**Supplemental Methods.**

**Determination of significant principle components.**

The numbers of significant principle components were determined based on $Q^2$ value. If $Q^2$ value of a principal component was greater than the significance limit of 0.05 or if the $Q^2V$ ($Q^2$ value for individual variable) was greater than 0.05 for at least sqrt(M) where M is number of Y-variables, that PC was regarded as valid. $Q^2$ is defined as $Q^2$=(1-PRESS/SS) where prediction error sum of square (PRESS) $= \sum_i \sum_i \left(Y_{im} - \hat{Y}_{im}\right)^2$ and SS is the residual sum of squares of the previous component.[52] Predictability was calculated based on either root mean square error of estimation (RMSEE) for cross-validated predictions or root mean square error of prediction (RMSEP) for *a priori* predictions. Predictability was defined as [1-RMSEE (or RMSEP)] × 100 and expressed as percent.

**Supplemental Figures.**

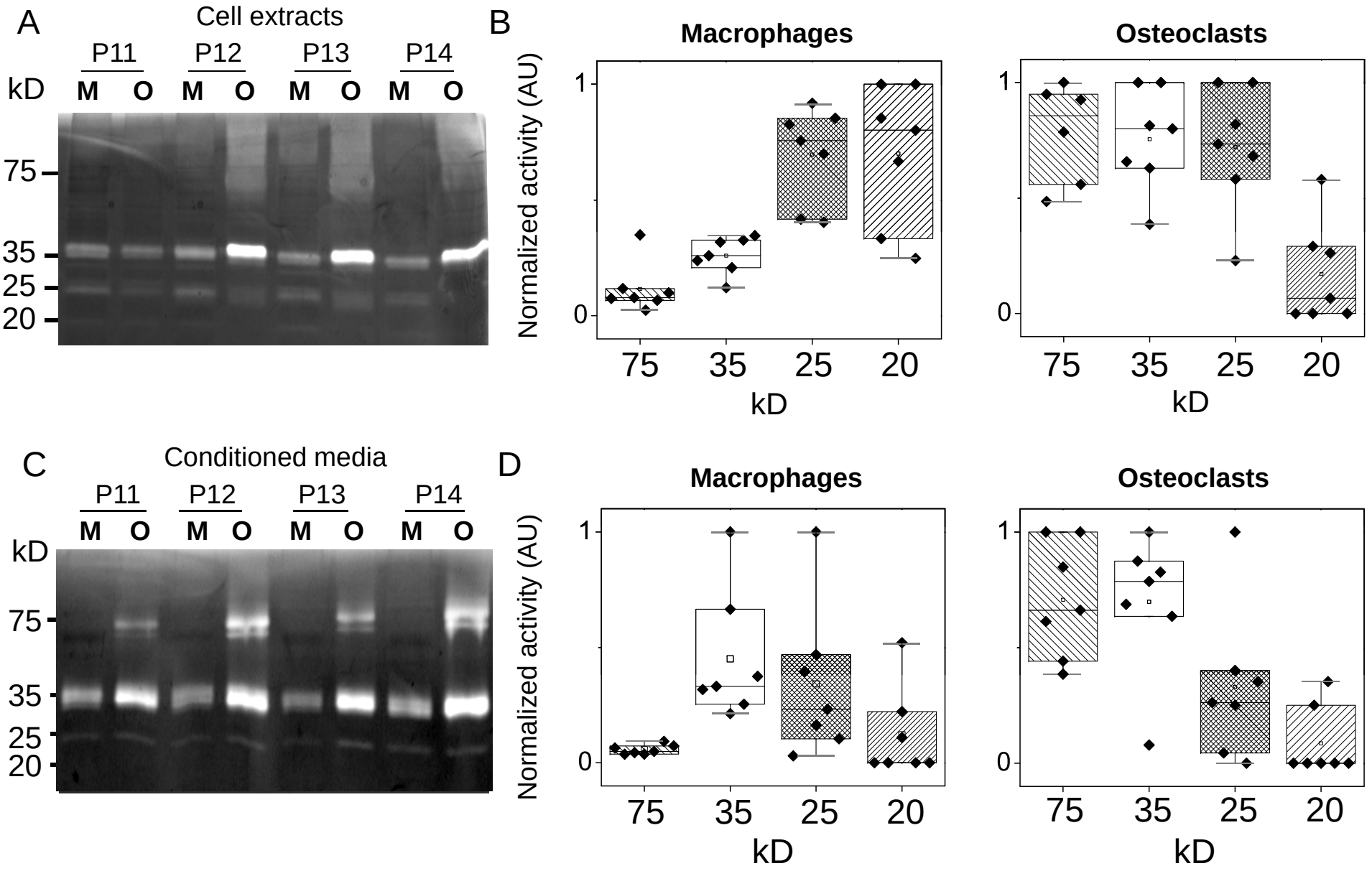
**Supplemental figure 1. Cathepsin proteolytic profiles of differentiated macrophages and osteoclasts in assay buffer, pH 6.** Multiplex cathepsin zymography (assay buffer, pH 6) and quantification of **(A, B)** cell extracts or **(C, D)** conditioned media for macrophage and osteoclast differentiation from patient monocytes. Quantification of cathepsin activity and patient variability is represented in the box and whisker plots. As with zymograms incubated in pH 4, the 75kD cathepsin activity was apparent in osteoclasts and cathepsin V activity was higher in osteoclasts as well. Cathepsin L activity was higher in cell extracts of macrophages.

**Supplemental figure 2. Multivariate analysis of kinase activation was not highly predictive of secreted cathepsin proteolytic activity of patient monocyte derived macrophages and osteoclasts.** Predictability of secreted cathepsins K, L, S, and V activity using a PLSR model trained with kinase measurements of differentiating macrophages **(A)** **(**$R^2Y$ = 0.693, $Q^2$ = 0.541, 1 significant PC**)** or of differentiating osteoclasts **(B)** ($R^2Y$ = 0.478, $Q^2$ = 0.073, 1 significant PC).

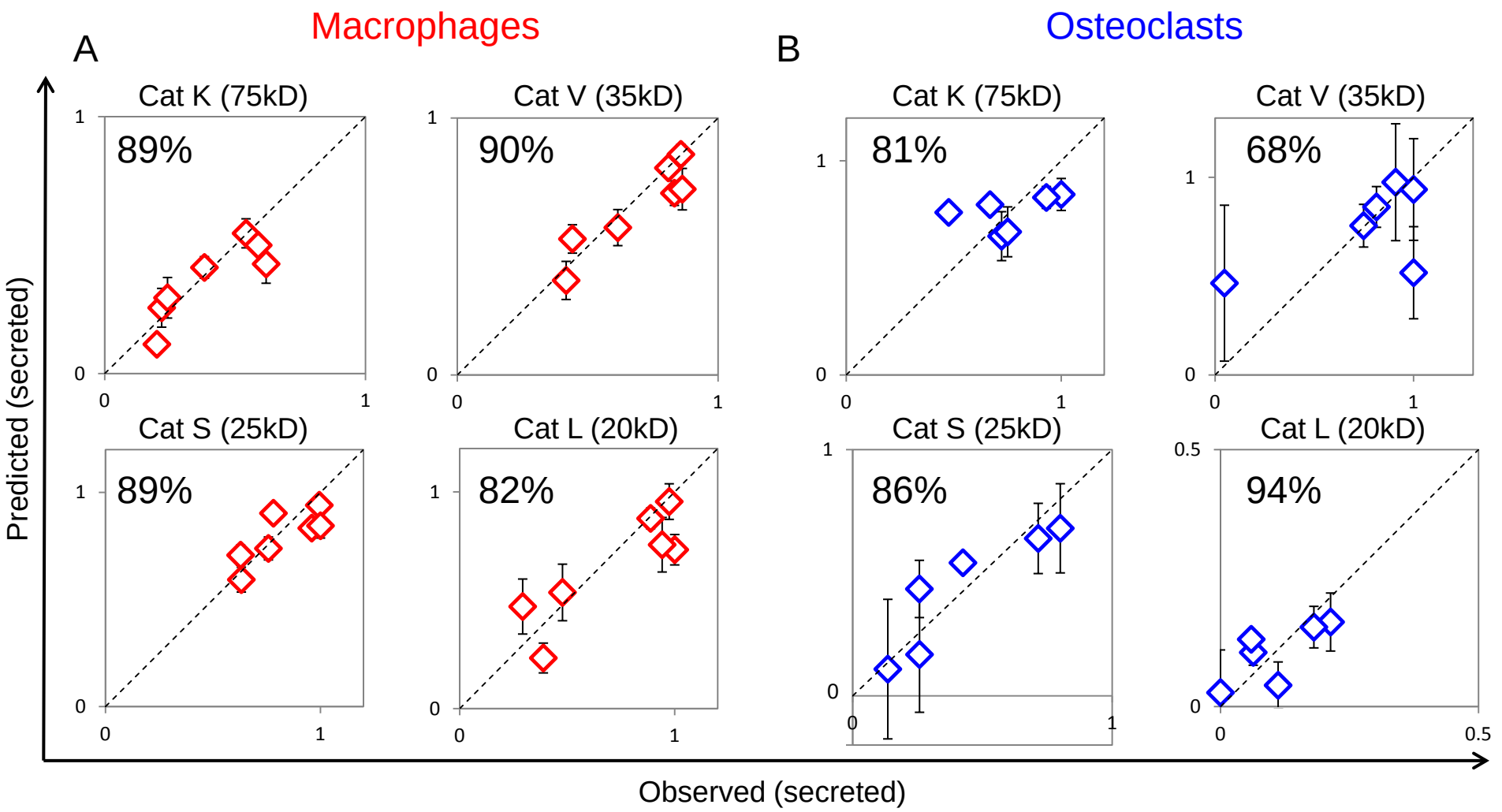
Electronic Supplementary Material (ESI) for Integrative Biology


**Supplemental table 1. Variable importance of projection (VIP) for macrophage diameter and osteoclast diameter and number of nuclei.** Kinase signals with significant VIP values for the PLSR model predictive of macrophage diameter, and osteoclast diameter and number of nuclei. Kinase signals were regarded as significant if the VIP value was greater than 1. Kinase signals with significant VIP values for both macrophages and osteoclasts were highlighted.

**Supplemental table 2. VIPs for cell-associated cathepsin activity of macrophages and osteoclasts.** Kinase signals with significant VIP values for the PLSR model predictive of cell-associated cathepsin activity of monocyte-derived macrophages and for monocyte-derived osteoclasts**.**




Supplemental figure 1




Supplemental figure 2

| Macrophages | | Osteoclasts | |
|---|---|---|---|
| **Variables** | **VIP** | **Variables** | **VIP** |
| **p-JNK day 6** | **1.782** | **p-JNK day 1** | 1.710 |
| **p-JNK day 3** | **1.596** | p-Akt day 1 | 1.685 |
| **p-JNK day 1** | **1.439** | **p-JNK day 6** | 1.593 |
| p-NFkB p65 day 1 | 1.292 | p-p38 MAPK day 6 | 1.207 |
| p-ERK1/2 day 9 | 1.086 | p-ERK1/2 day 6 | 1.189 |
| p-p38 MAPK day 9 | 1.044 | p-p38 MAPK day 1 | 1.162 |
| p-IkBa day 3 | 0.918 | p-ERK1/2 day 1 | 1.100 |
| p-IkBa day 9 | 0.875 | p-NFkB p65 day 1 | 1.096 |
| p-NFkB p65 day 6 | 0.869 | p-IkBa day 1 | 1.092 |
| p-Akt day 9 | 0.800 | p-IkBa day 9 | 1.065 |
| p-JNK day 9 | 0.751 | p-Akt day 6 | 1.058 |
| p-Akt day 3 | 0.746 | **p-JNK day 3** | 1.053 |
| p-p38 MAPK day 1 | 0.669 | p-p38 MAPK day 3 | 1.053 |
| p-IkBa day 6 | 0.586 | p-Akt day 9 | 1.035 |
| p-Akt day 6 | 0.505 | p-NFkB p65 day 9 | 0.781 |
| p-Akt day 1 | 0.272 | p-JNK day 9 | 0.710 |
| p-IkBa day 1 | 0.156 | p-Akt day 3 | 0.684 |
| | | p-IkBa day 3 | 0.536 |
| | | p-NFkB p65 day 6 | 0.397 |
| | | p-IkBa day 6 | 0.316 |
| | | p-ERK1/2 day 3 | 0.285 |
| | | p-NFkB p65 day 3 | 0.277 |
| | | p-ERK1/2 day 9 | 0.156 |
| | | p-p38 MAPK day 9 | 0.156 |

Supplemental table 1

| Macrophages | | Osteoclast | |
|---|---|---|---|
| **Variables** | **VIP** | **Variables** | **VIP** |
| p-IkBa D6 | 1.550 | **p-c-Jun day 6** | **1.349** |
| **p-c-Jun day 1** | **1.517** | **p-c-Jun day 3** | **1.243** |
| p-Akt day 1 | 1.478 | **p-c-Jun day 9** | **1.182** |
| **p-c-Jun day 3** | **1.360** | p-IkBa day 6 | 1.152 |
| p-IkBa day 1 | 1.073 | p-Akt day 3 | 1.103 |
| p-JNK day 9 | 1.063 | p-Akt day 6 | 1.031 |
| p-IkBa day 3 | 0.933 | p-JNK day 1 | 1.018 |
| p-IkBa day 9 | 0.865 | p-JNK day 9 | 0.993 |
| p-JNK day 6 | 0.842 | p-IkBa day 3 | 0.932 |
| p-Akt day 9 | 0.816 | p-IkBa day 1 | 0.908 |
| p-JNK day 1 | 0.746 | p-Akt day 9 | 0.879 |
| p-c-Jun day 9 | 0.667 | p-c-Jun day 1 | 0.878 |
| p-c-Jun day 6 | 0.665 | p-Akt day 1 | 0.836 |
| p-Akt day 3 | 0.496 | p-p38 MAPK day 1 | 0.762 |
| p-p38 MAPK day 1 | 0.419 | p-JNK day 6 | 0.761 |
| p-Akt day 6 | 0.345 | p-IkBa day 9 | 0.714 |

Supplemental table 2