Human filariasis—contributions of the *Litomosoides sigmodontis* and *Acanthocheilonema viteae* animal model

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Abstract

Filariae are vector-borne parasitic nematodes that are endemic worldwide, in tropical and subtropical regions. Important human filariae spp. include *Onchocerca volvulus*, *Wuchereria bancrofti* and *Brugia* spp., and *Loa loa* and *Mansonella* spp. causing onchocerciasis (river blindness), lymphatic filariasis (lymphedema and hydrocele), loiasis (eye worm), and mansonelliasis, respectively. It is estimated that over 1 billion individuals live in endemic regions where filarial diseases are a public health concern contributing to significant disability adjusted life years (DALYs). Thus, efforts to control and eliminate filarial diseases were already launched by the WHO in the 1970s, especially against lymphatic filariasis and onchocerciasis, and are mainly based on mass drug administration (MDA) of microfilaricidal drugs (ivermectin, diethylcarbamazine, albendazole) to filarial endemic areas accompanied with vector control strategies with the goal to reduce the transmission. With the United Nations Sustainable Development Goals (SDGs), it was decided to eliminate transmission of onchocerciasis and stop lymphatic filariasis as a public health problem by 2030. It was also requested that novel drugs and treatment strategies be developed. Mouse models provide an important platform for anti-filarial drug research in a preclinical setting. This review presents an overview about the *Litomosoides sigmodontis* and *Acanthocheilonema viteae* filarial mouse models and their role in immunological research as well as preclinical studies about novel anti-filarial drugs and treatment strategies.

Keywords Lymphatic filariasis · Onchocerciasis · Rodent models · *Acanthocheilonema viteae* · *Litomosoides sigmodontis* · Drug development

Human filarial species

Important human filariae spp. are *Onchocerca volvulus*, *Wuchereria bancrofti*, *Brugia* spp., *Loa loa* and *Mansonella* spp. Although the majority of infected individuals remain asymptomatic due to filarial-driven suppression of host immunity (Hoerauf and Brattig 2002; Adjohimey and Hoerauf 2010; Maizels et al. 2018; Ritter et al. 2018b, 2019; Alvar et al. 2020), filariae can influence disease outcome of concomitant infections and vaccination efficacy (Chatterjee et al. 2015; Santiago and Nutman 2016; Kroidl et al. 2016; Kabagenyi et al. 2020; Muhangi et al. 2007; Hillier et al. 2008; Elliott et al. 2010; Stensgaard et al. 2016; Mhimbira et al. 2017). Moreover, *O. volvulus*, *W. bancrofti*, and *Brugia* infections can lead to severe clinical symptoms and diseases in a subset of patients that develop strong inflammatory responses against the filariae. For example, the disease onchocerciasis caused by *Onchocerca volvulus* can lead to vision loss, blindness, and dermatitis including its severest form sowda (Adewole and Ayeni 2009; Edungbola et al. 1987; Katowa et al. 2015; Njim et al. 2015). Thus, onchocerciasis is a major public health problem (WHO Oncho 2020) and approximately 90 million people live at risk of contracting the disease worldwide, especially in Sub-Saharan Africa including 17 million infected and 270,000 permanently blind individuals (WHO 2018). Similarly, lymphatic filariasis (LF) caused by *Wuchereria bancrofti*, *Brugia timori* and *B. malayi* can lead to severe clinical symptoms including hydrocele, lymphedema, lymphangitis, and elephantiasis (WHO LF 2020; Rebollo and
Bockarie 2017). It is estimated that 68 million LF patients with 19 million hydrocele and 17 million lymphedema cases exist worldwide (Ramaiah and Ottesen 2014). In addition, loiasis caused by *Loa loa*, also known as African eye worm, is characterized by distinct clinical manifestations like Calabar swelling, pruritis, arthralgia, and sporadic sub-conjunctival migration of the adult worms (Lukiana et al. 2006; Akue et al. 2011). Recent studies have highlighted both increased mortality and significant increases in DALYs associated with loiasis (Chesnais et al. 2017; Veletzky et al. 2020). In contrast to onchocerciasis and LF, loiasis is geographically restricted to forested areas in 11 Western and Central African countries (Zouré et al. 2011; Kelly-Hope et al. 2012) with approximately 13 million infected individuals (Fernandez-Soto et al. 2014). In contrast, despite mild clinical manifestations (subcutaneous swellings, skin rashes, and pleuritis), a distinct clinical symptom as shown by other filarial infections is missing in *Mansonella perstans*, *M. streptocerca*, or *O. ozzardi*–infected individuals (Simonsen et al. 2011; Hoerauf 2009; Asio et al. 2009a; Downes and Jacobsen 2010). Mansonellosis is endemic in tropical parts of Latin America and large proportions of Sub-Saharan Africa. It is estimated that over 600 million people are at risk of infection in over 33 countries and 114 million people are infected with *M. perstans* (Simonsen et al. 2011; Kamtechum Tatuene et al. 2014). The absence of a specific clinical condition has resulted in a shortfall on mansanellosis research. However, it was shown that *M. perstans* strongly modulates host immune responses (Ritter et al. 2018b) which might explain the increased susceptibility and worsened disease course of HIV, tuberculosis (TB), and malaria as well as lowered efficacy of bacillus Calmette-Guerin vaccination against TB in endemic regions (Muhangi et al. 2007; Hillier et al. 2008; Elliott et al. 2010; Stensgaard et al. 2016; Mhimbira et al. 2017).

Vector control and mass drug administration (MDA) programs like OCP (Onchocerciasis Control Programme), APOC (African programme for Onchocerciasis control), and OPEA (Onchocerciasis Elimination Program of the Americas) were implemented decades ago (WHO 2018; Tsalikis 1993), achieving the interruption of *O. volvulus* transmission in Cuba, Ecuador, Mexico, and Guatemala (Mauricio et al. 2017) and elimination in Mali and Senegal (Diawara et al. 2009; Traore et al. 2012). GPELF (Global Programme to Eliminate LF) prevented an estimated number of 96 million new LF cases over the last 13 years, and it is now estimated that infections dropped to 68 million LF patients and 19 million hydrocele and 17 million lymphedema cases (Ramaiah and Ottesen 2014; WHO 2015).

However, it is becoming obvious that onchocerciasis and LF cannot be eliminated from Africa in the near future solely depending on the microfilaricidal and temporally embryostatic drugs currently used for MDA (ivermectin with or without albendazole) (Dadzie et al. 2003; Basañez et al. 2008; Chucher et al. 2009; Chandy et al. 2011; Rebollo and Bockarie 2017; Koudou et al. 2018; Babu and Kar 2004). Moreover, some *Loa loa*–infected individuals with high microfilariae numbers in the peripheral blood suffered from severe adverse events (SAEs) following intake of ivermectin or DEC during MDA programs (Chippaux et al. 1996; Gardon et al. 1997; Boussinesq et al. 1998; Padgett and Jacobsen 2008). This issue has compromised the elimination of onchocerciasis and LF in co-endemic areas (Boussinesq 2006; Padgett and Jacobsen 2008). Finally, regarding treatment for mansanellosis, ivermectin has been shown to have little effect on *M. perstans* infection in Africa (Asio et al. 2009a, 2009b, 2009c; Wanji et al. 2016). Thus, further research on alternative treatment strategies and novel, macrofilaricidal drugs are urgently needed to achieve the goal of eliminating transmission of onchocerciasis and stop lymphatic filariasis as a public health problem by 2030. Interestingly, at the end of the 20th century, rickettsiae-like intracellular bacteria, called *Wolbachia*, which are present in human filarial nematodes except *Loa loa*, opened up novel possibilities for anti-filarial treatment strategies (reviewed in detail by Kozek and Rao 2007).

Indeed, studies and clinical trials revealed that antibiotics such as doxycycline deplete *Wolbachia* from the adult filariae leading to permanent sterility and finally death of the adult filariae (macrofilaricidal activity) which is an advantage compared to microfilaricidal drugs such as ivermectin and diethylcarbamazine (Bandi et al. 1999; Hoerauf et al. 2000; Hoenuf et al. 2001, 2002, 2003a, 2003b).

Research about human filariae is limited due to the restricted access to human parasitic life stages. In *vitro* and *in vivo* models of human pathogenic filariae are urgently needed for the investigation of the parasite’s biology and immunomodulatory capacity as well as detection of novel treatment strategies and anti-filarial drugs. Thus, model organisms and rodent models of filariasis mimicking human filarial infections are mandatory for research and this review will focus on the *Litomosoides sigmodontis* and *Acanthocheilonema viteae* rodent models and their role in immunological research as well as preclinical studies on novel anti-filarial drugs and treatment strategies.

### Important aspects for the development of drugs for human filarial infections

Safety and efficacy are universal aspects for novel drugs that have to be evaluated before large scale human trials can be conducted. In the case of drugs intended for human filarial infections, there are three additional important properties that need to be addressed during preclinical development:

First, filariae have a complex life cycle during which the nematodes may pass through different organs and go through various stages of development. It is therefore challenging for a single drug to target all life cycle stages of any given filaria.
As a result, drugs against filariae are commonly separated into microfilaricidal (ivermectin, diethylcarbamazine) and macrofilaricidal (flubendazole, oxfendazole, anti-Wolbachia compounds) drugs. Microfilaricidal drugs target the progeny of filarial worms (microfilariae), which are taken up by the vector to transmit the parasite, whereas macrofilaricidal drugs target the adult stage. A significant amount of research capacities is currently focused on the development and validation of novel macrofilaricidal treatment strategies (Bakowski and McNamara 2019; Jacobs et al. 2019; Taylor et al. 2019; Hübner et al. 2019a; Ehrens et al. 2020; Geary et al. 2019; Hübner et al. 2020; Hawryluk 2020). Since human pathogenic filariae can survive in the host for years (Geary and Mackenzie 2011), microfilaricidal strategies generally only block the transmission of infections temporarily and are unable to completely eliminate the parasite. MDA strategies based on macrofilaricidal drugs may be able to achieve elimination much quicker (Hawryluk 2020).

The second important property in the case of filaricidal drugs concerns the speed at which the filariae are cleared from the host. Rapid killing of the parasite may lead to a significant release of both worm antigen and Wolbachia which may trigger significant host immune responses and cause adverse reactions (reviewed in more detail in Geary and Mackenzie 2011; Budge et al. 2018). Two examples of this are as follows: (1) adverse reactions after MDA treatment against lymphatic filariasis are more common in microfilaremic than amicrofilaremic patients (Budge et al. 2018); (2) the aforementioned adverse reactions in Loa loa–infected patients with high microfilariae numbers after treatment with ivermectin (Chippaux et al. 1996; Gardon et al. 1997; Boussinesq et al. 1998; Padgett and Jacobsen 2008). As a result, it may be desirable for novel macrofilaricidal drugs to slowly eliminate worms over time (Geary and Mackenzie 2011). It has been shown that doxycycline, the prototype anti-wolbachial drug, shows this effect (Supali et al. 2008).

The third property concerns the question whether elimination of the parasite itself is necessary. Some filariae that infect humans cause only limited pathology (e.g., Loa loa, Mansonella spp.). In the case of onchocerciasis, the aetiological agents involved in blindness are the microfilariae and their Wolbachia endosymbionts (Saint André et al. 2002; Geary and Mackenzie 2011). Permanent sterilization is therefore a potentially acceptable alternative to macrofilaricidal activity. In addition, sterilization of worms that is achieved via elimination of Wolbachia may be used in conjunction with directly acting filaricidal drugs to lessen potential adverse reactions. Such a strategy, a combination of doxycycline (targeting Wolbachia) with melarsomite (macrofilaricide), is commonly used for the treatment against adult Dirofilaria immitis in dogs (American Heartworm Society 2014).

**Rodent models—a historical perspective**

Rodents are among the most widely used model organisms in both basic and translational medical and biological research which includes filarial diseases. Model organisms like the nematodes Acanthocheilonema viteae (Krepkogorskaia 1933) and Litomosoides sigmodontis (Chandler 1931) have been studied for over 70 years and have contributed to major discoveries to the filarial research community.

In the following part of this review, we will focus on the history of biological and medical research using the filariae Acanthocheilonema viteae and Litomosoides sigmodontis in small rodents (mice, rats, hamsters). In addition, we will discuss how these two organisms have been instrumental in discovering and understanding the role of excretory-secretory products of helminths (Harnett et al. 1989; Haslam et al. 1999; Goodridge et al. 2005), improve and develop novel chemotherapies (Hewitt et al. 1947; Rao et al. 1990; Reddy et al. 1983; Hoerauf et al. 1999) as well as vaccines (Hartmann et al. 1997a; Lucius et al. 1991), and unravel the importance of the intracellular bacteria Wolbachia that is present in most human pathogenic filariae with the exception of Loa loa (McLaren et al. 1975; Vincent et al. 1975; Sironi et al. 1995; Hoerauf et al. 1999).

**Acanthocheilonema viteae (Krepkogorskaia 1933)**

A. viteae (formerly Litosoma witei, L. vitei, Dipetalonema vite, D. blanci, D. viteae, D. viteae) was initially described in 1933 by Krepkogorskaia (Bain 1978). The natural hosts are the Libyan jird Meriones libycus and the great gerbil Rhombomys opimus. The parasite is transmitted via the tick Ornithodoros tartakovskyi. Under laboratory conditions, the parasite can also infect other rodents, such as the Mongolian jird Meriones unguiculatus (Johnson et al. 1974), the golden hamster Mesocricetus auratus (Pacheco 1970; Neilson and Forrester 1975), rats, the multimammate rat Mastomys nataliensis (Holdstock 1974; Sänger and Lämmler 1979), and to a limited extend mouse strains (Haque et al. 1980; Storey et al. 1989) as well as Shaw’s jird Meriones shawi (Lumb et al. 2020). A. viteae adult worms reside in the subcutaneous tissue and start releasing microfilariae (MF) 6–9 weeks postinfection. MF may be detectable for up to 15 months postinfection, while the adult worms themselves have a maximum lifespan of up to 2 years (Johnson et al. 1974; Worms et al. 1961).

The first experimental infections were described in 1953 by Baltazard et al. (the parasite was known as Dipetalonema blanti at the time) and in the following decade research focussed on describing the general biology, life cycle, and laboratory maintenance (Baltazard et al. 1953; Chabaud 1957; Worms et al. 1961; Terry et al. 1961). Following this fundamental work, investigations into host-parasite interactions,
immune responses, and chemotherapeutic agents were carried out by numerous groups. Frank Hawking, the father of the famous Physicist Stephen Hawking, demonstrated the importance of the spleen in controlling the number of MF of *A. viteae* (and *L. sigmodontis*, *Dirofilaria immitis*, and *Dirofilaria repens*) (Hawking 1962) and postulated the proximate reason for the periodicity of MF in the peripheral blood based on MF movement and changes in oxygen tension and body temperature (Hawking and Clark 1967).

*A. viteae* was one of the first rodent filarial models used for preclinical drug testing, demonstrating (in parallel with *Brugia pahangi*) macrofilaricidal efficacy of flubendazole in jirds in the 1970s/1980s (Denham et al. 1979; Denham 1980; Court et al. 1988) and the recrudescence of MF in amicrofilaremic golden hamsters after treatment with immunosuppressive drugs (e.g., methyl prednisolone acetate and cyclophosphamide) (Neilson 1978). Subsequent studies in the *A. viteae* *Mastomys* model showed a predominant microfilaricidal efficacy of the macrocyclic lactones ivermectin and moxidectin (Zahner et al. 1987; Rao et al. 1987; Schares et al. 1994) and addressed the adverse reactions caused by diethylcarbamazine (DEC) (Singh et al. 1985).

While *A. viteae* is nowadays not regularly used for preclinical studies, the model became most famous by the discovery of two excretory-secretory (ES) immunomodulatory molecules (Fig. 1). With the discovery of Av17, a homologue to the human cystatin C (Hartmann et al. 1997a, 1997b), and ES-62 (Harnett et al. 1989), respectively, the area of filarial immunomodulation was introduced and this has led to the discovery of numerous other ES products (reviewed in detail in Maizels et al. 2018). The anti-inflammatory and immunomodulatory properties of excretory-secretory products such as ES-62 and cystatin and their potential application in treatments for autoimmune diseases such as arthritis and allergies as well as their use as therapeutics to influence the gut microbiome have been studied in great detail since their discovery and we refer the reader to the following publications for a more in-depth review on the topic (Harnett et al. 1999, Harnett and Harnett 2001a, 2001b, Harnett et al. 2004, Harnett and Harnett 2009; Al-Riyami and Harnett 2012; Pineda et al. 2014a, 2014b, 2015; Ebner et al. 2014; Rausch et al. 2018; Midha et al. 2018; Doonan et al. 2019; Langdon et al. 2019; Crowe et al. 2020).

In addition to the groundbreaking discovery of immunomodulatory excretory-secretory products, *A. viteae* has also been instrumental during the initial development of anti-*Wolbachia*-based treatment strategies for filarial diseases. *A. viteae*, unlike a number of human pathogenic filariae, such as the causative agents of lymphatic filariasis (*Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori*) and onchocerciasis (*Onchocerca volvulus*) as well as the second rodent model to be covered in this review (*Litomosoides sigmodontis*), does not contain Wolbachia. As such, *A. viteae* has been used to show that the anti-filarial properties of certain antibiotics (tetracyclines like doxycycline and others) are indeed dependent on the presence of Wolbachia, since they do not affect *A. viteae* infection (Hoerauf et al. 1999).

**Litomosoides sigmodontis (Chandler 1931)**

*Litomosoides sigmodontis* (prior to 1989 conflated with *Litomosoides carinii* [Travassos 1919]) was described in 1931 as a filariae of the cotton rat *Sigmodon hispidus* and designated as the type species of the novel genus *Litomosoides* (Chandler 1931; Bain et al. 1989). Three years later, *L. sigmodontis* was erroneously synonymized with *L. carinii* (Travassos 1919) due to similarities in their morphology (Vaz 1934). Later studies by the group of Odile Bain established that *L. sigmodontis* and *L. carinii* are indeed two separate species and the names were corrected (Bain et al. 1989; Martin 2014).

Apart from the natural host *S. hispidus*, other experimental hosts include *Meriones unguiculatus* (Schneider et al. 1968), albino rats *Rattus norvegicus* (Ramakrishnan et al. 1961), *Mastomys nataliensis* (Pringle and King 1968), and mice *Mus musculus* (Hawking et al. 1947; Patra and Basu 1970; Petit et al. 1992). Mice in particular exhibit a variety of different responses to the infection with *L. sigmodontis* and display a more resistant or susceptible phenotype depending on the strain (Petit et al. 1992). BALB/c mice and to a lesser degree

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**Fig. 1** Publications on *Acanthocheilonema viteae* sorted by year and topic. List of publications was generated via PubMed search (see supplement table 1 for search parameters and complete list) and assigned one main topic each
BALB/c and BALB/b mice were shown to be susceptible for infection with *L. sigmodontis* with a subset of animals developing microfilaria (around 50%, 28%, and 6%, respectively), whereas CBA/HN, CBA/Ca, C3H/HeN, DBA/2N, B10, B10Br, and B10D2 do not develop microfilaria, although all strains (in B10, B10Br, and B10D2 only in 28, 12, and 7% of mice) allowed the development into adult filariae (Petit et al. 1992). Therefore, the *L. sigmodontis* BALB/c mouse model mirrors the situation in humans infected with lymphatic filariasis where only a proportion of patients develops microfilaremia. This is one of the reasons why this mouse model has become widely used for filarial research.

*L. sigmodontis* is transmitted by the hematophagous mite *Ornithonyssus bacoti* which takes up MF from infected animals and transmits L3 larvae to (naive) animals during blood meals. The larvae then migrate through the skin and lymphatic system, enter the pulmonary blood circulation, and reach the pleural cavity within the first week postinfection (Karadjian et al. 2017; Kilarski et al. 2019). In susceptible mice (for example BALB/c mice), adult worms can be found in the pleural cavity after 28–30 days and MF are detectable in the peripheral blood after ~8 weeks (Hübner et al. 2009), whereas in semi-susceptible mice like C57BL/6 adult worms are cleared after 45 days and thus no MF are released (Petit et al. 1992). Therefore, the usage of different mouse strains allows the investigation of distinct research questions about parasite biology (e.g., latent vs patent infections), filarial-driven immune responses, associated morbidity, and treatment strategies.

The migration of L3 larvae through the pulmonary vessels and the presence of later worm stages in the pleural cavity makes the *L. sigmodontis* model ideal to study the pathogenesis of lung disease that can be associated with human pathogenic nematode infections (Vijayan 2007; Simonsen et al. 2011). Recent studies showed that the entry of L3s into the pleural cavity is associated with hemorrhages, granuloma formation, inflammation, and infiltration of neutrophils expressing calprotectin (Karadjian et al. 2017). The role of calprotectin, one of the most abundant proteins in neutrophils, during filarial infections is still unclear, but a follow-up study with calprotectin-deficient mice suggested an anti-inflammatory role of calprotectin that facilitates the migration of *L. sigmodontis* L3 larvae (Frohberger et al. 2020). Similarly, the *L. sigmodontis* rodent model has been used to investigate lung morbidity during chronic infections and different studies highlighted the role of the Th2 cytokines IL-4 and IL-5 in regulating inflammation at the site of infection (Ritter et al. 2017; Fercoq et al. 2019). The presence of MF in particular has a significant impact on inflammation in the lung and pleural cavity. Recent studies by Fercoq et al. (2020) demonstrated the formation of polyps on the pleura that consisted of up to 60% immune cells. The formation of these polyps which consisted mainly of CD3+ lymphocytes, CD68+ macrophages, and eosinophils correlated with the MF load (Fercoq et al. 2020).

Experimental studies on *Litomosoides sigmodontis* began in the 1940s with the discovery of the vector (Williams and Brown 1945) and the subsequent development of the required rearing techniques for the vector (Bertram et al. 1946; Scott et al. 1947; Hawking and Burroughs 1946). Similar to the work with *A. viteae*, the first studies in the following years focused on the basic biology of the parasite with investigations on the transmission by the vector (Freer 1953), life cycle (Williams 1948; Kershaw and Plackett 1948; Kershaw 1953), and identification of lymphatic vessels as the migratory pathway of infective larvae in the rodent host (Wenk 1967).

By the mid to late 1950s, initial immunological studies in cotton rats were able to show a degree of immunity with slower worm growth, reduced molting, and fewer adult worms in animals with prior *L. sigmodontis* infections (Scott and Macdonald 1958) and that this protection persists for >1 year even after the death of the worms from the primary infection (Macdonald and Scott 1958). Studies on the biology of the parasite, immune response to the infection, and development of new therapies have continued unabated in the following decades. Key results that helped to facilitate experimental studies include improvements to the laboratory maintenance and in particular generation of large numbers of L3 larvae via the “pelting method” (McCall 1976), dissection of mites (Nakamura et al. 1984), isolation of L3 larvae from the pleural cavity of Mongolian jirds 5 days after the infection (Hübner et al. 2009), and the validation of mice as an experimental host (Hawking and Burroughs 1946; Patra and Basu 1970; Petit et al. 1992). Mice have become the main experimental host for immunological research since the seminal paper by Petit et al. (1992) showed the susceptibility and maturation of *L. sigmodontis* in mice with a BALB/c background (Hoffmann et al. 2000; Finlay and Allen 2020). An overview about publications on *L. sigmodontis* is shown in Fig. 2.

**Key results in immunological research** include the discovery of a strong cross-reactivity between *Onchocerca volvulus* and *L. sigmodontis* antigen (Marcoullis and Gräsbeck 1976), the development of various vaccine protocols (primarily focused on attenuated L3 larvae with different adjuvants and treatment regiments) with varying degrees of success (reviewed in depth in Morris et al. 2013), IgE dependent killing of MF by neutrophils and macrophages (Mehta et al. 1980; 1982), and the significance of IL-4, IL-4R, IL-5, and IL-17 for the containment of the infection (Le Goff et al. 2000; Martin et al. 2000a, 2000b; Volkmann et al. 2001, 2003a; Taylor et al. 2006; Jenkins et al. 2011; Ritter et al. 2017, 2018a; Frohberger et al. 2019). Various studies have further shown that the protective immune responses against *L. sigmodontis* consist of both type 1 (Saefte1 et al. 2003; Muhsin et al. 2018; Babayan et al. 2003) and type 2 immune responses. With regard to granulocytes, eosinophils were shown to mediate...
protection via the major basic protein, eosinophil peroxidase, eotaxin-1 (Specht et al. 2006; Gentile et al. 2014), and eosinophil extracellular DNA traps (EETosis; Ehrens et al. 2021), which contributes to MF and adult worm clearance (Martin et al. 2000a). Neutrophils on the other hand are required for protective responses to invading infective L3 larvae and adult worms (Al-Qaoud et al. 2000; Ajendra et al. 2016; Frohberger et al. 2020; Pionnier et al. 2016). Studies on basophils during L. sigmodontis infection showed that basophil responses are suppressed during chronic infection, and basophils have no effect on the adult worm burden during primary infection (Larson et al. 2012; Torrero et al. 2010; Hartmann et al. 2018). However, basophils amplify type 2 immune responses during primary L. sigmodontis infection and support vaccine responses using irritated L3 larvae (Torrero et al. 2010, 2013).

Adaptive immune responses were also shown to be involved in protective immune responses against L. sigmodontis. Depletion of CD4+ T cells enhanced microfilaremia and L. sigmodontis adult worm recovery, while B cells and antibodies were shown to impact microfilaremia (Al-Qaoud et al. 1997; Martin et al. 2001). Studies with different B cell–deficient mouse strains have suggested a nuanced role of B cell subtypes in controlling microfilaremia as “μMT” (no mature B cells) and “B- less” mice (no immature or mature B cells) presented with equal or reduced MF numbers compared to BALB/c controls while B1 cell–deficient BALB Xid mice had an increased microfilariae load and increased adult worm burden (Al-Qaoud et al. 1998; Martin et al. 2001; Volkmann et al. 2001). The importance of T and B cells was further demonstrated in RAG2IL-2Rγ−/− deficient mice which are on the semi-resistant C57BL/6 background, but lack B, T, and NK cells. These mice are highly susceptible to L. sigmodontis infection with 100% of mice developing microfilaremia (Layland et al. 2015).

BALB/c mice which develop a patent infection show a hypo-responsive phenotype compared to C57BL/6 mice (Finlay and Allen 2020). This difference in responsiveness appears to be strongly dependent on an expansion of regulatory T cells which suppresses the immune response to L. sigmodontis (Taylor et al. 2005, 2007, 2012). Furthermore, a distinct subset of dysfunctional Th2 cells occurs during the course of infection (Knipper et al. 2019, Taylor et. al. 2005; Finlay and Allen 2020). In addition to hyporesponsive CD4+ T cells (Knipper et al. 2019; Haben et al. 2013; van der Werf et al. 2013), cytotoxic T cell responses were also shown to be inhibited during L. sigmodontis infection (Kolbaum et al. 2012; Buerfent et al. 2015). CD4+ T cell hyporesponsiveness was shown to also be mediated by the expansion of alternatively activated macrophages via the release of the immunomodulatory mediator TGFβ (Taylor et al. 2006). These alternatively activated macrophages expand locally at the site of L. sigmodontis infection (Jenkins et al. 2011) and their discovery led to a series of groundbreaking studies concerning their role in tissue repair and immunoregulation (Taylor et al. 2006; Finlay and Allen 2020). Blocking the recruitment of monocye-derived macrophages to the pleural cavity leads to an increase in T cell IL-4 production and reduced worm numbers in BALB/c mice suggesting a protective role of alternatively activated macrophages during L. sigmodontis infection (Campbell et al. 2018).

Similar to A. viteae, L. sigmodontis was shown to actively modulate the immune system of its host via cystatin (Pfaff et al. 2002). Furthermore, L. sigmodontis releases immunomodulatory small RNAs and exosomes (Buck et al. 2014; Quintana et al. 2019). This filarial immunomodulation was shown to impair vaccine responses (Haben et al. 2014; Hartmann et al. 2019), alter the course of co-infections (Hübner et al. 2012a; Gondorf et al. 2015; Dietze et al. 2016; Karadjian et al. 2014; Specht et al. 2010) and allergic sensitization (Ditrich et al. 2008), prevent the development of type 1 diabetes (Hübner et al. 2009, 2012b), and reduce diet-induced insulin resistance (Berbudi et al. 2016).

Moreover, the L. sigmodontis mouse model has been instrumental in understanding the role of Wolbachia beyond the mutualistic relationship with the parasite itself. For example, several studies showed that Toll-like and nucleotide-binding oligomerization domain (NOD)–like receptors and downstream signalling pathways are important for sensing Wolbachia, worm development, MF embryogenesis, and immunity against filariae (Pfarr et al. 2003; Brattig et al. 2004; Ajendra et al. 2016; Rodrigo et al. 2016; Wiszniewsky et al.
For a more in-depth review of immune responses to *L. sigmodontis* in mice, we refer the reader to the recent review by Finlay and Allen (2020).

Key results in the field of drug development with the *Litomosoides* model include showing the microfilaricidal efficacy of diethylcarbamazine (DEC) in cotton rats (Hewitt et al. 1947), the lack of macrofilaricidal efficacy of DEC (Hawking et al. 1950), the loss of the microfilarial sheath following DEC treatment and co-localization of neutrophils and phagocytes with remaining MFs (Hawking et al. 1950; Schardein et al. 1968), the activity of ivermectin against developing stages (Campbell 1982), the suppression of microfilaraemia by emodepside (Zahner et al. 2001), the macrofilaricidal activity of the benzimidazoles flubendazole (Zahner and Schares 1993; Hübner et al. 2019a) and oxfendazole (Hübner et al. 2020), and the development of treatment strategies against *Wolbachia* (Hoerauf et al. 1999; Specht et al. 2018).

These and other studies have been pivotal in the preclinical development of the above-mentioned drugs. DEC was tested against infections with *W. bancrofti* in humans in the same year and a significant reduction in MF was observed (Santiago-Stevenson et al. 1947). First clinical trials for onchocerciasis in humans were started in 1981 and confirmed the microfilaricidal efficacy of ivermectin for up to 1 year after treatment (Aziz et al. 1982). Flubendazole, an inhibitor of tubulin polymerization, was also tested against *O. volvulus* but presented with two major issues (Domínguez-Vazquez et al. 1983; Geary et al. 2019). Firstly, flubendazole had very limited oral bioavailability and only achieved 100% macrofilaricidal activity in parenteral formulations. Secondly, flubendazole caused abscesses at the injection site during the original trial against *O. volvulus* in humans. Even though a formulation with high bioavailability after oral treatment was eventually found, the novel formulation has the risk to cause aneuploidia and was therefore not considered for further testing in humans (Lachau-Durand et al. 2019). Oxfendazole is one of the more recent macrofilaricidal candidates. Unlike flubendazole, oxfendazole has a high macrofilaricidal efficacy after oral administration against *L. sigmodontis* in BALB/c mice (Hübner et al. 2020). In addition, results from a phase I ascending dose study in humans showed that oxfendazole was well tolerated and caused no major side effects in relevant dosages (Bach et al. 2020).

As discussed earlier, rodent models have been instrumental in discovering the significance of *Wolbachia* in filariae and discovering antibiotics as novel therapeutic approaches and safe macrofilaricidal drugs for human pathogenic filariae. The current recommendations for doxycycline therapy for onchocerciasis and lymphatic filariasis are daily oral treatments for 4 to 6 weeks to achieve macrofilaricidal efficacy (Debrah et al. 2015; Klarmann et al. 2012; WHO 2019). Daily treatments with antibiotics for 4 to 6 weeks are not feasible for MDA and miss the target product profile (TPP) for novel (macrofilaricidal) drugs for onchocerciasis as defined by the Drugs for Neglected Diseases initiative (DNDi) and Bill & Melinda Gates Foundation. Therefore, *in vitro* screenings in *Wolbachia* insect cell lines and testing in animal models have been used to identify improved drugs (Clare et al. 2019; Bakowski and McNamara 2019). Studies with the *L. sigmodontis* rodent model identified and validated rifampicin (Volkmann et al. 2003b), ABBV-4083 (Taylor et al. 2019; Hübner et al. 2019b), corallopyronin A (Schiefer et al. 2012; Schiefer et al. 2020), and AWZ1066S (Hong et al. 2019) as promising novel anti-*Wolbachia* compounds (an overview of the current drugs and candidates and their mode of action is given in Table 1). Rifampicin belongs to the class of rifamycins and targets the bacterial DNA-dependent RNA-polymerase (McClure and Cech 1978). ABBV-4083 is an analogue of TylosinA which was designed to improve the bioavailability of TylosinA after oral treatment (von Geldern et al. 2019). Corallopyronin A was isolated from the myxobacterium *Coralloccocus coralloides* and inhibits the bacterial DNA-dependent RNA-polymerase (Schaberle et al. 2015). AWZ1066S is an azaquainozine that is highly specific and effective against *Wolbachia* (Hong et al. 2019).

Corallopyronin A and AWZ1066S are in preclinical development (with phase I studies in preparation) while ABBV-4083 has already completed phase I trials (Alami et al. 2019; von Geldern et al. 2019). In contrast, Rifampicin was already evaluated in a clinical study in Ghana in the early 2000s (Specht et al. 2008). The treatment failed to show a sufficient reduction in *Wolbachia* numbers, but this has been attributed to a suboptimal dose in humans (Aljayyoussi et al. 2017). Later studies with other rodent models, i.e., experimental infection of *M. unguiculatus* with *B. malayi* and implantation of *O. ochengi* in CB.17 SCID mice, showed that a shorter, high dose regimen has a higher speed of action than doxycycline, achieves >90% *Wolbachia* reduction, and is not expected to lead to increased toxicity compared to low dose rifampicin (Aljayyoussi et al. 2017; Velásquez et al. 2018). As such, treatment with high dose rifampicin for <2 weeks may be sufficient to achieve macrofilaricidal efficacy against the causative agents of lymphatic filariasis in humans (Aljayyoussi et al. 2017).

**Current trends and developments**

There have been a number of exciting developments in our field in the last decade. The search for novel treatment strategies has yielded a variety of drug candidates that may achieve safe, macrofilaricidal activity against human pathogenic filariae. ABBV-4083 (von Geldern et al. 2019; Taylor et al. 2019), emodepside (Kulke et al. 2017), and oxfendazole (Hübner et al. 2020; Bach et al. 2020) have already completed phase I clinical trials and phase II studies are in preparation (DNDi 2020). Corallopyronin A (Schiefer et al. 2020) and AWZ1066S (Hong et al. 2019) are in preclinical development and have so far shown promising results. Phase I studies for these candidates...
| Name          | Mode of action                        | Status                                                                 | Effect                                | Class          | Clinical trials [ID]                  | Source                     |
|---------------|---------------------------------------|------------------------------------------------------------------------|---------------------------------------|----------------|---------------------------------------|----------------------------|
| Doxycycline   | Binds 30S ribosomal subunit, inhibition of protein synthesis | Used in individual therapy for onchocerciasis and lymphatic filariasis | Wolbachia depletion/-macrofilaricide  | Tetrazycline   | ISRCTN65756724 [LF] ISRCTN14042737 [LF] ISRCTN06010453 [Oncho] ISRCTN68861628 [Oncho] ISRCTN71141922 [Oncho] | Klarman-Schulz et al. 2017 Taylor et al. 2010 Debrah et al. 2007 Debrah et al. 2015 |
| Rifampicin    | Binds DNA-dependent RNA-polymerase, inhibition of translation | Phase II clinical studies with the standard low dose have been performed. High dose clinical studies are scheduled. | Wolbachia depletion/potential macrofilaricide | Rifamycin      | ISRCTN68861628 [Oncho] ISRCTN5216778 [LF] | Aljayoussi et al. 2017 |
| ABBV-4083     | Binds 50S ribosomal subunit, inhibition of protein synthesis | Phase I clinical studies completed. Phase II clinical studies under preparation. | Wolbachia depletion/potential macrofilaricide | Macrolide      | Taylor et al. 2019                   | Hong et al. 2019           |
| AWZ-1066S     | Inhibits protein synthesis             | Under preparation for phase 1 clinical studies                         | Wolbachia depletion/potential macrofilaricide | Azaquinazoline | Jacobs et al. 2019                    |                                    |
| AN11251       | Binds 50S ribosomal subunit, inhibition of protein synthesis | Backup clinical candidate                                              | Wolbachia depletion/potential macrofilaricide | Pleuromutilin  |                                    | Schiefer et al. 2019        |
| Coralpyronin A| Inhibits DNA-dependent RNA-polymerase  | under preparation for phase 1 clinical studies                         | Wolbachia depletion/potential macrofilaricide | α-Pyrole       | Schiefer et al. 2020                  | Macfarlane et al. 2019      |
| Ivermectin (IVM) | Interferes with ligand-gated chloride channels | Used against onchocerciasis and lymphatic filariasis as mass drug administrations. | Microfilaricide | Avermectin | ISRCTN50035143 [Oncho] | Richard-Lenoble et al. 2003 Laing et al. 2017 |
| Moxidectin    | Exact mode of action is unknown         | Potential alternative to ivermectin for mass drug administrations       | Microfilaricide | Milbemycine | ISRCTN50035143 [Oncho] | Milton et al. 2020 Opoku et al. 2018 |
| Diethylcarbamazine (DEC) | Alters metabolism of arachidonic acid | Used against lymphatic filariasis as part of mass drug administrations. Contraindicated in onchocerciasis patients | Microfilaricide | Piperazines | ISRCTN76875372 [Oncho] | Maizels and Denham 1992 |
| Albendazole   | Inhibits tubulin polymerization         | Used against lymphatic filariasis as part of mass drug administrations; used in conjunction with diethylcarbamazine and/or ivermectin | May improve microfilaricidal efficacy of IVM/DEC | Benzimidazole  | ISRCTN50035143 [Oncho] ISRCTN06010453 [Oncho] ISRCTN25831558 [Loiasis] ISRCTN56578422 [LF] | Geary et al. 2019 |
| Flubendazole  |                                        |                                                                        | Potential macrofilaricide             | Benzimidazole  |                             |                            |
are in preparation. Although *in vitro* culture models for human filariae have been developed (Tippawangkosol et al. 2002; Falcone et al. 1995; Njouendou et al. 2017, 2018, 2019; Zofou et al. 2018; Fombad et al. 2019; Voronin et al. 2019), until now it is not possible to mimic the parasite biology in the human host and obtain all life stages, especially reproductive adult worms, *in vitro*. Therefore, *in vivo* models of filariasis are urgently needed for the investigation of the parasite’s biology, immunomodulatory capacity, and development of novel treatment strategies and anti-filarial drugs. Indeed, artificial human filarial infections in animal models, e.g., *B. malayi* in BALB/c SCID mice and *O. volvulus* in NSG mice (Duke 1957; Trees 1992; Lawrence et al. 1994; Patton et al. 2018; Halliday et al. 2014), have been established and recent studies showed that distinct mouse models, especially the RAG2IL-2Rγ-deficient mice, might be suitable to answer unresolved questions about human filarial infections and open up new avenues to develop, test, and validate novel treatment strategies against filariae (Fombad et al. 2019; Pionnier et al. 2019; Chunda et al. 2020). However, those results are limited since no complete life cycle of human filariae could be established *in vivo* until now and drug efficacy may be impaired in immunocompromised animals. Thus, further research on animal models is required that improves our testing of novel treatment strategies in preclinical studies and would allow the access of all parasite life stages, which is until now a critical issue also in regards to ethical concerns.

To summarize, rodent models for human filarial diseases have been studied for over 70 years and have been instrumental in uncovering basic biological properties of filariae, understanding immune responses to and immunomodulation by nematodes as well as developing novel therapies. While rodent models have been influential and successful, it is nonetheless important for researches to remember the limitations of model infections. Thus, additional validations with different model parasites or hosts are important factors in effective preclinical development.

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