#36. Preclinical Models of Multiple Myeloma

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Introduction and Background

Multiple myeloma is a clonal B cell malignancy characterized by the accumulation of terminally differentiated, antibody-producing plasma cells in the bone marrow that is invasive and drug resistant. Patients are generally asymptomatic until very late state disease. There are few preclinical models that recapitulate human disease. In this work, we have evaluated the human MM.1S model and the murine 5TGM1 model.

- MM.1S was derived from a 42-year-old African-American woman and has been documented to express CD25, CD38, CD52 and CD59. It also expresses the glucocorticoid receptor and is dexamethasone sensitive.
- 5TGM1 is a syngeneic model generated from the C57BL/KaLwRij mouse that is predisposed to develop several monoclonal B-cell proliferative disorders.

Materials and Methods

MM.1S(pMMP-LucNeo) Human

- MM.1S cells were transfected to express luciferase to enable *in vivo* imaging.
- Female SCID Beige mice (Envigo) and female NSG mice (Jackson Laboratories) were acquired and cells (5x10^6 cells/mouse) were injected IV (intravenously).
- Standard of Care testing in the MM.1S(pMMP-LucNeo) model in SCID Beige mice:
  - bortozomib at 2mg/kg, IP, (Q3Dx2; 3off)x4
  - bortozomib at 1.5mg/kg, IP, Q7Dx4
  - bortozomib at 0.5mg/kg, IV, (Q3Dx2; 3off)x4

5TGM1-luc Murine

- 5TGM1 cells were transfected to express luciferase to enable *in vivo* imaging.
- Female C57/KaLwRij (Envigo; Netherlands) and female NIH III (bg/nd/xid) mice (Envigo) were acquired and cells (5x10^6 cells/mouse) were injected IV (intravenously).
- Standard of Care testing in the 5TGM1-Luc model in C57/KalwRij and NIH III (bg/nd/xid) mice:
  - Carfilzomib at 3mg/kg, IP, QDx2

In vivo bioluminescence imaging (BLI) was performed with an IVIS 50 optical imaging system (Perkin Elmer, Waltham, MA) to quantify whole-body disease burden. Total burden was calculated using Living Image 4.3.1 (Perkin Elmer, Waltham, MA) software from a fixed volume ROI covering the whole mouse.

Results and Conclusions

MM.1S(pMMP-LucNeo) Human

- Aggressive and reliable growth seen in both SCID Beige mice and NSG mice. In the more immune-deficient NSG mouse, disease progresses more quickly with about 30 days to 50% survival vs. ~45 days in the SCID Beige mouse.
- Expression of CD138 is a hallmark of plasma cells and multiple myeloma cells. In an NSG study we determined, by flow cytometry, that >85% of the CD45- gate in the bone marrow was CD138+ on study day 21 suggesting significant engraftment of the tumor cells within the bone marrow.
- The optimization of MM.1S in NSG mice makes it an appealing model for novel CAR-T, TCR and other cell-based therapies.

5TGM1-luc Murine

- Aggressive and reliable growth in both the syngeneic C57/KaLwRij strain and the immune-deficient NIH III (bg/nd/xid) mouse strains. Disease progression behaves similarly in both strains of mice, with significant tumor cells localizing in the spine and the long bones.
- This model is suitable for testing immunotherapies and other classes of drugs.

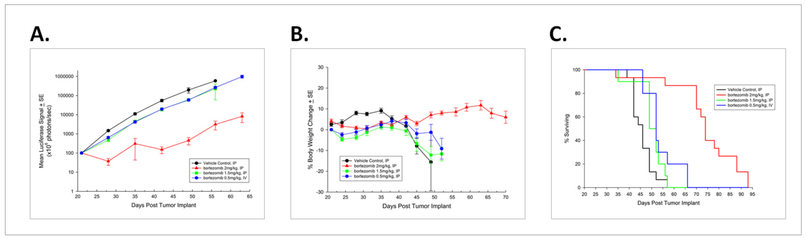

Figure 1. MM.1S(pMMP-LucNeo) model in SCID Beige mice.

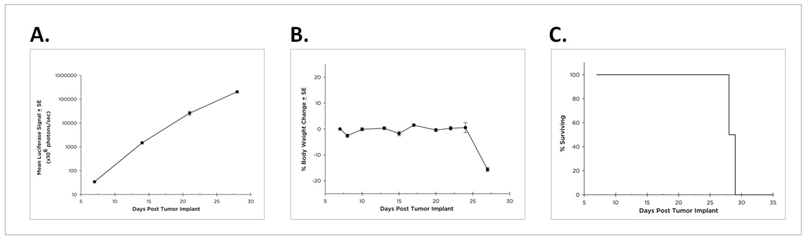

Figure 2. MM.1S(pMMP-LucNeo) model in NSG mice.

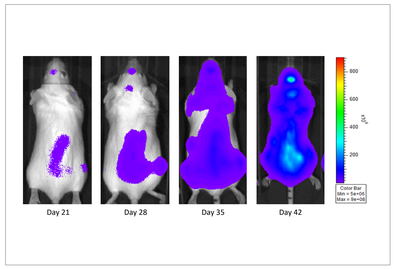

Figure 3. BLI images in SCID Beige tumor-bearing mice.

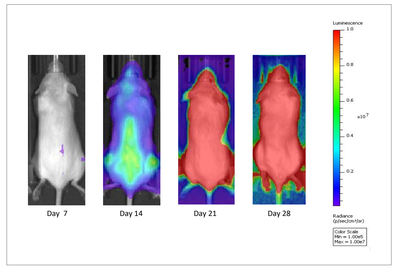

Figure 4. BLI images in NSG tumor-bearing mice.

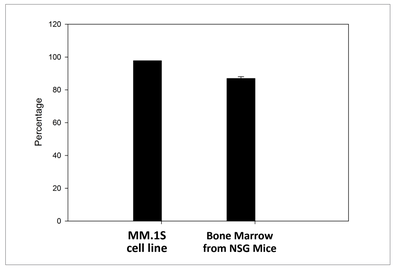

Figure 5. %CD138+ cells in bone marrow of NSG tumor-bearing mice.

MM.1S(pMMP-LucNeo) Human

- Aggressive growth in both SCID Beige (Figures 1 & 3) and NSG (Figures 2 & 4) mice, with disease progressing more rapidly in the NSG mice.
- CD138+ cells can be observed in the bone marrow of mice IV implanted with MM.1S(pMMP-LucNeo) (Figure 5), suggesting that this model mimics an important aspect of human multiple myeloma.

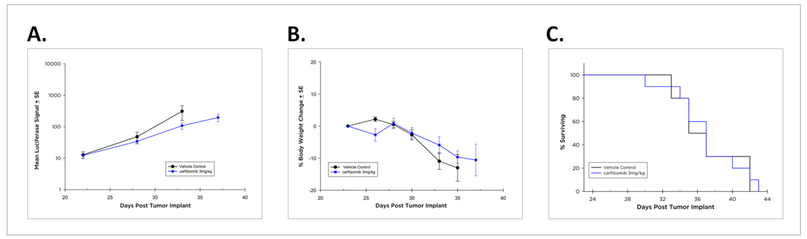

Figure 6. 5TGM1-luc model in syngeneic C57/KaLwRij mice.

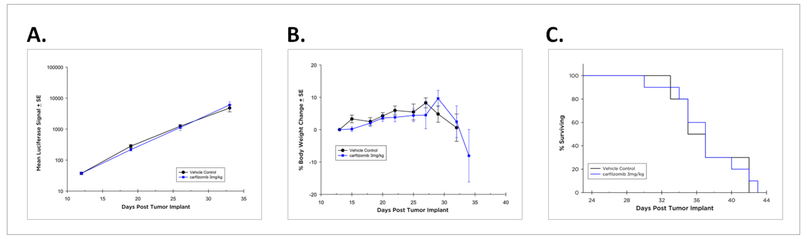

Figure 7. 5TGM1-luc model in immune-deficient NIH III (bg/nd/xid) mice.

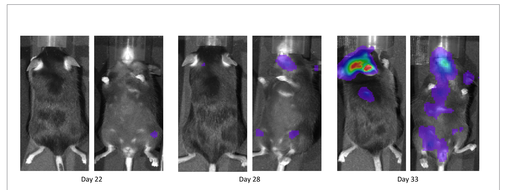

Figure 8. BLI images in C57/KaLwRij tumor-bearing mice.

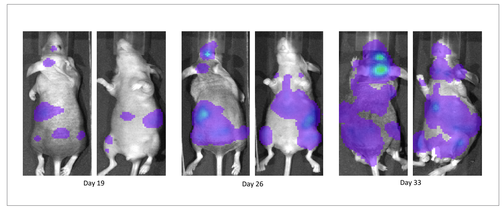

Figure 9. BLI images in tumor-bearing NIH III (bg/nd/xid) mice.

Table 1. Incidence of Tumor Burden by *Ex Vivo* BLI

Tumor Line	MM.1S (pMMP-LucNeo)	5TGM1-luc	5TGM1-luc
Mouse Strain	SCID Beige	C57/ KaLwRij	NIH III (bg/nd/xid)
Head	93%	59%	58%
Lung	93%	100%	40%
Hand Limbs	93%	88%	92%
Spine	93%	100%	

5TGM1-luc Murine

- Aggressive growth with similar disease progression is observed in both the syngeneic (Figures 6 & 8) and the immune-deficient mouse strains (Figures 7 & 9).
- Both models result in significant tumor burden by *ex vivo* BLI (Table 1).

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