**Supplementary Information for**

Plasma linoleate diols are potential biomarkers for severe of COVID-19 infections

**Cindy McReynolds1,2, Irene Cortes-Puch1,2,3, Resmi Ravindran4, Imran Khan4, Bruce G. Hammock5, Pei-an Betty Shih6, Bruce D. Hammock1,2,7\*, Jun Yang1,2\***

1Department of Entomology and Nematology, University of California, Davis, CA, USA

2EicOsis Human Health Inc., Subsidiary of EicOsis LLC, 1930 5th Street, Suite A, Davis, CA, ISA

3Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Internal Medicine, University of California, Davis, CA, USA

4Department of Pathology and Laboratory Medicine, University of California, Davis, CA, USA

5Department of Veterinary Medicine, Aquatic Health, University of California, Davis, CA

6Department of Psychiatry, University of California, San Diego, San Diego, CA, USA

7UCD Comprehensive Cancer Center, University of California, Davis, CA, USA

**\* Correspondence:**Jun Yang

[junyang@ucdavis.edu](mailto:junyang@ucdavis.edu)

Bruce D. Hammock

[bdhammock@ucdavis.edu](mailto:bdhammock@ucdavis.edu)

Keywords: linoleate diol1, lipid mediators2, COVID-193, inflammation4, leukotoxin5, EpOME, DiHOME, ARDS

**This PDF file includes the following:**

Table 1: average cytokine levels ± standard deviation over 5-day sampling period

Figure 1: EpOME and DiHOME values from COVID-19 patients and controls and calculated EpOME: DiHOME ratios over a 5-day sampling period in COVID-19 patients compared to a single assessment in healthy controls.

**Supplementary Table 1.** Average cytokine levels ± standard deviation over 5-day sampling period in 6 COVID-19 positive patients and single timepoints in 16 healthy controls.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | **COVID negative** | | | **COVID positive** | | |
| Significant |  | IP-10 | 377.51 | ± | 422.00 | 8,319.04 | ± | 13,197.36 |
|  | MCP-1 | 51.76 | ± | 46.99 | 198.07 | ± | 151.81 |
|  | IL-2R alpha | 75.96 | ± | 19.89 | 228.93 | ± | 221.50 |
|  | G-CSF | 32.15 | ± | 24.92 | 243.96 | ± | 185.23 |
|  | SCGF-b | 65,516.58 | ± | 23,927.79 | 457,401.32 | ± | 182,805.76 |
|  | IL-1ra | 1,464.07 | ± | 458.91 | 6,627.30 | ± | 5,657.16 |
|  | IL-18 | 69.87 | ± | 45.05 | 218.21 | ± | 165.27 |
|  | MIG | 652.77 | ± | 1,241.35 | 5,011.68 | ± | 8,872.44 |
|  | RANTES | 6,886.20 | ± | 9,986.27 | 82,607.91 | ± | 119,032.58 |
|  | IL-1 alpha | 3.64 | ± | 4.86 | 26.21 | ± | 13.29 |
|  | IL-1 beta | 1.73 | ± | 2.33 | 6.62 | ± | 3.10 |
|  | IL-2 | 13.08 | ± | 22.02 | 8.73 | ± | 3.42 |
|  | IL-3 | 0.01 | ± | 0.02 | 0.55 | ± | 0.44 |
|  | IL-4 | 1.01 | ± | 0.41 | 2.30 | ± | 0.82 |
|  | IL-5 | 7.78 | ± | 11.10 | 8.20 | ± | 5.06 |
|  | IL-6 | 0.41 | ± | 1.28 | 30.14 | ± | 18.98 |
|  | IL-7 | 4.41 | ± | 3.27 | 11.95 | ± | 4.90 |
|  | IL-8 | 4.90 | ± | 6.03 | 57.68 | ± | 38.85 |
|  | IL-9 | 318.33 | ± | 123.79 | 492.35 | ± | 63.57 |
|  | IL-10 | 9.78 | ± | 12.19 | 16.75 | ± | 5.56 |
|  | IL-12 (p70) | 4.45 | ± | 2.32 | 7.34 | ± | 3.13 |
|  | IL-12 (p40) | 46.89 | ± | 15.93 | 99.21 | ± | 58.28 |
|  | IL-13 | 0.91 | ± | 0.46 | 1.91 | ± | 0.55 |
|  | IL-16 | 94.16 | ± | 26.94 | 383.52 | ± | 258.54 |
|  | PDGF-BB | 611.54 | ± | 312.83 | 4,918.12 | ± | 2,593.90 |
|  | MIP-1b | 264.54 | ± | 97.06 | 419.52 | ± | 131.09 |
|  | SDF-1a | 1,657.55 | ± | 506.14 | 3,115.42 | ± | 717.18 |
|  | MCP-3 | 0.65 | ± | 0.88 | 25.38 | ± | 27.26 |
|  | LIF | 70.61 | ± | 53.20 | 77.78 | ± | 30.40 |
|  | IFN-a2 | 3.39 | ± | 2.01 | 9.38 | ± | 4.21 |
|  | IFN-g | 10.33 | ± | 9.83 | 50.09 | ± | 33.68 |
|  | TNF-a | 48.24 | ± | 16.31 | 128.00 | ± | 53.16 |
|  | TNF-b | 561.01 | ± | 223.51 | 840.87 | ± | 91.47 |
|  | MIF | 4,453.54 | ± | 2,413.46 | 15,533.21 | ± | 7,131.58 |
|  | Basic FGF | 3.70 | ± | 0.01 | 21.34 | ± | 18.93 |
|  | MIP-1a | 0.37 | ± | 0.56 | 8.72 | ± | 7.98 |
|  | M-CSF | 14.02 | ± | 5.30 | 58.77 | ± | 38.03 |
|  | HGF | 234.77 | ± | 61.06 | 6,463.33 | ± | 8,283.03 |
|  | SCF | 66.05 | ± | 12.63 | 204.00 | ± | 119.30 |
|  | TRAIL | 126.49 | ± | 36.31 | 222.80 | ± | 56.63 |
|  | CTACK | 400.80 | ± | 134.88 | 833.03 | ± | 391.99 |
|  | Eotaxin | 98.23 | ± | 33.87 | 147.76 | ± | 78.73 |
|  | VGEF | 61.21 | ± | 158.03 | 204.95 | ± | 99.50 |
| Not significant |  | GRO-a | 906.44 | ± | 222.88 | 905.37 | ± | 195.31 |
|  | IL-2 | 8.16 | ± | 22.02 | 7.83 | ± | 5.39 |
|  | IL-5 | 5.00 | ± | 11.10 | 5.00 | ± | 11.89 |
|  | IL-15 | 12.70 | ± | 0.00 | 12.70 | ± | 0.00 |
|  | IL-17 | 2.80 | ± | 0.00 | 2.80 | ± | 0.00 |
|  | b-NGF | 0.38 | ± | 0.00 | 0.38 | ± | 0.00 |
|  | GM-CSF | 0.50 | ± | 0.10 | 3.70 | ± | 0.97 |

**Supplementary Figure 1.** Individual epoxide and diol levels in patients and controls (A) and calculated EpOME: DiHOME ratios over a 5-day sampling period in COVID-19 patients compared to a single assessment in 44 healthy controls (B).

A.



B.



1. Plasma concentration (nM) of EpOME and DiHOME in five sequential samples collected from six hospitalized COVID-19 positive patients and control samples collected separately from healthy volunteers (n=44). Data from individual days is represented for each COVID patients and for each individual healthy control.
2. Ratio of EpOME: DiHOME values in healthy controls vs. hospitalized COVID-19 patients. Control values are averaged for one point ± SEM while COVID-19 patient samples are represented in chronological order of sampling after hospital admission. Lower ratios indicate that the DiHOME concentration was higher or the EpOMEs were lower and are commonly used to infer sEH activity [1]. Considering the large increase in EpOMES in COVID-19 patients compared to healthy controls, the decreased valie of the ratios in COVID-19 patients are largely driven by inceased DiHOME concentrations.

[1] D. Stefanovski, P.B. Shih, B.D. Hammock, R.M. Watanabe, and J.H. Youn, Assessment of soluble epoxide hydrolase activity in vivo: A metabolomic approach. Prostaglandins & other lipid mediators 148 (2020) 106410.