Quantifying Intra- and Extracellular Aggregation of Iron Oxide Nanoparticles and its Influence on Specific Absorption Rate

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Supplemental Information

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INFORMATION AVAILABLE

- Figure S1. Transmission electron microscopy images of SPION aggregates around and within LNCaP Cells 3, 4 and 5.
- Formulae for the four, two-dimensional geometric descriptors used in in analyzing aggregate images.

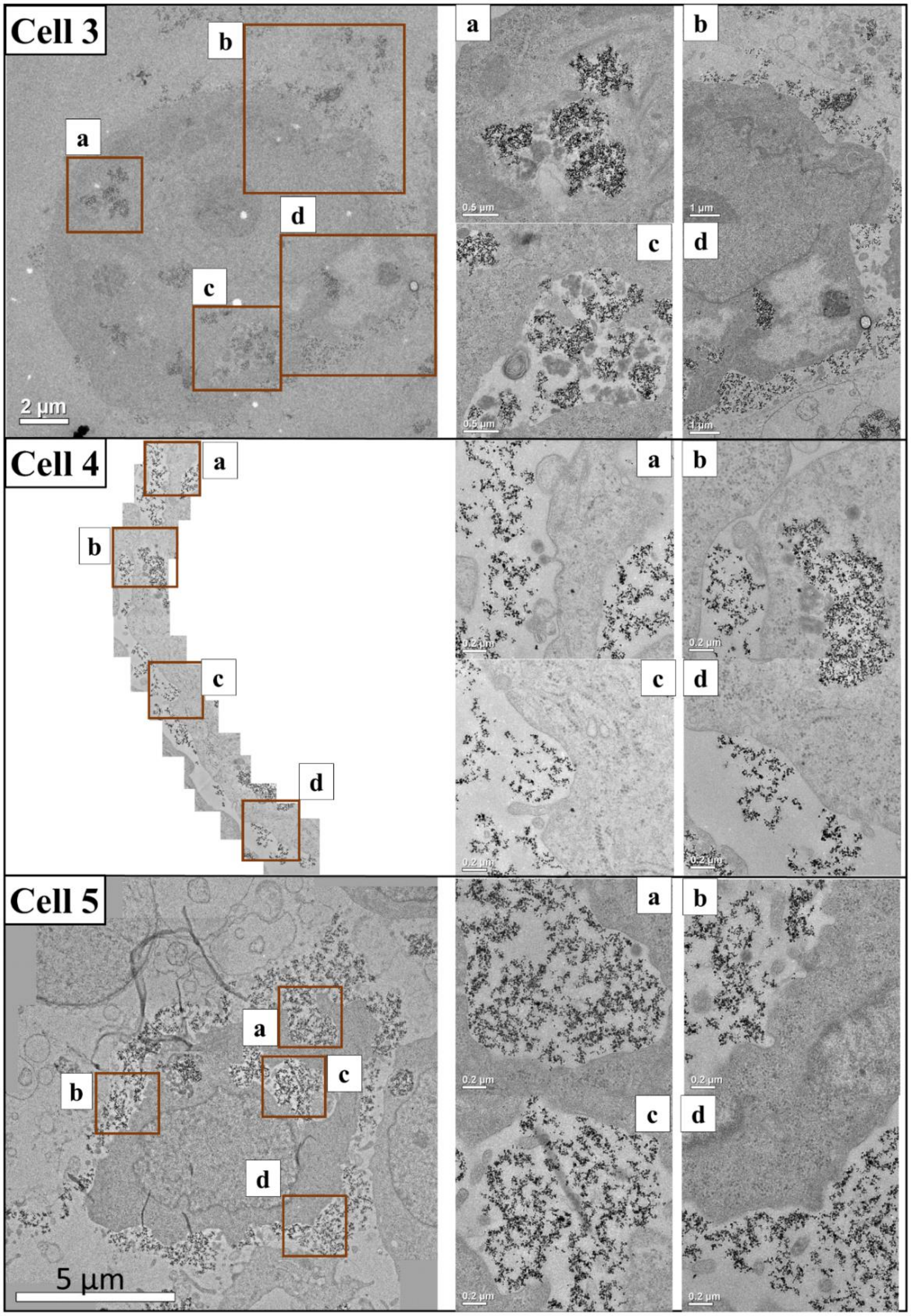

Figure S1. Transmission electron microscopy images of cells 3, 4 and 5. TEM images of Cell 1, 3 and 5 are also presented in Etheridge et al[1]and Hurley et al[2].

Four geometric parameter calculations in the image processing

Once a TEM image of an SPION aggregate was converted to a bit matrix (aggregate pixel=1.0 and background pixel=0.0), four geometric parameters (P, L_{max}, $R_{g,2D}$ and PA) were calculable. To determine the perimeter (P), the number of unit pixel edges at the boundary of an aggregate image was multiplied by the unit pixel length (L_p), and the maximum extent of the aggregate (L_{max}) was obtained by finding the longest scalar distance between two pixels within an aggregate image, as shown in Figure 2 (c). The 2D radius of gyration ($R_{g,2D}$) and the 2D projected area (PA) were calculated with following equations:

$$R_{g,2D} = \sqrt{\frac{1}{N}\sum_{i=1}^{i=N_{(x,y,\alpha=1)}}(x_i - x_{cm})^2 + (y_i - y_{cm})^2} \quad \text{(S1)}$$

$$PA = N_{(x,y,)} \times L_p^2 \quad \text{(S2)}$$

where $N_{(x,y,)}$ is the number of aggregate pixels, (x_i, y_i) is a spatial coordinate of an aggregate pixel i, and (x_{cm}, y_{cm}) is a spatial coordinate of aggregate image's the center of mass:

$$x_{cm} = \frac{\sum_{i=1}^{N_{(x,y,\alpha=1)}} x_i}{N_{(x,y,\alpha=1)}} \quad \text{(S3)}$$

$$y_{cm} = \frac{\sum_{i=1}^{N_{(x,y,\alpha=1)}} y_i}{N_{(x,y,\alpha=1)}} \quad \text{(S4)}$$

Calculated P, L_{max}, $R_{g,2D}$, and PA were non-dimensionalized by an aggregate's projected area weighted mean primary particle radius (a_p).

To obtain the four geometric parameters of a CCA generated quasifractal aggregate, a projection of the generated aggregate was obtained, and the two-dimensional spatial center coordinates of all primary particles of the aggregate were placed on an hypothetical image domain. To determine whether an image domain pixel was a part of the aggregate projection, the distances between the pixel and the centers of primary particles were calculated. If the distance between the pixel and any primary particle of the aggregate was less than 1.0 (the dimensionless primary particle radius), 1.0 was assigned to the pixel's bit matrix location, otherwise the pixel was considered background and its bit matrix location was assigned a zero value. This pixel identification process was performed for all image domain pixels, enabling the calculations of P/a_p, L_{max}/a_p, $R_{g,2D}/a_p$, and $PA/\pi a_p^2$.

REFERENCES

1. M. L. Etheridge, K. R. Hurley, J. Zhang, S. Jeon, H. L. Ring, C. Hogan, C. L. Haynes, M. Garwood and J. C. Bischof, *Technology*, 2014, **02**, 214-228.
2. K. R. Hurley, H. L. Ring, M. Etheridge, J. Zhang, Z. Gao, Q. Shao, N. D. Klein, V. M. Szlag, C. Chung, T. M. Reineke, M. Garwood, J. C. Bischof and C. L. Haynes, *Molecular Pharmaceutics*, 2016, DOI: 10.1021/acs.molpharmaceut.5b00866.