CCR frontiers IN SCIENCE

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Contents

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■ STRUCTURAL BIOLOGY

Structure of the 12-Helix Oxalate Transporter Determined by 3D Electron Microscopy

Hirai T, Heymann JA, Maloney PC, and Subramaniam S. Structural model for 12-helix transporters in the major facilitator superfamily. *J Bacteriol* 185: 1712-8, 2003.

Transport proteins represent approximately 30 percent of integral membrane proteins in several prokaryotic and eukaryotic genomes. We hope to contribute to a detailed mechanistic understanding of transport proteins by determining the molecular structure of selected transporters. Only a handful of atomic-resolution structures are available for these proteins, and then only rarely is there insight into the atomic basis of how protein structural changes are coupled to ion transport.

The class of transporters called facilitators (or carriers) mediates the reactions of uniport, symport, or antiport. Within this class, the major facilitator superfamily (MFS) encompasses the largest number of evolutionarily related examples. Individual MFS members function in settings that range from the accumulation of nutrients by bacteria to the cycling of neurotransmitters across synaptic membranes in humans, but it is believed that all MFS members share a common structural basis, such as 12 transmembrane α-helices. This structural theme is noted in many other transport systems, including those within the ATP-binding cassette transporter superfamily.

We obtained 2D crystals of the oxalate transporter (OxlT) in lipid bilayers by detergent dialysis starting from protein purified in the oxalate-bound state in the

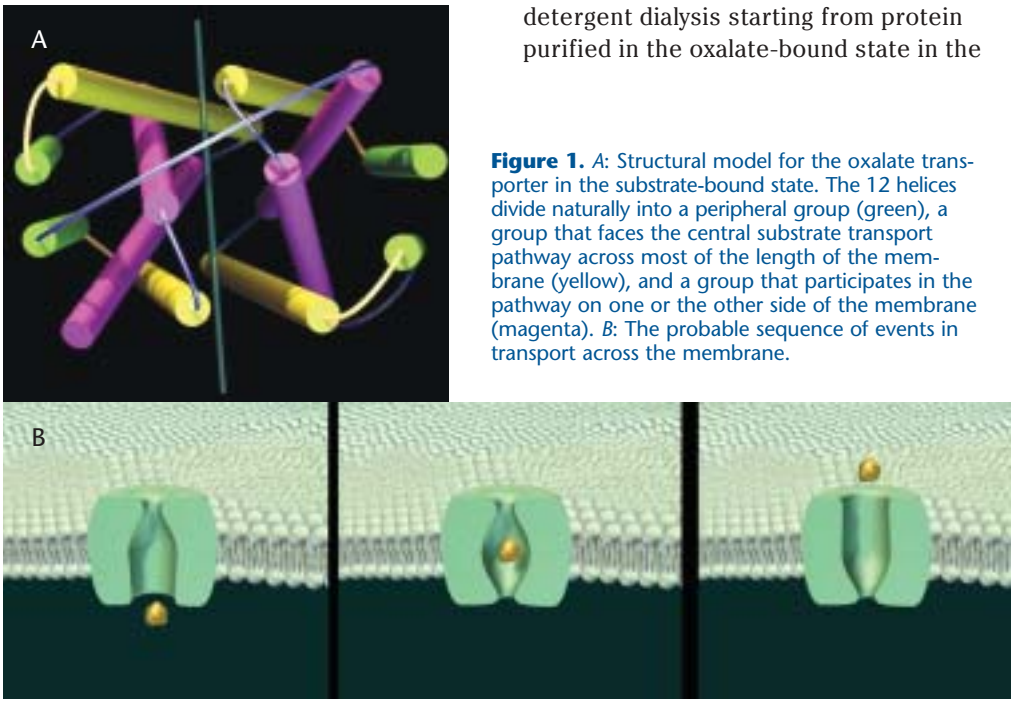

Figure 1. *A*: Structural model for the oxalate transporter in the substrate-bound state. The 12 helices divide naturally into a peripheral group (green), a group that faces the central substrate transport pathway across most of the length of the membrane (yellow), and a group that participates in the pathway on one or the other side of the membrane (magenta). *B*: The probable sequence of events in transport across the membrane.

presence of lipid/detergent micelles. Images of oxalate-bound crystals cooled to liquid nitrogen temperatures were then recorded in an electron microscope at –180°C. Because the specimen-containing stage can be tilted to varying angles relative to the electron beam, we were able to combine information from images recorded at different specimen tilts to reconstruct the 3D structure of the protein at 6.5-Å resolution (Hirai T et al. *Nat Struct Biol* 9: 597-600, 2002).

The 12 helices in the molecule are arranged around a central cavity, which is widest in the center of the membrane (Figure 1A). The helices divide naturally into a peripheral group, a second group that faces the central substrate transport pathway across most of the length of the membrane, and a third group that participates in the pathway on one or the other side of the membrane. A unit of an OxlT molecule consists of one helix from each group. Each half of the molecule consists of two units (that is, six helices). The interface between the two halves represents the transport pathway of the substrate. Within each half, the two units appear to be in structurally equivalent positions. In each unit, one highly tilted helix (from the third group) interdigitates into the space occupied by the neighboring unit. This arrangement of helices represents a novel fold for a membrane protein, and its provocative symmetry suggests a plausible explanation for bi-directional substrate transport by proteins in this family.

The high symmetry in the molecular architecture of OxlT in our proposed model is not only consistent with the idea that MFS proteins are the result of a gene duplication, but also suggests that MFS proteins may have developed from an ancestral precursor that contained three transmembrane segments.

Our work with OxlT represents the first glimpse into the architecture of an MFS transporter. In principle, there are about one billion ways in which the helices can be positioned into the 6-Å density map we obtained by electron microscopy. However, by combining the density map with extensive bioinformatic analysis of proteins in the family, we proposed a helix assignment for all MFS proteins (Hirai T et al. *J Bacteriol* 185: 1712-8, 2003). Two papers have just been published that report the X-ray structure of two other MFS proteins (lac permease and the glycerol transporter) (Abramson J et al. *Science* 301: 610-5, 2003; Huang Y et al. *Science* 301: 616-20, 2003). In our work on OxlT, we described the structure of the central state (Figure 1B), whereas the X-ray structures of the other two MFS proteins have revealed the structure of the cytoplasmically open state. Regardless, the helix assignment reported for these two proteins is identical to ours, confirming our assignment and proposal of a common structural model for all MFS proteins.

High-resolution imaging with electron microscopy is a field still in its infancy. So far the atomic structures of only four proteins have been obtained using electron microscopy. Yet this slow and often tedious process is leading to the development of unprecedented and powerful imaging methods to study the structures of large protein complexes and cellular assemblies. Reconstructions of 3D volumes of even whole cells at resolutions one to two orders of magnitude better than that achieved by optical microscopy now seem within reach. Such reconstructions may provide a cell-based context for unifying other structural data obtained from conventional crystallographic and single-molecule imaging approaches. Thus it may become possible to determine the spatial arrangements of key proteins and other complexes within specific microbial (or other) cell types, with the exciting prospect of following how these arrangements change during different stages of cellular signal transduction.

■ **Sriram Subramaniam, PhD**
Principal Investigator
Laboratory of Cell Biology
NCI-Bethesda, Bldg. 50/Rm. 4306
Tel: 301-594-2062
Fax: 301-480-3834
ss1@nih.gov

■ CARCINOGENESIS

Loss of *Brca1* and Development of Breast Cancer in Mice

Weaver Z, Montagna C, Xu X, Howard T, Gadina M, Brodie SG, Deng CX, and Ried T. Mammary tumors in mice conditionally mutant for *Brca1* exhibit gross genomic instability and centrosome amplification yet display a recurring distribution of genomic imbalances that is similar to human breast cancer. *Oncogene* 21: 5097-107, 2002.

Loss of one copy of the *BRCA1* tumor suppressor gene is responsible for increased susceptibility to familial breast and ovarian cancer. To examine the genetic pathways that lead to *BRCA1*-related tumorigenesis, we constructed a mouse model of this inherited form of breast cancer (Xu X et al. *Nat Genet* 22: 37-43, 1999). Our conditional knockout approach demonstrated that excision of exon 11 of *Brca1* in the mouse results in mammary tumor formation after long latency. The latency period suggests that additional genetic changes are necessary for tumorigenesis. We were thus able to use the tumors from this model to characterize the genetic changes that occur secondarily to *Brca1* mutation. We also characterized several *Brca1* conditional tumors from a $p53^{+/-}$ background. Our study found that all tumors exhibit chromosomal instability, as evidenced by structural chromosomal aberrations and aneuploidy,

yet they display a pattern of chromosomal gain and loss similar to the pattern in human breast carcinomas.

DNA gains and losses in the tumors were mapped using comparative genomic hybridization (CGH), which allowed us to compare the distribution of genomic imbalances between human and mouse. For example, a commonly gained region on mouse chromosome 11 centered on bands 11D–E, a region orthologous to human chromosome 17q11–qter, which is frequently amplified in human breast carcinomas. Additionally, the locus containing the c-*Myc* gene in the mouse (15D2–D3) is subject to recurring copy number increase in the *Brca1*-deficient mouse tumors. Primary tumor cells cultured for up to 31 passages exhibited some chromosome instability, yet the majority of the aberrations found in the primary tumor were continuously selected for, suggesting that these consistent aberrations convey a selective growth advantage upon the tumor cells.

The genomic instability present in the tumors was best visualized by spectral karyotyping (SKY). Every tumor displayed structural aberrations (such as insertions, deletions, dicentric chromosomes, and chromatid breakage), numerical chromosome aberrations, and multiple clones. By analyzing multiple metaphases for each tumor, we clearly saw that new structural aberrations were continuously arising as the cells were dividing (Figure 1). Even though the ploidy varied within some tumors, the recurrent marker chromosomes were replicated along with the chromosomal complement and therefore resulted in overall copy number changes. Analysis of the specific chromosome regions involved in the most recurrent rearrangements enabled us to elucidate the mechanism behind the gains and losses found in the CGH profiles. For example, SKY revealed a +Del(11) in several tumors, and we used gene-specific fluorescence *in situ* hybridization probes to show that an interstitial deletion occurred that left only the distal region of chromosome 11, the same region found to be amplified by CGH. The gene-specific probes showed that the region does not always include the *Erbb2* gene but always includes the band distal to that gene. Interestingly, although the *Erbb2* gene is amplified in many breast carcinomas, evidence suggests that this locus is not commonly gained or overexpressed in *BRCA1*-related breast or ovarian cancers. In fact, recent data suggest that the Septin 9 gene, which maps to chromosome 11E2, is a key gene that is amplified and overexpressed in several models of breast cancer (Montagna C et al. *Cancer Res* 63: 2179-87, 2003).

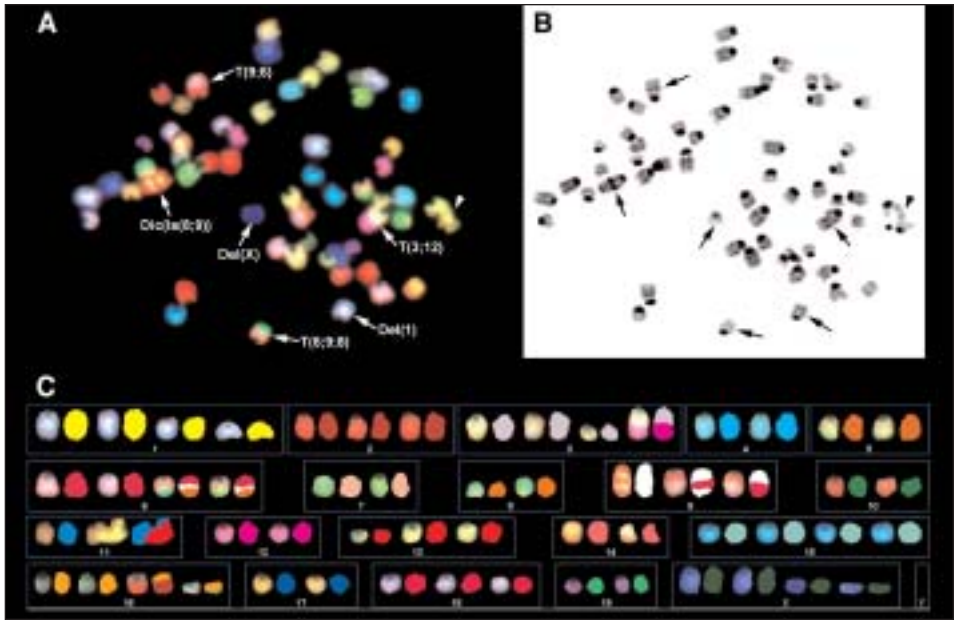

Figure 1. Spectral karyotype analysis of a representative metaphase from a *Brca1*-deficient tumor. Arrows indicate aberrant chromosomes (including dicentric, translocated, and deleted structures), and arrowheads indicate broken chromosomes 11 and 13 in the process of rearranging. *A:* Display (RGB) colors. *B:* Corresponding inverted DAPI image. *C:* Full karyotype with display colors on the left of the spectrally classified chromosomes.

In this study we also followed up previous work in which we found that fibroblasts from *Brca1*-null embryos exhibit abnormal numbers of centrosomes, aneuploidy, and deficiency in a G2–M checkpoint (Xu X et al. *Mol Cell* 3: 389-95, 1999). The *Brca1*-deficient mammary tumor cells maintain this centrosome amplification, but we found the centrioles to be structurally normal by electron microscopy. We suggest the segregation defects associated with supernumerary functional centrosomes in this mouse model of breast cancer may contribute to the generation of aneuploidy. BRCA1 in human cells colocalizes with the centrosome during mitosis (Hsu LC and White RL. *Proc Natl Acad Sci U S A* 95: 12983-8, 1998); therefore, the absence of BRCA1 could directly trigger the emergence of centrosome abnormalities.

Our findings firmly establish the similarity between mice conditionally deficient for *Brca1* and human *BRCA1*-related breast cancer. We conclude that despite the tremendous shuffling of chromosomes during the course of mammalian evolution, the pattern of genomic imbalances is conserved. Analyses of this kind help validate murine experimental tumor systems as models for human cancer.

- **Zoë Weaver, PhD**
  Staff Scientist
  Avalon Pharmaceuticals
  Germantown, MD
  Tel: 301-556-9826
  Fax: 301-556-9910
  ZWeaver@avalonrx.com
- **Thomas Ried, MD**
  Principal Investigator
  Genetics Branch
  NCI-Bethesda, Bldg. 50/Rm. 1408
  Tel: 301-594-3118
  Fax: 301-435-4428
  riedt@mail.nih.gov

CD4+ T Cells Require Self to Remain Self-tolerant

Bhandoola A, Tai X, Eckhaus M, Auchincloss H, Mason K, Rubin SA, Carbone KM, Grossman Z, Rosenberg AS, and Singer A. Peripheral expression of self–MHC-II influences the reactivity and self-tolerance of mature CD4+ T cells: evidence from a lymphopenic T cell model. *Immunity* 17: 425-36, 2002.

Adaptive immune responses are dependent on signals emanating from interactions between antigens and receptors clonally distributed on lymphocytes. The immune system maintains a diverse repertoire of lymphocytes that recognizes and eliminates pathogens even as it remains unresponsive to the host's own tissues, a phenomenom termed self-tolerance.

During development in the thymus, only those immature T cells bearing T cell receptors (TCRs) with low affinity to intrathymic self-peptide–major histocompatibility complexes (spMHC) are able to mature. Interactions between TCRs and spMHCs continue in the periphery and regulate many aspects of T cell biology, including proliferation, self-tolerance, and reactivity to foreign antigens. While the role of spMHCs in shaping the T cell repertoire is well documented, its role in controlling peripheral T cell reactivity is far from understood. Two mechanisms have been proposed to explain why autoimmunity does not normally occur. The first proposal, referred to as "tuning," postulates that TCR engagements with spMHCs in the periphery raise the signaling threshold that must be exceeded for subsequent T cell activation (Grossman Z and Paul WE. *Proc Natl Acad Sci U S A* 89: 10365-9, 1992; Grossman Z and Singer A. *Proc Natl Acad Sci U S A* 93: 14747-52, 1996). The second proposal, referred to as "suppression," postulates that autoimmunity is prevented by $CD4^+CD25^+$ regulatory T cells, which dampen the reactivity of other T cells (Sakaguchi S. *Curr Opin Immunol* 12: 684-90, 2000).

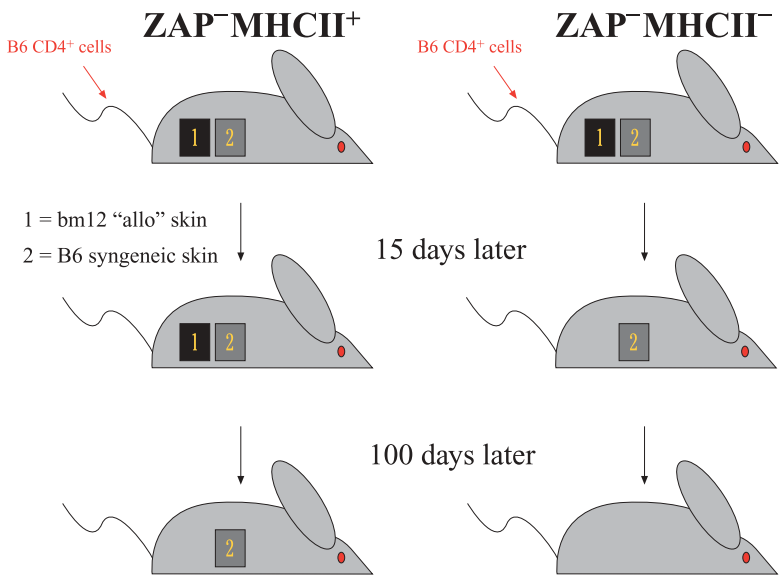

Figure 1. Host mice that were deficient for the zeta-associated protein 70 gene and that expressed or lacked the major histocompatibility II I-Aβ gene (ZAP^-MHCII^+ and ZAP^-MHCII^-, respectively) received skin grafts from bm12 mice (expressing allo MHCII molecules) and B6 mice (expressing syngeneic MHCII molecules). The mice were then reconstituted with 2 x 10^6 B6 $CD4^+$ lymph node T cells. By Day 15 accelerated rejection of foreign bm12 allo skin grafts was observed in the $MHCII^-$ host. By Day 100 $CD4^+$ T cells in ZAP^-MHCII^- mice initiated rejection responses against syngeneic B6 skin grafts.

To test the hypothesis that peripheral TCR–spMHC interactions dampen T cell reactivity, we transferred $CD4^+$ T cells from B6 mice into host mice lacking MHCII and also lacking endogenous T cells because of a mutation in the zeta-associated protein 70 gene (ZAP70, a protein required for lymphocyte development). Reactivity of the transferred $CD4^+$ T cells was assessed by measuring skin graft rejection responses. Specifically, we transferred B6 $CD4^+$ cells into mice deficient for ZAP70 and expressing or lacking the MHCII I-Aβ gene (ZAP^-MHCII^+ and ZAP^-MHCII^-, respectively) (Figure 1). Transferred T cells expanded rapidly in both hosts. $CD4^+$ T cells rejected allografts much more rapidly when transferred into ZAP^-MHCII^- mice than into ZAP^-MHCII^+ mice. Surprisingly, $CD4^+$ T cells in ZAP^-MHCII^- mice initiated rejection responses against syngeneic B6 skin grafts and infiltrated many organs, leading to autoimmunity. The recovered T cells were more sensitive to anti-TCR stimulation *in vitro*, as measured by the up-regulation of the early activation marker CD69, than were $CD4^+$ T cells transferred into $MHCII^+$ hosts.

The observed hyperreactivity of the $CD4^+$ T cells transferred into $MHCII^-$ hosts could be due to failure in the maintenance or function of regulatory T cells. The number of regulatory T cells we recovered after transfer into $MHCII^-$ hosts was extremely low, confirming an essential role of spMHCs in maintaining regulatory T cells. Comparing skin graft rejection responses in ZAP^-MHCII^+ hosts reconstituted with $CD4^+$ T cells with or without $CD4^+CD25^+$ regulatory cells allowed us to test whether the presence of these cells influences *in vivo* activity. Both groups retained syngeneic B6 skins but rejected allografts. ZAP^-MHCII^+ mice reconstituted with $CD4^+CD25^-$ cells rejected allografts much faster than did mice reconstituted with unfractionated $CD4^+$ T cells. These experiments show that the removal of regulatory T cells increased the reactivity

of $CD4^+$ T cells in $MHCII^+$ hosts against skin allografts, but was not by itself sufficient to lead to loss of tolerance to syngeneic skin grafts.

These results suggested that MHCII dampens T cell reactivity independently of its role in maintaining regulatory T cells. To test this hypothesis, we inoculated ZAP^-MHCII^+ and ZAP^-MHCII^- mice with $CD4^+$ T cells depleted of regulatory cells and measured *in vitro* reactivity. $CD4^+$ T cells recovered from $MHCII^-$ hosts maintained their higher reactivity, as measured by CD69 up-regulation upon anti-TCR stimulation.

Therefore, both suppressing and tuning mechanisms explain how peripheral MHCII influences $CD4^+$ T cell reactivity. In normal conditions, peripheral MHCII decreases the reactivity of $CD4^+$ T cells both by maintaining regulatory cells and by directly dampening their reactivity. For $CD4^+$ T cells whose ligands are encountered in the periphery, spMHCII will dampen their reactivity. For $CD4^+$ T cells that do not encounter their peripheral ligands, exogenous regulation by regulatory T cells is used.

This work provides one explanation why autoimmunity frequently occurs in humans with low levels of MHC expression. In addition, it should be possible to design peripherally expressed TCR ligands to control T cell responsiveness.

- **François Van Laethem, PhD**
  Visiting Fellow
  Experimental Immunology Branch
  NCI-Bethesda
- **Avinash Bhandoola, MD, PhD**
  Department of Pathology and Laboratory Medicine
  University of Pennsylvania School of Medicine
  Philadelphia, PA
  Tel: 215-573-0274
  Fax: 215-898-2401
  bhandooa@mail.med.upenn.edu

MOLECULAR BIOLOGY

Sphingolipids and Retinal Degeneration in *Drosophila*

Acharya U, Patel S, Koundakjian E, Nagashima K, Han X, and Acharya JK. Modulating sphingolipid biosynthetic pathway rescues retinal degeneration. *Science* 299: 1740-3, 2003.

Sphingolipids are integral components of eukaryotic cell membranes and are essential for the survival of yeast, *Drosophila*, mammals, and other organisms. Sphingolipids have a hydrophobic backbone moiety, ceramide, linked to a variable polar head group. Ceramide is converted to sphingosine, and sphingosine is phosphorylated to sphingosine 1-phosphate. These lipid derivatives are second messengers for signaling events that encompass a wide range of cell fates, from apoptosis to differentiation. Enzymes of sphingolipid metabolism (e.g., ceramidase) are regulated in response to these signaling events and in turn serve as regulators of the metabolites they generate, and they have been implicated in endocytic membrane trafficking events in yeast mutants (D'Hondt K et al. *Annu Rev Genet* 34: 255-95, 2000). We modulated the sphingolipid biosynthetic pathway *in vivo* in *Drosophila* and examined the effects on mutants with endocytic photoreceptor defects.

Each of the 800 ommatidia of a *Drosophila* compound eye consists of eight photoreceptor cells. Each cell has a rhabdomere, a specialized microvillar structure derived from the plasma membrane that houses the phototransduction machinery. Rhabdomere architecture is sensitive to perturbations in the phototransduction cascade and has been used to monitor photoreceptor degeneration. *Drosophila* phototransduction is a prototypical G protein-coupled receptor (GPCR) cascade that is initiated by light activation of rhodopsin. Association of arrestin 2 with phosphorylated rhodopsin leads to deactivation of rhodopsin. Arrestin 2 also mediates endocytosis of arrestin-rhodopsin complexes. Loss-of-function mutants of arrestin 2 ($arr2^3$) undergo rapid retinal degeneration and are defective in rhodopsin deactivation. The $arr2^3$ mutants make less than 1 percent of the protein, are defective in endocytosis, accumulate multivesicular bodies, show extensive cellular degeneration, and undergo necrotic cell death. These changes also result in a precipitous drop in rhodopsin levels, which is indicative of massive destruction of photoreceptors (Alloway PG et al. *Neuron* 28: 129-38, 2000). The *Drosophila* $arr2^3$ mutant thus provides a sensitive background to examine the *in vivo* effects of modulating the sphingolipid pathway in endocytosis.

We expressed *Drosophila* ceramidase by using a Gal4-UAS binary expression system. Ceramidase expression *per se* does not affect the morphology or function of wild-type photoreceptors. Expression of the gene is accompanied by increased ceramidase activity in extracts prepared from these photoreceptors and by decreased ceramide content in these tissues. Ceramidase transgene expressed in an $arr2^3$ background suppresses the retinal degeneration in these mutants; $arr2^3$ mutants expressing ceramidase closely resemble wild-type photoreceptors. In addition, $arr2^3$ flies expressing ceramidase maintain wild-type rhodopsin levels.

Because $arr2^3$ photoreceptors are defective in endocytosis and because defective endocytosis of arrestin-rhodopsin complexes has been implicated in retinal degeneration, we reasoned that ceramidase suppresses degeneration by modulating endocytosis. We examined the effects of ceramidase expression in a *Drosophila* dynamin mutant. Flies that express dominant-negative dynamin show general defects in endocytosis, and

targeted expression causes massive retinal degeneration. We also studied the effects of ceramidase expression in phospholipase C mutant (*norpA*) flies, which are blind and whose endocytic machinery is implicated in apoptotic photoreceptor degeneration. We found that ceramidase suppresses the photoreceptor degeneration observed in the dynamin and *norpA* mutants. These observations suggest ceramidase exerts its beneficial effects by modulating endocytosis.

The enzyme ceramidase converts ceramide to sphingosine; thus, the beneficial effects of ceramidase expression in dynamin or *norpA* mutants could be due to decreased ceramide levels or to sphingosine formation. We addressed this issue by examining the fate of photoreceptor cells in $arr2^3$, dynamin, and *norpA* mutants in a *lace* mutant background. Lace encodes for a subunit of the rate-limiting enzyme in the *de novo* ceramide biosynthetic pathway. Lace mutants are homozygous lethal, and heterozygotes are expected to have a decreased flux in the ceramide biosynthetic pathway. Indeed, loss of one copy of the *lace* gene suppressed degeneration in $arr2^3$, dynamin, and *norpA* mutant backgrounds, which suggests that decreased ceramide biosynthesis could explain some of the beneficial effects we observed. Moreover, $arr2^3$ flies fed on sphingosine did not exhibit suppressed degeneration, indicating that reduced photoreceptor degeneration in $arr2^3$ mutants correlates with decreased ceramide levels rather than sphingosine generation.

Regardless of the mode of cell death—necrotic as in $arr2^3$ or apoptotic as in *norpA*—ceramidase expression, decreased ceramide production (*lace* mutant), or both ameliorate photoreceptor degeneration. They also suppress degeneration in a dynamin mutant, so we infer that the sphingolipid pathway alters the dynamics of the endocytic process. That synthesis of a sphingoid base is required for yeast endocytosis, where it acts as a signaling molecule, supports this inference. In mammalian cells, addition of ceramide analogs modulates fluid-phase and receptor-mediated endocytosis. The molecular details of suppression of retinal degeneration in ceramidase over-expressors and *lace* mutants remain to be elucidated.

Several inherited forms of retinal degeneration in humans have been identified to result from mutations in key players of event signaling (e.g., rhodopsin and arrestin) (Wang Q et al. *Ophthalmic Genet* 22: 133-54, 2001). Our results, demonstrating rescue of degeneration in *Drosophila* visual mutants, provide a strong basis for exploring strategies that manipulate sphingolipid enzymes for therapeutic management of retinal degeneration in higher organisms. Furthermore, because *Drosophila* phototransduction is a prototypical GPCR signaling system, our results raise the possibility that sphingolipid metabolism is important in other systems as well. In fact, more than 600 GPCR genes have been identified in the human genome alone (Sadee W et al. *AAPS PharmSci* 3: E22, 2001). A large volume of work suggests that receptor endocytosis plays a crucial role in GPCR signaling (Claing A et al. *Prog Neurobiol* 66: 61-79, 2002). In light of our recent findings, the role of enzymes of sphingolipid metabolism in GPCR-mediated processes should be critically analyzed in higher organisms.

- **Usha Acharya, PhD**
  Research Fellow
- **Jairaj Acharya, PhD**
  Principal Investigator
  Regulation of Cell Growth Laboratory
  NCI-Frederick, Bldg. 560/Rm. 22-6
  Tel: 301-846-7051
  Fax: 301-846-1666
  acharyaj@mail.ncifcrf.gov

FROM THE DIRECTOR'S OFFICE

Reengineering the Intramural Research Program: An Interview with the CCR Director, J. Carl Barrett

How would you describe the Reengineering the Intramural Research Program? Is it another reorganization?

The Reengineering the Intramural Research Program (IRP) is *not* another reorganization. The IRP was reorganized in 2001 by merging the Division of Basic Sciences (DBS) and the Division of Clinical Sciences (DCS). The reengineering of the IRP is an *opportunity* for principal investigators (PIs) in the Program to work together to develop a vision and plan that will enrich the scientific opportunities for NCI staff and that will realize NCI's potential to accelerate scientific discovery and its application to clinical medicine and public health.

Do the PIs have a voice in this process?

Absolutely. The draft document regarding reengineering (http://ccrintra.cancer.gov/IRP/default.asp) has been distributed and is a platform on which the community can build and shape the direction of the IRP. The PIs have been given opportunities to voice their concerns and participate in this process through All-PI meetings, open meetings to discuss the four Centers of Excellence, Intramural Advisory Board-hosted All-PI meetings, and a web-based feedback form. The IRP leadership continues to solicit comments, suggestions, and ideas to help improve it. PIs are invited to visit the website, read the draft document, view the presentation, and provide feedback.

This draft document was presented to the Board of Scientific Counselors in July. What was their reaction?

The Board's response to the document was very positive, and they were pleased

to participate in the reengineering at an early stage. The Board's input into the shaping of this document may help the extramural community as they face similar issues, such as reviewing basic and clinical researchers involved in collaborative studies.

Please describe, in general, your vision for the Centers of Excellence.

The four Centers will be a focus of resources and infrastructure and will have the goal of accelerating the discovery, development, and delivery of interventions for the therapy or prevention of cancer. The Centers' leadership will be stewards of resources and infrastructure; facilitate interactions among PIs and with other Institutes, extramural investigators, and the private sector; and provide collaborations and interactions to achieve this goal. The leadership includes J. Carl Barrett (Advanced Biomedical Technologies), Joseph F. Fraumeni, Jr. (Molecular Epidemiology), and Kathryn Zoon (Tumor Immunology and Vaccines). The leadership for Molecular Oncology remains to be recruited.

Will funding mechanisms change with the reengineering?

IRP funding will fall into two broad categories, investigator-initiated research and what we could term collaborative initiatives. Investigator-initiated research will be funded through existing mechanisms, such as PI base budgets, Intramural Research Awards, Collaborative Project Assurances, Bench-to-Bedside Awards, and non-recurring special requests to the Division Directors. Collaborative initiatives developed by Faculties or Working Groups may receive additional funds to achieve specific objectives.

You have often mentioned a Matrix in your discussions about reengineering. Please describe this Matrix.

The Matrix is a tool for viewing some of the work done within the IRP. Each block represents points of intersection between organ-specific cancer sites and areas of research along the discovery-development-delivery continuum. The Matrix includes very broad descriptors of basic, clinical, and population research and is intended to demonstrate the research activity level for all cancer sites. With it we can analyze and present our research efforts.

If a box on the Matrix is empty, will PIs be required to change their areas of emphasis to fill it?

The Matrix is a tool to visualize in which areas the IRP has strength and activity as well as to identify those areas where additional emphasis could be placed. This format will help us determine whether we should enhance the latter areas, perhaps by initiating new recruits to create a comprehensive translational research program.

Will PIs' reviews be better if they collaborate more?

It is up to the individual PIs how to do their most outstanding research, and each will be reviewed on his or her research accomplishments. However, the IRP community will be encouraged to find ways to apply their basic science

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■ ADMINISTRATIVE LINKS

Information Technology Help Desk Consolidation
As of August 19, 2003, six information technology infrastructure functions were consolidated under the Center for Information Technology (CIT). NIH and the Office of the Secretary for DHHS agreed on the consolidation plan. The functions now under CIT are Email, Help Desk (Tier 1), Wireless Networking, Security, Enterprise Architecture, and Enterprise Authentication (NIH Login). Each area of this plan has an assigned project manager from CIT and a representative from the NIH Information Technology Management Committee. The previous NCI computer staff ensured work continued on problems that couldn't be resolved over the phone and they worked closely with the current CIT staff during the transition. To learn more, go to http://itconsolidation.nih.gov/.

Employee Express
The use of Employee Express was made mandatory October 1, 2003, by NIH and the DHHS. This system allows employees to make changes to personal information on their taxes, insurance, direct deposit, thrift savings plan, and home address. Employee Express is to be used by Federal civilian employees of DHHS and *not* by Guest Researchers, Commissioned Corps Officers, Visiting Fellows, and other non–full-time employees. To access Employee Express a personal identification number (PIN) is needed, which can be obtained by mail or online at http://www3.od.nih.gov/ohrm/ee/pin.htm. For further assistance call the Employee Express Helpdesk at 800-573-0940 or the assigned Human Resources Office.

Once a PIN is received and transactions begin to be conducted through Employee Express, employees should elect to receive an Email confirmation of each transaction, which will aid in follow-ups. Employees should wait two full pay periods and check pay slips before reporting problems with transactions. If the expected changes have not occurred by then, the Employee Express Helpdesk or the Human Resources Office should be contacted. For more information visit http://www3.od.nih.gov/ohrm/ee/niheeinfo.htm.

Institute of Medicine Releases NIH Reorganization Study
On July 29, 2003, the Institute of Medicine of the National Academies released its study on the reorganization of NIH, "Enhancing the Vitality of the National Institutes of Health: Organizational Change to Meet New Challenges" (http://www.nap.edu/catalog/10779.html). The study focused on "whether the current structure and organization of NIH are optimally configured for the scientific needs of the 21st century" and accompanied the FY 2001 appropriation for DHHS that directed NIH to have the study done by the National Academy of Science. The Institute of Medicine issued 14 recommendations, including assuring that centralization of management functions will not undermine NIH's ability to identify, fund, and manage the best research and training; strengthening the Office of the NIH Director; and increasing funding for Research Management and Support. To see all 14 recommendations, go to http://camp.nci.nih.gov/admin/news/admin/200309/IOM_Report.htm.

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discoveries to further development for delivery into the clinical setting.

Will the way PIs are reviewed and rewarded change?

The existing review and reward process may not meet the needs of all PIs. Established review criteria for PIs in the Division of Cancer Epidemiology and Genetics recognize that investigators collaborate in large groups with an identifiable leader who is rewarded for that role. Review criteria in the CCR do not yet fully recognize in a similar manner the contributions to programmatic missions or large-group efforts. A review and reward structure should take into account each PI's roles, responsibilities, and resources. PIs demonstrating excellence in achieving the objectives associated with their respective roles will be recognized and rewarded.

How will long-term, high-risk research be rewarded?

We need to think differently and develop a review and reward system that values taking risks and having long-term goals. Are retrospective reviews always the best, and could prospective reviews play an important role in the process? We look forward to receiving suggestions and to evaluating proposals and strategies to enhance this process.

How do training and mentoring fit in?

The IRP needs to foster an environment in which excellence in training and mentoring is encouraged, valued, and rewarded. A critical component of training is mentoring, which can take place at many levels—guiding graduate students, helping postdoctoral fellows make their mark and decide their direction, working with tenure track investigators to establish themselves in their fields, and providing opportunities for mentors to improve their skills. Excellence in mentorship within the IRP will contribute to the overall excellence in training the next generation of scientists and national leaders in cancer research.

■ **L. Michelle Bennett, PhD**
Associate Director for Science

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SCIENTIFIC ADVISORY COMMITTEE

If you have scientific news of interest to the CCR research community, please contact one of the scientific advisors (below) responsible for your area of research.

Biotechnology Resources

David J. Goldstein, PhD
dg187w@nih.gov
Tel: 301-496-4347

David J. Munroe, PhD
dm368n@nih.gov
Tel: 301-846-1697

Carcinogenesis, Cancer and Cell Biology, Tumor Biology

Joseph A. DiPaolo, PhD
jd81a@nih.gov
Tel: 301-496-6441

Stuart H. Yuspa, MD
sy12j@nih.gov
Tel: 301-496-2162

Clinical Research

Frank M. Balis, MD
fb2y@nih.gov
Tel: 301-496-0085

Caryn Steakley, RN, MSW
cs397r@nih.gov
Tel: 301-435-3685

Immunology

Jonathan D. Ashwell, MD
ja9s@nih.gov
Tel: 301-496-4931

Jay A. Berzofsky, MD, PhD
jb4q@nih.gov
Tel: 301-496-6874

Molecular Biology

Ira O. Daar, PhD
id13e@nih.gov
Tel: 301-846-1667

Carl Wu, PhD
cw1m@nih.gov
Tel: 301-496-3029

Structural Biology, Chemistry

Victor E. Marquez, PhD
vm3p@nih.gov
Tel: 301-846-5954

Christopher J. Michedja, PhD
cm304t@nih.gov
Tel: 301-846-1216

Sriram Subramaniam, PhD
ss512h@nih.gov
Tel: 301-594-2062

Translational Research

Anita B. Roberts, PhD
ar40e@nih.gov
Tel: 301-496-6108

Elise C. Kohn, MD
ek1b@nih.gov
Tel: 301-402-2726

Virology

Vinay K. Pathak, PhD
vp63m@nih.gov
Tel: 301-846-1710

John T. Schiller, PhD
js153g@nih.gov
Tel: 301-496-6539