Characterising the role of HDAC6 in the control of human macrophage IL-10 production

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Background

❖ Histone deacetylate 6 (HDAC6) is a protein deacetylase implicated in diverse cellular processes including cell signalling and motility.

❖ Interleukin 10 (IL-10) is a pleiotropic cytokine with both immunosuppressive and proinflammatory activity.

❖ Clinical trials of therapeutic IL-10 administration have been undertaken in cancer and inflammatory disorders including rheumatoid arthritis and Crohn's disease.

❖ Potentially counter to this, inhibition of IL-10 has also been linked with anti-tumour and anti-inflammatory properties.

❖ KA2309 & KA2508 are potent and selective inhibitors of HDAC6 identified as part of a clinical drug development programme; a closely related compound (KA2507) has completed a Phase I clinical trial in cancer without adverse tolerability signals (NCT03008018).

Methodology

❖ M0 macrophages were derived from the peripheral blood mononuclear cells of healthy human donors.

❖ M0 macrophages were differentiated *in vitro* into M2 macrophages in the presence or absence of test compounds at increasing concentrations.

❖ Inhibitors of PI3-kinase and p38 MAP kinase were run as positive controls.

❖ At the end of the differentiation process, culture supernatants were collected for IL-10 quantification.

In vitro macrophage studies were performed by Explicyte, Bordeaux, France

Results

1. KA2309 & KA2508 are potent inhibitors of HDAC6 that are free from significant effects on other HDAC family enzymes.

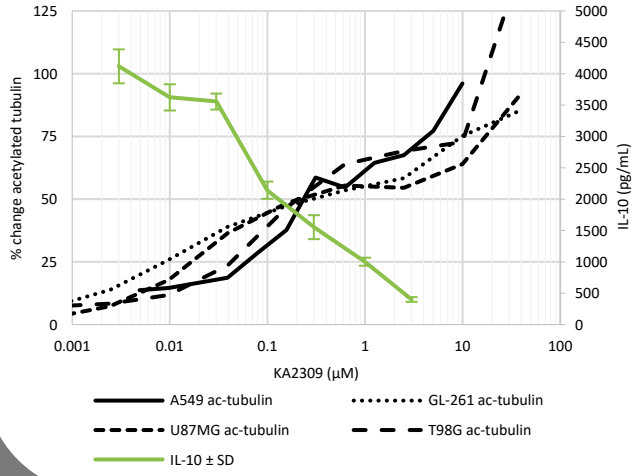
	HDAC family biochemical IC_{50} (nM)										
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
KA2309	>10,000	>10,000	>10,000	>10,000	3,369	3	3,007	927	6,138	>10,000	>10,000
KA2508	7,935	>10,000	>10,000	2,615	701	4.1	695	162	2,356	>10,000	>10,000

	Ac-tubulin EC_{50} (nM)	**Ac-histone EC_{50} (nM)**
KA2309	153	15,753
KA2508	104	*Not tested*

Acetylated α-tubulin, a cellular marker of on-target HDAC6 inhibition, and acetylated histone H3, a cellular marker of off-target class I HDAC family inhibition, were quantitated in A549 human lung cancer cells.

2. KA2309 demonstrates dose-dependent inhibition of IL-10 release from human *in vitro* cultured macrophages. The IC_{50} of this effect is similar to the EC_{50} for the induction of acetylated α-tubulin in human and mouse tumour cell lines.

Comparable data were obtained for KA2508.



Conclusions

Selective inhibition of HDAC6 blocks the release of IL-10 from human macrophages.

❖ Small molecule HDAC6 inhibition is feasible and well tolerated in man (based on a recent Phase I clinical trial of a sister compound).

❖ Inhibition of IL-10 may enhance the anti-tumour immune response, although further work is required to understand the mechanisms.

❖ It has recently been suggested that IL-10 may play a role in the pathogenesis of severe COVID-19; inhibition of IL-10 may be beneficial in this setting[1].

❖ Small molecule inhibitors of IL-10 release open the door for novel therapeutic avenues to be explored.

1. Lu et al, Trends Immunol. Epub 2 Nov 2020; PMID: 33214057

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