SSDV
derma.swiss
SGDV

05 | 2024

DERMATOLOGICA HELVETICA

Société Suisse de Dermatologie et Vénéréologie
Società Svizzera di Dermatologia e Venereologia
Swiss Society of Dermatology and Venereology
Schweizerische Gesellschaft für Dermatologie und Venerologie

WHAT'S NEW

Innovation of chronic wound therapy through patient-specific cell-based assays and novel therapeutic substances

This section is a contribution from the SKINTEGRITY.CH interdisciplinary research consortium. Akribes Biomedical is a small Vienna-based biotech company, founded in 2015*. It is dedicated to improving the healing of chronic wounds and became the first company member of SKINTEGRITY.CH. A recent article, entitled «Development of a cellular assay as a personalized model for testing chronic wound therapeutics», in the Journal of Investigative Dermatology (JID) [1] introduced the company's basic strategy to the public.

*https://akribes-biomedical.com

Petra Doerfler, Akribes Team.

Chronic wounds – «a high unmet medical need»

Chronic human skin wounds, e.g., venous -, arterial -, pressure - or diabetic foot ulcers, are a major health issue worldwide with 10-20 million patients in Western countries alone. This number is expected to increase due to the aging population and growing incidence of metabolic diseases [2]. While extensive efforts have been made in the past to develop diagnostic markers and imaging devices for chronic wounds, systems to develop and/or pretest drug treatment options in a personalized manner are still lacking [3].

No new drugs have been approved in this field within the last >20 years, and drug development for chronic wounds is hampered by the lack of translatability from preclinical animal models to patients. Therefore, Akribes established a cell-based assay system using wound exudates as a «humanized model of chronic wounds».

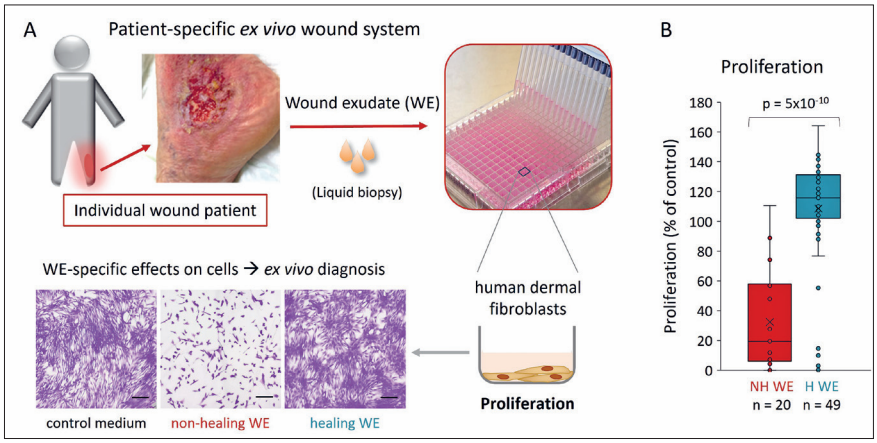

Figure 1: Effects of exudates from individual wounds on the proliferation of healthy primary human dermal fibroblasts reflect the in vivo wound status. (A) Concept of the fibroblast proliferation assay in the presence of exudates from non-healing or healing wounds, including microscopic pictures after 72 hours in culture. (B) Statistical evaluation of fibroblast proliferation in the presence of exudates from non-healing (NH) or healing (H) wounds.

Development of patient-specific wound assays

Wound exudates (WEs), obtained from patients by negative pressure wound therapy (NPWT) or swabbing, contain the pathogenic drivers of chronicity of individual wounds. Exposing primary human dermal fibroblasts (HDF) from healthy donors to sterile-filtered WEs from individual patients was found to transfer important functional characteristics of the wound condition to the cell culture system. Typically, WEs from non-healing wounds impair fibroblast proliferation, matrix formation and collagen production and enhance secretion of inflammatory cytokines, while WEs from healing wounds do not, thus reflecting the in vivo wound status.

Akribes established miniaturized cell assays (384-well format, 72 hours cell culture) to accommodate large WE numbers and sample volumes as low as 7µl, allowing the analysis of a vast array of non-healing as well as healing wounds. *Figure 1* shows the concept of the fibroblast proliferation assay (A) and summarizes the evaluation for the example of NPWT samples (B). A strong correlation was observed between wound chronicity and inhibitory effects of individual WEs on fibroblast proliferation. Moreover, sequential WEs from the same wounds permitted the monitoring of transitions from a clinically non-healing to a healing status. Overall, Akribes found that the results of this functional assay were in excellent agreement with clinical diagnosis, as illustrated in *Figure 2*. Based on results for >800 exudates from >300 wounds of different etiologies, collected under «real-world» conditions, fibroblast proliferation proved a straight-forward, quick and meaningful functional biomarker of the wound condition.

Dr. Barbara Wolff-Winiski, Co-CEO and CSO of Akribes, acknowledged the large number of contributors to this success,

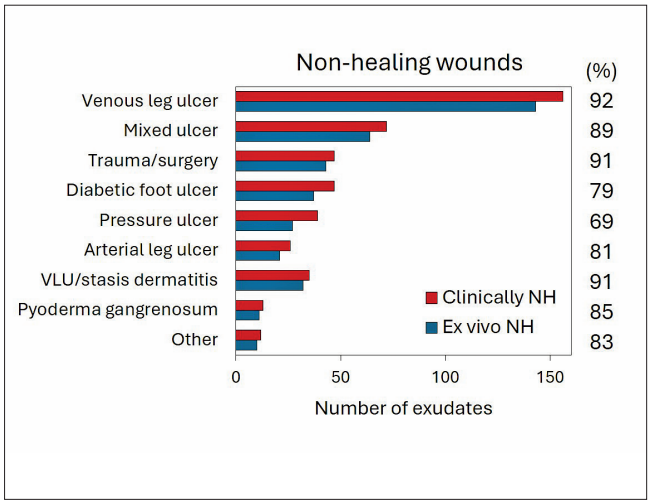

Figure 2: Agreement of clinical and ex vivo assessments of non-healing (NH) wounds of different etiologies. Bars represent the absolute numbers of test samples per wound type, percent values indicate the accordance of assessment methods. WEs were obtained by swabs.

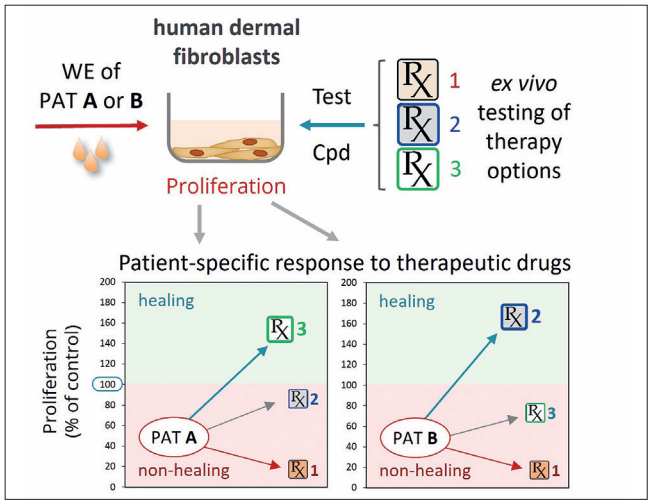

Figure 3: Cellular test system with exudates from individual non-healing wounds to detect patient-specific rescue effects of various therapeutic substances (cpd: compound).

«The extensive collaboration with many clinical partners for sample collection and documentation provided the basis to establish this assay».

Personalized model for testing chronic wound therapeutics

Akribes also investigated the impact of non-healing WEs on gene expression profiles of fibroblasts to elucidate early changes underlying the inhibition of cell proliferation and aiming to reveal common targets for therapeutic intervention. Already 6 hours after stimulation with three WEs of different etiologies, transcriptional analysis revealed an induction of inflammatory cytokine- and chemokine-pathways and the unfolded protein response (UPR), indicating that these changes may contribute to the pathology of non-healing wounds. The relevance of these findings was confirmed by previous reports that these pathways are also upregulated in cells isolated from chronic wounds or biopsies of venous ulcers.

However, the targeted interference with key players of these common pathways did not rescue fibroblast proliferation, likely because additional mechanisms are involved.

Therefore, Akribes decided to utilize fibroblast proliferation as a functional assay platform to identify compounds which rescue fibroblasts from adverse WE-effects regardless of the mode of action. Unlike most biomarkers, the proliferation readout does not depend on a single molecule. It summarizes the cellular response to the specific combination of components within each WE. Thus, it is suitable to test (potential) therapeutics affecting various molecular targets and pathways, with differential outcomes for individual patients and wounds (see schematic outline in *Figure 3*).

As a proof of concept, Akribes tested two therapeutics currently employed in the clinical management of chronic wounds, platelet derived growth factor and silver sulfadiazine, and both led to patient-specific responses in line with clinical experience, indicating the usefulness of the assay. In an effort to screen for and profile new therapeutics (not yet published), Akribes successfully identified compounds and compound classes with previously unknown potential for chronic wound therapy. Profiling of selected candidates is ongoing, with one compound to be tested in a clinical Proof-of-Concept study in 2025.

Moreover, Akribes plans to evaluate the performance of the fibroblast assay for predicting treatment responses of individual patients in comparison to the actual clinical response. Ultimately, this test may support the decision as to which treatment promises the most favorable outcome for the respective patient.

Author

Petra Doerfler, Akribes Team

References

1. *Doerfler, P., Schoefmann, N., Cabral, G., Bauer, W., Berli, M.C., Binder, B., Borst, C., Botter, S., French, L.E., Goerge, T., Hafner, J., Hartmann, D., Høgh, A., Hoetzenecker, W., Holzer-Geissler, J.C.J., Kamolz, L.P., Kofler, K., Luger, T., Nischwitz, S.P., Popovits, M., Rappersberger, K., Restivo, G., Schlager, J.G., Schmuth, M., Stingl, G., Stockinger, T., Stroelin, A., Stuetz, A., Umlauft, J., Weninger, W.P., Wolff-Winiski, B. (2024). Development of a cellular assay as a personalized model for testing chronic wound therapeutics. Journal of Investigative Dermatology. https://doi.org/10.1016/j.jid.2024.05.029*
2. *Gould, L., Abadir, P., Brem, H., Carter, M., Conner-Kerr, T., Davidson, J., DiPietro, L., Falanga, V., Fife, C., Gardner, S., Grice, E., Harmon, J., Hazzard, W.R., High, K.P., Houghton, P., Jacobson, N., Kirsner, R.S., Kovacs, E.J., Margolis, D., McFarland Horne, F., Reed, M.J., Sullivan, D.H., Thom, S., Tomic?Canic, M., Walston, J., Whitney, J., Williams, J., Zieman, S., Schmader, K. (2015). Chronic wound repair and healing in older adults: Current status and future research. Wound Repair Regeneration 23, 1–13. https://doi.org/10.1111/wrr.12245*
3. *Weigelt, M.A., Lev-Tov, H.A., Tomic-Canic, M., Lee, W.D., Williams, R., Strasfeld, D., Kirsner, R.S., Herman, I.M. (2022). Advanced Wound Diagnostics: Toward Transforming Wound Care into Precision Medicine. Advances in Wound Care 11, 330–359. https://doi.org/10.1089/wound.2020.1319*