Targeting the Adenosine Axis to Treat Cancer

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The Complexity of the Tumor Microenvironment

Modulation of the TME may dramatically augment cancer therapies
Targeting the Adenosine Axis to Activate the Immune System

- Extracellular adenosine suppresses tumor immunity
- Extracellular ATP stimulates innate immunity
NZV930 (Formerly SRF373) – an Antibody Targeting CD73

- High affinity, fully human antibody against human CD73
- Potent inhibitor of CD73 enzymatic activity
- Promotes reduction of adenosine and increased T cell proliferation
- Cooperativity with checkpoint inhibitors (PD-1) in pre-clinical models
- Novartis Phase 1/1b initiated June 2018
NZV930 Blocks Membrane Bound and Soluble CD73 Activity

SKOV3 Cells

![Graph showing %NH AMP Conversion vs log Ab ng/ml for SKOV3 Cells. The graph compares NZV930 and Isotype controls.]

MDA-MB-231 Supernatant

![Graph showing %NH AMP Conversion vs log Ab ng/ml for MDA-MB-231 Supernatant. The graph compares NZV930 and Isotype controls.]

The graphs illustrate the inhibition of AMP conversion by NZV930 compared to isotype controls in both cell lines and supernatant.
NZV930 Restores Suppression of Adenosine-Mediated T Cell Proliferation

CD4 T cell proliferation

![Graph showing CD4 T cell proliferation](image)

- **Proliferation Index**
- **log mAb (ng/ml)**
- **Beads Only**
- **Beads + AMP**
- **NZV930**

**Legend**
- **Beads Only**
- **Beads + AMP**
- **10 ng/ml NZV930 + Beads + AMP**

**Proliferation Index**
- **Prolif. Index = 70**
- **Prolif. Index = 8**
- **Prolif. Index = 67**

**Beads = αCD3 + αCD28**
NZV930 Decreases Extracellular Adenosine In Vitro and In Vivo

Pancreatic cancer cells in vitro

MDA-MB-231 tumor in vivo

% Adenosine Inhibition

log mAb (ng/ml)

NZV930
Isotype

Plasma Adenosine (nM)

Control
CD73 Ab
NZV930
CD73 Blockade Improves Activity of Anti-PD1 in the CT26 Syngeneic Tumor Model

CT26 syngeneic model

Isotype

CD73

PD-1

PD-1 + CD73

Mu-reactive CD73: 400 µg 2x/wk x 2
PD-1: 300 µg 2x/wk x 2
Soluble CD73 is a Potential Biomarker for Anti-PD-1 Responsiveness

- sCD73 detected in human cancer patient serum
- Decreased sCD73 in melanoma patients treated with Nivo + multi-peptide vaccine
- High CD73 predicts poor anti-PD-1 and anti-CTLA-4 responses

Optimal cutpoint

Logrank P = 7.8E-03

mean OS_weeks

J. Stagg unpublished

Study described in Gibney et al CanRes, 2015

NZV930 Phase 1 Trial Design

NZV930 Single Agent Dose Escalations

- NZV930 with PDR001 (anti-PD-1) Doublet Therapy
- NZV930 with NIR178 (A2AR antagonist) Doublet Therapy
- NZV930 with NIR178 & PDR001 Triplet Therapy

N= ~344 patients

**Indications:**
- NSCLC
- TNBC
- Ovarian Cancer
- MSS Colorectal
- Pancreatic Ductal Adenocarcinoma
- Renal Cell Carcinoma
SRF617 – an Antibody Targeting CD39

- High affinity, fully human antibody against human CD39
- Potent inhibitor of CD39 enzymatic activity
- Reduction of adenosine and increased ATP leads to increased T cell proliferation and dendritic cell maturation
- Cooperativity with checkpoint inhibitors (PD-1) in pre-clinical models
- IND-enabling studies ongoing
CD39 is Upregulated on TIL and Expression is Increased Following PD-1 Blockade

TIL profiling

PBMC with Nivolumab

- None
- Nivo

% CD39 Positive Cells

CD45+ TIL

% CD39 Positive

Cell Type
SRF617 Binds to CD39 and Blocks Enzymatic Activity on MOLP8 Myeloma Cells

**CD39 Cell Binding**

**CD39 Enzymatic Inhibition**

![Graph showing CD39 Cell Binding](image)

![Graph showing CD39 Enzymatic Inhibition](image)
SRF617 Mediated CD39 Blockade is Immunostimulatory

**CD4⁺ T Cells**

- **Proliferation**
  - Graph showing proliferation index vs. log antibody concentration.
  - Blue line for SRF617, gray line for isotype.

- **Activation/Exhaustion**
  - Bar graph showing % PD-1⁺ TIM-3⁺ LAG-3⁺ positive cells:
    - Beads
    - ATP
    - ATP + SRF617

**Monocyte Derived Dendritic Cells**

- **CD86 Expression**
  - Bar graph showing CD86 expression (gMFI) with different conditions:
    - Isotype
    - SRF617
    - anti-CD39
    - ATP
    - SRF617 + anti-CD39

- **Cytokine Secretion**
  - Bar graph showing cytokine secretion (pg/ml) with different conditions:
    - No ATP
    - 300 μM ATP
SRF617 Shows Anti-Tumor Activity in a Xenograft Setting

**Graph:**
- **MOLP8 Xenograft**
  - Isotype
  - SRF617 (20 mg/kg)
  - SRF617 (60 mg/kg)

**Legend:**
- Days on Study
- Tumor Volume (mm$^3$)

**Stats:**
- **Iso Control**: 367.41 (60 mg/kg)
- **SRF617 (60 mg/kg)**
- **SRF617 (20 mg/kg)**

**Notes:** Abs dosed BiW/2 wk
SRF617 Modulates Macrophage Trafficking and Tumor Infiltrate

F4/80+ cells in tumor

Tumor chemokine analysis

F4/80+ cells in tumor

MOLP8 xenograft
Samples collected d14
CD39 Combination Strategies Test Different Hypotheses

- Immunogenic Cell Death
- ATP
- αCD39
  - Innate Immune Activation
  - Adaptive Immune Responses
CD39 Combination Strategies Test Different Hypotheses

Immunogenic Cell Death

**SRF617 + Doxorubicin**

MOLP8 xenograft day 19
CD39 Combination Strategies Test Different Hypotheses

![Graph showing tumor volume over days on study for different treatments]

- **Isotype**
- **SRF617**
- **SRF617 + SRF231**
- **SRF617 + Anti-CD47**

**MOLP8 xenograft**

- **Innate Immune Activation**
- **Adaptive Immune Responses**
CD39 Combination Strategies Test Different Hypotheses

CT26 model

Innate Immune Activation

Adaptive Immune Responses
# SRF617 Inhibits CD39 Enzymatic Activity in Uterine Tissue from Dosed Cynomologus Monkeys

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- Uterine sections from 3 cynomologus monkeys dosed with SRF617
- Colorimetric assay detects phosphate released by CD39 hydrolyzing ATP
- SRF617 also blocks ADP hydrolysis (data not shown)

ATP 15 minutes
Summary

• Adenosine production via the CD39-CD73 adenosinergic pathway is a critical mediator of immunosuppression in the TME

• NZV930 is a fully human CD73 antibody that potently inhibits CD73 enzymatic activity
  • Shows activity in pre-clinical settings

• CD73 in serum and tumors may have utility as clinical biomarkers

• NZV930 is currently in Ph1/1b clinical studies

• SRF617 is a fully human CD39 antibody that potently inhibits CD39 enzymatic activity
  • Shows activity in pre-clinical settings

• NZV930 and SRF617 provide alternative strategies for blocking adenosine production in the TME
Shared and Unique Characteristics of Targeting Adenosine via CD73 or CD39

Implications for Rational Combination Approaches

Tumor Intrinsic Effects
- Induced by MAPK on tumors
- Increases TNBC cell motility
- Expression reduced by Raf/Mek inhibitors in melanoma
- Inhibits anti-ErbB2 activity on breast tumor cells
- Adenosine independent effects on adhesion, migration

Immune Cell Effects
- Promotes DC antigen tolerance
- Prevents myeloid recruitment, chemotaxis
- Involved in Th17 cell expansion

T Cell Effects
- Key mediators of extracellular adenosine production
- Cell autonomous T cell inhibition via A2AR signaling

CD73

CD39

RTK inhibitors, targeted therapies

Chemotherapy, innate immune agonists

CKI, co-stimulatory TCR agonists, CART therapies

Reinhart, Can Res 2017
Young, Can Res, 2017
Turcotte Can Res 2017
Qiao, Int J Mol Sci, 2019
Allard, Immunol Rev, 2017
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