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What is This?
Mouse Models of Otitis Media: Strengths and Limitations

Mahmood Fazal Bhutta, MRCS, DOHNS¹,²

Abstract
There has been a rapid rise in the use of the mouse to investigate pathobiology of otitis media. This is for good reason, including easy husbandry, but also capacity for genetic manipulation of the mouse. Insights into human disease have been gleaning from mouse models, but there are limitations of the mouse-to-man approach. First, important differences exist between mouse and man, particularly in immune function. Second, functional equivalence of genes in the two species is not ensured. Third, laboratory mice of a uniform genetic background and environment are an inadequate model of the plethora of factors affecting complex disease in humans. Finally, gene function in mouse models is often obliterated using gene knockout technology, but this is a poor mimic of normal gene variation in man. These drawbacks of the mouse may in the future limit its usefulness in otitis media research.

Keywords
otitis media, mouse

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Limitations

Although there has been recent great enthusiasm for the mouse model in the field of OM, the limits of this model have not been enunciated. There are caveats to the mouse-to-man approach, some generic and some specific to OM (Table 1).

The first caveat is that although man and mouse are similar in structure and function, there are some important differences. Mouse and man evolved from a common ancestor 65 to 75 million years ago and have been subject to divergent evolutionary pressures, amplified by species differences in ecology and life span. This is pronounced for immune function,7 which reflects the prominence of infectious disease as a driver of evolution. For example, blood in man is neutrophil rich, whereas that of mouse is lymphocyte rich. Man has a ring of nasal-associated lymphoid tissue (NALT) aggregations at the pharyngeal inlet (most prominent at the nasopharyngeal tonsil or adenoid), whereas in mice, NALT aggregations are restricted to the opening of the Eustachian tube.8 Some mucins expressed in human middle ear mucosa are not expressed in mouse.9 Microbiota have coevolved with their hosts, and so pathogens are eutrophic: the human middle ear pathogens *Stereptococcus pneumoniae* and nontypeable *Haemophilus influenzae* are not known to cause OM in mouse other than under experimentally induced conditions, whereas *Moraxella catarhalis* is cleared rapidly from the mouse middle ear.

Differences of the immune system may also be important. Hominids, including man, have a complex posterior extension of the middle ear cleft in the form of a mastoid air cell system, rather than the simple bulla found in most mammals (Figure 2). A small mastoid volume is associated with OM in man (perhaps because chronic or recurrent inflammation disrupts growth), but bulla shape has not been correlated with OM susceptibility in mouse. The overall impact on disease susceptibility arising as a result of species differences in immune or nonimmune structure and function is not known, but such interspecies immune differences have been considered important in other inflammatory disorders, fuelling the development of humanized mice.

The second caveat is that even if mouse and man share genes, the functional equivalence of these genes cannot be assumed. There may be alternate splicing of genes between mouse and man, or these genes may have assumed new roles in the course of evolution. For example, mutation at the genes *STAT3* or *ELA2* increases susceptibility to acute OM in man, yet corresponding mouse models demonstrate no immune dysregulation. Similarly, monosomy X (Turner syndrome) is associated with recurrent acute OM, but in the mouse model, phenotypic effects are mild with no OM reported. Mutation at genetic loci causing primary ciliary dyskinesia often leads to chronic middle ear effusion in man, but knockout mouse models show embryonic or early lethality.

The third caveat is that although mice have been used to identify highly penetrant loci underlying many single-gene disorders, they have proven less successful for analysis of complex traits, where multiple factors determine risk of disease. Contemporary genetic mapping techniques necessitate that mice are inbred (genetically identical except for the mutation of interest) and housed in a controlled and pathogen-free environment. This is clearly a deficient representation of the multitude of genetic and environmental
factors affecting OM. Almost by definition, any single factor that leads to the onset of disease in such mice will be more severe than the small effect of a single variant leading to disease in man. The relevance of genetic and environmental homogeneity of mouse models is further questioned by the sometimes profound effects on disease that can result from modification of these variables. For example, both the Jeff and Junbo mouse models of chronic OM develop disease at an earlier stage and with greater severity if caged in conventional rather than specific pathogen-free facilities. Genetic background can also modify disease: the Hush Puppy10 and Jeff4 mutations frequently lead to chronic OM in a C3He strain of mouse, but disease is rarely seen with the same mutations carried on a C57/BL6 strain. Conversely, the Junbo5 mutation causes more severe disease in the C57/BL6 strain than in C3He.

The final caveat to the use of the mouse is that although the toolkit to manipulate mouse genetics has proven valuable, it is still a poor mimic of the genetic variations underlying common heritable disease. In particular, the gene knockout approach produces total loss of function of a gene rather than a change in function. Many knockout models of OM display a plethora of anatomic and functional deficits as well as middle ear inflammation. For example, OM can coexist with widespread disruption of hematopoiesis (the E2f4 and Rpl38 mouse), altered morphogenesis of epithelium (the IκBαΔN, SalI4, and p73 mouse), abnormal ciliary function (the Dnahc5, Dnahc11, and Chy1 mouse), defective glycosaminoglycan storage (the Gus, Ids, Idua, and Nagu mouse), or widespread defects in fibrin breakdown (the Plg mouse). Gene knockout models can mimic some forms of syndromic OM (and indeed, some knockout models have been created specifically to mimic these syndromes), but where the disease in mouse is so widespread, the argument that this represents a good model for nonsyndromic human OM is not persuasive.

### Conclusion

For good reason, the mouse is becoming the preferred animal model in OM research and has already proven beneficial in understanding molecular mechanisms in human disease. It

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**Table 1. Factors That Differ between Man and the Laboratory Mouse and That Could Affect Susceptibility to Otitis Media**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Man</th>
<th>Laboratory Mouse</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common natural middle ear pathogens</td>
<td>Steptococcus pneumoniae Nontypeable Haemophilus influenzae Moraxella catarrhalis</td>
<td>Sendai virus Mycoplasma pulmonis</td>
<td>Streptococcus pneumoniae and nontypeable Haemophilus influenzae can induce short-lived otitis media in mouse; Moraxella Cattarhalis is nonpathogenic</td>
</tr>
<tr>
<td>Natural incidence of otitis media</td>
<td>High in childhood</td>
<td>Minimal</td>
<td>Some laboratory mice develop chronic otitis media in later life</td>
</tr>
<tr>
<td>Inflammatory response</td>
<td>Variation in inflammatory response</td>
<td></td>
<td>Mouse blood is lymphocyte rich, whereas that in man is neutrophil rich</td>
</tr>
<tr>
<td></td>
<td>Recognized mucoid effusion phenotype (OME)</td>
<td>No recognized mucoid effusion phenotype</td>
<td>Muc7, Muc8, Muc11/12, and Muc17 are not expressed in mouse</td>
</tr>
<tr>
<td></td>
<td>Mastoid air cell system</td>
<td>Bulla only</td>
<td>A smaller mastoid volume is correlated to susceptibility to otitis media in man</td>
</tr>
<tr>
<td>Anatomy</td>
<td>Nasal-associated lymphoid tissue in a broad ring</td>
<td>Nasopharyngeal lymphoid aggregates at Eustachian tube only</td>
<td>—</td>
</tr>
<tr>
<td>Environment</td>
<td>Exposure to many pathogens</td>
<td>Often kept in high health status or pathogen-free conditions</td>
<td>There is variable health status of laboratory mice in different units</td>
</tr>
</tbody>
</table>

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will have an assured place in OM research for decades to come, but given the limitations outlined above, this role may eventually be exhausted in favor of human tissues.

**Author Contributions**

Mahmood Fazal Bhutta, conceptualized and wrote the article.

**Disclosures**

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**References**


**Figure 2.** A comparison of the mouse and human middle ear cleft, as demonstrated on axial computed tomography (CT). In the mouse, as in most mammals, the posterior extension of the middle ear space is limited to the bulla (*). In man, the extension includes the mastoid antrum (*) and the mastoid air cell system (m). CT of mouse ear reproduced. Permission granted with courtesy from Erik L. Ritman, MD, PhD, Mayo Clinic College of Medicine, Rochester, Minnesota.