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ONE HEALTH—ONE MEDICINE—RISKS AND BENEFITS. A SHORT REVIEW

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Pet and farm animals have accompanied humans for thousands of years. This coevolution and coexistence comes with both risks and benefits. As 75% of emerging human infectious diseases are zoonotically transmitted directly or are vector-borne, zoonoses are seen as a major human health risk. The «One health—one medicine» concept for a worldwide strategy should include interdisciplinary collaboration and communication for all aspects of health care for humans, animals, and the environment. The evaluation of risks is mainly focused on infectious diseases transmitted directly or indirectly from pet or farm animals to humans, e.g., rabies, echinococcosis, toxoplasmosis, anthrax, brucellosis, chlamydiosis, and tuberculosis.

There are many benefits to sharing your life with a pet, such as the positive effects of bonding and increased exercise. In addition, there is increased research into spontaneous canine and feline tumor cases that serve as models for analogous human cancer cases. Dogs or cats are possible epidemiological models (e.g., for comparing the geographic distribution of cancer). Genetic, proteomic, and molecular comparison of cancer in humans to canine cases imply possible models for tumor pathogenesis. To demonstrate the anti-tumor efficacy in a relevant in vivo situation, dogs might be used as possible therapeutic models.

Keywords: *zoonotic diseases, pet, human, risk*

Introduction. Pet and farm animals have accompanied humans for thousands of years. Dogs are believed to be the first domesticated pets, accompanying humans since 12,000–15,000 years ago (Davis and Valla, 1978; Perri, 2016). Following human settlement, the domestication of goats, sheep, and pigs followed (Larson, 2014).

In 2016, a GfK global study on pet ownership (http://www.gfk.com/global-studies/global-studies-pet-ownership/), which interviewed more than 27,000 consumers (aged 15 years and older) in 22 countries online, showed that over 50% of people worldwide have at least one pet. Dogs are the most common pets (33%), followed by cats (23%). In 2015, the livestock population statistics of the European Union (28 member states) recorded 89.2 million bovines, 148.7 million pigs, 85.5 million sheep, and 12.5 million goats (http://ec.europa.eu/eurostat/statistics-explained/index.php/File:Livestock_population,_2015_(million_head)_T1.png#filelinks). The coevolution and coexistence of humans and animals is accompanied by both risks and benefits. As 75% of emerging human infectious diseases are zoonotically transmitted directly or are vector-borne, zoonoses are seen as a major human health risk. Over the last decades, zoonotic infections have increased due to the increase of the human population worldwide, the effects of globalization, world trade, and intensified agribusiness.

Rudolf Virchow (fig. 1 A; 1821–1902) first noted the link between diseases of humans and animals and coined the term “zoonosis” while investigating the life cycle of Trichinella spiralis in swine and its zoonotic consequences (Schultz, 2008). Theobald Smith (fig. 1 B; 1859–1934; Dolman and Wolfe, 2003) and Karl-Friedrich Meyer (fig. 1 C; 1884–1974) were two of the other important forefathers of the «One health—one medicine» movement (Pospischil, 2015). Later, this led to the establishment of the One Health Initiative, a movement to forge collaborations primarily between human and veterinary medicine. This concept for a worldwide strategy should include interdisciplinary collaboration and communication in all aspects of health care for humans, animals, and the environment. The synergy achieved will advance health care for the 21st century and beyond by accelerating biomedical research discoveries, enhancing public health efficacy, expeditiously expanding the scientific knowledge base, and improving medical education and clinical care. When properly implemented, it will help protect and save untold millions of lives in present and future generations (http://www.onehealthinitiative.com/about.php). The term «One health—one medicine» was originally coined by Calvin Schwabe (*1927–, fig. 1; Dolman and Wolfe, 2003; Kaplan and Echols, 2009).

Evaluation of risks. The evaluation of risks is mainly focused on infectious diseases transmitted directly or indirectly from pet or farm animals to humans.

Examples of zoonotic diseases transmitted from pet animals to humans.

Rabies. Rabies is probably by far the most dangerous threat in table 1. Most of the 59,000 deaths caused yearly by rabies occur in Asia and Africa. The virus is transmitted in 99% of cases by rabid dogs (Hampson et al., 2015). Traditionally, rabies diagnosis in animals was based on the detection of intracytoplasmic Negri bodies in the neuronal cells (fig. 2 A). Later, antigens in tissue sections could be labeled using immunohistochemistry (fig. 2 B). The gold standard for diagnosis remains direct fluorescent antibody (DFA) staining of tissue sections (https://www.cdc.gov/rabies/diagnosis/accuracy.html).

Echinococcosis. Human echinococcosis is a parasitic disease caused by tapeworms of the genus Echinococcus. The two most important forms of the disease in humans are cystic echinococcosis (hydatidosis) and alveolar echinococcosis. Humans are infected through the ingestion of parasite eggs in contaminated food, water, or soil, or through direct contact with animal hosts (table 1; http://www.who.int/mediacentre/factsheets/fs377/en/). Carnivores act as definitive hosts and rarely as intermediate hosts for the parasite,

and host the mature tapeworm in their intestines. They are infected through the consumption of viscera of intermediate hosts that harbor the parasite (fig. 3 A–C). In human patients, cysts can be detected with ultrasound, X-ray, computed tomography, or other imaging techniques. Anti-echinococcus antibodies can be detected with serodiagnostic tests, e.g., indirect fluorescent antibody, complement fixation, ELISA, western blotting, and the like (Wenbao et al., 2012).

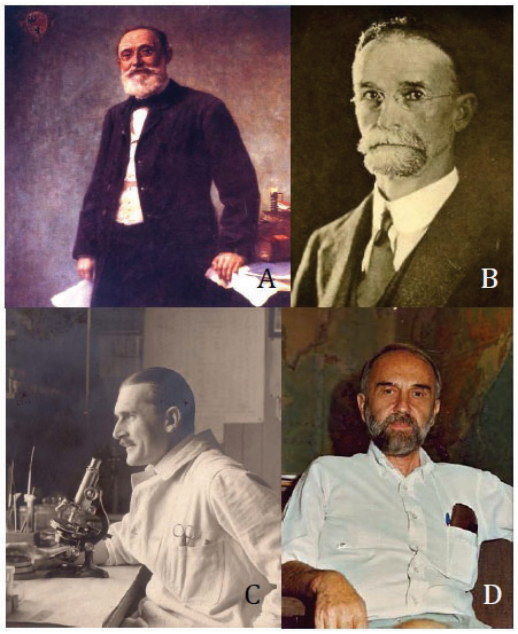

Figure 1. A: Rudolf Virchow (1821-1902), **B:** Theobald Smith (1859-1934), **C:** Karl-Friedrich Meyer (1884-1974), **D:** Calvin Schwabe (1927-)

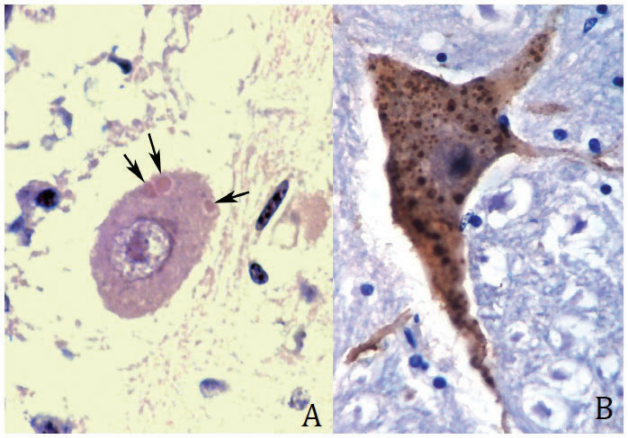

Figure 2. A: Negri bodies characteristic for rabies in a neuronal cell, **B:** Imunohistochemical demonstration of rabies virus antigen in a neuronal cell

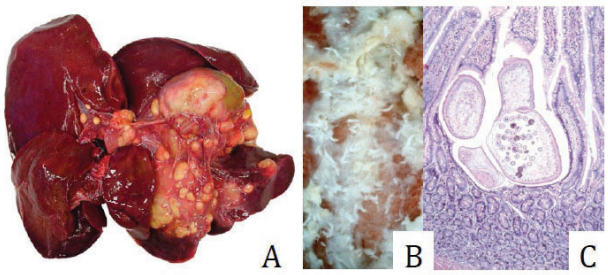

Figure 3: A: Cystic echinoccocosis, dog, liver, **B:** Echinococcus: tapeworm-like proglottides in the small intestine, dog, **C:** Echinococcus: tapeworm-like proglottides inembedded in the small intestinal mucosa, no signs of direct contact to enterocytes no signs of inflammation

Toxoplasmosis. Toxoplasmosis (Toxoplasma gondii) usually does not cause lesions in the majority of human patients. The parasite is found worldwide; data from the United States indicate that more than 60 million people may be infected with it.

However, immunodeficient patients develop severe symptoms such as seizures and poor coordination (fig. 4 A, B). If an infection occurs during pregnancy, congenital toxoplasmosis may affect the child. Tachyzoites develop in feline large intestinal enterocytes and are shed in the feces (fig 5 A, B). Recently, a negative association of Toxoplasma seropositivity with multiple sclerosis was reported (Stascheit et al., 2015).

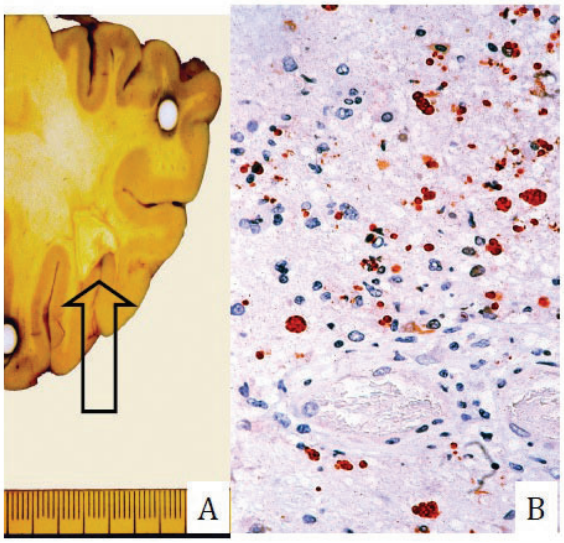

Figure 4. A: Human immunodeficient patient, 1.2cm single necrotic lesion, cortico-subcortial region, frontal lobe., **B:** Immunohistochemical labeling of Toxoplasma antigen in the CNS

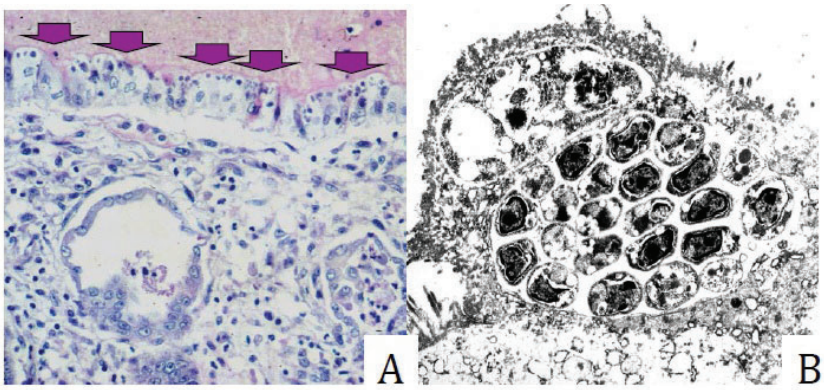

Figure 5. A: Intestine, feline, enterocytes containing toxoplasma, PAS stain, **B:** Intestine, feline, enterocytes containing toxoplasma, electron microscopy

Table 1 – Examples of infectious diseases transmitted by pet animals (e.g., dogs and cats) to humans

Disease	Pathogen(s)	Animals involved	Mode of transmission
Cat-scratch disease	*Bartonella henselae, B. quintana*	cats	bites or scratches from infected animals
Echinococcosis	*Echinococcus* spp.	dogs, foxes, wolves	oral ingestion of infective eggs from the feces of an infected definitive host
Leptospirosis	*Leptospira interrogans*	dogs	direct or indirect contact with urine of infected animals
Toxocariasis	*Toxocara canis, T. cati*	dogs, cats	exposure to feces
Toxoplasmosis	*Toxoplasma gondii*	cats	exposure to feces
Rabies	*Rabies virus*	dogs, cats	through saliva by biting or through scratches from an infected animal

Examples of zoonotic diseases transmitted from farm animals to humans.

Anthrax. Anthrax is an infection caused by the bacterium Bacillus anthracis. It can occur in four forms: skin (95% of cases; fig. 6 A), inhalation, intestinal, and injection. Risk factors include people who work with animals or animal products, travelers, postal workers, and military personnel. Globally, at least 2,000 cases occur a year (https://www.cdc.gov/anthrax/basics/index.html). Different methods can be applied for diagnosing clinical cases; specimens may be Gram-stained. Bacillus anthracis grows in long chains that stain gram-positive (fig. 6 A, B). Polymerase chain reactionвЂ“based assays and immunofluorescence microscopy may be used to confirm the organism.

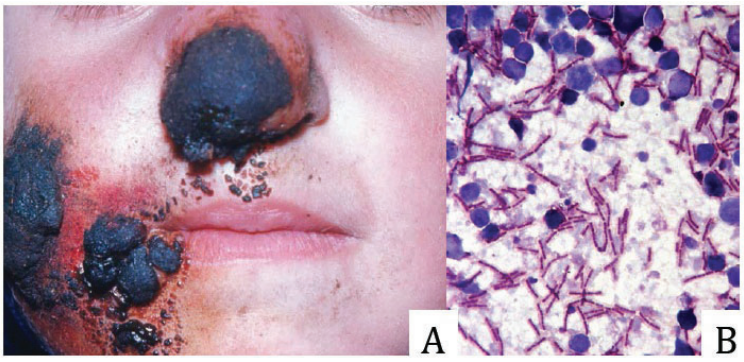

Figure 6. A: Anthrax, human skin, B: Bacillus anthracis rods, bovine blood smear Giemsa stained

Brucellosis. Domestic or wild animals are the major source of human Brucella infections. The routes of infection are multiple: foodborne, occupational, or recreational, and even bioterrorism. Brucella melitensis is the most important zoonotic agent, followed by Brucella abortus and Brucella suis. The control of bovine brucellosis (due to Brucella abortus) has been more successful than the control of sheep and goat brucellosis (due to Brucella melitensis). The occurrence of brucellosis is directly linked to the status of animal brucellosis in a region (Godfroid et al., 2005). The diagnosis of brucellosis in humans relies on the serologic demonstration of antibodies against the agent or histologic evidence of granulomatous hepatitis on hepatic biopsy. In animals, many cases are detected in post-mortem samples (fig. 7 A, B). The World Health Organization classifies brucellosis as one of the neglected endemic zoonoses that contributes to the perpetuation of poverty in developing countries. Due to regular control measures for brucellosis in developed countries, the number of cases was reduced dramatically.

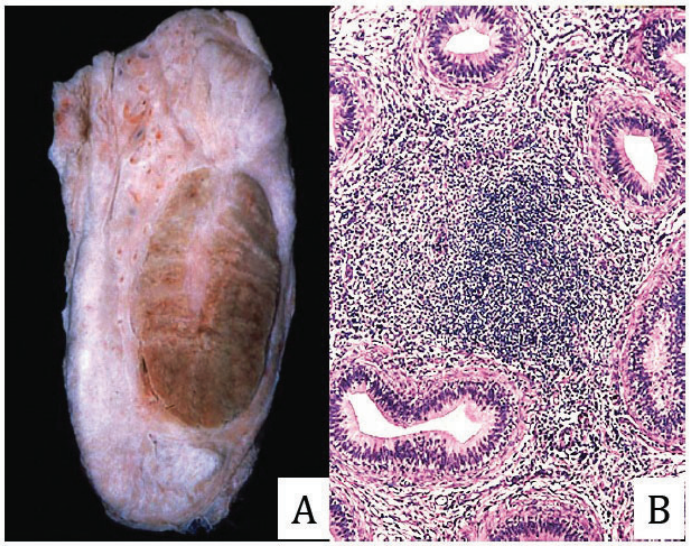

Figure 7. A: Granulomatous periorchitis in an infected bull, B: Chronic epididymitis in a bull indicative for brucellosis

Chlamydiosis. Chlamydiae cause several diseases, some of which, such as psittacosis and enzootic abortion of ewes, are of public health interest and others of economic importance in farm animals. They induce clinical ocular, pulmonary, genital, articular, and intestinal diseases, but very often manifest as persistent, chronic, or subclinical infections that are difficult to diagnose and treat. Chlamydiaceae are involved in human miscarriages abortions (Pospischil et al., 2002; Baud et al., 2011; 2014).

Chlamydial strains are usually host-related; however, improved diagnostic techniques are increasingly identifying infections of other animal species with a given strain. This is causing concern about the zoonotic potential of human chlamydial strains in animals, and vice versa. Psittacosis is a chlamydial disease that affects a wide range of bird species. It is transmissible from birds to humans. As the human disease is usually associated with parrots (including parakeets or budgerigars), physicians often refer to the infection as “parrot fever.” Several diagnostic procedures using morphologic and molecular technologies have been described (Borel et al., 2014).

Table 2 – Examples of infectious diseases transmitted from farm animals to humans

Disease	Pathogen(s)	Animals involved	Mode of transmission
African sleeping sickness	*Trypanosoma brucei* ¯*hodesiense*	range of wild animals and domestic livestock	the bite of the tsetse fly
Anthrax	*Bacillus anthracis*	grazing herbivores: cattle, sheep, goats, camels, horses, pigs	ingestion, inhalation, or skin contact with spores
Brucellosis	*Brucella spp.*	cattle, goats	infected milk or meat
Chlamydiosis/enzootic abortion	*Chlamydia abortus*	domestic livestock, particularly sheep	close contact with postpartum ewes
Variant Creutzfeldt–Jakob disease	PrP^{vCJD}	cattle	eating meat from animals with bovine spongiform encephalopathy (BSE)
Cysticercosis, taeniasis	*Taenia solium, Taenia saginata*	commonly pigs and cattle	consuming water or food contaminated with tapeworm eggs, or consuming raw or undercooked pork contaminated with cysticerci
Foodborne illnesses	*Campylobacter* spp., *Escherichia coli, Salmonella* spp., *Shigella* spp., *Trichinella* spp.	animals domesticated for food production (cattle, poultry)	raw and/or undercooked food made from infected animals
Glanders	*Burkholderia mallei*	horses	direct contact
Swine influenza	Any strain of the influenza virus endemic in pigs	pigs	close contact
Tuberculosis	*Mycobacterium bovis*	cattle, deer, llamas, pigs	milk, exhaled air, sputum, urine, feces, or pus from infected animals
Q fever	*Coxiella burnetii*	livestock	inhalation of spores, contact with bodily fluid or feces

Tuberculosis. The majority of human tuberculosis (TB) cases are caused by Mycobacterium tuberculosis. M. bovis is another Mycobacterium that can cause TB in humans. M. bovis is most commonly found in cattle and other animals such as bison, elk, and deer. Humans are most commonly infected with M. bovis by eating or drinking contaminated unpasteurized dairy products. Two tests are used to detect TB bacteria in the body: the TB skin test (TST) and TB blood tests (https://www.cdc.gov/tb/publications/factsheets/general/mbovis.htm). In most developed countries, animals with a positive skin test usually are culled. Macroscopic post-mortem findings in animals are pathognomonic (fig. 8 A). Mycobacteria are diagnosed in specially stained histopathologic sections (fig. 8 B, C).

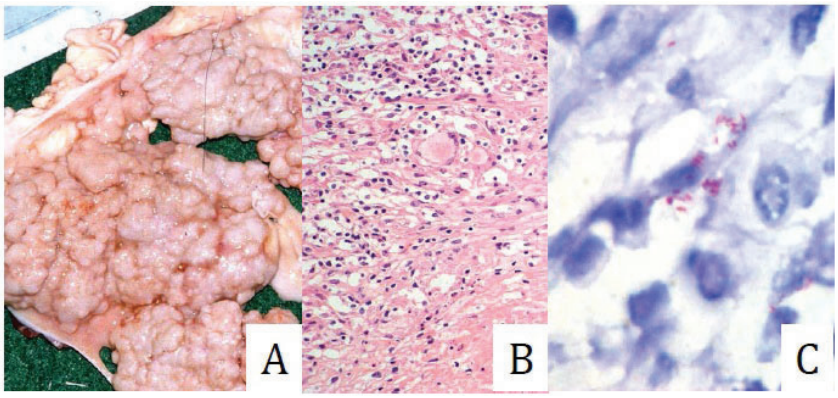

Figure 8. Bovine tuberculosis: A: granulomatous pleuritis, B: histopathology (HE), C: Acid fast bacilli (ZN stain)

Evaluation of benefits. An increasing number of studies have reported on the many benefits of sharing one's life with a pet (Mestel, 2017).

Bonding, exercise, and companionship. Direct eye contact between humans and dogs increased oxytocin levels, promoting relaxation and trust in dogs and their owners (Nagasawa et al., 2015). Dog owners were more likely to go for a walk in their free time compared to non-dog owners (Reeves et al., 2011). Male and female pet owners aged 60 years or over were less likely to report loneliness (Stanley et al., 2014).

Comparative oncology. Spontaneous canine and feline tumor cases can serve as models for analogous human cancer cases. In developed countries, the level of veterinary health care for pet animals such as dogs and cats is almost similar to that of human

health care with respect to diagnostic procedures, surgical techniques, and the use of therapeutic approaches and applied substances (Pospischil et al., 2016).

Facts in favor of using a canine and/or feline model of cancer (MacEwen, 1990):

- Like humans, dogs/cats are outbred species;
- Dogs share major ancestral gene sequences with humans (Rowell et al., 2011);
- Canine breeds show phenotypic diversity but a high level of inbreeding is associated with a predisposition to a distinct set of diseases, including tumors (Rowell et al., 2011; Pedersen et al., 2012; Mellanby, 2013);
- Dogs/cats share the human environment closely;
- During their much shorter lifespans, dogs/cats can develop tumors, many of them closely related to those in humans (Tamburini et al., 2009);
- Canine/feline cancers progress more rapidly compared to human tumors;
- The number of pet dogs and cats receiving a high level of veterinary care is increasing (Herberman, 1989);
- Dogs/cats respond similarly to most treatment regimens as humans.

There are several means of using dogs/cats with cancer as models for human patients:

- As possible epidemiological models (e.g., to compare geographic distribution, i.e., disease clusters) of cancer in dogs/cats and humans (Pospischil et al., 2008; Dorn and Schneider, 1972; Dorn, 1967; Sasco, 1993; Walter and Schwegler, 1992; Grüntzig et al., 2015, 2016; Graf et al., 2015, 2016; Boo et al., 2017);
- The dog as a possible model for tumor pathogenesis (e.g., with respect to genetic, proteomic, and molecular comparison of cancer in humans (O'Brien et al., 2000);
- The dog as a possible therapeutic model (e.g., to demonstrate the anti-tumor drug efficacy in a relevant in vivo situation (Marcanato et al., 2013; Pinho et al., 2012).

A direct comparison of tumor incidences in humans and dogs in a defined geographic catchment area and during a similar temporal frame had been attempted in Michigan, USA, using data from 1964вЂ“1994. The results of that study showed a similar spatial distribution for human and animal tumors. It appears, however, that the influence of geographic/geologic factors on tumorigenesis was more pronounced in dogs than in humans (ОвЂ™Brien et al., 2000). No temporal clusters were observed. Pet animals such as cats and dogs are the closest human companions, sharing human environmental conditions and sometimes food. Cats and dogs with spontaneous cancer could be ideal comparative models of cancer, as they are outbred species like humans; many of their genes are directly comparable to human genes, and spontaneous cancer in dogs/cats progresses more rapidly compared to humans. However, their relative lifespan is shorter compared to humans, although they respond similarly to most treatment regimens used in humans. As recent, detailed, extensive comparative human-animal studies in defined geographic regions are not available, the current value of canine and feline models cannot be evaluated conclusively.

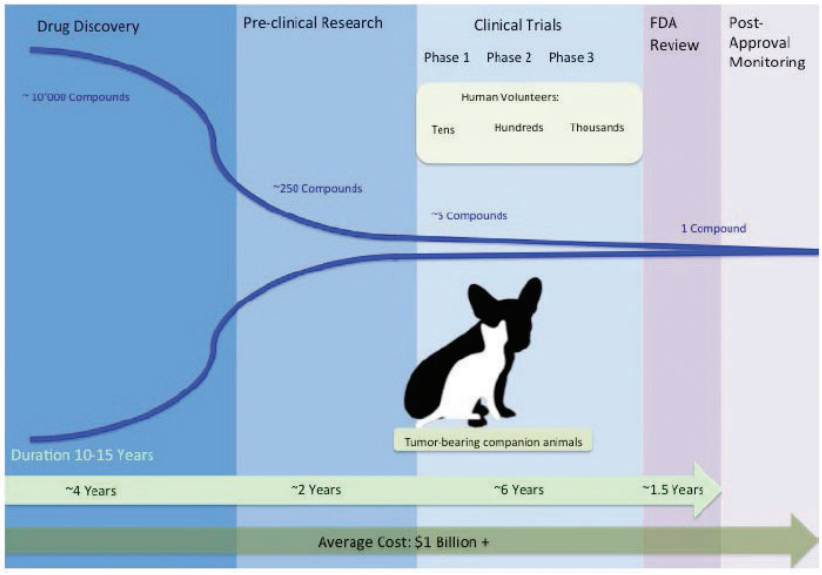

Figure 9. Companion animals in the drug development process

Outlook. For a broader and more general application of such models, the following requirements are necessary:

1. Population-based cancer registries (Pospischil et al., 2016; Grüntzig et al., 2015, 2016; Graf et al., 2015, 2016);
2. Comparative investigation of cancer registry data from different species (Pospischil et al., 2016; Grüntzig et al., 2015, 2016; Graf et al., 2015, 2016);
3. Comparative (human/feline/canine) geographic and environmental risk assessment for tumor incidences (Boo et al., 2017);
4. Tissue banks/biobanks for tumor samples.

Comparative testing of genetic/proteomic tumor markers.

The improvement of oncological clinical trials is due to the contribution to the drug development process by companion animals with naturally occurring cancer. Clinical trials in animals are not constrained by traditional Phase I, Phase II, and Phase III trial designs (fig. 9). This allows novel agents to be offered to companion animals before conventional therapies are administered or during the period of minimal residual disease, as opposed to human clinical trials, where patients enrolled often have advanced, treatment-resistant disease (Khanna et al., 2009). Another major advantage is the significantly shorter lifespan of companion animals, allowing more rapid collection of survival data. The disease-free interval in dogs treated for cancer is 18 months, whereas over 7 years are needed to assess treatment outcomes in humans (MacEwen, 1990; Paoloni and Khanna, 2008).

Dogs with naturally occurring tumors have contributed successfully to clinical trials: Kurzman and colleagues (Kurzman et al., 1995) demonstrated the anti-tumor activity of the immune stimulator liposomal muramyl tripeptide phosphatidylethanolamine (L-MTP-PE) in dogs with osteosarcoma. Re-evaluation of the mature human data from these studies found remarkably similar results to the earlier canine studies, which eventually led to approval of L-MPT-PE (MEPACT) for osteosarcoma in children in Europe (Kleinerman, 1995; Kleinerman et al., 1995; Meyers et al., 2005).

In the United States, 20 academic comparative oncology centers have formed the Comparative Oncology Trials Consortium (COTC) to provide the infrastructure and resources needed to integrate clinical trials on pets with naturally occurring cancers into the development pathways for new drugs, devices, and imaging techniques for human cancers (Gordon et al., 2009). However, the cancer research community has not yet succeeded in communicating the value of companion animals in clinical trials, and their useful integration into these trials remains a challenge.

References

1. Baud D, Goy G, Jaton K, Osterheld MC, Blumer S, Borel N, Vial Y, Hohlfeld P, Pospischil A, Greub G. Role of Chlamydia trachomatis in miscarriage. Emerg Infect Dis, 17:1630-1635,
2. Baud D, Goy G, Osterheld MC, Croxatto A, Borel N, Vial Y, Pospischil A, Greub G. Role of Waddlia chondrophila placental infection in miscarriage. Emerg Infect Dis, 20:460-464,
3. Boo G, Leyk S, Fabrikant SI, Graf R, Pospischil A. Assessing effects of structural zeros on models of canine cancer incidence: a case study of the Swiss Canine Cancer Registry. Submitted to Geospat Health, 2017.
4. Borel N, Frey CF, Gottstein B, Hilbe M, Pospischil A, Franzoso FD, Waldvogel A. Laboratory diagnosis of ruminant abortion in Europe. Vet J, 200:218-229, 2014.
5. Davis SJM, Valla FR. Evidence for domestication of the dog 12,000 years ago in the Natufian of Israel. Nature, 276:608-610, 1978.
6. Dolman CE, Wolfe RJ. Suppressing the diseases of animals and man; Theobald Smith. Harvard University Press, 2003, ISBN 0674012208.
7. Dorn CR, Schneider R. Public health aspects of cancer in pet dogs and cats. Am J Public Health, 62:1460-1462, 1972.
8. Dorn CR. The epidemiology of cancer in animals. Calif Med, 107:481-489, 1967. Godfroid J, Cloeckaert A, Liautard J-P, Kohler S, Fretin D, Walravensa K, Garin-Bastujie B, Letessonf J-J. From the discovery of the Malta fever's agent to the discovery of a marine mammal reservoir, brucellosis has continuously been a re-emerging zoonosis. Vet Res, 36:313-326, 2005.
9. Gordon I, Paoloni M, Mazcko C, Khanna C. The Comparative Oncology Trials Consortium: using spontaneously occurring cancers in dogs to inform the cancer drug development pathway. PLoS Med, 6, 2009.
10. Graf R, Grüntzig K, Boo G, Hässig M, Axhausen KW, Fabrikant S, Welle M, Meier D, Guscetti F, Folkers G, Otto V, Pospischil A. Swiss Feline Cancer Registry 1965–2008: the Influence of Sex, Breed and Age on Tumour Types and Tumour Locations. J Comp Pathol, 154:195–210, 2016.
11. Graf R, Grüntzig K, Hässig M, Axhausen KW, Fabrikant S, Welle M, Meier D, Guscetti F, Folkers G, Otto V, Pospischil A. Swiss Feline Cancer Registry: A Retrospective Study of the Occurrence of Tumours in Cats in Switzerland from 1965 to 2008. J Comp Pathol, 153:266–277, 2015.
12. Grüntzig K, Graf R, Boo G, Guscetti F, Hässig M, Welle M, Meier D, Folkers G, Pospischil A. Swiss Canine Cancer Registry 1955-2008: Occurrence of the Most Common Tumour Diagnoses and Influence of Age, Breed, Body Size, Sex and Neutering Status on Tumour Development. J Comp Pathol, 152:1–15, 2016.
13. Grüntzig K, Graf R, Hässig M, Welle M, Meier D, Lott G, Erni D, Schenker NS, Guscetti F, Boo G, Axhausen K, Fabrikant S, Folkers G, Pospischil A. The Swiss Canine Cancer Registry: A Retrospective Study on the Occurrence of Tumours in Dogs in Switzerland from 1955 to 2008. J Comp Pathol, 152:161–171, 2015.
14. Hampson K, Coudeville L, Lembo T, Sambo M, Kieffer A, Attlan M, Barrat J, Blanton JD, Briggs DJ, Cleaveöand S, Costa P, Freuling CM, Hiby E, Knopf L, Leanes F, Meslin FX, Metlin A, Miranda ME, Müller T, Nel LH, Recuenco S, Rupprecht CE, Schumacher C, Taylor L, Vigilato MAN, Zinstag J, Dushoff J. Estimating the global burden of endemic canine Rabies. PLOS Neglected Trop Dis, 9:1-20, 2015.
15. Herberman RB. Second counterpoint: Animal tumour models and their relevance to human tumour immunology. J Biol Response Med, 2:217-226, 1989.
16. Kaplan B, Echols M. 'One Health'—the Rosetta stone for 21st century health and health providers. Veter Ital, 45:377–382, 2009.
17. Khanna C, London, C, Vail, D, Mazcko C, Hirschfeld S. Guiding the optimal translation of new cancer treatments from canine to human cancer patients. Clin Cancer Res, 15:5671–5677, 2009.
18. Kleinerman E, Gano J, Johnston D, Benjamin R, Jaffe, N. Efficacy of liposomal muramyl tripeptide (CGP 19835A) in the treatment of relapsed osteosarcoma. Am J Clin Oncol, 18:93–99, 1995.
19. Kleinerman E. Biologic therapy for osteosarcoma using liposome-encapsulated muramyl tripeptide. Hematol Oncol Clin North Am, 9:927–938, 1995.
20. Kurzman D, MacEwen, E, Rosenthal, C, Fox, L, Keller T, Helfand C. Adjuvant Randomized encapsulated Therapy Clinical for Osteosarcoma Trials Using Tripeptide and in Dogs: Combined Cisplatin ' Results of Muramyl. Clin Cancer Res, 1:1595–1601, 1995.
21. Larson G. The Evolution of Animal Domestication. Annu Rev Ecol Evol Syst, 45:115–136,
22. MacEwen EG. Spontaneous tumors in dogs and cats: Models for the study of cancer biology and treatment. Cancer Metastasis Rev, 9:125–136, 1990.
23. Marconato L, Gelain ME, Comazzi S. The dog as a possible animal model for human non-Hodgkin lymphoma: a review. Hematol Oncol, 31:1–9, 2013.
24. Mellanby RJ, Ogden R, Clements DN, French AT, Gow AG, Powell R, Corcoran B, Schoeman JP, Summers KM. Population structure and genetic heterogeneity in popular dog breeds in the UK. Vet J, 196:92-97, 2013.

25. Mestel R. Millenia together. Nature, 543:29-30, 2017.
26. Meyers PA, Schwartz, CL, Krailo, M, Kleinerman ES, Betcher D, Bernstein ML. Osteosarcoma: A Randomized, Prospective Trial of the Addition of Ifosfamide and/or Muramyl Tripeptide to. J Clin Oncol, 23:9–16, 2005.
27. Nagasawa M, Mitsui S, En S, Ohtani N, Ohta M, Sakuma Y, Onaka T, Mogi K, Kikusui T. Social evolution. Oxytocin-gaze positive loop and the coevolution of human-dog bonds. Science, 348:333-336, 2015.
28. O'Brien DJ, Kaneene, JB, Getis A, Lloyd JW, Swanson M, Leader RW. Spatial and temporal comparison of selected cancers in dogs and humans, Michigan, USA, 1964–1994. Prev Vet Med, 47:187–204, 2000.
29. Paoloni M, Khanna C. Translation of new cancer treatments from pet dogs to humans. Nat Rev Cancer, 8:147–156, 2008.
30. Pedersen N, Liu H, Theilen G, Sacks, B. The effects of dog breed development on genetic diversity and the relative influences of performance and conformation breeding. J Anim Breed Genet, 130:236-248, 2012.
31. Perri, A. A wolf in dog's clothing: Initial dog domestication and Pleistocene wolf variation. J Archaeolog Sci, 68:1–4, 2016.
32. Pinho SS, Carvalho S, Cabral J, Reis CA, Gärtner F. Canine tumours: a spontaneous animal model of human carcinogenesis. Transl Res, 159:165-172, 2012.
33. Pospischil A, Grüntzig K, Graf R, Boo G. Spontaneous animal tumor models. In Animal models for human cancer, Martic-Kehl MI, Schubiger PA, eds. Wiley-VCH, Weinheim, D,
34. Pospischil A, Hässig M, Vogel R, Salvini MM, Fabrikant S, Axhausen K, Schenker SN, Erni D, Guscetti F. Dog population and breed distribution in Switzerland from 1955 to 2008. Schweizer Archiv für Tierheilkunde, 155:219-228, 2008.
35. Pospischil A, Thoma R, Hilbe M, Grest P, Gebbers JO. Abortion in woman caused by caprine Chlamydophila abortus (Chlamydia psittaci serovar 1). Swiss Med Wkly, 132:64- 66, 2002.
36. Pospischil A. Human and animal health on three continents-a biography of the early life of Karl Friedrich Meyer (1884-1974). Pathog Dis, 73: ftv039, doi:
37. 10.1093/femspd/ftv039, 2015.
38. Reeves MJ, Rafferty AP, Miller CE, Lyon-Callo SK. The impact of dog walking on leisure-time physical activity: results from a population-based survey of Michigan adults. J Phys Act Health, 8:436-444, 2011.
39. Rowell JL, McCarthy DO, Alvarez CE. Dog models of naturally occurring cancer. Trends Mol Med, 17:380-388, 2011.
40. Sasco AJ. Comparative epidemiology of cancer. Epidemiology, 5:484-485, 1993. Schultz M. Rudolf Virchow. Emerg Inf Dis, 14:1480-1481, 2008.
41. Stanley IH, Conwell Y, Bowen C, Van Orden KA. Pet ownership may attenuate loneliness among older adult primary care patients who live alone. Aging Ment Health, 18:394-399,
42. Stascheit F, Paul F, Harms L, Rosche B. Toxoplasma gondii seropositivity is negatively associated with multiple sclerosis. J Neuroimmunol, 285:119–124, 2015.
43. Tamburini BA, Trapp S, Phang TL, Schappa JT, Hunter LE, Modiano JF. Gene expression profiles of sporadic canine hemangiosarcoma are uniquely associated with breed. PLoS ONE, 4:1-12, 2009.
44. Walter JH, Schwegler K. Untersuchungen zur Häufigkeit von Neoplasien bei sezierten Hunden in Berlin (West). Journal Veterinary Medicine A, 39:328-341, 1992.
45. Wenbao Z, Hao W, Jun L, Renyong L, McManus DP. Immunology and Immunodiagnosis of Cystic Echinococcosis: An Update. Clin Dev Immunol, doi: 10.1155/2012/101895, 2012.