Impact of the *Xenopus* system on the missions of the NINDS

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The mission of the NINDS is to reduce the burden of neurological disease. This mission is supported by a robust portfolio of basic research efforts aimed at understanding the structure and activities of the brain, knowledge essential for diagnosing and treating human brain disease. Some important areas of NINDS basic research include: biology of the cells of the nervous system, brain and nervous system development, genetics of the brain, cognition and behavior, neurodegeneration, brain plasticity and repair, neural signaling, learning and memory, motor control and integration, sensory function, and neural channels, synapses, and circuits.

As an overview, because of the ease with which its developing and adult nervous system can be studied, *Xenopus* has been an important model system for understanding brain function. Among the most prominent early examples of general biological insights were Gurdon's studies demonstrating that a cell nucleus from embryonic intestine could drive development of an entire embryo, using nuclear transplantation at the one-cell stage[1]. The use of informative (e.g. animal cap) assays for early tissues interactions (induction) demonstrated that this model system is an engine for gene discovery in neural development[2]. Important insights into synapse formation and refinement came from studies of neuromuscular junctions, especially those in very early development[3] and from the establishment of topographic maps in the retinotectal system[4]. Our understanding of ion channel function in the nervous system has been heavily dependent on expression in *Xenopus* oocytes[5]. Neuroendocrine discoveries included the identification and isolation of melanocyte stimulating hormone[6]. These historical strengths have been followed by a series of very important new discoveries, falling within the NINDS mission, whose insights would have been much more difficult, or impossible, to obtain with other systems. Selected examples from the recent literature (2006 – 2009) are given below.

The fundamental contributions of research in *Xenopus* is documented in the recent papers listed below that were selected to illustrate the facilitation of NINDS mission objectives through use of this model system. The topics range widely and the contributions are substantive and highly visible.

Cell biology of neurons

Agathocleous Michalis; Iordanova Ilina; Willardsen Minde I; Xue Xiao Yan; Vetter Monica L; Harris William A; Moore Kathryn B **A directional Wnt/beta-catenin-Sox2-proneural pathway regulates the transition from proliferation to differentiation in the Xenopus retina**. Development (Cambridge, England) (2009), 136(19), 3289-99.

Bollmann Johann H; Engert Florian **Subcellular topography of visually driven dendritic activity in the vertebrate visual system**. Neuron (2009), 61(6), 895-905.

W. Shen, J.S. Da Silva, H. He and Hollis T. Cline **Type A GABA-receptor-dependent synaptic transmission sculpts dendritic arbor structure in *Xenopus* tadpoles *in vivo*.** (2009) J Neurosci. 29:5032-43.

Bertolesi GE, Michaiel G, McFarlane S. **Two heparanase splicing variants with distinct properties are necessary in early Xenopus development.** J Biol Chem. (2008) 283:16004-16

Carlos Carmona-Fontaine, Helen K. Matthews, Sei Kuriyama, Mauricio Moreno, Graham A. Dunn[2], Maddy Parsons[2], Claudio D. Stern[1] and Roberto Mayor **Contact inhibition of locomotion *in vivo* controls neural crest directional migration**. Nature (2008) 456:957-961.

Ly Alice; Nikolaev Anatoly; Suresh Geetha; Zheng Yufang; Tessier-Lavigne Marc; Stein Elke

DSCAM is a netrin receptor that collaborates with DCC in mediating turning responses to netrin - 1. Cell (2008) 133: 1241-54.

Green Jeremy B A; Davidson Lance A **Convergent extension and the hexahedral cell**. Nature cell biology (2007) 9: 1010-5.

Mitchell Brian; Jacobs Richard; Li Julie; Chien Shu; Kintner Chris **A positive feedback mechanism governs the polarity and motion of motile cilia**. Nature (2007), 447: 97-101.

Nervous system development

Strate Ina; Min Tan H; Iliev Dobromir; Pera Edgar M **Retinol dehydrogenase 10 is a feedback regulator of retinoic acid signalling during axis formation and patterning of the central nervous system**. Development (2009) 136: 461-72.

Linda W. Chang and Nicholas C. Spitzer **Spontaneous calcium spike activity in embryonic spinal neurons is regulated by developmental expression of the Na^+, K^+-ATPase β3 subunit.** (2009) J Neurosci. 29:7877-85.

N. Bardine, C. Donow, B. Korte, A.J. Durston, W. Knöchel and S.A. Wacker **Two Hoxc6 transcripts are differentially expressed and regulate primary neurogenesis in *Xenopus laevis*.** (2009) Dev Dyn. 238:755-65.

Denver, Robert J.; Hu, Fang; Scanlan, Thomas S.; Furlow, J. David. **Thyroid hormone receptor subtype specificity for hormone-dependent neurogenesis in Xenopus laevis.** Developmental Biology (2009) 326: 155-168.

Hassenklöver T, Schwartz P, Schild D, Manzini I. **Purinergic signaling regulates cell proliferation of olfactory epithelium progenitors.** Stem Cells. (2009) 27:2022-31.

CNS genetics; *Xenopus* models of neurological disease

Tam Beatrice M; Moritz Orson L **Dark rearing rescues P23H rhodopsin -induced retinal degeneration in a transgenic Xenopus laevis model of retinitis pigmentosa: a chromophore-dependent mechanism characterized by production of N-terminally truncated mutant rhodopsin**. The Journal of Neuroscience (2007), 27(34), 9043-53

Barela Arthur J; Waddy Salina P; Lickfett Jay G; Hunter Jessica; Anido Aimee; Helmers Sandra L; Goldin Alan L; Escayg Andrew **An epilepsy mutation in the sodium channel SCN1A that decreases channel excitability**. The Journal of Neuroscience (2006), 26(10), 2714-23.

Cognition and behavior; neuroendocrine regulation

Davide Dulcis and Nicholas C. Spitzer **Illumination controls differentiation of dopamine neurons regulating behaviour.** Neuron (2009) 64, 240-250.

Hu, F., Crespi, E.J. and Denver, R.J. (2008) **Programming neuroendocrine stress axis activity by exposure to glucocorticoids during postembryonic development of the frog Xenopus laevis.** Endocrinology 149:5470-5481.

Elliott Taffeta M; Kelley Darcy B **Male discrimination of receptive and unreceptive female calls by temporal features**. The Journal of experimental biology (2007) 210: 2836-42.

Vignal C, Kelley D. **Significance of temporal and spectral acoustic cues for sexual recognition in *Xenopus laevis*.** Proc Biol Sci. (2007) 274:479-88.

Yang Eun-Jin; Nasipak Brian T; Kelley Darcy B **Direct action of gonadotropin in brain integrates behavioral and reproductive functions**. Proceedings of the National Academy of Sciences of the United States of America (2007) 104: 2477-82.

Crespi, E.J. and Denver, R.J. **Leptin (ob gene) of the South African clawed frog *Xenopus laevis***. Proceedings of the National Academy of Sciences, USA (2006) 103:10092-10097.

Neurodegeneration

Mazabrand, A. and Pollet N. **Reduced levels of survival motor neuron protein leads to aberrant motoneuron growth in a *Xenopus* model of muscular atrophy.** Neurogenetics. (2009) Jun 11. DOI 10.1007/s10048-009-0200-6

Waters Michael F; Minassian Natali A; Stevanin Giovanni; Figueroa Karla P; Bannister John P A; Nolte Dagmar; Mock Allan F; Evidente Virgilio Gerald H; Fee Dominic B; Muller Ulrich; Durr Alexandra; Brice Alexis; Papazian Diane M; Pulst Stefan M **Mutations in voltage-gated potassium channel KCNC3 cause degenerative and developmental central nervous system phenotypes**. Nature genetics (2006), 38(4), 447-51.

Boorse, G.C., Kholdani, C.A., Seasholtz, A.F. and Denver, R.J. **Corticotropin-releasing factor is cytoprotective in *Xenopus* tadpole tail: Integration of ligand, receptor and binding protein in tail muscle cell survival**. Endocrinology (2006) 147:1498-1507.

Plasticity and repair

Bonett, R.M., Hu, F., Bagamasbad, P. and Denver, R.J. **Stressor and glucocorticoid-dependent induction of the immediate early gene Krüppel-like factor 9: implications for neural development and plasticity**. Endocrinology (2009) 150:1757–1765.

Chiu Shu-Ling; Chen Chih-Ming; Cline Hollis T **Insulin receptor signaling regulates synapse number, dendritic plasticity, and circuit function in vivo**. Neuron (2008), 58(5), 708-19.

Pineda Ricardo H; Ribera Angeles B **Dorsal - ventral gradient for neuronal plasticity in the embryonic spinal cord**. The Journal of neuroscience (2008), 28(14), 3824-34.

Kumar Anoop; Godwin James W; Gates Phillip B; Garza-Garcia A Acely; Brockes Jeremy P **Molecular basis for the nerve dependence of limb regeneration in an adult vertebrate**. Science (New York, N.Y.) (2007), 318(5851), 772-7.

Neural signalling

X.F. Liu, P.K. Tari and K Haas K. **PKM zeta restricts dendritic arbor growth by filopodial and branch stabilization within the intact and awake developing brain.** (2009) J Neurosci. 29:12229-35.

N. Schwartz**,** A. Schohl and Edward S. Ruthazer **Neural activity regulates synaptic properties and dendritic structure in vivo through calcineurin/NFAT signaling**. (2009) Neuron 62:655-69.

Nishiyama Makoto; von Schimmelmann Melanie J; Togashi Kazunobu; Findley William M; Hong Kyonsoo **Membrane potential shifts caused by diffusible guidance signals direct growth - cone turning**. Nature neuroscience (2008) 11: 762-71

Sharon B. Sann, Lin Xu, Hiroshi Nishimune, Joshua R. Sanes and Nicholas C. Spitzer **Neurite outgrowth and *in vivo* sensory innervation mediated by a $Ca_V2.2$ – laminin β2 stop signal.** (2008) J. Neurosci. 28: 2366-2374.

Nicol Xavier; Voyatzis Sylvie; Muzerelle Aude; Narboux-Neme Nicolas; Sudhof Thomas C; Miles Richard; Gaspar Patricia **cAMP oscillations and retinal activity are permissive for ephrin signaling during the establishment of the retinotopic map**. Nature neuroscience (2007), 10(3), 340-7.

Learning and memory

Du JL, Wei HP, Wang ZR, Wong ST, Poo MM. **Long-range retrograde spread of LTP and LTD from optic tectum to retina** Proc Natl Acad Sci U S A. (2009) Nov 3. [Epub ahead of print]PMID: 19887635

R.C. Ewald and Hollis T Cline **Cloning and phylogenetic analysis of NMDA receptor subunits NR1, NR2A and NR2B in *Xenopus laevis* tadpoles**. (2009) Front Mol Neurosci. 2:4

Maguschak, Kimberly A.; Ressler, Kerry J. **β -catenin is required for memory consolidation.** Nature Neuroscience (2008) 11: 1319-1326

Motor control and integration

Dong W, Lee RH, Xu H, Yang S, Pratt KG, Cao V, Song YK, Nurmikko A, Aizenman CD. **Visual avoidance in Xenopus tadpoles is correlated with the maturation of visual responses in the optic tectum**. J Neurophysiol. (2009)10:803-15.

Soffe Stephen R; Roberts Alan; Li Wen-Chang **Defining the excitatory neurons that drive the locomotor rhythm in a simple vertebrate: insights into the origin of reticulospinal control**. The Journal of physiology (2009), 587(Pt 20), 4829-44.

Zornik Erik; Kelley Darcy B **Regulation of respiratory and vocal motor pools in the isolated brain of Xenopus laevis**. Journal of Neuroscience (2008), 28(3), 612-21

Rhodes, Heather J.; Yu, Heather J.; Yamaguchi, Ayako. **Xenopus vocalizations are controlled by a sexually differentiated hindbrain central pattern generator.** Journal of Neuroscience (2007), 27(6), 1485-1497.

Sensory function

Chen TW, Lin BJ, Schild D. **Odor coding by modules of coherent mitral/tufted cells in the vertebrate olfactory bulb**. Proc Natl Acad Sci U S A. (2009)106:2401-6.

Garcia-Morales Carla; Liu Chiung-Hui; Abu-Elmagd Muhammad; Hajihosseini Mohammad K; Wheeler Grant N **Frizzled - 10 promotes sensory neuron development in Xenopus embryos**. Developmental biology (2009), 335(1), 143-55

Rossi, Christy Cortez; Hernandez-Lagunas, Laura; Zhang, Chi; Choi, Irene F.; Kwok, Letitia; Klymkowsky, Michael; Bruk Artinger, Kristin. **Rohon - Beard sensory neurons are induced by BMP4 expressing non-neural ectoderm in Xenopus laevis.** Developmental Biology (2008), 314(2), 351-361.

Elliott Taffeta M; Christensen-Dalsgaard Jakob; Kelley Darcy B **Tone and call responses of units in the auditory nerve and dorsal medullary nucleus of Xenopus laevis**. Journal of comparative physiology. A, Neuroethology, sensory, neural, and behavioral physiology (2007), 193(12), 1243-57.

Channels

Bosmans Frank; Martin-Eauclaire Marie-France; Swartz Kenton J **Deconstructing voltage sensor function and pharmacology in sodium channels**. Nature (2008), 456(7219), 202-8.

Keith, Ryan K.; Poage, Robert E.; Yokoyama, Charles T.; Catterall, William A.; Meriney, Stephen D.. **Bidirectional modulation of transmitter release by calcium channel/syntaxin interactions in vivo.** Journal of Neuroscience (2007), 27(2), 265-269.

Ben-Chaim Yair; Chanda Baron; Dascal Nathan; Bezanilla Francisco; Parnas Itzchak; Parnas Hanna **Movement of 'gating charge' is coupled to ligand binding in a G-protein-coupled receptor**. Nature (2006), 444(7115), 106-9.

Synapses

Berghuis Paul; Rajnicek Ann M; Morozov Yury M; Ross Ruth A; Mulder Jan; Urban Gabriella M; Monory Krisztina; Marsicano Giovanni; Matteoli Michela; Canty Alison; Irving Andrew J; Katona Istvan; Yanagawa Yuchio; Rakic Pasko; Lutz Beat; Mackie Ken; Harkany Tibor **Hardwiring the brain: endocannabinoids shape neuronal connectivity**. Science (2007), 316(5828),

Xu, Chun; Zhao, Man-xia; Poo, Mu-ming; Zhang, Xiao-hui. **GABAB receptor activation mediates frequency-dependent plasticity of developing GABAergic synapses.**

Nature Neuroscience (2008), 11(12), 1410-1418

Borodinsky, Laura N.; Spitzer, Nicholas C.. **Activity-depending neurotransmitter-receptor matching at the neuromuscular junction.** Proceedings of the National Academy of Sciences of the United States of America (2007), 104(1), 335-340.

Circuits

Dunfield Derek; Haas Kurt **Metaplasticity governs natural experience-driven plasticity of nascent embryonic brain circuits**. Neuron (2009), 64(2), 240-50

Ramdya P, Engert F. **Emergence of binocular functional properties in a monocular neural circuit.** Nat Neurosci. (2008) 11:1083-90.

Pratt Kara G; Dong Wei; Aizenman Carlos D **Development and spike timing-dependent plasticity of recurrent excitation in the Xenopus optic tectum**. Nature neuroscience (2008) 11: 467-75.

Technical innovation

Berndt, Andre; Yizhar, Ofer; Gunaydin, Lisa A.; Hegemann, Peter; Deisseroth, Karl. **Bi - stable neural state switches.** Nature Neuroscience (2009), 12(2), 229-234

Viczian Andrea S; Solessio Eduardo C; Lyou Yung; Zuber Michael E **Generation of functional eyes from pluripotent cells**. PLoS biology (2009), 7(8); PubMed ID 19688031

Butts, Christopher A.; Xi, Jin; Brannigan, Grace; Saad, Abdalla A.; Venkatachalan, Srinivasan P.; Pearce, Robert A.; Klein, Michael L.; Eckenhoff, Roderic G.; Dmochowski, Ivan J. **Identification of a fluorescent general anesthetic, 1- aminoanthracene.** Proceedings of the National Academy of Sciences of the United States of America (2009), 106(16), 6501-6506.

Junek Stephan; Chen Tsai-Wen; Alevra Mihai; Schild Detlev **Activity correlation imaging : visualizing function and structure of neuronal populations**. Biophysical journal (2009), 96(9), 3801-9

Xenopus Grants funding by the NINDS

According to NIH RePORTER Search Tool, in the fiscal year of 2009, the National Institute of Neurological Disorders & Strokes (NINDS) **funded 46 grants** for projects involving *Xenopus*. These grants total **$11,306,510**. See appendix for a complete list.

2009 *Xenopus* White Paper – Community Needs

Executive Summary

Xenopus - a crucial model organism for biomedical research:

Experiments in model animals are a cornerstone of biomedical research and have a massive impact on our understanding of human health and disease. The frog, *Xenopus,* is a widely used and crucial vertebrate model organism that offers a unique combination of three powerful advantages: strong conservation of essential biological mechanisms, a remarkable experimental repertoire, and unparalleled cost-effectiveness when compared to murine or other mammalian models.

In fact, for many experimental applications, *Xenopus* is the only viable model system. For example, in cell and molecular biology, *Xenopus* extracts allow for individual components of the cell cycle or DNA replication/repair machinery to be analyzed in a manner that cannot be recapitulated *in vivo* or in cell culture. For developmental biology, no other model system allows for high-throughput genomic/proteomic screening and at the same time allows for transplant/explant analysis (i.e. "experimental embryology"). The *Xenopus* oocyte is unique as a system for studying channel physiology using the patch-clamp and as a system for protein expression. Finally, *Xenopus* is the only vertebrate model that readily produces enough biological material for biochemical purification from eggs, intact embryos, or isolated embryonic tissues. The combination of these characteristics offers a wide range of experimental opportunities for studies using the *Xenopus* system in contrast to other vertebrates such as the mouse or zebrafish.

NIH Investment in *Xenopus:*

The NIH has made a substantial and continuing investment in *Xenopus* research. Indeed, a search of the NIH rePORT database for R01's or equivalent grants using the search term "*Xenopus*" returned **427 grants for a total cost of $127,583,776** for FY08 and FY09. Despite this investment in individuals' research, the *Xenopus* community lacks many resources that are considered entirely essential for other model systems, including a complete genome sequence, stock and training centers, and a comprehensive model organism database.

Xenopus as a Model System and Human Disease:

Given the tremendous advantages of the *Xenopus* system, the pace of new biological discovery by the *Xenopus* Community is brisk. Using *Xenopus*, we have significantly improved our understanding of human disease genes and their mechanisms, justifying the NIH's investment in *Xenopus*. Below we provide examples of just a few of the human health discoveries made in the last two years:

Xenopus embryos are used for *in vivo* analysis of gene expression and function:

Nephronophthisis - *Hum Mol Genet.* 2008. 17, 3655-62; *Nat Genet. 2005*. 37, 537-43.
Cutis laxa - *Nat Genet.* 2009. 41, 1016-21.
Meckel-Gruber syndrome - *Am J Hum Genet.* 2008. 82, 959-70.
Colorectal cancer - *Genome Res.* 2009. 19, 987-93.

Xenopus egg extracts are used for *in vitro* biochemical studies:

Fanconi Anemia - *Mol. Cell.* 2009. 35, 704-15; *J Biol Chem.* 2009, 284, 25560-8.
C-myc oncogene - *Nature*. 2007. 448, 445-51.
BRCA1 - *Cell*. 2006. 127, 539-552

Xenopus oocytes are used to study gene expression and channel activity:
Trypanosome transmission - *Nature* 2009. 459, 213-217.
Epilepsy, ataxia, sensorineural deafness - *N Engl J Med.* 360, 1960-70.
Catastrophic cardiac arrhythmia (Long-QT syndrome) - *PNAS* 2009. 106,13082-7.
Megalencephalic leukoencephalopathy - *Hum Mol Genet.* 2008. 17, 3728-39.

Xenopus as a Model System and Basic Biological Processes:

Xenopus also plays a crucial role in elucidating the basic cellular and biochemical mechanisms underlying the entire spectrum of human pathologies. Again only a few of the many discoveries in the last two years are highlighted here:

Xenopus embryos were used for studies of TGF-® signal transduction.
(*Cell*. 2009. 136,123-35; *Science*. 2007. 315, 840-3).
Xenopus egg extracts revealed fundamental aspects of cell division.
(*Nature*. 2008. 453, 1132-6; *Science*. 2008. 319, 469-72).
Xenopus embryos were used for studying mucociliary epithelia.
(*Nat Genet.* 2008. 40, 871-9; *Nature*. 2007. 447, 97-101).
Xenopus embryos were used for studying development of the vasculature.
(*Cell*. 2008.135, 1053-64).
Xenopus egg extracts provided key insight into DNA damage responses.
(*Mol Cell.* 2009. 35,704-15; *Cell.* 2008. 134, 969-80).
Xenopus embryos linked telomerase to Wnt signaling.
(*Nature*. 2009. 460, 66-72).
Xenopus was used for small molecule screens to develop therapeutics.
(Nat Chem Biol. 2008. 4, 119-25; Blood. 2009. 114, 1110-22).

Immediate Needs of the *Xenopus* Community:

It is the consensus of the *Xenopus* community that their biomedical research could be greatly accelerated by the development of key resources that are currently lacking. These resources would be of use to the entire *Xenopus* research community. In this White Paper, the community identifies seven resources in two categories: Three Immediate Needs and four Essential Resources:

The **Immediate Needs** are a common set of key resources that were identified as the most pressing by three committees established to identify needed resources across the broad and diverse *Xenopus* community. There is a broad, community-wide consensus that these resources would have an immediate impact on all *Xenopus* users and should be assigned the highest priority in order to accelerate the pace of biomedical research using *Xenopus* as a model system.

These Immediate Needs and the resulting improvements in biomedical research are as follows:

1. *Establishment of the Xenopus Resource and Training Center at the MBL in Woods Hole.*
   -Will allow rapid distribution of transgenic *Xenopus laevis* lines expressing fluorescent reporters and tagged proteins (for example histone-RFP for visualizing the mitotic spindle or organ specific GFP in embryos)
   -Will allow centralized generation, housing, and distribution of genetically modified *X. tropicalis* lines, including both mutants and transgenics.
   -Will allow both current investigators and the next generation of researchers to get hands-on training in *Xenopus*-based biomedical research methods (including cell, molecular, and developmental methods).
2. *Expansion and improvement of Xenbase, a Xenopus model organism database.*
   -Maintain and curate data for the essential primary database for *Xenopus* researchers.
   -Enhance the functionality of *Xenbase* by introducing a phenotypes feature.

-Support new content on *Xenbase*, including proteomics support, a new genome browser, and Wiki for *Xenopus* methods.
-Continue and expand collaborative and service efforts (e.g. provide *Xenopus* data to other databases including NCBI, UniProtK, Mascot and Tornado).

3. *Complete sequencing of the Xenopus laevis genome.*
-Will allow the deconvolution of data in mass-spectrometry-based proteomic studies.
-Will facilitate identification of conserved gene regulatory regions to build gene-regulatory networks.
-Will facilitate site-specifc studies of DNA transaction (repair and replication)
-Will facilitate identification of all ORFs to build an ORFeome for rapid functional characterization of genes
-Will facilitate the design of morpholino oligonucleotides for gene depletion studies
-Will faciliate the analysis of chromatin-immunoprecipitations to identify DNA-bound to transcription factors and DNA modifications.

Essential Resources Needed by the *Xenopus* Community:

In addition to these immediate, community-wide needs, the committees identified four **Essential Resources** that should be developed as soon as possible, so that *Xenopus* biologists can more effectively fulfill the missions of the NIH. The *Xenopus* community considers all four of these additional resources to be essential, but understands that priorities must be set, and ranks these behind the Immediate Needs. These Essential Resources are as follows:

4. *Xenopus ORFeome in recombineering vectors.*
5. *Improvement of the X. tropicalis genome sequence and annotation*
6. *Development of methods for disrupting gene function in Xenopus.*
7. *Generation and Distribution of antibodies for Xenopus research.*

Anticipated Gains for Biomedical Research:

Xenopus is a crucial model organism for biomedical research. With the development of large-scale community-wide resources, *Xenopus* is poised to be become the premier vertebrate model for systems-level approaches to understanding biological mechanisms in cell, molecular, and developmental biology.

The National Research Council and the National Academy of Sciences have recently called on the Unites States “to launch a new multiagency, multiyear, and multidisciplinary initiative to capitalize on the extraordinary advances recently made in biology”. This report (http://www.nap.edu/catalog.php?record_id=12764) recommends the term "new biology" to describe an approach to research where “physicists, chemists, computer scientists, engineers, mathematicians, and other scientists are integrated into the field of biology.” The promise of systems-level analysis in *Xenopus*, combined with its already proven strengths, make *Xenopus* the ideal model organism for pursuing this “new biology.”

Genome improvements will provide *Xenopus* researchers with the ability to perform genome-wide screens for biological activities that will in turn allow the rapid assembly and analysis of gene regulatory networks. The ORFeome will greatly facilitate such genome-wide screening by allowing all ORFs to be rapidly analyzed or large numbers of proteins to be tagged for analysis of protein-protein interaction or for *in vivo* visualization. Using extracts and biochemical purification coupled with mass-spectrometry and genomic sequence, protein interactomes can be rapidly identified and validated. Because *Xenopus* can be so easily manipulated and because vast amounts of biological material can be generated, cell-type specific interactomes can also be identified. Large-scale genetic screens will identify important novel genes in developmental pathways, especially given the relatively simple genome of *X. tropicalis* compared to zebrafish. Finally, the flexibility of both *Xenopus* extracts and embryos make this system ideal for chemical biology screens. Identifying these gene-regulatory networks, interactomes, and novel genes will be only the first steps, of course. The well-established power of *Xenopus* for rapid analysis of gene function will then allow deeply mechanistic analyses to complement the systems-level approaches described above.

It is the combination of these characteristics that distinguishes *Xenopus* from other vertebrate model systems such as mouse and zebrafish and allows for a systems-level approach to understanding biological mechanisms. The tremendous promise of the *Xenopus* model cannot be realized, however, without the immediate development of community-wide research resources. This White Paper presents the needed resources, and we look to the NIH for guidance in how to best achieve these goals.

For complete details of the 2009 Xenopus White Paper, please visit
http://www.xenbase.org/community/xenopuswhitepaper.do

Appendix

Xenopus Grants funded by the NINDS

Project Number	Activity	Project Title	Principal Investigator	Organization	Total
5K02NS050345-06	K02	CONNEXIN 32 MUTATIONS IN X-LINKED CMT	ABRAMS, CHARLES K	SUNY DOWNSTATE MEDICAL CENTER	$149,283
2R01NS046653-06A2	R01	NA/BICARBONATE COTRANSPORTERS IN BRAIN	BEVENSEE, MARK OLIVER	UNIVERSITY OF ALABAMA AT BIRMINGHAM	$402,646
5R01NS018400-25	R01	MOLECULAR PHYSIOLOGY OF BICARBONATE TRANSPORT IN THE BRAIN	BORON, WALTER F	CASE WESTERN RESERVE UNIVERSITY	$463,271
5R01NS052372-05	R01	INTERNEURONAL MECHANISMS FOR THE CONTROL OF WALKING	CHENG, JIANGUO	CLEVELAND CLINIC LERNER COL/MED-CWRU	$329,613
3R01NS034727-13S1	R01	STRUCTURE OF THE GABA A RECEPTOR BINDING SITES	CZAJKOWSKI, CYNTHIA M	UNIVERSITY OF WISCONSIN MADISON	$359,313
5R01NS059854-02	R01	STRUCTURAL REARRANGEMENTS IN GABA-A RECEPTORS	CZAJKOWSKI, CYNTHIA M	UNIVERSITY OF WISCONSIN MADISON	$318,174
5R01NS036267-11	R01	MOLECULAR MECHANISMS OF NEURONAL MIGRATIONS	DEREWENDA, ZYGMUNT S	UNIVERSITY OF VIRGINIA CHARLOTTESVILLE	$331,406
3R01NS036267-11S1	R01	MOLECULAR MECHANISMS OF NEURONAL MIGRATIONS	DEREWENDA, ZYGMUNT S	UNIVERSITY OF VIRGINIA CHARLOTTESVILLE	$48,729
5R37NS034407-15	R37	PROBING RECEPTOR STRUCTURES WITH UNNATURAL AMINO ACIDS	DOUGHERTY, DENNIS A	CALIFORNIA INSTITUTE OF TECHNOLOGY	$414,564
3R37NS034407-15S1	R37	PROBING RECEPTOR STRUCTURES WITH UNNATURAL AMINO ACIDS	DOUGHERTY, DENNIS A	CALIFORNIA INSTITUTE OF TECHNOLOGY	$93,632
1R21NS063053-01A1	R21	MONAKA - MODULATOR OF NORMAL AND NEUROPATHOLOGICAL SYNAPTIC TRANSMISSION	FERGUSON, TANYA S.	UNIVERSITY OF PENNSYLVANIA	$220,041

5R01NS058505-03	R01	A NEW FAMILY OF VOLTAGE-GATED POTASSIUM CHANNEL REGULAORY SUBUNITS	GOLDSTEIN, STEVE A N	UNIVERSITY OF CHICAGO	$460,517
5F31NS059562-02	F31	ROLE OF LRP6 IN THE REGULATION OF WNT SIGNALING DURING BRAIN DEVELOPMENT	GRAY, JASON D	WEILL MEDICAL COLLEGE OF CORNELL UNIV	$41,170
1ZIANS003019-03	ZIA	RNA EDITING OF TRANSPORTERS AND PUMPS	HOLMGREN, MIGUEL		$262,571
5R01NS064671-02	R01	CRCNS: ACTIVITY-DEPENDENT GROWTH CONE GUIDANCE	HONG, KYONSOO	NEW YORK UNIVERSITY SCHOOL OF MEDICINE	$366,524
5K08NS052454-05	K08	GABA-A RECEPTOR FUNCTION IN PEDIATRIC FOCAL CORTICAL DYSPLASIA	JANSEN, LAURA A	SEATTLE CHILDREN'S HOSPITAL	$168,291
2R01NS023684-26A2	R01	NEURAL SUBSTRATES FOR MATCHING HEARING TO UTTERANCE	KELLEY, DARCY B	COLUMBIA UNIV NEW YORK MORNINGSIDE	$352,188
5R01NS045937-07	R01	ROLE OF TH1 SPECIFIC CELL SURFACE MOLECULE TIM-3 IN EAE.	KUCHROO, VIJAY K	BRIGHAM AND WOMEN'S HOSPITAL	$382,813
1F31NS069510-01	F31	MOLECULAR REGULATION OF EXPERIENCE-DEPENDENT SYNAPSE AND DENDRITE STABILIZATION	LESLIE, JENNIFER HELEN	MASSACHUSETTS INSTITUTE OF TECHNOLOGY	$41,176
5R01NS011756-33	R01	CHEMICAL SYNAPSES - BIOPHYSICAL STUDIES	LESTER, HENRY A.	CALIFORNIA INSTITUTE OF TECHNOLOGY	$340,872
3R01NS011756-33S1	R01	CHEMICAL SYNAPSES - BIOPHYSICAL STUDIES	LESTER, HENRY A.	CALIFORNIA INSTITUTE OF TECHNOLOGY	$16,181
5R01NS029967-17	R01	NEURAL CALCIUM CHANNELS-REGULATION AND FUNCTION	LIPSCOMBE, DIANE	BROWN UNIVERSITY	$292,226
3R01NS029967-17S1	R01	NEURAL CALCIUM CHANNELS-REGULATION AND FUNCTION	LIPSCOMBE, DIANE	BROWN UNIVERSITY	$16,281

5F32NS063512-02	F32	ROLE OF MSPS AND TACC DURING AXON GUIDANCE	LOWERY, LAURA A	HARVARD UNIVERSITY (MEDICAL SCHOOL)	$48,860
3R01NS035812-12S1	R01	ANALYSIS OF GLUTAMATE RECEPTOR FUNCTION IN C. ELEGANS	MARICQ, ANDRES VILLU	UNIVERSITY OF UTAH	$90,000
5R01NS057674-02	R01	VITAMIN C TRANSPORTERS IN THE BRAIN	MAY, JAMES M	VANDERBILT UNIVERSITY	$302,203
5R01NS056415-02	R01	NEUROMUSCULAR JUNCTION FORMATION	MEI, LIN	MEDICAL COLLEGE OF GEORGIA (MCG)	$294,000
3R01NS056415-02S1	R01	NEUROMUSCULAR JUNCTION FORMATION	MEI, LIN	MEDICAL COLLEGE OF GEORGIA (MCG)	$224,522
1ZIANS003000-07	ZIA	CONFORMATIONAL CHANGES IN CIC CHLORIDE TRANSPORTERS	MINDELL, JOSEPH A		$62,410
5K01NS052551-03	K01	UNDERSTANDING DIRECTED RETINAL CELL AXON GUIDANCE.	MORRIS, ANDREA R	HAVERFORD COLLEGE	$117,218
7R01NS049417-04	R01	THE NIPA 1 PROTEIN IN SPASTIC PARAPLEGIA AND DEVELOPMENT	NICHOLLS, ROBERT D	UNIVERSITY OF PITTSBURGH AT PITTSBURGH	$278,677
5R01NS062156-02	R01	COMBINED COMPUTATIONAL AND WET LAB SCREENING FOR DRUGS TESTED VIA OATS	NIGAM, SANJAY K	UNIVERSITY OF CALIFORNIA SAN DIEGO	$337,969
1R21NS058330-01A2	R21	NOVEL ANALGESICS FROM AUSTRALIAN FUNNEL-WEB SPIDER VENOM	NITABACH, MICHAEL NATHAN	YALE UNIVERSITY	$248,250
5P01NS035985-10	P01	MOLECULAR DETERMINANTS OF EXTRASYNAPTIC GABA RECEPTOR FUNCTION ON CEREBELLAR GRAN	OTIS, THOMAS S	UNIVERSITY OF CALIFORNIA LOS ANGELES	$238,894
5R01NS038296-09	R01	APOPTOSIS AND RENEWAL OF NEURAL PROGENITOR CELLS	RAKIC, PASKO	YALE UNIVERSITY	$313,357
1R15NS067566-01	R15	NEUROTRANSMITTER FATE SPECIFICATION AND THE ROLE OF VOLTAGE-GATED	SAHA, MARGARET S	COLLEGE OF WILLIAM AND MARY	$213,017

		CALCIUM CHANNEL			
5R01NS040972-09	R01	DEVELOPMEBNT OF THE VERTEBRATE NERVOUS SYSTEM	SOKOL, SERGEI Y	MOUNT SINAI SCHOOL OF MEDICINE OF NYU	$412,472
1R01NS057690-01A2	R01	GENETIC SCREENS FOR ANALYSIS OF CA-DEPENDENT TRANSMITTER SPECIFICATION	SPITZER, NICHOLAS C	UNIVERSITY OF CALIFORNIA SAN DIEGO	$280,389
1R21NS064417-01	R21	PHARMACOLOGY OF CONNEXIN CHANNELS: STRUCTURE-ACTIVITY STUDIES.	SRINIVAS, MIDUTURU	STATE COLLEGE OF OPTOMETRY	$219,927
1F31NS063668-01A1	F31	ROLE OF CPEB IN DENDRITIC CAMKLLA MRNA TRANSPORT AND TRANSLATION	SWANGER, SHARON ANN	EMORY UNIVERSITY	$28,866
1RC1NS068966-01	RC1	GENOME WIDE SCREENING OF TRANSMEMBRANE ACCESSORY SUBUNITS OF ION CHANNELS	TOMITA, SUSUMU	YALE UNIVERSITY	$500,000
5R21NS062204-02	R21	IDENTIFICATION OF LIGANDS THAT BIND TO THE ORPHAN DELTA2 RECEPTOR	TRAYNELIS, STEPHEN F.	EMORY UNIVERSITY	$169,531
5R01NS035909-13	R01	GENES ESSENTIAL TO MOTOR AXON GUIDANCE IN DROSOPHILA	VAN VACTOR, DAVID L	HARVARD UNIVERSITY (MEDICAL SCHOOL)	$371,658
1R01NS063878-01A2	R01	MACROPHAGES, NR2B-CONTAINING NMDA RECEPTORS AND HIV DEMENTIA	XIONG, HUANGUI HANK	UNIVERSITY OF NEBRASKA MEDICAL CENTER	$371,250
5R01NS048834-05	R01	ANDROGEN MODULATION OF VOCAL NEURONS	YAMAGUCHI, AYAKO	BOSTON UNIVERSITY	$283,294
5F31NS057872-03	F31	THE ROLE CELLULAR METABOLISM IN REGULATING APOPTOSIS	YI, CAROLINE H	HARVARD UNIVERSITY (MEDICAL SCHOOL)	$28,264
				Total	$11,306,510