in patients with congenital or acquired immunodeficiencies, which show striking expression of CD8, in association with a dermal infiltrate and a granulomatous pattern. The behaviour of such lesions appears to be somewhat dependent on the status of immunosuppression.[6]

Because there is morphological overlap between these three conditions, an accurate clinicopathological correlation that includes immunophenotypic studies is key to differentiate between them. To this end, Kempf *et al.*[4] present the largest series of these three conditions ever reported to date (n = 47), with special focus on $CD8^+$ ATCL. This comprehensive study collected cases from numerous European centres, and the clinical, pathological and immunophenotypic features, and the treatments used, were subsequently reviewed at an EORTC Cutaneous Lymphoma Group workshop. Notably, cases of $CD8^+$ ATCL were solitary acral small nodules of small-to-medium-sized $CD8^+$ lymphocytes, lacking significant cytologic atypia. Immunophenotypically, a dot-like pattern of immunoreactivity with CD68,[7] expression of TIA-1, and absence of granzyme B were characteristic. Like primary cutaneous small-to-medium $CD4^+$ LPD, the Ki67 activity was always below 30%. In contrast, cases of $CD8^+$ PTCL had a higher rate of multifocality (~27%), a higher degree of cellular pleomorphism and higher expression of multiple cytotoxic markers (granzyme B, perforin). They also lacked the CD68 dot-like pattern and had much higher Ki67 proliferation (55% of cases with >50%). Local recurrences were seen in 45% of cases and one patient died from the disease. The patients with immunodeficiency-associated LPD were much younger and had multiple lesions clinically.

From a clinical perspective, a diagnosis of PTCL of the skin has strong clinical connotations, and usually patients receive systemic treatment with chemo- and/or radiotherapy.[8] Separating reproducible diagnostic categories is key to individualizing therapeutic regimens and discovering their molecular profile. This study shows that appropriate distinction of $CD8^+$ dermal LPDs into specific diagnostic categories is possible and reproducible (Figure 1).

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Is heat shock protein 90 inhibition a relevant treatment strategy for psoriasis?

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Over recent decades, several targeted therapies – biologics and small molecules – have been successfully developed and approved for the treatment of moderate-to-severe psoriasis vulgaris. This intense development has been driven by compelling evidence for the major pathogenic contributions of key inflammatory effector cytokines such as tumour necrosis factor (TNF)-α and the interleukin (IL)-23–IL-17 family axis.[1] Among the key regulators of TNF-α- and IL-17-driven inflammatory pathways lies heat shock protein (HSP)90, a protein playing major functions in physiology and in carcinogenesis.[2]

In this issue of the *BJD*, Bregnhøj *et al.* report results from a proof-of-concept, phase Ib study investigating the safety and efficacy of the novel HSP90 inhibitor RGRN-305 in 11 patients with plaque psoriasis over 12 weeks.[3] Although RGRN-305 was primarily developed for cancer, serendipitous observation of psoriasis remission in one patient, and alleviation of psoriasis-like inflammation in a xenografted mouse model provided a rationale for this study. Administered orally at two dosages (250 and 500 mg daily), the drug was associated with ≥50% improvement of Psoriasis Area and Severity Index (range 71–94%) at 12 weeks vs. baseline in six of 11 patients, without a clear dose effect.

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The authors also conducted skin transcriptome analysis using microarrays, showing early and sustained reduction of TNF-α- and IL-17-induced inflammatory transcripts with pathophysiological relevance, including *IL36G* and *CXCL8*, and delayed downregulation of IL23/STAT3-driven activities in clinical responders. However, the impacts of HSP90 are likely to be broader, and obviously beyond keratinocytes. In *in vitro* studies of a THP-1 monocytic cell line, HSP90 inhibition has been shown to reduce pyroptosis, a proinflammatory mode of cell death, through alteration of the NLRP3 inflammasome.[4]

NLRP3 gene polymorphisms have been reported to increase the risk of developing psoriasis in the Swedish population,[5] but evidence for a central contribution of the NLRP3 inflammasome in human psoriasis is still missing. Therefore it would be interesting to complement studies showing alleviation by RGRN-305 of TNF-α- and IL17-driven inflammatory transcripts in keratinocytes, with assessment of its capacity to alter the NLRP3 inflammasome in different cellular subtypes. As this target cannot be accurately investigated by transcriptome studies, such research may open perspectives in other immune-mediated skin diseases.[6] However, safety concerns related to HSP90 inhibition should not be neglected, given their broad physiological functions that are in line with their multiple protein–protein interactions. Likewise, the adverse events reported by Bregnhøj *et al.* in their study sound like a warning, with eczema-like skin rashes reported in four of the five patients receiving the higher dose, while only mild adverse events were observed in the lower-dose group.

Taken together, these results still carry the promise for a new mode of action in psoriasis. Whether HSP90 inhibitors will fill remaining gaps in the context of a broader and more diversified set of oral and biologic therapies for psoriasis is not clear yet. However, with the development of precision medicine approaches, there is no doubt that innovative targeted drug development still has a future in psoriasis, and that new relevant modes of action will continue to emerge.

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