Microdialysis in Profiling Cytokines and Other Macromolecules in the Skin in Health and Disease: A Comment to Falcone et al.

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The article by Falcone et al. (1) shows the outcome of a systematic review of human, minimally invasive techniques for the *in-vivo* measurement of interleukin 1a (IL-1α) and IL-1 receptor (IL1R).

The search has been well performed according to the criteria of systematic review, but we take the opportunity to comment that the search terms for target macromolecules are restrictive. Whilst these restrictions are to be lauded according to the authors' current expert opinion of the IL-1 family, the interests of researchers over the many years covered by the literature search may not have had similar knowledge (e.g. that it is more appropriate that IL-1α rather than IL-1β should be analyzed) or may have had entirely different interests as to relevant cytokines, biomarkers of other macromolecules. The result is, in our view, exclusion of valuable papers on the actually "minimally invasive" techniques because the "wrong" cytokines had been the subject of analysis.

In order to illustrate what this might result in we have chosen our own "field of competence" microdialysis to generate an alternative (but because of space not exhaustive) view of which papers might be relevant for researchers (whether they be an individual PhD student or a research team leader) considering use of the technique for IL-1α/IL-1R or indeed any other biomarker/macromolecule.

The paper's search technique yielded 3 articles on microdialysis which is but a fraction of e.g. a simple PubMed search of "microdialysis and cytokines" which yielded 143 peer reviewed articles of 4,042 human microdialysis articles. Restriction of articles to publication in the present journal gives two articles of direct relevance to the authors motive for search (2, 3). A broader perusal of the work of the research groups actually referred to by Falcone et al. would also reveal further interesting articles. If we were to add our own favorite articles exemplifying use of microdialysis we would add papers covering correlation of microdialysis to histologic findings (4) and use in skin disease (5). In the paper by Hersini et al. (3) there are numerous articles referred to for their demonstration of cytokines in action (6, 7) or for their role over the years in elucidation basic principles of the technique (e.g. 8, 9).

If we had been given the question "Could microdialysis be used to collect quantifiable amounts of IL-11α, IL-1RA and other biomarkers from the skin causing no or minimal discomfort?", we would have answered "Yes, without a doubt". But the evidence for this is not provided adequately by the 3 articles surviving the cull in the review of Falcone et al. (1).

In our view microdialysis is a sampling methodology with many advantages and is well established in studies of inflammatory mediators (3). Using microdialysis one has the opportunity to discard the samples reflecting the individual innate reactivity that is caused by tissue or blood sampling. Thus the *in vivo* milieu is more accurately reflected in samples obtained by microdialysis than by other methods. Additionally the microdialysate is a more "pure" sample.

We are in full agreement with Falcone et al. (1) that we should try to measure in our target tissue the skin, the proteins involved in disease processes. We offer the content of this commentary as ancillary information on one of the techniques (microdialysis) reviewed in their article in the full knowledge that proponents of the other 7 techniques mentioned may well have similar views on useful papers that the article's search methodology precluded.

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Response to the Comment by Anderson & Ghafouri

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We appreciate the comment of Anderson & Ghafouri on our results regarding a systematic literature review on minimally-invasive methods to sample interleukin 1α (IL 1α) and IL1RA from human skin *in vivo* [1]. Using the terms "interleukin 1 alpha", "interleukin 1 receptor antagonist", "skin", "human", including all possible abbreviations and synonyms, we found 10 different methods. Among these, one employed microdialysis to sample IL1α and other biomarkers. Anderson & Ghafouri argue that the search strategy was restrictive, leading to the exclusion of valuable papers on the actually minimally-invasive techniques, and use the search "microdialysis and cytokines" on PubMed to exemplify the high number of articles using this technique. We are fully aware that the limitation of our review was the restriction of the search strategy to IL-1α and IL-1RA: as we stated in the discussion, the addition of relevant cytokines and chemokines such as IL-1β, IL-6 and IL-8 would have strengthened and, possibly, broadened the overview of minimally-invasive sampling methods. We invite the readers not to view our work as a compendium of all minimally-invasive methods to sample cytokines and chemokines in general from human skin *in vivo*. Rather, it should be seen as the (to our best knowledge) first attempt to provide a systematic overview of all available methods to sample two specific protein biomarkers from human skin *in vivo*. In this respect, the number of articles found for each method should be considered in light of the exclusion and inclusion criteria of the article selection process, bearing in mind that valuable papers might have been excluded on the mere basis of such criteria.

We thank Anderson & Ghafouri for sharing their expert opinion on the minimally-invasive sampling of cytokines and chemokines using microdialysis and, in agreement with them, we welcome proponents of the other methods found in our review to share their views on valuable papers that, because of the exclusion and inclusion criteria, might have been omitted in our work.