Acne, one of the most common skin diseases, is caused by multiple factors, including *Propionibacterium acnes*. Studies suggest that responses to *P. acnes* by host immunity play important roles in its pathogenesis. Identifying immune modulators that attenuate inflammatory responses against *P. acnes* and the inhibition of bacterial growth may lead to novel avenues of immunologic intervention. 


Acne vulgaris is one of the most common skin diseases, affecting approximately 50 million people in the United States. The disease is important because it has significant morbidity and profoundly affects patients’ self-esteem. Although acne is common, its pathogenesis is still uncertain. Multiple etiological factors, including follicular hyperkeratinization, sebum, *P. acnes*, and inflammation, are thought to contribute. Perhaps it is the multifactorial etiology of acne that makes it challenging to treat. There is a high unmet clinical need for new and better treatments, given the increase in antibiotic-resistant strains of *P. acnes* and the restrictions placed on the use of isotretinoin. In this issue, Nakatsuji et al. (2008b) describe an alternative strategy to conventional therapy: a *P. acnes* vaccine that exerts protective immunity.

Although *P. acnes* is present in normal skin, its importance in acne pathogenesis has been well demonstrated because a reduction in bacterial count with antibiotic therapy improves the clinical outcome. What is less clear, however, is whether *P. acnes* is a true pathogen or whether unwanted host immune responses to this commensal microbe determine the disease outcome, because the number of bacteria present in lesions does not always correlate with disease severity (Leyden et al., 1988). Several previous studies have demonstrated that both cellular and humoral immunity against *P. acnes* are present in patients, and recent studies have provided a better understanding of the innate immune response produced by hosts in response to *P. acnes*. Upon activation, host innate cells elicit a protective antimicrobial response against *P. acnes* by inducing the production of antimicrobial peptides such as human β-defensin 2 (Nagy et al., 2005, 2006). On the other hand, the same mechanism may be responsible for producing inflammatory mediators by innate cells such as keratinocytes, monocytes, and sebocytes in response to *P. acnes* (Kim et al., 2002; Nagy et al., 2005, 2006), causing tissue injury and inflammatory disease. The balance between these innate responses, in addition to adaptive immune responses elicited by *P. acnes* likely determines whether the host will present with clinically active lesions.

Many of the current therapies focus primarily on reducing inflammation. The use of lower doses of antibiotics for their anti-inflammatory properties is currently being evaluated. In addition, recent studies suggest that in addition to its well-known effect on "normalizing" the follicular epithelium, retinoic acid demonstrates anti-inflammatory and antimicrobial effects (Liu et al., 2005, 2008), underscoring the need to investigate further the immunomodulatory effects of acne therapies. Despite substantial interest in basic acne research, acne vaccines that modulate host immune responses to *P. acnes* are not available.

In the study reported in this issue, Nakatsuji et al. (2008b) generated antibodies using inactivated *P. acnes*, postulating that they might provide protective immunity. The authors demonstrated that intranasal immunization of mice with this inactivated vaccine generated in vivo protective immunity against *P. acnes* challenge. Specifically, the antibodies elicited by inactivated *P. acnes* attenuated IL-8 production in human sebocytes; however, there was no effect on *P. acnes* growth. The clinical improvement observed in this *P. acnes* inflammatory murine model suggests that for acne treatment, antibodies that primarily exhibit anti-inflammatory properties might be sufficient for clinical improvement but without an antimicrobial effect.

**Immunization with** *P. acnes* **holds promise for acne therapy.**

The inactivated *P. acnes* vaccine used in this study targeted the whole bacterium, most likely without specificity. Therefore, developing vaccines against specific *P. acnes* antigens might be even more useful, as previously demonstrated by the same research group (Nakatsuji et al., 2008a). This would require that *P. acnes* antigens first be
identified and then characterized for the types of response that each antigen elicits; this information could then be used to develop a component acne vaccine. Very few P. acnes antigens have been identified and studied.

It will be important to evaluate the antibodies generated against P. acnes for other immunomodulatory effects, including their ability to induce proinflammatory mediators and cytokotoxicity, which might lead to tissue injury. It has been shown that some patients have antibodies against P. acnes, and positive correlations between antibody titers and the severity of the disease have been reported (Ashbee et al., 1997; Ingham et al., 1987; Webster et al., 1985). Thus, not all antibodies directed against P. acnes may be beneficial, and they may even worsen the disease.

Part of the difficulty in developing any acne therapy is that there is no perfect animal model. Although the mouse model used by Nakatsuji et al. (2008b) demonstrated a decrease in ear swelling in vaccinated mice, the lesions produced by injection of P. acnes into the ears of mice do not reproduce clinical acne lesions exactly. For this reason, it is not certain that similar clinical improvement will occur in humans, in whom other varying factors, such as the presence of inflammatory lipids in sebum, may influence the growth and behavior of P. acnes. Nonetheless, the authors of this study offer an important and interesting concept—that focusing on attenuating the inflammatory component of the disease could be therapeutically beneficial. Because the induction of cytokines, chemokines, and metalloproteinases by P. acnes occurs via a Toll-like receptor 2 (TLR2)-dependent pathway, the development of vaccines or other immune therapies that target TLR2 and other TLRs may provide other alternatives to conventional therapy. We are already familiar with agents that modulate TLR response, such as imiquimod, which enhances TLR7 and TLR8 function, and retinoic acid, which downregulates TLR2 expression and function, suggesting that vaccines with potent anti-TLR immunity may hold promise for the future of acne therapy.

CONFLICT OF INTEREST
The author serves as a consultant and is on a scientific advisory board for Galderma, Medicis, Sanofi-Aventis and Stiefel.

REFERENCES

See related article on pg 2485

Germline MC1R Variants and BRAF Mutant Melanoma
Elke Hacker1 and Nicholas K. Hayward1

Recent studies have demonstrated that melanocortin-1 receptor (MC1R) variants increase the risk of melanomas harboring BRAF mutations. This finding provides insight into the relationship between host genotype and selection for somatic mutation type. Additional larger studies are required in diverse populations to further examine the interaction between MC1R and BRAF in different melanoma subtypes.


MC1R function
MC1R is a well-known G-protein-coupled receptor found on melanocytes that plays an important role in the regulation of pigmentary genes (reviewed in Abdel-Malek et al., 2008). The gene is highly polymorphic, with more than 60 variants documented, the majority of which compromise the function of the receptor so that it inadequately responds to its ligands, α-melanocyte-stimulating hormone (α-MSH) and β-defensin (Abdel-Malek et al., 2008, Candille et al., 2007). Variant MC1R isoforms affect the signal transduction pathways that normally result in a switch from pheomelanin to eumelanin production after exposure of skin to UVR (Abdel-Malek et al., 2008). They are also strongly associated with red hair

1Oncogenomics Laboratory, Queensland Institute of Medical Research, Brisbane, Queensland, Australia
Correspondence: Professor Nicholas Hayward, Queensland Institute of Medical Research, 300 Herston Road, Herston, Queensland 4029, Australia.
E-mail: Nick.Hayward@qimr.edu.au