Introduction:

- Despite considerable advances in therapy over recent years, multiple myeloma (MM) remains largely incurable with a clinical course characterised by ever-shortening periods of treatment and relapse; new therapies with novel mechanisms of action are needed.
- The immunomodulatory agents (IMiDs) in current clinical practice can augment immune effector function and combination with other immunologically active agents is a rational avenue of investigation - indeed trials of IMiDs with agents such as monoclonal antibody therapies are already underway.
- The naturally occurring oncolytic virus reovirus serotype 3 Dearing (Reolysin, Oncolytics Biotech Inc) has been shown to be safe in the context of advanced solid cancers, and more recently in patients with MM.
- In this study we demonstrate the potential of reovirus in combination with IMiDs and steroids to induce both direct tumour cell killing and an anti-tumour immune response, especially in the context of the cytoprotective effect of stromal cell interactions.

Figure 1: HMCLs express JAM1 and are killed by Reovirus in a time- and dose-dependent manner; a JAM1-negative tumour cell is resistant

A-C) KMS11, JIM3 and OPM2 were treated with combinations of Reovirus, dexamethasone and lenalidomide; cell death was assessed by intracellular amine staining at the specified time points.

D) Primary myeloma cells from a patient bone marrow sample at diagnosis was treated with Reovirus-IMiD combinations and cell death assessed in CD138+ cells at 48 hours.

Conclusion:

- Reovirus exerts oncolytic effects on a range of human myeloma cell lines and primary samples; the virus is effective in combination with immunomodulatory drugs (IMiDs) in current clinical use.
- Immune cells are activated by reovirus treatment; IMiDs augment this effect.
- Reovirus-activated NK cells exhibit enhanced degranulation against and killing of tumour cells, including the OPM2 line, which is resistant to direct oncolysis.
- Stromal cells confer protection to myeloma cells against current clinical agents; in combination with these agents, reovirus can mitigate stromal cell-mediated tumour protection.
- Reovirus-IMiD combinations now warrant clinical evaluation.

Figure 2: Reovirus and IMiDs exert effects in combination against human myeloma cell lines and primary malignant bone marrow plasma cells

A) Expression of the Reovirus receptor JAM1 on HMCLs at baseline and after incubation with lenalidomide for 72h, measured by flow cytometry.

B-F) HMCLs were treated with Reovirus at a range of multiplicities of infection (MOIs) and assessed for viability at 4 time points by intracellular amine staining and flow cytometry.

Figure 3: Reovirus and IMiDs activate immune effectors from healthy donors’ peripheral blood, and from patients with multiple myeloma

Figure 4: Reovirus-activated NK cells kill tumour targets, including those resistant to direct viral oncolysis

Figure 5: Reovirus overcomes stromal-mediated cytoprotection

Human myeloma cells lines were incubated either alone, or on a layer of stromal cells (HS-27, HS-5, M2-10B4, CD40L+L929) and treated with combinations of dexamethasone, IMiDs and reovirus. A) The action of dexamethasone on U266 is inhibited by HS-27 co-culture; reovirus remains effective. B) Combination therapies with H929 in culture with stroma.

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