanian, John A. Hey and Neng-Yang Shih, Schering-Plough Research Institute, Kenilworth, New Jersey</i> | |
| 5. Phosphodiesterase 4 Inhibitors | 41 |
| <i>John G. Montana and Hazel J. Dyke, Celltech R&D Ltd, Great Abington, Cambridge, United Kingdom</i> | |

- | | | |
|----|--|----|
| 6. | Recent Advances in the Science and Treatment of Atherosclerosis
<i>Duane A. Burnett and Harry R. Davis, Jr., Schering-Plough Research Institute, Kenilworth, New Jersey</i> | 57 |
| 7. | Progress in the Treatment of Pulmonary Disease in Cystic Fibrosis
<i>Pallav L. Shah, Royal Brompton Hospital, London, United Kingdom</i> | 67 |
| 8. | Anticoagulants: Inhibitors of Thrombin and Factor Xa
<i>Philip E. J. Sanderson, Merck Research Laboratories, West Point, Pennsylvania</i> | 79 |

III. CANCER AND INFECTIOUS DISEASES

Section Editor: Jacob J. Plattner, Chiron Corporation, Emeryville, California

- | | | |
|-----|---|-----|
| 9. | Recent Developments in Antibacterial Research
<i>Joanne J. Bronson and John F. Barrett, Bristol-Myers Squibb Pharmaceutical Research Institute, Wallingford, Connecticut</i> | 89 |
| 10. | New Therapies for Parasitic Infection
<i>Patrick M. Woster, Wayne State University, Detroit, Michigan</i> | 99 |
| 11. | Growth Factor Receptor Kinases in Cancer
<i>Paul A. Renhowe, Chiron Corporation, Emeryville, California</i> | 109 |
| 12. | Non-HIV Antiviral Agents
<i>Larry L. Klein and John T. Randolph, Abbott Laboratories, Abbott Park, Illinois</i> | 119 |
| 13. | <i>In Vitro</i> and <i>In Vivo</i> Approaches to Studying Antiretroviral Therapy (ART)-Induced Metabolic Complications
<i>James E. Weiel and James M. Lenhard, GlaxoSmithKline, Research Triangle Park, North Carolina</i> | 129 |
| 14. | Cell Cycle Kinases and Checkpoint Regulation in Cancer
<i>S. David Kimball and Kevin R. Webster, Bristol-Myers Squibb, Princeton, New Jersey</i> | 139 |

IV. IMMUNOLOGY, ENDOCRINOLOGY AND METABOLIC DISEASES

Section Editor: William K. Hagmann, Merck Research Laboratories, Rahway,
New Jersey

15. Targeting the Estrogen Receptor with SERMs 149
Chris P. Miller and Barry S. Komm, Wyeth-Ayerst Research, Radnor, Pennsylvania
16. Vasopressin Receptor Modulators: From Non-peptide Antagonists to Agonists 159
Eugene J. Trybulski, Wyeth Ayerst Research, Princeton, New Jersey
17. Selective Androgen Receptor Modulators (SARMs) 169
Lin Zhi and Esther Martinborough, Ligand Pharmaceuticals, San Diego, California
18. Antagonists of $\beta 2$ Integrin-Mediated Cell Adhesion 181
Patricia A. Giblin and Terence A. Kelly, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut
19. DPP-IV Inhibition and Therapeutic Potential 191
Edwin B. Villhauer, Gary M. Coppola and Thomas E. Hughes, Novartis Institute for Biomedical Research, Summit, New Jersey

V. TOPICS IN BIOLOGY

Section Editor: Janet M. Allen, Pfizer Global Research & Development,
Fresnes Laboratories, Fresnes, France

20. Bioinformatics in the Drug Discovery Process 201
Sarah Pollock and Hershel M. Safer, Compugen Ltd., Tel Aviv, Israel
21. The Role of Protein Structure Prediction in Drug Discovery 211
*David T. Jones, Brunel University, Uxbridge, Middlesex, United Kingdom;
Mark B. Swindells and Richard Fagan, Impharmatica LTD., London, United Kingdom*
22. Proteomics: Defining Protein Function in the Post Genomics Era 227
Brent L. Kreider, Phyllos, Inc., Lexington, Massachusetts

23. Therapeutic Monoclonal Antibodies: History, Facts and Trends 237
László Takács, Pfizer Global Research & Development, Fresnes Laboratories, Fresnes, France; Maria-Dolores Vazquez-Abad and Eileen A Elliott, Pfizer Global Research & Development, Groton Laboratories, Groton, Connecticut

VI. TOPICS IN DRUG DESIGN AND DISCOVERY

Section Editor: George L. Trainor, DuPont Pharmaceuticals Company,
Wilmington, Delaware

24. Pharmacokinetics and Design of Aspartyl Protease Inhibitors 247
Lorin A. Thompson and Andrew J. Tebben, DuPont Pharmaceuticals Company, Wilmington, Delaware
25. ADME by Computer 257
Matthew D. Wessel and Scot Mente, Pfizer Global Research & Development, Groton Laboratories, Groton, Connecticut
26. PET Ligands for Assessing Receptor Occupancy In Vivo 267
H. Donald Burns, Terence G. Hamill, Wai-si Eng, and Richard Hargreaves, Merck Research Laboratories, West Point, Pennsylvania
27. Existing and Emerging Strategies for the Analytical Characterization and Profiling of Compound Libraries 277
Gregory A. Nemeth, DuPont Pharmaceuticals, Wilmington, Delaware; Daniel B. Kassel, DuPont Pharmaceuticals Research Laboratories, San Diego, California

VII. TRENDS AND PERSPECTIVES

Section Editor: Annette M. Doherty, Pfizer Global Research & Development,
Fresnes Laboratories, Fresnes, France

28. To Market, To Market – 2000 293
Bernard Gaudillière, Patrick Bernardelli and Patrick Berna, Pfizer Global Research & Development, Fresnes Laboratories, Fresnes, France

29. New Developments in Animal Healthcare	319
<i>Ashley E. Fenwick, Pfizer Veterinary Medicine Discovery Chemistry, Sandwich Laboratories, Sandwich, Kent, England</i>	
30. Intellectual Property Issues Impacting the Pharmaceutical Industry	331
<i>Amy E. Hamilton and Mark J. Stewart, Eli Lilly and Company, Indianapolis, Indiana</i>	
COMPOUND NAME, CODE NUMBER AND SUBJECT INDEX, VOLUME 36	341
CUMULATIVE CHAPTER TITLES KEYWORD INDEX, VOLUMES 1-36	351
CUMULATIVE NCE INTRODUCTION INDEX, 1983-2000	367
CUMULATIVE NCE INTRODUCTION INDEX, 1983-2000, BY INDICATION	383

CONTRIBUTORS

Aslanian, Robert	31	Kreider, Brent L.	227
Barett, John F.	89	Lenhard, James M.	129
Berna, Patrick	293	Martinborough, Esther	169
Bernardelli, Patrick	293	Mente, Scot	257
Bronson, Joanne J.	89	Miller, Chris P.	149
Burnett Duane A.	57	Montana, John G.	41
Burns, H. Donald	267	Nemeth, Gregory A.	277
Carroll, William A.	11	Pollock, Sarah	201
Coghan, Michael	11	Randolph, John T.	119
Coppola, Gary M.	191	Renhowe, Paul A.	109
Coyle, Joseph T.	1	Safer, Hershel M.	201
Davis, Jr., Harry R.	57	Sanderson, Philip E. J.	79
Decker, Michael W.	1	Saunders, John	21
Dyke, Hazel J.	41	Shah, Pallav L.	67
Elliott, Eileen A.	237	Shaikh, Sanobar	1
Eng, Wai-si	267	Shih, Neng-Yang	31
Fagan, Richard	211	Stewart, Mark J.	331
Fenwick, Ashley E.	319	Swindells, Mark B.	211
Gaudillière, Bernard	293	Takács, László	237
Giblin, Patricia A.	181	Thompson, Lorin A.	247
Gopalakrishnan, Murali	11	Tebben, Andrew J.	247
Hamill, Terence G.	267	Trybulski, Eugene J.	159
Hamilton, Amy E.	331	Vazquez-Abad, Maria-Dolores	237
Hargreaves, Richard	267	Villhauer, Edwin B.	191
Hey, John A.	31	Webster, Kevin R.	139
Hughes, Thomas E.	191	Weiell, James E.	129
Jones, David T.	211	Wessel, Matthew D.	257
Kassel, Daniel B.	277	Williams, John P.	21
Kelly, Terence A.	181	Williams, Michael	1
Kimball, S. David	139	Woster, Patrick M.	99
Klein, Larry L.	119	Zhi, Lin	169
Komm, Barry S.	149		

SECTION I. CNS AGENTS

Editor: David W. Robertson, Pharmacia Corporation
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Chapter 1: Same Brain, New Decade: Challenges in CNS Drug Discovery in the Postgenomic, Proteomic Era

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Introduction. The brain is a highly complex organ that mediates conceptual thought, cognition, volition, self-consciousness and emotion (1,2). As "the interpreter and responder to environmental challenges", the brain, working via the peripheral nervous system, processes information and controls behavioral responses via "systems replete with specialized circuits, parallel pathways, and redundant mechanisms to protect the individual, thus ensuring propagation of the genome and survival of the species (3,4). Accordingly, brain dysfunction resulting from genetic, environmental and/or aging factors has a major negative impact on the quality of life and individual survival.

CNS COMPLEXITY AND DRUG DISCOVERY

The human brain contains approximately 100 billion neurons and expresses greater than 60% of known human genes. In comparison, the nervous system of the threadworm, *C. elegans*, a model system for studying genomic function, has a mere 302 neurons, 3×10^{-6} % the number in the human brain. Neurons in *C. elegans* are interconnected via 600 electrical and 5000 chemical synapses (5). The *C. elegans* genome codes for approximately 1000 G-protein coupled receptors (GPCRs), 90 ligand-gated ion channels, 80 potassium-selective ion channels and 228 nuclear receptors providing a virtually infinite number of postgenomic molecular substrates through which neuronal function can be regulated (6,7). Understanding this complexity at the level of the human brain and postgenomic interactions between genes and their products (epigenetics; 8) is a key challenge in understanding human CNS disease pathophysiology and in designing new drugs that are safer and more efficacious to treat these diseases.

The characterization of simpler systems like *C. elegans*, has prompted a shift away from an increasingly reductionistic approach to the study of the brain and nervous system, focused almost exclusively on molecular function at the synaptic level, to a renewed appreciation of the hierarchical complexity (gene, synapse, pathway, phenotype) of the nervous system (9) and the need to: a) integrate structure with function at the tissue and whole animal level; and b) integrate and iterate animal studies with emerging clinical research at both the systems and compound levels. Given emerging knowledge regarding the intrinsic complexity of the human brain, the success resulting from serendipity in the last 40 years is impressive and has provided a number of highly effective CNS drugs, the majority of which act synaptically, either mimicking (agonists), facilitating (transmitter uptake blockers, allosteric modulators) or antagonizing the effects of endogenous neurotransmitters and neuromodulators (10,11). Not only neurons but also glial cells - astrocytes, microglia, etc. are potential drug targets.

The function of the brain is extremely dynamic. Neonate, adult and aged brains are morphologically and phenotypically very distinct. Diseased brain can be very different from the 'normal', healthy brain. Transmitters and receptors present during development disappear in adult brain, while receptors change in number and function due to disease and nervous system trauma. Mechanisms to sustain brain homeostasis, including trophic factor maintenance of neuronal viability, are negatively impacted by aging, leading to an accumulation of environmental insults. Brain function is influenced by hormones, via the hypothalamic-pituitary axis (HPA; 3) and by peripheral e.g. cardiovascular/vascular, system function.

Global sales of CNS drugs in 1999, including pain, exceeded \$50 billion, approximately 15% of the total global drug sales. This market will continue to grow as the aging population increases (by 2030, the number of Americans 65 or older will double; 11) and life-style factors, including stress and information overload resulting from a breakdown in societal support systems for the individual (3,12,13).

The Decade of the Brain initiative of the 1990s was intended to "enhance the awareness of the benefits to be derived from brain research" and thus elucidate the cause(s) of CNS disorders, enabling development of effective treatments (14). Despite this and newer drug discovery technologies, both chemical and biological, that include draft sequences of the human genome (15), the discovery and timely development of CNS drugs remains one of the most challenging in pharmaceutical research (11). Factors contributing to this include: the inherent complexity of the brain; a paucity of knowledge regarding function at the molecular level - especially in disease states; animal models with limited predictive value; a lack of robust, quantitative diagnostic tools to track disease occurrence and progression; imprecise physician diagnoses of symptomatically related psychiatric disease states that frequently involve ethnic and cultural factors; and challenges in defining efficacy in human trials due to high placebo responses (16,17).

CNS drug discovery to date has thus been highly iterative in nature, building on established mechanism(s) of action of clinically effective compounds with improvements in tolerance and/or safety. The successful antidepressant SSRIs (selective serotonin reuptake inhibitors), e.g., fluoxetine, are mechanistically similar to the traditional tricyclic antidepressants (TCAs), e.g. imipramine. In addition, the reason for the superior efficacy of the 'atypical' antipsychotic medication, clozapine - the mechanism(s) of action of which has been repeatedly redefined as new CNS receptors have been identified - as compared with other dopamine (DA) receptor antagonists, has not been elucidated.

An additional complication in developing new CNS drugs is that drugs currently used for one indication can be used to treat different CNS disorders - e.g. valproate for epilepsy, bipolar affective disorder (BPAD), migraine (18) and dementia-associated agitation, and anticonvulsants, e.g. gabapentin, that modulate neuronal firing are used for the treatment of neuropathic pain and, potentially, BPAD.

Diagnosis and classification of CNS disorders relies on two key reference works: the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) and the International Classification of Diseases - Revision 10 (ICD-10), the European equivalent of DSM-IV. While invaluable tools, their use is confounded by ethnic -, societal - and gender- related differences in patient diagnosis. CNS diseases also have a high incidence of co-morbidities - depression is associated with chronic pain and excessive stress and alcoholism with depression, anxiety and cognitive impairment. The neuronal loss associated with stroke leads to cognitive dysfunction, mood disorder(s) and

TABLE 1: TRENDS IN PSYCHIATRIC DRUG TREATMENT

Disease State	Current Approaches	Experimental Approaches
Schizophrenia	DA receptor blockers – haloperidol, clozapine, chlorpromazine, risperidone, olanzapine	DA: Clozapine-like agents, partial agonists, D4 receptor antagonists. NMDA receptor/glycine modulators – D-serine, serine racemase α -7 nicotinic receptor agonists 5HT _{2A} inverse agonists – AC 90179 Neurokinin-3 and cholecystokinin ₁ antagonists
Depression	TCAs - imipramine, amitriptyline: Monoamine oxidase inhibitors (MAOIs) - tranylcypromine SSRIs - citalopram, fluoxetine SNRIs (5HT/ NE reuptake inhibitors) - venlafaxine	Improved monoamine uptake inhibitors 5HT _{1A} receptor ligands NK-1 receptor antagonists Corticotropin releasing factor (CRF) receptor antagonists
Bipolar Affective Disorder	Lithium, valproic acid, carbamazepine	Antiepileptics: pregabalin, topiramate etc. Valproate analogs - TV-1901 etc.
Anxiety: panic disorder, OCD (obsessive-compulsive disorder) GAD (generalized anxiety disorder), PTSD (posttraumatic stress disorder), acute stress disorder	Benzodiazepines (BZs)- diazepam, clonazepam 5HT _{1A} partial agonists - buspirone SSRIs	Newer BZs: pagaclone, deramcidane 5HT _{1A} agonists: lesopitron, S-15535 Orphanin FQ receptor agonists – Ro 64-6198 CRF receptor antagonists
Attention deficit hyperactivity disorder (ADHD)	Psychostimulants – methylphenidate d-amphetamine	α 4 β 2- nicotinic receptor agonists – ABT-089 Histamine H ₃ antagonists - GT 2331 Monoamine uptake blockers - atomoxetine
Compulsive/addictive disorders : cocaine, amphetamine, heroin, alcohol, nicotine (smoking) addiction Recreational drug use Cannabinoid, PCP Compulsive disorders: Gambling, sexual behavior, eating (obesity, anorexia, bulimia)	Methadone, LAAM Naloxone Disulfiram Acamprosate Nicotine patches Bupropion Phenylpropanolamine Sibutramine Orlistat PPAR γ antagonists - troglitazone	DA transport blockers - RTI -113 D1 receptor ligands - DAS-431, CEE 03-310 Cocaine vaccine (TA-CD) and catalytic antibodies - mAb 15A10 Obesity: Leptin modulators, CART, GLP1, amylin, galanin, neuropeptide Y, α - MSH, famoxin, fatty acid synthase (FAS) inhibitors, orexin, melanocortin - 4 (MC-4)/SLC-1 and SOCS3 antagonists
Sleep disorders: sleep pattern disruption (jet lag) Insomnia, narcolepsy	Hypnotics- Secobarbital, triazolam, estazolam Modafinil, Melatonin	Agomelatine, Adenosine agonists H ₃ agonists – SCH 50971 Orexin agonists, NBI 34060
Sexual disorders Erectile dysfunction/ Female sexual dysfunction	Sildenafil Apomorphine	IC-531, BAY 38-9456 DA agonists

dementia; and the loss in cognitive function occurring in Alzheimer's disease (AD) leads to aggression, anxiety and depression. The overlap in symptoms between diagnostically distinct disease states and the high co-morbidity with other distinct CNS disorders makes clinical experimentation an absolute necessity in defining the utility of CNS drugs. The area is historically replete with compounds advancing to the clinic for one indication and being found to be useful for another (10).

TARGET DYNAMICS

Ongoing research, basic and applied, has continued to identify a number of new approaches to the treatment of CNS disorders that are currently to or through clinical trial validation. These are shown alongside existing approaches in Tables 1 and 2; some are incremental improvements on existing mechanisms (D4 antagonists for schizophrenia; valproate analogs) while others (D-serine for schizophrenia (19); caspase inhibitors for neurodegenerative disorders; vaccines for AD and stroke (20,21)) are highly novel approaches. In many instances however, the challenge in CNS drug R & D is in improving (reducing) the side effect liabilities for compounds active at a known CNS drug target (e.g. D2 receptor) to allow higher levels of drug to be administered. This can be accomplished by understanding the mechanism(s) by which known compounds produce their side effects and by then 'tuning out' this property or adding additional properties to newer compounds to overcome side effects. Side effects, while never a trivial issue, are of increasing importance, especially in CNS disorders requiring chronic therapy in a young population that is, apart from their disease-related disability, relatively healthy. For example, antipsychotics show a class-related phenomenon of QT-syndrome prolongation that can result in ventricular tachycardia, heart block and fatalities. This has been a major factor in the comparative lack of new drug approvals for this class (22).

A less obvious instance of potential side effect liability results from approaching the process of compound identification using a highly reductionistic molecular approach that lacks an integrated, pharmacological framework. The logic, *a priori*, is that by identifying a compound interacting with high affinity at a defined molecular target, it will lack interactions with other molecular targets. Leptin, the 167mer secreted from adipocytes, acts via leptin receptors to reduce food intake and was thought to represent a promising anorectic agent (23). However, acting via the hypothalamus, leptin also inhibits bone formation, an effect that would limit the chronic use of the peptide in obesity (24).

EXPLOITING THE GENOME OF THE BRAIN

A large number of chromosomal loci containing susceptibility genes potentially involved in disease etiology as well as gene candidates for schizophrenia, BPAD, etc. have been identified (25,26). Validation of these is based on epidemiological data showing a significant genetic contribution to disease etiology. Interactions between more than one susceptibility gene and environmental risk factors (the "envirome"; 27) clearly contribute to disease incidence, the norm of reaction factor - indicating that biology - and human behavior - cannot be classified simply in terms of DNA sequences (28). In schizophrenia, concordance rates between monozygotic and dizygotic twins are 50% and 15% with an overall heritability of 68% (29). Focusing on disease genes within chromosomal regions implicated through genetic linkage analysis (using DNA from affected family pedigrees) requires a case control study design involving large cohorts (200-500 of patients and controls) derived from ethnically homogeneous populations matched for age and sex. The quality of the case histories is crucial in assuring the validity of diagnosis and in identifying ethnically unmatched individuals who contribute to stratification effects. The identification of putative disease-associated genes in an initial population should be replicated in additional populations. However, gene association studies often fail to replicate due to locus or genetic heterogeneity or simply because of the poor quality of the collection. With the sequencing of the human genome and identification of more than 2.5 million single nucleotide polymorphisms (SNPs; 30), phenotypic traits will be increasingly correlated with genetic variability with the