

# Mouse Models of Alopecia Areata: C3H/HeJ Mice Versus the Humanized AA Mouse Model



Amos Gilhar<sup>1</sup>, Rimma Laufer Britva<sup>1</sup>, Aviad Keren<sup>1</sup> and Ralf Paus<sup>2,3,4</sup>

The C3H/HeJ model has long dominated basic alopecia areata (AA) in vivo research and has been used as proof-of-principle that Jak inhibitors are suitable agents for AA management in vivo. However, its histologic features are not typical of human AA, and it is questionable whether it is sufficiently clinically predictive for evaluating the therapeutic effects of candidate AA agents. Instead, the humanized mouse model of AA has been used to functionally demonstrate the role of key immune cells in AA pathogenesis and to discover human-specific pharmacologic targets in AA management. Therefore, we advocate the use of both models in future preclinical AA research.

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## INTRODUCTION

The mainstream autoimmunity research community has been slow to recognize and acknowledge that the hair loss disorder, alopecia areata (AA), is one of the most common human autoimmune diseases (Gilhar et al., 2012; McElwee et al., 2013), exceeded in incidence and prevalence only by type 1 diabetes mellitus and rheumatoid arthritis. The clinical and psychosocial importance of this disease is notoriously underestimated because AA is neither life-threatening nor recognized to be life-shortening or physically crippling. However, patients affected by AA, namely by its maximal variants, alopecia totalis or universalis, often experience AA as a psychologically devastating illness, whose burden of disease is very substantial (Gilhar et al., 2012; Matzer et al., 2011; Monselise et al., 2013). This finding is aggravated by the fact that there is neither fully satisfactory, universally effective therapy available for the established disease, nor convincing management strategies for the reliable prevention of AA progression (Harries et al., 2010; Paus et al., 2018).

<sup>1</sup>Skin Research Laboratory, Rappaport Faculty of Medicine, Technion - Israel Institute of Technology, Haifa, Israel; <sup>2</sup>Department of Dermatology & Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, Florida, USA; <sup>3</sup>Centre for Dermatology Research, University of Manchester, and NIHR Biomedical Research Centre, Manchester, United Kingdom; and <sup>4</sup>Monasterium Laboratory Skin & Hair Research Solutions GmbH, Muenster, Germany

Correspondence: Amos Gilhar, Laboratory for Skin Research, Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel. E-mail: doritg2000@gmail.com or gilhar@technion.ac.il

Abbreviation: AA, alopecia areata

These facts alone call for clinically relevant AA research models, in which the as yet insufficiently understood pathobiology of AA can be systematically and mechanistically dissected and in which new AA treatment and prevention strategies can be explored in vivo at the preclinical level, ideally with good predictive value for the outcomes that can realistically be expected in patients with AA. Mouse models have provided invaluable research tools for dissecting the roles of extrinsic and intrinsic factors and various underlying immune pathologies in various autoimmune skin diseases (Yu et al., 2015; Yu and Petersen, 2018). Lessons that have been learned from mouse models for psoriasis (Jin et al., 2018; Mykicki et al., 2017; Nakajima and Sano, 2018), atopic dermatitis (Lin et al., 2018; Nakajima et al., 2019; Yamada et al., 2018), and vitiligo (Riding et al., 2019) have greatly advanced our understanding of disease pathogenesis and for exploring novel therapeutic strategies at the preclinical level.

According to the literature, there are at least 20 models for psoriasis, 19 for atopic dermatitis, and 11 for vitiligo but only three for AA. Because one of the latter, that is, the Dundee experimental balding rat model (McElwee et al., 1999, 1995), is no longer available, this has left us with just two in vivo models of AA: the most widely used murine AA model that has long dominated preclinical AA in vivo research, that is, aging C3H/HeJ mice (Dai et al., 2016; de Jong, et al., 2018; Shin et al., 2018; Sundberg et al., 1995; 1994), in which spontaneously developing AA-like lesions can be studied, and the humanized AA mouse model (Gilhar et al., 2016, 2013a).

The C3H/HeJ mouse model has produced many novel results with important implications for human AA by accessing the powerful tools of mouse genetics (de Jong et al., 2018) and has helped to identify candidate autoantigens (Wang et al., 2016) and novel treatment strategies (Dai et al., 2016; Jalili et al., 2018; Xing et al., 2014). It also provided insight into the role that could be played by psychoemotional stressors and associated neuropeptides in AA pathogenesis (Paus and Arck, 2009; Peters et al., 2007; Siebenhaar et al., 2007; Zhang et al., 2009) and has confirmed the key role of IFN- $\gamma$  in AA pathogenesis (Freyschmidt-Paul et al., 2006; Ito et al., 2004). Advanced variations of this model that accelerate the development of AA by transplanting lesional skin from older mice to young ones (McElwee et al., 1998) or that transfer draining lymph node-derived cells from affected older to as yet unaffected young C3H/HeJ cells (Wang et al., 2015) have further facilitated the use of this murine AA model.

The C3H/HeJ mouse model was also used to identify key immune cell and molecular principles in murine AA and proof-of-principle that Jak inhibitors are suitable agents for

**Table 1. Differences between C3H/HeJ and Humanized AA Mouse Model**

Typical Properties	C3H/HeJ Mice <sup>a</sup>	Humanized AA Mouse Model
Ease of use	Basic surgical skills	Advanced surgical skills
Cost	Relatively low	Relatively high
Convenience	Good	Difficult to find donors willing to provide both scalp skin and blood
Grooming-induced hair loss	Present	Absent
Predictiveness	Unclear	Good
Disadvantages	<ol style="list-style-type: none"> <li>1. The histologic feature is not characteristic to human AA</li> <li>2. Absence of MICA, a recognized pathogenic key NKG2D ligand in human AA</li> <li>3. Mouse-specific hair follicle immunopathology</li> </ol>	<ol style="list-style-type: none"> <li>1. Need specific conditions</li> <li>2. Lack of genetic background</li> <li>3. Small area of scalp skin xenotransplants</li> </ol>
Advantages	Can easily be employed as first stage assay for in vivo candidate drug testing, even though a negative outcome may not be predictive	<ol style="list-style-type: none"> <li>1. The histologic feature is characteristic to human AA</li> <li>2. Mimics human AA more closely than any other animal model, good predictive power</li> </ol>

Abbreviation: AA, alopecia areata.

<sup>a</sup>Skin graft-induced hair loss variant (McElwee et al., 1998).

AA management in vivo because both IFN-γ and IL-15 signal through the Jak pathway, thus rendering Jak inhibitor therapy a highly promising intervention strategy in AA management (Phan and Sebaratnam, 2019; Wang et al., 2018; Xing et al., 2014). However, their potential adverse effects deserve to be more rigorously contemplated and evaluated, especially when Jak inhibitors are systemically administered long-term to children (Gilhar et al., 2019).

Despite its undisputed usefulness for and major contributions to preclinical AA research, the C3H/HeJ mouse model carries several important disadvantages that are often ignored, yet must be kept in mind (Table 1). These include a major constitutive toll-like receptor signaling defect (Kamath et al., 2005; Sundberg et al., 1994) that is absent in patients with AA and alopecic lesions induced itch-related grooming behavior-induced (Sundberg et al., 1994; King et al., 2014). A key disease-promoting “danger” signal in AA pathobiology, the NKG2D agonistic ligand, MICA (Ito et al., 2008; Li et al., 2016; Petukhova et al., 2010), is strikingly absent in mice (the murine homolog protein has only 27% amino acid identity with human MICA) (Sundberg et al., 1994). Moreover, the histologic features are not typical for human AA (McElwee et al., 1998; Sundberg et al., 1994) because in the murine AA-like phenotype, the inflammatory cell infiltrate extends to the distal follicle between the hair bulb and sebaceous gland, sometimes reaching the bulge, whereas human AA is characterized by a largely peribulbar lymphocytic infiltrate (Sundberg et al., 1994; King et al., 2014). In addition, these mice cannot serve as a valid model for evaluating therapeutic effects of selected immunoinhibitory agents of interest in AA, such as Kv1.3 blockers because the K<sup>+</sup> channel expression pattern of mouse T cells is different from that of human T cells (Beeton et al., 2006). It has been argued that, given the major differences between the immune systems of mice and

humans (Zschaler et al., 2014), spontaneous models of autoimmunity that arise in mice do not satisfactorily recapitulate the human condition and thus make the development of new therapeutic strategies that will also work in the human system particularly challenging (Walsh et al., 2017). Unsurprisingly, there is growing concern that laboratory mice do not reflect relevant aspects of the human immune system, which may account for failures to translate disease treatments (Beura et al., 2016).

Furthermore, the major differences between nonconventional T cells populations in humans and mice must be taken into account when using mice as preclinical models of human disease (Zschaler et al., 2014). For example, there are several distinct subsets of γδ T cells in mice and humans, but mouse and human subsets have notably different TCR use, antigen reactivity, and patterns of tissue homing (Godfrey et al., 2015). Buscher et al. (2017) demonstrated that mouse models failed to account for the natural diversity in human immune responses, and as a result, insights gained in the laboratory may be lost in translation.

Therefore, it constituted an important advance in the field when lesional human skin from patients with AA was successfully transplanted onto SCID mice (Gilhar et al., 2002, 2001, 1998). This advance permitted one, for the first time, to study and experimentally manipulate the AA-affected human target organ directly in a preclinical in vivo setting. Moreover, this model confirmed the proposed key role of CD8<sup>+</sup> T cells and anagen hair follicle-derived autoantigens in AA (Paus et al., 2018; 1993) and the importance of CD4<sup>+</sup> T cell help for developing a maximal AA phenotype (Gilhar et al., 2003; 2002). However, this model has not been adopted by the field because it is too unpractical as it requires the availability of substantial amounts of diseased human scalp skin from patients with AA as well as autologous,

intracutaneous T cell populations from lesional skin (Gilhar et al., 1998).

Therefore, a more practical “humanized” mouse model of AA with a wider range of applications had been developed. Helpful leads for this came from the previous observation that the intracutaneous injection of PBMCs enriched in cell populations that express NK cell markers into split-thickness transplants of healthy human corporeal skin onto beige SCID mice (which lack T, B, and have a low level of NK cells [Thomsen et al., 2008] suffices to induce psoriasis [Bracke et al., 2014; Guerrero-Aspizua et al., 2010; Nickoloff, 1999; Nousbeck et al., 2011]).

In the new model, AA-like hair loss lesions are induced in normal, full-thickness human scalp skin transplanted onto SCID beige mice by injecting autologous PBMCs enriched for NKG2D<sup>+</sup>/CD56<sup>+</sup> cells treated stimulated with IL-2 (Gilhar et al., 2013a, 2013b). Given that PBMCs from the same patient are used who has donated the scalp skin xenotransplants, a graft-versus-host scenario, which would anyway not generate an AA phenotype but permanent, cicatricial alopecia, is avoided (Gilhar et al., 2016).

Using this model permits one to circumvent many of the disadvantages of the C3H/HeJ AA model, as they do not apply to the humanized one (Table 1). This model should encourage investigators to widely use the humanized AA model, for example, as a second step after initial screening experiments in C3H/HeJ mice, to optimize preclinical AA in vivo research and its predictive power for clinical outcomes. Moreover, this in vivo model should facilitate at least initial progress in the long-overdue challenge to dissect which role human hair follicles and their immune privilege actually play in the establishment, maintenance, and collapse of peripheral autoantigens (Oelert et al., 2017).

By using the humanized AA mouse model, it has been elucidated that AA pathogenesis in human skin is also affected by unconventional T cell subtypes such as NKT, iNKT10, ILC1,  $\gamma/\delta$ -T, and  $\gamma/\delta$ -regulatory T cells, whose numbers are significantly increased in AA compared with healthy human skin (Ghraieb et al., 2018; Kaufman et al., 2010; Laufer Britva et al., 2019), whose likely role in AA pathobiology had previously escaped murine AA research. Because the experiments demonstrated that nonconventional T cells might play a role in human AA (Ghraieb et al., 2018; Laufer Britva et al., 2019), they suggest that targeting these immunocytes offers new opportunities for innovative therapeutic intervention. The humanized mouse model has been used to discover human-specific pharmacologic targets such as the potassium channel Kv1.3 (Gilhar et al., 2013). In addition, the model demonstrated both preventive and therapeutic effects of  $\alpha$ -galactosylceramide, which stimulates IL-10 production by iNKT cells and their expansion (Ghraieb et al., 2018), thus introducing a promising a new candidate treatment strategy into translational AA research. Finally, in vivo results in the humanized AA mouse model elegantly recapitulate the reported differential clinical trial results in patients with AA with the Jak inhibitor, tofacitinib versus the phosphodiesterase type 4 inhibitor, apremilast (Liu et al., 2018; Mikhaylov et al., 2019): just as in patients with AA, poor therapeutic effects were seen in the humanized AA

mouse model with apremilast, contrasted by a strong therapeutic effect of tofacitinib (Gilhar et al., unpublished data).

## CONCLUSION

In summary, we advocate making it a routine practice in future preclinical AA research to use both the C3H/HeJ (e.g., for screening purposes) and the humanized AA model as perfectly complementary investigation tools and to test new candidate AA therapeutics also in the humanized AA model before entering into clinical trials.

## ORCIDs

Amos Gilhar: <http://orcid.org/0000-0002-4267-2986>  
Rimma Laufer Britva: <http://orcid.org/0000-0001-7202-8254>  
Aviad Keren: <http://orcid.org/0000-0002-6204-5007>  
Ralf Paus: <http://orcid.org/0000-0002-3492-9358>

## CONFLICT OF INTEREST

RP is the founder & CEO of a CRO (Monasterium Laboratory GmbH; <https://www.monasteriumlab.com>) that is involved in research on the humanized alopecia areata model described here. The remaining authors state no conflict of interest.

## AUTHOR CONTRIBUTIONS

Conceptualization: AG; Supervision: AG; Writing: AG and RP; Data curation: AK and RLB; Visualization: AK and RLB

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