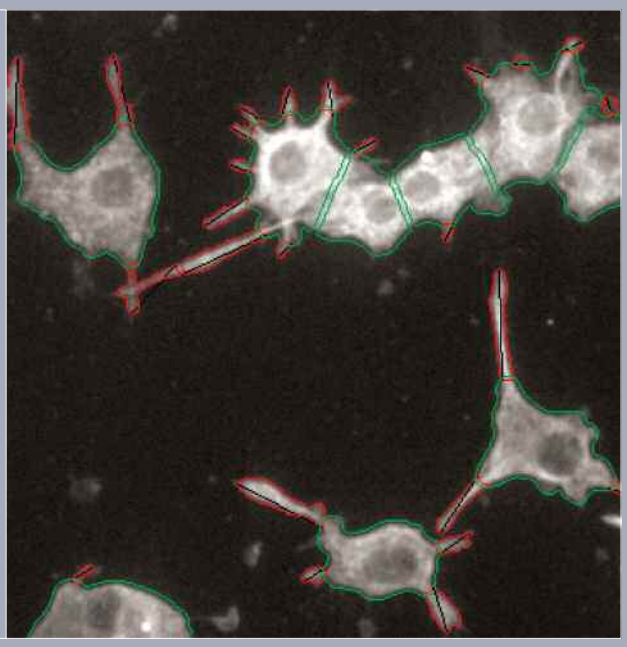
Translational Research Institute

Neuronal differentiation is essential for the formation of the mammalian nervous system. Activation of the Rho Kinase (ROCK) pathway by lysophosphatidic acid (LPA) causes neurite retraction. In order to examine the effect of ROCK inhibitors on the prevention of LPA-induced neurite retraction, PC12 cells were allowed to differentiate for 4 days in the presence of nerve growth factor before treatment with ROCK inhibitors and then stimulation with LPA. Cells were fixed and stained for α-tubulin, and nuclei were visualized by using Hoechst 33342 dye. Cells were imaged in a 96-well format with the IN Cell 1000 platform. Images were analyzed for neurite length (red) and cell count (green) by using the Developer Toolbox. Work done in the laboratory of Thomas Schröter, Ph.D., senior scientist.



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Director's Overview

The Translational Research Institute merges drug discovery efforts at the Scripps Research Florida campus with advanced technology platforms to rapidly identify and validate biological pathways that can be targeted for therapeutic intervention. The goal of the drug discovery operation is to discover and develop small-molecule therapeutic agents for unmet medical needs in neurodegeneration, Parkinson's disease, acute respiratory distress syndrome, glaucoma, spinal cord injury, cancer, and metabolic disorders, including insulin resistance, type 2 diabetes, and obesity, by targeting G protein–coupled receptors, proteases, ion channels, and kinases.

Patrick R. Griffin, Ph.D.

The drug discovery component of the Translational Research Institute is fully integrated with the following groups: Lead Identification and High-Throughput Screening, headed by Peter Hodder, Department of Molecular Therapeutics; Medicinal Chemistry, headed by William Roush, Department of Chemistry; Discovery Biology, headed by Phil LoGrasso, Department of Molecular Therapeutics; Drug Metabolism and Pharmacokinetics, headed by Mike Cameron, Department of Molecular Therapeutics; and Informatics, headed by Mark Southern.

The Lead Identification team enables drug-target lead identification via ultra-high-throughput screening technology. Using state-of-the-art automation and instrumentation, members in this group are responsible for developing and executing biochemical or cell-based high-throughput screening assays in a miniaturized 1536-well microtiter plate format. In addition to its support of internal Scripps Research objectives, the group participates in the National Institutes of Health Molecular Libraries Probe Production Centers Network (MLPCN), in which qualified assays are screened against the network's high-throughput screening compound library. Several internal and external investigators have accessed the group's expertise via collaborative or core-charge mechanisms.

The genomics core is headed by Brandon Young. Scientists in this core oversee genotyping and gene expression profiling. The services provided by the core allow Scripps Research investigators to examine the genome at both the genetic and the transcriptional level for the genes that underlie common diseases. In collaboration with colleagues on the Florida campus, members of the core have been involved in projects to identify the genes responsible for pathologic conditions, such as addiction and alcoholism, systemic lupus erythematosus, autism, obsessive-compulsive disorder, diabetes, obesity, and prion diseases.

The cell-based screening platform is headed by Julie Conkright, Department of Molecular Therapeutics. The faculty advisor to the core is Michael Conkright, Department of Cancer Biology. In this group, high-throughput technologies are used to provide a systematic description of the function of genes encoded by the human genome and a more comprehensive understanding of the genetic basis for human disease. Members of the group provide investigators access to genome-wide collections of cDNAs and short interfering RNAs that can be used to examine cellular models of signal transduction pathways and phenotypes. In addition, the cell-based screening platform participates in one of the center-based initiatives of the Scripps Research MLPCN center.

The proteomics platform is headed by Jennifer Caldwell Busby, Department of Molecular Therapeutics. The focus of this core is using liquid chromatography and state-of-the-art mass spectrometry technology to identify, quantify, and characterize proteins and protein modifications. Researchers in the core are involved in scientific collaborations in which novel technologies are used to identify biologically important proteins and protein modifications. Large-scale differential analysis is being used to map the pathways related to insulin sensitization and adipogenesis. In other projects, chromatographic enrichment techniques are used to identify sites of phosphorylation and other posttranslational modifications. Researchers in the proteomics core collaborate with other scientists to create experiments that will provide meaningful mass spectrometric results.

Investigators' Reports

Drug Discovery: Medicinal Chemistry Efforts

T.D. Bannister, Y. Feng, T.M. Kamenecka, C. Liang, W.R. Roush, Y. Chen, S. Chowdhury, X. Fang, Y. He, R. Jiang, M. Koenig, R. Noel, E.H. Sessions, Y. Shin, X. Song, T. Vojkovsky, Y. Yin

We seek to discover new compounds to treat diseases for which current therapies are inadequate. In our major programs during the past year, we targeted glaucoma, Parkinson's disease, and breast cancer. In each program, we have attempted to block the action of a specific protein kinase that is overactive or overabundant in affected patients and that hastens the progression of disease. In 2 of the programs, we began by identifying chemical leads from a high-throughput biochemical screen of the Scripps collection of more than 700,000 compounds. The structural information from these screens, in combination with computational and biological analysis of compounds made in other laboratories targeting the same enzymes, provides insights for modifying the structures to obtain unique and patentable leads with the required druglike biochemical, physical, and pharmacologic properties. All of these are evaluated internally by Scripps scientists in the biology, pharmacology, and drug metabolism and pharmacokinetics groups of the Translation Research Institute, who work closely with the medicinal chemists on fully integrated interdisciplinary project teams.

GLAUCOMA

We are designing inhibitors of the serine-threonine kinase ROCK, or Rho kinase, which regulates intraocular pressure by controlling the outflow of aqueous humor. Excess ROCK activity is associated with high intraocular pressure, which is a primary risk factor for glaucoma, and with retinal damage. Application of a ROCK inhibitor increases outflow, lowers intraocular pressure, and preserves retinal neurons. Current antiglaucoma drugs have limited efficacy or cause side effects, including discomfort, hyperemia (red eye), and/or undesired changes in cardiovascular function. No glaucoma drugs on the market act by directly altering the Rho kinase pathway, but ROCK inhibitors have strong pressure-lowering and neuroprotective effects and thus could be a valuable new treatment. An ideal ROCK inhibitor applied topically to the eye must simultaneously have many properties, including high ROCK affinity, aqueous solubility, excellent corneal permeability, high cellular penetration, and low ocular clearance, to provide a long-lasting effect. Most importantly, the inhibitor must be selective for ROCK over other enzymes and receptors so that no serious side effects occur.

We have synthesized thousands of new ROCK inhibitors in multiple chemical classes; many have low nanomolar potency in both biochemical and cell-based assays, high selectivity, and a profile of properties appropriate for preclinical development. For example, SR-3677 was tested in an animal model for glaucoma by our collaborator, V. Rao, Duke University, Durham, North Carolina. The inhibitor lowered intraocular pressure more than 30% within 1 hour, an efficacy comparable to that of antiglaucoma drugs in current use. The reduction in pressure waned after 2 hours, however, so we are designing other compounds intended to have a similarly powerful yet more sustained effect. As expected, the reduction in pressure was due to an increased rate of fluid outflow.

We have also made compounds that distinguish between the enzyme isoforms ROCK-I and ROCK-II to test their precise roles. An inhibitor selective for ROCK-II, for example, would lack any unwanted side effects due to ROCK-I inhibition. Such effects are unclear, because no other isoform-selective ROCK inhibitors targeting glaucoma are known.

PARKINSON'S DISEASE

In collaboration with the National Institute of Neurological Disorders and Stroke, we are developing a therapy to interrupt the loss of dopamine-containing neurons in the midbrain that is a hallmark of Parkinson's disease. Activation of the transcription factor c-Jun by c-Jun N-terminal kinase (JNK) promotes neurodegeneration. Inhibitors of JNK, which exist in 3 isoforms, JNK1, JNK2, and JNK3, are neuroprotective in animal models of Parkinson's disease. Our approach, using inhibitors selective for JNK2 and JNK3, would be a quantum leap in the clinical treatment of Parkinson's disease for several reasons. All current therapies merely treat the symptoms of the disease rather than address the underlying pathologic changes, they tend to lose therapeutic efficacy over time, and they typically elicit undesired side effects. Our challenge is to develop a compound that is a potent, selective, and cell-permeable JNK2/3 inhibitor; has the pharmacokinetic properties for oral dosing (ideally once a day); has good brain penetration; and has a benign toxicology profile.

We have synthesized thousands of new JNK inhibitors in multiple chemical scaffolds and are evaluating compounds with the best combination of properties in several preclinical animal models for Parkinson's disease. For example, in a pilot study, the Scripps JNK inhibitor SR-3306 delivered systemically to rodents via osmotic minipump at 10 mg/kg reduced CNS-mediated behaviors that occur after a chemically induced brain lesion used to mimic the parkinsonian condition. Newer generation compounds, including SR-3562, will soon be evaluated in animal models and are particularly promising because of improved properties, including high oral bioavailability (45%), high cell-based potency (0.06 μM), and excellent distribution to the brain of rodents after oral dosing.

CANCER

In collaboration with Poniard Pharmaceuticals, South San Francisco, California, we have synthesized many potent and selective novel inhibitors of focal adhesion kinase (FAK). FAK inhibitors could be an important new means of treating solid tumors, including breast cancer. FAK has been implicated in promoting detachment of tumor cells and metastasis, characteristics of almost all advanced-stage solid tumors that are responsible for most of the suffering and death related to cancer. By blocking FAK and thus stopping the first step of metastasis, the detachment of cancer cells from their primary site, we hope to halt this process and thereby interrupt progression of the disease. We have recently completed our FAK chemistry efforts after identifying highly potent and selective FAK inhibitors, including SR-2516. This lead compound is effective in in vitro tumor metastasis models, is efficacious in animal models of tumor progression, has desirable pharmaceutical properties suitable for convenient once-a-day oral dosing, and is being licensed for further development.

FUTURE DIRECTIONS

We are continuing our research on glaucoma and Parkinson's disease and have smaller or exploratory efforts in other areas, including methods for treating diabetes, for curbing drug addiction, and for targeting cancer progression by other mechanisms. We hope to expand these efforts. Many of the compounds identified in the ROCK and JNK inhibitor programs are also likely to be useful in the treatment of other diseases. For example, animal data suggest that ROCK inhibitors might be an effective treatment for multiple sclerosis. Strong preclinical evidence shows that JNK inhibitors, in addition to treating Parkinson's disease, also may prevent neuronal damage in a host of other disorders including stroke, Alzheimer's disease, and amyotrophic lateral sclerosis.

We anticipate that in each of our research programs we can continue to synthesize novel compounds with the right combination of properties that would permit development of the compounds as safe and effective agents for stopping the progression of important diseases.

PUBLICATIONS

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LoGrasso, P., Kamenecka, T. Inhibitors of c-jun-N-Terminal Kinase (JNK). Mini Rev. Med. Chem. 8:755, 2008.

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Proteomics Laboratory

J.A. Caldwell Busby, V. Cavett

The Proteomics Laboratory at Scripps Florida provides proteomics services and expertise to scientific collaborators at Scripps Research facilities in both Florida and California, universities within the state of Florida, and other educational institutions. We use cutting-edge mass spectrometry technology to identify proteins, map modifications that occur after translation, and do relative quantitation experiments with a variety of sample types.

In its lifetime, a protein can have several locations and functions within a cell. Location, function, and 3-dimensional structures of proteins are all influenced by static and dynamic chemical modifications that occur after translation. These modifications vary from small methyl and acetyl groups, which are part of the histone codes, to large lipid and glycosylation modifications, which act as cellular markers and signaling molecules. With mass spectrometry, we can detect both the small

and the large changes in mass that occur in proteins because of these modifications, and we can identify the specific amino acids modified.

Relative changes in protein levels or level of post-translational modification between multiple samples provide biologically relevant information about cellular pathways and proteins of interest. Large-scale studies of this type require rigorous sample preparation and highly tuned algorithms for comparing different mass spectrometric analyses. We are currently validating methods for both sample fractionation and data analysis for these types of large-scale differential protein experiments.

Mass spectrometers at the facility include an ion trap spectrometer, which is used mostly to identify proteins and peptides, and a triple quadrupole mass spectrometer, which is used for relative quantitation experiments. A new addition is a mass spectrometer that can be used to perform accurate mass and high-resolution experiments. Each mass spectrometer is interfaced to nano-flow electrospray ionization sources and capillary high-performance liquid chromatography columns.

Data analysis is performed primarily via automated workflow on a cluster maintained by the bioinformatics group. Automation of the front-end processing allows a more thorough review of the data and more time for development of innovative software in collaboration with information technology groups at Scripps Research and beyond.

Drug Metabolism and Pharmacokinetics Laboratory

M.D. Cameron, L. Lin, C. Ruiz, S. Khan, Z. Li

The Drug Metabolism and Pharmacokinetics Laboratory at Scripps Florida provides in vitro and in vivo evaluation of the pharmacokinetic and pharmacodynamic properties of new chemical entities. We work on project teams within the drug discovery group of the Department of Molecular Therapeutics and support chemistry efforts within the Scripps Research Institute Molecular Screening Center. We help bridge medicinal chemistry and pharmacology by evaluating the metabolic fate and identifying the liabilities of compounds. Pharmacokinetic studies provide basic parameters, including peak plasma concentration, bioavailability, exposure, half-life, clearance, volume of distribution, and tissue distribution. Research interests include P450 structure-function relationships and the formation of reactive intermediates during metabolism. The laboratory is equipped with a liquid chromatography–tandem mass spectrometry system and a Q-trap hybrid triple quadrupole/linear ion-trap mass spectrometer.

PUBLICATIONS

Cameron, M.D., Wen, B., Roberts, A.G., Atkins, W.M., Campbell, A.P., Nelson, S.D. Cooperative binding of acetaminophen and caffeine within the P450 3A4 active site. Chem. Res. Toxicol. 20:1434, 2007.

Cameron, M.D., Wright, J., Black, C.B., Ye, N. In vitro prediction and in vivo verification of enantioselective human tofisopam metabolite profiles. Drug Metab. Dispos. 35:1894, 2007.

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Miller, B.H., Schultz, L.E., Gulati, A., Cameron, M.D., Pletcher, M.T. Genetic regulation of behavioral and neuronal responses to fluoxetine. Neuropsychopharmacology 33:1312, 2008.

Cell-Based Screening Core

J.J. Conkright, G. Zastrow, J. Cartzendafner, M. Morris

The Cell-Based Screening Core provides high-throughput screening of functional genomic platforms and consults with researchers from Scripps, both in California and Florida; universities in Florida; and other outside academic institutions to perform these screens. We curate 2 large libraries: the Mammalian Genome Collection cDNA library and the Qiagen Druggable siRNA library. Screening these libraries allows investigators to determine if overexpression of a single gene (Mammalian Genome Collection cDNA library) or reduction in expression levels of a single gene (Qiagen siRNA library) positively or negatively influences their particular biological readout. These libraries provide investigators a unique tool to identify novel factors and pathways involved in biological systems. The findings can lead to new areas of research and novel targets for drug development.

In addition to our large libraries, we have 2 small libraries that we built: a transcription factor library and a nuclear receptor library. These libraries are important new tools for investigators who study the effects of proteins and signaling pathways on gene expression. These libraries are also a mechanism for studies of the specificity of new potential drugs and chemical probes that modulate gene expression.

A third area of expertise we provide is the generation of mutagenesis screens. Determining the regions

or residues in a protein that are important for its biological function can be a key component in dissecting how the protein interacts with other factors. Chemical mutagenesis of a gene permits an unbiased approach to identifying these biologically critical residues of the protein. We perform the mutagenesis and provide screening sets for investigators to examine the effect the mutation has on a chosen biological end point.

Last, we counsel researchers on how to validate their screens and counterscreen the rank-order hits. These tasks are extremely important to prove the statistical significance of a finding and to ascertain the specificity of the finding for that precise biological function or pathway.

PUBLICATIONS

Amelio, A.L., Miraglia, L.J., Conkright, J.J., Mercer, B.A., Batalov, S., Cavett, V., Orth, A.P., Busby, J., Hogenesch, J.B., Conkright, M.D. A coactivator trap identifies NONO ($p54^{nrb}$) as a component of the cAMP-signaling pathway. Proc. Natl. Acad. Sci. U. S. A. 104:20314, 2007.

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Discovery Biology: Kinases

D.R. Duckett, J. Anderson, W. Chen, D. Harmey, Y.Y. Ling

We are investigating the use of small-molecule kinase inhibitors of biologic interest and therapeutic potential. Protein kinases are important components of signal transduction pathways, and deregulation of kinase activity in humans can lead to disease. Kinases have become one of the most important target classes for drug development. We are optimizing a novel class of kinase inhibitors for treatment of Parkinson's disease. Although the cause of Parkinson's disease is unknown, a strong correlation exists between loss of primary dopaminergic neurons within the substantia nigra and progression to the diseased state.

Our current goal is to develop an inhibitor of the Jun N-terminal family of kinases; our aim is to protect the primary dopaminergic neurons from cell death, thus slowing or halting the progression of the disease. Working closely with scientists in other disciplines necessary for lead optimization (chemistry, pharmacology, and drug metabolism), we were successful in securing funding from the National Institute of Neurological Disorders and Stroke for this research.

We are also investigating the role of MAP kinases in primary brain cancers. In 2008, brain tumors will be diagnosed in approximately 20,000 patients in the United States. The prognosis for these patients is poor, and treatment options are limited. We will focus on defining the role Jun N-terminal kinase signaling plays in tumor maintenance and cell dispersal and whether inhibition of this kinase has therapeutic potential in this devastating disease.

In addition, we are involved in the Scripps-Pfizer collaboration that was started in 2007. Since then, several assays have been designed for high-throughput screening of targets of therapeutic interest to Pfizer.

PUBLICATIONS

Jiang, R., Duckett, D., Chen, W., Habel, J., Ling, Y.Y., LoGrasso, P., Kamenecka, T.M. 3,5-Disubstituted quinolines as novel c-Jun N-terminal kinase inhibitors. Bioorg. Med. Chem. Lett. 17:6378, 2007.

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Probe and Drug Discovery: The Lead Identification Department

P. Hodder, A. Abovich, P. Baillargeon, P. Chase, M. Crisp, L. DeLuca, R. Einsteder, K. Emery, F. Madoux, B. Mercer, D. Minond, M. Petrillo, A. Porto, S. Saldanha, L. Scampavia, M. Spaargaren, T. Spicer, V. Fernandez-Vega

The Lead Identification Department is responsible for developing and executing high-throughput screening (HTS) assays and for supporting downstream medicinal chemistry and related "hit-to-lead" efforts (Fig. 1). The anchors of the department are 2 fully automated robotic platforms. One supports screening of 384- and 1536-well microtiter plates in a variety of biochemical and cell-based assay formats. The other is used to manage and distribute the more than 600,000 compounds used for drug discovery at Scripps Research and 300,000 compounds for the Molecular Libraries Probe Production Centers Network. The facility also contains an assay development laboratory, equipped with bacterial culture, protein purification, compound characterization, and tissue culture laboratories as well as semi-automated equipment for liquid handling and

Fig. 1. The uHTS laboratory of the Lead Identification Department houses equipment and instrumentation necessary to develop and support a uHTS campaign and medicinal chemistry follow-up efforts. The anchor of the department is a fully automated uHTS platform (center right), which is used to screen libraries of compounds for biological activity in a variety of pharmacologically relevant assays, including cell-based, protein, RNA, and DNA targets. Flanking the uHTS platform are an assay development laboratory (left and center) containing equipment and instrumentation necessary to develop an HTS assay and a mammalian tissue culture suite (upper right). Behind the uHTS platform (not shown) is a fully automated compound management platform capable of storing, retrieving, and aliquoting desirable compounds from the screening file and a liquid chromatography–mass spectrometry platform (bottom right) used to perform routine compound quality assurance/quality control. Not shown are fully equipped protein expression/purification and microbiology laboratories.

detection. Supporting this operation is an integrated laboratory information management system, which tracks HTS assay data and compound usage and quality. Additionally, we are involved in developing metallo-β-lactamase class B1 chemical probes.

THE SCRIPPS RESEARCH INSTITUTE MOLECULAR SCREENING CENTER

Established in July 2005, the Scripps Research Institute Molecular Screening Center is a national resource for small-molecule screening and the development of chemical probes. It is 1 of 9 members in the Molecular Libraries Probe Production Centers Network, a translational research initiative sponsored by National Institutes of Health (NIH) and part of the NIH Roadmap. The mission of the Scripps center is to screen the NIH library of more than 300,000 individual compounds against peer-reviewed targets; the goal is to discover proof-of-concept probes. The results are available to the scientific community through the PubChem Web site of the National Center for Biotechnology Information: http://pubchem.ncbi.nlm.nih.gov. Currently, the Lead Identification department serves as the HTS core within the Scripps screening center; our responsibilities are to develop biological and biochemical assays, perform HTS campaigns, manage the resulting data, act as steward of the NIH screening library, and provide assay support for the development of probes.

OTHER SCREENING ACTIVITIES

Since the inauguration of the ultra-HTS (uHTS) operation in November of 2005, we have also been actively screening the Scripps collection of compounds against drug discovery targets not only from the MLPCN but also from scientists at Scripps Research and from outside partners. So far, members of the department have initiated and successfully completed more that 50 uHTS-related collaborations (Table 1) and have contributed to the discovery more than 10 novel leads (chemical probes) of G protein–coupled receptors, metalloproteinases, nuclear receptors/transcription factors, and kinases (http://molscreen.florida.scripps.edu/).

DISCOVERY AND DEVELOPMENT OF CLASS B METALLO-β-LACTAMASE INHIBITORS

The diversity of bacterial β-lactamases continues to outpace the development of useful β-lactam–based antibiotics. Although the development of class B β-lactamase inhibitors has been an active area of past research, an array of potent, class-specific small-molecule inhibitors has yet to be fully characterized in the clinically relevant VIM-2 metallo-β-lactamase system. Additionally, VIM-2 inhibitors that are effective inhibitors of other class B β-lactamases will be of great interest. Such compounds will be useful as tools for characterizing gram-negative pathogens or as adjuvant in antibiotic therapy.

One of our goals is to develop HTS-ready assays suitable for rapid identification of compounds that modulate the activity of Ambler molecular class B (Bush-Jakoby-Medeiros group 3) metallo-β-lactamases, specifically VIM-2 and IMP-1 enzymes. In preliminary research efforts, we have developed HTS-ready fluorescence- and absorbance-based VIM-2 and IMP-1 inhibition assays. In collaboration with K.B. Sharpless, Department of Chemistry, we have screened a diverse click-chemistry library or compounds designed specifically to inhibit metallo-β-lactamases. Currently we are developing several novel scaffolds that appear to be specific inhibitors.

PUBLICATIONS

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Table 1. Summary of collaborations in the development of HTS and HTS assays.

Target class	Target name (Abbreviation)	Collaborator, affiliation
Antibacterial	*Pseudomonas aeruginosa*	R. Miller, Pfizer, Groton, Connecticut
ATPase	p97	R. Deshaies, California Institute of Technology, Pasadena, California
β-Lactamase	VIM-2	P. Hodder, Scripps Research, Jupiter, Florida
	IMP-1	
G protein–coupled receptor	$5HT_{1a}$	M. Teitler, Albany Medical College, Albany, New York
	$5HT_{1e}$	
	GalR2	S. Brown, Scripps Research, La Jolla, California
	GPR7	O. Civelli, University of California, Irvine, California
	$S1P_1$	H. Rosen, Scripps Research, La Jolla, California
	$S1P_2$	
	$S1P_3$	
	$S1P_4$	
	AGTRL-1 (APJ)	L. Smith, Burnham Institute for Medical Research, Orlando, Florida
	GLP-1	P. LoGrasso, Scripps Research, Jupiter, Florida
	GPR119	P. McDonald. Scripps Research, Jupiter, Florida
	m Opioid heterodimers	L. Devi, Mt. Sinai School of Medicine, New York, New York
	NPY- Y1	C. Wahlestedt, Scripps Research, Jupiter, Florida
	NPY- Y2	
Hydrolase	RBBP9	B. Cravatt, Scripps Research, La Jolla, California
	b-gluc	J. Kelly, Scripps Research, La Jolla, California
Ion channel	Aquaporins (AQP)	M. Yeager, Scripps Research, La Jolla, California
	TRPML3	S. Heller, Stanford University, Stanford, California
	TRPN1	
Kinase	JAK2	R. Levine, G. Gilliland, Sloan Kettering, New York, New York
	JNK3	P. LoGrasso, Scripps Research, Jupiter, Florida
	ROCK2	T. Schröter, Scripps Research, Jupiter, Florida
	PKA	
	FAK	P. Hodder, Scripps Research, Jupiter, Florida
Metalloproteinase	ADAMTS4	G. Fields, Florida Atlantic University, Boca Raton, Florida
	MMP13	
	MMP8	
	Falciparum M18 metalloprotease	D. Gardiner, Queensland Institute of Medical Research, Queensland, Australia
	IDE	M. Leissring, Mayo Clinic, Jacksonville, Florida
NADPH oxidase	Nox-1	G. Bokoch, Scripps Research, La Jolla, California
Nuclear receptor	SHP-1	P. Griffin, Scripps Research, Jupiter, Florida
	Estrogen receptor	K. Nettles, Scripps Research, Jupiter, Florida
	RAR	P. Griffin, Scripps Research, Jupiter, Florida
	SF1 (NR5A1)	X. Li, Orphagen Pharmaceuticals, San Diego, California
	RORa (NR1F1)	
Phosphotransferase	TPT1	H. Harding, New York University, New York, New York
Proliferation/viability	Jurkat E6.1 cells	P. Hodder, Scripps Research, Jupiter, Florida
Protein/protein	EphB4-ephrinB2	P. Kuhn, Scripps Research, La Jolla, California
	HCV core homodimer	D. Strosberg, Scripps Research, Jupiter, Florida
	NS5B/CYPB	
Protein misfolding	Hsp70	R. Morimoto, Northwestern University, Chicago, Illinois
	AL-09	M. Ramirez-Alvarado, Mayo Clinic, Rochester, Minnesota
	PERK	D. Ron, New York University, New York, New York
Protein/RNA	HIV Rev-RRE RNA	J. Williamson, Scripps Research, La Jolla, California
Reductase	msrA	H. Weissbach, Florida Atlantic University, Boca Raton, Florida
Stem cell proliferation	Notch	H. Petrie, Scripps Research, Jupiter, Florida
Transcription factor	PPARg/Src1	P. Griffin, Scripps Research, Jupiter, Florida
	PPARg/Src2	
	PPARg/Src3	
	NF-kB	J. Reed, Burnham Institute for Medical Research, La Jolla, California
	STAT1	D. Frank, Dana-Farber Cancer Institute, Boston, Massachusetts
	STAT3	
	KLF5	V. Yang, Emory University, Atlanta, Georgia
	AHR	M. Denison, University of California, Davis, California
Ubiquitin proteolysis	WEE1	N. Ayad, Scripps Research, Jupiter, Florida

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Discovery Biology: G Protein–Coupled Receptors

P. McDonald, D. Obradovich, A. Smith, E. Sturchler, S. Tabrizifard

G protein–coupled receptors (GPCRs) are the largest and most versatile family of cell-surface receptors. The ubiquitous cell-surface distribution and involvement of these proteins in almost all biological processes explain why the largest percentage of currently marketed therapeutic drugs target these receptors. We focus on developing biochemical and cell-based functional assays to monitor GPCR activity that involve high-throughput and high-content technologies. Using a multidisciplinary approach that involves collaborations with disciplines such as lead identification, chemistry, drug metabolism and pharmacokinetics, and in vivo pharmacology, we aim to identify and develop small-molecule modulators of GPCRs for the treatment of metabolic diseases such as type 2 diabetes mellitus and obesity.

We have developed a series of novel cell-based assays for the glucagon-like peptide 1 receptor (GLP-1R) to promote a drug discovery program for this clinically validated target of type 2 diabetes. In parallel with the GLP-1R assays, we have developed similar assays for 2 other closely related receptors, GLP-2R and glucagon receptor, which serve as counterscreens for selectivity against GLP-1R. We are also working on an orphan GPCR that has been implicated in type 2 diabetes and obesity and that signals and functions in an analogous manner to GLP-1R. In collaboration with P. Kenny, Molecular Therapeutics, we are also developing small-molecule inhibitors of a GPCR previously shown to be involved in drug dependence that may lead to a novel therapy for substance abuse.

As part of the collaboration between Scripps and Pfizer, Inc., that was initiated in 2007, we are designing and developing 3–4 assays per year for GPCR targets of therapeutic interest to Pfizer.

In Vivo Pharmacology

A.S. Pachori, M. Ganno, S. Khan, S. Clapp, D. Hansen

The In Vivo Pharmacology group at Scripps Florida is an integrated group of investigators involved in preclinical studies in support of drug discovery efforts at Scripps Research in both Florida and California. We develop appropriate animal models of diseases for ongoing projects such as studies in hypertension, glaucoma, Parkinson's disease, diabetes, and heart failure. These models are then used to test the efficacy of new compounds for a particular therapeutic area. An important aspect of establishing the efficacy of a compound is to determine if the compound is altering its intended target. We initially evaluate the role of a particular target in primary cell culture and then evaluate the target in vivo. The cell culture experiments are also used to screen novel compounds for the effects of the compounds on targets.

In addition, we evaluate the pharmacodynamic properties of new chemical entities in vivo by doing dose-response and time-course studies to determine the effects of the compounds on the intended target. For these evaluations, we use standard techniques such as Western blotting, enzyme-linked immunosorbent assays and immunohistochemistry. We also collaborate with the drug metabolism and pharmacokinetics laboratory to monitor plasma and tissue concentrations of chemical entities; the results help us further refine and develop the disease models. Finally, we evaluate the compounds for toxicity.

In the past year, we have successfully developed animal models of hypertension to test the efficacy of Rho kinase inhibitors as novel antihypertensive agents. We have screened several novel Rho kinase inhibitors for their efficacy and toxicity and established the need for isoform-selective inhibitors to avoid toxicity issues.

We have also established the use of primary dopaminergic neurons in an in vitro target modulation assay to screen compounds for treatment of Parkinson's disease. In addition, we have adopted a strategy to explore and seek alternative therapeutic uses for novel compounds currently under development. For example, we have expanded the use for novel Jun N-terminal kinase inhibitors for Parkinson's disease to include their use as cytoprotective agents against heart failure induced by ischemia-reperfusion injury. Our preliminary data indicate that in rodents, these inhibitors can successfully reduce tissue damage in a dose-dependent manner. We are also exploring the use of Rho kinase inhibitors, which were originally developed as antihypertensive agents, in the treatment of glaucoma. This strategy will help us not only expand our portfolio but also discover new approaches for some of the biggest unmet needs of patients.

Omics Informatics

B.D. Pascal

The Omics Informatics group at Scripps Florida addresses support and software needs of various laboratories. Our goals are to identify and integrate existing solutions where possible and to build new solutions only when necessary. A primary specialization is the analysis and management of mass spectrometric data and development of proteomics software research tools that enable proteomics researchers to validate, visualize, and share their data.

HD DESKTOP

Scientists at Scripps Florida are using hydrogen-deuterium exchange mass spectrometry to characterize protein dynamics and protein-protein or protein-ligand interactions. The Deuterator software, released last year, addresses some of the data analysis bottlenecks by providing a platform to automate and visualize centroid calculations. Despite these efforts, the task of assembling and visualizing the resulting data is still a manual operation left to the end user. The current software, HD Desktop, leverages the existing code base and stores all data in a relational database. Novel rendering and analysis tools have been presented in an integrated user interface (Fig. 1).

MASS SPECTROMETRY CALIBRATION SOFTWARE

Although every mass spectrometry laboratory will vary in instrument manufacturer and experimental designs, most proteomics laboratories have a common need to measure and validate the calibration of the instruments. An automated method to process and display the mass calibration shift at various time points allows the maximization of instrument run time and contributes to the standardization and validation of proteomics data.

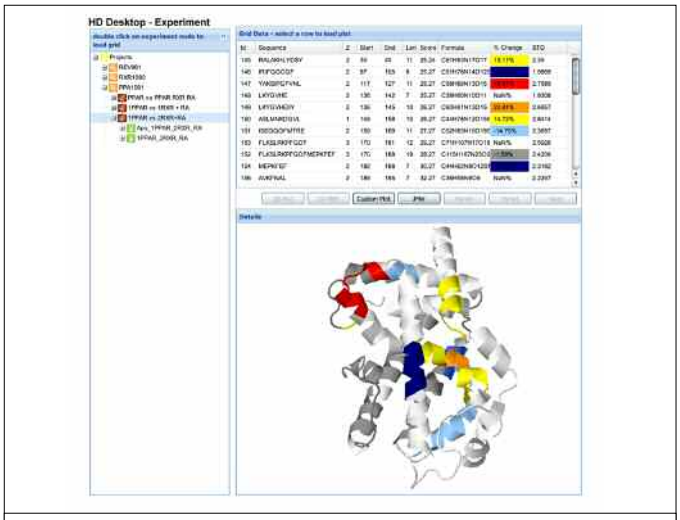

Fig. 1. HD Desktop experiment view.

We have developed an automated method for determining calibrated mass drift on high-resolution instruments. On a daily basis, the quality of the data collection is monitored by routine analysis of a tryptic digest of a β-casein standard. The resulting binary files are collected, moved into the laboratory information management system, and then processed through an automated workflow, which conducts file conversions and peak quality assessments and sends the files to a compute cluster for peptide identification search. The results are then parsed, and the difference between the observed and calculated mass is stored in a database; the data are made available through a Web-based interface (Fig. 2, page 377).

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Drug Discovery Biology: Cell Biology

T. Schröter, A.M.W. Handy, E. Griffin, J.R. Pocas, K. Clarke, C. Hahmann

With more than 500 members, protein kinases are important drug discovery targets for a wide variety of therapeutic indications. These

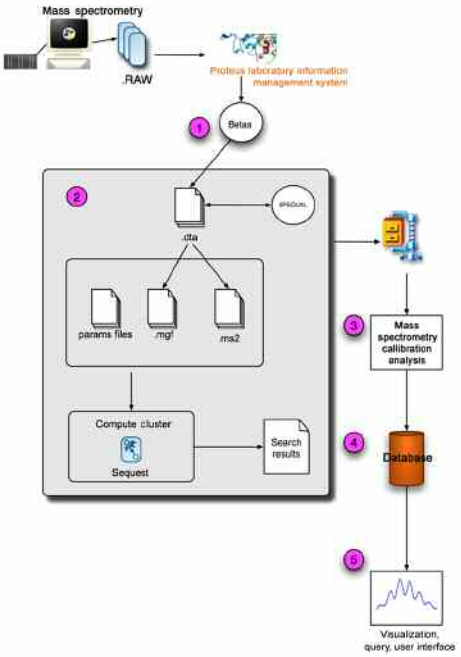

Fig. 2. Data flow of mass spectrometry calibration software.

kinases control signal transduction pathways, and in humans, deregulation of their activity can lead to diseases such as glaucoma and cancer. The serine-threonine kinase Rho kinase (ROCK) regulates intraocular pressure by controlling the outflow of aqueous humor. In glaucoma, increased intraocular pressure leads to loss of retinal ganglion cells and, ultimately, loss of vision. Inhibition of ROCK activity increases outflow, lowers intraocular pressure, and preserves retinal neurons. We concentrate on developing biochemical and cell-based functional assays to monitor ROCK activity via both high-content and high-throughput screening technologies.

Working closely with researchers in high-throughput screening, medicinal chemistry, pharmacology, and drug metabolism and pharmacokinetics, we identified small-molecule lead compounds from a high-throughput screening of the Scripps collection of more than 700,000 compounds. During lead optimization, we screened thousands of new ROCK inhibitors for the biochemical activity against the enzyme and the close family members protein kinase A, Akt1, and MRCKα. Hundreds of these compounds were chosen, and their cell-based activity against ROCK was tested by using target modulation and functional assays. Changes in myosin light-chain phosphorylation were measured by using a 96-well immunocytochemical assay and infrared imaging, and changes in the formation of stress fibers and neurite protection were evaluated by using a high-content imaging system.

For the cancer program, in 2007, we successfully finished a collaboration with scientists at Poniard Pharmaceuticals, Inc., South San Francisco, California, to discover novel inhibitors of focal adhesion kinase. This kinase has been implicated in tumor cell detachment and metastasis. We supported the program by developing biochemical and cell-based assays to monitor the effect of newly discovered small molecules on biochemical inhibition of focal adhesion kinase and on cellular growth, migration, and invasion. We are also collaborating with researchers at Pfizer, Inc., in developing biochemical and cell-based high-throughput screening assays for a diverse set of novel disease targets, including protease inhibitors, hydrolases, and membrane transporters.

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Chemical Informatics Program

S.C. Schürer, D. Vidović, C. Chung

We collaborate with scientists in the Scripps Research Institute Molecular Screening Center, and we also received a grant from the Columbia University Molecular Library Screening Center. Both of these centers are part of the national Molecular Libraries Screening Centers Network. We are also involved in drug discovery efforts within the Translational Research Institute. We have developed a platform of industry-standard software tools for analysis, visualization, hypothesis building, and modeling of large and focused experimental screening data sets. Our platform enables us to generate and evaluate a large variety of structural, pharmacophore, and physicochemical 2- and 3-dimensional descriptors. The platform includes computational chemistry tools for 3-dimensional pharmacophore-alignment ligand-based quantitative structure-activity relationships, ligand-protein docking (in a variety of approaches and scoring functions), homology modeling, molecular modeling and dynamics, and statistical tools.

We have also developed various interactive reporting and visualization protocols that are used in collaborative research. Our platform provides broad chemical informat-

ics and computational chemistry capabilities. Examples of research projects in which these technologies play a key role include analysis of data on toxic effects in cells and animals; development of small-molecule modulators of a broad variety of targets, including metalloproteases, phosphatases, kinases, nuclear receptors, and sphingosine lipid receptors (for which we also modeled the receptor structures); and image-based high-content assays, including probing the inflammatory pathway at the stage of NF-κB translocation and expression of E-selectin or vascular adhesion molecule 1 and targeting the aggregation of the protein huntingtin.

In collaboration with the screening informatics team, we play a key role in implementing work flow, procedures, and business rules and in integrating discovery informatics with the operational informatics infrastructure to facilitate discovery processes. Examples include the Scripps Research compound registration system; integration of the Molecular Libraries Screening Centers Network chemoinformatics server, which is hosted at Scripps Research, with PubChem; integration of images from image-based screening with the operational infrastructure; and publication of screening data to PubChem. To date, more than 5.5 million data points and more than 120 assays obtained by using these protocols have been published.

Other chemoinformatics research efforts are focused on structure-based comprehensive analyses of target-similarity relationships in the phosphatase and kinase gene families, ligand-based and target "fishing," and the development of integrative applied chemoinformatics methods.

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Screening Informatics Program

M.R. Southern, K. Hoda, Y. Cruz

Scientists in the Screening Informatics Program at Scripps Florida collaborate broadly with researchers in the Scripps Research Institute Molecular Screening Center, part of the national Molecular Libraries Screening Centers Network, and in drug discovery efforts within the Translational Research Institute. Our responsibilities include high- and low-throughput screening assays and downstream drug metabolism and pharmacology, medicinal chemistry, and probe development. We have an operational environment for data management and quality assurance and a knowledge environment that facilitates efficient optimization of probes. These activities take place at both the Florida and the California sites.

The software systems have been built primarily by using the MDL Discovery Experiment Management Framework from Symyx Technologies, Inc., Santa Clara, California, and support specific work flows involving tasks such as chemical compound registration, plate and sample registration, assay development, and entire screening campaigns. On top of these systems, we have developed in-house software that is tightly coupled to provide additional functionality and to improve our efficiency. Examples include robotic automation, plate mapping operations, and structure search. A key component is our Assay Exploration Data Warehouse, which along with its Web-based front end is known to end users as ChemInfo.

ChemInfo is assay metric and structure centric, enabling exploration of assay data by compound, target, or assays. It integrates chemical descriptors, physical properties, and data on drug metabolism and pharmacokinetics to facilitate probe optimization. Complicated Venn-like queries are possible. ChemInfo contains individual and aggregated assay data from our internal assays as well as from PubChem. The database has up to 30 users within Scripps Research.

PUBLICATIONS

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