

## Drs. Mavragani and Moutsopoulos reply

To the Editor:

We were delighted to read the letter by Killian, *et al*, which challenges the use of the terms *primary* and *secondary* human Sjögren syndrome (SS) even in experimental animal models of SS<sup>1</sup>. These terms were coined almost 40 years ago on the basis of a study that revealed clinical, immunologic, and genetic differences among patients expressing sicca manifestations alone and patients with rheumatoid arthritis (RA) and SS. Despite the lack of appropriate studies, the rheumatology community expanded the term *secondary* SS to include all patients with autoimmune disorders who expressed sicca manifestations. Of note, subsequent reports on patients with systemic lupus erythematosus (SLE) or scleroderma and sicca features did not confirm observations similar to those seen in RA with sicca complaints<sup>2</sup>.

The MRL/MpJ mouse is an autoimmune strain that develops lacrimal and salivary gland inflammation (dacryoadenitis and sialadenitis) and has been long considered a model for human SS. Two main substrains of MRL/MpJ mice are recognized: the MRL/MpJ-Fas+/Fas+ (MRL/+) and the MRL/MpJ-Faslpr/Faslpr (MRL/lpr). In the latter model, defective Fas mediated apoptosis of lymphocytes in peripheral lymphoid organs occurs as a result of a Fas ligand mutation, and systemic autoimmune disease develops with a wide range of manifestations [e.g., arthritis, glomerulonephritis, vasculitis central nervous system (CNS)/peripheral NS (PNS) inflammation, or massive lymphadenopathy]. In addition to dacryoadenitis and sialadenitis, both strains developed antinuclear antibodies, with the MRL/lpr mice displaying also autoantibodies against Ro/SSA and La/SSB autoantigens<sup>3,4</sup>.

With this in mind, SS experimental animal models sharing features related to both glandular (diminished salivary and lacrimal secretions) and extraglandular involvement reminiscent of those seen in SLE (e.g., glomerulonephritis, CNS/PNS inflammation) could be erroneously classified as models of “secondary” SS and therefore characterized as “inadequate” for studies investigating the potential efficacy of novel targeted therapies for primary SS<sup>1</sup>. However, it should be emphasized that these immunological treatment approaches are indeed expected to be effective in SS patients with systemic extraglandular manifestations and excessive immune activation rather than those with local inflammation confined to salivary glands. Moreover, it is worth mentioning that though glomerular involvement is considered mainly an SLE-related rather than an SS-related feature, earlier and more recent works documented the presence of membranoproliferative and membranous glomerulonephritis in patients with “primary” SS<sup>5,6</sup>. These patients were characterized by the presence of mixed monoclonal cryoglobulins and kidney immunopathology revealing predominant tissue deposition of IgM<sup>5</sup>. Peripheral neuropathy is another well-known manifestation of primary SS<sup>7</sup>, which together with glomerulonephritis, lymphadenopathy, and autoantibodies against Ro/SSA and La/SSB autoantigens, among other manifestations, has been shown to be highly predictive for lymphoma development in these patients<sup>8,9</sup>. The MRL/MpJ experimental animal model is an excellent model for the evaluation of therapeutic modalities because in addition to sicca manifestations, the model expresses extensive lymphopro-

liferation affecting parenchymal organs<sup>3</sup>. Unfortunately, at present, management of SS is mainly limited to secretagogues and excretion replacement, while immunosuppressive agents are efficacious neither for alleviation of SS features nor for the prevention of disease progression<sup>10</sup>.

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