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**Selective antisense oligonucleotide inhibition of human IRF4 prevents malignant myeloma regeneration via cell cycle disruption.**

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**Public Summary:**

In multiple myeloma, inflammatory and anti-viral pathways promote disease progression and cancer stem cell generation. Using diverse pre-clinical models, we investigated the role of interferon regulatory factor 4 (IRF4) in myeloma progenitor regeneration. In a patient-derived xenograft model that recapitulates IRF4 pathway activation in human myeloma, we test the effects of IRF4 antisense oligonucleotides (ASOs) and identify a lead agent for clinical development (ION251). IRF4 overexpression expands myeloma progenitors, while IRF4 ASOs impair myeloma cell survival and reduce IRF4 and c-MYC expression. IRF4 ASO monotherapy impedes tumor formation and myeloma dissemination in xenograft models, improving animal survival. Moreover, IRF4 ASOs eradicate myeloma progenitors and malignant plasma cells while sparing normal human hematopoietic stem cell development. Mechanistically, IRF4 inhibition disrupts cell cycle progression, downregulates stem cell and cell adhesion transcript expression, and promotes sensitivity to myeloma drugs. These findings will enable rapid clinical development of selective IRF4 inhibitors to prevent myeloma progenitor-driven relapse.

**Scientific Abstract:**

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