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## Review

# Model organisms — A historical perspective

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## ABSTRACT

Much of our knowledge on heredity, development, physiology and the underlying cellular and molecular processes is derived from the studies of model, or reference, organisms. Despite the great variety of life, a common base of shared principles could be extracted by studying a few life forms, selected based on their amenability to experimental studies. Very briefly, the origins of a few model organisms are described, including *E. coli*, yeast, *C. elegans*, *Drosophila*, *Xenopus*, zebrafish, mouse, maize and *Arabidopsis*. These model organisms were chosen because of their importance and wide use, which made them systems of choice for genome-wide studies. Many of their genomes were between the first to be fully sequenced, opening unprecedented opportunities for large-scale transcriptomics and proteomics studies.

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**1. Introduction**

Much of our knowledge on heredity, development, physiology and the underlying cellular and molecular processes is derived from the studies of model, or reference, organisms. Despite the great variety of life, a common base of shared principles could be extracted by studying a few life forms, selected based on their amenability to experimental studies (Fig. 1). Gregor

Mendel is believed to be the first who carefully chose an organism to experimentally address universal questions of heredity. Mendel was aware and intrigued by questions of evolution [1,2]. In his publication from 1866 he stated that his experiments were “the only right way by which we can finally reach the solution of a question the importance of which cannot be overestimated in connection with the history of the evolution of organic forms”. He was also very careful about the

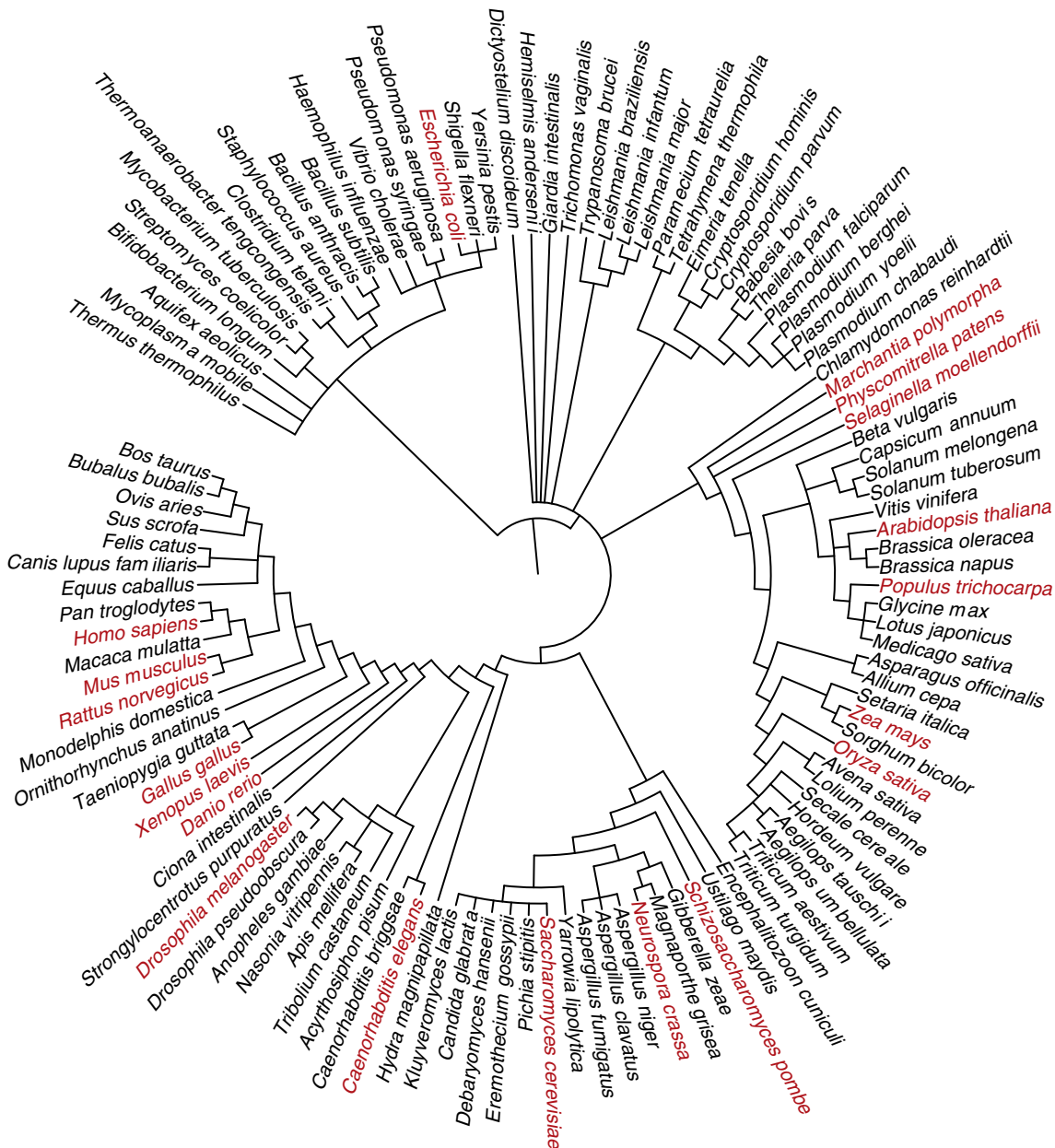


Fig. 1 – Tree of life, drawn based on [169,170], showing a selection of various organisms. Model organisms referred to in the text are indicated in red types.

characteristics, which the organism “must exhibit to avoid questionable results” [3]. These two aspects: phylogenetic position, and experimental amenability to specific research interests have guided the selection of model organisms for the time after Mendel. Typically, an initial phase to establish a core set of experimental protocols is necessary to attract a critical mass of researchers, a prerequisite for the long-term success of a model organism. The greater the accumulated body of knowledge, the easier it is to address biological questions by experiments without being tied down by technical obstacles. Quite often, after the research community has surpassed a critical size, the model organism is self-perpetuating, attracting more interest due to its popularity. Not all advantages of a given model organism may be recognized initially — a portion of luck is often involved. For example, the ease to transform *Arabidopsis thaliana* [4,5] could not be anticipated initially [6]. The opposite happened to the proverbial guinea pig, which lost its appeal due to the difficult genetics [7]. Very briefly, the origins of a biased selection of model organisms will be described. These model organisms were selected because of their importance and wide use, which made them systems of choice for genome-wide studies. Many of their genomes were among the first to be fully sequenced, opening unprecedented opportunities for large-scale transcriptomics and proteomics studies (Table 1). We provide a short historic introduction to the model systems whose proteomes are the focus of the review articles in this issue (see Fig. 2). Excellent in-depth articles and reviews focusing on other aspects exist for each model organism, and the interested reader is referred to these for further information.

## 2. *Drosophila*

The rediscovery of Mendel’s work in 1900 by Hugo de Vries [8], and Carl Correns [9] stimulated interest to explain Mendel’s laws at the level of the chromosomes, which at the time were known to bear the genetic information [10]. To analyze the problem that more segregating traits exist than the number of chromosomes, Thomas Hunt Morgan chose *Drosophila melanogaster*, which was earlier introduced and described as a laboratory animal by the entomologist Charles W. Woodworth [11]. Combining cytology and genetics, he and his co-workers

were able to re-interpret the Mendelian laws by the chromosome theory [12]. In the 1970s and 80s, genetics, embryology and molecular biology first merged in research done with *Drosophila*. Ed Lewis characterized mutants that caused dramatic transformations of the body plan [13,14]. The molecular analysis of the affected genes uncovered a related set of proteins with a conserved universal role in the generation of diversity along body axes [15–17]. Around this time, Christiane Nüsslein-Volhard and Eric Wieschaus began working together to isolate mutants affecting pattern formation in *Drosophila*. They systematically searched for mutants that disrupted the segmentation pattern of the larvae, reflecting abnormal patterning processes during embryogenesis [18]. The outcome of this screen was extremely rewarding [18,19]. The mutants and corresponding genes could be grouped into a hierarchical network leading to an understanding of the logic of pattern formation that was without precedent [20]. Interestingly, the involved genes turned out to be conserved in vertebrates and were shown to be important for normal development and in disease [21–23].

## 3. *Neurospora*

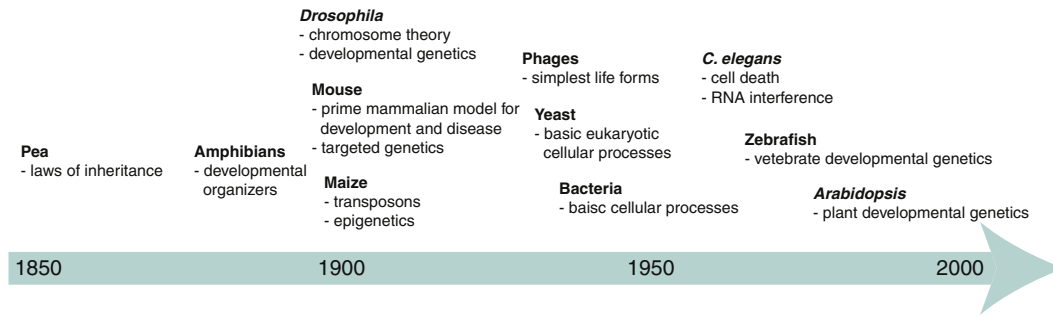
In the thirties of the last century, many researchers were unimpressed by the complexity of *Drosophila*. To study the fundamental cellular processes, simpler life forms proved more appropriate. George Beagle and Edward Tatum chose *Neurospora crassa* based on previous studies [24–26] that reported *Neurospora*’s advantages, such as easy cultivation and the haploid life cycle, which simplifies genetic analysis because recessive traits manifest themselves directly in the offspring. Furthermore, analysis of genetic recombination is facilitated by the ordered arrangement of the products of meiosis in *Neurospora* ascospores. Beadle and Tatum exposed *Neurospora* to X-rays, causing mutations. They then observed failures in metabolic pathways caused by errors in specific enzymes. This led them to propose the “one gene–one enzyme” hypothesis, stating that specific genes code for specific proteins [27]. *Neurospora* is still popular to study metabolism, gene regulation, chromosome behavior, DNA repair, DNA methylation and epigenetic phenomena, genome defense, photobiology, circadian rhythms, differentiation, development, and other biological phenomena of relevance to higher eukaryotes [28–30].

## 4. Bacteria

Joshua Lederberg was inspired by Oswald Avery, Colin MacLeod, and Maclyn McCarty’s seminal paper identifying deoxyribonucleic acid (DNA) as a transforming agent in *Pneumococcus* bacteria [31]. Lederberg considered Avery’s findings “the most exciting key” to study the chemical nature of the gene. Initial attempts to transform auxotrophic *Neurospora* strains failed, as these showed spontaneous reversions [32]. Lederberg then decided to use the bacterium *Escherichia coli*, encouraged by the possibility that bacteria might reproduce also by sexual methods and, thus, could be used for genetic studies [33]. He and Tatum showed that the bacterium *E. coli* entered a sexual phase during which it

**Table 1 – Proteome coverage for a selection of model organisms. The numbers result from a comparison of experimental data against the hypothetical proteome. The number of protein-coding genes that have orthologs in humans is indicated in the right column.**

Organism	Number of protein-coding genes ( <a href="http://www.ensembl.org/">http://www.ensembl.org/</a> )	Proteome coverage [%]	Orthologs of human genes [162]
<i>E. coli</i>	4237	94 [163]	541
<i>S. cerevisiae</i>	6532	67 [164]	2154
<i>C. elegans</i>	20,158	68 [165]	4649
<i>D. melanogaster</i>	14,076	65 [166]	5527
<i>M. musculus</i>	22,931	34 [167]	16,376
<i>H. sapiens</i>	22,286	67 [167]	
<i>A. thaliana</i>	24,408	50 [168]	3239



**Fig. 2 – Timeline to indicate the emergence of a few model organisms. Keywords referring to the main features of each model organism are added.**

could exchange genetic information through bacterial conjugation [34]. In parallel, Tatum applied the approach of mutagenizing *Neurospora* to bacteria [35]. These marked the beginnings of using *E. coli* as a model system. The discovery of the structure of DNA opened a whole new area of research [36], and *E. coli* continued to be used as a very popular model organism. For example, the first DNA polymerase was isolated from *E. coli* [37,38], and the basic concepts of transcriptional regulation were unraveled using this model organism [39]. Besides being the workhorse of recombinant DNA laboratory practices, *E. coli* still occupies an important place as a model system, such as in studies of chemotaxis [40], or as a model for bacterial pathogens [41].

## 5. Phages

Phages, viruses infecting bacteria, were established as models through the initiative of Max Delbrück [42]. Working in Morgan's laboratory at Caltech, he joined Emroy Ellis to study bacteriophages, intrigued by their simplicity, which allows straightforward isolation and quantification, yet showing a key feature of life: the ability to replicate [43]. The "Phage group", an informal group of people, then started around 1940, after Delbrück and Salvador Luria had met at a physics conference [44]. Delbrück and Luria began a series of collaborative experiments culminating in the famous Luria–Delbrück experiment, where they showed that mutations for antibiotic resistance occur randomly in the absence of selection, rather than being a response to selection [45]. The main legacy of the Phage group resulted from the yearly summer phage course at Cold Spring Harbor Laboratory. Beginning in 1945 and continuing to 1960, Delbrück and colleagues taught biologists and physicists phage biology and experimentation. Many of the leaders of the emerging field of molecular biology were alumni of the phage course.

## 6. Yeast

Baker's yeast is one of the simplest eukaryotic organisms, allowing simple cultivation, but many essential cellular processes are conserved between yeast and humans. Øyvind Winge can be considered the founder of yeast genetics, as much of the pioneering work was performed in his group at

the Carlsberg Laboratory in Copenhagen [46]. Not surprisingly working at Carlsberg Laboratory, his interests included hops, barley and yeast, with increasing focus on yeast. In 1935, when Winge began to work genetically with yeast [47], advances in genetics using other model organisms helped to make the experiments with yeast practicable, among them four-strand crossing over [48], chromosome mapping [49], the identification of lethal genes [50], and transformation of *Pneumococcus* [51], to pick a few. Knowledge of the genetics of *Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*, achieved by Winge and many others [46], has made it possible to use these two yeasts for research on the cell cycle. Investigations on both, by several teams of scientists, have made major contributions toward understanding the way cell division is controlled in eukaryotes. Leland H. Hartwell developed the concept of cell-cycle checkpoints based on the isolation and characterization of temperature-sensitive mutants in *S. cerevisiae* [52–54], while Paul Nurse proceeded to isolate cell-cycle defective mutants of *Sz. pombe*. By 1976, Nurse and his colleagues had identified 14 genes involved in DNA synthesis, nuclear division and the formation of the septum, which separates the two daughter cells [55]. Subsequently, the wild-type alleles affected in these mutants were isolated, and their biochemical and cell-biological roles investigated, leading to a reconstruction of cell-cycle control in normal cells and uncontrollably proliferating cancer cells [56]. Apart from studies on the cell cycle, yeast continues to be an excellent model system for cell morphogenesis [57], chromosome stability [58], and even aging [59]. Being one of the easiest and most accessible eukaryotic models, *S. cerevisiae* has repeatedly been used to introduce new high-throughput technologies, as will be further discussed subsequently.

## 7. *Caenorhabditis elegans*

The nematode *Caenorhabditis elegans* was chosen in 1963 by Sydney Brenner [60] as a model organism due its simplicity compared to other multicellular organisms, for example *Drosophila*: it contains fewer than 1000 cells that divide in a stereotypical manner, which means that the lineage of every cell can be traced back to the egg. Furthermore, its life cycle allows handling it like a microbe. At the same time, *C. elegans* displays all the hallmarks of a multicellular organism, such as a complex organ system [61,62], or social, sexual, and learning behaviors [63]. Conserved mechanisms involved in

programmed cell death [64], insulin signaling and aging [65,66], and neurobiology [67], have been elucidated using *C. elegans*. The worm has also been instrumental in the dissection of the mechanism of RNA interference (RNAi) [68], which was originally described in transgenic plants [69–71]. RNAi has added a powerful and easy tool for generating targeted loss-of-function mutations. The power of this method was demonstrated by the first genome-wide RNAi screens in *C. elegans* [72,73], and has since been extended to other organisms [74–76].

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## 8. Zebrafish

Similar to *C. elegans*, zebrafish (*Danio rerio*), has been introduced as a model organism relatively recently, by George Streisinger. The motivation was to choose a vertebrate model that would combine the power of forward genetic screens with easy access due to its transparency and external embryonic development [77]. Large-scale forward genetic screens have resulted in a collection of mutations that cover many aspects of embryonic development [78]. More recently, it was discovered that a genome-wide duplication event occurred in the teleost lineage [79,80], which is absent in the mammalian lineage. Therefore, essential functions may be covered by redundantly acting genes, hindering their detection in forward genetic screens [81–83]. Nevertheless, and also due to advances in reverse genetic approaches, zebrafish continues to gain popularity as a model organism. Notably, it is currently the only genetically accessible model for appendage and heart regeneration [84,85].

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## 9. Amphibians and chicken

Amphibians and chicken constitute classical model systems to study vertebrate development [86,87]. The embryos are large and easily accessible, which allows straightforward experimental manipulation, especially microsurgery. Our knowledge of developmental organizers, neural induction [88], and pattern formation during appendage development [89] is owed to the studies of these model organisms. Building on a German tradition of embryology, Wilhem Roux put these organisms and the associated questions to the forefront of the biological mainstream at the time [86]. Extrapolating from the results of his experiments, Roux formulated the mosaic theory of development with a very early determination of cell fates [90], while Hans Driesch came to different conclusions through experiments he conducted with sea urchins that led him to refute Roux's theory and postulate regulative development, where a loss of cells can be compensated during development [91]. This historic dispute may illustrate the limitations of extracting general concepts based on observations made with a single model organism.

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## 10. Mouse

*Xenopus laevis*, chicken, as well as other vertebrate models, for example the rat and monkeys are less amenable to genetic

studies than the mouse, which has become the leading mammalian model organism. The mouse is closely related to humans [92] and shares the developmental strategies and diseases, including cancer, atherosclerosis, hypertension, diabetes, osteoporosis and glaucoma. In addition, certain human diseases that normally do not strike mice, such as cystic fibrosis and Alzheimer's, can be induced by manipulating the mouse genome and environment. Mouse is also the prime model organism for stem-cell biology [93]. Targeted manipulation of the genome [94], forward genetic mutagenesis screens [95,96], and *in vivo* imaging techniques [97] are highly developed, which facilitates conducting tailored experiments at cellular resolution. After the rediscovery of Mendel's work in 1900 the question arose whether his laws would apply to animals as well [98]. Indeed, Lucien Cuénot could show Mendelian ratios for the transmission of coat color factors in mice [99], followed by a similar report from William Castle and Clarence Little for a lethal mutation [100]. Little is probably best known for the development of inbred mouse strains that are still used today. Genetic mapping in the mouse began with J.B.S. Haldane's report in 1915 [101] of linkage between the pinkeye dilution and albino loci, only two years after the first report of genetic linkage in *Drosophila* [49]. The genetic map grew slowly over the next 50 years as new loci and linkage groups were added. With the application of DNA polymorphisms as markers the recombination map grew denser at a fast pace, and advances in recombinant DNA technology allowed building a physical map of the genome [98,102], which culminated in the complete genome sequence [92]. In parallel, the development of embryonic stem cells and homologous recombination lead to the establishment of targeted genetics [94], a hallmark of today's mouse genetics.

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## 11. Maize and rice

Ever since Mendel's experiments, plants have been used as model organisms in genetic studies. For many years, the focus was on agriculturally important plants, such as maize, barley and potato, and it is only recently that plant biologists have adopted their favorite model system, *Arabidopsis thaliana* [103]. Maize in particular has a long history in genetic studies, going back to Edward M. East and Rollins A. Emerson who studied kernel pigmentation genes shortly after the rediscovery of Mendel's work [104,105]. The genetic map of maize grew rapidly and contained as many as 350 genes already in 1935 [106]. Many fundamental processes were discovered through work with maize, among others hybrid vigor [107,108], the physical exchange of chromosomes during crossing over [109], transposition [110], and genomic imprinting [111]. *Zea mays* continues to be a widely used model system, in particular for developmental genetics [112] and the elucidation of agriculturally important traits [113]. Over recent years, rice (*Oryza sativa*) has gained importance as a model organism for genetic and molecular studies. This is largely due to its relatively small genome of 420 Mb whose full sequence was released as early as 2002 [114]. The many tools and experimental approaches now available for rice have made it the most widely studied model for cereals [115,116].

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## 12. Arabidopsis

*Arabidopsis* may be regarded as the plant equivalent to the animal models *Drosophila* or *C. elegans*, and is sometimes jokingly referred to as *Drosophila botanica*. Although *Arabidopsis* was first proposed as a model system early in the 20th century, it only gained popularity in the 1980s [117], largely based on its small and simple genome, making it amenable for molecular approaches. In addition, its short life cycle and large number of seeds make it suitable for sophisticated genetics, while at the same time representing the complexity of a flowering plant [6]. *Arabidopsis* has lived up to the expectations and is the most popular model organism of the plant kingdom. Major insights have been obtained, for instance, into organ development, plant stem-cell biology [118], pattern formation [119–121], innate immunity [122,123], circadian rhythm [124], natural variation of diverse traits [125], and many developmental mechanisms. *Arabidopsis* allows the study of phenomena earlier described by plant physiologist, such as responses to light [126], gravity [127], or phytohormones [128], at the level of molecular genetics. The vast knowledge accumulated serves as a platform that now guides studies of economically important plants such as rice [114,115,129], maize [130], or populus [131]. To better understand the evolution of plants, species representing different realizations of plant life cycles have become more popular, such as the moss *Physcomitrella* [132,133], the spikemoss *Selaginella* [134], and the liverwort *Marchantia* [135]. Studies of these plants have been greatly facilitated by the advancement of next-generation sequencing technologies [136].

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## 13. Pathogens

Human pathogens infect a large number of people worldwide and, thus, constitute a serious threat to mankind. Robert Koch's discovery of the tubercle bacillus in 1882 [137], and the isolation of antibiotics by Alexander Fleming in 1928 [138] have been instrumental in treating infections. However, drug-resistant strains emerge and spread increasingly fast [139]. A multitude of pathogen-host models have been established to study the steps of infection, and how various pathogens bypass defense mechanisms [140]. Early steps in the infection appear to be shared by various pathogens and may provide potential therapeutic targets [141]. Studying infectious processes at the system level will assist in designing more efficient defense strategies that can anticipate potential adaptations of the pathogen [142,143, this issue 144]. Along the same line, comparing the genomes of pathogens and closely related non-pathogens will reveal the changes that are associated with infectious potential [145,146]. Interestingly, most genes providing antibiotic resistance are homologous to genes with functions unrelated to antibiotic resistance, suggesting that resistance proteins have evolved from inconspicuous precursors into highly specific proteins that plague the health sector today [147]. Genome sequencing of soil bacteria has uncovered a surprisingly large number of previously uncharacterized antibiotic resistance genes [148]. Studying these antibiotic resistance mechanisms can help in

anticipating novel mechanisms that may emerge clinically, as well as provide a basis for the development of new antibiotic drugs.

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## 14. Pushing technological boundaries: forerunner *S. cerevisiae*

The recent advancements in technology have allowed researchers to increasingly study organisms at the system level. Many of the resources and technologies were first developed in *S. cerevisiae* and subsequently applied to other, more complex, eukaryotic model organisms. For example, *S. cerevisiae* was the first eukaryotic organism with a completely sequenced genome [149], with a complete collection of knock-out strains [150,151], with large-scale protein–protein interaction datasets [152,153], and where systematic functional screens have been performed [154,155]. Furthermore, ChIP-chip technology [156] and RNA-Seq [157] were established using baker's yeast, and *S. cerevisiae* continues to take a leading role: integrating the large-scale datasets to build gene-centric network models will reveal the potential to perform predictive biology [158,159, this issue 160].

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## 15. Outlook

The revolutionary knowledge that was gained since Mendel's pea experiments is very much owed to the studies of model organisms. Many of the core molecular mechanisms elucidated were found conserved in related species. Therefore, model organisms have uncovered the relatedness of life on this planet at the level of the blueprint, the beauty of which is hidden to the naked eye. And many more basic secrets await discovery. New technologies will enable us to understand the model organisms at the system level, eventually allowing the logical reconstruction of many processes *in silico*. However, studying model organisms represents a reductionist approach that is chosen for practical reasons, and fails to explain the particularities of many life forms. Excitingly, high-throughput sequencing technologies have started to blur the borders of model and non-model organisms, as they allow explorations from the known ground into uncharted territory, making it possible to study organisms that do not fulfill the criteria of classical model organisms, including disease-associated life forms, exotic species, species closely related to model organisms at the sequence level but with strikingly different phenotypes [161]. Undoubtedly, starting from experiments using model systems, future studies will also reveal the genetic basis for the enormous diversity of life forms.

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