Echinobase White Paper 2022

Enhancing the Impact of Echinoderm Research Systems

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This document briefly outlines the current significance of echinoderm research models for understanding evolutionary and developmental mechanisms, with emphasis on their central role in experimentally validating gene function, gene regulation and gene regulatory networks. The core mission of Echinobase is to provide accessible and easily searchable, high-quality, curated sets of genomic resources for the echinoderm, and wider research communities. This white paper identifies the priorities of the research community and the Scientific Advisory Board concerning the future enhancement of these resources in support of core NICHD missions.

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1. Echinoderms as a model system for biomedical research

1.1 For over 150 years Echinoderms have served as model systems for developmental and evolutionary studies

Echinoderms possess many practical experimental features:

- Inexpensive maintenance of adults and embryo cultures
- Gravid adults are abundant and readily available
- Optically transparent, externally developing embryos are ideal for live imaging
- Availability of large numbers (many millions) of highly synchronized embryos in a single culture for provides material for high throughput and biochemical analysis

Properties of echinoderms make them models for developmental and evolutionary research:

- Simple model system to understand deuterostome development (Figure 1.A)
- Very rapid embryonic development, with larval organs fully formed within three days
- Ease of embryo micromanipulation, such as blastomere removal and transplantation
- Reliable fate mapping and lineage tracing
- Multiple robust methods exist for perturbing gene expression and function
- Well-established approaches are available for cis-regulatory DNA analysis, including high-throughput approaches
- Models of environmental impact including mutagens and teratogens
- Multiple experimentally tractable species within the phylum (Figure 1.B) to provide a continuum of evolutionary distances needed to identify functional noncoding regions and reliable gene orthology.
- No whole genome duplication providing simpler gene orthology and nomenclature

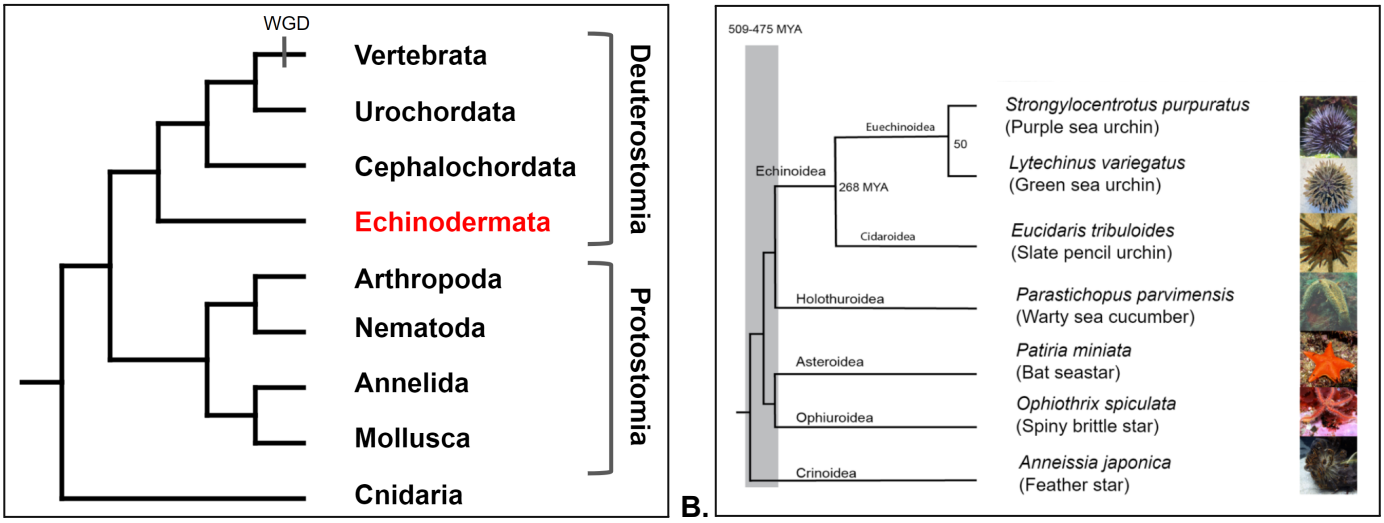


Figure 1. A. Echinoderms are deuterostomes. **B.** Phylogenetic relationships and times of divergence of species of Echinoderms. The shaded region is the period of rapid divergence at the Cambrian boundary.

1.2 Investment in research in echinoderms has driven a wealth of insight into biological mechanisms

Studies with sea urchins and other echinoderms are making far-reaching contributions to many fields of biology. For example, a Google Scholar search reveals that the term, “Echinoderm” has been used in the text of ~12,300 publications since 2018. Most significantly, echinoderms have contributed uniquely to understanding the role of the genome in controlling the process of development. Currently, the gene regulatory networks (GRNs) of sea urchin development are the most thoroughly understood and experimentally validated. The strengths of this experimental model (section 1.1) will continue to make it a preeminent system for the

analysis of the genomic control of embryogenesis. New methodologies including CRISPR/Cas gene editing and single-cell RNA-seq approaches have been employed and are contributing to our understanding of GRN function.

Gene Regulatory Networks: In 1969 Roy Britten and Eric Davidson suggested a theoretical framework of networks for the regulation of gene expression (Britten and Davidson, 1969). Presentation of the first detailed animal gene regulatory network model for development (Davidson et al., 2002a, 2002b) heralded the beginning of a new and ever more important research role for sea urchins and is still cited today (Day et al., 2022; Rothenberg and Göttgens, 2021; Verd et al., 2019). This work was tremendously augmented by the genome sequence announced in 2006 (Sea Urchin Genome Sequencing Consortium et al., 2006) and by the use of arrayed library resources. The sea urchin embryo is now the leading model system for analyzing the regulatory networks that underlie all animal development. Current work in this important field is expanding our:

- understanding of the architecture of GRNs (Andrikou et al., 2015; Damle and Davidson, 2011; Dylus et al., 2016; Erkenbrack, 2016; Erkenbrack et al., 2018; Fernandez-Valverde et al., 2018; Hinman et al., 2009, 2003; Khor and Ettensohn, 2022; Peter and Davidson, 2017, 2010, 2009; Shashikant et al., 2018a, 2018b; Wang et al., 2019),
- GRN evolution (Ben-Tabou de-Leon, 2022; Cary et al., 2020; Erkenbrack et al., 2016; Hatleberg and Hinman, 2021; Hogan et al., 2020; Israel et al., 2016; Khadka et al., 2018; Khor and Ettensohn, 2017; Levin et al., 2022; Yamazaki et al., 2021),
- linkages between GRNs and tissue morphogenesis (Annunziata et al., 2014; Khor and Ettensohn, 2022; Martik and McClay, 2015; Rafiq et al., 2012; Satoh et al., 2022; Tarsis et al., 2022),
- the regulation of GRNs by intercellular signaling pathways (Cui et al., 2014; Range, 2018; Sun and Ettensohn, 2014; Tsironis et al., 2021),
- and the potential utility of GRNs in re-engineering the process of embryogenesis (Damle and Davidson, 2012; Pieplow et al., 2021).

This work has pioneered the use of systems and GRN approaches into many other models of biology (Day et al., 2022; Dutkowski and Ideker, 2011; Krumlauf and Wilkinson, 2021; Kubo et al., 2010; Papadogiannis et al., 2022; Parker and Krumlauf, 2020; Rothenberg and Göttgens, 2021; Rothenberg, 2021; Sánchez Alvarado, 2012; Verd et al., 2019; Zmasek and Godzik, 2013; Zmasek et al., 2007). As evidence of impact in this cardinal area, there are ~8,430 Google Scholar citations using the terms “sea urchin gene regulatory network” since 2018.

Immunology: Sea urchins have potent non-adaptive immune systems that utilize hundreds of receptors of classes such as Toll-like Receptors (TLR) (Buckley and Rast, 2015). Elucidation of echinoderm immune function has the potential to inform our understanding and evolution of vertebrate immune function (Buckley and Rast, 2019, 2017, 2015; Buckley et al., 2019, 2017; Chiaramonte et al., 2019; Reinardy et al., 2016; Smith and Davidson, 1994).

Cell Signaling: The genome sequence has also made possible important new insights regarding cell signaling processes in early development and their role in embryonic patterning (Annunziata et al., 2019; Byrne et al., 2015; Carlisle and Swanson, 2021; Chiaramonte et al., 2020; Meaders and Burgess, 2020; Sun and Ettensohn, 2017; Wessel and Wong, 2009). Current research on environmental stress involves the sea urchin (Chiarelli et al., 2022; Garrett et al., 2020; Martino et al., 2017; Masullo et al., 2021; Ragusa et al., 2017). The sea urchin has a long history of contributions to fertilization biology (reviewed in (Briggs and Wessel, 2006)) and echinoderms continue to be an important model system for the study of this biological phenomenon

(Carlisle and Swanson, 2021; Chassé et al., 2019; Meaders and Burgess, 2020; Wessel and Wong, 2009; Wozniak and Carlson, 2020). Further, because of the high resolution imaging capabilities, cell cleavage and developmental processes continue to be informed by studies with echinoderms (Hansen et al., 2021; Henson et al., 2021, 2019; Martik and McClay, 2017).

Neurobiology: In the realm of neurobiology, genome sequences have enabled studies of development and regeneration (McClay, 2022; Slota and McClay, 2018; Slota et al., 2019; Zheng et al., 2022).

Cell Type Development and Evolution: The definition of cell type is being transformed by the new technology of single cell RNA sequencing, allowing cells to be characterized by their transcriptome. The echinoderm community is actively involved in this research (Foster et al., 2022, 2020; Massri et al., 2021; Meyer et al., 2022; Paganos et al., 2021; Perillo et al., 2020; Satoh et al., 2022).

Germ Cell Specification: The sea urchin has emerged as an important model for the study of germ cell specification by conditional mechanisms, work that has also been spurred by the availability of genomic data (Foster et al., 2020; Fresques and Wessel, 2018; Massri et al., 2021; Perillo et al., 2022).

Regeneration and Aging: The extraordinary capacity that echinoderms have for regeneration, and studies showing exceptional longevity are now being exploited by researchers. These works are currently directed at understanding the molecular and cellular mechanisms of biological phenomena (Alicea-Delgado and García-Arrarás, 2021; Byrne, 2020; Medina-Feliciano and García-Arrarás, 2021; Meyer and Hinman, 2022; Piovani et al., 2021; Wolff and Hinman, 2021).

Pharmacology and Toxicology: Echinoderm models are used to study the effects of compounds on embryo development and are important for assessing toxicity (Gökirmak et al., 2012; Li et al., 2020; Nesbit et al., 2019; Nogueira et al., 2021; Shipp and Hamdoun, 2012; Vyas et al., 2022).

Education and Outreach: The availability of sea urchin gametes and the ease of their manipulation have made the sea urchin a popular source of educational material for many years. There are two widely used and complementary educational websites. “Sea Urchin Embryology” (http://seaurchineducation.stanford.edu/) provides essential information concerning animal procurement and handling, gamete collection, and fertilization, as well as detailed protocols for simple wet-lab exercises related to fertilization and early development. “Virtual Urchin” (https://depts.washington.edu/vurchin/) supports unique, interactive web-based educational modules related to sea urchin development, including a virtual lab bench for simulating complex experimental manipulations. “Embryology Experiment” kits are commercially available from Carolina Biological Supply Company and Gulf Specimen Marine Lab, attesting to the widespread use of sea urchin gametes and embryos as educational materials.

2. Echinobase amplifies the return on investment of federal funding and accelerates research progress

2.1 Echinoderm community NIH funded projects

The investigators who use sea urchins and other echinoderms as models for evolution, development and cell biology are an active and intellectually important community of researchers. Currently, this community comprises about 150 investigators, as measured by the number of people who attend the Developmental Biology of the Sea Urchin and other Marine Invertebrates (DBSUMI meeting; see below). There are about 60 laboratory directors on the current mailing list for this meeting. NIH RePORTer search results are below (Table 1) and shows the impact of echinoderm related funded projects and publications resulting from research involving echinoderms.

Table 1. Results from NIH RePORTer search showing numbers of echinoderm related projects and publications.

Search term	Projects	Publications
echinoderm	82	944
sea urchin	490	23,539
sea star	72	1,017

2.2 Echinobase features support echinoderm research

The current Echinobase (www.echinobase.org) has been developed from previous sites including SpBase (RO1 to Andy Cameron, 2007-2012) and EchinoBase (P41 to Cameron, 2012-2018). Echinobase development is now funded through a collaborative P41 between Carnegie Mellon University (Hinman/Ettensohn) and the University of Calgary (Karimi/Vize). Echinobase is a clone of Xenbase, the *Xenopus* Model Organism Knowledgebase, and shares many features with Echinobase. The current Echinobase (www.echinobase.org) is the third generation resource supporting genomic research on echinoderms, with new improved genome assemblies of species used for genomics, developmental biology and gene regulatory network analyses. In brief, Echinobase provides:

- Search and BLAST tools are available via the landing page or through over 38,000 gene pages.
- Gene pages also display gene models, HGNC compliant names, multispecies orthology, GO terms, a link to the JBrowse genome browser, and a gene expression plotting tool.
- Tabs beyond the summary gene page provide gene specific literature, transcripts, expression data, protein sequences and protein-protein interactant predictions (based on human protein data).
- Automated literature collection has retrieved over 18,000 publications for automated and manual curation.
- The Echinoderm Anatomical Ontology has been developed with standardized anatomy terms for developmental stages and parts that have been organized into a hierarchy with a visualization tool to graph the relationships between anatomical structures as they develop.
- To support the community, collections of data, protocols and other resources are shared using EchinoWiki and an FTP site.
- To enable interdisciplinary and collaborative studies, research, descriptions and contact information of community members and groups are available and searchable.

2.3 Overview of the most recent release - Echinobase 5.6.0

Web interface. Model organism knowledgebases serve to centralize specialized resources for the research community and to make their unique content broadly available to the wider biomedical research world. Echinoderm researchers have worked closely with Xenbase developers and leveraged many of the existing features of Xenbase to rapidly release the Echinobase clone (Arshinoff et al., 2022). Echinobase provides echinoderm specific content including the support of multiple classes of representative species. The new production and testing environments are now hosted in a private cloud at the University of Calgary where Xenbase is hosted. These knowledgebases have simple user interfaces designed to minimize clicks required to access information. Genes and supporting information are searchable from the landing page using the search bar or pull-down menus and this finds the gene page of interest directly. The gene pages contain links to a variety of gene specific information. Some of the features are shown in Figure 2.

Echinobase is implemented as a fully virtualized federation of Virtual Machines (VMs). It runs on a private cloud powered by two Lenovo x3850 M6 servers with 48 CPU cores and 1 TB of RAM each. VMware vSphere serves as the hypervisor. The VMs are behind a secure firewall and only accessible inside a VPN. Public access to the knowledgebase is via a standard Apache http web server.

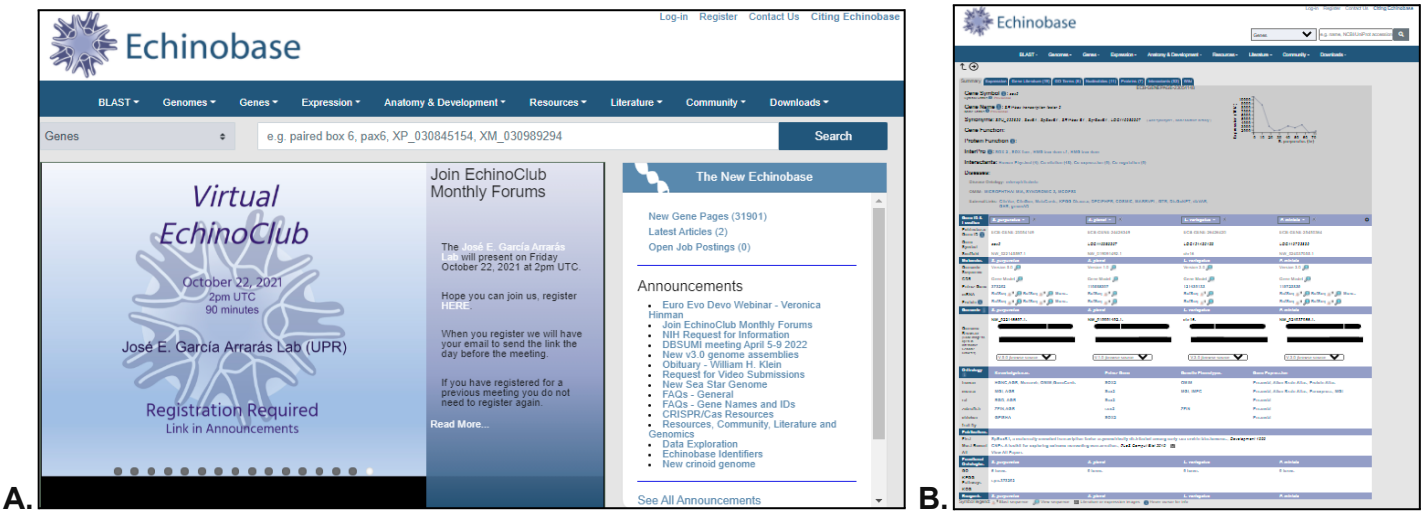


Figure 2. A. The Search bar can be used for directly searching from the landing page and pull-down menus are available if the user has a specific inquiry or purpose for visiting. **B.** An example gene page shows all of the information gathered and displayed on the Summary page. The tabs can be used to access more specific supporting information that has more details than the Summary page. Note that this gene is orthologous for *S. purpuratus*, *A. planci, P. miniata and L. variegatus*.

Genomes. The new *S. purpuratus* v5.0, *P. miniata* v3.0 and *L. variegatus* v3.0 are available along with *A. planci* v1.0 genomes and are fully supported in the new framework, the *A. japonica* (featherstar) and *A. rubens* (sugar star) genomes are partially supported (JBrowse and BLAST).

Table 2. A. Genome statistics for *Strongylocentrotus purpuratus,* Assembly name: Spur_5.0 | Date: 2019-09-06 | Genome coverage: 123.0x | BioSample: SAMN00829422; *Patiria miniata*, Assembly name: Pmin_3.0 | Date: 2020/12/01 | Genome coverage: 150.0x | BioSample: SAMN13694171 | BioProject: PRJNA597964; *Lytechinus variegatus,* Lvar_3.0 | Date: 2021-05-14 | Genome coverage: 83x | BioSample: SAMN025949. **B.** Echinobase data since release on July 13, 2020.

A.

	S. purpuratus		*P. miniata*		*L. variegatus*
	v5.0 (2019)	v4.2 (2015)	v3.0 (2020)	v1.0 (2012)	v3.0 (2021)
span (bp)	921,855,793	990,915,289	608,344,308	811,028,858	869,598,128
N (%)	0.04	8.93	0.1	1.5	0.02
GC (%)	37.39	37.32	40.57	40.5	36.3
AT (%)	62.61	62.68	59.43	58	63.7
scaffold count	871	31,897	30	60,183	33
longest scaffold (bp)	62,154,208	2,525,675	48,504,769	670,900	96,709,854
scaffold N50 length (bp)	37,282,239	419,550	23,093,800	52,614	45,571,165
scaffold N50 count	11	6734	9	4,640	7
scaffold N90 length (bp)	4,944,709	500,171	10,063,795		31,652,786
scaffold N90 count	22	3,125	23		16
contig count	1,546	146,295	1,191	179,756	395
contig N50 length (bp)	2,052,140	16,785	2,102,889	23,955	5,852,084
contig N50 count	139	13,763	87	9,466	44
contig N90 length (bp)	633,415	2,625	234,404		1,346,333
contig N90 count	439	65,224	405		159

B.

Echinobase Data Statistics

Genes			
Year	2022	2021	2020
Gene Pages	31912	31912	31912
S. purpuratus genes	31912	31912	31912
P. miniata genes	5935	5935	0
L. variegatus genes	6577	6577	0
A. planci genes	6261	6261	6261
Manually Curated Genes	3605	3605	3605
Entrez Genes	169581	169581	105562
S. purpuratus	81356	81356	81356
P. miniata	32041	32041	0
L. variegatus	31978	31978	0
A. planci	24206	24206	24206
Community			
Year	2022	2021	2020
People	151	151	140
Labs	15	15	15
Organizations	257	257	76
External Links	373038	373038	254932

Developmental ontology. The current Echinoderm Anatomical Ontology (ECAO) describes anatomical entities and developmental stages for *S. purpuratus,* the most widely studied echinoderm. This ontology has recently expanded to include two additional, widely-used euechinoids (*Lytechinus variegatus* and *Paracentrotus lividus*), a representative (and the most widely studied) cidaroid (*Eucidaris tribuloides*), and the batstar (*Patiria miniata*). By integrating the developmental stages and anatomical features of diverse echinoderm species into a single, unified developmental ontology (the Echinoderm Embryo Ontology, or EEO) we now have a powerful tool for the curation of diverse, gene-related data across the phylum and the comparative analysis of these data across species.

Literature. The literature associated with a set of echinoderm search terms (4) has been collected (Karimi et al., 2021) and associated with both genes and tissues in the ECAO and will be updated weekly, making Echinobase a destination for relevant literature. Links in publication reports jump straight to gene pages, tissue descriptions, author pages and more.

Orthology. Echinobase uses a DIOPT approach for orthology analysis (Foley et al., 2021). Pairwise comparisons of protein sequences are analyzed using several tools and a threshold of 3 tools was selected for calling orthologs. Seven tools were used to compare *S. purpuratus* and human proteins for determining gene names and gene symbols (3). Five tools were used to analyze *S purpuratus* vs. other echinoderms and this information is used for the display of the 1:1 orthologs of multiple species on a gene page. This display is being expanded to 1:many, many:1 so genes duplicated in echinoderms can be mapped to the related human gene. Paralog analysis for *S. purpuratus* has been completed and display of paralogs on the gene pages is under development.

Nomenclature. Naming of the genes is a multistep process using the guidelines prepared by the Echinobase Nomenclature Steering Committee and Working Group (Beatman et al., 2021). Curators manually named another set of genes that have been in the published literature such as those involved in gene regulatory networks (GRNs).

Functional genomics. Our understanding of the evolution and functions of genomes and genes will be improved by providing high-quality, accurate genome assemblies, ortholog identification, and collection and annotation of transcriptome, chromatin accessibility, and other functional genomics datasets.

RNAseq data of *S. purpuratus* is displayed as TPM vs. hours plots on the gene pages and RNAseq and ATACseq developmental expression datasets can be visualized in JBrowse as tracks or downloaded from the FTP site. As more data becomes available at NCBI, it will be updated on Echinobase. Genome-wide maps of enhancer RNAs (eRNAs) across multiple developmental stages are also displayed as JBrowse tracks and are useful for enhancer identification and analysis (Khor et al., 2021).

Usership. User statistics for 2021 are shown in Figure 3. The statistics show 25-50 users per weekday, fewer on the weekends and some periods of higher use, predominantly viewing gene pages, and an international group of users.

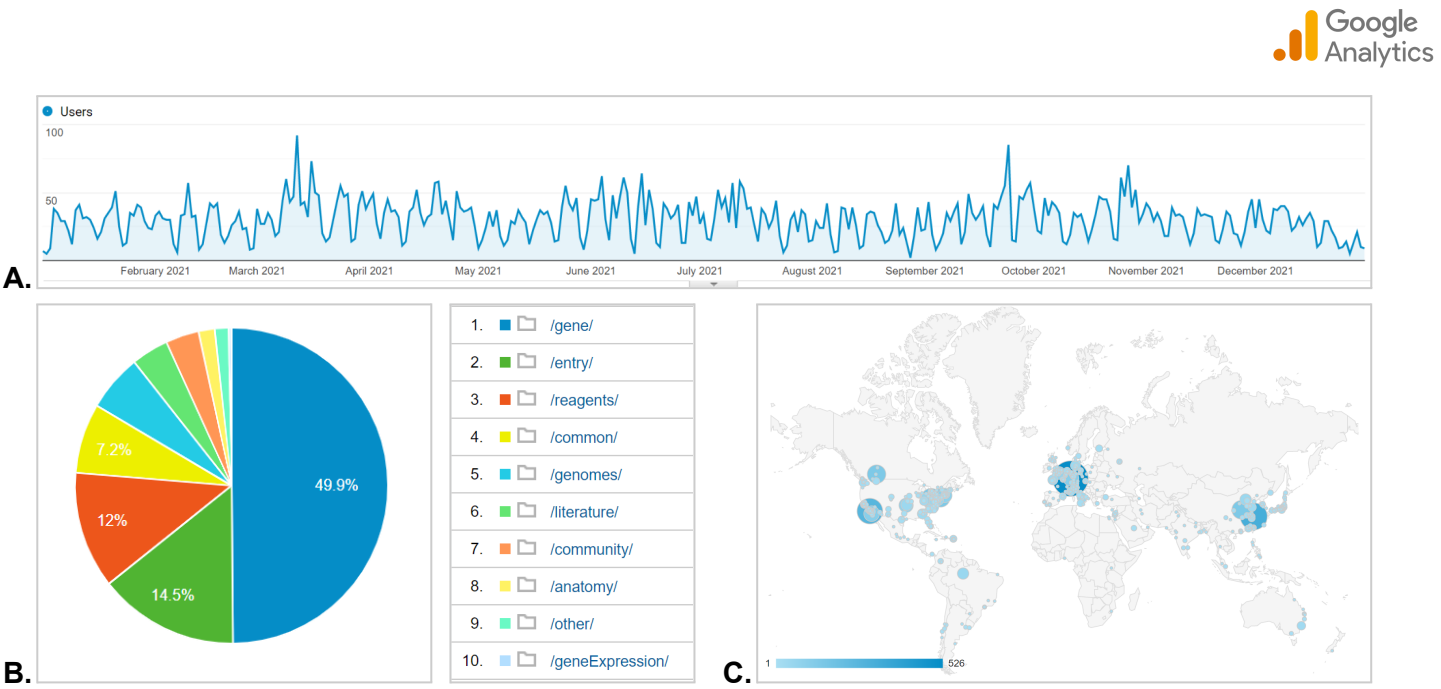


Figure 3. User data from Google Analytics showing **A.** Users per day at Echinobase, **B.** Pageviews as a percentage eg. 49.9% of pageviews were to view a gene, and **C.** the cities where users were located.

Dissemination. Four manuscripts have been published describing components of Echinobase (see the Publications section below). In April 2022, Echinobase presented a poster and a talk at the DBSUMI Meeting at MBL and in September 2021 at the Virtual EchinoClub where there were over 100 participants. We have an email list of nearly 400 community members for communicating updates and sending surveys in order to engage the community and collect feedback. The PIs are presenting research talks and noting the contributions of Echinobase. We have nearly 80 letters of support from the community for our upcoming renewal application.

As a web-based resource it is vital that Echinobase's appearance and functionality remain current and therefore the site will continue to be updated with the recent research news, results, functions and discoveries.

2.4 Community contributed datasets

Currently Echinobase hosts ATAC-seq data for timepoints from 18-70 hours (Shashikant et al., 2018b), RNA-seq (Tu et al., 2014, 2012), and genome-wide eRNAs profiles across nine early developmental stages (Khor et al., 2021). RNA-seq time course data was contributed by the Wray Lab (Davidson et al., 2020). The HiC data for the *S. purpuratus* and *P. miniata* genomes have been contributed by the Skarmeta lab (unpublished data).

2.5 Other resources related to Echinobase

The Resource for Developmental Regulatory Genomics (RDRG) was a community research resource that produced ATAC-seq chromatin accessibility profiles of several purified embryonic cell types at different developmental stages, for the purpose of enhancing CRE identification and GRN analysis. RDRG also developed a large number of new reagents for the research community, including fluorescent BAC reporters, NanoString codesets, and photoactivatable morpholinos. For researchers to benefit from these resources it will be critically important that Echinobase continue to host these data tracks on our JBrowse system and maintain up-to-date lists of these reagents. The activities of Echinobase and RDRG were highly synergistic.

The orthology analysis for Echinobase used the Pittsburgh Supercomputing Center (PSC), established in 1986, PSC is supported by several federal agencies, the Commonwealth of Pennsylvania and private industry and is a leading partner in ACCESS (Advanced Cyberinfrastructure Coordination Ecosystem: Services & Support) (formerly XSEDE (Extreme Science and Engineering Discovery Environment)), the National Science Foundation cyberinfrastructure program. PSC provides university, government and industrial researchers with access to several of the most powerful systems for high-performance computing, communications and data storage available to scientists and engineers nationwide for unclassified research.

2.6 Research dependent upon Echinobase

In collecting letters of support we have researchers identifying Echinobase as an essential and therefore critical resource (Felipe Aguilera, Vanessa Barone, Smadar Ben-Tabou de-Leon, Andrea Bodnar, Maria Byrne, Christine Byrum, Tyler Carrier, Jenifer Croce, Philip Davidson, Maurice Elphick, José E. García-Arrarás, Amro Hamdoun, John Henson, Elliot Jackson, Jimmy Khor, Pei Yun Lee, Thomas Onorato, Douglas Pace, Catherine Schrankel, L Courtney Smith, Billie Swalla,Greg Wray) and important for other NIH funding (José E. García-Arrarás, David McClay, Charles Shuster, Gary Wessel). Studies of GRNs are possible (Maria Ina Arnone, Christina Calestani, Sally Moody, Gary Wessel). The new orthology analysis is important for many (Felipe Aguilera, Vanessa Barone, Kate Buckley, Irene Diedda, Tyler Carrier, Annie Meyer). Studies of gene expression and transcriptomics (Felipe Aguilera, Maria Ina Arnone, Vanessa Barone, Andrea Bodnar, Christine Byrum, Tyler Carrier, Maurice Elphick, Manuel Irimia, Elliot Jackson, Darío Lupiáñez, Sally Moody, Roberta Russo, Catherine Schrankel, Charles Shuster, L Courtney Smith, Shunsuke Yaguchi), enhancers (César Arenas-Mena), single cell RNA-seq (Thomas Onorato, Periklis Paganos, Lina Sun), and comparative genomics (Felipe Aguilera, Andrea Bodnar, Philip Davidson, José E. García-Arrarás, Billie Swalla). It was also noted that Echinobase is a resource for training and educating new scientists (Katherine Buckley, Maria Byrne, Christina Calestani, José E. García-Arrarás, Pei Yun Lee, Paola Oliveri, Thomas Onorato, Catherine Schrankel).

2.7 Content interfacing with community initiatives

Echinobase interfaces with two large community resources: the Alliance of Genome Resources and the UCSC Cell Browser. Our partner knowledgebase, Xenbase, is currently in the process of AGR integration and will be part of that resource in late 2022. The API developer being designed to export Xenbase content will work seamlessly with Echinobase content, and therefore we will be ready to provide content when AGR is ready to add additional members. The UCSC Cell Browser, an online resource for viewing single cell RNA-seq data, has already processed and displayed on echinoderm dataset, and expressed willingness to work with us to do the same for other echinoderm datasets (pers comm Max Haessler, UCSC). We will work with this group to provide dataset curation to streamline and standardize data submissions and ensure the maximum visibility and leveraging of all qualifying single-cell datasets.

2.8. Echinobase publications

(1) Arshinoff BI, Cary GA, Karimi K, Foley S, Agalakov S, Delgado F, Lotay VS, Ku CJ, Pells TJ, Beatman TR, Kim E, Cameron RA, Vize PD, Telmer CA, Croce J, Ettensohn CA, Hinman VF, **Echinobase: leveraging an extant model organism database to build a knowledgebase supporting research on the genomics and biology of echinoderms,** *Nucleic Acids Research*, Volume 50, Issue D1, 10.1093/nar/gkab1005
(2) Foley S, Ku C, Arshinoff B, Lotay V, Karimi K, Vize PD, Hinman V, **Integration of 1:1 orthology maps and updated datasets into Echinobase,** *Database (Oxford)*, Volume 2021, baab030, 10.1093/database/baab030
(3) Beatman, TR, Buckley, KM, Cary, GA, Hinman, VF, Ettensohn, CA, **A nomenclature for echinoderm genes,** *Database (Oxford)*, Volume 2021, baab052, 10.1093/database/baab052
(4) Karimi, K, Agalakov, S, Telmer, CA, Beatman TR, Pells, TJ, Arshinoff, BI, Ku, CJ, Foley, S, Hinman, VF, Ettensohn, CA, Vize, PD, **Classifying domain-specific text documents containing ambiguous keywords**, *Database (Oxford),* Volume 2021, baab062, 10.1093/database/baab062
(5) Foley S, Vlasova A, Marcet-Houben M, Gabaldón T, Hinman VF, **Evolutionary analyses of genes in Echinodermata offer insights towards the origin of metazoan phyla.** *Genomics.* 2022 Jul 11, 10.1016/j.ygeno.2022.11043

3. Establishing Community Consensus of Priorities for Echinobase

3.1 A highly collaborative echinoderm research community

The echinoderm research community is a remarkably cooperative group. This collection of investigators has held an international meeting (Developmental Biology of the Sea Urchin; DBSU) every 18 months since 1981 (except during the COVID pandemic) with only a rotating, ad hoc committee of organizers and no other official structure. Many investigators, graduate students, and postdoctoral scholars have spent time in echinoderm research laboratories other than their own for sabbaticals or short training experiences. Interdisciplinary work ranging from paleontology to molecular developmental biology is evident within the community. The exchange of unpublished sequence data and reagents occurs seamlessly among laboratories. In this context, the support of community resources returns much more than it costs while still supporting innovative efforts.

3.2 EchinoClub virtual research series

A new community collaboration, “EchinoClub” initiated by Echinobase in 2021, kicked off with a series of presentations. From March to December there were 6 presentations, each with around 100 attendees for 2 hour presentations.

- Hamdoun Lab: Protective mechanisms during echinoderm development and the generation of a homozygous mutant drug transporter knockout line.
- García Arrarás Lab: Regeneration in holothurians; a different view of echinoderm development.
- Echinobase Team: Echinobase, a genomics knowledgebase.
- Arnone Lab: Gene regulatory networks in development and evolution.
- Wray Lab: What can extreme biology teach us about the evolution of development?
- Lepage Lab: Old friends and new family members: a novel mechanism for activation of the MAPK signaling pathway.
- Wessel Lab: Echinoderms Rock!

This presents an ongoing, monthly series for sharing recent research updates, methods development and community feedback.

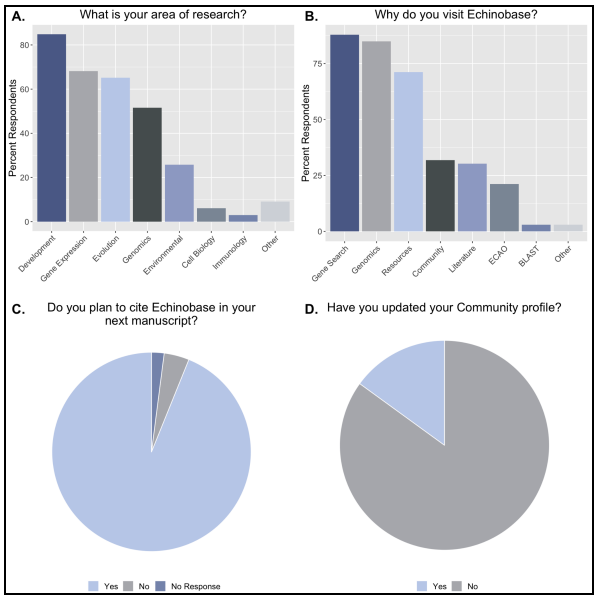
EchinoClub is now run by a group of young investigators; Catherine Schrankel, Margherita Perillo, Zak Swartz and Vanessa Barone, for them to gain experience with organizing community events.

3.3 Establishing community consensus for future goals for Echinobase

The development of Echinobase has been guided by feedback from the echinoderm research community and the SAB. A scientific advisory board meeting was held at the Developmental Biology of the Sea Urchin meeting (XXIV; April, 2017), along with a public forum to discuss the needs of the research community with respect to Echinobase and other resources. Approximately 60 people attended the public meeting. The group unanimously supported the continuation and expansion of Echinobase. Based on these meetings, we established a survey to assess the needs and priorities of the community, which was emailed to the Echinobase email list and posted on the website. We received 105 responses, including 47 identified as faculty and lab PIs (https://www.surveymonkey.com/results/SM-P363JRL6/). 96% of respondents stated that echinobase was essential for their research, or that it would be difficult to do their work without it. This survey provided a clear set of priorities for the Echinobase user community. These were implemented by 2021:

- Added genome assemblies of species of Echinoderms used as model organisms for genomic research.
- Improved gene annotations and ortholog identities.
- Provided a resource for sharing protocols, reagents and community news.
- Echinobase continues to include genome-wide data of features of a regulatory nature
- (including ATAC-seq data) for all species.
- Incorporates expression data into Echinobase.
- Improved accessibility and ease of use of the web resource.

At the SAB meeting at the DBSUMI meeting in April 2022, members discussed the past survey results and another survey was distributed. These results are in Figure 4.



What features would you like to see on Echinobase?

Responses were sorted and summarized.

In summary, users requested:

- additional genomes eg *Lytechinus pictus* and *Paracentrotus lividus*
- expanded GO terms
- expanded gene orthology including PhylomeDB
- gene expression (RNA and protein) visualization matrix
- expanded curation of in situ images, including an imagebase
- additional data tracks on the genome browser including SNPs
- improved search capability of legacy *P. miniata*
- support for single cell transcriptomics
- sgRNA tool available on Echinobase
- a Newsletter describing new changes and features of Echinobase
- training modules for its using Echinobase

Figure 4. Results from the April 2022 User Survey.

3.4 Consensus for Echinobase priorities going forward

(A) To add genome assemblies of species of Echinoderms used as model organisms for genomic research. The genomes of echinoderms are large and polymorphic. Indeed, efforts to sequence and assemble them have often served as experiments for this kind of effort in general. The community has requested that annotated genomes of *Lytechinus pictus* and *Paracentrotus lividus* be made available on Echinobase. The *L. pictus* genome annotations are currently being finalized.

(B) To improve gene annotations and ortholog identities. A central objective in many research programs in our community is to assay gene expression and function. Efforts should be made to generally improve gene annotations (e.g. splicing isoforms, non-coding RNAs, translation starts sites, and UTRs). This will globally improve the utility of Echinobase for all researchers and facilitate CRISPR guide RNA design (Cui et al., 2017; Lin and Su, 2016; Lin et al., 2019). A DIOPT-like pipeline has been developed for ortholog prediction of *S. purpuratus* to humans (for gene names) and to other fully supported echinoderm species on Echinobase. This analysis will be expanded to include PhylomeDB phylogenetic analysis. GO terms will be expanded to improve gene expression studies and visualization tools will be incorporated for display of data. The number of user-generated echinoderm transcriptomes is ballooning. There are 292 echinoderm transcriptomes in the NCBI sequence read archive (SRA) representing 81 species. Most of these were collected for an explicit experimental purpose and no consolidation has been undertaken. Thus a huge amount of data is lost to the experimentalist. A further goal therefore is to collate transcriptomes from these many sources to provide high quality reference transcriptomes from multiple species and, where possible, provide details of time points and tissue types.

(C) To provide a resource for sharing protocols, reagents and community news. The EchinoWiki is available for posting of protocols and validated reagents. Morpholinos and gRNAs have been curated and are incorporated into Echinobase. Links to gRNA tools will be provided in addition. Images are curated from articles and an image gallery is available. The Announcements on the landing page serve to notify the community of events and news.

(D) To continue including genome-wide regulatory sequences, including ATAC-seq, for all species. Echinoderms are famous for the ease with which synchronous embryo cultures can be obtained, suiting them perfectly for developmental profiling of chromatin architecture. Most importantly, echinoderm embryos are unusually well suited for functional cis-regulatory analyses of gene expression, an essential component of GRN studies. Such data are emerging from many labs and it will be crucial to provide genome browser tracks or other portals to these data on Echinobase. This will greatly facilitate improved annotations of functional noncoding DNA and the use of echinoderms for regulatory functional genomics. Such data are also routinely needed by researchers from other models systems and, in particular, the growing body of researchers performing comparative functional genomics that would like to use this major phylum in their analyses.

(E) To further incorporate expression data including single cell RNA-seq data into Echinobase. New endeavors to include spatial and quantitative expression should be included for S. purpuratus and other important experimental species. Significant individual lab efforts are directed at identifying spatial and quantitative gene expression profiles that can benefit the community as a whole. Providing these data in a format that can be readily accessed and cross-referenced from multiple species will aid comprehensive syntheses of gene regulatory network analyses, including for researchers from other communities. These should, as much as possible, also follow standards for other models systems outside of the echinoderms, to facilitate broader accessibility. Controlled vocabularies for developmental anatomy, and developmental stages, should be developed with the intent of coordinating with other taxa.

(F) To improve accessibility and ease of use of the web resource. As the types (e.g. annotation and expression) and the quantity of data expand, it becomes imperative to remodel the Echinobase web information system to ensure that it remains easily accessible to researchers, regardless of their experience with echinoderms. This will include use of uniform nomenclature and searching tools, as well as intuitive links to external resources and databases. Efforts will be made to seek input from researchers in other systems, and in particular other genomic web resource developers, to stimulate outreach efforts to service a broader community. The goal is to increase the impact of Echinobase and Echinoderm research, and to ensure that researchers from other communities can take advantage of the work done in echinoderms. These recommendations address critically important needs identified by the community, seek to make best use of current resources, and are directed at enhancing the unique strengths of the echinoderm model system for the coming decade. Echinobase is a critically important source of genomic information for the Echinoderm Phylum. Without it, most of the important research resources that have been developed over the past decade (including the genome sequence itself) would be almost useless. The continual improvement of this vital resource is therefore of the highest priority. Echinobase also leads the way in working with highly polymorphic genomes, which are typical for many species with large population sizes. Echinobase therefore serves as a technical resource to scientists establishing new organisms for genomic studies. As a medium sized competitive community we are also well placed to trial new approaches for data sharing. Echinobase therefore serves as an important resource for a wide community beyond echinoderm-specific researchers.

4. Specific Aims for Echinobase renewal derived from community consensus

The above priorities were used to establish the following specific aims for the renewal of the Echinobase funding, which was identified as the most important goal for the knowledgebase.

1: Maintain and expand Echinobase and disseminate echinoderm research data.

1.1 Maintain and expand database infrastructure, software, capability, interfaces and usability.
1.2 Maintain, integrate and improve support for new and existing echinoderm genomic content.
1.3 Enhance data sharing infrastructure with other resources for interoperability and align Echinobase with external resources.
1.4 Provide open access dissemination using FAIR principles and foster communication among all stakeholders.

2: To improve genome and expression resources, annotations and provide gold standard curated data.

2.1 Expand and improve genome assemblies and gene model predictions.
2.2 Improve gene orthology using controlled vocabularies and DIOPT best practices.
2.3 Continue to provide “gold standard” curated data using FAIR principles.
2.4 Leverage the echinoderm developmental ontology to curate gene expression data and the expression patterns of tissue- and stage-specific transcriptional drivers.

3: Enhance integrated Omics support.

3.1 Process GEO data adding new data types (ATAC, Methyl-seq HiC) and visualization tools.
3.2 Develop support for single cell data (RNA-seq, ATAC-seq) and link to human cell Atlas/UCSC.
3.3 Continue to develop and improve efficiency of data mining tools to increase data integration.

Current personnel.

Carnegie Mellon University
Veronica Hinman
Charles Ettensohn
Saoirse Foley, Bioinformatician
Cheryl Telmer, Project Manager

University of Calgary
Peter Vize
Kamran Karimi
Sergei Agalakov, Database Administrator
Brad Arshinoff, Software Developer
Eugene Kim, Software developer

Past personnel: Thomas Beatman, Andrew Cameron, Greg Cary, Francisco Delgado, Carolyn Ku

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