Impact of the *Xenopus* system on the mission of the NIDDK

Oliver Wessely, PhD. - Louisiana State University Health Science Center

*Xenopus* has played a very important role in the mission of NIDDK for a long time. *Xenopus* oocytes have been and still are an invaluable system to study the conductive properties of many channels and transporters expressed on renal epithelial cells. Many recent technological advances such as antisense morpholino oligomers for gene knockdowns, transgenic GFP lines for imaging and the genome information for *X. tropicalis* have promoted *Xenopus* as a valuable model not only to study early embryonic development, but also to investigate organogenesis. This has been realized by NIDDK and projects exploring the pronephric kidney, the pancreas and the liver are among the currently funded grants.

**Electrophysiology using Xenopus oocytes:** *Xenopus* oocytes express a low number of endogenous membrane transporters and channels because they are virtually independent from exogenous nutrients. As such they have been and are the preferred *in vivo* model to characterize channels, receptors and transporters present on renal epithelial cells that are crucially important for kidney function. Oocytes are used to study electrophysiological properties, stoichiometries and the role of post-translational modification. The system is also very amendable to high-throughput screening approaches. As such it has been a powerful tool to perform functional screens for genes encoding ion channels and transporters. In addition to their basic science component these studies have significant impact in respect to human diseases. For example, studies on hypertension have used *Xenopus* oocytes to demonstrate that defects in With no Lysine kinase 4 (WNK4) causes increased activity of the renal transporter molecules NKCC2 and NCC and thereby directly interferes with blood pressure control.

**Kidney Development:** *Xenopus* embryos due to their aquatic life develop a functional pronephric kidney within 31 hours post fertilization. Thus, *Xenopus* has been established as a valuable animal model to study kidney development. Over the years, it has become evident that the process of kidney development is evolutionary conserved and findings in *Xenopus* are directly applicable to studies in higher vertebrates such as humans and mouse. One of the most recent advances was the realization that *Xenopus* is a powerful model organism to study the patterning of the nephron along its proximal-distal axis. With the availability of the *Xenopus tropicalis* genome it was possible to identify many structural proteins that are specifically expressed in defined segments of the pronephros. This patterning was highly reminiscent to the one found in individual nephrons of the metanephric kidney. It provided a novel angle to understand how transcription factors actually pattern the kidney along its proximal distal axis as illustrated by the recent study on the Iroquois (Irx) gene family. Similarly, the synchronous development of the *Xenopus* pronephros has also provided many novel insights in how kidney progenitors differentiate into their mature counterparts (e.g. the blood-filtering podocyte) or how microRNAs regulate terminal differentiation of the renal epithelial cells.

In addition to understanding the processes that regulate normal kidney development, the pronephric kidney of *Xenopus* is also a valuable tool to study kidney diseases. Knockdown of genes mutated in human forms of Polycystic Kidney Disease result in a “PKD-like” phenotype in *Xenopus* that is used to better understand the molecular mechanisms leading to kidney cyst formation. In particular, the speed of analysis and the nearly unlimited availability of embryos provide an ideal *in vivo* test system to study aspect of Polycystic Kidney Disease that cannot be performed in mouse as easily.
Finally, the *Xenopus* kidney is a great system to study tissue engineering. *Xenopus* was the first organism, where it could be shown that the combined action of Retinoic Acid and Activin can convert primitive ectoderm into a functional kidney that can even be transplanted in nephrectomized *Xenopus* embryos. Ongoing work has extended these studies to several cell types in the kidney and has played an important role in identifying novel kidney-specific genes as well as ways to generate kidney epithelial cells *in vitro*.

**Pancreas Development:** The formation of the pancreas and the control of islet cell differentiation is one of the most coveted models of lineage specification. It is of high clinical importance due to its disturbance during diabetes. While mouse and chick have been the traditional models to study pancreas formation, the *Xenopus* pancreas has been developed as a viable alternative. Even though there are differences at later stages of pancreas development and its reorganization during metamorphosis, the early pancreas development in *Xenopus* is very similar to that of mice and humans. Many results are directly applicable to mammalian systems. In fact, one of the most important genes in pancreatic development, *Pdx1*, was initially discovered in *Xenopus*. The current research in *Xenopus* pancreas development follows similar avenues as outlined for the kidney. However, one particular interest is directed towards developing a transcriptional network of pancreas development in an effort to understand how early endodermal progenitors are specified first to a pancreatic fate, then to an endocrine fate and finally to a beta cell fate. For this approach *Xenopus* is uniquely suited since combinatorial knockdown studies using antisense morpholino oligomers allow analyses that are much more time-effective than compound mouse mutants.

**Liver Development:** Another organ system that has recently found more attention in *Xenopus* is the liver. The liver is an essential organ, yet the molecular basis of liver development is still poorly understood. Therefore, liver transplantation is often the only option for life threatening liver malfunctions. In an effort to develop alternative treatment options such as tissue replacement therapies from stem cells, the processes involved in hepatic tissue specification and the initial patterning of the foregut domain that will give rise to the liver are of high interest. Using the advantages of *Xenopus* it was recently shown that liver development relies on canonical and noncanonical Wnt signaling. Both pathways are necessary, but their activities have to be coordinated correctly to promote proper outgrowth of the liver bud.

**Selected References:**


**Xenopus grants funded by the Institute:**

According to NIH RePORTER Search Tool, in the fiscal year of 2011, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) funded thirty-one grants for projects involving Xenopus. These grants total to $6,882,566.

**2011 Xenopus White Paper - Community Needs:**

**Executive Summary**

**Xenopus: An essential vertebrate model system for biomedical research:**

Model animals are crucial to advancing biomedical research. Basic studies in vertebrate animals rapidly accelerate our understanding of human health and disease. Among the commonly used model animals, the frog, *Xenopus*, has great impact because of its close evolutionary relationship with mammals. Moreover, the remarkable experimental repertoire of the *Xenopus* system has made it a cornerstone of neurobiology, physiology, molecular biology, cell biology, and developmental biology.
Current NIH investment in research using Xenopus:
Consistent with its broad utility, the NIH has made a large and continuing investment in Xenopus research. Indeed, a search of the NIH rePORT database for R01 or equivalent grants using the search term “Xenopus” returned 678 grants for a total of over $217,000,000 for FY09-10. The NIH has also recently demonstrated its commitment to Xenopus community resources by approving $2.5 million to establish the National Xenopus Resource in Woods Hole, MA and a similar amount to maintain and expand Xenbase, the Xenopus Community’s online database.

Xenopus as a model system for human disease gene function
Given the tremendous power of the Xenopus system, the pace of new biological discovery by the Xenopus Community is vigorous. Using Xenopus, we have significantly improved our understanding of human disease genes and their mechanisms of action, justifying the NIH’s investment. For example:

**Xenopus** embryos are used for *in vivo* analysis of gene expression and function:
- **Congenital Heart Disease** – *PNAS* 2011. 108, 2915-2920

**Xenopus** egg extracts are used for *in vitro* biochemical studies:
- **BRCA1** – *Cell*. 2006. 127, 539-552

**Xenopus** oocytes are used to study gene expression and channel activity:

**Xenopus** as a model system for understanding basic biological processes:
*Xenopus* also plays a crucial role in elucidating the basic cellular and biochemical mechanisms underlying the entire spectrum of human pathologies. Just a small fraction of the many recent discoveries are highlighted here:

**Xenopus** contributes to or understanding of vertebrate genome organization.

**Xenopus** egg extracts reveal fundamental aspects of cell division.

**Xenopus** reveals new aspects of eukaryotic nuclear structure and function.

**Xenopus** embryos are used for studies of Wnt and TGF-β signal transduction.

**Xenopus** embryos are used for studying mucociliary epithelia.

**Xenopus** embryos are used for studying development of the vasculature.

**Xenopus** egg extracts provide key insights into DNA damage responses.
Xenopus embryos link telomerase to Wnt signaling.

Xenopus are used for small molecule screens to develop therapeutics.

Despite its demonstrated utility and despite the recent investments by the NIH, 
Xenopus still lacks many resources that are considered entirely essential for other model 
systems. It is the consensus of the Xenopus community that their biomedical research 
could be greatly accelerated by the development of key resources of use to the entire 
Xenopus research community.

At the 2010 International Xenopus Conference, developmental, cell, and molecular 
biologists gathered to discuss the resources needed and the priority that should be 
assigned to each. There was broad community-wide consensus that eleven resources 
are currently needed, and these were prioritized into two categories: Immediate Needs 
and Essential Resources:

The Immediate Needs of the Xenopus research community:

1. **Generation of the Xenopus ORFeome:**
   - Will enable genome-wide *in vivo* analyses of gene function.
   - Will enable genome-wide *in vivo* analyses of protein localization.
   - Will enable, when combined with transgenesis, the first large-scale biochemical 
     determination of protein-protein interactions in specific tissues and at specific 
     embryonic stages.
   - Will facilitate more-rapid functional characterization of specific proteins.

2. **Improvement of the Xenopus genome sequence:**
   - Will accelerate molecular studies by providing a complete catalogue of Xenopus 
     genes.
   - Will enable completion of the Xenopus ORFeomes.
   - Will enable genomic analyses & systems biology approaches for novel gene 
     discovery.
   - Will facilitate proteomics approaches and peptide analysis.

Essential Resources for Xenopus research community:

In addition to these most-pressing needs, the community has identified nine other 
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 of these additional resources to be essential, but understands that priorities 
must be set, and therefore ranks these as indicated below:

3. **Improvement of long-range contiguity in the Xenopus laevis genome**
4. **Improvement of Xenopus antibody resources**
5. **Loss of function: Zinc Finger Nucleases/TILLING**
6. **Loss of function: Small inhibitory hairpin RNAs**
7. **Novel loss of function/knockdown/knockout technologies**
8. **Intergenic annotation of the Xenopus genome**
9. **Improvements of the X. tropicalis genome – long range contiguity**
10. **Additions and improvements to Xenbase: the Xenopus Model Organism Database**
11. **Frogbook: A comprehensive resource for methods in Xenopus biology**

**Community Recommendations for Attaining Resources:**

The *Xenopus* Community feels that in order to attain these much needed resources it will be imperative to renew the PAR-09-240/1: “Genetic and Genomic Analyses of *Xenopus*.” This mechanism can help to direct funding to the establishment of resources that will accelerate research by the entire community. Development of research resources is essential to the NIH mission, but because such work is not hypothesis-driven, these proposals fare poorly in standard CSR study sections. Moreover, the standard study sections typically lack the depth of expertise that is needed to properly evaluate these proposals. The “Genetics and Genomic Analyses of *Xenopus*” PAR allows for a focused and expert review of resource development proposals, and its renewal will help to ensure a continuing return on the current NIH investment in biomedical research using *Xenopus*.

The *Xenopus* Community also feels that, given the ease with which massive amounts of biological samples can be obtained using this organism, a new PAR to support systems biology using *Xenopus* is warranted. A new PAR in this area would allow all biomedical researchers to exploit the emerging genomic resources for *Xenopus* to perform systems-level analyses *in vivo*, in a vertebrate, and in a cost-effective manner. Such research would generate significant advances into the “New Biology” described below.

**Anticipated Gains for Biomedical Research:**

*Xenopus* as an animal model continues to have a broad impact for biomedical research. Given its already long history of large-scale screens of gene function and its broad use in molecular, cell, and developmental biology, the establishment of additional community-wide resources will greatly facilitate the impact of *Xenopus* as a premier vertebrate model for systems-level analyses.

The National Research Council and the National Academy of Sciences have recently called on the United 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](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 “New Biology.”

Specifically, 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 and their relationship to phenotypes. 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. *Xenopus* offers a unique resource because it is the only *in vivo* vertebrate animal model that couples vast amounts of biological material and a sequenced genome, thus 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 gene-regulatory networks, interactomes, and novel genes will be only the first steps. 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 impact 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 2011 *Xenopus* White Paper, please visit [http://www.xenbase.org/community/xenopuswhitepaper.do](http://www.xenbase.org/community/xenopuswhitepaper.do)
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