# Old knowledge and new technologies allow rapid development of model organisms

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**ABSTRACT** **Until recently the set of "model" species used commonly for cell biology was limited to a small number of well-understood organisms, and developing a new model was prohibitively expensive or time-consuming. With the current rapid advances in technology, in particular low-cost high-throughput sequencing, it is now possible to develop molecular resources fairly rapidly. Wider sampling of biological diversity can only accelerate progress in addressing cellular mechanisms and shed light on how they are adapted to varied physiological contexts. Here we illustrate how historical knowledge and new technologies can reveal the potential of nonconventional organisms, and we suggest guidelines for selecting new experimental models. We also present examples of nonstandard marine metazoan model species that have made important contributions to our understanding of biological processes.**

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> In scientific investigation the fortunate choice of animal often suffices to resolve general questions of the greatest importance.
>
> Claude Bernard, *Introduction a l'étude de la médecine expérimentale*

This sentiment, expressed by Claude Bernard in 1865 (Bernard *et al.*, 1865, p. 27 [translation from French by the authors]), was echoed 60 years later by August Krogh: "For such a large number of problems there will be some animal of choice, or a few such animals, on which it can be most conveniently studied" (Krogh, 1929, p. 202). It is as true today in the era of genomics as it was in those days, that choosing experimental organisms on the basis of particular physiological features or practical suitability for a given technique is often the key to unlocking a biological question.

Individual species used for scientific investigation, in particular those used repeatedly, are commonly referred to as "models." In practice, the term is generally used more restrictively to refer only to those organisms that have been heavily studied and that are tractable to genetic and/or molecular analysis, obvious examples being the fruit fly, mouse, yeast, *Arabidopsis*, nematode, zebrafish, and *Xenopus*. Such heavily studied species having many resources may be described as "traditional," "conventional," "standard," "canonical," "favored," "well-established," or "dominant," whereas organisms studied by a small number of labs and having fewer molecular tools may be called "emerging," "historical," "unusual," "nonstandard," "marginal," or "understudied." It is worth pointing out that the adjective "emerging," does not imply recent introduction into the laboratory: many of the "emerging models" have been studied since the 19th century; in this usage, "emerging" indicates a recent increase in molecular tools and methodologies, speed of scientific progress, or the number of laboratories working with a particular organism.

The "traditional" model organisms are very well understood through accumulated knowledge and intense study and have proven broad utility for research in many different fields, but they are unable to cover the full range of biological enquiry. This is because, as Claude Bernard implied 150 years ago, many biological processes are absent, masked, or not accessible in these organisms, and only a tiny fraction of existing molecular and taxonomic biodiversity is represented (Abzhanov *et al.*, 2008; Bolker, 2012;

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| Model species or group | Key biological features and breakthroughs | Awards | Key references |
|---|---|---|---|
| Sea urchin (*Arbacia punctulata*, *Strongylocentrotus purpuratus*,[a] *Lytechinus variegatus*, *Paracentrotus lividus*) | • Rapid, synchronous development and "biochemical" quantities of the easy-to-handle sea urchin embryos make them a key model for cell and developmental biology.<br>• Circa 1900, Boveri proposed the chromosome theory of inheritance and discovered centrosomes in sea urchins.<br>• Important models for studying mechanisms of cell cycle and transcriptional regulation. | 2001 Nobel Prize in Physiology or Medicine: identification of the key mitotic protein cyclin | Dorée and Hunt, 2002; Davidson, 2009 |
| Starfish (e.g., *Patiria pectinifera*, *Patiria miniata*[a], *Marthasterias glacialis*) | • Concept of "maturation (M-phase) promoting factor" was established by cytoplasmic transfer experiments in amphibian and starfish oocytes, providing the foundation for much of cell cycle research.<br>• Starfish were among the first organisms in which the meiosis-inducing hormone was identified. | | Kanatani *et al.*, 1969; Kishimoto and Kanatani, 1976 |
| Clam (*Spisula solidissima* and other bivalve mollusks, e.g., mussel, oyster) | • Extremely large number of oocytes allows establishment of cell-free systems that recapitulate cell cycle transitions, which has led to significant advances in the understanding of the cell cycle and translational control. | 2001 Nobel Prize in Physiology or Medicine: cyclins<br>2004 Nobel Prize in Chemistry: discovery of ubiquitin-mediated protein degradation system | Sudakin *et al.*, 1995 |
| Sea hares/slugs (*Aplysia californica*[a], other *Aplysia* species) | • The nervous system is composed of a small number of large cells, many of which are invariant and identifiable, rendering sea slugs an ideal model to understand the physiological basis of learning and memory. | 2000 Nobel Prize in Physiology or Medicine: discoveries concerning signal transduction in the nervous system | Carew and Kandel, 1973 |
| Squid (*Loligo* spp.) | • Squids feature a giant axon (up to 1 mm in diameter) in which voltage clamp electrodes can be inserted, allowing electrophysiology studies.<br>• Observations of axonal transport led to the discovery of kinesin, the first microtubule motor protein. | 1963 Nobel Prize in Physiology or Medicine: discovery of the ionic mechanism of the action potential | Vale *et al.*, 1985; Schwiening, 2012 |
| Sea squirts (*Ciona intestinalis*[a], *Ciona savigny*,[a] *Phallusia mammillata*[a], *Halocynthia roretzi*[a], *Botryllus schlosseri*[a], *Styela partita*) | • Owing to their copious gametes and easy culture methods, sea squirts (ascidians) are a historical model for basic cell and developmental biology.<br>• In 1905, observations of the reorganization and partitioning of the pigmented myoplasm led Conklin to propose the concept of maternal determinants and the role of asymmetric division in specifying cell fates. | | Nishida and Sawada, 2001; Brozovic *et al.*, 2016 |
| Hydrozoan jellyfish (*Aequorea victoria*, *Clytia hemisphaerica*) | • Hydrozoans have been used to study bioluminescence and for traditional experimental embryology.<br>• Laboratory model hydrozoans have provided evidence for the evolutionarily ancient and conserved roles of signaling pathways in embryo polarity, development, and oocyte maturation. | 2008 Nobel Prize in Chemistry: discovery of GFP and the intracellular calcium sensor aequorin | Zimmer, 2009 |
| Ragworm (*Platynereis dumerilii*) | • This organism has a short generation time and synchronous and stereotypic development of thousands of transparent embryos.<br>• Research has addressed diverse questions in development, evolution, and neurobiology concerning phototaxis, introns, microRNA, the control of diel vertical migration via melatonin, and nervous system cell types. | | Tosches *et al.*, 2014 |

This table is far from exhaustive and omits many laboratory models with huge potential such as the amphipod crustacean *Parhyale hawaiensis*, the larvacean *Oikopleura dioica*, and important fish models such as medaka (*Oryzias latipes*) and puffer fish (*Takifugu rubripes*).

[a]Genome available publicly in January 2016.

**TABLE 1:** Examples of contributions from marine model organisms.

Sullivan, 2015; Warren, 2015). In the past, there was no good alternative to explore this diversity: developing a new organism as a model was time-consuming and costly.

Today, many of the limitations in developing new model organisms are disappearing. With the advent of molecular methods, in particular low-cost high-throughput sequencing and easier approaches

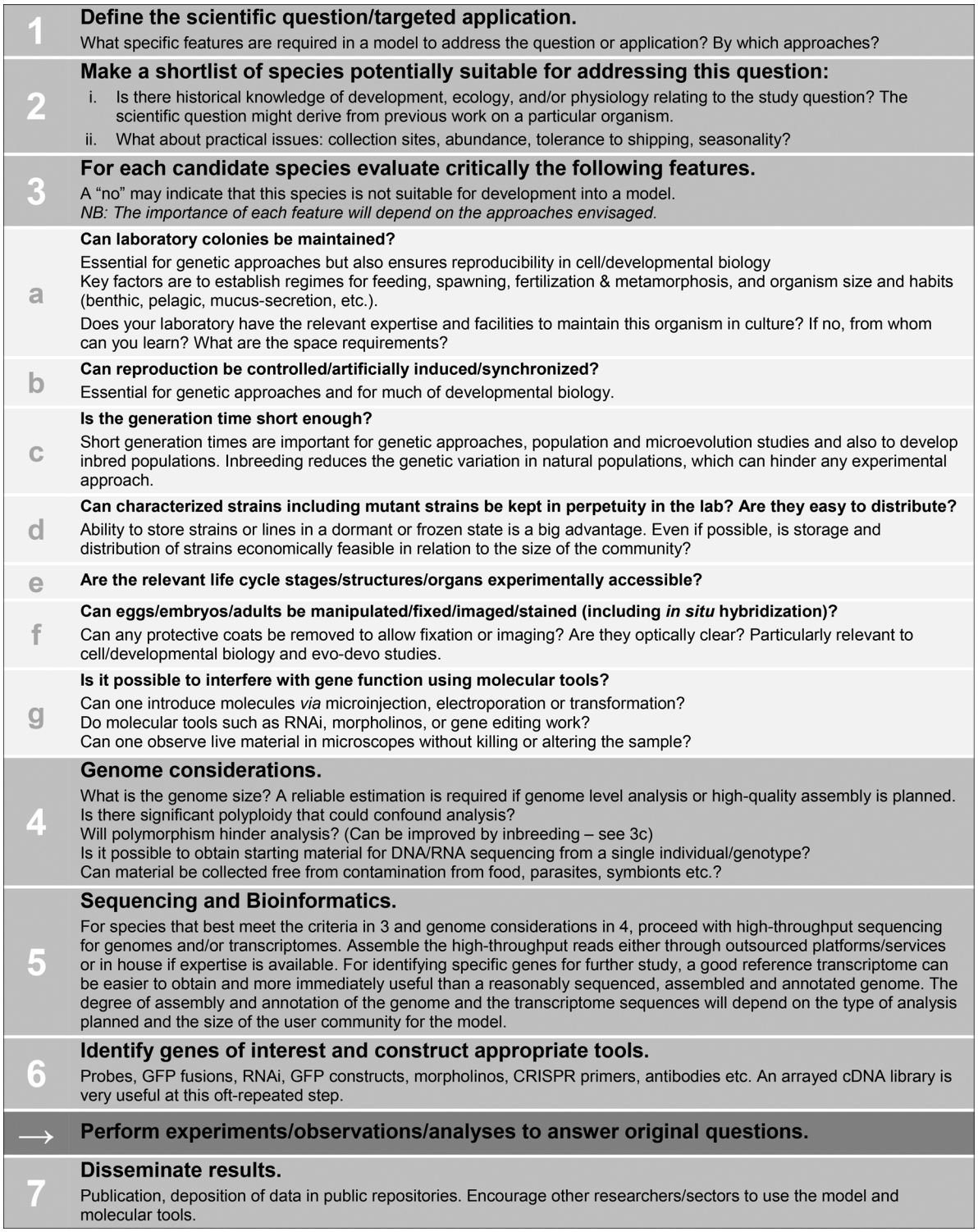
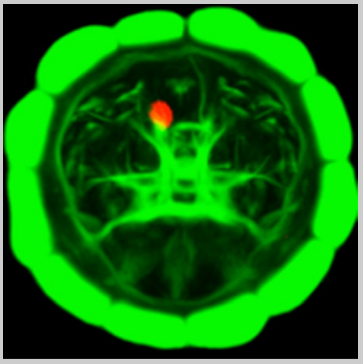



FIGURE 1: Considerations and workflow for developing a new model organism.

to genetic, epigenetic, and functional analysis without the need for conventional genetics, it is now possible to develop genomic resources and adapt analytical methods for new models fairly rapidly. These molecular resources can then allow rapid progress in addressing research questions that are intractable using current models and permit the exploration and development of new biotechnologies based on the unique biological characteristics of a particular species.

In this new era, cross-talk between communities exploiting living organisms for applied aims and for basic research is facilitated. Organisms already cultured or collected for commercial purposes can be readily tested for their use in the laboratory, while better understanding of particular biological processes or traits in laboratory models can open up translational research avenues. Moreover, models of interest to multiple disciplines (basic biology, industry, medicine,

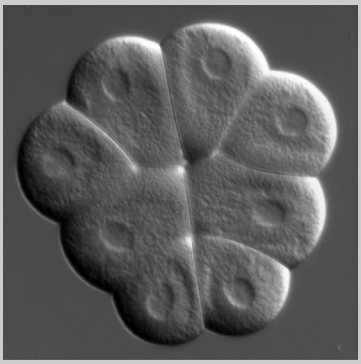
## *Platynereis dumerilii*



Interest: Phylogenetic considerations make the marine annelid Platynereis dumerilii particularly suitable for studies in evolution and development [1, 2]. Platynereis belongs to the Spiralia/Lophotrochozoa, one of the three major lineages of bilaterians, which is under-represented amongst experimental/molecular models compared to deuterostomes (e.g. vertebrates) and ecdysozoans (e.g. insects and nematodes). Attractive features: synchronous and stereotypic development of thousands of transparent embryos from a single spawning [3f]; small adult size (around 4 cm in length) and relatively short generation time (minimum 3 months) [3c], easy husbandry and breeding in the laboratory [3a] (Fischer and Dorresteijn, 2004). Simple and reliable control of spawning using artificial lunar light cycles [3b]; larval development has been described in great detail [2] (Fischer et al., 2010). High-throughput injections into one (and few) cell-stage embryos are easily possible and open up the system for all kinds of molecular manipulation [3f, g]. Contributions: Platynereis has helped answer questions relating to eye evolution, phototaxis and plankton swimming behavior as well intron evolution, microRNA evolution and nervous system evolution. It has also proved valuable for toxicology studies. Tools: Sequencing of the 0.9 Gb genomes of one inbred line and one natural population was recently completed [4]; multiple transcriptomes are available from different tissues, stages and populations (http://4dx.embl.de/platy/) [5]. A reliable and easily reproducible whole-mount in situ hybridization protocol in combination with highly stereotypic development are the prerequisite for multi-gene expression atlases at cellular resolution [3f] (Tomer et al., 2010). These in turn allow reliable mapping of single cell transcriptomes that have been generated for several larval stages (Achim et al., 2015) [5]. Furthermore, knock-down and knockout-techniques and stable transgenesis methods have been established and successfully applied by several laboratories [6].

## *Phallusia mammillata*

Interest: Ascidian eggs develop via stereotypic reorganizations and an invariant cleavage pattern which are remarkably conserved among species (Sardet et al., 2007; Lemaire et al., 2008). Over a century ago it was noted that the embryos of the European ascidian Phallusia mammillata are exceptionally transparent [2] and more recently Phallusia has been developed as a species favorable for microscopy approaches [3f] (McDougall et al., 2015). Attractive features: In addition to their transparency, Phallusia eggs readily translate injected mRNAs such as those encoding GFP fusions, allowing fluorescent live cell imaging of all stages at single cell resolution [3e, f, g]. Gametes are very abundant and embryonic development is synchronous and fast. Phallusia will reproduce year-round and adult hermaphrodites can be maintained in aquaria for months [2, 3a, b]. The major drawback for Phallusia is limited geographical distribution although animals can be shipped from Mediterranean and northeastern Atlantic locations and potentially cultured in laboratory seawater tanks (life cycle <6 months). Tools: The genome (234 Mb, about 20,000 genes) and several transcriptome sequences are available [4, 5] (http://www.aniseed.cnrs.fr/) (Brozovic et al., 2016) as well as an arrayed cDNA library and an expanding repertoire of GFP-tagged constructs. Ascidian eggs can be efficiently electroporated with plasmid DNA, and many of the molecular constructs and methods developed for the ascidian species of reference Ciona intestinalis are applicable to Phallusia. Specific gene function can be perturbed by the addition of chemical inhibitors, injection of morpholinos or dominant negative constructs, and gene editing [3g, 6]. Contributions: Phallusia allows in vivo imaging of the earliest stages of ascidian development and has contributed to our understanding of many dynamic processes, including calcium oscillations, cytoskeletal reorganizations, meiotic and embryonic cell cycles, spindle positioning, and gastrulation.



## *Clytia hemisphaerica*

Interest: Cnidaria (corals, sea anemones, hydra, jellyfish) include highly diverse species with the familiar set of developmental regulators coded in their genomes, and provide a fresh perspective on animal development as the sister group of the bilaterian clade [1]. The genus Clytia (Phialidium) had previously provided choice experimental material to uncover many properties of hydrozoan larval development (Freeman, 1981) [2]. We tested C. hemisphaerica (Houliston et al., 2010) as a model because of wide availability and ease of culture [3a] and after consultation with Villefranche zoologist Dany Carré (Carré and Carré, 2000). Other attractive features: Transparent eggs and embryos for microscopy [3f], large enough (180 µm diameter) for easy micromanipulation; small jellyfish (1 cm in diameter) facilitating culture [3a]; short life cycle (2-3 months) [3c], including a vegetative polyp stage, which provides a continuous supply of genetically identical jellyfish; convenient light-induced spawning and peptide-induced metamorphosis [3b]. Tools: Assembled genome sequence (450 MB) and many transcriptome resources are soon to be published and become publically available. Clonal male medusa from an individual polyp colony produced by 3 generations of self-crossing were used as starting material for genome sequencing [4], although these showed lower homozygosity than expected, and polymorphism between the two haplotypes initially hindered genome assembly. The immortal polyp colonies can be easily distributed as 'cuttings' between laboratories [3d]; gene knockdown during larval development is routine and gene-edited colonies are now being successfully developed, although as yet RNA interference has been unsuccessful [3g]. Other unforeseen drawbacks include fluorescence from endogenously expressed GFPs in wild-type strains, which restricts imaging possibilities, and generalized translational repression in immature oocytes hampering expression of exogenous mRNAs at this stage. Contributions: Since Clytia hemisphaerica began to emerge as a molecular model in 2006, it has helped illuminate numerous diverse biological questions including the regulation of oogenesis, origins of embryo polarity, embryonic pattering genes, germ-line origins and muscle evolution (Houliston et al., 2010; Steinmetz et al., 2012; Lapébie et al., 2014).

## *Patiria miniata*

Interest: Starfish have long proved to be a choice model for studying oocyte maturation [1]. They have the rare advantage that meiosis can be induced with a defined compound (the maturation hormone, 1-methyl-adenine). Patiria miniata and the related species Patiria pectinifera (formerly known as Asterina miniata and pectinifera) are used by several laboratories to study meiosis and cell cycle regulation [2]. Attractive features: P. miniata, from the West Coast of the United States, is not endangered or protected and tolerates shipping well; adult starfish can be maintained in a standard animal facility at any research institute [3a]. Meiosis is extremely synchronous and occurs on a convenient time scale of 1.5 hours. Cellular events of meiosis can be followed at room temperature in seawater in oocytes available year around [3b, e]. Exogenous mRNAs can be expressed in oocytes that are transparent allowing high resolution imaging by light microscopy [3f]. Contributions: Patiria has contributed significantly to the large knowledge base on the molecular and cellular events of meiosis (Kishimoto and Kanatani, 1976; Kishimoto, 1999; Lenart et al., 2005). Tools: A draft genome assembly and transcriptome data are available for P. miniata (http://www.ncbi.nlm.nih.gov/genome/?term=txid46514[Organism:noexp]), though assembly was complicated by the unexpectedly high heterozygosity [4, 5]. The available sequence information allows the use of all standard molecular biology tools for the study of the cell biology of meiotic divisions. Drawbacks: the generation time is very long (years) rendering classical genetics and establishment of transgenic lines impractical. Variation within the species and heterozygosity of the sequenced individuals is very high. This complicates genome assembly.

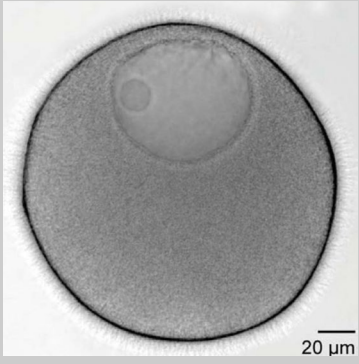



FIGURE 2: Case histories for four marine model animal species. Numbers in square brackets correspond to the points listed in Figure 1.

teaching) acquire synergistic added value, as each increase in knowledge or resources will benefit all sectors that use it.

Importantly, "non-model" organisms have an excellent track record contributing to major discoveries in cell biology. Table 1 presents a nonexhaustive list to highlight some of the most prominent examples, many of which have led to Nobel Prize–winning discoveries. Notably, these discoveries were made before the new molecular technologies became available. These examples illustrate the potential for virtually any organism to become a "model," and developing new models, while still not straightforward, is less daunting since the advent of new molecular technologies.

It is not a coincidence that the examples in Table 1 are all marine organisms, because these organisms are, for historical and practical reasons, often suitable for development as experimental models. Since the 19th century, marine stations around the world have provided access to biological material covering a spectacular range of biodiversity; all animal phyla are present in the sea, several of them uniquely so. Marine stations have thus pushed forward research into all aspects of biology and ecology, thereby generating a large body of knowledge concerning where to find organisms, particularities of their physiology and life cycles, and how to manipulate them in the laboratory. This knowledge is of enormous importance in guiding the efficient choice and development of new models. On the practical side, many marine organisms produce vast quantities of freely accessible eggs, embryos, and larvae that are naturally transparent and therefore ideal for microscopy; and many, too, lack the robust protective cell walls, shells, cuticles, and exoskeletons that are common in terrestrial organisms and render the latter less amenable to experimental manipulation.

The motivation to find a new model organism is usually driven by a particular research challenge; existing models may not be suitable for the approaches envisaged to address particular biological processes; or an unexplored species or taxonomic group may have characteristics that are unique, exaggerated, or especially accessible to analysis. The rapidly decreasing start-up costs and technical investment needed to establish molecular and technical resources for any organism now make it economically feasible for a single laboratory or small consortium to test a number of possible new model species, then choose to develop and explore one (or more) of these for specific research aims. However, "lower" costs are not necessarily negligible: developing a new model can require establishing laboratory cultures and determining whether the biology of the organism is suitable for the desired experiments, and this effort can be quite labor- and material-intensive.

We have used our own experience developing models to outline some of the factors to be considered before developing resources for new models (Figure 1). We identify decision points that can help researchers to develop new models efficiently or to abandon those organisms that do not meet key criteria. We emphasize that prior biological knowledge is essential in the selection of potential models and that existing expertise can significantly decrease the financial and time costs for developing a new model. We have included in the outline the development of genomics resources such as a transcriptome or genome sequences, facilitated by high-throughput sequencing approaches. These resources are essential for many approaches in modern biology (such as comparative transcriptomics and promoter analysis) and greatly accelerate others, including genetics, biochemistry/proteomics, and gene function studies. Our own expertise is marine organisms, but our criteria will be useful when considering any potential new model, and in principle, any new tissue and cell cultures.

We emphasize that the considerations listed in Figure 1 are a thinking aid, not a recipe to be followed to the letter. Many potential models may return a "no" to the criteria queried in part 3 of Figure 1 but nevertheless prove valuable. This is demonstrated by the first five models in Table 1, none of which meet every criterion. The main aim of this figure is to alert researchers to potential bottlenecks involved in developing a new organism as a model and to weigh them against potential benefits.

Four model species for which we have firsthand experience are presented in Figure 2 (Kishimoto and Kanatani, 1976; Kishimoto, 1999; Freeman, 1981; Carré and Carré, 2000; Fischer and Dorresteijn, 2004; Fischer *et al.*, 2010; Lenart *et al.*, 2005; Sardet *et al.*, 2007; Lemaire *et al.*, 2008; Houliston *et al.*, 2010; Tomer *et al.*, 2010; Steinmetz *et al.*, 2012; Lapébie *et al.*, 2014; Achim *et al.*, 2015; McDougal *et al.*, 2015; Brozovic *et al.*, 2016). We have for each case matched the relevant features of these species with the considerations listed in Figure 1. For the annelid *Platynereis dumerilii* and the jellyfish *Clytia hemisphaerica*, for instance, paying attention to these criteria paid off and expectations have largely been fulfilled. Furthermore, some unexpected advantages emerged (e.g., vegetatively propagating *Clytia* polyp colonies being extremely convenient for maintenance of wild-type and gene-edited strains, *Phallusia* eggs readily translating exogenous mRNA even before fertilization), but also some unforeseen drawbacks.

As demonstrated by the examples in Table 1, nonstandard model organisms provide tremendous opportunities for increasing our understanding of biological processes, and their study has resulted in the development of a range of new technologies that have benefited academic research, health care, and the biotechnology industry. Particular scientific and technological advances are not necessarily anticipated directly, but can emerge progressively once sufficient resources and know-how have accumulated to allow in-depth analyses. We hope that this overview will provide a stimulus to turn from the beaten path of standard models and explore new avenues: the time is ripe to do so!

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