A major risk factor for cardiovascular disease (CVD) is elevated LDL-cholesterol, which can undergo oxidative modification (mLDL). Experimental models show that mLDL in atherosclerotic plaques can be taken up by scavenger receptors on circulating blood monocyte subsets, contributing to the progression of atherosclerosis.
prone vascular beds leads to increased monocyte derived macro-
phage foam cell formation and atherosclerosis. However, an
increasing appreciation of blood monocyte functional heterogeneity
has complicated this model and the subset specific functions of
blood monocytes in atherosclerosis is unknown. In humans, 3 cir-
culating monocyte subsets can be identified based on CD14 and
CD16 expression and 2 subsets in mice based on Gr1 expression.
CD14^{high}CD16^{low} (Gr1^{high}) monocytes are well-characterized
inflammatory monocytes that respond to bacterial cues, while
CD14^{low}CD16^{high} (Gr1^{low}) monocytes can crawl on the vascular
endothelium in the steady state, although their role in homeostatic
conditions is largely unresolved. CD14^{high}CD16^{high} are poorly
described in mice, but are shown to have increased frequency in
human inflammatory disease. We aimed to characterise the blood
monocyte subset response to mLDL by addressing the quantitation
and mechanisms of uptake, subsequent functionality and how
intravascular crawling monocytes may regulate mLDL endothelial
deposition.

We have demonstrated differential intracellular uptake kinetics
of mLDL in vitro by human monocyte subsets via quantitative
imaging and flow cytometry. CD14^{high}CD16^{high} monocytes
showed greatest uptake after 2 hours, via the scavenger receptor
CD36. In-vivo experiments in mice showed similar uptake in
monocyte subsets, peaking at 4 hours post mLDL infusion
(Gr1^{high}: 4hrs 6.9+/-2.8, 24hrs 5.7+/-3.9; Gr1^{low}: 4hrs 10.3
+/-4.4, 24hrs 4.3+/-2.8. Percentage cells mLDL positive, mean
+/-SEM, n=3). Currently, we are developing whole body
imaging modalities and high-resolution intravitral microscopy in
mice to attempt to understand the fate and function of
‘LDL-loaded’ blood monocytes. Preliminary data suggests LDL
loaded monocytes localise to discrete tissues and that crawling
Gr1^{low} (CD14^{low}) monocytes can scavenge LDL at the endothelial
interface. Further work will determine whether they transmigrate
into the arterial wall, undergo differentiation or apoptosis, localise
to draining lymph nodes and/or efflux lipid to anti-inflammatory
HDL. In summary, these complementary approaches add to exist-
ing knowledge on the role of mLDL and blood monocytes in
atherosclerosis.