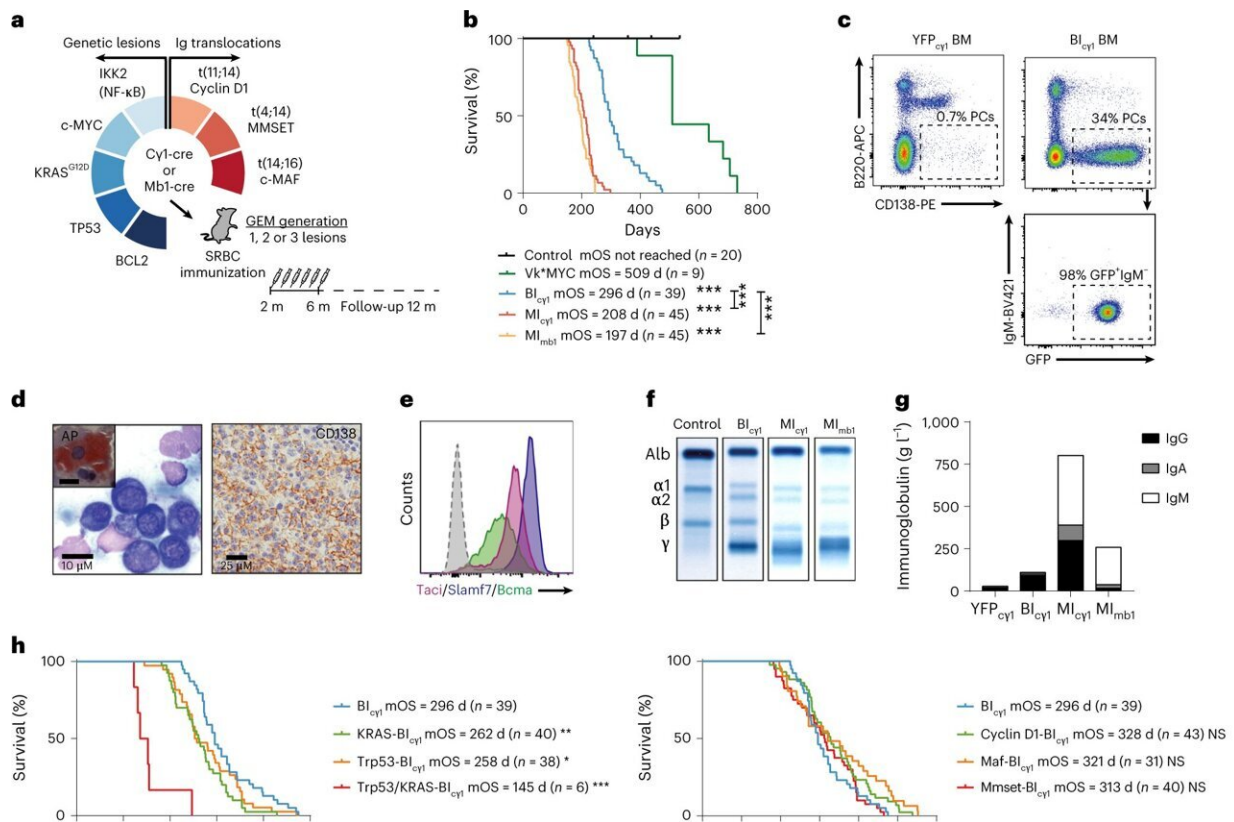# Scientists create mouse avatars to treat multiple myeloma

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Genetically heterogeneous mouse models of human-like multiple myeloma. **a**, Schematic of the genetic screen strategy, whereby transgenic mice were crossed with cγ1-cre or mb1-cre mice. Among 31 genetically heterogeneous mouse lines generated, MI_{mb1}, $MI_{c\gamma1}$ and $BI_{c\gamma1}$ strains developed MM. GEM, genetically engineered mice; m, months. **b**, Kaplan–Meier OS curves of MI_{mb1}, $MI_{c\gamma1}$, $BI_{c\gamma1}$, control ($YFP_{c\gamma1}$ and YFP_{mb1}) and Vk*MYC mice. **c**, Representative flow cytometry analysis in the BM of $BI_{c\gamma1}$ mice at the time of death, which shows an increased number of $GFP^+CD138^+B220^-sIgM^-$ MM cells. **d**, Giemsa staining of

a representative BM sample in BI$_{c\gamma1}$ mice revealed human-like PCs with expression of acid phosphatase (AP; left). On the right, immunohistochemical examination in BI$_{c\gamma1}$ mice revealed CD138 surface expression by MM cells. **e**, MM cells show increased surface expression of Bcma, Slamf7 and Taci according to flow cytometry analyses. **f**, Representative electrophoresis of immunoglobulin secretion in serum samples from MI$_{mb1}$, MI$_{c\gamma1}$ and BI$_{c\gamma1}$ mice shows M spikes corresponding to the gamma fraction. **g**, Quantification of immunoglobulin isotypes in serum samples by ELISA in MI$_{mb1}$ ($n = 3$), MI$_{c\gamma1}$ ($n = 2$), BI$_{c\gamma1}$ ($n = 4$) and YFP$_{c\gamma1}$ control ($n = 9$) mice. **h**, Kaplan–Meier survival curves of mouse lines that develop MM derived from the BI$_{c\gamma1}$ strain with additional $KRAS^{G12D}$ mutation, heterozygous $Trp53$ deletion, or expression of cyclin D1, c-MAF or MMSET. **i**, Kaplan–Meier survival curves of mouse lines that develop MM derived from MI$_{c\gamma1}$ mice with additional $KRAS^{G12D}$ mutation, heterozygous $Trp53$ deletion, c-MAF expression or BCL2 expression. **j**, Kaplan–Meier survival curves in mice with MMSET/NSD2 expression crossed with lines carrying either $IKK2^{NF\text{-}\kappa B}$ activation or c-MYC expression, which developed MM at old ages. **k**, Flow cytometry analyses in BI$_{c\gamma1}$ and MI$_{c\gamma1}$ mice revealed that precursor states precede clinically evident MM in genetically heterogeneous mice. **l**, Analysis of Igh clonality according to RNA-seq of immunoglobulin gene loci and classification by the presence of explicit clonotypes for each sample. B cell receptor (BCR) repertoires and the most expanded clone groups in control, MGUS and MM samples. Log-rank (Mantel–Cox) test was used. *P