

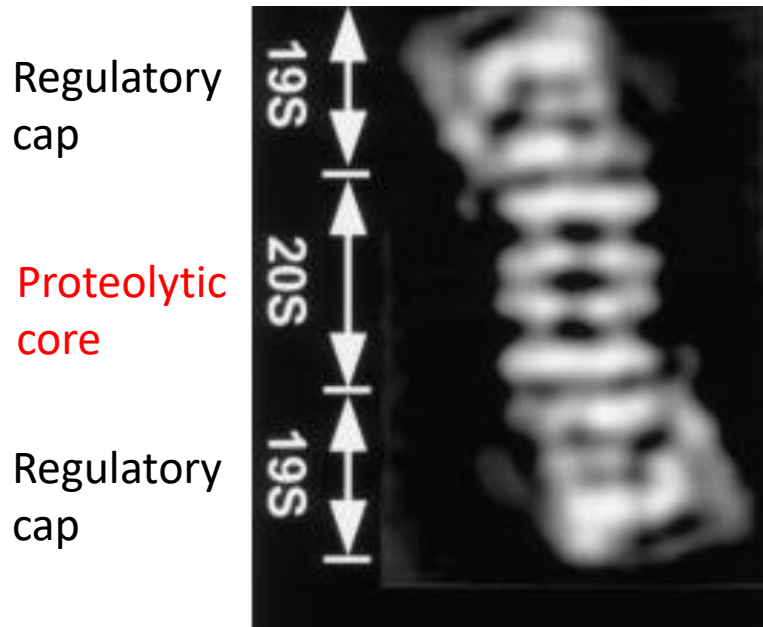
KZR-616, A Selective Inhibitor of the Immunoproteasome, Attenuates the Development of Murine Lupus Nephritis

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Henry W B Johnson, Eric Lowe, Christopher J Kirk

Disclosures

Employee and Shareholder of Kezar Life Sciences

The Proteasome: Primary Means of Intracellular Protein Degradation

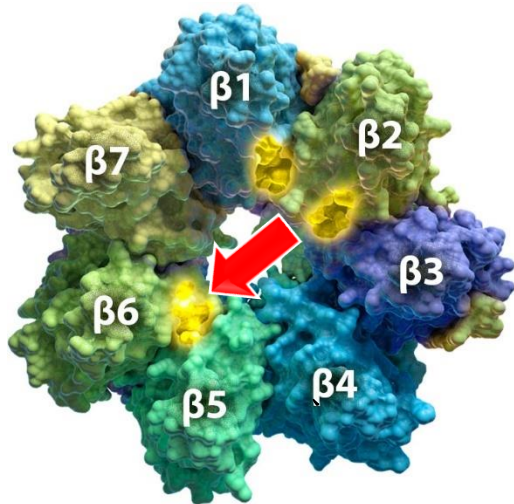


J. Struct. Biol. 1998, 121, 19.

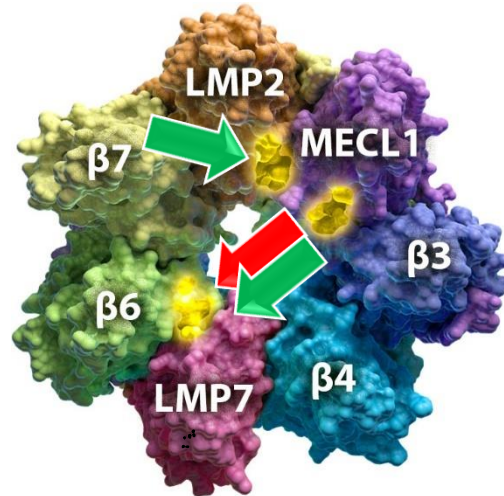
- Ubiquitously expressed and highly conserved
- Controls cellular functions *via* protein degradation
 - Degradation of misfolded/damaged proteins
 - Regulates cellular function (e.g. cell cycle) via targeted protein degradation
- Validated target in plasma cell neoplasms
 - Bortezomib (VELCADE®)
 - Carfilzomib (KYPROLIS®)
 - Ixazomib (NINLARO®)
- 2 major forms of the 20S core
 - Constitutive proteasome
 - Immunoproteasome

The Immunoproteasome is a Unique Form of the Proteasome

Constitutive proteasome



Immunoproteasome



↑ Chymotrypsin-like (CT-L):
1^o Targets of approved proteasome
inhibitors
(bortezomib/carfilzomib/ixazomib)
(BTZ/CFZ/IXA)

↑ Targets of KZR-616

Unique N-terminal Threonine protease active sites



Ubiquitous Expression
(e.g. Heart and Liver)

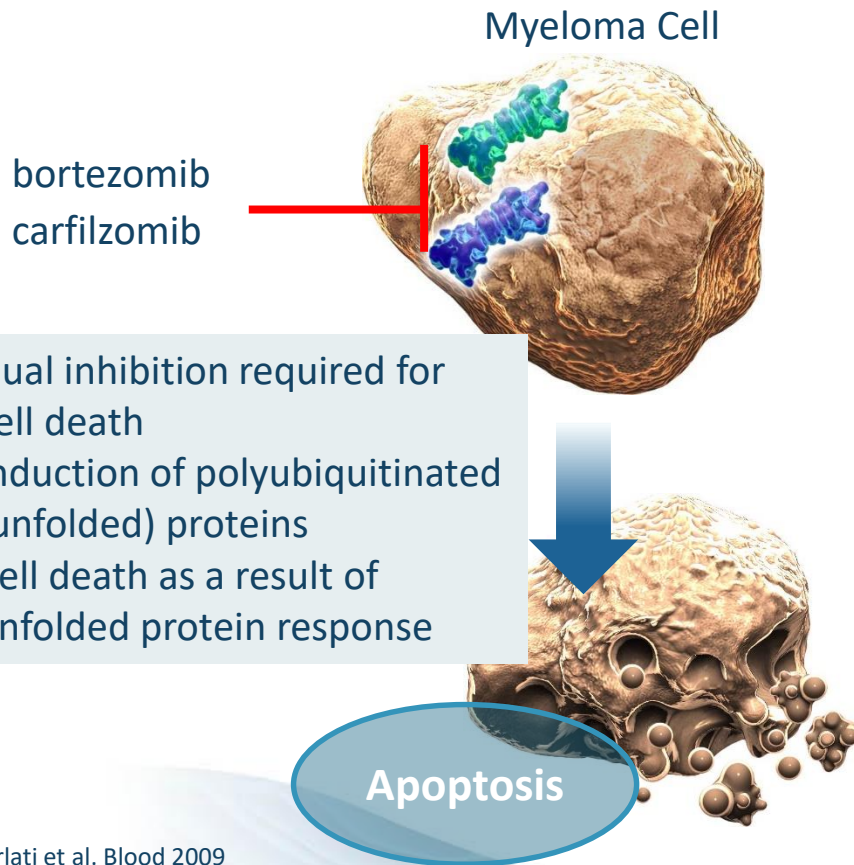


Immune System
(e.g. lymphocytes)

- Immunoproteasome active site subunits induced in non-immune cells upon exposure to inflammatory cytokines (e.g. IFN- γ)
- Expression is increased in multiple autoimmune disorders

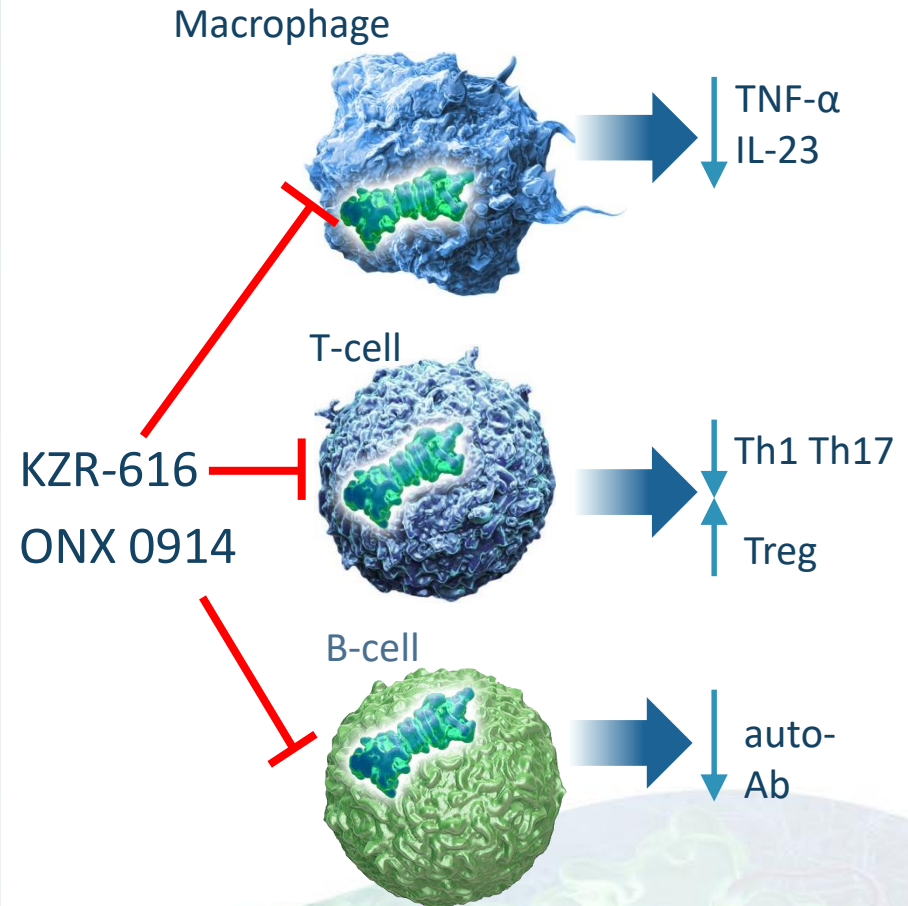
Distinct Cellular Effects of Dual Proteasome Inhibition vs. Selective Immunoproteasome Inhibition

Dual-Targeting Proteasome Inhibitors



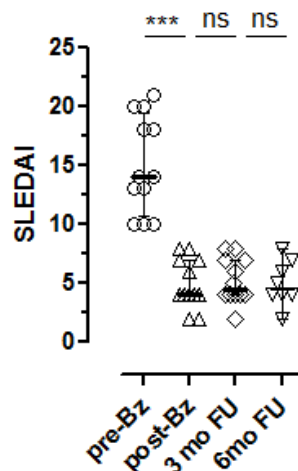
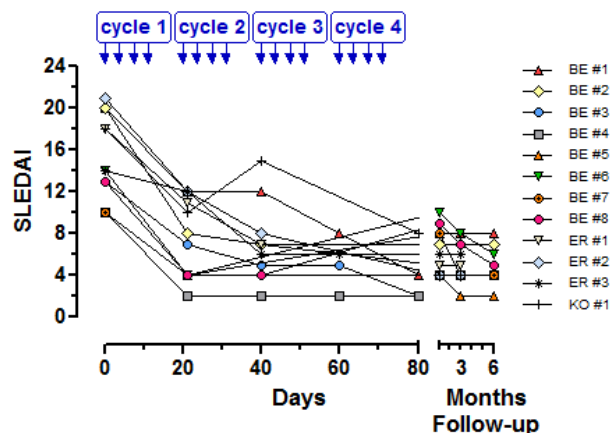
Parlati et al. Blood 2009

Selective Immunoproteasome Inhibitors

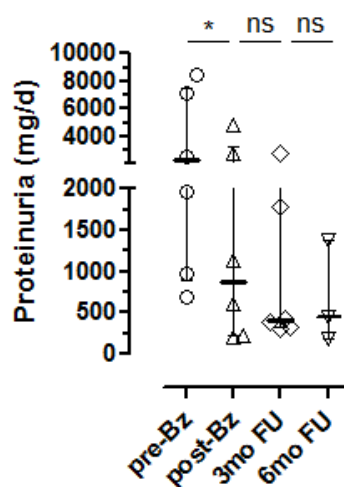
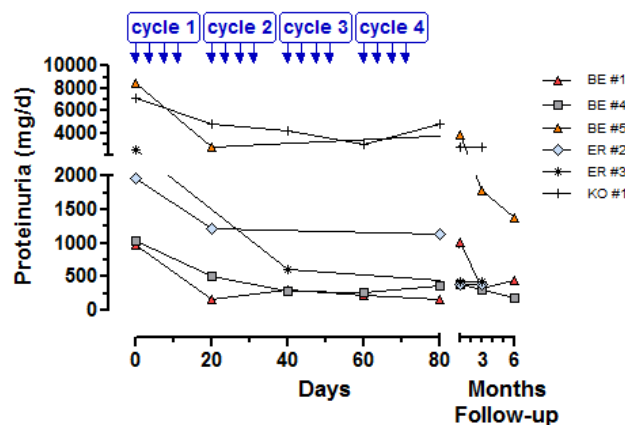


Muchamuel et al Nat Med 2009, Ichikawa et al. Arthritis and Rheumatism 2011, Khalim et al. JI 2012

Rapid Improvement in Systemic Lupus Erythematosus (SLE) Symptoms and Lupus Nephritis (LN) Disease Seen with Bortezomib Therapy

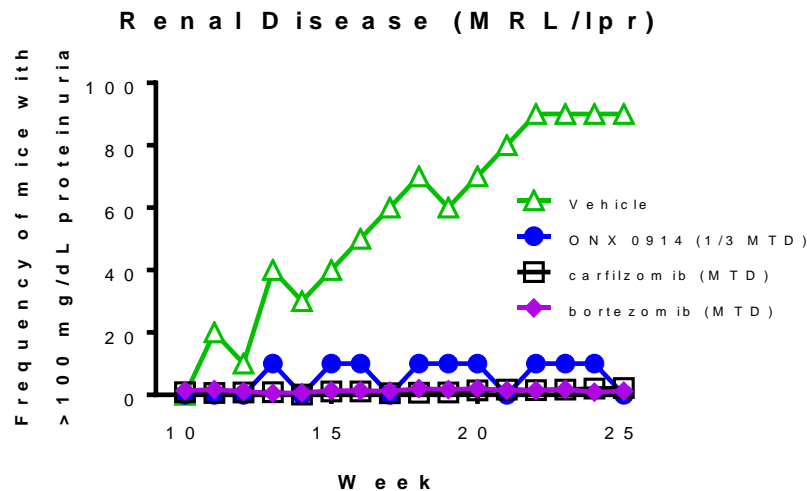


- Median SLEDAI
 - Baseline: 14
 - Post BTZ: 4
- Durable reduction in SLEDAI improvements
- Reintroduction of other therapies maintains responses



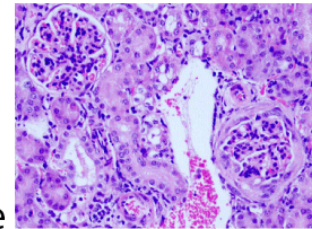
- Median proteinuria
 - Baseline: 2.2 g/day
 - Post BTZ: 0.87 g/day
- Continued reduction in proteinuria seen post treatment
- AEs occurred in 92% of patients and 58% discontinued due to AEs

Immunoproteasome Inhibition Replicates the Activity of Bortezomib in Mouse Models of SLE and LN

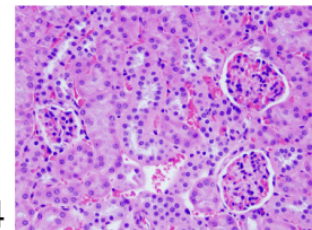


Kidney Histology

Vehicle

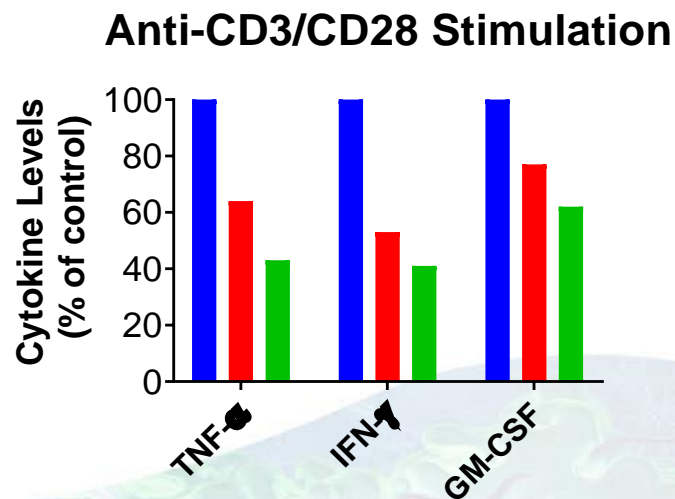
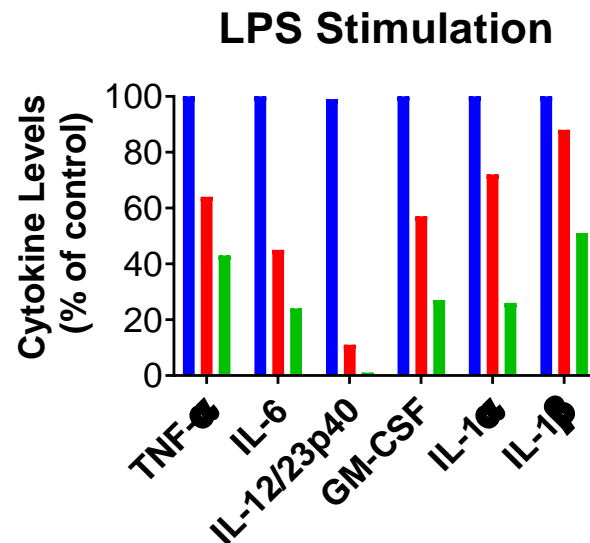
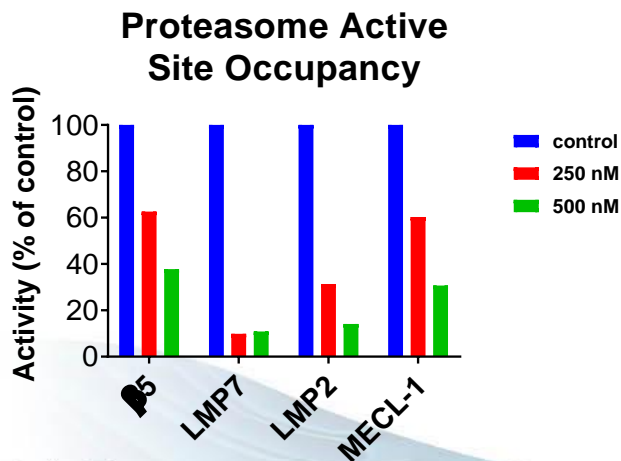
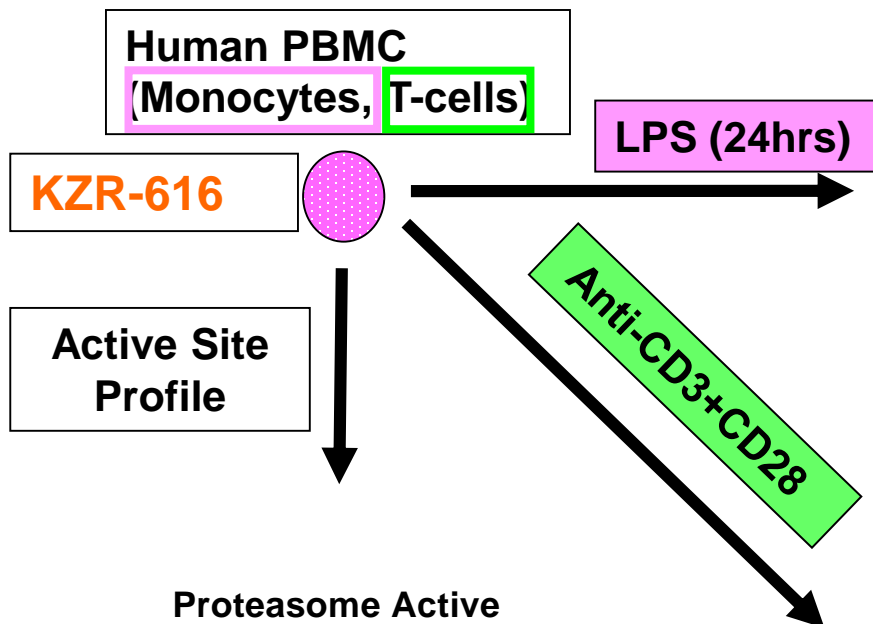


ONX 0914



- Selective immunoproteasome inhibition (ONX 0914) resulted in equivalent efficacy as dual inhibitors
- Therapeutic benefit of ONX 0914 seen at sub-maximum tolerated doses (MTD)
- Equivalent improvements in autoantibody reduction, blockade of IFN- α production and reduced antibody secreting cell (ASC) formation

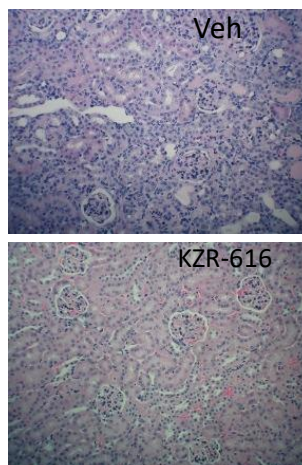
KZR-616 Blocks Inflammatory Cytokine Production In Vitro



KZR-616 Blocks LN Disease Progression in NZB/W F1 Mice

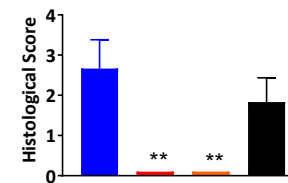
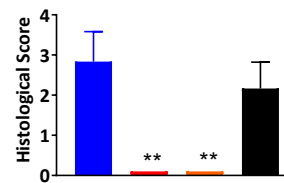
KZR-616 IV or SC

NZB/W F1
24 weeks



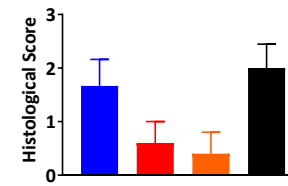
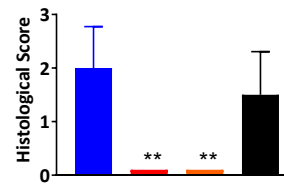
Glomerular Nephritis

Glomerular Sclerosis



Tubular Changes

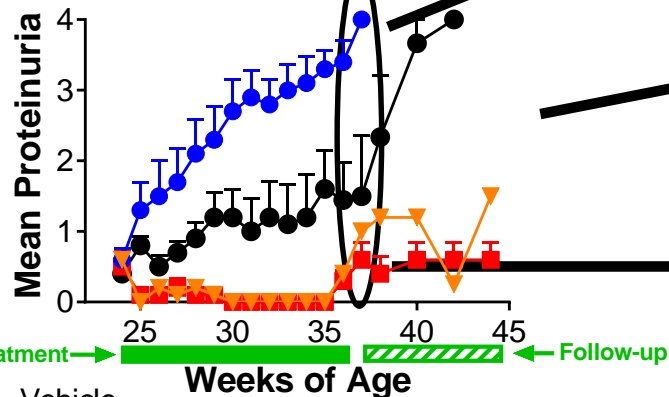
Lymphoid Infiltrate



Vehicle 10 mg/kg SC QODX3
5 mg/kg IV QODX3 MMF 30 mg/kg QD

** = P<0.01

Total Proteinuria



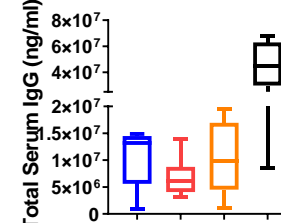
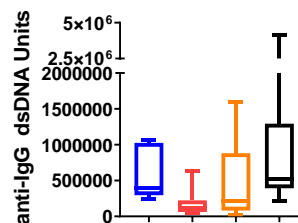
Weeks of Age

● Vehicle ● MMF 30 mg/kg QD
■ 5 mg/kg IV QODX3 ▲ 10 mg/kg SC QODX3

MMF-Mycophenolate Mofetil

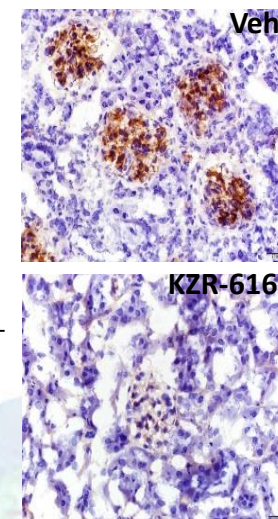
anti-IgG dsDNA Ab

Total IgG



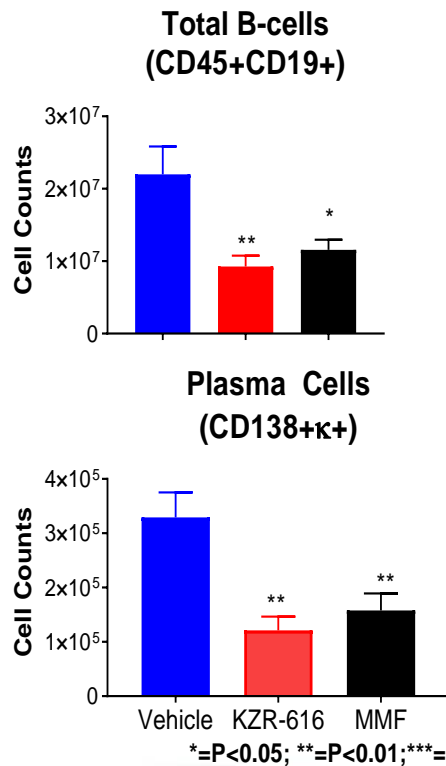
Vehicle 5 mg/kg IV QODX3
10 mg/kg SC QODX3 30 mg/kg MMF PO

IgG Deposition

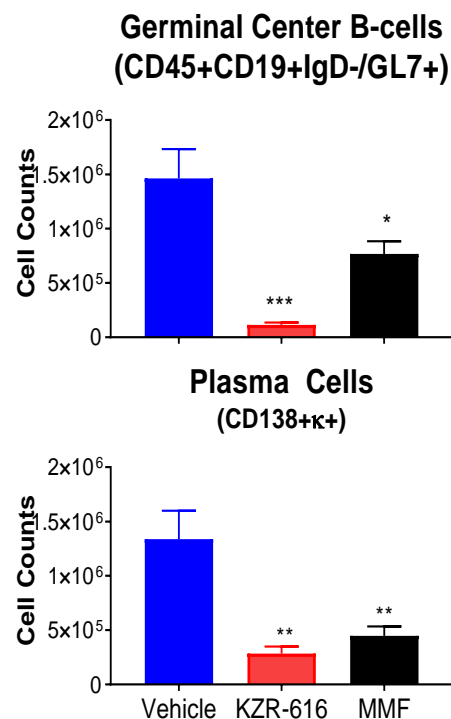


KZR-616 Treatment in NZB/W F1 Mice Reduces Plasma Cell Formation

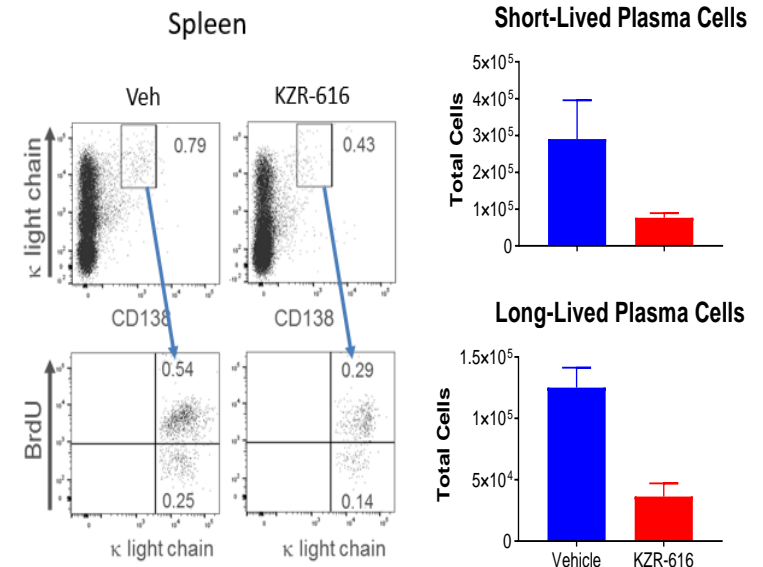
Bone Marrow



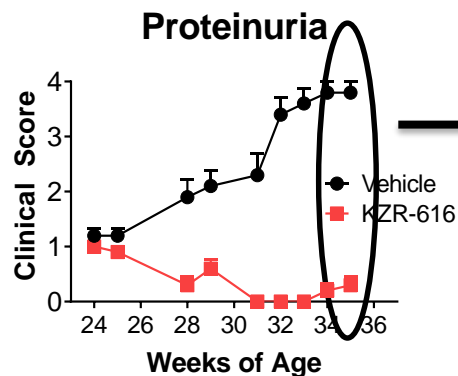
Spleen



Splenic Plasma Cells (BrdU incorporation)

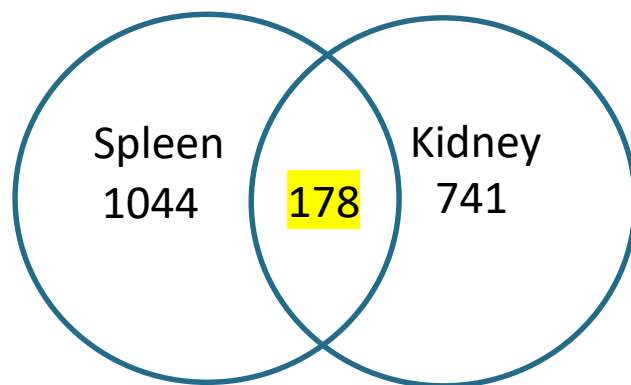


KZR-616 Treatment Results in Inhibition of Immune Response Pathways



RNA Sequencing
GoStat
Ingenuity Pathway
Analysis (IPA)

Genes Inhibited

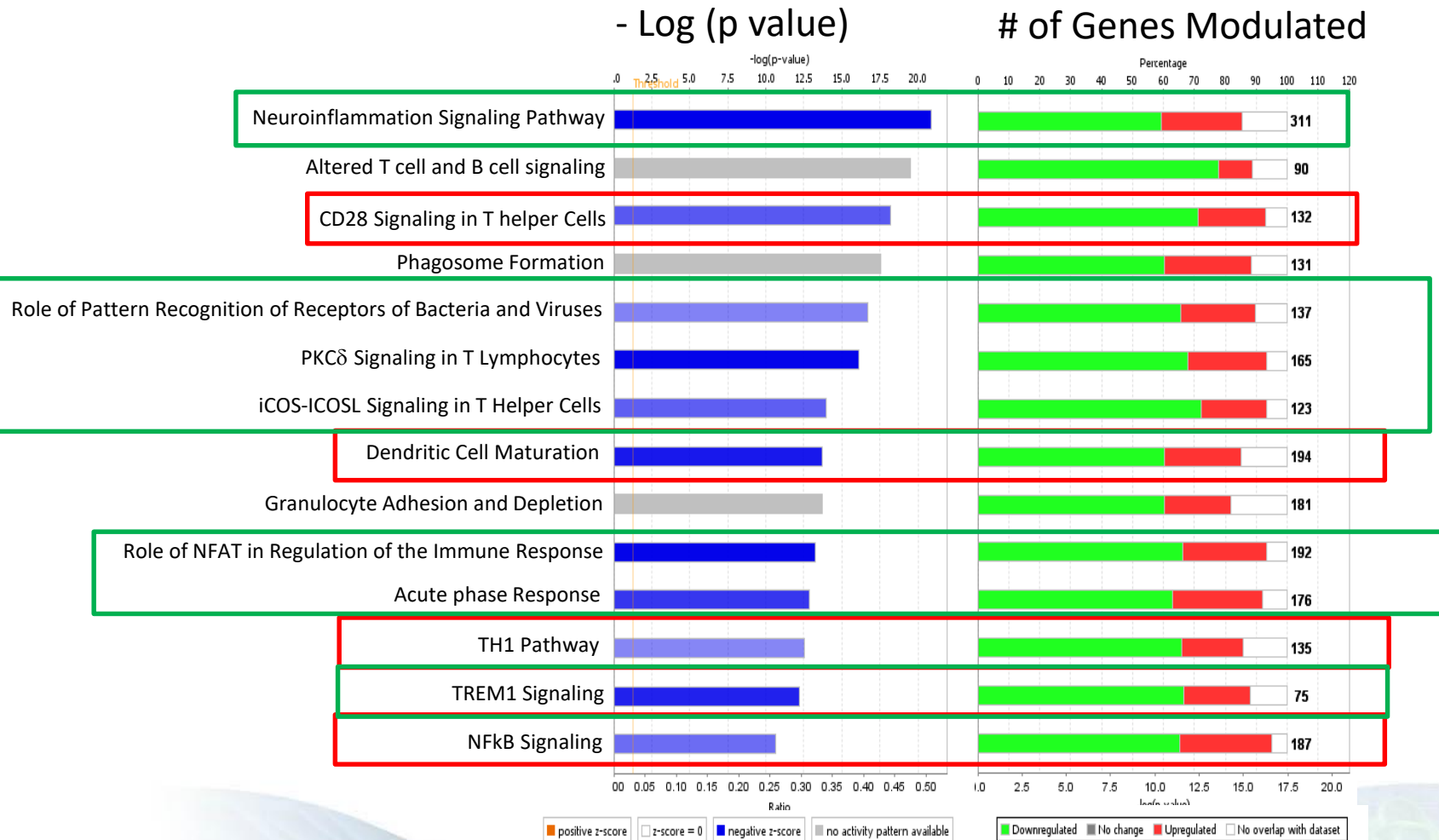


Log2 FC cutoff	FDR cutoff/P value
1	0.001, p<0.1
# Genes at Cutoff	
Spleen	1222
Kidney	919

Most Significant Gene Ontologies Inhibited

- immune response
- immune system process
- external side of plasma membrane
- cell surface
- leukocyte activation
- MHC class II
- cell activation
- regulation of lymphocyte activation
- antigen processing and presentation of exogenous lymphocyte activation
- antigen processing and presentation
- regulation of T cell activation

KZR-616 Treatment Modulates Multiple Immune Response Pathways in the Kidneys of Diseased Mice



Top Canonical and Disease Functions Modulated in the Spleen and Kidney of KZR-616 Treated NZB/W F1 Mice

Top Canonical Pathways

S K

PKCθ Signaling in T Lymphocytes		
Role of NFAT in Regulation of the Immune Response		
Neuroinflammation Signaling Pathway		
Dendritic Cell Maturation		
B Cell Receptor Signaling		
Calcium-induced T Lymphocyte Apoptosis		
PI3K Signaling in B Lymphocytes		
TREM1 Signaling		
Phospholipase C Signaling		
iCOS-iCOSL Signaling in T Helper Cells		
Th1 Pathway		
CD28 Signaling in T Helper Cells		
Interferon Signaling		
Production of Nitric Oxide and Reactive Oxygen Species in Macrophages		
Acute Phase Response Signaling		
GP6 Signaling Pathway		
FAT10 Cancer Signaling Pathway		
Inflammasome pathway		
Tec Kinase Signaling		
T Cell Exhaustion Signaling Pathway		
HMGB1 Signaling		
Role of Pattern Recognition Receptors in Recognition of Bacteria and Viruses		
PPAR Signaling		
Th17 Activation Pathway		
NF-κB Signaling		
FcγRIIB Signaling in B Lymphocytes		

-5.196 3.900

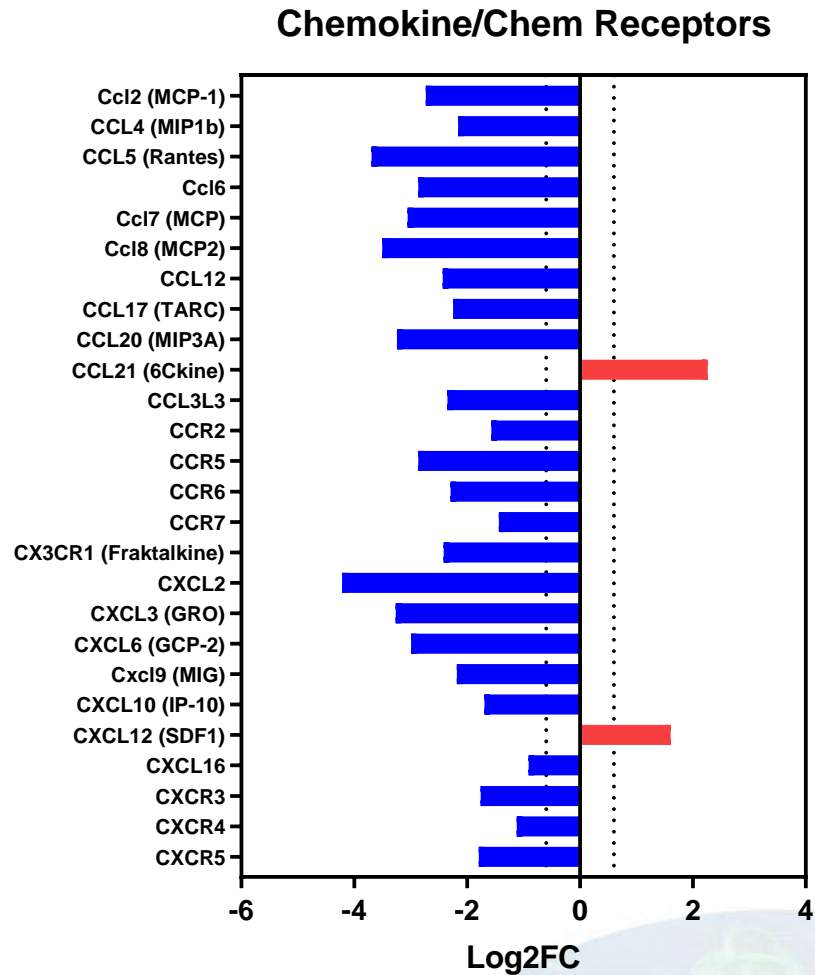
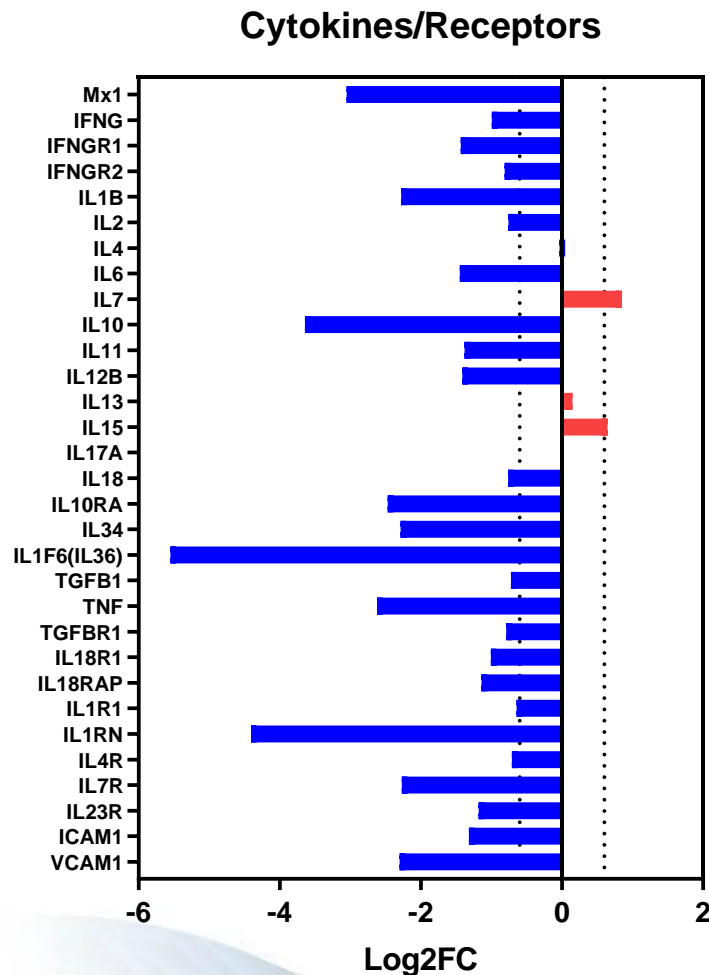
Top Disease and Biofunctions

S K

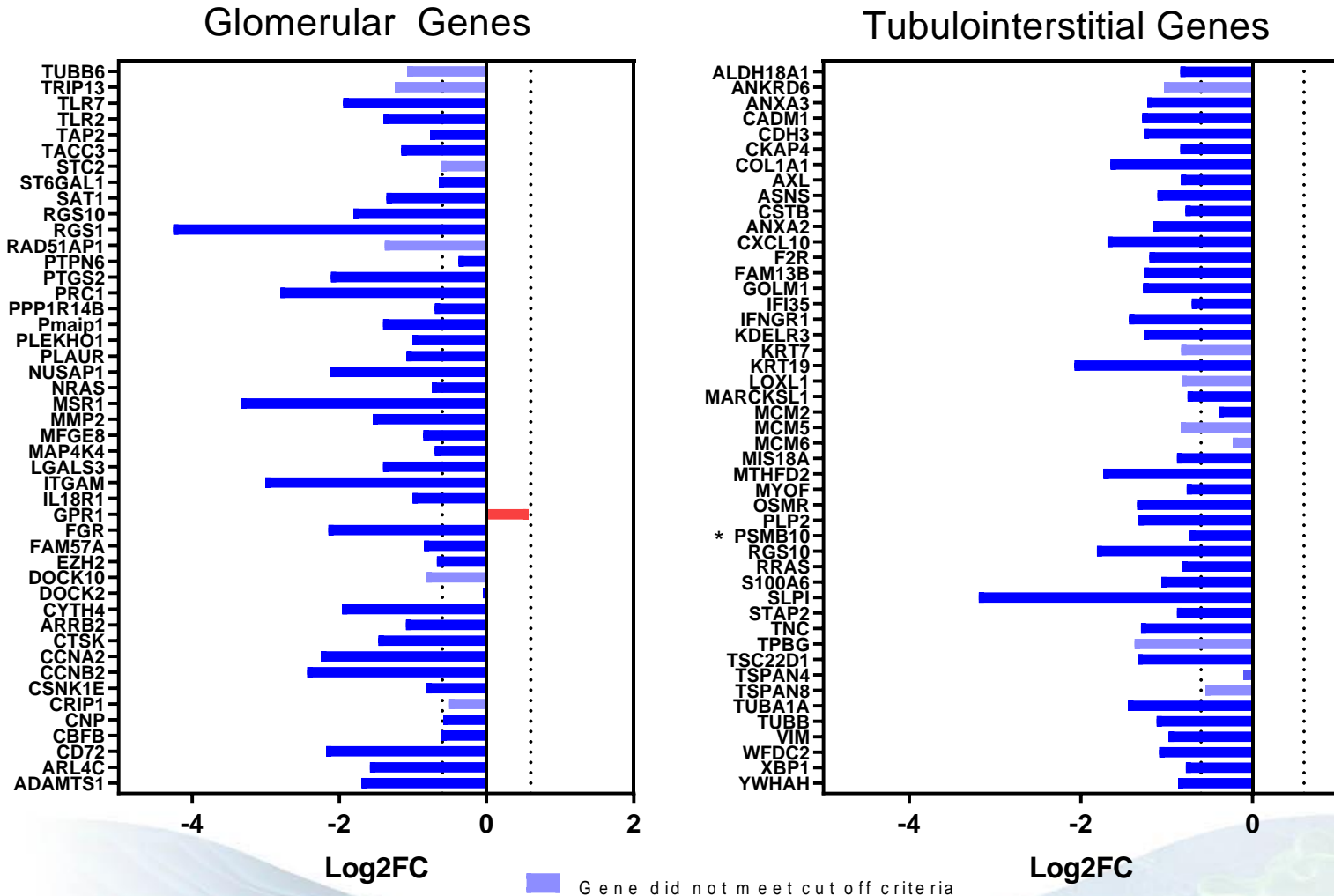
Leukopoiesis		
Hematopoiesis of mononuclear leukocytes		
Lymphopoiesis		
Homeostasis of leukocytes		
Homeostasis of blood cells		
Lymphocyte homeostasis		
T cell homeostasis		
T cell development		
Cell movement		
Differentiation of T lymphocytes		
Infection of mammalia		
Migration of cells		
Cell survival		
Cell movement of blood cells		
Leukocyte migration		
Cell viability		
Differentiation of phagocytes		
Cell movement of myeloid cells		
Differentiation of antigen presenting cells		
Cellular homeostasis		
Immune response of cells		
Cell movement of leukocytes		
Cell movement of phagocytes		
Quantity of lymphatic system cells		
Cell movement of neutrophils		
Cell viability of leukocytes		
Quantity of lymphocytes		
Development of phagocytes		
Hematopoiesis of phagocytes		
Quantity of IgG		
Engulfment of cells		
Phagocytosis		
Quantity of mononuclear leukocytes		
Chemotaxis of neutrophils		

-7.131 6.326

Mice Treated with KZR-616 Showed Broad Reduction of Inflammatory Cytokine and Chemokine Gene Expression in the Kidneys

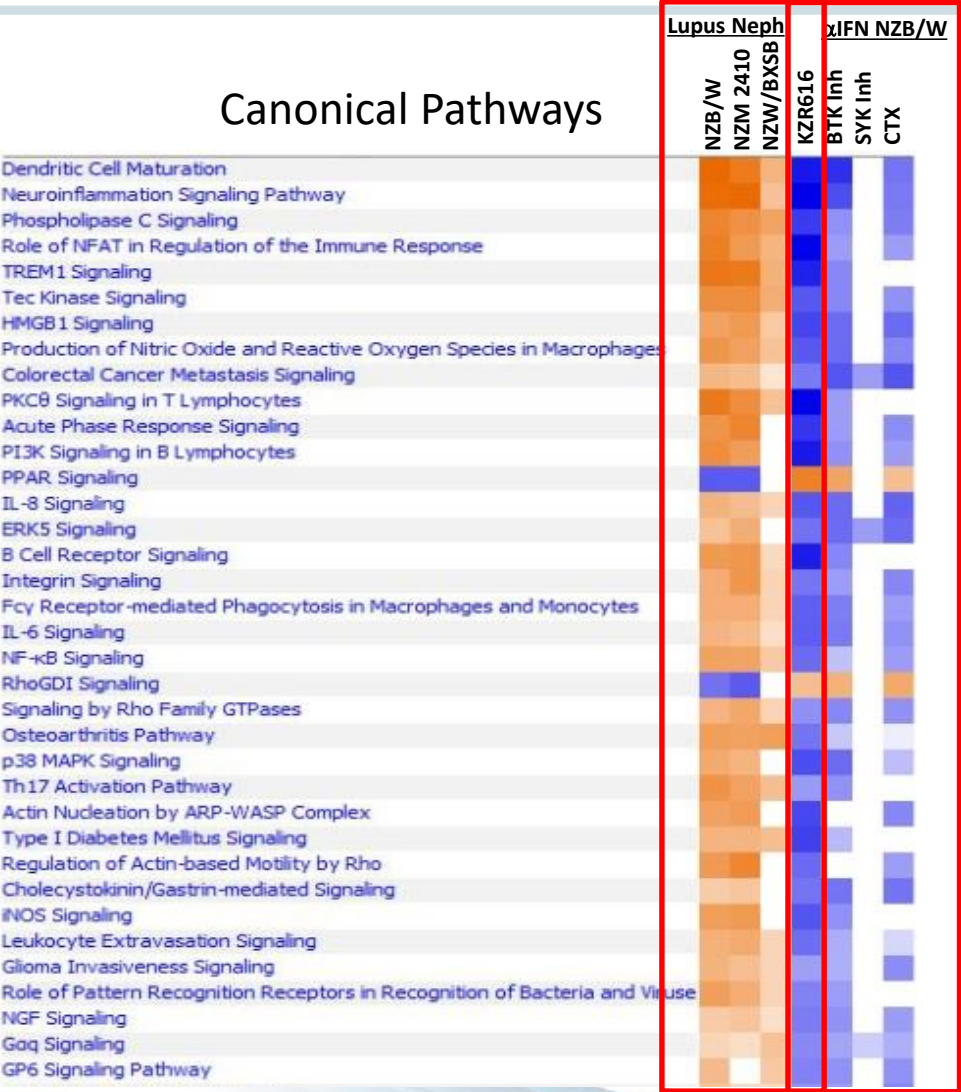


KZR-616 Treatment in Mice Inhibits Genes Upregulated in the Glomerulus and Tubulointerstitium of LN Patients

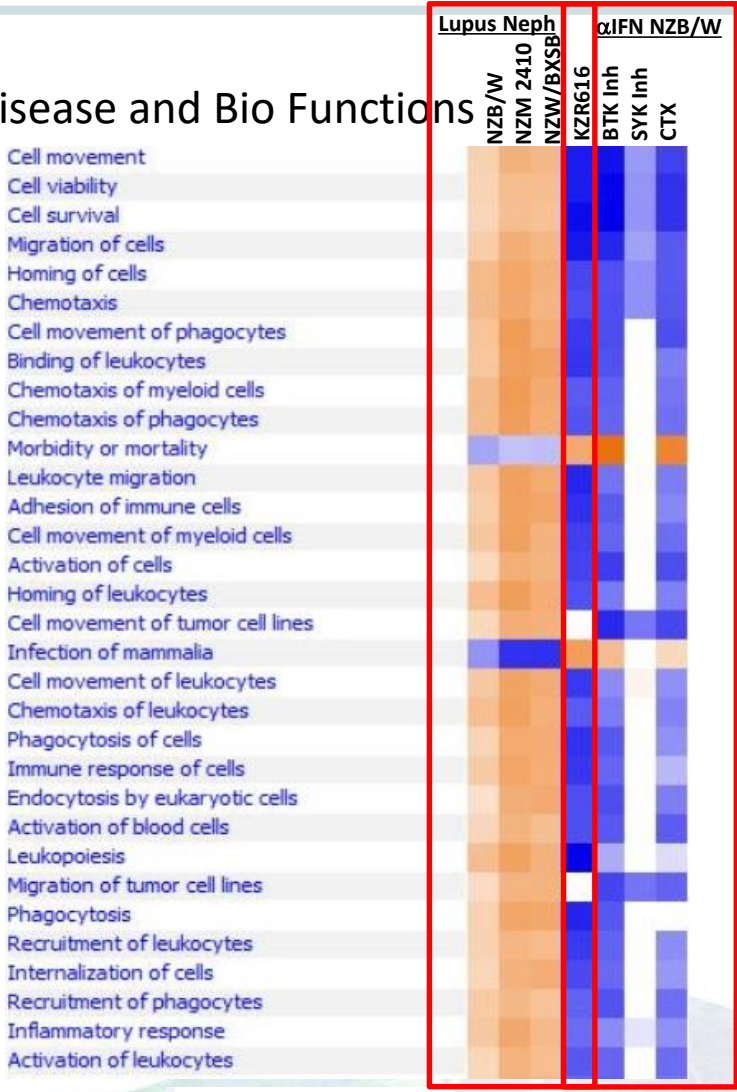


Comparison of Pathway Changes in Kidneys to KZR-616 Treatment with Various Lupus Models and Therapeutic Agents

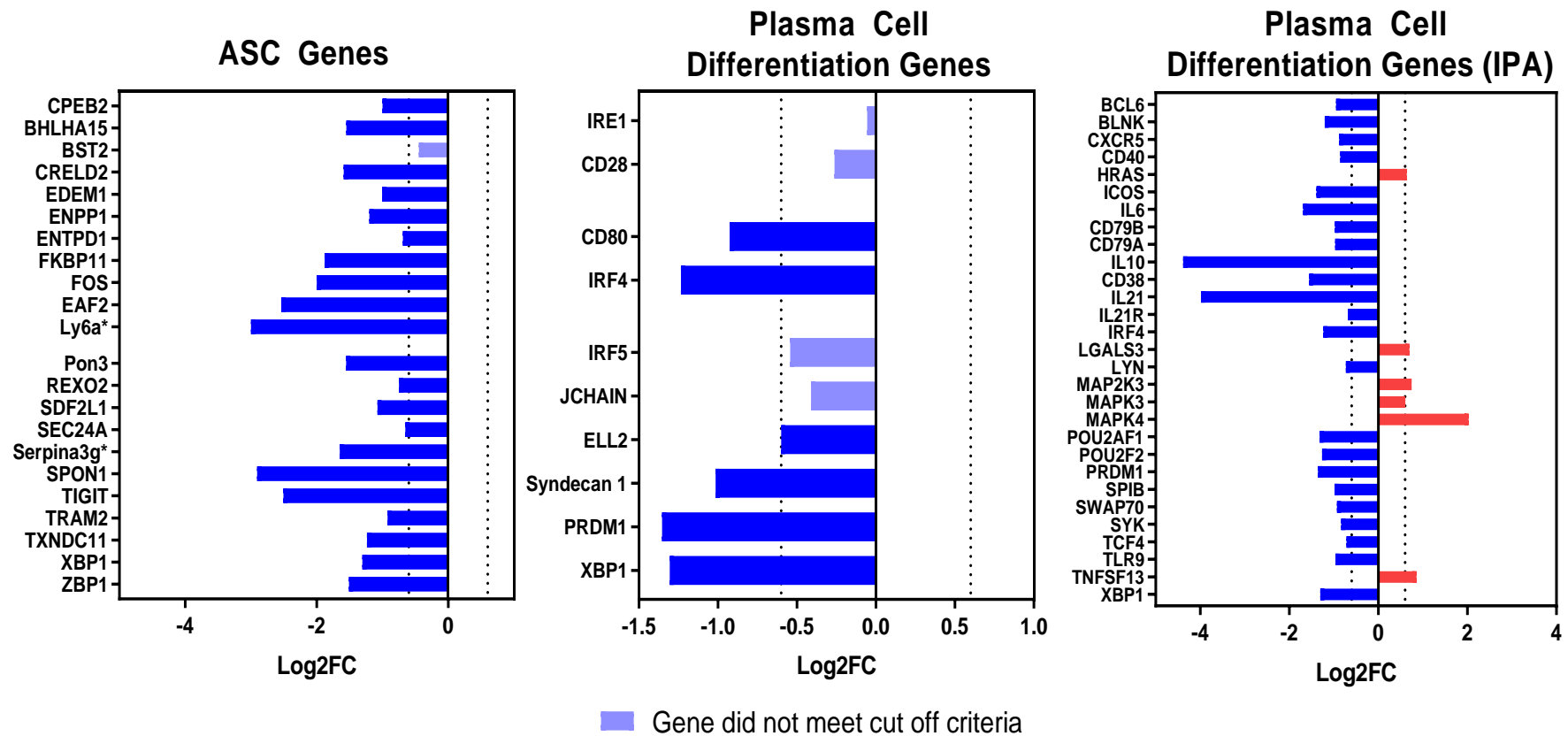
Canonical Pathways



Disease and Bio Functions



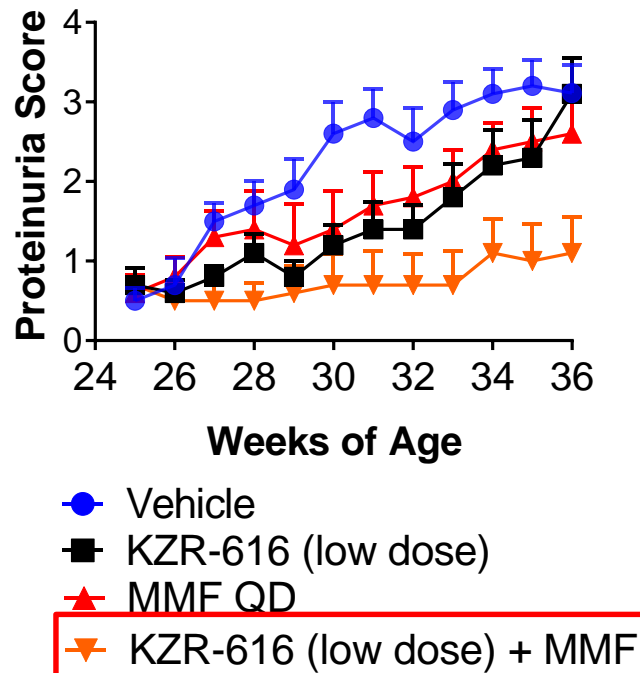
KZR-616 Reduces Splenic Expression of Genes Associated with ASC Generation and Plasma Cell Differentiation



Gene list from Shi et al. Nature 2015

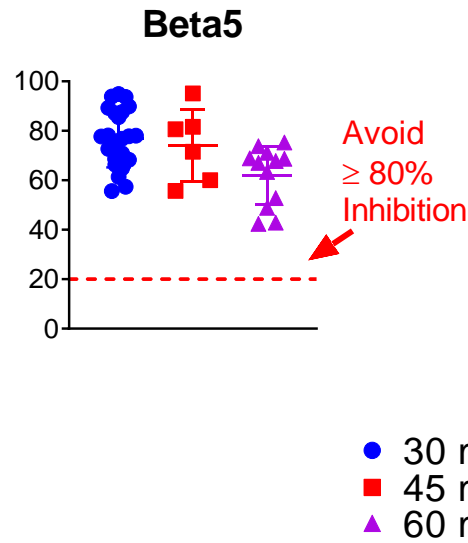
KZR-616 Synergizes with MMF in NZB/W F1 Mice and Induces Selective Inhibition of the Immunoproteasome in Healthy Volunteers

Mouse Model Efficacy



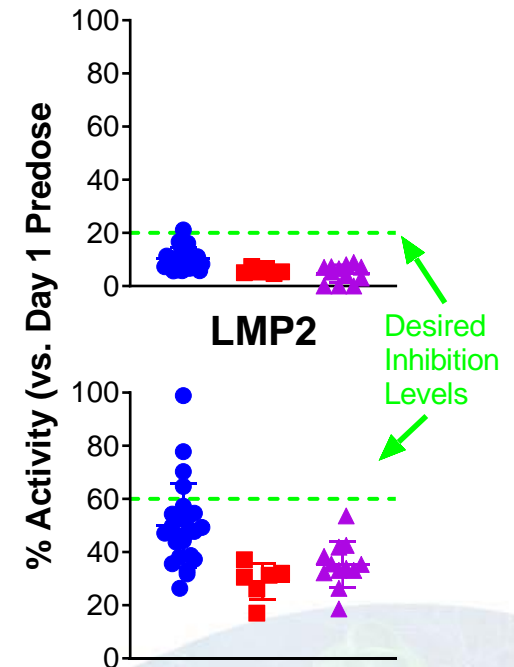
Phase 1 Healthy Volunteers

Constitutive Proteasome



Immunoproteasome

LMP7

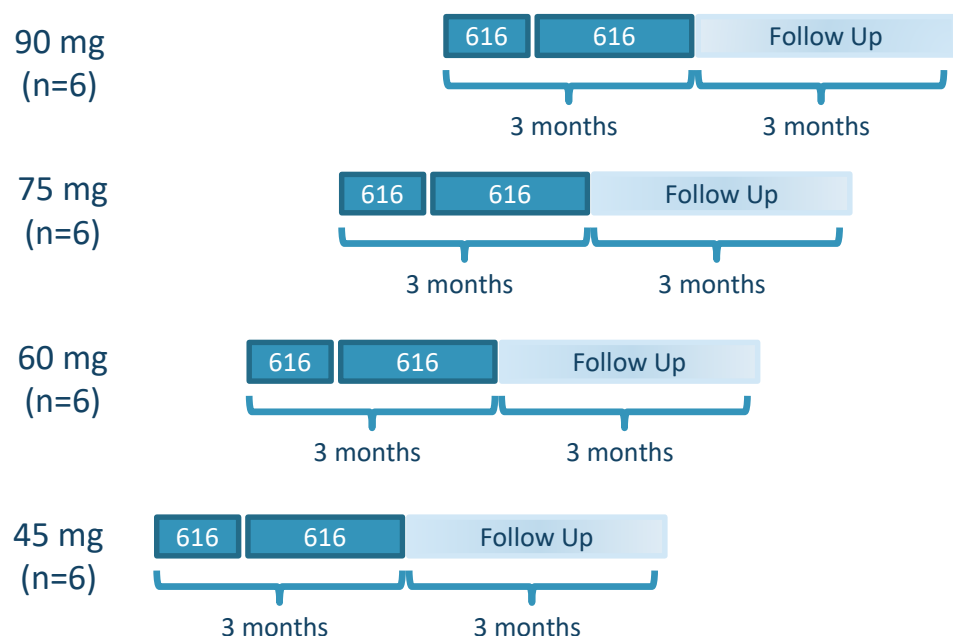


SC dosing (4hr post-dose)

Muchamuel ACR 2017
Lickliter ACR 2017 18

KZR-616-002: A Phase 1b/2 Study of KZR-616 in SLE and LN Patients

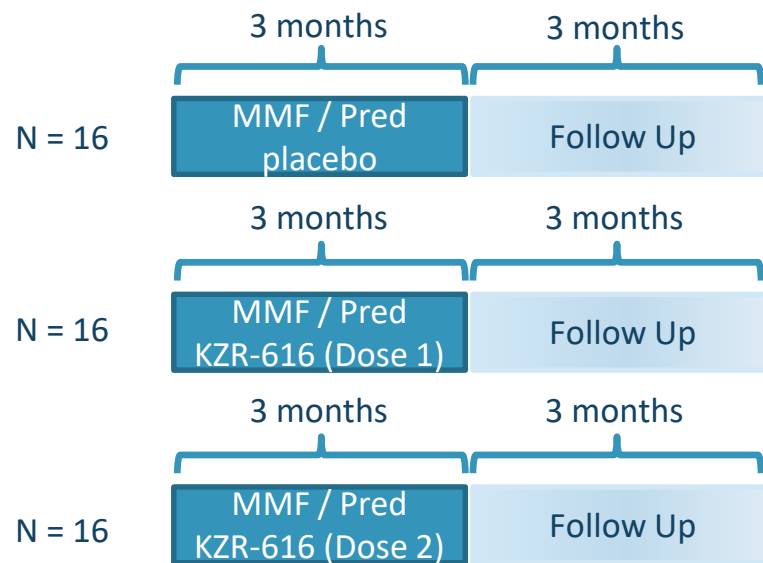
Phase 1b SLE and LN (SLEDAI ≥ 4) Prior SOC treatment required



Endpoints

1°: Safety
2°: Recommended Phase 2 doses, Plasma PK
Exploratory: Efficacy, PD & Biomarkers, Pharmacogenomics

Initial Phase 2 Lupus Nephritis Treatment during induction phase of therapy



Endpoints

1°: Safety
2°: Efficacy (Complete and partial renal response rates, SLEDAI-2K, BILAG, corticosteroid use)
Exploratory: PD, Biomarkers, Pharmacogenomics

Summary of KZR-616 Effects in Mouse Models of Lupus

- Highly active in the NZB/W F1 mouse model of SLE/LN
 - Complete resolution of proteinuria
 - Reduced autoantibody levels
 - Reduced renal IgG deposition
 - Prolonged renal response in mice even after treatment withdrawal
- Effect due in part to depletion of activated B-cells and plasma cells
- Gene expression profiling reveals inhibition of multiple pathways
 - Down regulation of multiple immune response pathways
 - Glomerular and tubulointerstitial renal pathology
 - Decreases multiple cytokines and chemokines in spleen and kidney
 - Plasma cell differentiation and ASC generation
- Synergizes with MMF in NZB/W F1 mice
- KZR-616 is currently being evaluated in a Phase 1b/2 trial in SLE and LN

Acknowledgements

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