

Blockade of Cytokine Production and Attenuation of Experimental Arthritis Progression by Novel Small Molecule Inhibitors of Sec61-Dependent Protein Secretion

Janet L Anderl¹, R Andrea Fan¹, Jing Jiang¹, Henry WB Johnson¹, Annalise Kanicki¹, Christopher J Kirk¹, Evan R Lewis¹, Eric Lowe¹, Dustin L McMinn¹, Beatriz Millare¹, Tony Muchamuel¹, Meera Rao¹, Jack Taunton², Christine Tun¹, Jinhai Wang¹, Jennifer A Whang¹, Jean Zhang¹, Patricia Zuno¹

¹Kezar Life Sciences, Inc., South San Francisco, CA, USA;

²University of California, San Francisco, San Francisco, CA, USA

Disclosures

Employees and Shareholders of Kezar Life Sciences

JL Anderl	A Kanicki	DL McMinn	J Wang
RA Fan	CJ Kirk	B Millare	JA Whang
J Jiang	ER Lewis	T Muchamuel	J Zhang
HWB Johnson	E Lowe	M Rao	P Zuno

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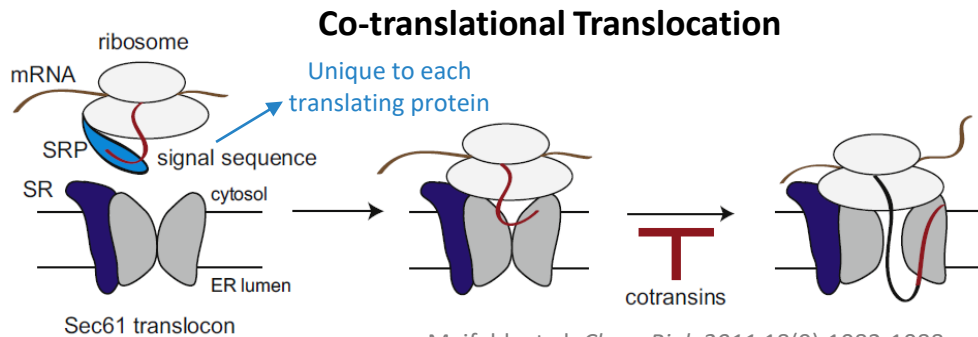
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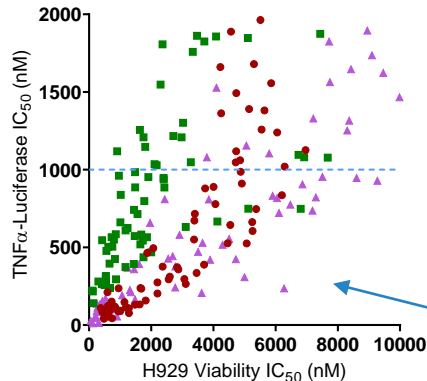
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Discovery of Sec61 Inhibitors with Anti-Cytokine Activity



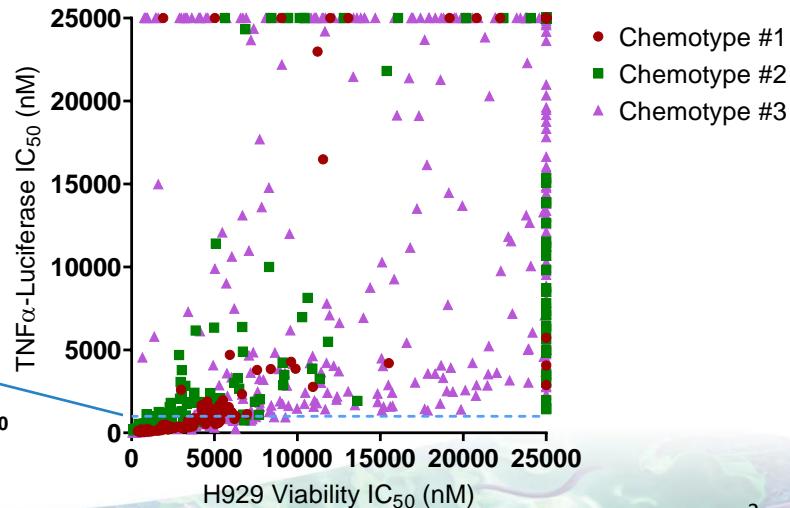
Maifeld, et al. *Chem Biol.* 2011;18(9):1082-1088.

Sec61 inhibition by distinct chemotypes exhibits range of potency on TNF α -luciferase reporter cell line and viability of Sec61-sensitive H929 multiple myeloma cells



Sec61-gated secretion of proteins via the endoplasmic reticulum can be selectively inhibited by small molecules

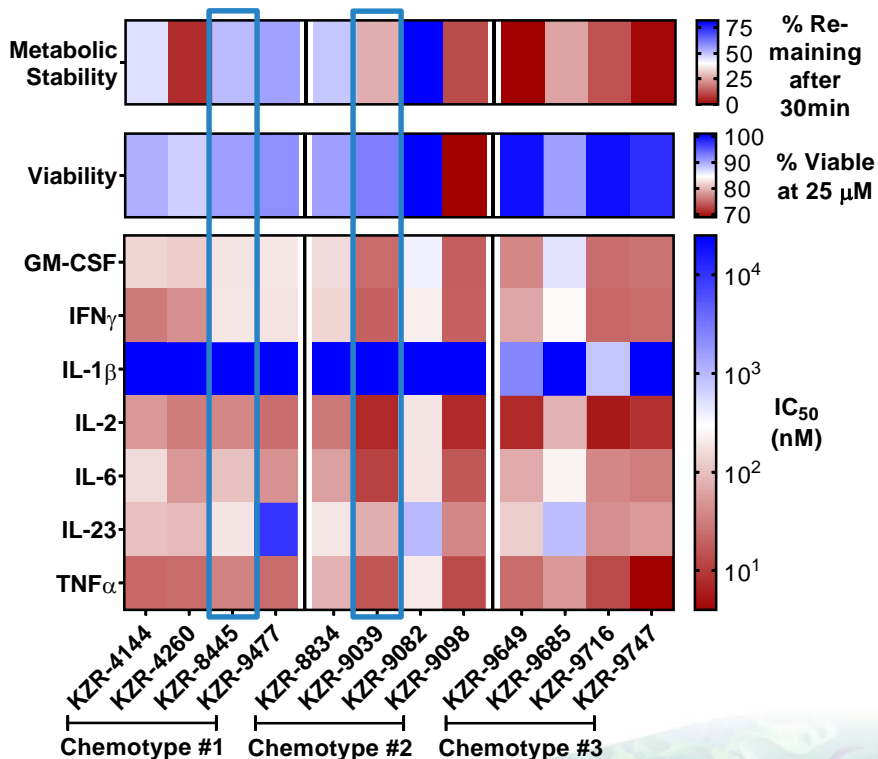
Small Molecule Inhibition of TNF α Reporter and H929 Viability



Sec61 Inhibitors Block Expression of Multiple Pro-Inflammatory Cytokines in Stimulated Primary Immune Cells

- Potent TNF α suppressors selected for 24-hour treatment of LPS or anti-CD3/anti-CD28-stimulated human PBMCs
- Tool compounds selected for in vivo studies based on chemotype, anti-cytokine potency, low cytotoxicity, and in vitro mouse liver microsome stability

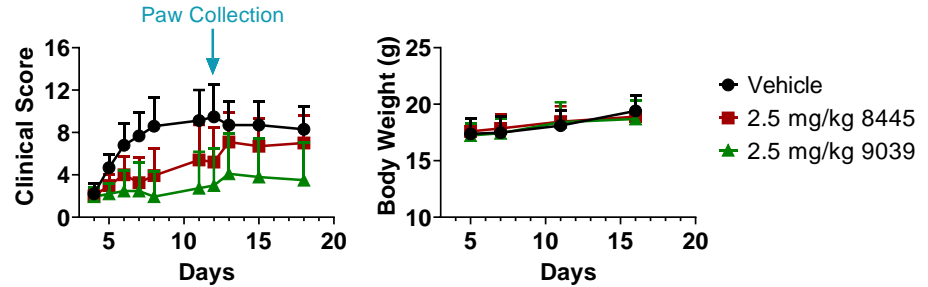
Viability and Cytokine Effects in Human PBMC



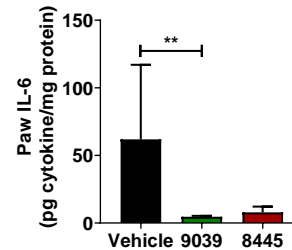
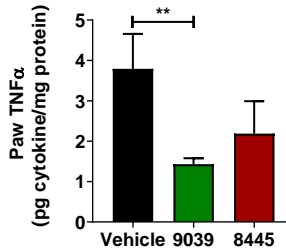
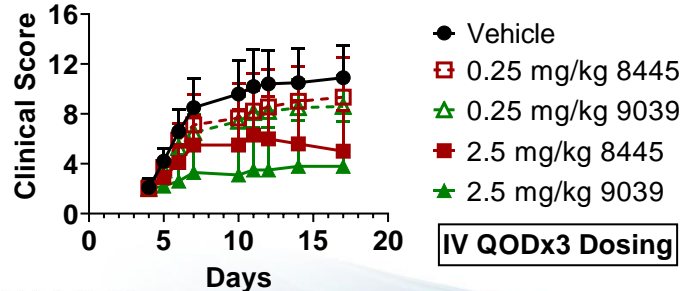
KZR-8445 and -9039 Demonstrate Amelioration of Disease Activity in Mouse Collagen Antibody-Induced Arthritis Model

- Dose-dependent improvements in clinical score at doses $<1/8^{\text{th}}$ MTD
- Significant reductions in pro-inflammatory cytokines in paws measured at disease peak
- **Small molecule targeting of Sec61 is a promising therapeutic target for inflammatory and autoimmune disorders**

CAIA Disease Activity, Body Weight, and Paw Cytokine Levels



CAIA Disease Activity Dose Responses



Thank you!

Selective Targets. Broad Impact.

*Uniquely Powerful Approaches to Tackling the
Toughest Diseases*

OUR STORY



For more information, visit our
website at www.kezarlifesciences.com
or email us: contact@kezarbio.com