RoR yt inhibitor program

Preclinical candidates targeting multiple Auto-immune disorders

RoR yt inhibitor for Auto-immune and Inflammatory Diseases

Auto-immune and Inflammatory diseases cover a vast therapeutic space, driven by common underlying pathophysiology

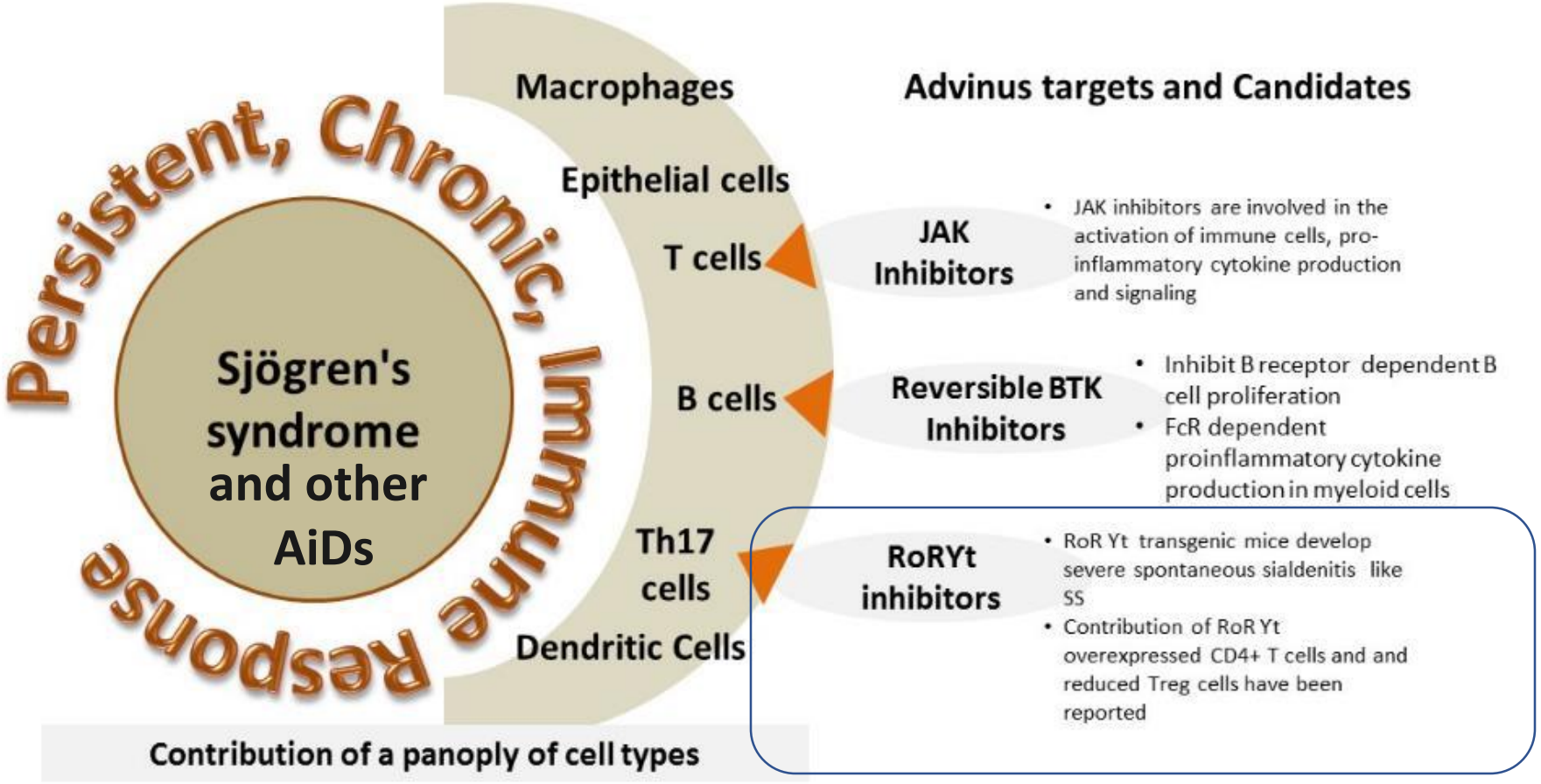
Advinus has developed an rich and diverse portfolio of candidates for Auto-immune and anti-inflammatory diseases that can be targeted for 1st time application in specific, niche indications

Sjogren's Syndrome* is a potential primary indication common to the 3 Advinus programs where they are likely to have great therapeutic impact

Advinus candidates will also have application in multiple other indications, to be decided during the course of clinical development

**** Sjögren's Syndrome has been selected as an example of a niche indication for which the candidate can be positioned. Similar other indications can be identified.***

Multi-Modal Approach to Sjogren's Syndrome



Advinus candidates address the different mechanisms that contribute to development of Sjögren's Syndrome

Competitive Landscape

Most pipeline therapies are mABs and other biologic approaches. IP3K and BTK are 2 targets for which inhibitors are in early preclinical development for some of these indications

Drug	Target	Mechanism of Action	Phase of Study
UCB5857	PI3Kδ	Selective inhibitor of PI3Kδ preventing transmission of cell surface receptor signaling	II
CFZ533	CD40	Fc silent antibody to CD40 preventing B cell stimulation and differentiation without depletion	II
AMG557	ICOS	Inhibit activation of TFH	II
VAY736	BAFF-R	Antibody to BAFF-R preventing BAFF-mediated B cell proliferation and survival	II
Low-dose IL-2	$CD4^{+}CD25^{+}$ T cells	Low-dose interleukin 2 expands Treg cells	II
Rituximab + belimumab	CD20 B cells, BAFF	Anti-CD20-dependent depletion of B cells combined with BAFF blockade to decrease survival of self-reactive B cells	II
Tocilizumab	IL-6R	Blockade of IL-6R preventing IL-6-dependent TH17 and TFH cell differentiation	II
Abatacept	CD80/86	CTLA4-Ig binding of CD80/86 prevents co-stimulation-dependent activation of CD4 T Cells	III

A safe, oral agent can be a very inexpensive and attractive therapeutic alternative to biologics currently in the pipeline

Impetis **RORγt** Inhibitor Program for Sjogren's Syndrome, Atopic Dermatitis and other Autoimmune and Inflammatory diseases

Impetis **RORγt** Inhibitor Program

Potential "First-in-Class" opportunity for targeted Autoimmune diseases with secondary positioning in a broad range of auto-immune diseases including Type 1 Diabetes, Multiple Sclerosis and Psoriasis

Competitive Landscape

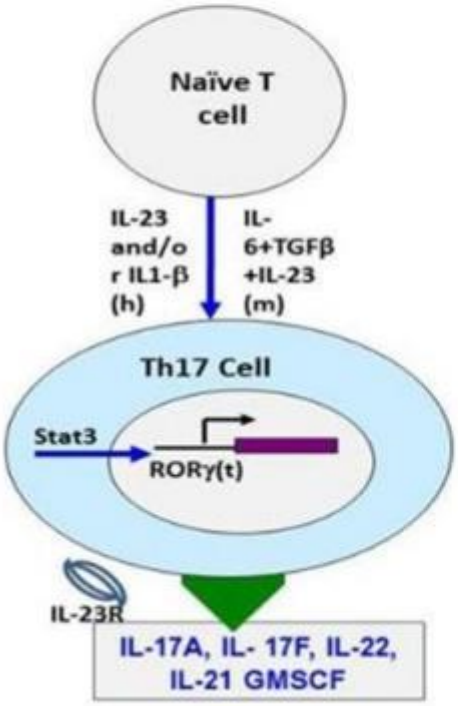
- A new approach to target Th17 dependent disorders
- Retinoic acid-related orphan nuclear receptor gamma (RORγt) is a hot, but "difficult-to-drug" target.
- Difficult to assess competitiveness within the class

Advinus Program: Status

- Early program with multiple potent and selective ROR γ t inhibitors identified
- Demonstrated efficacy in multiple preclinical models
- Two patents filed on two different chemotypes
- Candidate nomination stage

Impetis RORγt Inhibitor Program

Small molecule inhibitors of RORγt are expected to have great potential as novel therapeutic agents for Sjögren's Syndrome



- RORγt - key transcription factor involved in Th17 cell differentiation from naïve T cells and production of Th17 cytokines IL-17, IL-21 & IL-22
- Th17-targeted therapy for inflammatory/auto-immune diseases (e.g., psoriasis, RA, MS) is an established concept
  - Preclinical PoC (genetic/antibody therapeutics) and clinical (antibody therapeutics) PoC exist with Th17-related cytokines
- Targeting Th17 cells directly by blocking RORγt could potentially shut down inflammation more effectively and thus may provide greater efficacy

In vitro Profile –Comparison

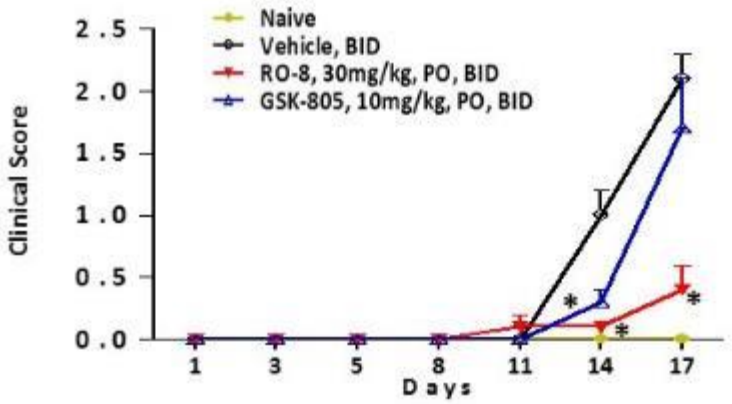
Properties	VTP-43742*	RO-8	RO-9	RO-10
Primary assay (**Transactivation**): IC_{50}, (nM)	17[a]	9	5	11
Functional assay **Mouse splenocyte** IC_{50}, nM	Not reported	79	106	170
Functional assay **Human whole blood:** IC_{50}, nM	221	379	80	627
Selectivity over RORα (Transactivation) : IC_{50}, nM)/ Ki+	4712+	10000	2700	~10000

- Advinus molecules exhibit potency & selectivity comparable/superior to advanced candidates in pipeline

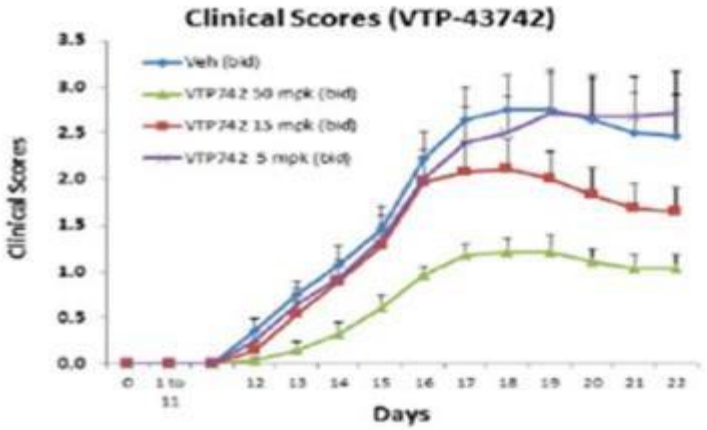
Efficacy Demonstrated in Multiple Autoimmune Disorders

EAE Model of Multiple Sclerosis

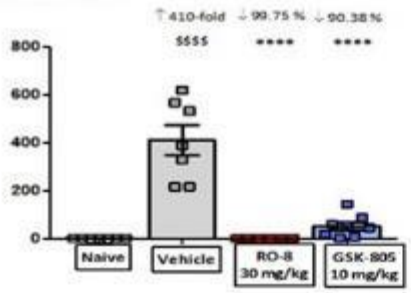
Clinical Score : RO-8



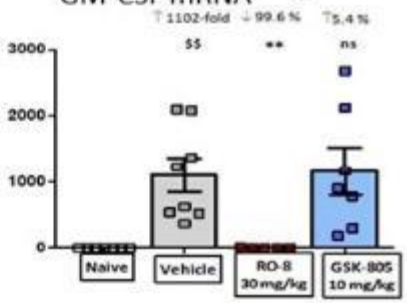
Clinical score: VTP -43742



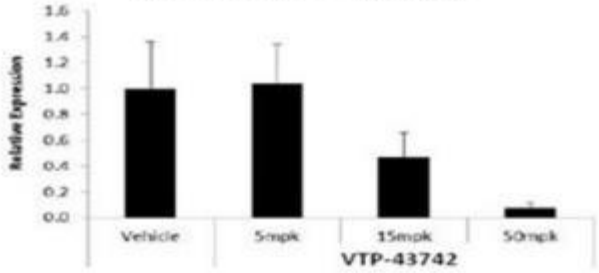
IL-17A mRNA



GM-CSF mRNA



Spinal Cord IL-17A mRNA



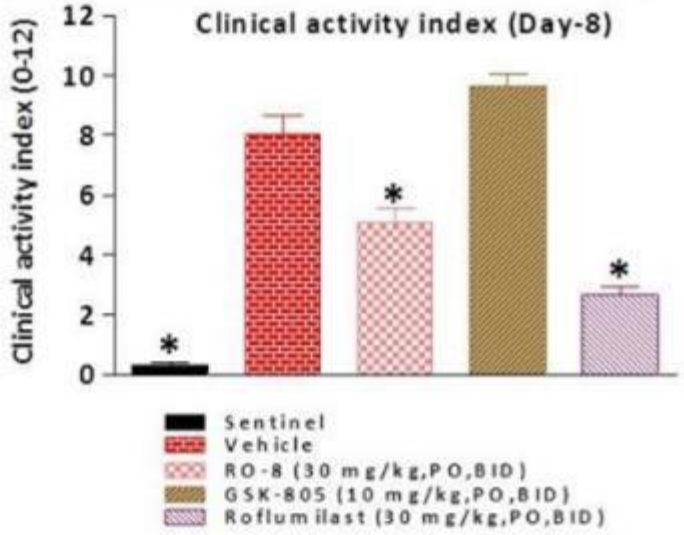
- Better efficacy than VTP43742
- Significant reduction in IL-17A, GM-CSF, CCR6 and IL-23R expression

Efficacy in Multiple Models: Representative Data for RO-8

Psoriasis
Ear Thickness Day 7

EAE Model of Multiple Sclerosis
Clinical Score

DSS Induced Ulcerative Colitis
Clinical Activity Index



- Advinus molecules exhibit efficacy in several preclinical models of autoimmune disorders

RORγt program : Way Forward

- Potent and selective lead molecules identified, with single digit potency, in transactivation and whole blood (Th17) assays
  - Lead Optimization aimed at improving ADMET properties to attain adequate exposure in dogs and rats for safety studies

- Molecules to be profiled towards clinical candidate
  - All assays, models, and know-how in place for speedy execution
  - Demonstrated inhibition in human whole blood assay
  - Acceptable ADME profile for further progression
  - Efficacy and effect on biomarkers demonstrated in multiple autoimmune disease models.
  - Candidate selection to be done based on PK/PD correlation

Thank You