Trends in Parasitology

CellPress

Review

25 Years of the *Onchocerca ochengi* Model

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Although of limited veterinary significance, *Onchocerca ochengi* has become famous as a natural model or 'analogue' of human onchocerciasis (river blindness), which is caused by *Onchocerca volvulus*. On the basis of both morphological and molecular criteria, *O. ochengi* is the closest extant relative of *O. volvulus* and shares several key natural history traits with the human pathogen. These include exploitation of the same group of insect vectors (blackflies of the *Simulium damnosum* complex) and formation of collagenous nodules with a similar histological structure to human nodules. Here, we review the contribution of this natural system to drug and vaccine discovery efforts, as well as to our basic biological understanding of *Onchocerca* spp., over the past quarter-century.

History and Basic Biology

In 1992, *Parasitology Today* published an article by Alexander (Sandy) Trees entitled '*Onchocerca ochengi*: Mimic, Model or Modulator of *O. volvulus*?' that introduced a relatively obscure filarial species to a wider audience [1]. In our view, the intervening two-and-a-half decades have clearly demonstrated that *Onchocerca ochengi* has lived up to its initial promise and fulfilled its potential as a superlative natural system for the study of onchocerciasis.

O. ochengi was first described by Bwangamoi [2] from bovine skins collected from an abattoir in Uganda. The nodules were reported to damage hides at several locations across East Africa and reduce their market value (the sole veterinary impact of this disease) [3]. Interestingly, this effect on the leather reflected one of the few significant biological differences between *O. ochengi* and *Onchocerca volvulus:* adults of the former are located in intradermal nodules, whereas human *O. volvulus* nodules are usually subcutaneous. Several years later, Bussieras *et al*. [4] described a similar *Onchocerca* spp. from cattle in Togo that had shorter **microfilariae** (see Glossary), which was named *Onchocerca dermata.* Subsequent investigations by Bain *et al*. [5] determined that Bwangamoi had published incorrect measurements for *O. ochengi* microfilariae and, thus, *O. dermata* was abandoned as a junior synonym of *O. ochengi*.

For over a decade, *O. ochengi* was neglected for onchocerciasis research in favour of other bovine *Onchocerca* species from temperate regions, such as *Onchocerca gibsoni* and *Onchocerca lienalis*. However, as entomological monitoring to assess the efficacy of onchocerciasis control came to the fore during the late 1980s, the potential for larvae of bovine *Onchocerca* spp. in blackflies to complicate the calculation of transmission potentials was recognised. This drew increasing attention to *O. ochengi*, because it is challenging to discriminate between the **L3** of this species and that of *O. volvulus* without recourse to molecular assays [6–8].

During the early 1990s, the remarkable parallels between the natural history of *O. ochengi* and *O. volvulus* began to attract more international interest and, through collaborations between the Liverpool School of Tropical Medicine, Eberhard Karls University (Tübingen), and veterinary

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The *Onchocerca ochengi* system has consistently shown that strong, albeit incomplete, natural immunity exists in cattle and that partial protection can be induced by both irradiated and recombinant vaccines.

In accordance with human data, the *O. ochengi* system has demonstrated that *Wolbachia* induce a profound local neutrophilia within nodules. Recent proteomic data obtained from nodule fluid showed that adult worms are 'bathed' in liberated neutrophil granule contents, especially antimicrobial proteins.

The *Wolbachia* endosymbiont of *O. ochengi* has a highly reduced genome that can produce few vitamins and cofactors, although it may generate energy in the form of ATP for its host. The most abundant *Wolbachia* proteins induce neutrophil activation and chemokinesis.

Small RNAs with diagnostic potential are released by *Onchocerca* spp. into nodule fluid and human (and bovine) blood.

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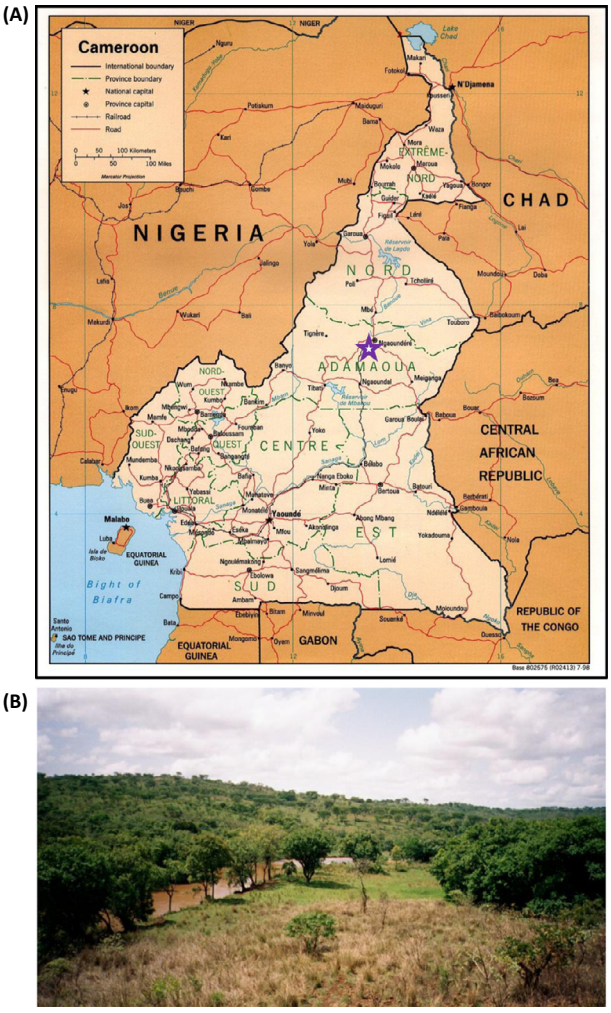

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Figure 1. Key Field Site for *Onchocerca ochengi* Research under Natural Conditions. (A) Location of the field site (purple star) on the Adamawa Plateau of northern Cameroon. (B) The River Vina du Sud near Ngaoundéré, where the main vector for *Onchocerca ochengi* in the region, *Simulium squamosum* [13,81], breeds in high densities.

Glossary

Aposymbiotic: lacking symbiotic relations in the natural state.
Embryostatic: an outcome of drug or vaccine action defined by the cessation of embryonic development in the female reproductive tract.
L3: the third-stage infective larva.
Macrofilaricidal: capable of killing adult filarial worms.
Microfilariae: the highly motile, transmissible first-stage larvae of filarial nematodes, which are born live and accumulate in either the skin or the blood depending on the species.
Microfilaridermia: the presence of microfilariae in the skin.
Synteny: conservation of blocks of gene order between different chromosomes.
Zooprophylaxis: reduced disease transmission to humans due to the diluting effect of animal populations.

researchers from Cameroon, *O. ochengi* eventually supplanted the other bovine *Onchocerca* spp. as the model of choice for chemotherapeutic and immunological investigations. Almost everything we know about *O. ochengi* in cattle has been derived from data collected at a single field site adjacent to the River Vina du Sud, a blackfly-breeding site located near the town of Ngaoundéré in the Adamawa Region of Cameroon (Figure 1). The first experiment in naturally infected cattle examined the relation between nodule load and microfilarial density in animals of different ages, exploiting the accessibility of the nodules, which are easily numerated by palpation and can be removed surgically under local anaesthesia. This study suggested that immunity to microfilariae, but not adult worms, develops in older animals [9]. Other aspects of the natural history of *O. ochengi* in its natural host were rapidly established, such as the pre-patent period for microfilarial appearance in the skin (a minimum of 10 months) and their predilection site (the posterior ventral region) in comparison with other bovine *Onchocerca* spp. found in Cameroon [10,11]. Subsequently, longer-term experiments were conducted that revealed fascinating patterns of differential susceptibility to infection among cattle, with bulls exhibiting