These results illustrate that the application of dermal OFM on fresh human skin explants has the potential to generate data that serve as an integrated model for preclinical assessment of topical drug candidates.

57.4.2 In Vivo Clinical Dermal OFM Study: PK/PD

57.4.2.1 Biomarker: PK/PD Profile Assessment

Dermal OFM has demonstrated its feasibility to assess PK/PD profiles of a lipophilic topical drug and a high-molecular-weight compound in a clinical trial [48]. The target drug was BCT194 (logP = 3.1), which acts by inhibiting the p38 pathway and thus the intradermal release of pro-inflammatory cytokines. The clinical dermal OFM study with psoriasis patients monitored the PK/PD profiles of the lipophilic topical drug and the inflammatory biomarker and high-molecular-weight compound TNF-alpha (molecular weight: 51 kDa as a trimer) in vivo in the skin of psoriasis patients.

Another clinical dermal OFM application with psoriatic patients successfully assessed intradermal PK/PD profiles of the highly lipophilic corticoid clobetasol-17-propionate (CP-17) (logP = 3.49) [47]. CP-17 is a topical drug widely used for the treatment of psoriasis, which activates glucocorticoid receptors and triggers antiinflammatory and immunosuppressive activities. PK and PD data of the drug and vehicle were comparatively assessed in lesional and non lesional skin. Further, time-resolved and probe-depth-dependent kinetic data were collected, which revealed slower penetration kinetics of CP-17 into lesional than into non lesional skin and showed that skin penetration into lesional skin normalized after repeated dosing. Results also showed that CP-17 does not significantly accumulate in the dermis independently of the skin condition.

The reduced penetration rate into hyperkeratosed psoriatic skin supported the assumption that the thickened psoriatic stratum corneum functions as a trap compartment for lipophilic topical drugs. The results of this clinical dermal OFM study further highlight the accuracy, sensitivity, and reproducibility of in vivo dermal OFM to assess dermal PK/PD profiles of lipophilic topical drugs and inflammatory biomarkers.

57.4.2.2 Antibody Assessment

Dermal OFM sampling was used in a clinical study with healthy participants and psoriatic patients to perform absolute quantification of a fully human monoclonal antibody. The concentration profile of the therapeutic antibody secukinumab was determined to assess the ability of a single subcutaneous dose to neutralize IL-17A in the skin [50]. The absolute tissue concentration of secukinumab was determined using dermal OFM in combination with no net flux in the skin of healthy human participants. No net flux was performed with an external reference substance, and the results were validated with results from suction blisters and punch biopsies. Secukinumab levels in the dermal ISF of psoriatic patients were quantitatively assessed one week after drug injection, and the resulting secukinumab levels were sufficiently high to completely neutralize IL-17A in the lesional skin of psoriatic patients.

57.4.2.3 Proteomics

The ISF samples collected during this antibody study [50] underwent proteomic and gene transcription analyses. A total of 170 proteins were further analyzed, including cytokines, chemokines, growth factors, cell adhesion molecules, and soluble receptors [65]. Early proteomic changes that occur in the dermis after secukinumab treatment were complemented with gene expression changes extracted from skin biopsy. Beta-defensin-2 was identified as a biomarker of IL-17A–driven pathology in patients with psoriasis.

57.4.3 In Vivo Clinical Dermal OFM Study: Bioequivalence Assessment

The utility of clinical dermal OFM as a dermal PK approach to assess BE was recently performed as part of an FDA-granted collaborative research effort to evaluate PK-based methods for topical BE assessment [49]. Acyclovir, a hydrophilic, poorly permeating topical drug, was used to assess the rate and extent of percutaneous penetration by continuous sampling with dermal OFM and