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Title of Presentation	A novel transgenic Kit+/D814V mouse model of SM-AHN reveals Th17/Th22-skewed inflammation and increased susceptibility to Mrgprb2-mediated anaphylaxis
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Abstract of Presentation	Progress in developing effective therapies for systemic mastocytosis (SM) continues to be limited by the absence of well-characterized pre-clinical models. To address this gap, we generated an inducible transgenic Scl-CreERT2;Kit+/D814V mouse line expressing KitD814V in hematopoietic stem and progenitor cells. This model reproduces core features of advanced SM with an associated hematologic neoplasm (SM-AHN), including increased mast cell (MC) numbers, altered blood counts, extramedullary hematopoiesis and reduced survival. Here, we characterized the systemic immune environment and anaphylactic responses in this model. Multiplex serum proteomic profiling (Olink® Target 48 cytokine panel) revealed a distinct inflammatory signature in Kit+/D814V mice already at baseline, dominated by cytokines associated with Th17/Th22-type immune responses (IL-17A, IL-17F, IL-22, IL-21, IL-31), alongside elevated CXCL11, CCL5 and CTLA4. This points to disease effects extending well beyond MC expansion toward broader immune remodeling. Anaphylaxis was induced via IgE- and Mrgprb2-mediated MC activation, with body temperature monitored to assess severity; cytokines were profiled before and after the anaphylactic reaction, and a subset of mice received avapritinib for 16 consecutive days.

	KitD814V-mutant mice responded similarly to controls following IgE-mediated anaphylaxis, but showed a significantly greater drop in body temperature after Mrgprb2-mediated anaphylaxis using ciprofloxacin. Both groups exhibited a shared "core" anaphylaxis cytokine signature (e.g., IL-10, IL-16, CCL12), whereas e.g. IL-17F and IL-22 were selectively elevated in mutant mice. Avapritinib treatment furthermore reduced anaphylaxis severity in mutant mice. Together, these findings demonstrate that KitD814V drives a systemic Th17/Th22-skewed inflammatory state and increased susceptibility to Mrgprb2-mediated anaphylaxis, both of which respond to KIT-targeted therapy.
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