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BEYOND MICE AND MEN: ALTERNATIVE VERTEBRATE AND INVERTEBRATE MODELS IN CANCER BIOLOGY

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ABSTRACT

While cancer looms large in the public and scientific minds, this can result in a quite narrow view of its range and manifestations. The centering of human clinical investigations and popularity of mouse models lead many to be unaware of fascinating findings about cancer in other species. The field of comparative oncology shows that cancer can be found not just in mammals but widely across the tree of animals, a realization that broadens views of the disease in fundamentally important ways. Examples include mechanisms of cancer-resistant species, transmissible cancers, and questions about whether cancer risk is intrinsic to metazoan life. I highlight strong evidence for cancer in invertebrates, focusing on *Drosophila* which show not only many hallmarks of cancer but also induce host responses mimicking those of human patients, including anti-tumor immunity. A wide-ranging study of cancer-bearing species enhances potential for transformative advances in battling this ancient disease.

INTRODUCTION

Cancer can dominate views of health and mortality, especially in the global North. Four in ten Americans will be diagnosed with cancer, and nearly everyone has a loved one affected by it. Cancer is a public enemy whose threat is appreciated by all, regardless of their understanding of the underlying disease mechanisms. However, this permeation of cancer awareness means that much about it is tacitly accepted.

Everyone knows that humans, if they don't die from other causes, will get cancer. Many are aware that their pet dogs and cats can also develop tumors, and some have read that scientists use mice and rats to study cancer in the laboratory. But few have wondered whether other animals beyond mammals can develop this disease –and what we might learn from these creatures.

The field that studies how different species do or do not experience cancer is called Comparative Oncology. Comparative oncology has a long history but has been overshadowed in recent decades by laboratory cancer models including cultured cells and mice. Acknowledging the foundational impact of these focused models, there is now interest in what may be learned by exploring cancer more widely across the animal kingdom. To give one striking example, although human cancer is not a communicable disease, Tasmanian devils can pass a carcinoma from one individual to another through biting. This transmissible cancer is decimating the species in the wild; transmissible cancers also exist in feral dogs and devastate populations of marine mussels and clams (Hart et al. 2023; Murchison 2008; Ostrander et al. 2016) (**Fig. 2B**). Such phenomena illustrate how comparative oncology can broaden views of metastasis, tumor evolution and immune defense. They dramatize the remarkable perspectives that come from considering cancer beyond the familiar.

To hazard an analogy, comparative oncology can bring benefits akin to that of learning a second language. If one only speaks English, one might never know that some languages (e.g. Romance languages) assign gender to nouns. One might further never know that other languages (e.g. Mandarin Chinese) convey information through spoken

tones as well as words. So a comparative approach can bring to light elements that are, but should not be, taken for granted; it can also sharpen appreciation of truly core elements. Moreover, though languages do not develop via a biological evolutionary model, they nevertheless show descent with divergence over time, and can preserve elements that reveal shared heritage. Comparative oncology can similarly yield insights into how cancer has shaped animal evolutionary history.

In the millennia-long human quest to understand cancer and mitigate its effects, new techniques are creating remarkable opportunities to leverage information about the breadth of cancer across the animal kingdom. And the scope of this work can expand experimental work to species not conventionally considered within the realm of oncology. To extend the analogy above, a scientist studying only cancer in mammals might be akin to a Spanish-speaker studying only the closely related Romance languages. The Spanish speaker would miss insights about fundamental language structures from Sino-Tibetan and African languages, akin to what the scientist could learn from a study of avian and ectothermic vertebrates as well as invertebrate species. As the latter are more widely diverged from the familiar but nevertheless share essential elements, they provide a rich opportunity for new and transformational discoveries. This review will therefore specifically argue for the value of a broad scope of comparison within comparative oncology.

HOW SHOULD WE DEFINE CANCER?

When considering cancer across the tree of life, it is necessary to define terms, and to ask whether the terminology may intrinsically limit the species to which studies may be applied. Clear definitions of *cancer* and *tumor* are more elusive than generally appreciated. For instance, the standard textbook *The Biology of Cancer* (Weinberg 2023) offers largely circular definitions of *cancer* and *neoplasia* that invoke *tumors*, a word that is not specifically defined. The murkiness can be understood by appreciating the history of cancer terminology, originating with Hippocrates' '*karkinos*' and '*oncos*' 2400 years ago and subsequently shaped by clinicians in ways that do not always map on to current understanding of molecular mechanisms. One example is 'carcinoma in situ', commonly used to describe a dysplastic set of non-invasive cells in breast tissue that are not in fact carcinomas (which are defined as malignant). A separate point of contention is whether a tumor must be *metastatic* to be truly cancerous, wherein metastasis involves not just crossing a basement membrane at its site of origin ('*invasion*') but undergoing intravasation into blood vessels followed by extravasation and growth at a secondary site. Such a definition would intrinsically rule out any possible recognition of cancer in invertebrates, which do not have vascular circulatory systems; a similar objection applies to the 'angiogenesis' criterion offered by the famed Hallmarks of Cancer review (Hanahan & Weinberg 2000). Overall, the origins of cancer-related terms in human clinical medicine can present a challenge to broad comparative oncology, particularly when considering species with anatomies and life histories that differ from our own.

For this review, we will use the following definitions, which approach consensus without relying on criteria that would limit applicability to vertebrates. A *tumor* is the accumulation of excess cells –due to increased proliferation, growth and/or reduced cell death-- in a time or place that is inappropriate to the animal, with morphological changes that indicate changes beyond hyperplastic growth alone (hence *neoplasia*). When such cells leave their normal site and cross a basement membrane to *invade* other tissues, the tumor can be termed *malignant*; when they do not, the tumor is called *benign*. Though often used as a synonym for the malignant tumor itself, *cancer* may be also usefully considered as the whole-body disease of disrupted physiology that is caused by malignant tumors.

A BRIEF HISTORY OF COMPARATIVE ONCOLOGY

Comparative oncology as a discipline dates back centuries, and is inextricably intertwined with foundational advances in cancer biology. A list of 13 unanswered questions about cancer posed in 1802 by a British scientific society includes ‘*Query 10: Are brute creatures subject to any disease resembling cancer in the human body?*’ (Dawe 1969; The Medical Committee of the Society for Investigating the Nature and Cure of Cancer 1967) An affirmative answer could be found in 1792 descriptions of dog tumors by Jean-Baptiste Muzard. Detailed observations were subsequently made by Johannes Muller, whose 1838 work pioneering the microscopic analysis of tumors –to which we owe the distinction between benign and malignant-- included samples from domestic animals. Muller’s work influenced Rudolf Virchow, the famous originator of ‘cell theory’, whose foundational work on cellular pathology examined tumors in cattle as well as dogs. Virchow’s work prompted his striking 1858 declaration: “Between animal and human medicine there are no dividing lines—nor should there be”.

Consistent with Virchow’s program, the late 19 and early 20th century saw a rapid recognition of tumor-like growths in non-mammalian species. From oysters in 1887 to trout in 1903 (Dawe 1969), what these reports lacked in pathological detail was countered by the confidence that there was no reason to limit cancer to domestic or even wild mammals. These observations aroused skepticism, and it is instructive that skepticism also extended to reports of tumors in mice (Dunn 1962). By not succumbing to skeptics, scientists paved the way for the ‘model organism’ contention that a variety of animals could be useful models for human cancer research.

The open-minded approach bore immediate fruit whose roots are often forgotten today.

The discovery of oncogenes, culminating in the cloning of Src and the 1989 Nobel Prize given to Bishop and Varmus, began when a Long Island farmer brought her prize hen to Peyton Rous at the Rockefeller institute in 1909 (Rous 1911). Rous’s recognition that this chicken bore a sarcoma, and his isolation of the transforming principle from it, led to his own 1966 Nobel prize. Perhaps the earliest experiment in cancer genetics came in the 1920s when investigators found that intercrossing two closely related fish of the genus *Xipophorus* led to hybrids that develop spontaneous and lethal melanomas (Gordon 1927; Johnson & Phadnis 2021); these melanomas were later found to be driven by a mutated EGF Receptor (Wittbrodt et al. 1989). Thus, non-mammalian

tumors lay at the birth of cancer genetics and molecular mechanisms in experimental oncology.

Recognizing the value of such investigations, in 1966 the National Cancer Institute established the Registry of Tumors in Lower Animals (RTLA) at the Smithsonian Institute (Harshbarger 1969). Though repositories of mammalian tumors existed since the 19th century, the RTLA was specifically charged with the collection of specimens to ‘facilitate the comparative study of tumorigenesis and related disorders in invertebrate and poikilothermic vertebrate animals’. Donated tumors were preserved and underwent expert analysis to distinguish likely neoplastic lesions from hyperplasia, granulomas, and other non-oncogenic processes (Harshbarger 1984). When the RTLA was closed in 2007, it contained more than 7000 specimens; the collection is still extant though not actively managed.

APPROACHES WITHIN COMPARATIVE ONCOLOGY

Comparative oncology today has gone past specimen collection to embrace a variety of approaches. The first looks for tumors in wild animals (Giraudeau et al. 2024; Madsen et al. 2017; Pesavento et al. 2018). While of compelling relevance, this approach has an obvious challenge beyond logistics. Selection bias eliminates most cancer-harboring individuals from any surveyed population, both because malignant tumors are lethal in themselves and because any sub-lethal loss of fitness may lead to culling from the population by predation or disease. In addition to the likelihood that wild populations may not reach age ranges in which cancer may be prevalent, less obvious challenges (e.g. the rapid rate of carcass disappearance (Vittecq et al. 2013), bias towards benign surface tumors) also exist. Overall, there is quite limited data on animal cancer in the wild; ideally this gap would be closed. Wild animals can also serve as sentinels for carcinogenic pollution, particularly in aquatic environments, where cancer rates in fish as well as marine mammals increase in habitats exposed to industrial or agricultural use (Baines et al. 2021). For land animals, in addition to charismatic megafauna that are actively managed, global wildlife health surveillance programs in place to detect zoonotic disease emergence have potential to contribute information about cancer rates.

A second approach surveys cancer in animals held in zoos and similar facilities. More than 1200 zoos share a medical database, managed by the non-profit organization Species360, that records routine monitoring of animals under care as well as necropsies where cancer can be identified (Compton et al. 2025; Vincze et al. 2022). This database covers 21,000 species, albeit with a bias towards mammals and birds, and provides fascinating information about relative cancer risk. In addition to limitations, the data have many strengths, one of which is that the age of individual is usually known. A second is a comparison of neoplasia versus malignancy rates, which reveals that there are not species that get solely benign tumors. It must be remembered that animals held in zoos are immune from predation, leading to average lifetimes that far exceed their wild counterparts. They also subsist on a different diet from that of their natural habitat and trade native health stressors (e.g. parasites) for artificial (e.g. altered light and temperature, human interaction). The same, of course, is true in the laboratory: one

estimate is that most wild mice die within less than a year, a fraction of their 2-3 year lifespan in captivity and before most naturally occurring tumors have been documented in the species (Anisimov et al. 2005). Interestingly, a recent analysis found that most diagnoses of neoplasia in zoo necropsies occurred prior to the average lifespan of the animal, that is, not preferentially in 'old' individuals (Compton et al. 2025).

A third approach is veterinary oncology, which is powered by the close medical observation of pets (mostly small mammals such as cats and dogs) as well as livestock. Perhaps 4 million dogs are diagnosed with cancer in the US each year, a risk that elevates sharply with age; malignancy is the major source of mortality in aged dogs in several Western countries (LeBlanc & Mazcko 2020; Ostrander et al. 2019). In addition to documenting naturally occurring tumors in animals that share an environment with humans, research with companion animals involves clinical trials, including testing therapies that go beyond the options limited for human patients by governmental regulations (LeBlanc & Mazcko 2020; Lenz & Atherton 2025). Canine trials on tumors such as osteosarcoma, melanoma, and glioma were included in a comparative oncology component of the multi-billion dollar US Cancer Moonshot Initiative.

A fourth approach is to bring wild animal tissue into the lab, through isolating cells and immortalizing them through well-established culture methods. Such cells are thereafter an inexhaustible source of material for cancer-related assays. Fresh samples of vertebrate skin can yield fibroblasts, which can either be directly studied or reprogrammed to other tissue fates. This approach has been powerful in revealing species-specific aspects of tumor-relevant biology (e.g. (Firsanov et al. 2024), with the caveat that it is limited to cell-intrinsic mechanisms and that the fibroblast is not the cell of origin for most tumors. Moreover, not all animal tissues are prone to convenient cell immortalization.

Finally, the fifth approach is to use diverse animal species in laboratory cancer research. Mice have been the overwhelmingly favorite laboratory model, displacing the rat during the revolution in transgenesis and knockout technologies. Alongside the many advantages there are also relevant limitations (e.g. (Anisimov et al. 2005; Bulls et al. 2024; Cheon & Orsulic 2011; Rangarajan et al. 2004; Schuh 2004). Other well-known 'model organisms', such as the zebrafish and the fruit fly (Bilder et al. 2021; Cagan et al. 2019; Chatterjee & Deng 2019) (Astell & Sieger 2020; Weiss et al. 2022), are now explicitly studied as *in vivo* cancer models; the cost, generation time, and ethical regulations on these species are lower than on rodents. Excitingly, as new technologies for genome engineering and sequencing have emerged, this range can expand to 'non-model' species with phylogenetically interesting positions.

IS CANCER RISK INTRINSIC TO THE METAZOAN LIFESTYLE?

A central question of comparative oncology is: Can all animals get cancer? To form a fertile adult, all metazoans must create organs through stimulating cell division, but then must cease proliferation when the appropriate size is reached, which often also involves programmed cell death. These cells must differentiate into appropriate fates, including exiting from proliferative progenitor status, in a manner coordinated with surrounding

neighbors. The cells must further organize physically in an appropriate manner, including being separated from other tissues by a basement membrane. Cancer results from the misregulation of these normal programs of proliferation, differentiation, and morphogenesis that ensure both embryonic development and adult homeostasis. Since core molecular pathways –signaling and otherwise– that control proliferation, differentiation and morphogenesis are conserved and evolved before separation of the vertebrate and invertebrate lineages, a reasonable perspective is that central phenotypes of cancer cells that corrupt these processes –e.g. uncontrolled proliferation, aberrant differentiation, invasive behavior—are a latent risk to any metazoan species. Thus, for the purpose of this review, one could reframe the central question as follows: is there a reason to think that some animals CANNOT get cancer?

For the myriad species where there are no reports of cancer-stricken individuals, one can easily invoke a sampling problem. A 1952 paper (Brown et al. 1952) provides an object lesson: it begins '*IT IS COMMONLY STATED that cancer does not occur in the Eskimos, and to our knowledge no case has so far been reported*' before going on to document the first case. No one today would consider that any human ethnic group is immune to cancer. Might the same be true for branches of the animal tree of life? Certainly for many species, no one has bothered to look, a problem fed by the perception of cancer as a disease of mammals, and amplified by animal care regulations that require closer health monitoring of mammals than other vertebrates, with very few required for invertebrates. Moreover, observers are trained to recognize mammalian tumors. Such biases are just one obstacle to a comprehensive evaluation of relative cancer susceptibility.

Nevertheless, we can say that there are animals that do not, and probably cannot, get cancer. The nematode *C. elegans* has been studied intensively in laboratories for over 50 years, including with saturating genetic screens that have yielded fundamental discoveries in cancer-relevant mechanisms such as apoptosis, Ras signaling, and cell invasion (Kimble & Nüsslein-Volhard 2022). Nevertheless, no phenotypes fit the definition of cancer used here. The organism's well-known lifestyle provides some explanation. *C. elegans* consists of only 959 cells, with the longest somatic lineage having just 10 divisions; it has no somatic stem cells, limiting the possibility of genetic changes within any lineage over the animal's 2-3 week lifespan. Interestingly, somatic hyperplasia has in fact been achieved through careful hypomorphic reduction of SWI/SNF-mediated differentiation in combination with inactivation of G1/S inhibitors, which in one lineage retains the mutant cell in a proliferative precursor state. These studies reveal a complex network that ensures the robust cell cycle exit associated with the invariant cell lineage of the animal (Ruijtenberg & Van Den Heuvel 2015).

This instructive example illustrates that small, short-lived species which do not require somatic stem cells are unlikely to suffer from cancer in the wild, although it also reveals that related phenotypes might indeed be experimentally induced. While such lifestyles are much more prevalent amongst invertebrates, they are certainly not exclusive to the vertebrate clade. For instance, lobsters can live for more than 100 years, growing throughout this period to reach more than three feet long. The longest-lived non-colonial

animal is thought to be a 507 year-old clam, of a clade that likely produces immune cells throughout their lifetime. And indeed, tumors have been reported in related bivalve species (see below).

Rather than sampling error, short lifetime or inherent inability to be transformed, a lack of reported cancer in a species can have a fourth interpretation: that the species has evolved potent anti-cancer defenses. Elephants and naked mole rats are nearly though not entirely cancer free. Rather than assuming that these species have some biology that is intrinsically incompatible with cancer formation, their position on the phylogenetic tree close to cancer-experiencing species has prompted a rich investigation of molecular mechanisms by which they resist tumors. Thus, how are we to view the invertebrates, where arguably clear cases of cancer –as well as cancer-fighting defenses-- are reported? If we adopt the view that invertebrate species are generally incapable of oncogenesis, we risk missing interesting lessons about cancer's breadth and perhaps informative anti-cancer strategies that have evolved in this lineage.

CANCER ACROSS THE TREE OF ANIMAL LIFE

Extensive current data on cancer across animal phyla allow two important points to emerge. First, cancer is ubiquitous across the vertebrates, but with varying prevalence that highlights unexpectedly cancer-resistant species (**Fig. 1**). Second, tumors have been described in a number of invertebrate species, with two examples –*Drosophila* and bivalves-- particularly well-studied with modern methods (**Fig. 2A**). Recent reviews provide an overview of vertebrate data (Aktipis et al. 2015; Boddy et al. 2020; Compton et al. 2025; Vincze et al. 2022), which I will summarize briefly below.

MAMMALS

Amongst the vertebrates, mammals are the most carefully analyzed, primarily using the Species360 database (Vincze et al. 2022). This database includes postmortem evaluation of nearly 12,000 individuals in which cancer is noted if suspected of contributing to demise (i.e. 'incidentalomas' are not recorded). Neoplasia is found widely across the mammals, with a median prevalence of 12% at death. However, there is substantial diversity of rates amongst the major orders, as well as of individual species. This includes from ferrets (63% dead with a neoplasm, largely lymphoma) and opossums (56% dead with a neoplasm, largely lung adenocarcinoma) to the common porpoise and Rodrigues fruit bat, with neoplasia prevalences of ~1% (**Fig. 1B**). Amongst this diversity, it appears that carnivorous mammals, especially those that consume other mammals, face the highest average cancer-related mortality.

The most famous issue in comparative oncology is Peto's paradox, which points out the contrast with any *prima facie* expectation that large and long-lived animals should get more cancer. Analyses of the mammalian dataset, as well as its expansion to other vertebrates, has led to ongoing debates over whether any relationship between cancer rate and body size or average lifespan exists (Dujon et al. 2024; Lynch 2025)(Metzger 2025).

What is clear from the survey is that certain species have remarkably low cancer rates.

This observation has sparked the exciting discovery that species have evolved different tumor-suppressive mechanisms, and lessons learned may perhaps inspire new therapeutic approaches (Seluanov et al. 2018). Several examples will whet readers' appetite but it is evident that these species' potent resistance involves mechanisms beyond those listed.

The rarity of cancer in the enormous and long-lived Bowhead whale prompted analysis of immortalized fibroblasts from this species, which revealed high efficiency and accuracy in repairing DNA double-strand breaks compared to other mammals (Firsanov et al. 2024). Interestingly, malignant transformation of whale fibroblasts actually required fewer genetic changes than human cells, and p53-mediated apoptotic activity was also low. The hypothesis that whales may suppress mutagenic damage by elevating levels of two conserved DNA repair proteins—which can improve DNA repair when provided to human cells—points to a therapeutic direction.

The small but long-lived naked mole rat is famed for being almost entirely cancer free, with only a few confirmed cases despite widespread breeding. One mechanism implicated in this phenotype is the secretion of a specific, higher molecular weight form of Hyaluronic Acid (HA) into the extracellular matrix (Tian et al. 2013). This HA causes cultured naked mole rat cells to be highly sensitive to contact inhibition of proliferation, a phenotype associated with heightened growth control in vivo. Strikingly, mammalian cancer cells engineered to produce the naked mole rat form of HA showed inhibited proliferation and induction of apoptosis, consistent with a model in which high molecular weight HA can be tumor suppressive in transformed cells.

Blind mole rats, which are only distantly related to naked mole rats, have strong cancer resistance that involves an entirely different phenomenon (Zhao et al. 2021). These animals possess naturally low levels of DNA methyltransferase 1 (DNMT1) that leads to activation of retrotransposons during cellular hyperplasia in culture. The resultant cytoplasmic nucleic acids then trigger interferon-induced cell death, which could eliminate an overgrowing population and reduce risk of transformation in vivo.

This small sample provides just a taste of unexpected mechanisms by which exotic mammals may resist cancer; bats and elephants provide yet other examples (Abegglen et al. 2015; Karpinski et al. 2025; Koh et al. 2019; Sulak et al. 2016). The diversity of these mechanisms emphasizes how each species has independently evolved cancer defense strategies. Thus, one can only begin to imagine how many more distinct mechanisms exist to regulate cancer prevalence in other animals across the tree of life.

NON-MAMMALIAN VERTEBRATES

The literature on non-mammalian vertebrates is less prominent, but re-emphasizes the presence of tumors throughout these groups (Compton et al. 2025). In fact, the fossil record preserves evidence of osteosarcomas in ancestral turtles from the Triassic, dating back 240 million years (Haridy et al. 2019), as well as later dinosaurs (Ekhtiari et al. 2020). Although extant non-mammalian vertebrate classes have average neoplasia prevalence than mammals, including birds, many bird tumors are malignant. Blood

cancers are most common, but others (including sarcomas as in Rous's hen) are found both in pets and in the wild. Reptiles show a slightly greater neoplastic rate than birds, with prominent blood cancers as well as carcinomas of the skin, liver, and bile duct (Christman et al. 2017). Snakes showed a particularly high frequency of neoplasia as well as malignancy, including hematopoietic cancer as well as renal adenocarcinomas. By contrast, turtles are represented in the zoo database by a single non-malignant neoplasia; neoplasia in crocodilians was also remarkably low (Bulls et al. 2024). However, there is an independent report of malignant osteosarcoma in a land turtle (Boehm et al. 2013), while benign fibropapillomatosis of viral etiology is well-known to impact sea turtles (Jones et al. 2016). Amphibians exhibit the lowest neoplasia and cancer prevalence of the vertebrates; they are relatively understudied but reports exist of renal adenocarcinoma in the Leopard frog and melanomas in axolotls (Harshbarger et al. 1999; Ruben et al. 2007); invasive lesions were found in Tiger Salamanders from a sewage-contaminated lagoon (Rose & Harshbarger 1977).

Fish are not central to the Species360 database, but reports of tumors in bony fish (teleosts) in the wild are widespread (e.g. Romano, Luis Alberto & Pedros, Virginia Fonseca 2020; Vergneau-Grosset et al. 2017). An aquarium database with 883 fish necropsies showed a spontaneous neoplasm rate of 6%. Carcinomas exist, but melanomas beyond those found in *Xiphophorus* deserve special mention, as the laboratory model organism zebrafish has become a powerful model for studying melanoma as well as other tumor types (van Rooijen et al. 2017)(Weiss et al. 2022). While there was an early misconception that sharks and rays (chondrichthyans) rarely developed cancer, this belief has been shown to be inaccurate. Tumors are reported in six of the nine chondrichthyan orders, with about 1/3 categorized as malignant (Huveneers et al. 2016).

Finally, the order of agnathans (non-jawed vertebrates) is of particular interest. There are only two extant members of this order: the lamprey and the hagfish. Interestingly, the RTLA documents tumors in both, including hepatocellular carcinoma, and describes a lamprey melanoma with multiple subcutaneous, renal and branchial metastases (Harshbarger 1970). Thus, clear tumors are found throughout vertebrates, even in the most basally-derived vertebrate lineage.

INVERTEBRATES

As we consider cancers in invertebrates, let us remind ourselves of the obstacles. First, invertebrates are not monitored by zoo health programs and rarely treated by veterinarians. Second, only a few edible marine species are harvested in a manner that might allow chance notice of a neoplastic lesion. Third, invertebrate anatomy not only presents some challenges to conventional cancer definitions but is also unfamiliar to non-specialists, while invertebrate specialists are unfamiliar with cancer pathology. This latter point has caused old case reports with limited documentation to be viewed with skepticism.

One goal of the RTLA was to more rigorously examine reports of tumors in invertebrates. Their adjudication categorized hundreds of examples of invertebrate neoplasia,

including in insects, crustaceans, and mollusks (Newton & Lewbart 2017) (**Fig. 2A**). Of invertebrate tumors most were benign, including papilloma growths on lobster, shrimp, and a planarian; benign neoplasms have also been reported in slugs and other gastropods. But malignant tumors are also documented in crabs and mollusks; one report described ganglioneuroblastoma in a trematode. Anomalous growth in corals have also been proposed to be neoplastic although this is controversial, as are reports of neoplasms in tunicates and echinoderms. No reports of tumors in sponges exist, and only one of a potential tumor in the cephalochordate *Amphioxus* (Aktipis et al. 2015). More recently, studies of tumor-like growths in a non-bilaterian Cnidarian have emerged. Both wild-caught and laboratory-raised strains of *Hydra* can exhibit abnormal growths, which result from ectopically proliferating cells accumulating in the ectoderm (Boutry et al. 2023; Domazet-Lošo et al. 2014). These cells appear related to normal interstitial stem cells, but exhibit a distinct gene expression profile. In one strain, tumor growth is associated with a distinctive microbiome, but that is not the case in another. These tumors can be grafted into a healthy host, where they proliferate and invade the normal *Hydra* tissue. Interestingly, they can also be transmitted to progeny during budding in this asexually-reproducing species. Again, the organism's life history, including its reputation as an 'immortal animal' (Boehm et al. 2013), encourages one to consider how to apply conventional definitions of a tumor.

Drosophila tumors and the hallmarks of cancer

The best-studied tumors of invertebrates are found in *Drosophila*. These flies are also arguably the best-studied animals on earth, with 125 years of laboratory research using classical and cutting-edge methods that yielded seven Nobel prizes (Bilder & Irvine 2017). Spontaneous tumors are found in the guts of ~5-10% of aged wild-type laboratory flies, starting about $\frac{3}{4}$ of the way through the ~9 week lifespan (Siudeja et al. 2015). These tumors initiate in intestinal stem cells and are caused by various forms of genetic instability (Riddiford et al. 2021). Tumors with this genotype are driven by autocrine EGF signaling and stimulate IL-6-like mediated inflammation from neighboring cells; they disrupt architecture leading to tissue dysplasia (Patel et al. 2015). Spontaneous lethal tumors can also appear in laboratory larvae, through loss of heterozygosity uncovering a mutant TSG allele maintained at a low rate in natural populations; there have been no measurements of tumor rates in wild larvae (Golubovsky et al. 2006; Roegiers et al. 2009). Though those observed to date are not described as invasive, they fulfill many cellular and molecular criteria associated with benign tumors.

Fly tumors can be conveniently created in the laboratory by Genetically Engineered Fly Models (GEFMs) that overexpress oncogenes or knock out TSGs in a tissue-specific manner. These approaches and information about the tumors are detailed in reviews (Bilder 2004; Cagan et al. 2019; Chatterjee & Deng 2019; Gonzalez 2013); I note some pertinent information here. 1) Misregulation of a single fly gene can be sufficient to transform cells with many 'hallmarks of cancer' (see below), and these phenotypes, particularly malignant phenotypes, can be exacerbated when a cooperating oncogene such as activated Ras is added. 2) Transformation can take place either in developing organ primordia of the larva (both epithelial and neural) or in adult stem cell populations

that proliferate throughout the animal's lifetime. 3) Some genes that transform fly cells are also frequent drivers of human tumors, while others are not commonly mutated (though still conserved regulators of human biology).

It can be instructive to evaluate 'malignant' GEFMs against the well-known Hallmarks of Cancer (Hanahan & Weinberg 2000). The examples below include those drawn from epithelial cells overexpressing activated Ras along with loss of the tumor suppressor Scribble (Dillard et al. 2021; Pagliarini & Xu 2003), although different GEFMs including those that transform neural stem cell populations can act similarly.

The first three Cancer Hallmarks describe mechanisms that drive inexorable tumor growth ('sustained proliferative signaling, evading growth suppressors, resisting cell death'). Scrib/Ras tumors activate the JNK and Hippo signaling pathways, which fuel tumor growth in part through an autocrine IL-6-like/STAT feedback loop, as well as upregulating apoptosis inhibitors (Dillard et al. 2021). Phenotypically, malignant fly cells essentially become immortalized: though they kill the host, they can be transplanted into a new host where they continue their lethal growth (Rossi & Gonzalez 2015). Similar cells have been passaged over many years with unceasing proliferation. The tumor cells have thus achieved a fourth Hallmark: enabling replicative immortality, although *Drosophila* use a transposon-based rather than telomerase-based mechanism to prevent telomere shortening (Mason et al. 2008). At any rate, like human malignant tumors, these fly tumors are invariably lethal.

With the final two Hallmarks, we encounter the issue of anatomical differences. The fifth Hallmark is 'inducing angiogenesis'. This cannot strictly apply to invertebrates because they do not use vasculature to deliver blood to cells, but instead bathe their internal organs in an open circulatory system (the hemolymph). Nevertheless, insects face the same challenges in oxygen supply that humans do, and solve this challenge by supplying oxygen to cells through a tubular network called the trachea (Hayashi & Kondo 2018). The tracheal network is even constructed by the homologous VEGF and PDGF signaling pathway that shapes vertebrate vasculature. And indeed, some GEFMs upregulate PDGF/VEGF ligands to attract extra oxygen supply to the growing tumor (Calleja et al. 2016; Grifoni et al. 2015; Tamamouna et al. 2021).

The sixth Hallmark is 'activating invasion and metastasis', which is a central discriminator between benign and malignant tumors. It is clear that many fly GEFMs fill the invasion criterion (Sharpe et al. 2023). Fly epithelia are bounded by a basement membrane which shares high functional, ultrastructural, and molecular conservation with that of humans. Many fly tumors upregulate matrix metalloproteases which degrade the basement membrane, and activate motility programs that allow movement out of the primary site, even migrating onto neighboring organs. Moreover, conserved regulators of epithelial-mesenchymal transition can enhance long-distance dispersion of fly tumors (Campbell et al. 2019). Yet here the question of anatomy arises. Metastasis by definition encompasses steps beyond invasion, including intravasation into and extravasation from a vasculature which the insect simply does not possess. Thus while flies cannot be said to execute a conventional metastatic process, they certainly exhibit invasive migration out of the tissue of origin.

As the six hallmarks expand with regularly updated reviews on e.g. Next Generations (Hanahan & Weinberg 2011) and New Dimensions (Hanahan 2022), we wonder whether fly tumors will keep apace in the manner shown above: not a 100% match, but many thematic parallels when considering analogous rather than strictly homologous biology. Certainly features such as avoiding immune destruction (see below), dedifferentiation and tumor-promoting inflammation are already evident; recent papers demonstrate non-mutational epigenetic reprogramming, altered metabolism and senescent cell presence as well (Datta & Bangi 2024; Parreno et al. 2024; Wong & Verheyen 2021)(Floc'hlay et al. 2023).

Drosophila display tumor-host interactions analogous to human cancer patients

The latest Hallmarks review is entitled 'Embracing Cancer Complexity: Hallmarks of Systemic Disease', highlighting tumor-host interactions and systemic impacts of cancer including lethality unrelated to the 'mass effect' (Swanton et al. 2024). We can neatly place the most remarkable recent findings about fly cancer in this perspective as well. Astonishingly, the last decade has identified case upon case where fly tumors induce in their own hosts systemic manifestations that mimic those seen in human cancer patients. These phenomena include critical drivers of human mortality such as cancer cachexia and coagulopathy (detailed in e.g.(Bilder et al. 2021; García-López et al. 2021; Hsi et al. 2023; Liu et al. 2022)). Recent work has also identified 1) an early tumor-eliminating process mediated by circulating fly TNF (de Vreede et al. 2022); 2) renal failure caused by tumor-induced signals, at least one of which is conserved in mammals (Kwok et al. 2024; Xu et al. 2023, 2024); 3) Evidence for unappreciated cachexia mechanisms conserved with mammals discovered through new fly studies (Liu et al. 2025). Finally, 4) a fly tumor accelerates mortality by permeabilizing the blood-brain barrier through IL-6-like inflammation, with a similar phenotype demonstrated in one mouse cancer model (Kim et al. 2021).

Excitingly, flies also show anti-tumor immunity. Although differing biology again comes into play, flies display the therapeutically critical response of the vertebrate immune system in fighting cancer. Insects have no adaptive immune system, and instead defend themselves from non-self pathogens via a robust innate immune system with cellular and humoral arms (Banerjee et al. 2019). The cellular arm includes macrophages resembling those of mammals; the humoral arm is activated by the conserved Toll and the semi-conserved IMD signaling pathways. The output of these pathways is NfKb transcription factors that upregulate antimicrobial peptides (AMPs) secreted into circulation. A seminal study found that fly macrophages recognize malignant epithelial tumors and restrict their progression (Pastor-Pareja et al. 2008). In one tumor model, macrophages activate Toll signaling in humoral effector organs to secrete AMPs, which cooperate with tumor-associated macrophages to specifically kill tumor cells (Parisi et al. 2014; Parvy et al. 2019). Related immune reactions are seen against blood cell tumors and grafted neural tumors (Hirata et al. 2025; Voutyraki et al. 2023). So even without T cells and B cells, and even in a relatively short-lived species

with a modest propensity for cancer in the wild, an invertebrate has evolved an immune regulatory axis to recognize tumors and limit their growth.

To recap: in this well-studied organism, an invertebrate that spontaneously forms tumors can be genetically manipulated to transform cells that not only fulfill many of the Hallmarks of Cancer, but also induce host responses that resemble familiar and lethal manifestations of human cancer such as cachexia and coagulopathy. Moreover, the fly has a mechanism to surveil and eliminate small clones of malignant cells, and also raises an immune response that fights larger tumors in ways at least superficially related to human tumor immunology. These provocative findings suggest a profound evolutionary connection between cancer-like phenomena and the normal physiology of the fly. They also raise the possibility of deep homology in the way that animals across the phylogenetic tree respond to malignant growth.

Neoplasias in bivalves

In the wild, undoubtedly the most prevalent invertebrate neoplasias are found in bivalve mollusks. These cancers affect a wide variety of species including clams, oysters, mussels, and cockles. One such neoplasia, termed transmissible disseminated neoplasia (TDN), has led to massive die-offs in commercially important regions. Before dealing with TDN below, we will discuss conventional neoplasias of this taxon. Large numbers of bivalves are harvested for human consumption, and many are inspected before being served. Moreover, some species are quite long-lived, and expected to contain stem cells that can produce at least blood cells throughout the lifetime. All this may contribute to the substantial list of neoplasia which fall into three general categories (Carballal et al. 2015; Newton & Lewbart 2017).

The first are epithelial tumors, with descriptions of both benign and malignant neoplasms. These formed on various organs, but include invasive lesions with evident mitotic figures and associated inflammation. The second affects cells of the germinal epithelium, a tissue producing both soma and germline which must proliferate to ensure reproduction. In these gonadal neoplasms, normal tissue is replaced with cells showing altered cellular, nuclear and nucleolar morphology. Initially small foci proliferate to fill the reproductive follicle but then later invade into other gonadal organs.

The third is disseminated neoplasia (DN). In this lethal disease, anaplastic cells proliferate within the affected animal, gradually disrupting normal tissues and replacing them. Across 15 species worldwide (**Fig. 2B**), the condition presents with common features: large, rounded cells showing high nucleus:cytoplasm ratio, diminished organellar contents, and frequent mitotic figures that are seldom present in healthy cells. DN cells consistently show varied chromosomal imbalances as well as distinct mutation signatures (including independent events duplicating the mitochondrial control region). The DN cell of origin is likely the hemocyte, a circulating blood cell of invertebrates. However, DN cells are distinctly transformed and exhibit reduced cell death, reduced phagocytic ability, and inhibition of p53 activity. For all of these reasons, investigators have likened DN to a leukemia.

A bivalve transmissible neoplasia

Exciting findings first published in 2015 demonstrated that some, though not all, cases of DN result from horizontal transmission of clonal cancer cells from one member of a clam

population to another (Metzger et al. 2015). Affected animals across a large range shared neoplastic cells with nearly identical genotypes that were distinct from the hosts' own genotype. To date, eight independent lines of TDN behaving similarly have been characterized worldwide. These TDNs affect a variety of bivalve species, but are species-restricted, except in a striking case where one species carries a neoplasia derived from a second sympatric species that apparently can resist its own neoplastic cells (Metzger et al. 2016). Neoplastic cells can likely survive in the water column, and are taken up by the host but then aggressively replace the host tissues (Hart et al. 2025). Three distinct TDNs (one of clams and two of cockles) have now been examined genomically (Bruzos et al. 2023; Hart et al. 2023). The lineages have certain similarities (hemocyte origin, pronounced genetic instability) but differ in other aspects (two separate putative mechanisms of p53 functional interference, only one lineage is associated with mobile element reactivation).

Thus, TDN is an invertebrate transmissible cancer, analogous to the clonal vertebrate transmissible tumors of Tasmanian devils and canines. It can arise repeatedly and independently in different bivalve species, presumably originating from a specific nontransmissible DN of an individual. Certainly much is to be learned about fundamental biology (e.g. the bivalve functional equivalent of MHC systems which prevents most TDNs from crossing species), but TDN also raises fascinating larger questions about how an animal treats cancer on the self/non-self continuum of immune surveillance. It also raises questions about cancer evolution: TDN lineages are highly genetically unstable, even one that is dated to originate several hundred years ago. This provides an interesting comparison with the genomes of the Tasmanian devil transmissible tumors (Stammnitz et al. 2023), perhaps giving insight into adaptive immune selection against vertebrate tumors that are not present in invertebrates. The availability of many TDN lines will allow comparison of the remarkable ability for cancer cells to transcend the boundaries of an individual animal. Finally, given their prevalence and their high lethality, it is reasonable to expect that TDN is exerting a high selective pressure in a short amount of time, and could reveal elements of tumor defenses in the host as well as perhaps evasive response from the genetically mutable tumor population.

CONCLUSIONS

Comparative oncology shows us that animal diversity has provided a host of natural experiments that have much to tell us about the monumental problem of cancer. Expanding surveys of captive animals will sort out species that are extremely susceptible or resistant to cancer through intrinsic biology rather than extrinsic factors, particularly as non-mammalian vertebrates are scrutinized. Close examination might also identify species in which metastases are enriched or underrepresented.

It is clear that research on cancer-resistant species will lead to fundamentally new discoveries from those in popular rodent models. On the one hand, one could consider therapeutic export of exogenous tumor suppressive mechanisms into the human context (e.g. provision of naked mole rat HA synthase, which extends healthspan in mice (Zhang et al. 2023)). On the other hand, one can learn deeper information about known elements of human tumor biology (e.g. the multiple mechanisms that downregulate MHC in the mammalian transmissible cancers). For exotic vertebrates,

analyzing cultured cells for autonomous properties will be enhanced by in vivo studies, given appreciation of cancer as a systemic disease and systemic anti-cancer defenses including immunity. A striking question concerns how evolution of diversity in immune systems plays out in terms of tumor immunology. A considered choice of taxa could yield exciting research programs. Finally, there are well-established non-mammalian models like the zebrafish that will continue to yield insights complementary to those that rodent models supply.

What can we learn from invertebrate cancers? The track record of *Drosophila* research (e.g. recent Nobel prizes for widely conserved mechanisms such as developmental and oncogenic signaling pathways, innate immune signaling, and circadian rhythms) indicates that the answer is 'more than you think'. One has only to consider cell competition, a phenomenon studied for 50 years in the fly that is now emerging as a relevant player in human cancer (van Neerven & Vermeulen 2023). It is worth remembering that flies don't purport to be something they could never be --an exact model for mammalian tumors-- but are instead a rapid and rigorous in vivo experimental system that can point to conserved pathways and mechanisms of cancer biology. Certainly the striking similarities now documented between tumor-host interactions in flies and human patients fall into this category. To reiterate the familiar phrase: 'All models are wrong; some are useful'. In this light, *Drosophila* has proven its utility time and again.

Future investigations could go far beyond the fruit fly. Long-lived insects include ant and termite queens that thrive for decades while laying over 100 million eggs. Considering the stem cells needed to support such homeostasis and proliferation, might they be protected from transformation by undiscovered anti-cancer mechanisms? Are there extra cancer risks associated with invertebrate (and other) species undergoing indeterminate growth, or species primed for regeneration and de-growth like planaria (Hariharan et al. 2015)?

Overall, interrogating the presence and potential of cancer in invertebrates and non-jawed vertebrates allows us to ask fascinating questions about both overlapping and distinct mechanisms that react to general interruptions of epithelial homeostasis --such as sterile and septic injury-- compared to a rogue 'wound that does not heal'. Further, it will provide insight into how the potential and reality of this disease has shaped the evolution of the animal kingdom, as well as how animals have evolved anti-cancer defenses. It is this broad view of comparative oncology --not only in terms of species, but in terms of fascinating questions-- that will truly realize the promise of the field.

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FIGURE LEGENDS

Figure 1: Cancer in vertebrates. A) Phylogeny of vertebrates, with average neoplasia and malignancy rates of familiar groups from (Vincze et al. 2022). Birds and reptiles are measured together as sauropsids. 'Present' indicates that both neoplasia and malignancy are found, but rates have not been evaluated. B) Relative rates of neoplasia malignancy in select tetrapod species from (Compton et al. 2025). Tree information is from timetree.org.

Figure 2: Cancer across the tree of animal life. A) Phylogeny of animals, indicating taxa in which cancer has been identified. Within the chordate phylum, vertebrates, tunicates, and lancelets are distinguished. ID=insufficient data; Yes? (1)= single report in literature; No?= no well-documented report to date. B) Examples of species with transmissible cancers. Tree information is from timetree.org.

LITERATURE CITED

- Abegglen LM, Caulin AF, Chan A, Lee K, Robinson R, et al. 2015. Potential Mechanisms for Cancer Resistance in Elephants and Comparative Cellular Response to DNA Damage in Humans. *JAMA*. 314(17):1850–60
- Aktipis CA, Boddy AM, Jansen G, Hibner U, Hochberg ME, et al. 2015. Cancer across the tree of life: cooperation and cheating in multicellularity. *Phil. Trans. R. Soc. B*. 370(1673):20140219
- Anisimov VN, Ukraintseva SV, Yashin AI. 2005. Cancer in rodents: does it tell us about cancer in humans? *Nat Rev Cancer*. 5(10):807–19
- Astell KR, Sieger D. 2020. Zebrafish In Vivo Models of Cancer and Metastasis. *Cold Spring Harb Perspect Med*. 10(8):a037077
- Baines C, Lerebours A, Thomas F, Fort J, Kreitsberg R, et al. 2021. Linking pollution and cancer in aquatic environments: A review. *Environ Int*. 149:106391
- Banerjee U, Girard JR, Goins LM, Spratford CM. 2019. Drosophila as a Genetic Model for Hematopoiesis. *Genetics*. 211(2):367–417
- Bert H, Lamrous H, Sena MV de A. 2024. Living with a tumor: A case of osteosarcoma involving the medullary region in Phrynos cf. P. geoffroanus (Testudines: Chelidae). *Anat Rec (Hoboken)*. 307(10):3355–63
- Bilder D. 2004. Epithelial polarity and proliferation control: links from the Drosophila neoplastic tumor suppressors. *Genes Dev*. 18(16):1909–25
- Bilder D, Irvine KD. 2017. Taking Stock of the Drosophila Research Ecosystem. *Genetics*. 206(3):1227–36

- Bilder D, Ong K, Hsi T-C, Adiga K, Kim J. 2021. Tumour-host interactions through the lens of *Drosophila*. *Nat Rev Cancer*. 21(11):687–700
- Boddy AM, Harrison TM, Abegglen LM. 2020. Comparative Oncology: New Insights into an Ancient Disease. *iScience*. 23(8):101373
- Boehm A-M, Rosenstiel P, Bosch TCG. 2013. Stem cells and aging from a quasi-immortal point of view. *Bioessays*. 35(11):994–1003
- Boutry J, Buysse M, Tissot S, Cazevielle C, Hamede R, et al. 2023. Spontaneously occurring tumors in different wild-derived strains of hydra. *Sci Rep*. 13(1):7449
- Brown GM, Cronk LB, Boag TJ. 1952. The occurrence of cancer in an Eskimo. *Cancer*. 5(1):142–43
- Bruzos AL, Santamarina M, García-Souto D, Díaz S, Rocha S, et al. 2023. Somatic evolution of marine transmissible leukemias in the common cockle, *Cerastoderma edule*. *Nat Cancer*. 4(11):1575–91
- Bulls SE, Platner L, Ayub W, Moreno N, Arditi J-P, et al. 2024. Unraveling the relationship between cancer and life history traits in vertebrates
- Cagan RL, Zon LI, White RM. 2019. Modeling Cancer with Flies and Fish. *Dev Cell*. 49(3):317–24
- Calleja M, Morata G, Casanova J. 2016. Tumorigenic Properties of *Drosophila* Epithelial Cells Mutant for lethal giant larvae. *Dev Dyn*. 245(8):834–43
- Campbell K, Rossi F, Adams J, Pitsidianaki I, Barriga FM, et al. 2019. Collective cell migration and metastases induced by an epithelial-to-mesenchymal transition in *Drosophila* intestinal tumors. *Nat Commun*. 10(1):2311

- Carballal MJ, Barber BJ, Iglesias D, Villalba A. 2015. Neoplastic diseases of marine bivalves. *Journal of Invertebrate Pathology*. 131:83–106
- Chatterjee D, Deng W-M. 2019. Drosophila Model in Cancer: An Introduction. *Adv Exp Med Biol*. 1167:1–14
- Cheon D-J, Orsulic S. 2011. Mouse models of cancer. *Annu Rev Pathol*. 6:95–119
- Christman J, Devau M, Wilson-Robles H, Hoppes S, Rech R, et al. 2017. Oncology of Reptiles. *Veterinary Clinics of North America: Exotic Animal Practice*. 20(1):87–110
- Compton ZT, Mellon W, Harris VK, Rupp S, Mallo D, et al. 2025. Cancer Prevalence across Vertebrates. *Cancer Discov*. 15(1):227–44
- Datta I, Bangi E. 2024. Senescent cells and macrophages cooperate through a multi-kinase signaling network to promote intestinal transformation in Drosophila. *Dev Cell*. 59(5):566-578.e3
- Dawe CJ. 1969. Phylogeny and oncogeny. *Natl Cancer Inst Monogr*. 31:1–40
- de Vreede G, Gerlach SU, Bilder D. 2022. Epithelial monitoring through ligand-receptor segregation ensures malignant cell elimination. *Science*. 376(6590):297–301
- Dillard C, Reis JGT, Rusten TE. 2021. RasV12; scrib^{-/-} Tumors: A Cooperative Oncogenesis Model Fueled by Tumor/Host Interactions. *Int J Mol Sci*. 22(16):8873
- Domazet-Lošo T, Klimovich A, Anokhin B, Anton-Erxleben F, Hamm MJ, et al. 2014. Naturally occurring tumours in the basal metazoan Hydra. *Nat Commun*. 5(1):4222
- Dunn TB. 1962. The Value of Animal Research, and the Men Who Do This Research*. *Cancer Research*. 22(8_Part_1):898–905

- Ekhtiari S, Chiba K, Popovic S, Crowther R, Wohl G, et al. 2020. First case of osteosarcoma in a dinosaur: a multimodal diagnosis. *Lancet Oncol.* 21(8):1021–22
- Firsanov D, Zacher M, Tian X, Sformo TL, Zhao Y, et al. 2024. DNA repair and anti-cancer mechanisms in the long-lived bowhead whale. *bioRxiv.* 2023.05.07.539748
- Floc'hlay S, Balaji R, Stanković D, Christiaens VM, Bravo González-Blas C, et al. 2023. Shared enhancer gene regulatory networks between wound and oncogenic programs. *Elife.* 12:e81173
- García-López L, Adrados I, Ferres-Marco D, Dominguez M. 2021. A Blueprint for Cancer-Related Inflammation and Host Innate Immunity. *Cells.* 10(11):3211
- Giraudeau M, Vincze O, Dupont SM, Sepp T, Baines C, et al. 2024. Approaches and methods to study wildlife cancer. *J Anim Ecol.* 93(10):1410–28
- Golubovsky MD, Weisman NY, Arbeev KG, Ukraintseva SV, Yashin AI. 2006. Decrease in the Igl tumor suppressor dose in *Drosophila* increases survival and longevity in stress conditions. *Exp Gerontol.* 41(9):819–27
- Gonzalez C. 2013. *Drosophila melanogaster*: a model and a tool to investigate malignancy and identify new therapeutics. *Nat Rev Cancer.* 13(3):172–83
- Gordon M. 1927. The Genetics of a Viviparous Top-Minnow *Platyopocilus*; the Inheritance of Two Kinds of Melanophores. *Genetics.* 12(3):253–83
- Grifoni D, Sollazzo M, Fontana E, Foldi F, Pession A. 2015. Multiple strategies of oxygen supply in *Drosophila* malignancies identify tracheogenesis as a novel cancer hallmark. *Sci Rep.* 5:9061
- Hanahan D. 2022. Hallmarks of Cancer: New Dimensions. *Cancer Discov.* 12(1):31–46

- Hanahan D, Weinberg RA. 2000. The Hallmarks of Cancer. *Cell*. 100(1):57–70
- Hanahan D, Weinberg RA. 2011. Hallmarks of cancer: the next generation. *Cell*. 144(5):646–74
- Haridy Y, Witzmann F, Asbach P, Schoch RR, Fröbisch N, Rothschild BM. 2019. Triassic Cancer-Osteosarcoma in a 240-Million-Year-Old Stem-Turtle. *JAMA Oncol*. 5(3):425–26
- Hariharan IK, Wake DB, Wake MH. 2015. Indeterminate Growth: Could It Represent the Ancestral Condition? *Cold Spring Harb Perspect Biol*. 8(2):a019174
- Harshbarger JC. 1969. The registry of tumors in lower animals. *Natl Cancer Inst Monogr*. 31:XI–XVI
- Harshbarger JC. 1970. Cover Legend. *Cancer Resarch*. 30(5):i
- Harshbarger JC. 1984. Pseudoneoplasms in ectothermic animals. *Natl Cancer Inst Monogr*. 65:251–73
- Harshbarger JC, Chang SC, DeLanney LE, Rose FL, Green DE. 1999. Cutaneous mastocytomas in the neotenic caudate amphibians *Ambystoma mexicanum* (axolotl) and *Ambystoma tigrinum* (tiger salamander). *J Cancer Res Clin Oncol*. 125(3–4):187–92
- Hart SFM, Garrett FES, Kerr JS, Metzger MJ. 2025. Gene expression in soft-shell clam (*Mya arenaria*) transmissible cancer reveals survival mechanisms during host infection and seawater transfer. *PLoS Genet*. 21(3):e1011629
- Hart SFM, Yonemitsu MA, Giersch RM, Garrett FES, Beal BF, et al. 2023. Centuries of genome instability and evolution in soft-shell clam, *Mya arenaria*, bivalve transmissible neoplasia. *Nat Cancer*. 4(11):1561–74

- Hayashi S, Kondo T. 2018. Development and Function of the Drosophila Tracheal System. *Genetics*. 209(2):367–80
- Hirata M, Nomura T, Inoue YH. 2025. Anti-Tumor Effects of Cecropin A and Drosocin Incorporated into Macrophage-like Cells Against Hematopoietic Tumors in Drosophila mxc Mutants. *Cells*. 14(6):389
- Hsi T-C, Ong KL, Sepers JJ, Kim J, Bilder D. 2023. Systemic coagulopathy promotes host lethality in a new Drosophila tumor model. *Curr Biol*. 33(14):3002-3010.e6
- Huveneers C, Klebe S, Fox A, Bruce B, Robbins R, et al. 2016. First histological examination of a neoplastic lesion from a free-swimming white shark, *Carcharodon carcharias* L. *J Fish Dis*. 39(10):1269–73
- Johnson CM, Phadnis N. 2021. A cancer in hybrids. *Proc Natl Acad Sci U S A*. 118(3):e2023488118
- Jones K, Ariel E, Burgess G, Read M. 2016. A review of fibropapillomatosis in Green turtles (*Chelonia mydas*). *Vet J*. 212:48–57
- Karpinski E, Badey N, Mintzer E, Ashkenazy-Titelman A, Li L, Church GM. 2025. Engineering elephant models of cold-adaptation and cancer resistance
- Kim J, Chuang H-C, Wolf NK, Nicolai CJ, Raulet DH, et al. 2021. Tumor-induced disruption of the blood-brain barrier promotes host death. *Dev Cell*. 56(19):2712-2721.e4
- Kimble J, Nüsslein-Volhard C. 2022. The great small organisms of developmental genetics: *Caenorhabditis elegans* and *Drosophila melanogaster*. *Dev Biol*. 485:93–122

- Koh J, Itahana Y, Mendenhall IH, Low D, Soh EXY, et al. 2019. ABCB1 protects bat cells from DNA damage induced by genotoxic compounds. *Nat Commun.* 10(1):2820
- Kwok SH, Liu Y, Bilder D, Kim J. 2024. Paraneoplastic renal dysfunction in fly cancer models driven by inflammatory activation of stem cells. *Proc Natl Acad Sci U S A.* 121(42):e2405860121
- LeBlanc AK, Mazcko CN. 2020. Improving human cancer therapy through the evaluation of pet dogs. *Nat Rev Cancer.* 20(12):727–42
- Lenz JA, Atherton MJ. 2025. Maximizing the dual benefit of pet dogs in cancer trials. *Nat Rev Cancer.* 25(3):147–48
- Liu Y, Dantas E, Ferrer M, Miao T, Qadiri M, et al. 2025. Hepatic gluconeogenesis and PDK3 upregulation drive cancer cachexia in flies and mice. *Nat Metab.* 7(4):823–41
- Liu Y, Saavedra P, Perrimon N. 2022. Cancer cachexia: lessons from *Drosophila*. *Dis Model Mech.* 15(3):dmm049298
- Madsen T, Arnal A, Vittecoq M, Bernex F, Abadie J, et al. 2017. Chapter 2 - Cancer Prevalence and Etiology in Wild and Captive Animals. In *Ecology and Evolution of Cancer*, eds. B Ujvari, B Roche, F Thomas, pp. 11–46. Academic Press
- Mason JM, Frydrychova RC, Biessmann H. 2008. *Drosophila* telomeres: an exception providing new insights. *Bioessays.* 30(1):25–37
- Metzger MJ. 2025. Peto's Paradox Is Dead. Long Live Peto's Paradox. *Cancer Discovery.* 15(1):14–15
- Metzger MJ, Reinisch C, Sherry J, Goff SP. 2015. Horizontal Transmission of Clonal Cancer Cells Causes Leukemia in Soft-Shell Clams. *Cell.* 161(2):255–63

- Metzger MJ, Villalba A, Carballal MJ, Iglesias D, Sherry J, et al. 2016. Widespread transmission of independent cancer lineages within multiple bivalve species. *Nature*. 534(7609):705–9
- Murchison EP. 2008. Clonally transmissible cancers in dogs and Tasmanian devils. *Oncogene*. 27 Suppl 2:S19-30
- Newton AL, Lewbart GA. 2017. Invertebrate Oncology. *Veterinary Clinics of North America: Exotic Animal Practice*. 20(1):1–19
- Ostrander EA, Davis BW, Ostrander GK. 2016. Transmissible Tumors: Breaking the Cancer Paradigm. *Trends Genet*. 32(1):1–15
- Ostrander EA, Dreger DL, Evans JM. 2019. Canine Cancer Genomics: Lessons for Canine and Human Health. *Annu Rev Anim Biosci*. 7:449–72
- Pagliarini RA, Xu T. 2003. A genetic screen in *Drosophila* for metastatic behavior. *Science*. 302(5648):1227–31
- Parisi F, Stefanatos RK, Strathdee K, Yu Y, Vidal M. 2014. Transformed epithelia trigger non-tissue-autonomous tumor suppressor response by adipocytes via activation of Toll and Eiger/TNF signaling. *Cell Rep*. 6(5):855–67
- Parreno V, Loubiere V, Schuettengruber B, Fritsch L, Rawal CC, et al. 2024. Transient loss of Polycomb components induces an epigenetic cancer fate. *Nature*. 629(8012):688–96
- Parvy J-P, Yu Y, Dostalova A, Kondo S, Kurjan A, et al. 2019. The antimicrobial peptide defensin cooperates with tumour necrosis factor to drive tumour cell death in *Drosophila*. *Elife*. 8:e45061

- Pastor-Pareja JC, Wu M, Xu T. 2008. An innate immune response of blood cells to tumors and tissue damage in *Drosophila*. *Dis Model Mech*. 1(2–3):144–54; discussion 153
- Patel PH, Dutta D, Edgar BA. 2015. Niche appropriation by *Drosophila* intestinal stem cell tumours. *Nat Cell Biol*. 17(9):1182–92
- Pesavento PA, Agnew D, Keel MK, Woolard KD. 2018. Cancer in wildlife: patterns of emergence. *Nat Rev Cancer*. 18(10):646–61
- Rangarajan A, Hong SJ, Gifford A, Weinberg RA. 2004. Species- and cell type-specific requirements for cellular transformation. *Cancer Cell*. 6(2):171–83
- Riddiford N, Siudeja K, van den Beek M, Boumard B, Bardin AJ. 2021. Evolution and genomic signatures of spontaneous somatic mutation in *Drosophila* intestinal stem cells. *Genome Res*. 31(8):1419–32
- Roegiers F, Kavaler J, Tolwinski N, Chou Y-T, Duan H, et al. 2009. Frequent unanticipated alleles of lethal giant larvae in *Drosophila* second chromosome stocks. *Genetics*. 182(1):407–10
- Romano LA, Pedros VF. 2020. Neoplasias in Fish: Review of the Last 20 Years. A Look from the Pathology. *Annual Research & Review in Biology*. 35(12):134–53
- Rose FL, Harshbarger JC. 1977. Neoplastic and possibly related skin lesions in neotonic tiger salamanders from a sewage lagoon. *Science*. 196(4287):315–17
- Rossi F, Gonzalez C. 2015. Studying tumor growth in *Drosophila* using the tissue allograft method. *Nat Protoc*. 10(10):1525–34
- Rous P. 1911. A SARCOMA OF THE FOWL TRANSMISSIBLE BY AN AGENT SEPARABLE FROM THE TUMOR CELLS. *J Exp Med*. 13(4):397–411

- Ruben LN, Clothier RH, Balls M. 2007. Cancer resistance in amphibians. *Altern Lab Anim.* 35(5):463–70
- Ruijtenberg S, Van Den Heuvel S. 2015. G1/S Inhibitors and the SWI/SNF Complex Control Cell-Cycle Exit during Muscle Differentiation. *Cell.* 162(2):300–313
- Schuh JCL. 2004. Trials, tribulations, and trends in tumor modeling in mice. *Toxicol Pathol.* 32(Suppl 1):53–66
- Seluanov A, Gladyshev VN, Vijg J, Gorbunova V. 2018. Mechanisms of cancer resistance in long-lived mammals. *Nat Rev Cancer.* 18(7):433–41
- Sharpe JL, Morgan J, Nisbet N, Campbell K, Casali A. 2023. Modelling Cancer Metastasis in *Drosophila melanogaster*. *Cells.* 12(5):677
- Siudeja K, Nassari S, Gervais L, Skorski P, Lameiras S, et al. 2015. Frequent Somatic Mutation in Adult Intestinal Stem Cells Drives Neoplasia and Genetic Mosaicism during Aging. *Cell Stem Cell.* 17(6):663–74
- Stammnitz MR, Gori K, Kwon YM, Harry E, Martin FJ, et al. 2023. The evolution of two transmissible cancers in Tasmanian devils. *Science.* 380(6642):283–93
- Sulak M, Fong L, Mika K, Chigurupati S, Yon L, et al. 2016. TP53 copy number expansion is associated with the evolution of increased body size and an enhanced DNA damage response in elephants. *Elife.* 5:e11994
- Swanton C, Bernard E, Abbosh C, André F, Auwerx J, et al. 2024. Embracing cancer complexity: Hallmarks of systemic disease. *Cell.* 187(7):1589–1616
- Tamamouna V, Rahman MM, Petersson M, Charalambous I, Kux K, et al. 2021. Remodelling of oxygen-transporting tracheoles drives intestinal regeneration and tumorigenesis in *Drosophila*. *Nat Cell Biol.* 23(5):497–510

- The Medical Committee of the Society for Investigating the Nature and Cure of Cancer. 1967. Cancer problems 160 years ago. Institution for investigating the nature of cancer. *International Journal of Cancer*. 2(4):281–85
- Tian X, Azpurua J, Hine C, Vaidya A, Myakishev-Rempel M, et al. 2013. High-molecular-mass hyaluronan mediates the cancer resistance of the naked mole rat. *Nature*. 499(7458):346–49
- van Neerven SM, Vermeulen L. 2023. Cell competition in development, homeostasis and cancer. *Nat Rev Mol Cell Biol*. 24(3):221–36
- van Rooijen E, Fazio M, Zon LI. 2017. From fish bowl to bedside: The power of zebrafish to unravel melanoma pathogenesis and discover new therapeutics. *Pigment Cell Melanoma Res*. 30(4):402–12
- Vergneau-Grosset C, Nadeau M-E, Groff JM. 2017. Fish Oncology: Diseases, Diagnostics, and Therapeutics. *Veterinary Clinics of North America: Exotic Animal Practice*. 20(1):21–56
- Vincze O, Colchero F, Lemaître J-F, Conde DA, Pavard S, et al. 2022. Cancer risk across mammals. *Nature*. 601(7892):263–67
- Vittecoq M, Roche B, Daoust SP, Ducasse H, Missé D, et al. 2013. Cancer: a missing link in ecosystem functioning? *Trends Ecol Evol*. 28(11):628–35
- Voutyraki C, Choromidis A, Meligkounaki A, Vlachopoulos NA, Theodorou V, et al. 2023. Growth deregulation and interaction with host hemocytes contribute to tumor progression in a *Drosophila* brain tumor model. *Proc Natl Acad Sci U S A*. 120(33):e2221601120
- Weinberg R. 2023. *The Biology of Cancer*. Garland Science. 3rd Edition ed.

- Weiss JM, Lumaquin-Yin D, Montal E, Suresh S, Leonhardt CS, White RM. 2022. Shifting the focus of zebrafish toward a model of the tumor microenvironment. *Elife*. 11:e69703
- Wittbrodt J, Adam D, Malitschek B, Mäueler W, Raulf F, et al. 1989. Novel putative receptor tyrosine kinase encoded by the melanoma-inducing Tu locus in *Xiphophorus*. *Nature*. 341(6241):415–21
- Wong KKL, Verheyen EM. 2021. Metabolic reprogramming in cancer: mechanistic insights from *Drosophila*. *Dis Model Mech*. 14(7):1–17
- Xu J, Liu Y, Yang F, Cao Y, Chen W, et al. 2024. Mechanistic characterization of a *Drosophila* model of paraneoplastic nephrotic syndrome. *Nat Commun*. 15(1):1241
- Xu W, Li G, Chen Y, Ye X, Song W. 2023. A novel antidiuretic hormone governs tumour-induced renal dysfunction. *Nature*. 624(7991):425–32
- Zhang Z, Tian X, Lu JY, Boit K, Abulaeva J, et al. 2023. Increased hyaluronan by naked mole-rat Has2 improves healthspan in mice. *Nature*. 621(7977):196–205
- Zhao Y, Oreskovic E, Zhang Q, Lu Q, Gilman A, et al. 2021. Transposon-triggered innate immune response confers cancer resistance to the blind mole rat. *Nat Immunol*. 22(10):1219–30