8th. World Congress on Computational Mechanics (WCCM8)
5th. European Congress on Computational Methods in Applied Sciences and Engineering (ECCOMAS 2008)
June 30 – July 5, 2008
Venice, Italy

COMPUTATIONAL MODELS OF DENDRITIC CELL CHEMOTAXIS IN TISSUE ENGINEERED MICROENVIRONMENTS

***Margherita Cioffi[1], Simone Bottan[1], Ulrike Haessler[2], Brandon Dixon[2], Melody A Swartz[2], Federica Boschetti[1]**

[1]LaBS
Department of Structural Engineering,
Politecnico di Milano
Piazza Leonardo da Vinci 32
20133 Milano, Italy
margherita.cioffi@polimi.it

[2]Institute of Bioengineering
EPFL
Building AAB 043, Station 15
CH-1015 Lausanne
Switzerland
melody.swartz@epfl.ch

Key Words: *Chemotaxis, Interstitial flow, Chemokines, Finite Element Modelling.*

ABSTRACT

Active regulation of dendritic cells (DC) by the lymphatics is just beginning to be explored [1]. The importance of interstitial flow on CCR7 signaling has recently been demonstrated for breast cancer cells [2], which likely mimic DCs to home to lymph nodes. Both lymphatics and DCs secrete the CCR7 ligands CCL19 (which is not matrix-binding) and CCL21 (which is strongly matrix-binding), and both are important for lymph node homing of immune cells.

Here we develop a dynamic computational model to be used in parallel with in vitro tests to describe the specific response of DCs to both CCR7 ligands and flow.

In the computational model, which simulates the actual in vitro experimental system (Fig.1, left), a channel (5.55 x 1.6 x 1 mm) maintains dendritic cells embedded within a 3D gel and subjects them to chemokine gradients. Constant chemokine concentrations C0 and C1 are applied at the channel boundaries. The interaction between chemokines CCL19 and CCL21 with a single cell and the extracellular matrix were studied using the finite-element code Comsol Multiphysics, solving the following equation for each species Ci:

$$\rho v \cdot \nabla c + \rho \frac{\partial C_i}{\partial t} = \rho D \nabla^2 C_i + r_i$$

where D is the species diffusivity, ρ is the medium density, v is the flow velocity and r is the reaction term, which accounts for the chemokines binding and unbinding to the matrix. The equilibrium constants were derived experimentally using biacore.

Figure 1 (right) shows the transitory in CCL21 and CCL19 concentrations, respectively. CCL21 diffuses slowly and does not reach steady state conditions even after 12 hours (the duration of the considered in vitro tests). On the contrary, CCL19 diffusion is comparable to the experimental average velocity of dendritic cells (0.01µm/s). Figure 2

shows the concentration distribution around a cell with and without flow.

This preliminary computational model, integrated with experimental data, is giving a first insight into the interaction between dendritic cells, kemokines gradients and interstitial flow. Future developments of the model include the integration of cell movement, dependent by the species concentrations.

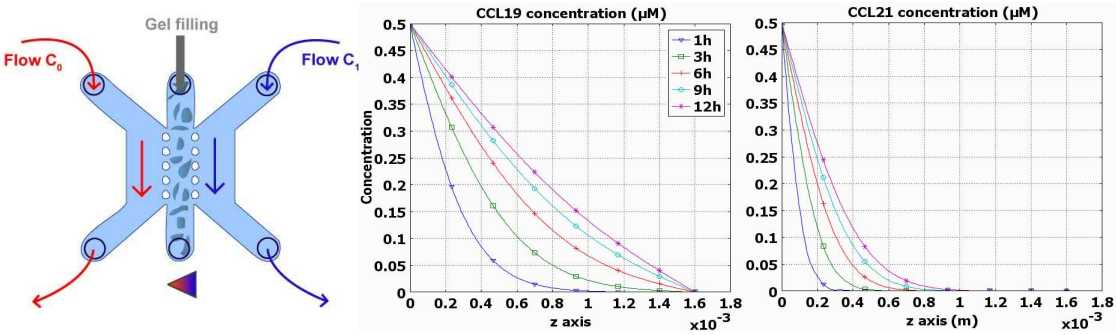

Figure 1. Left: Chamber used to measure concentrations and reaction constants. The chamber is filled with collagen gel seeded with DCs. Right: CCL19 and CCL21 concentration (mol/m^3) on the channel cross section (z axis), at different time points (0-12 hours).

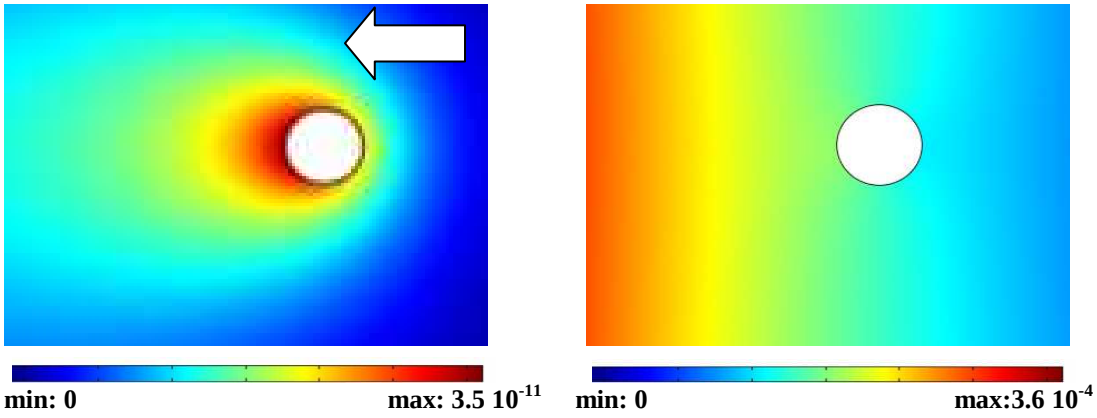

Figure 2: distribution of CCL19 concentration (mol/m^3) around a cell in the presence (left) or absence (right) of slow flow (6μm/s).The arrow shows the flow direction.

REFERENCES

[1] G.J. Randolph, V. Angeli and M.A. Swartz. "Dendritic-cell trafficking to lymph nodes through lymphatic vessels", *Nature Rev. Immunol.*, Vol. **5**(8), pp. 617-628, (2005).

[2] J.D. Shields, M.E. Fleury, C. Yong, A.A. Tomei, G.J. Randolph, M.A. Swartz. Autologous chemotaxis as a mechanism of tumor cell homing to lymphatics via interstitial flow and autocrine CCR7 signaling. *Cancer* Cell, Vol. **11**(6), pp.526-538, (2007).

[3] M.E. Fleury, K.C. Boardman, M.A. Swartz. Autologous morphogen gradients by subtle interstitial flow and matrix interactions. *Biophys J.*, Vol. **91**(1), pp. 113-121, (2006).