II inner root sheath keratins, previously K6irs1–K6irs4, are now named K71–K74 and are followed by K6hf, the type II keratin located in the companion layer. K77–K80 are the type II keratins, discovered by sequencing of the type II keratin locus. The gene designation for each keratin carries the same number as the protein with the prefix KRT.

Although we can be almost 100% confident that all the human keratins have been identified, enough flexibility in the nomenclature has been provided to allow for the discovery of new keratins in other mammals. Because keratins are cell type and differentiation specific, it is not hard to imagine that the vast differences in morphology of the skin that have evolved between mammals (for example, elephant, dolphin, armadillo, duck-billed platypus, deer, porcupine) might coincide with a requirement for keratins with different structural properties. Certainly several type II keratins have been identified that do not exist in humans, including a keratin in the gorilla and chimpanzee that is redundant in humans (Winter *et al.*, 2001).

In the last 24 years, Moll *et al.* (1982) has been cited more than 4,000 times. A lot has happened in that time, including many expression studies, the identification of almost 20 genetically inherited diseases caused by keratin mutations, the generation of more than 30 transgenic mice (either keratin knockouts or mice carrying altered keratin genes), and numerous *in vitro* structural studies and cellular functional studies. For Schweizer *et al.* (2006) to be cited as often in the next 24 years will depend on the future of research into keratins. Certainly the legacy of the last few years is the question: why are there are so many keratins? This question alone should keep scientists approaching keratin biology from all angles busy for some time to come.

CONFLICT OF INTEREST

The author states no conflict of interest.

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A New Nail in the CTCL Coffin

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The impact of immunotherapy on the natural progression of cutaneous T-cell lymphoma (CTCL), particularly the mycosis fungoides and Sézary syndrome variants, has been based on our evolving understanding of the disease's immunobiology.

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The characterization of the T-helper 2 (Th2) cytokine phenotype (IL-4, IL-5, and IL-10 predominance) of the malignant $CD4^+$ T lymphocytes of cutaneous T-cell lymphoma (CTCL) has provided an immunologic basis for the immune dysfunction correlated with advancing stages of CTCL (Vowels *et al.*, 1994). The Th2 phenotype is associated with IFN signal transduction pathway defects (Sun *et al.*, 1998), thus rendering the CTCL cell devoid of endogenous IFN immunoregulation. These observations provided the rationale leading to the therapeutic use of IFNs (INF-α and INF-γ) in CTCL (Olsen, 2003). Further

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immunopathologic correlations have shown that IFNs exert their Th1 therapeutic effects by inhibiting tumor-cell Th2 cytokine production and enhancing antitumor cell-mediated cytotoxicity (Kim *et al.*, 2005). Combination of IFNs with other immunomodulatory therapies appears to augment clinical responses, suggesting cooperative or synergistic Th1 antitumor effects (Suchin *et al.*, 2002).

> An exciting translation of the immunobiology of CTCL into a novel immunotherapeutic approach

Künzi *et al.* (2006) report mechanisms underlying the cytolytic effect of recombinant measles virus (rMV) on CTCL cells. Using cell lines and xenografted nude mice, they demonstrate that (1) CTCL cells express receptors for measles virus (CD150 and CD46); (2) rMV replicates lytically and is cytopathic in CTCL cells; and (3) intratumoral injections of rMV result in regression of CTCL xenografts. These studies, combined with the clinical responses obtained in a phase I trial of intratumoral rMV in CTCL patients pretreated with IFN-α (Heinzerling *et al.*, 2005), are an exciting translation of the immunobiology of CTCL into a novel immunotherapeutic approach.

The specificity of rMV therapeutic targeting of CTCL lies not with CD150 and CD46 expression (as these receptors are expressed on normal cells), but rather with CTCL's acquired defect in IFN signaling (Heinzerling *et al.*, 2005; Sun *et al.*, 1998). This renders CTCL cells a virtual IFN-free microenvironment in which rMV is unencumbered to replicate and induce cytolysis. This complements the current IFN-based immunotherapy strategies in CTCL.

Clinically, IFNs have been shown to be a highly active agent in CTCL with response rates as high as 70%, depending on the route of administration (Olsen, 2003). Low-dose subcutaneous IFN appears to be the most effective and best tolerated. It is often combined with other biologic response modifiers, and these combinations have been shown to impact disease survival in advanced stages (Suchin *et al.*, 2002).

The addition of an oncolytic virus in the context of IFN-based therapy has great potential to augment response rates. There still are significant issues, however, that require further investigation. Targeting rMV by intratumoral injection has been effective in the current models but has limited clinical application in many cases, such as Sézary's syndrome. Titrating the optimal dose is critical with any new therapeutic agent but is especially significant with oncolytic viruses. The therapeutic margin of this treatment interfaces with the host's immune protection of non-CTCL cells from measles infection. Acquired immunity to measles virus must be evaluated as a variable of both efficacy and safety. The effects of viral cytolysis in inducing a broader antitumor immunity, critical in other CTCL immunotherapies, require critical analysis. In addition, a broader toxicity profile is needed through further clinical testing. Nevertheless, the initial data are promising, and it appears that rMV used in combination with IFN-α and possibly other immunomodulatory therapies offers an exciting new avenue in immunotherapeutic targeting of CTCL.

CONFLICT OF INTEREST

The author states no conflict of interest.

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