

# Characterization of nuclear receptors from parasitic nematodes to overcome anti-infectious drug resistance.

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## Abstract

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Resistance to ivermectin (IVM), the most important broad-spectrum antiparasitic drug in use today, is widespread in parasites to the extent that it compromises successful control of human and animal parasites. New therapeutics are urgently needed to overcome resistance to actual treatments. Two nuclear hormone receptors NHR-8 and DAF-12, of parasitic nematodes play key roles in lipid metabolism, reproduction and longevity of worms as well as in drug detoxification<sup>1</sup>. Due to their central role in development of nematodes and in IVM resistance<sup>2</sup>, NHR-8 and DAF-12 are potential therapeutic targets to fight parasitic diseases. However, their mechanism of action needs to be deciphered. Using X-ray crystallography and biophysical characterization (Thermal Shift Assay, Isothermal Titration Calorimetry, fluorescence anisotropy assays, native mass spectrometry), new structural information about ligand and transcriptional coregulators binding are acquired and allow a better understanding of NHR-8 and DAF-12 biological functions. In addition, a number of ligands of interest are currently selected to validate their action in cellular assays in order to orient the design of DAF-12 and NHR-8 inhibitors.

(1) Wang, Z.; Schaffer, N. E.; Kliewer, S. A.; Mangelsdorf, D. J. Nuclear Receptors: Emerging Drug Targets for Parasitic Diseases. *J. Clin. Invest.* 2017, 127 (4), 1165–1171. <https://doi.org/10.1172/JCI88890>.

(2) Ménez, C.; Alberich, M.; Courtot, E.; Guegnard, F.; Blanchard, A.; Aguilaniu, H.; Lespine, A. The Transcription Factor NHR-8: A New Target to Increase Ivermectin Efficacy in Nematodes. *PLOS Pathog.* 2019, 15 (2), e1007598. <https://doi.org/10.1371/journal.ppat.1007598>.