To summarize, fruitflies and other animals such as zebrafish (107) (model for cardiovascular diseases), as well as treatment of mice by mutating a particular gene, are commonly used as animal models for human diseases. However, it is not likely that animals such as these will be accepted by the FDA to establish safety and efficacy for a given drug in humans, to the extent that the FDA will be persuaded to approve the initiation of a clinical trial. The present commentary helps to provide a definition of an acceptable animal model for treating a disease, by an example of what is *not an acceptable model*.

d. Developing an Accepted Animal Model for a Disease

The first step in arriving at an animal model for a disease is to develop an animal model that resembles the human condition, in view of the physiology of the disease, symptoms of the disease, and response to therapeutic interventions, such as to an administered drug. Varga et al. (108) used the term "valid animal model" to refer to an animal model that resembles the human condition, but this use of the word "valid" is not the same as the defined process of "validation."

Regarding the history of the development of animal models, one of the first steps in adopting the rat as a standard animal took place at the University of Wisconsin-Madison, where E.V. McCollum advocated using rats instead of cows. Initially, the idea was met with adversity, as documented by McCollum's statement that, "Professor Hart was astonished and offended at my pronouncement on the cow project. He was contemptuous of my suggestion that we turn to the rat as an experimental animal" (109). Over the course of decades, rats as well as other animals, became standard models for testing various pharmaceuticals, as demonstrated by a guidance document issued by the FDA (110).

A conventional animal model for arthritis involves the generation of arthritis-like symptoms by injecting antibodies raised against type II collagen into the animal (111,112). A conventional animal model for multiple sclerosis, called EAE, involves injecting myelin-derived proteins into the animal (113,114). Recombinant animals that are animal models for diseases include the PDAPP transgenic mouse model for Alzheimer's disease, which is engineered to express a mutant human amyloid precursor protein (115). An animal model

[107]Asnani A, Peterson RT. The zebrafish as a tool to identify novel therapies for human cardiovascular disease. Dis. Model Mech. 2014;7:763–7.

[108]Varga OE, et al. Validating animal models for preclinical research: a scientific and ethical discussion. Alternat. Lab Anim. 2010;38:245–8.

[109]McCollum EV. The paths to the discovery of vitamins A and D. J. Nutr. 1967;91(Suppl. 1):11–6.

[110]U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for industry. Estimating the safe starting dose in clinical trials for therapeutics in adult healthy volunteers; 2002.

[111]Nandakumar KS, et al. Collagen type II-specific monoclonal antibody-induced arthritis in mice: description of the disease and the influence of age, sex, and genes. Am. J. Pathol. 2002;163:1827–37.

[112]Stuart JM, et al. Collagen autoimmune arthritis. Annu. Rev. Immunol. 1984;2:199–218.

[113]Yednock TA, et al. Prevention of experimental autoimmune encephalomyelitis by antibodies against alpha 4 beta 1 integrin. Nature 1991;356:63–6.

[114]MacKay IR, et al. Immunopathological comparisons between experimental autoimmune encephalomyelitis and multiple sclerosis. Clin. Exp. Immunol. 1973;15:471–82.

[115]Schenk D, et al. Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology, the PDAPP mouse. Nature 1999;400:173–7.