VYNE™ THERAPEUTICS

KOL Event: Update on the BET InhiBET™ Platform and VYN201

May 17, 2022

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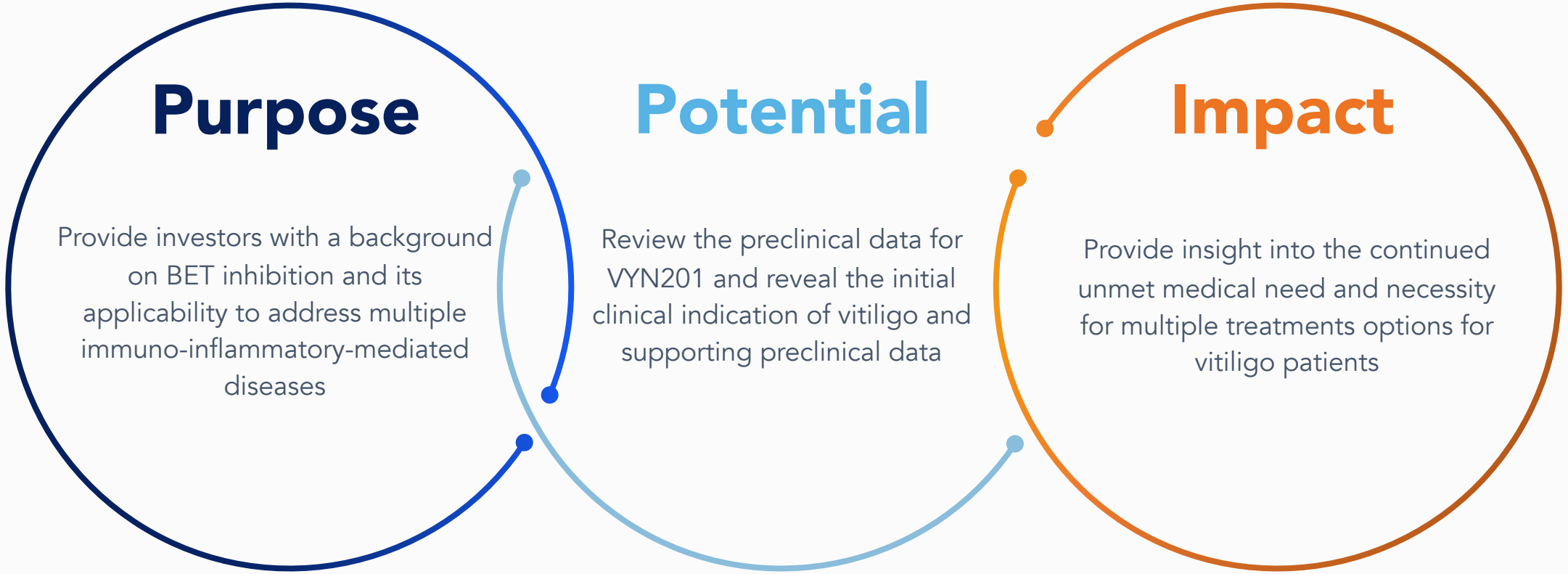
2022 KOL Event – InhiBET™ BET Inhibitor Platform

for Immunology and Inflammatory Diseases and Clinical Development Plan for VYN201



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Today's Agenda

KOL Event Focused on the InhiBET™ Platform and VYN201

Topic	Presenter	Time
Overview of VYNE	David Domzalski President and CEO	10:05 – 10:15
Introduction to BET proteins	Professor Gerald V. Denis, Ph.D. Boston University School of Medicine	10:15 – 10:30
Overview of VYN201	Iain Stuart, Ph.D. Chief Scientific Officer	10:30 – 10:55
Overview of Vitiligo	Professor Thierry Passeron, MD, Ph.D. University of Nice	10:55 – 11:10
Q&A	All Panelists	11:10 – 11:25
Future milestones/Wrap-up	David Domzalski President and CEO	11:25 – 11:30

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Investment Highlights (NASDAQ: VYNE)

VYNE is focused on developing proprietary, innovative, and differentiated therapies for the treatment of immuno-inflammatory conditions

Innovative Pipeline

- Pipeline focused on major markets (Atopic Dermatitis and I&I) and rare skin diseases with high unmet medical need
- Key Targets: JAK/ sphingosine-1 receptor modulator combo & BET inhibitors

InhiBET™ Platform

- New platform, based on a novel class of targets called BET inhibitors
- Pursuing locally administered (VYN201) and oral therapies (VYN202)
- Exclusive global access to a NCE library for any indication
- Substantial progress since August 2021 in-license

Proven Development Capabilities and Leading Advisory Infrastructure

- Seasoned R&D team with proven product development track record
- Strong network of discovery and preclinical science partners
- Well respected SAB provide strong advisory input to pipeline development activities
- Developed and received FDA approval for the first and only topical formulations of minocycline for acne and rosacea; Products were divested in January 2022

amzeeq® (minocycline) topical foam, 4%

zilxi® (minocycline) topical foam, 1.5%

Multiple Near-term Catalysts

- Numerous near-term catalysts across FMX114, VYN201 and VYN202 with potentially significant long-term value creation

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VYNE: Developing differentiated therapies for the treatment of I&I conditions

FMX114:

Combination therapy to address both the source & cause of inflammation associated with Atopic Dermatitis (AD)

Target Market: Mild-to-moderate atopic dermatitis

~19 million people (U.S.)

Combination Mechanism:

- Tofacitinib (JAK-1/3): to inhibit cytokine release
- Fingolimod (sphingosine 1-phosphate receptor modulator): to inhibit inflammatory cell migration

Phase 1b Safety & Efficacy:

- Well-tolerated, with no serious adverse events recorded; Systemic bioavailability of tofacitinib and fingolimod substantially lower compared to oral equivalents
- FMX114 demonstrated a statistically significant improvement of the signs and symptoms of AD at 2 weeks

Next Milestone: Topline results of Phase 2a trial:Q2 2022

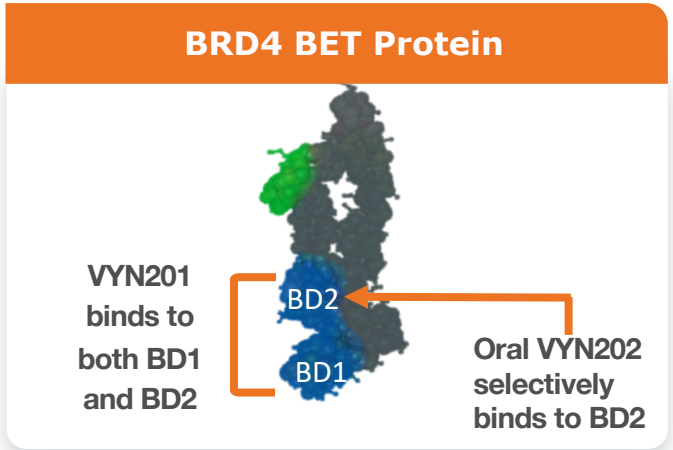
InhiBET™ BET Inhibitor Platform:

Global rights to library of NCE BET inhibitors for any indication

VYN201: Locally administered pan-BD BET inhibitor

- **Target Market:** Indications benefiting from local administration and "soft drug" approach
- **Preclinical Proof-of-Concept Data:** Data suggests potential "pipeline in a product" with broad utility of VYN201 across multiple routes of administration

VYN202: Oral, highly-selective BD2 BET inhibitor for major immuno-inflammatory diseases



Preclinical Proof-of-Concept Data Summary for VYN201

Based on established models, compared to active control and vehicle/placebo

TH7 Inflammation Model

- Reduced composite score of inflammation severity
- Dose-dependent reduction in pro-inflammatory cytokines

Fibrotic Tissue & IPF[1] Models

- Significantly lower fibrosis v. vehicle and negative control
- Preliminary IPF model data suggests VYN201 could have promising impact on IPF-related fibrosis and biomarkers

Rheumatoid Arthritis Model

- Two highest doses demonstrated statistically significant improvement in treatment response, measured by paw thickening and arthritis score
- Superior to locally-dosed active dexamethasone control

Vitiligo Model

- Highest doses demonstrated statistically significant improvement in reducing melanocyte loss & lowering key inflammatory biomarkers vs. vehicle
- Numerically superior to active control, ruxolitinib cream, 1.5%

VYN201
Potential "pipeline in a product" with broad utility across multiple routes of administration

1. Idiopathic pulmonary Fibrosis (IPF)
2. Data on file

Summary of Locally Administered Pan-BD BETi Candidate Selection Criteria

Based on an assessment of preclinical data, market research and SAB/KOL input

- ☑ Improved inflammation scores
- ☑ Reduction in inflammatory biomarker levels
- ☑ Good tolerability in animals
- ☑ Good local pharmacology
- ☑ Limited systemic drug accumulation
- ☑ Potential to address high unmet medical need
- ☑ Attractive market opportunity

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VYN201 Lead Indication

Vitiligo

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The Vitiligo Opportunity

A disabling disease and major unmet medical need

Unmet Need

- Vitiligo is a disabling disease impacting social, sexual and professional life. Resemblance to leprosy impacts QOL in some countries
- Treatments need to impact both pigmentation and Quality of Life

Preclinical Data Map to Clinical Plan

- Melanocyte histology metrics and *in vitro* biomarkers (TNF-α and IFN-ɣ, MMP9 and E-cadherin) translate well to clinical endpoints

Large Market

- 0.5 to 2.0% of worldwide population
- Non-segmental sub-type represents ~90% of patients
- Est. U.S. prevalence is between 1.9 and 3.2 million cases (diagnosed/undiagnosed)

Differentiated Characteristics

- Treatment is dominated by non-specific therapeutic options
- VYN201 is a topically applied "soft" drug, designed to maximize target engagement in the skin and minimize systemic exposure

Sources: Bergqvist. Dermatol. 2020;236:571-592; *JAMA Dermatology*, "Prevalence of Vitiligo Among Adults in the United States"; 2022; 158(1):43-50 (published online Nov. 17, 2021); Rangu S, McKenzie PL, Castelo-Soccio L (2021) Therapy Utilization among Children with Vitiligo at an Urban Tertiary Care Center J Clin Dermatol Ther 7: 070.

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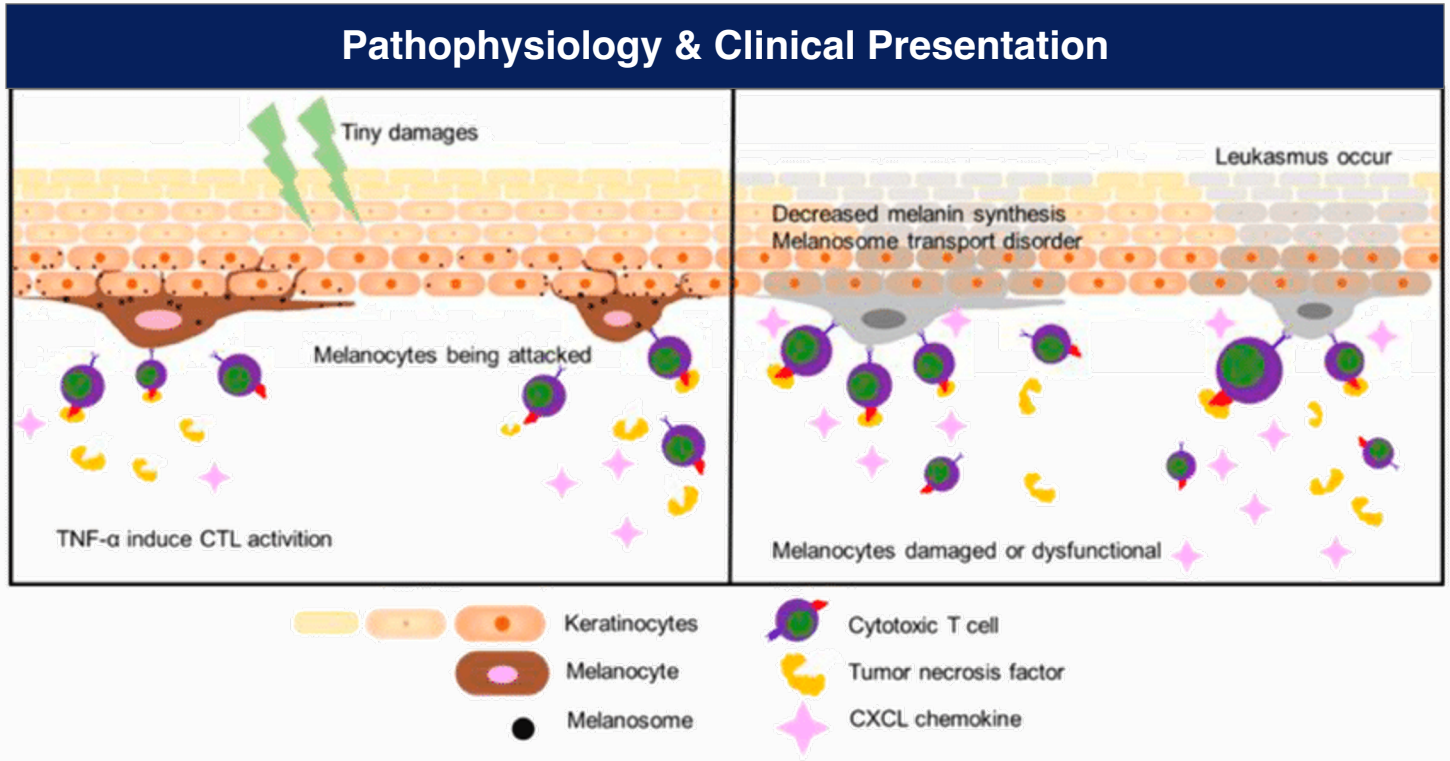
Vitiligo – Disease Overview

An acquired disorder of dermatologic pigmentation with high impact on self-esteem



- Vitiligo is a depigmenting skin disorder characterized by the **loss of melanocytes,** which causes typical non-scaly, chalky-white macules
- Pathogenesis is classified as **autoimmune in nature**; the disease is associated with a culmination of genetic and environmental factors with metabolic, oxidative stress, and cell detachment abnormalities
- Vitiligo can be classified as segmental or non-segmental; segmental presentation appears **unilaterally**, while non-segmental presents **bilaterally and occasionally mucosally** (i.e., around the mouth)
- Characteristic amelanotic lesions, while physically harmless, **tend to be psychologically devastating**

Source: UptoDate; Bergqvist. Dermatol. 2020;236:571-592; Karagaiah. Expert Opin Emerg Drugs. 2020;25(1):7-24

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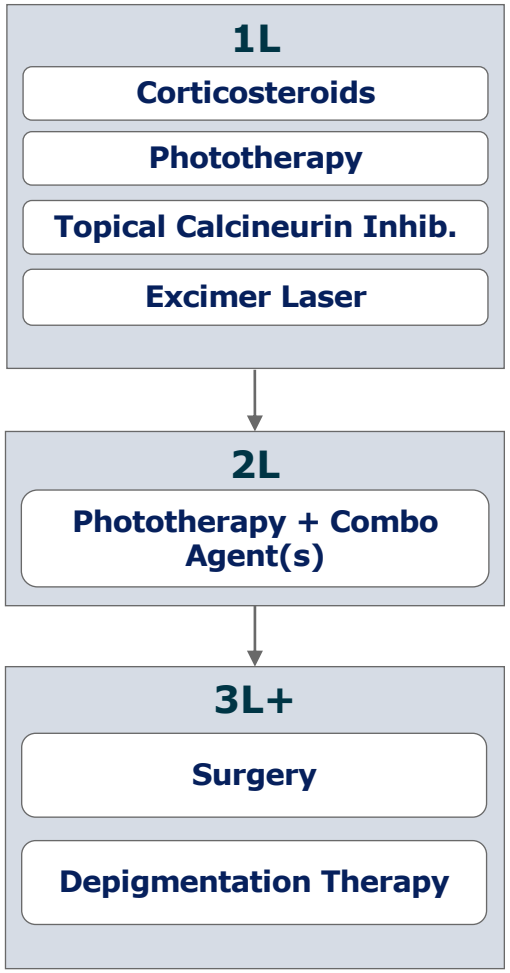
Vitiligo – Treatment Paradigm

Current vitiligo treatment is dominated by non-specific therapeutic options

Current Treatment Paradigm and Unmet Need



Treatment modality is dependent on **disease area** (segmental vs. non-segmental) as well as **activity** (controlled vs. uncontrolled); patients typically receive **NBUVB phototherapy, excimer laser procedure,** or an **oral / topical anti-inflammatory agent in the 1L**

1L agents are often **used in combination in the 2L** to enhance disease control

Surgeries include skin tissue / cellular grafting and hair follicle transplant, often **technically challenging and costly**; depigmentation therapy is a **less common FDA-approved modality for cosmetic improvement**

Vitiligo Key Unmet Need

Current vitiligo treatment is dominated by non-specific therapeutics; a **targeted, more efficacious treatment option is needed** that lowers the disease recurrence rate and is effective for all skin tones / scar types

Source: UptoDate; Bergqvist. Dermatol. 2020;236:571-592; Karagaiah. Expert Opin Emerg Drugs. 2020;25(1):7-24
NBUVB: Narrow-band ultraviolet-B light; 1L = 1st line, 2L = 2nd line, 3L+ = 3rd line or greater

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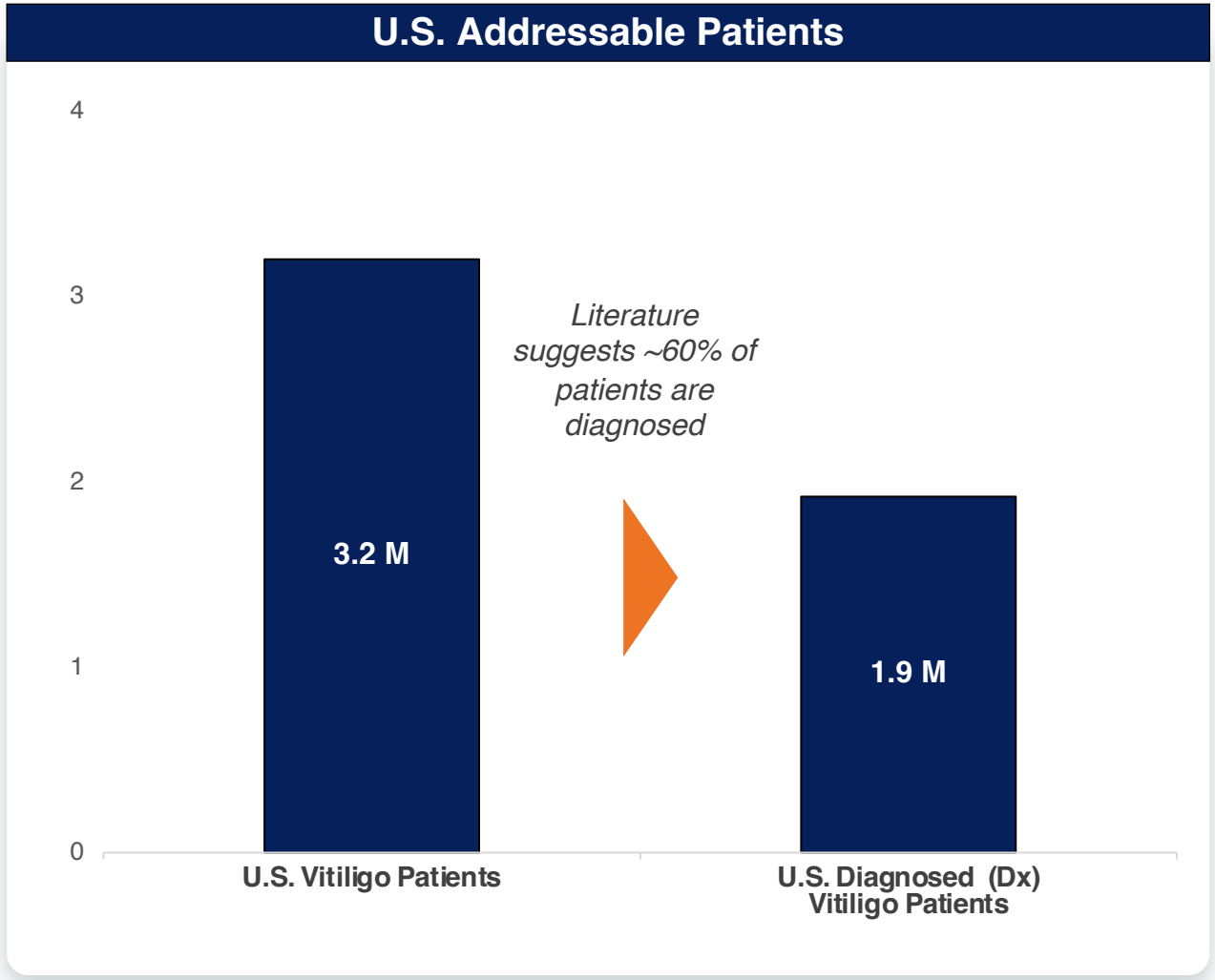
Vitiligo – Epidemiology

Large market with high unmet need and lack of approved prescription treatment options



- **Large U.S. market between 1.9 (diagnosed) and 3.2 million (diagnosed/undiagnosed) with no approved treatments**
  - Prevalence generally consistent across regions of the world with a range of 0.5% to 2.0% of the worldwide population
- **Literature suggests that many patients do not seek treatment due to lack of approved and effective treatment options**

Sources: *JAMA Dermatology*, "Prevalence of Vitiligo Among Adults in the United States"; 2022; 158(1):43-50 (published online Nov. 17, 2021); Rangu S, McKenzie PL, Castelo-Soccio L (2021) Therapy Utilization among Children with Vitiligo at an Urban Tertiary Care Center J Clin Dermatol Ther 7: 070. Bergqvist. Dermatol. 2020;236:571-592; Kreuger (2012)

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InhiBET™ BET Inhibitor Platform Panel

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2022 KOL Event:
BET Inhibition for I&I Diseases & Clinical Development of VYN201

Gerald V. Denis, PhD

- Professor, Boston University School of Medicine - molecular oncologist with experience in chromatin control of transcription in cancer
- Pioneered studies of the BET bromodomains proteins, a family comprised of BRD2 (originally named RING3), BRD3 and BRD4 in somatic cells
- First to report a function for a BET protein, and to link these co-regulators to human cancer
- Established that BET bromodomain proteins provide a functional link between abnormal metabolism, inflammation and breast cancer progression in post-menopausal African American women
- Now exploring how BET proteins regulate cytokine/chemokine production in the immune cells that infiltrate the breast cancer microenvironment, which are important for immune exhaustion, chemoresistance and metastasis

Thierry Passeron, MD, PhD

- Professor of Dermatology at the University Hospital of Nice
- Heads the laboratory INSERM U1065 team 12, C3M, dedicated to the study of molecular mechanisms involved in pigmentation and melanoma
- President of the Department of Clinical Research and Innovation of Nice University hospital
- Vice-president of Côte d'Azur University
- Seven international patents and more than 220 publications in scientific journals
- Co-founder of YUKIN therapeutics
- Fields of research include pigmentary disorders (including vitiligo and melasma), melanoma, hidradenitis suppurativa, alopecia areata and lasers

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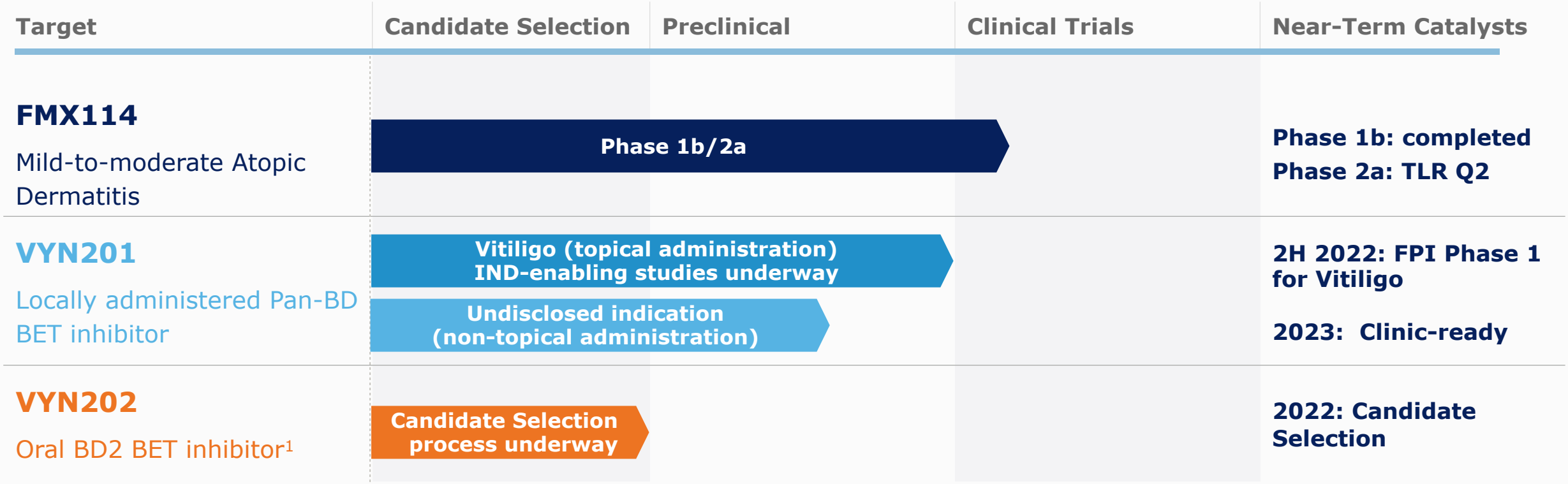
Note: Professor Gerald V. Denis, Ph.D. and Professor Thierry Passeron, MD, Ph.D. are consultants for VYNE and are receiving compensation for their presentations at today's event.

Targeted Clinical Milestones through 2023

Driving Pipeline to Proof-of-Concept



Exclusive Access to Library of NCE BET Inhibitors for Any Indication Worldwide

1. Initial indications for VYN202 to be communicated following completion of requisite pre-clinical evaluations

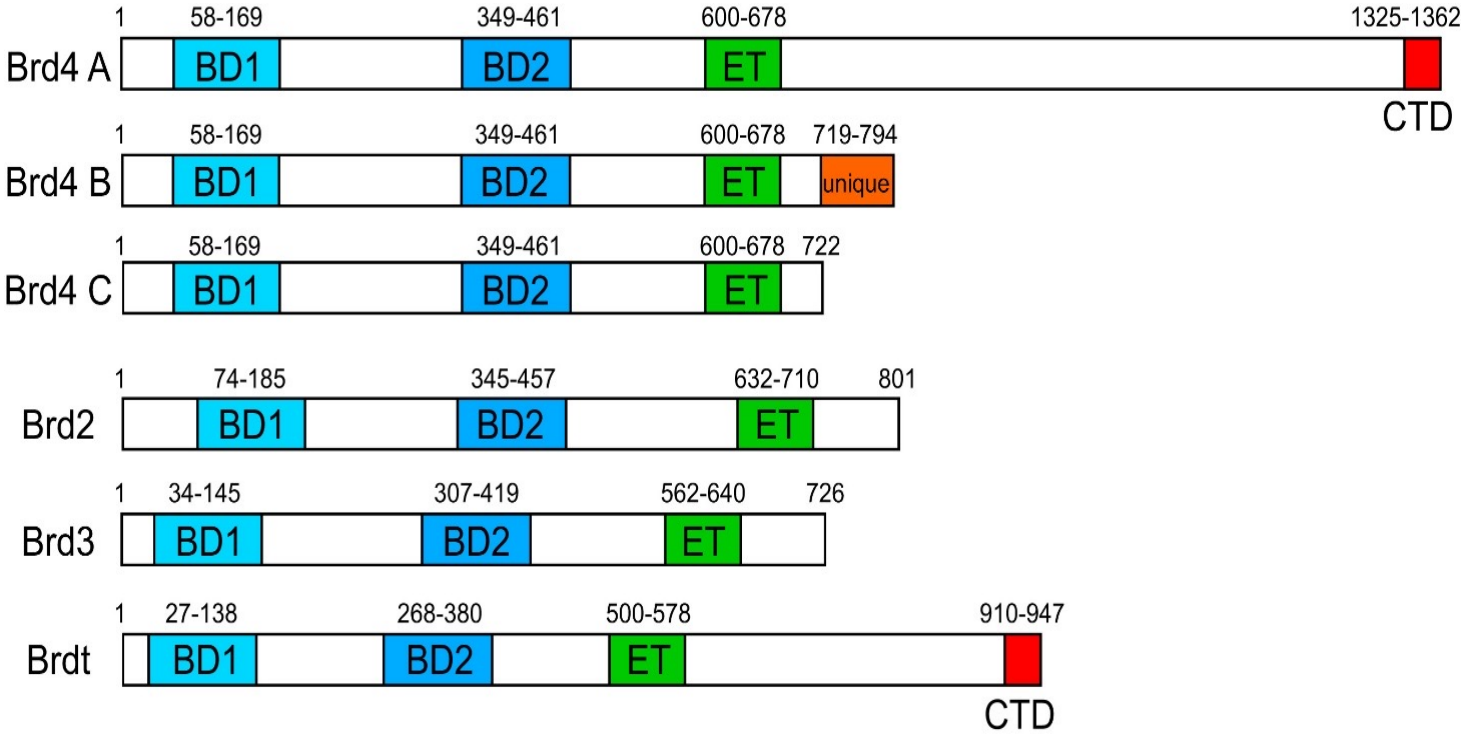
TLR = Top Line Results; FPI = First Patient In/Enrolled

Boston University

BET proteins, through their bromodomain motifs, control transcription of cytokine genes critical for inflammatory diseases

Gerald V. Denis, PhD
Boston University School of Medicine
Department of Pharmacology and Experimental Therapeutics

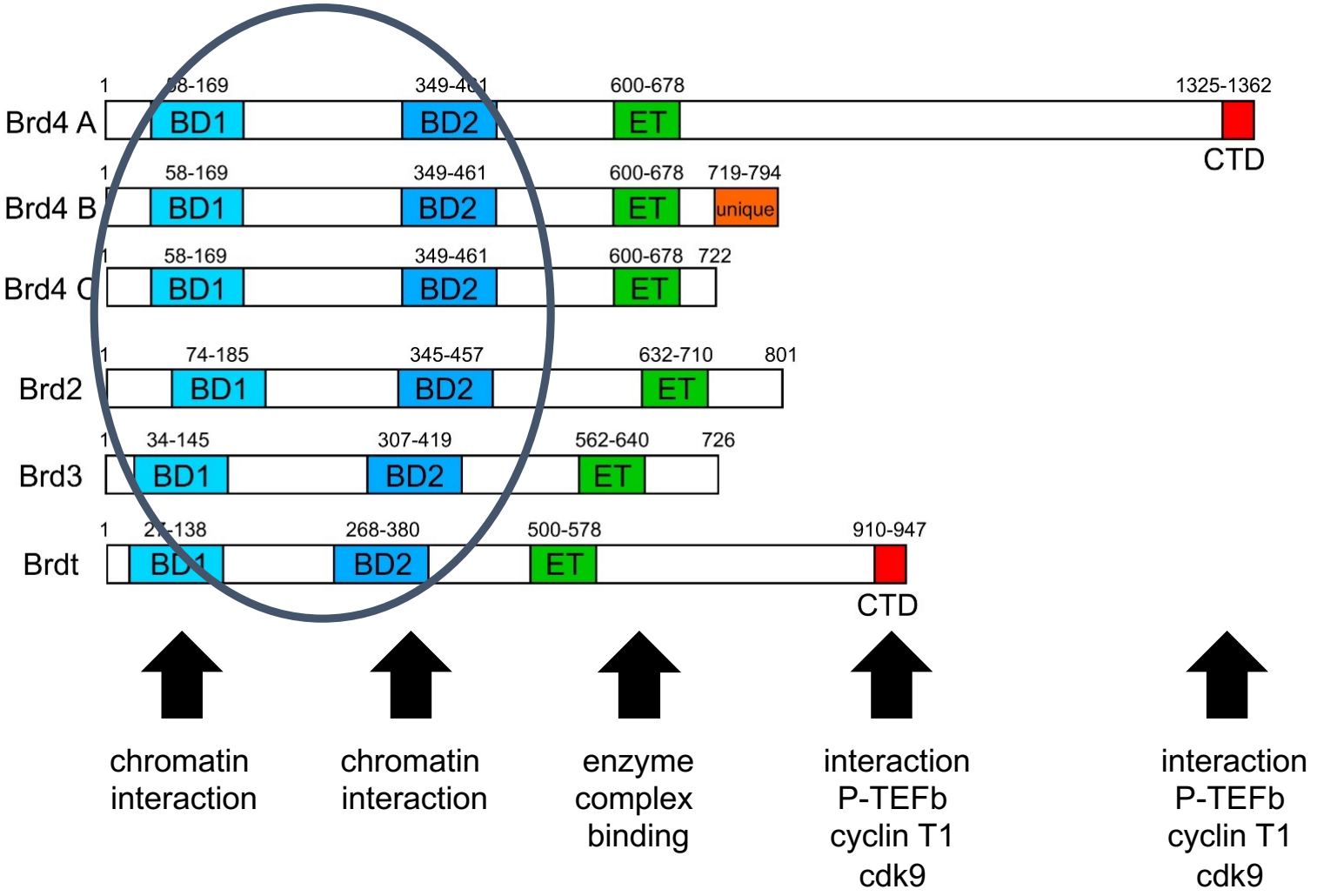
Domain structure of human BET proteins



- The bromodomain family (“Brd” or “BD”) is comprises of 4 members (BRD2-4, BRDT) and have two shared domains, bromodomain 1 and 2 (BD1 and BD2) with an extra-terminal domain
- The Brd family is different from other BD domain classes (i.e. acetylases/transcriptional co-regulators) so inhibitors do not tend to have a broad activity outside the Brd family

Shi & Vakoc, *Mol. Cell* 2014

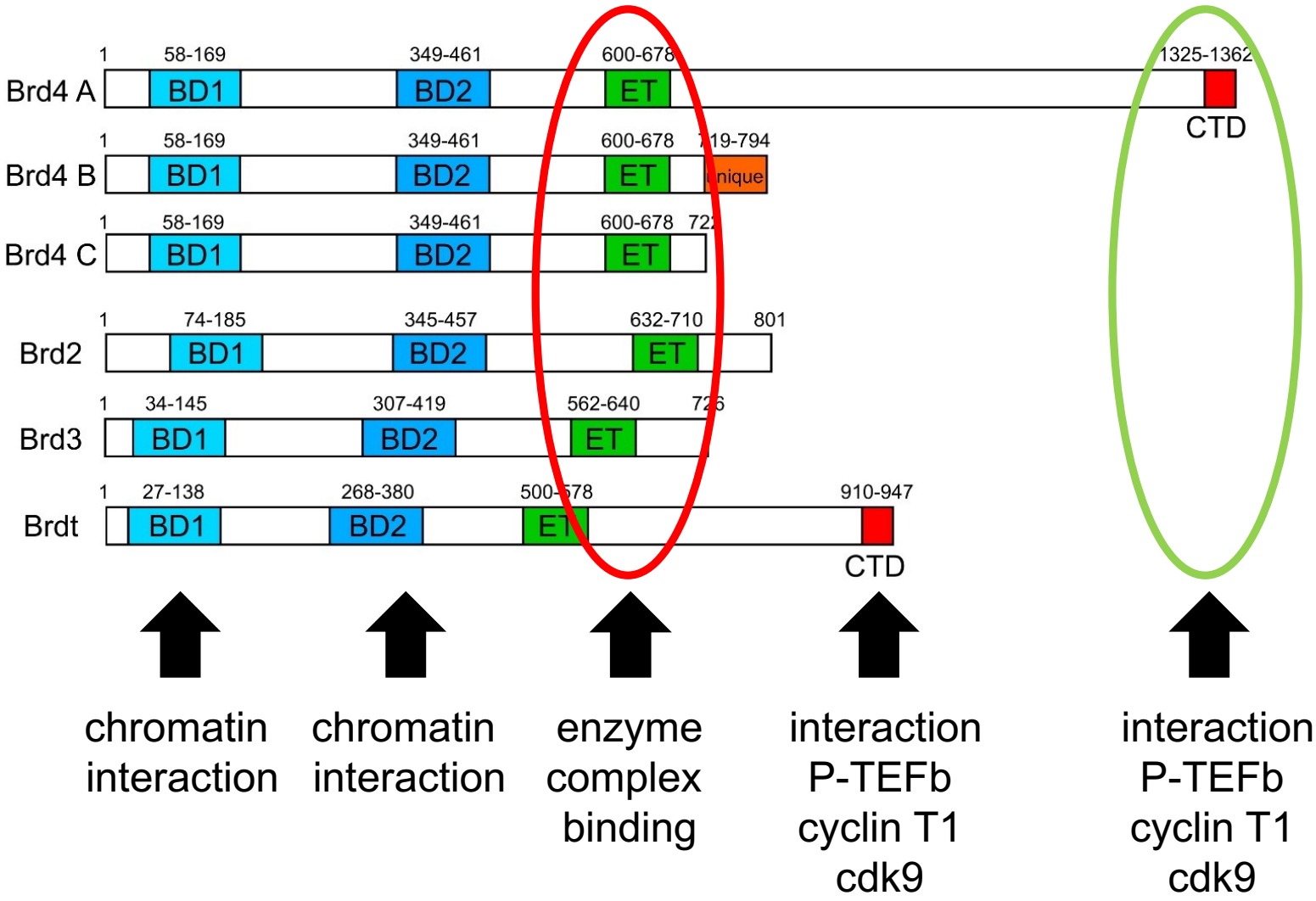
Domain structure of human BET proteins



- BD1 and BD2 primarily recognize acetylated lysines on histone termini of chromatin
- Both BD1 and BD2 are recognized as druggable small molecule inhibitor targets
- The difficulty in developing selective small molecule BET inhibitors (BETi) has been the high amino acid homology between BD1 and BD2

Shi & Vakoc, *Mol. Cell* 2014

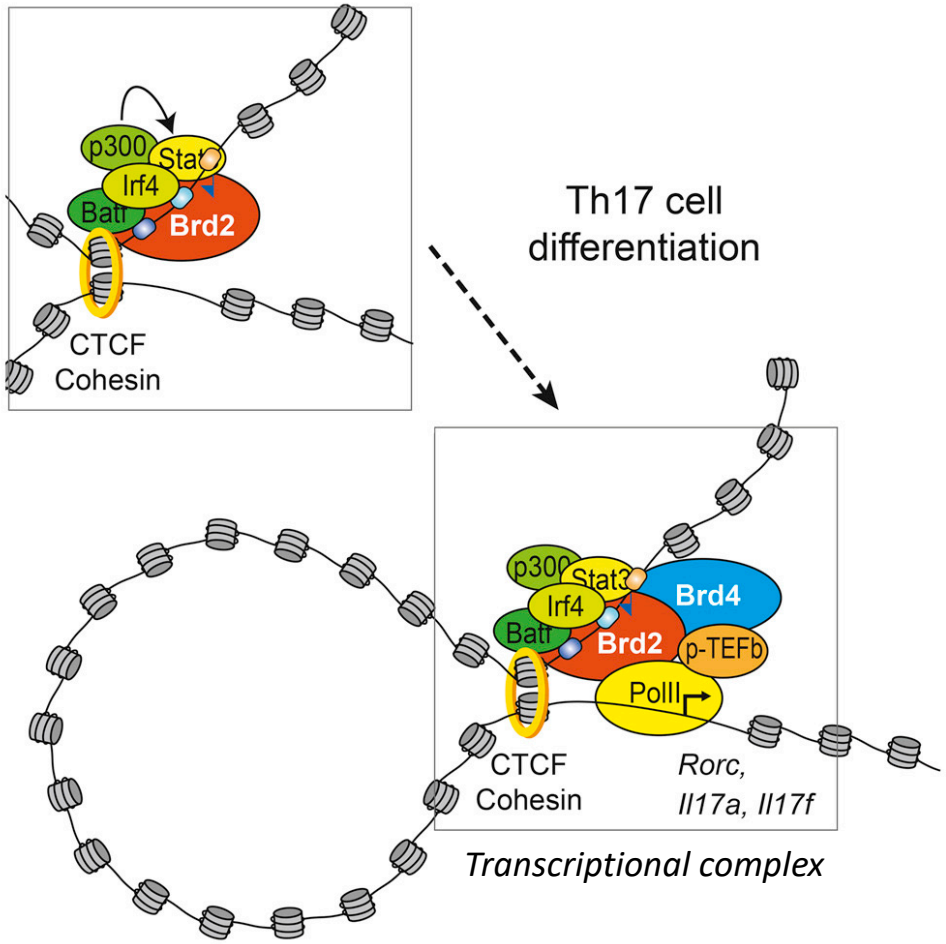
Domain structure of human BET proteins



- Remaining structure involved in recruiting/binding additional transcriptional factors that promote chromatin remodeling, which facilitates the initiation of gene transcription

Shi & Vakoc, *Mol. Cell* 2014

BET proteins bind to histones in chromatin and recruit co-regulator complexes

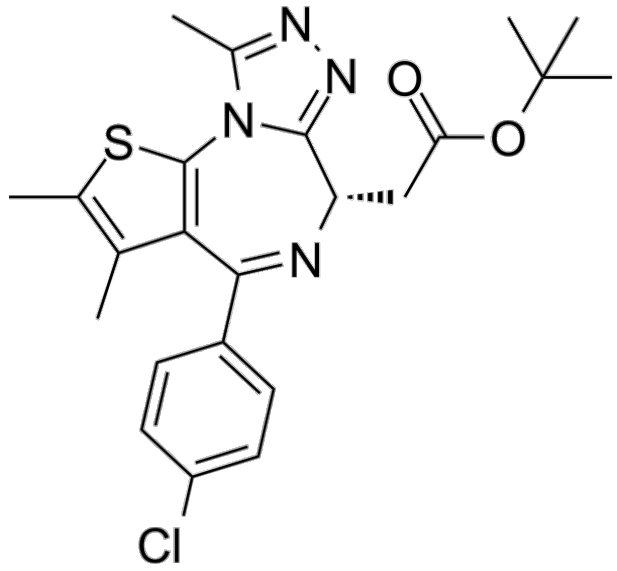


- Targeted loops is where all the “action” happens as transcription is a group effort among several recruited factors
- Inhibiting BET proteins prevents transcriptional complex formation, thereby inhibiting the whole pathway
- This targeting is different from drugs that inhibit a specific receptor (e.g. blocking the active site of tyrosine kinases such as JAKs) to prevent a specific downstream action/consequence from happening

Cheung, … & Ming-Ming Zhou, *Mol Cell* 2017

The History/Evolution of BET Inhibition

- JQ1, I-BET-151[1] and other first generation BETi: all pan-BD BET inhibitors for hematological and solid tumor applications
- Dose limiting toxicities have limited these first generation development programs (Gastro-intestinal stem cell, immuno- and reproductive toxicities)
- The multi-modal action of BETi on inhibiting T cell differentiation and cytokine expression has led to interest in their applicability to autoimmune and autoinflammatory diseases

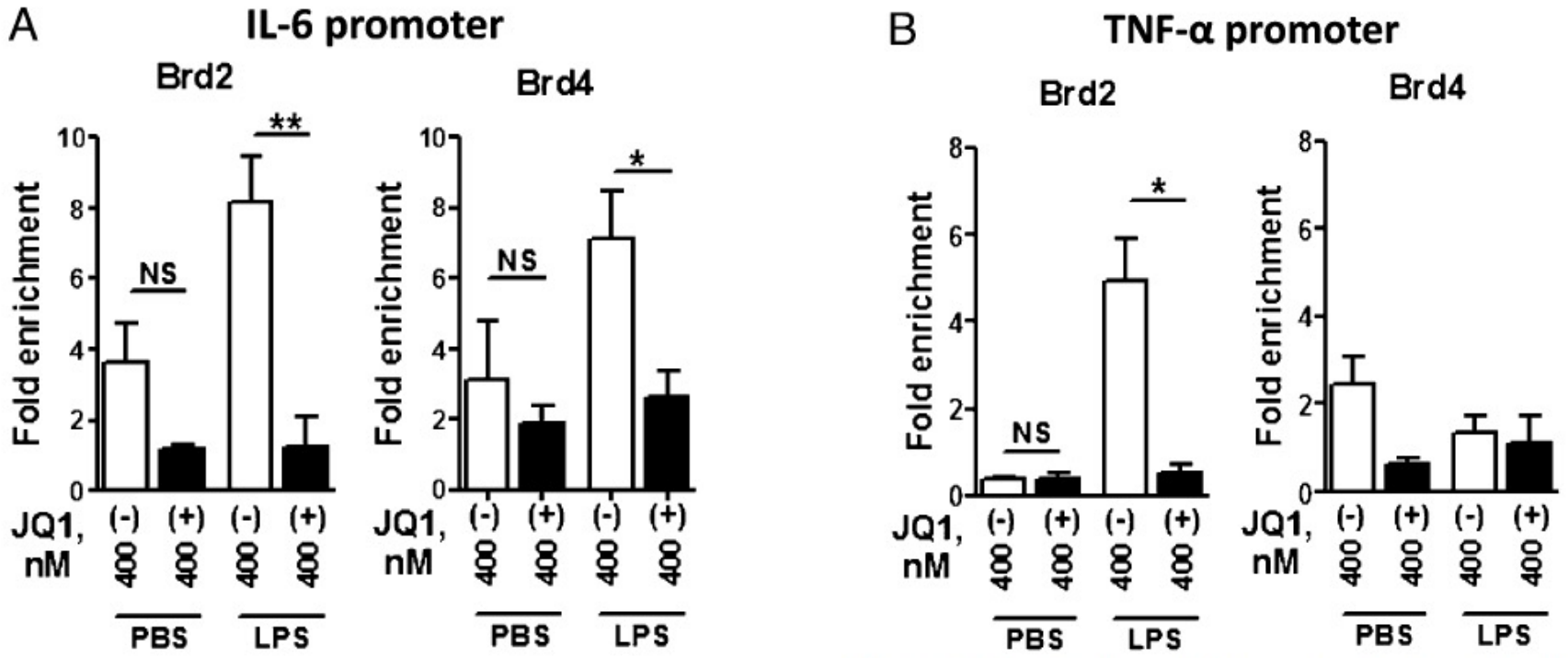


JQ1, pan-BD BET inhibitor, first described in 2010[2]

IC50 BRD4 BD1: 77nM
IC50 BRD4 BD2: 33nM

1. https://en.wikipedia.org/wiki/JQ1, 2. Munro et al, Nature 2010

BRD2 and BRD4 bind to promoters of macrophage inflammatory cytokine genes (JQ1)

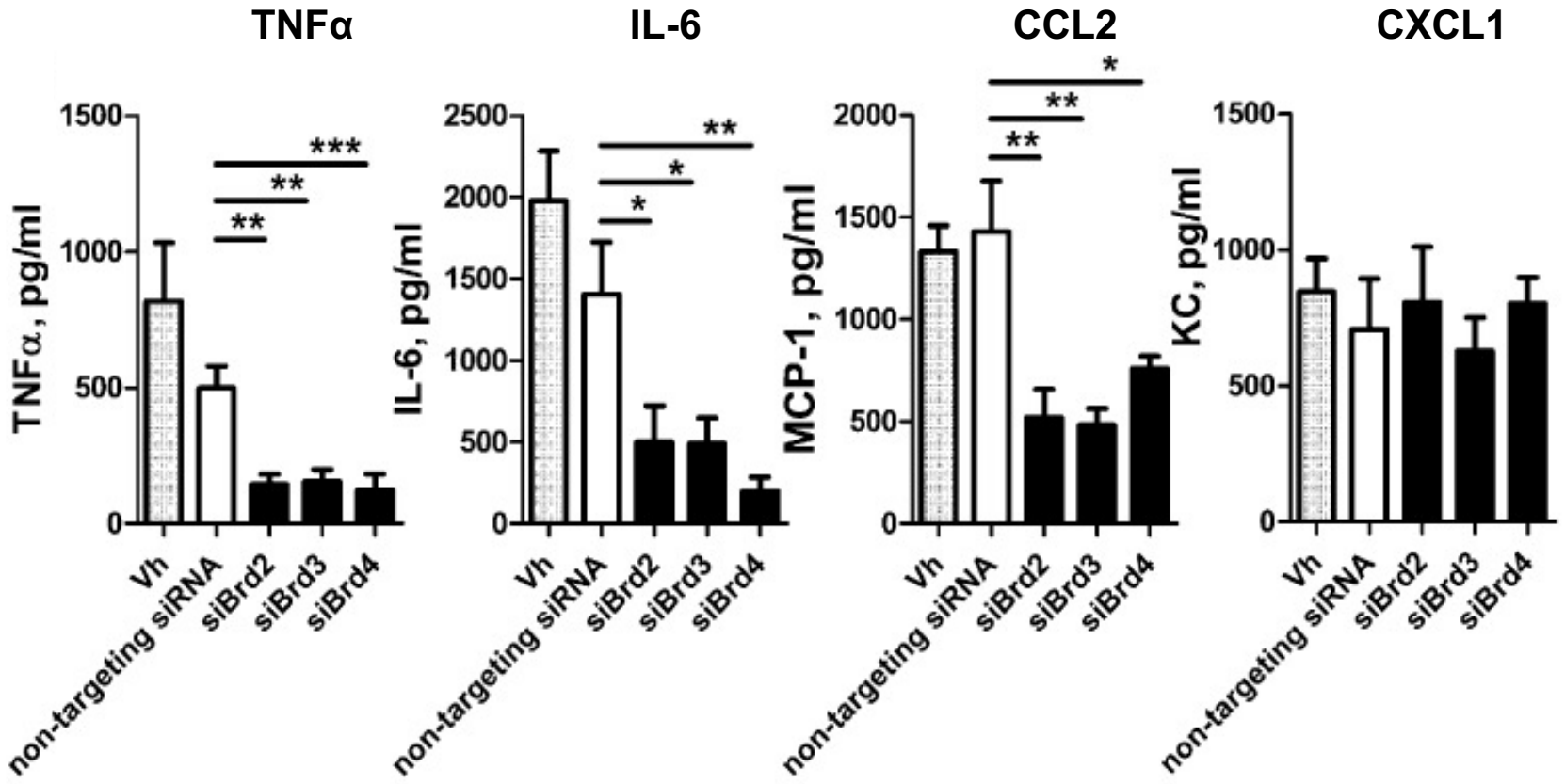


Chromatin immunoprecipitation shows pan-BET inhibitors displace BET protein from chromatin[1]

- Example of how a BETi impacts certain transcription factors to generate specific cytokines can demonstrate how the “multiplicative feature” of impacting the BET/Brd pathway works

1. Belkina, Nikolajczyk & Denis, *J. Immunol*. 2013. 2. https://en.wikipedia.org/wiki/JQ1

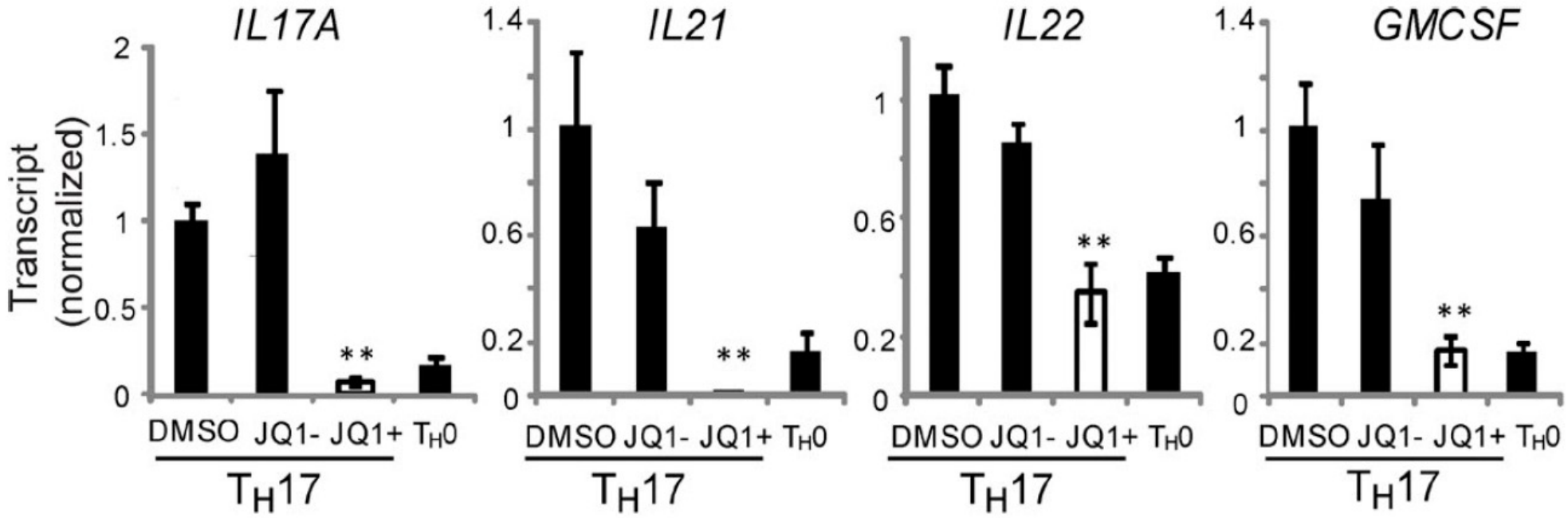
Knockdown of each BET protein in primary macrophages reduces cytokine production



- Example shows that not **all** cytokines are regulated by BETis (CXCL1 is not regulated)
- **Disease applications have to be targetable by BETis and specificity is possible**
- The key question is how to ensure that the mechanism of action connects to the targeted indications

Belkina, Nikolajczyk & Denis, *J. Immunol*. 2013

Pan-BET inhibition blocks Th17 differentiation in human naïve T cells (JQ1)



- Blocking Th17 with JQ1: this mechanism introduced the relevance of BETi for Th17-mediated diseases
- Th17-relevant diseases include: rheumatoid arthritis, psoriasis, systemic lupus erythematosus, ulcerative colitis/Crohn's disease

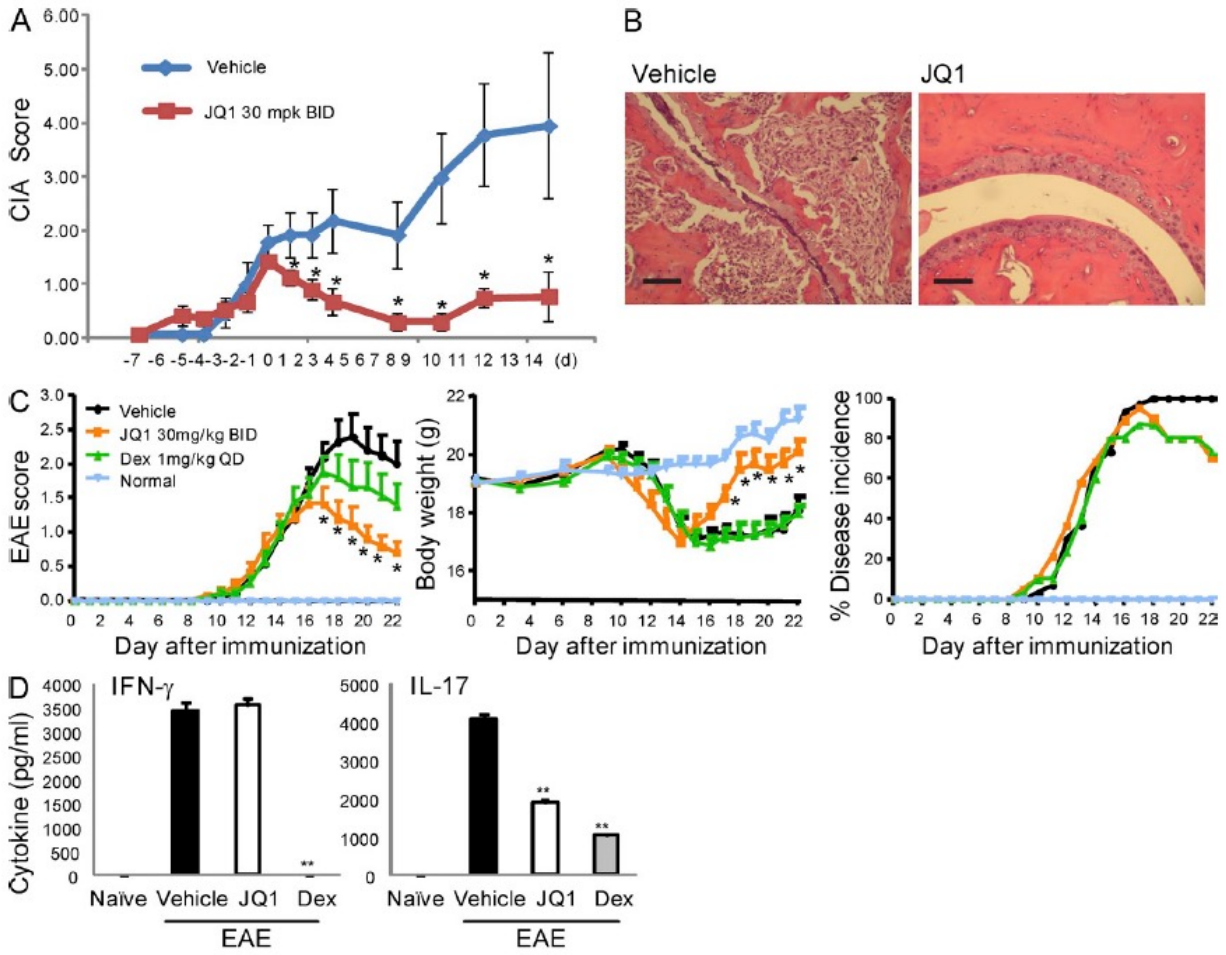
Note: The canonical paper showing Th17 regulation by BET proteins: Mele et al, J. Exp Med. 2013

Pan-BET inhibition protects mice from autoimmunity (JQ1)

collagen-induced arthritis model

experimental autoimmune encephalitis model

Th17 cytokine



- Potent anti-inflammatory effects seen in *in vitro* T cell differentiation studies was shown to translate in several *in vivo* animal models of inflammatory disease with JQ1

Mele et al, *J. Exp Med*. 2013

The Future of BETi's

- Improved medicinal chemistry efforts have enabled gains on on-target potency, with differentiated BD1/2 selectivity profiles being achievable for new BETis
- There is a greater (yet evolving) understanding of the role of bromodomain selectivity on both pharmacological/disease relevance and safety e.g BD1 v's BD2 selectivity[1]
- Newer approaches available to improve on benefit/risk for pan-BD BETi:
  - Specific tissue targeting (local effect)
  - Reduce or mitigate toxicities/systemic exposure through:
    - High on-target potency and BD selectivity (BD1 v. BD2 and vice versa)
    - Controlled release/modified release formulations
    - "Soft" and pro-drug approaches, as applicable

1. Galen et al, *Science* 2021

Summary

- The science of BET protein inhibition in immuno-inflammatory and oncology applications continues to evolve
- Work continues to elucidate the impact of BD selectivity on both oncogene and cytokine expression “signatures”
- Broad inhibitory networks have value because many inflammatory cytokines function in networks, not as single factors
- Equally, clinical relevance requires knowledge of specific cytokines involved, as not all cytokines are inhibited, even by a pan-BETi approach (*e.g.*, CXCL1)
- Targeting both BD1 and BD2 bromodomains using less-selective small molecules (*e.g.*, JQ1) has potent anti-inflammatory benefits, but also has undesirable toxicities that will necessitate more targeted therapies for pan-BD BETis
- There is a continuing need to understand the interplay between BETi potency and selectivity relating to the intended clinical application to optimize benefit/risk

InhiBET™ BET Inhibitor Platform

Bromodomain & Extra-Terminal Domain (BET) Inhibition for Immunology and Inflammatory Diseases

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InhiBET™ BET Inhibitor Platform Overview

Platform includes global rights to a library of NCEs for any indication

VYN201

Locally administered Pan-BD BET inhibitor

Designed to address diseases involving multiple, diverse inflammatory cell signaling pathways with low systemic exposure

Potential Target Market:

- Vitiligo
- Other indications benefiting from local application and "soft drug" approach

Broad activity:

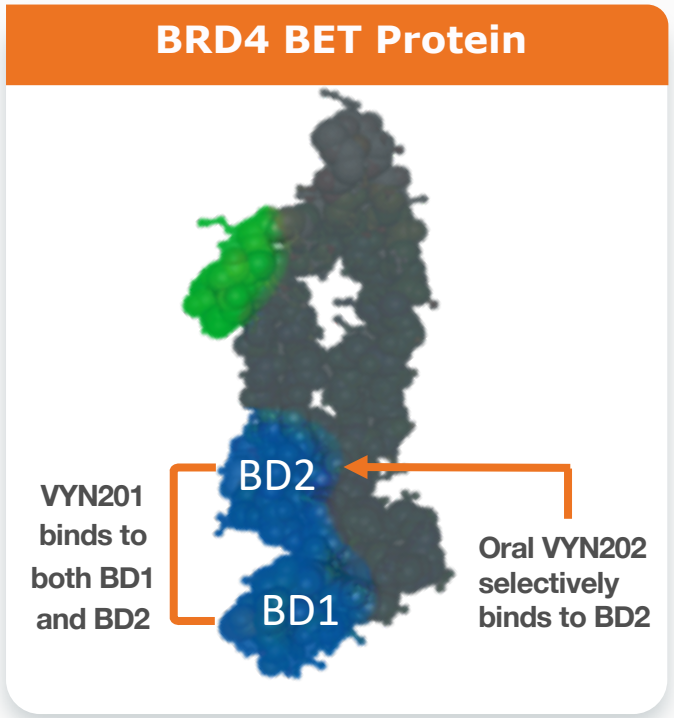
- Binds to BD1 and BD2 domains

Competition:

- Almost all BET inhibitors in development bind to BD1 and BD2 but are ***orally*** delivered with significant dose limiting toxicities

Targeted Near Term Milestones:

- Phase 1 Initiation in Vitiligo: 2H 2022



VYN202

Oral BD2-selective BET inhibitor

Designed to selectively bind to BD2 and is being developed for major immuno-inflammatory diseases

Potential Target Market[1]:

- Immuno-inflammatory indications such as rheumatoid arthritis, systemic lupus erythematosus, ulcerative colitis/Crohn's and multiple sclerosis; additional potential in myeloproliferative neoplastic disorders[2]

Focused activity:

- Highly selective inhibition of BD2 domain of the BRD4 protein (Selectivity vs. BD1)
- Targeting improved safety profile compared to oral pan-BD BET inhibitors

Targeted Near Term Milestones:

- Candidate Selection – 2022

1. Initial indication to be communicated following candidate selection, exercise of option and completion of requisite pre-clinical evaluations
2. List included is illustrative and not exhaustive of potential indications

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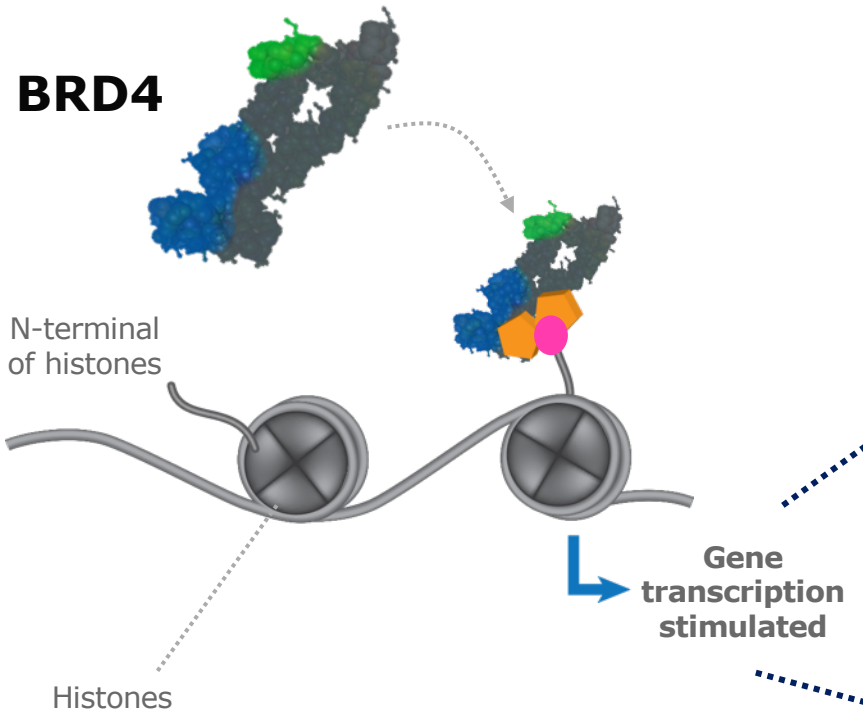
BET Proteins Play a Key Role
in the Regulation of Inflammatory and Oncogenic Genes involved in Several Diseases

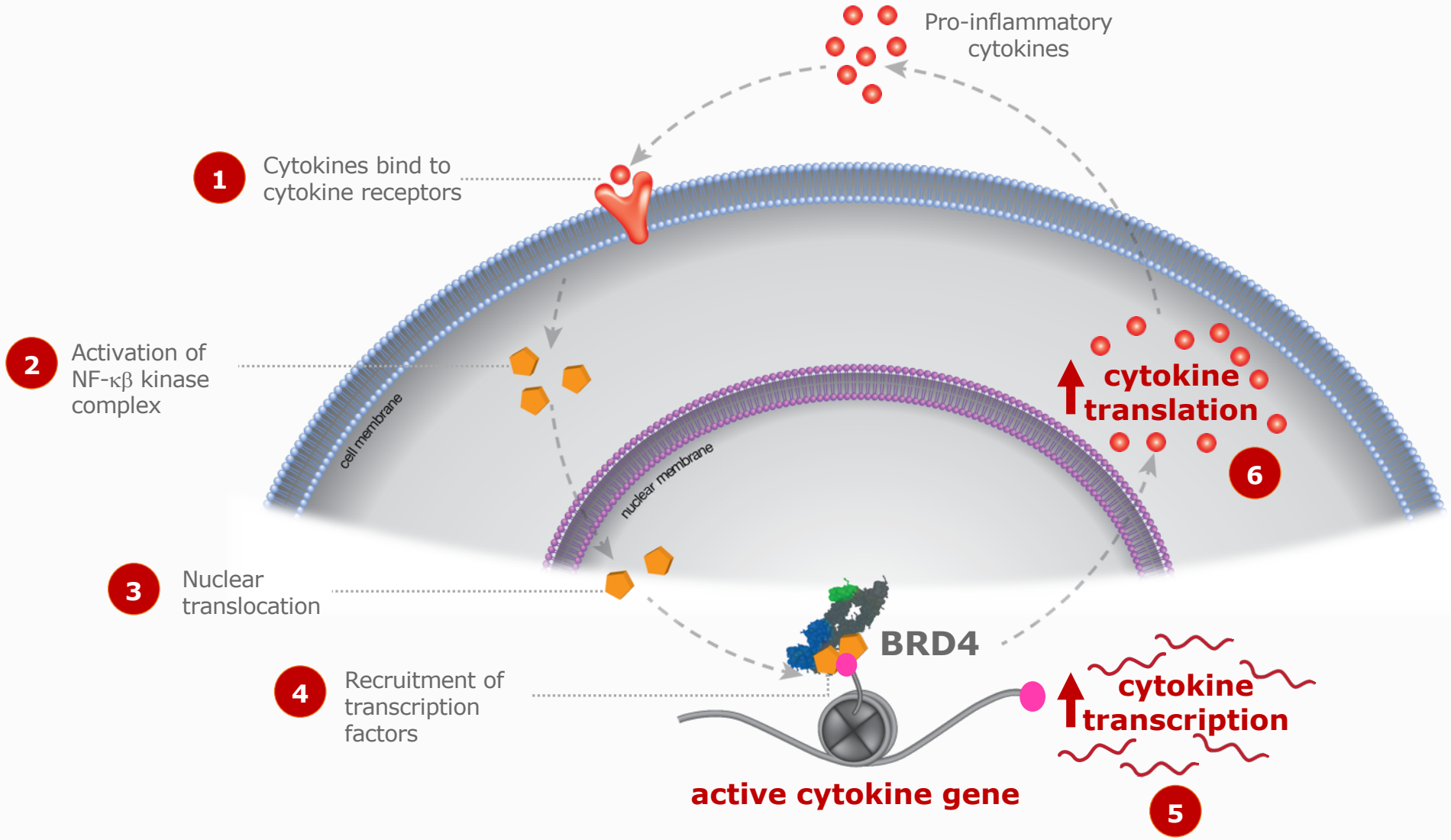


BET proteins "read" acetylated lysines and enable transcription of:

Pro-inflammatory genes, leading to:
- Increased cytokine expression that activate B&T cells
- An increase in autoimmune and cardiovascular diseases

Oncogenic genes, leading to:
- Increased cell proliferation/survival
- An increase in solid tumors and hematologic malignancies

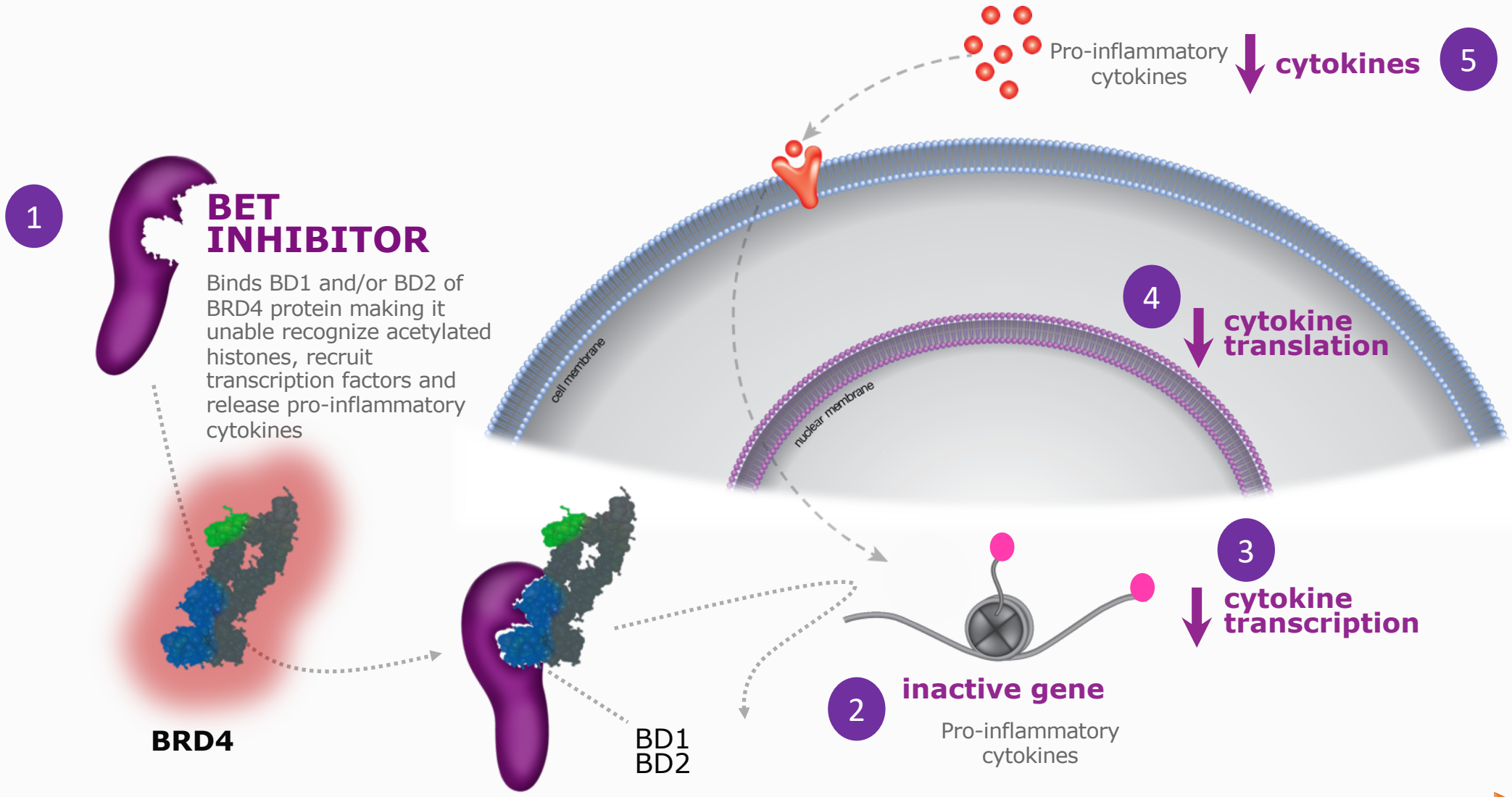
How BET Proteins Fuel the "Vicious Cycle"
of Pro-Inflammatory Cytokine Production in Autoimmune Diseases



NF-κB = Nuclear Factor Kappa B

BET Inhibitors Block BD1/BD2 Binding

to Acetylated Lysines and Stall Pro-inflammatory Protein Transcription



VYN201
Locally administered pan-BET inhibitor

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VYN201 Pre-Clinical Efficacy Model Evaluations

Program designed to investigate the targeted administration of a "soft drug" pan-BD BET inhibitor to maximize local effect and minimize systemic exposure

Indication/area	Model	Administration Route	Status
Th17 autoimmune diseases	IMI-induction mouse model	Topical	Complete
Th2 autoimmune diseases	DNCB-induction mouse model	Topical	Complete
Fibrosis	Wound healing outcomes mouse model	Topical	Complete
Vitiligo	Reconstituted human epithelial skin TNFα/IFNγ induction model	Topical	Complete
Idiopathic pulmonary fibrosis	Bleomycin-induction mouse model	Intra-nasal	Complete
Rheumatoid arthritis	Intra-articular cytokine cocktail mouse model	Intra-articular	Complete
Macular degeneration	Choroidal neovascularization rat model	Intra-orbital/vitreous	Complete
Colitis (gut restricted)	DSS-induction mouse model	Oral	Complete
Oncology (AML/melanoma)	Human cell line screening and biomarker discovery	In-vitro	On-going

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VYN201: Th17 autoimmune diseases

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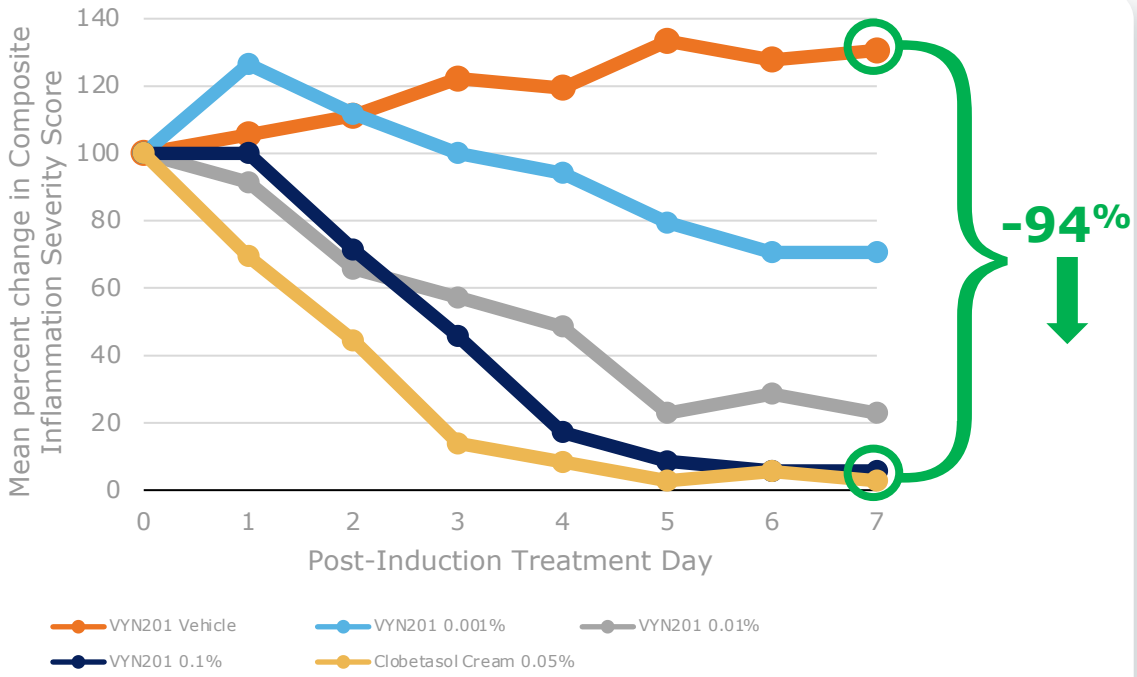
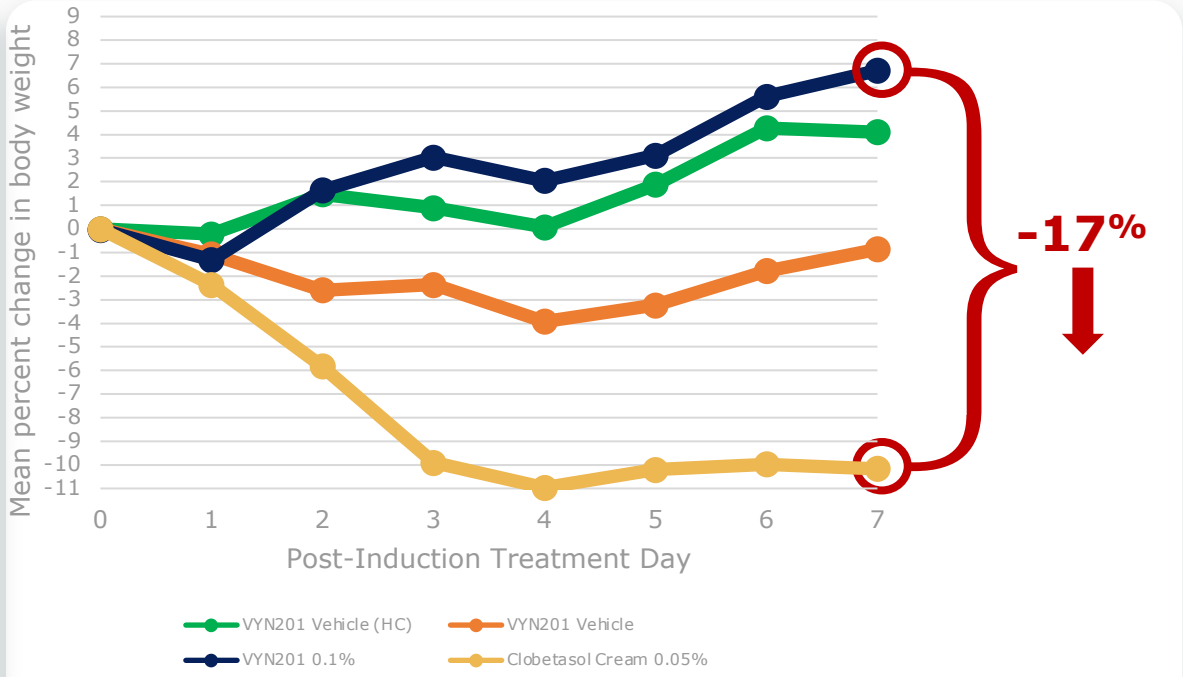
VYN201: Comparable Efficacy to Superpotent Steroid Clobetasol
in a TH17-Mediated Murine Inflammation Model; Potential for Greater Tolerability

Dorsal depilated BALB-C mice were dosed topically for 14 days with 100mg topical IMI cream (Day 1-7: induction phase, Day 8-14: treatment phase). N=4 animals were assigned to each treatment group with each group receiving 100mg of allocated treatment on Day 8-14 once daily



- Dose dependent response was observed over the VYN201 concentration range 0.001% to 0.1%
- There was a 94% reduction in composite score for VYN201 0.1% relative to vehicle control group at Day 7
- VYN201 0.1% had comparable efficacy to clobetasol propionate 0.05% cream



- Animals treated with VYN201 0.1% continued to gain body weight in a similar manner to healthy control group treated with vehicle
- Clobetasol cream 0.05% group had a 17% reduction in body weight compared to the VYN201 0.1% group at treatment day 7

IMI – Imiquimod.

*Composite Inflammation Severity Score is a composite mean score of erythema and peeling severity scored on a 4-point ordinal scale per domain (0=none, 1=mild, 2=moderate and 3=severe for a maximum score of 6), data expressed as a mean percentage change from initiation of treatment phase.

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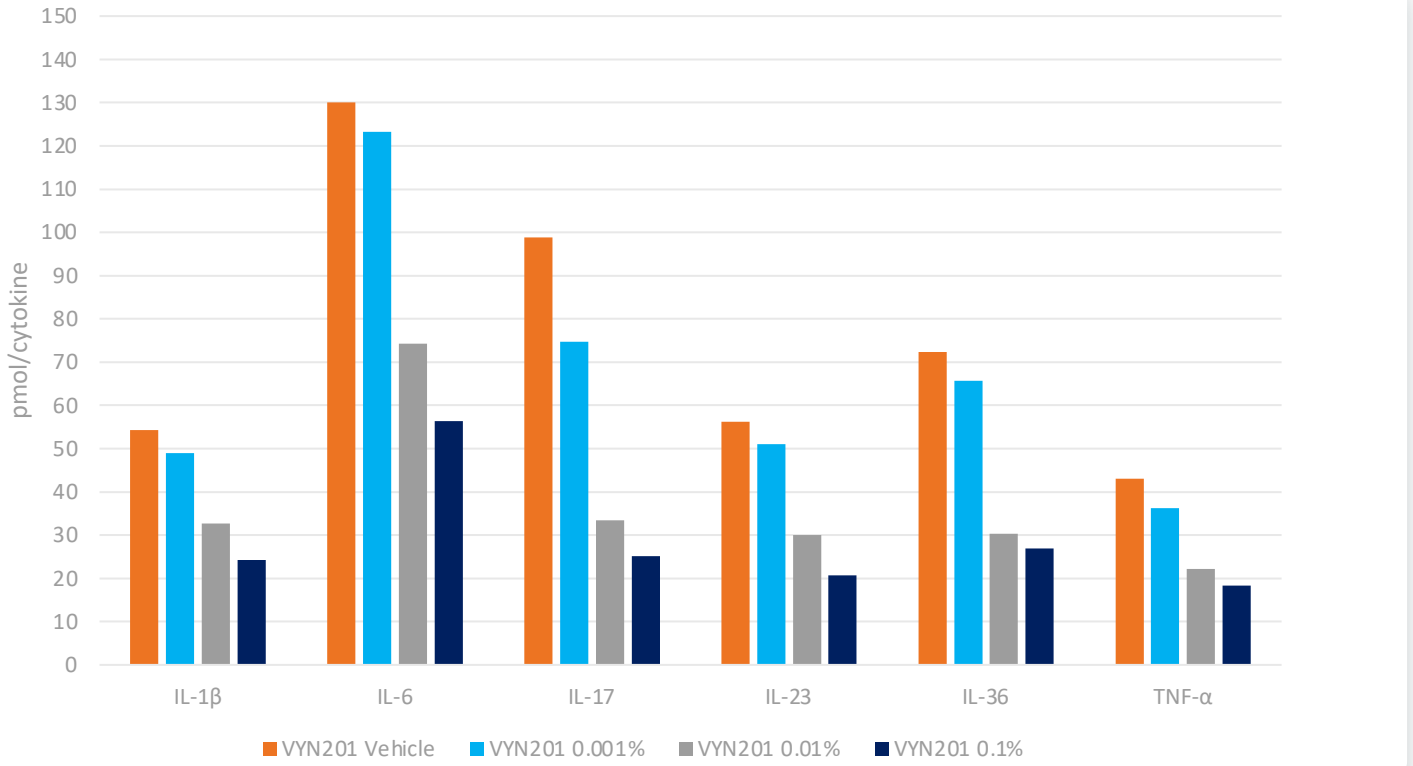
VYN201: Dose-Dependent Reduction in Pro-Inflammatory Biomarkers
in TH17-Mediated Murine Inflammation Model Indicates Target Engagement

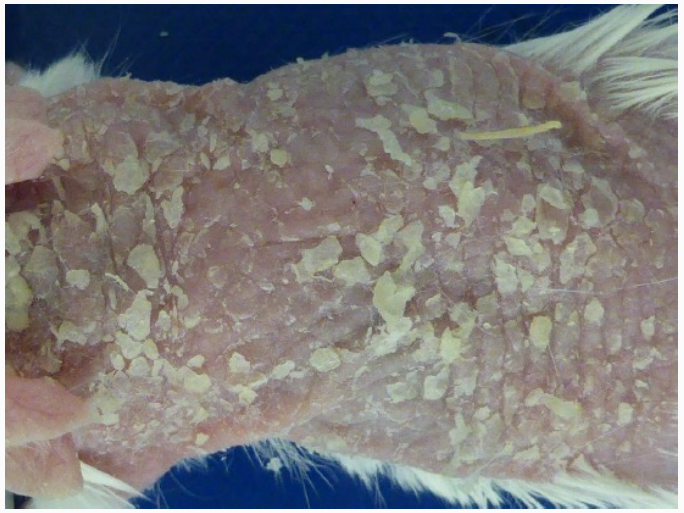
Dorsal depilated BALB-C mice were dosed topically for 14 days with 100mg topical IMI cream (Day 1-7: induction phase, Day 8-14: treatment phase). N=4 animals were assigned to each treatment group with each group receiving 100mg of allocated treatment on Day 8-14 once daily



- **Strong correlation between improvement in clinical severity scores and reduction in many pro-inflammatory biomarkers relevant to Th17-mediated autoimmune diseases**
- Dose-dependent reduction in biomarker expression was observed with VYN201 0.1% as having the greatest effect
- IL1β, IL-6 and IL-23 precipitate the differentiation of naïve Th0 immune cells to Th17 cells
- Th17 cells produce a range of cytokines that drive inflammation in autoimmune diseases. These include IL17, IL36 and TNFα

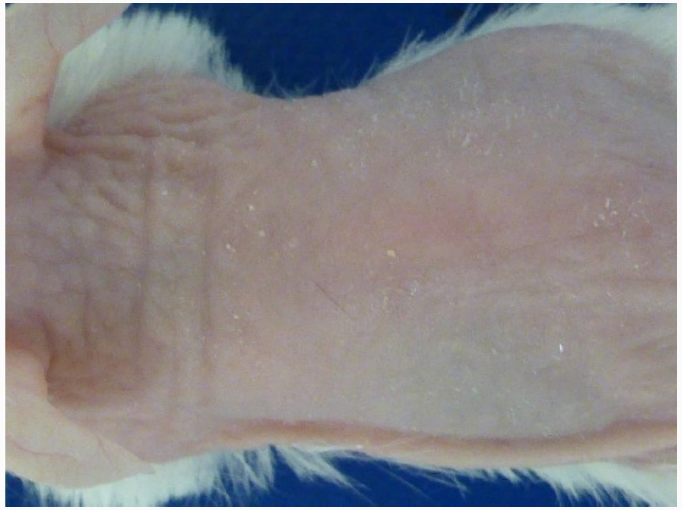
IMI – Imiquimod.

VYN201:
Normal Skin Physiology in TH17-Mediated Murine Inflammation Model Suggests VYN201 Well Tolerated (Day 7)



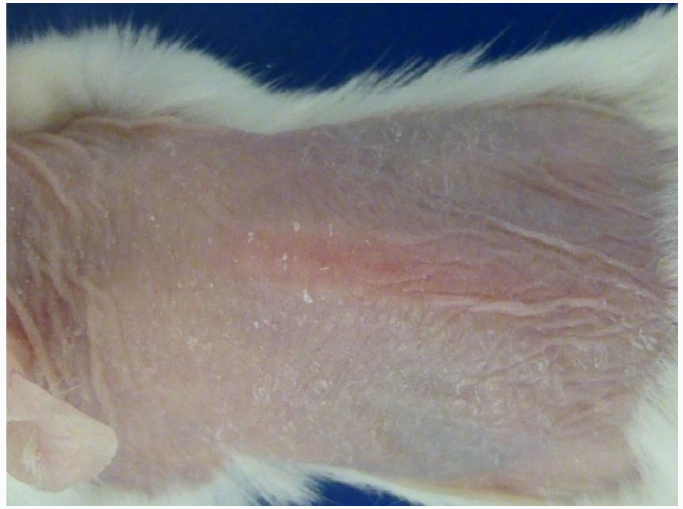
VYN201 Vehicle

- No appreciable improvement in clinical signs



VYN201 0.1%

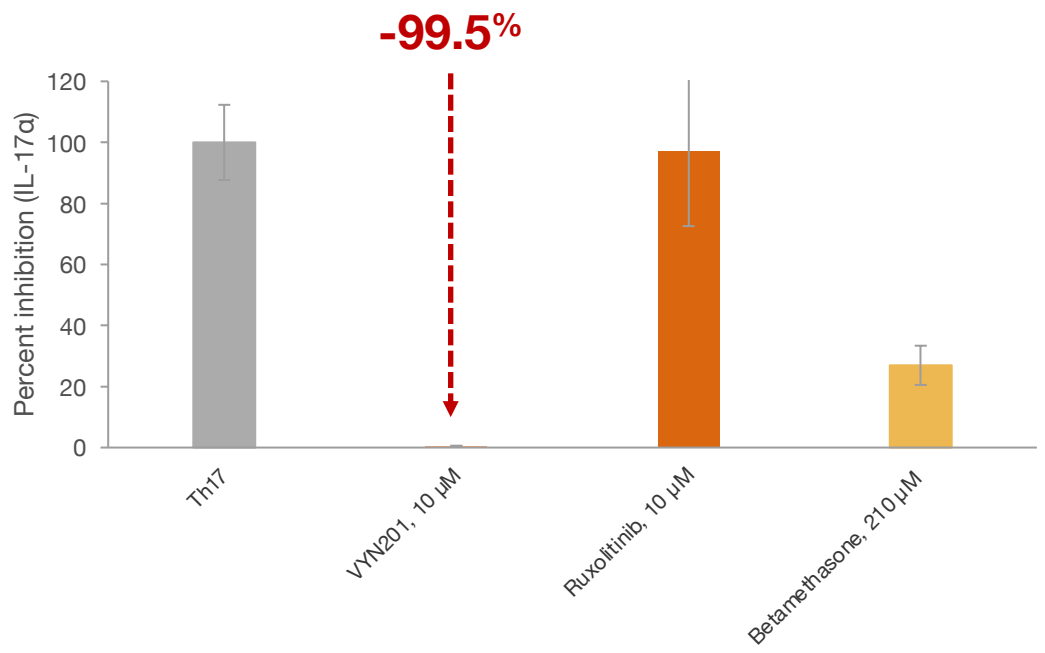
- Substantial resolution of clinical signs
- Skin presents with normal physiology with no evidence of striae rubrae or atrophy
- No evidence suggestive of intolerance



Clobetasol Cream 0.05%

- Substantial resolution of clinical signs
- Significant evidence of dermal atrophy (clear presence of both rhytides/fine wrinkles and deep wrinkles)
- Marked dermal translucency and elastolysis

VYN201 Significantly Reduced Expression of Several Key Pro-Inflammatory Proteins Relevant to Th17-mediated Autoimmune Diseases in Human Tissue[1]



Interleukin 17-alpha

T-cells are polarized to Th1 and Th17 cells, the latter of which drives the production of IL17a which further upregulates the migratory action of pro-inflammatory cells and further inflammatory cell activation.

>95% Inhibition seen with assays for IL-36γ & LP-10

Interleukin 36-gamma

IL36γ is implicated in upregulating IL-17A signaling-related genes and so able to amplify keratinocyte inflammatory responses by promoting not only their own expression but also that of other cytokines related to Th17 signaling

CXC motif chemokine ligand 10 (LP-10)

An inflammatory cell chemoattractant secreted in response to interferon gamma. LP-10 is significantly overexpressed in many autoimmune diseases (>25-fold) vs. healthy skin[1]

1. Data on file. Results presented from qPCR analysis of processed and Th17-stimulated ex vivo human skin tissue based on a method derived from Garrett S.M., Zhao Q., and Feghali-Bostwick C. (2019) Induction of a Th17 phenotype in human skin – a mimic of dermal inflammatory diseases, *Methods and Protocols*, 2, 45

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VYN201: Dermal and Lung Fibrosis

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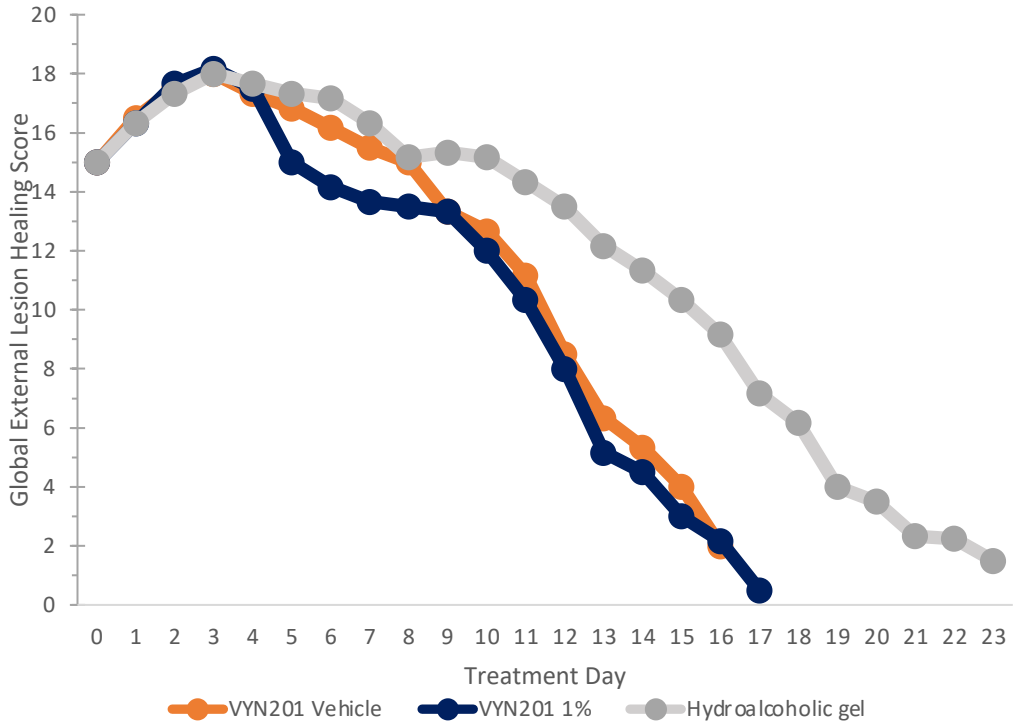
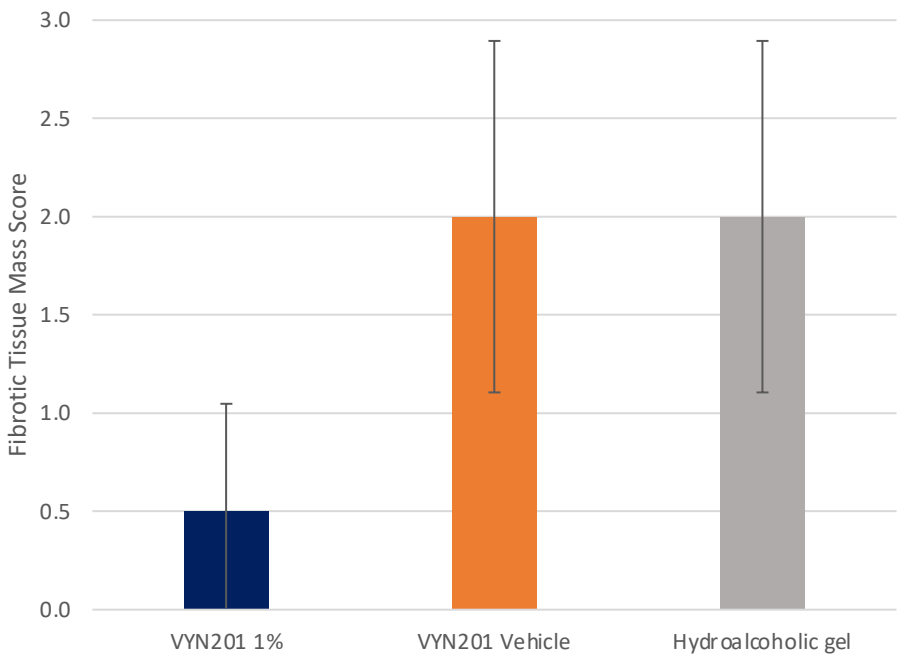
VYN201: Demonstrated Anti-Fibrotic Activity
without Delay in Healing Time in Murine Skin Healing Model

Female hairless mice (n=4/group) had two identical 10mm incisions made either side of the flank. Animals were topically dosed 1X daily with 100mg VYN201 vehicle, VYN201 1% or a Hydroalcoholic gel* until each wound had completely healed



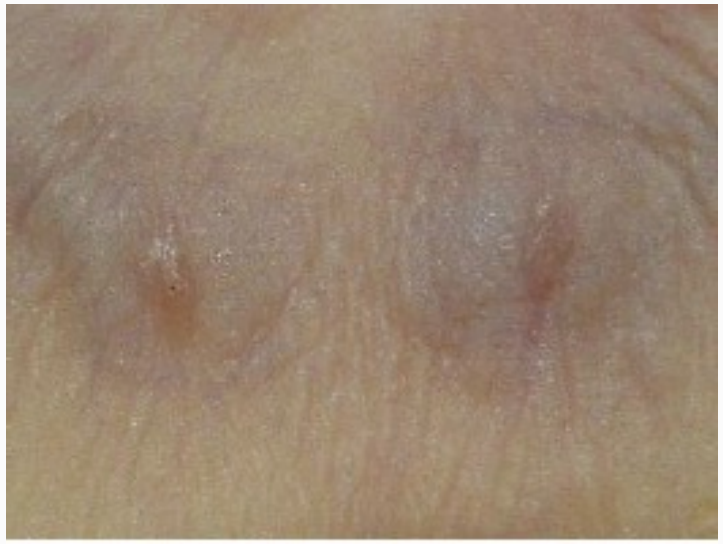
- Statistically significant difference ($p<0.05$) in composite global external healing score for VYN201 1% compared to Hydroalcoholic gel from Day 8
- Complete healing occurred for VYN201 1% and VYN201 vehicle approximately 5 days earlier compared to Hydroalcoholic gel (Mean day to heal:15.5 vs. 21 days)



- Animals treated with VYN201 1% had statistically significant less tissue mass/fibrosis compared to VYN201 vehicle or Hydroalcoholic gel, indicative of the known anti-fibrotic mechanism for BET inhibition ($P<0.05$ for VYN201 1% compared to VYN201 vehicle and Hydroalcoholic gel)

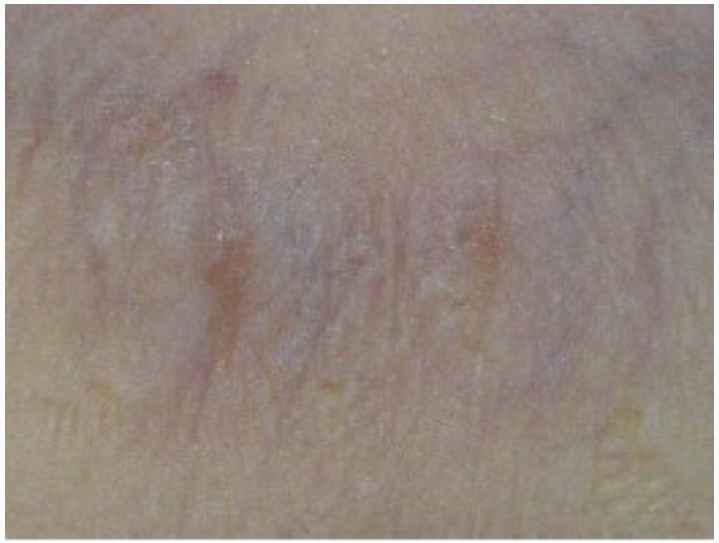
*A negative control known to delay wound healing
Global External Lesion Score is a composite severity score of lesion length, width, swelling and visibility
Fibrotic tissue mass is scored on a 4-point severity scale: 0=No tissue mass; 1=small tissue mass; 2=moderate tissue mass; 3=large tissue mass

VYN201: Little Evidence of Residual Swelling
and Macular Wound Appearance in Murine Skin Healing Model



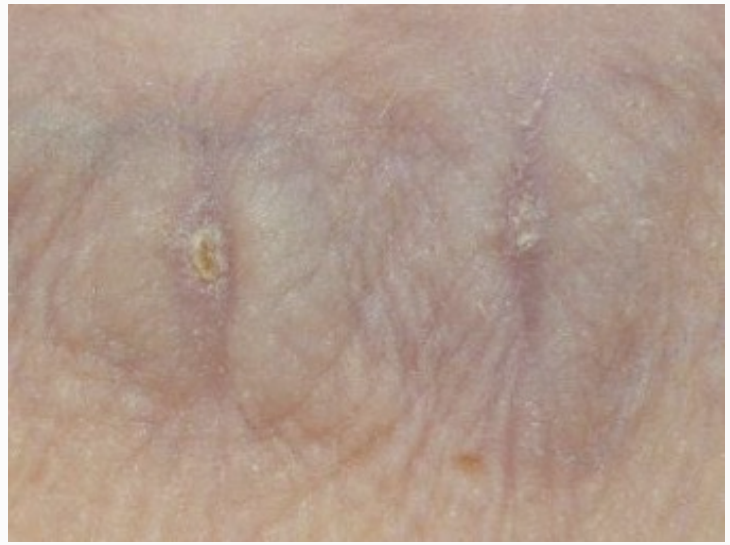
VYN201 Vehicle

- Still evidence of minor swelling around incision sites



VYN201 1%

- Little evidence of residual swelling
- Wound appears more macular in nature compared to VYN201 vehicle or the Hydroalcoholic gel
- Incision sites appear less distinct and leave a more aesthetic outcome compared to other treatments

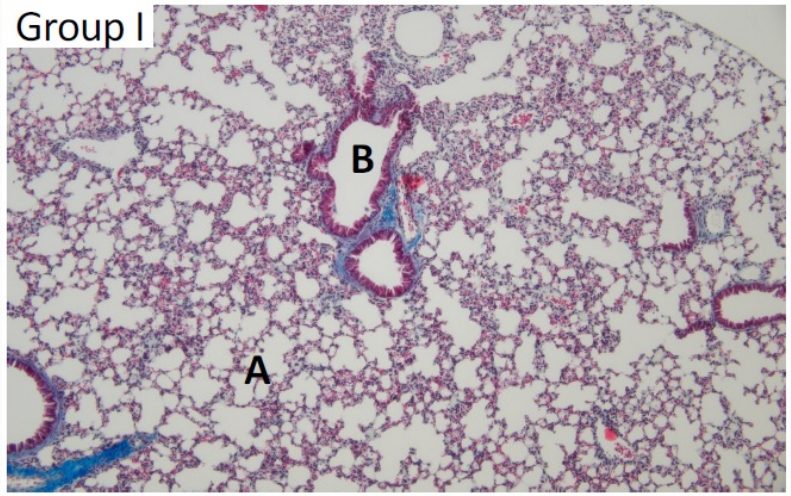


Hydroalcoholic gel

- Moderate swelling clearly evident at end of treatment
- Although healed, residual scabbing still remains
- Incision sites clearly visible

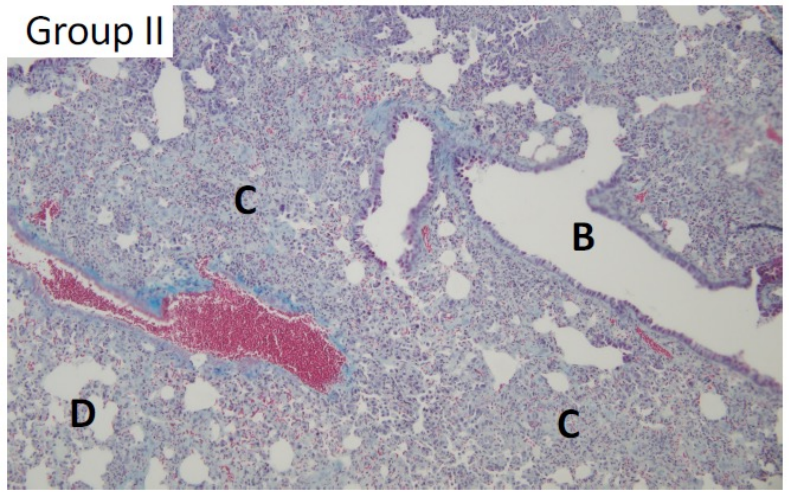
VYN201: Bleomycin-induced mouse model of IPF - Histology

Histology images indicate positive impact of VYN201 0.06mg/ml on fibrosis in lungs. Additional preclinical exploration planned



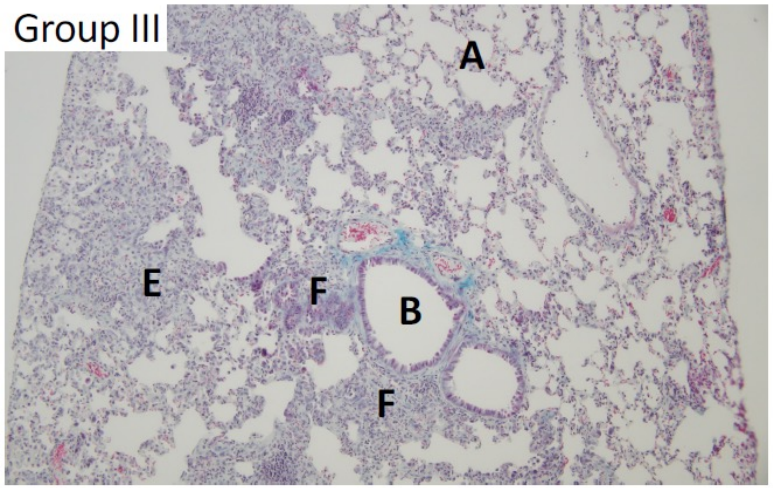
Healthy sham control

A: Normal lung parenchyma with open airways and airspaces.
B: Conducting airway



Bleomycin control

B: Conducting airway
C: Fibrotic lesions with abundant cellularity
D: Sporadic airways



Bleomycin + 0.06mg/ml VYN201

A: Normal lung parenchyma with open airways and airspaces.
B: Conducting airway
E: Less severe localized fibrosis: parenchyma
F: Less severe localized fibrosis: airway

*Lung fibrosis is induced in C57bl/6 mice using bleomycin at a dose of 4U/kg once daily by intranasal administration (N=10/treatment group). VYN201 treatment groups received nebulized, intra-nasal doses at 0, 0.06, 0.6 and 3mg/ml and bleomycin concomitantly for 21 days. A sham group received vehicle only.

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VYN201: Rheumatoid Arthritis

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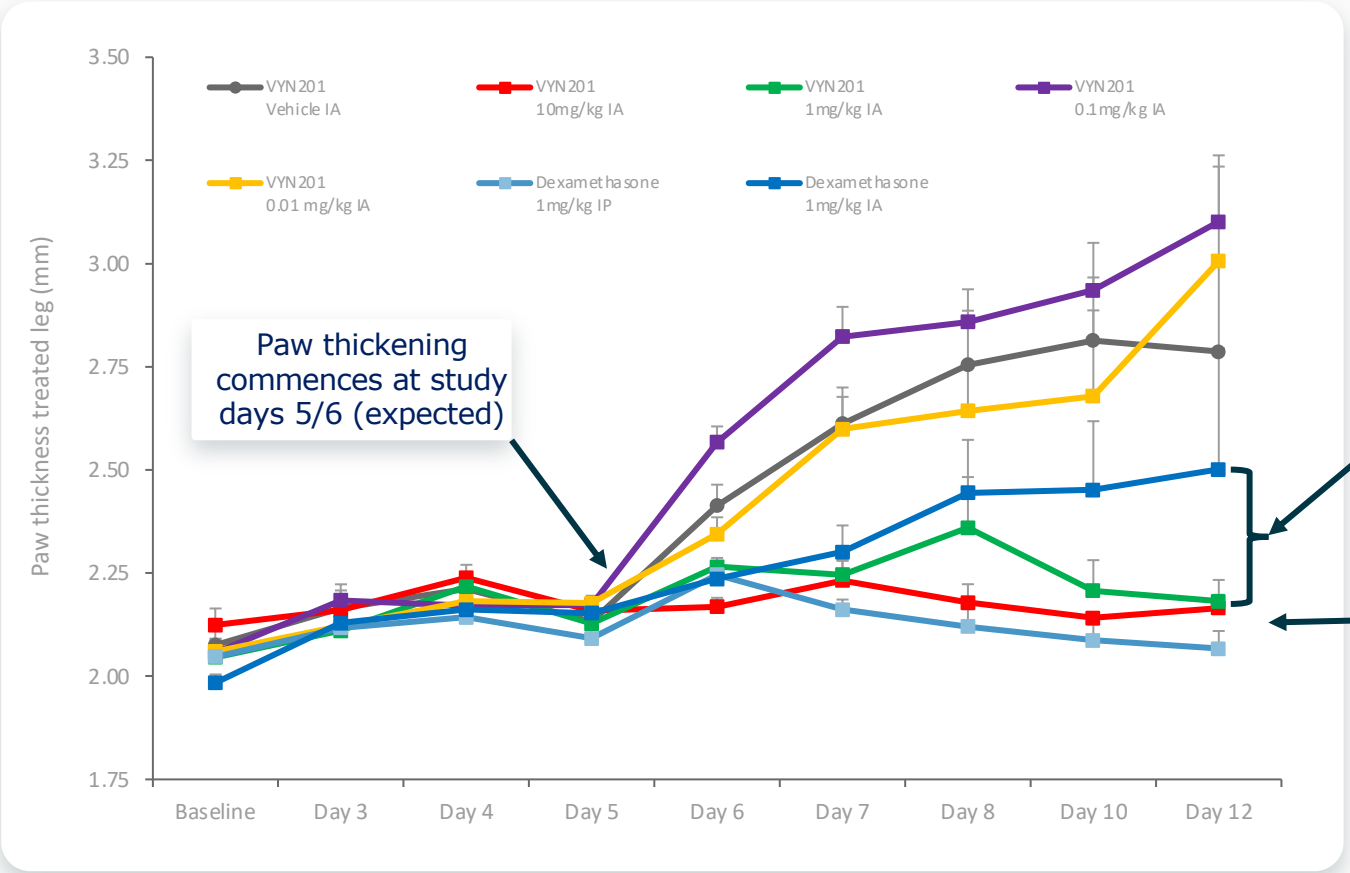
VYN201: CAIA Mouse Model of Arthritis – Paw Thickness

Marked inhibition of paw thickening/swelling

Inflammatory arthritis was induced in BALB/C mice using a mixture of four arthritogenic MAbs by IV injection at Day 0 and was further challenged with an LPS IV injection at Day 4 (N=7/treatment group). VYN201 treatment groups received 50µl intra-articular (IA) doses of VYN201 at 0, 0.01, 0.1, 1 or 10mg/kg on Days 0, 3, 6 and 9. Dexamethasone control animals received 50µl of 10mg/kg IA on Days 0, 3, 6 and 9 or 1mg/kg intraperitoneal (IP) on each treatment day (Day 0-11). Treatment response was evaluated based on an assessment of paw thickening/swelling.



Both VYN201 1 & 10mg/kg superior to dexamethasone IA 10mg/kg

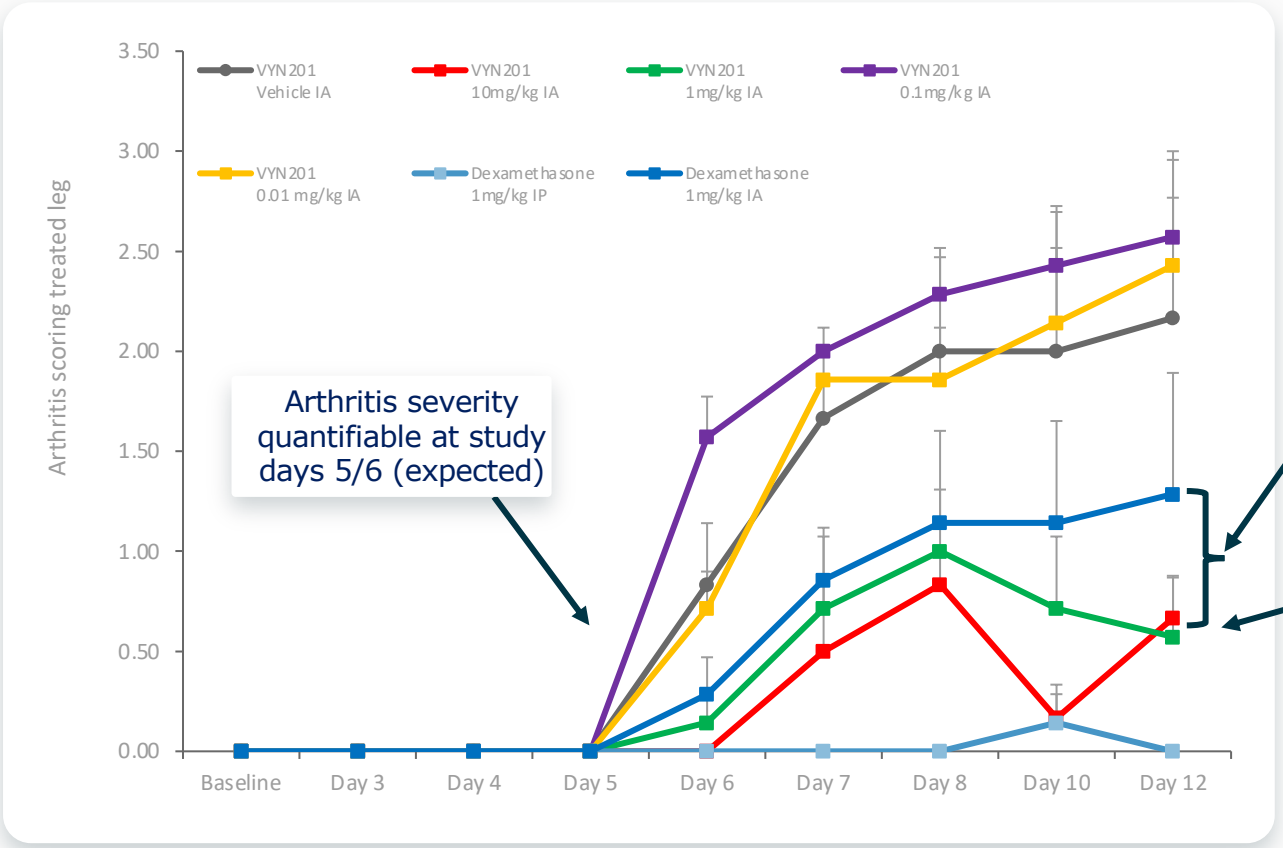
Marked inhibition of paw thickening for the VYN201 1 & 10mg/kg dose levels and in line with 1mg/kg dexamethasone systemic dose

CAIA = Collagen Antibody Induced Arthritis; IA = Intra-articular; IP = Intraperitoneal

VYN201: CAIA Mouse Model of Arthritis – Arthritis Score

Demonstrated dose dependent reduction in disease severity

Inflammatory arthritis was induced in BALB/C mice using a mixture of four arthritogenic MAbs by IV injection at Day 0 and was further challenged with an LPS IV injection at Day 4 (N=7/treatment group). VYN201 treatment groups received 50µl intra-articular (IA) doses of VYN201 at 0, 0.01, 0.1, 1 or 10mg/kg on Days 0, 3, 6 and 9. Dexamethasone control animals received 50µl of 10mg/kg IA on Days 0, 3, 6 and 9 or 1mg/kg intraperitoneal (IP) on each treatment day (Day 0-11). Treatment response was evaluated based on an assessment of arthritis score*



Both VYN201 1 & 10mg/kg superior to dexamethasone IA 10mg/kg

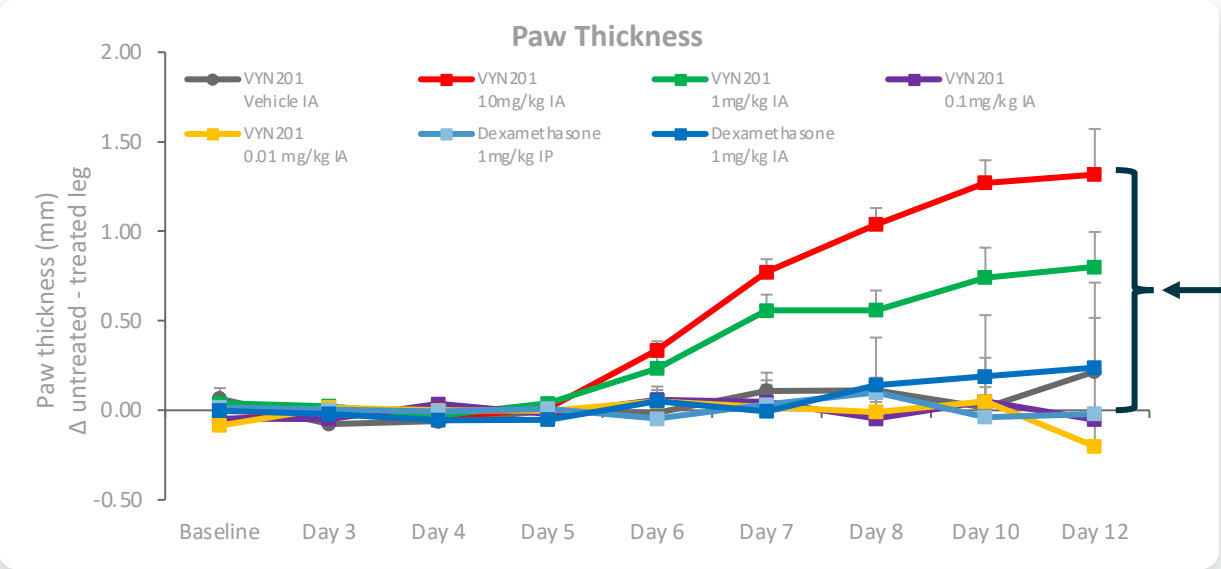
Marked inhibition of arthritis signs and symptoms for VYN201 at 1 & 10mg/kg dose levels with severity scores approaching "normal" (mean severity score <1)

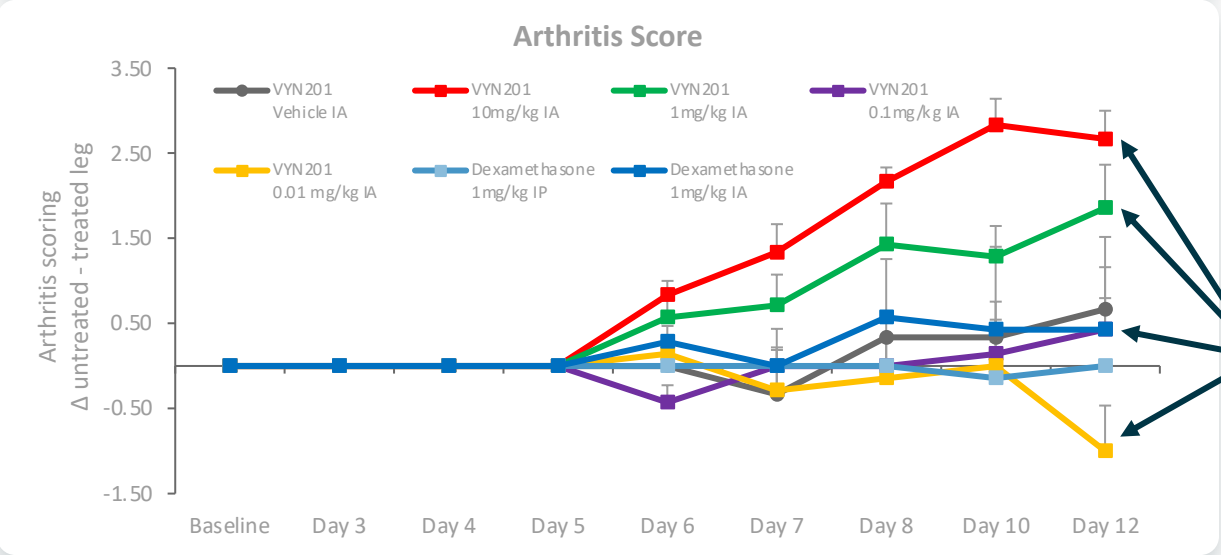
*Scoring based on a five-point composite severity scale of redness, swelling of the ankles and wrists, and paw thickness. Scoring ranges from 0 (normal) to 4 (extensive signs and symptoms of arthritis);
CAIA = Collagen Antibody Induced Arthritis; IA = Intra-articular; IP = Intraperitoneal

VYNE™ THERAPEUTICS

VYN201: CAIA Mouse Model of Arthritis – Systemic Impact

Demonstrated localized dose-dependent effect





Each animal treated with the intra-articular injections received the injection in the ankle of one rear paw. The untreated rear paw was assessed to evaluate any potential anti-inflammatory systemic effect. Anti-inflammatory systemic effect was evaluated based on an assessment vs. untreated paw

VYN201 1 & 10mg/kg results demonstrated the highest localized effect in the treated limb when compared to the untreated limbs (largest delta between treated and untreated limbs)

For the VYN201 10mg/kg dose:

- The average paw thickness at day 12 was 3.48 mm in the untreated paw versus 2.17 mm in the treated paw ($p<0.01$)
- The average arthritis score was 0.67 in the treated paw versus 3.33 in the untreated paw ($p<0.05$)

For the VYN201 1mg/kg dose:

- The average paw thickness at day 12 was 2.98 mm in the untreated paw versus 2.18 mm in the treated paw ($p<0.01$)
- The average arthritis score was 0.57 in the treated paw versus 2.43 in the untreated paw ($p<0.05$)

Treatment effect for VYN201 treated animals was dose-dependent over the dose range 0.01 to 10mg/kg

*Scoring based on a five-point composite severity scale of redness, swelling of the ankles and wrists, and paw thickness. Scoring ranges from 0 (normal) to 4 (extensive signs and symptoms of arthritis); CAIA = Collagen Antibody Induced Arthritis; IA = Intra-articular; IP = Intraperitoneal

VYN201: Vitiligo

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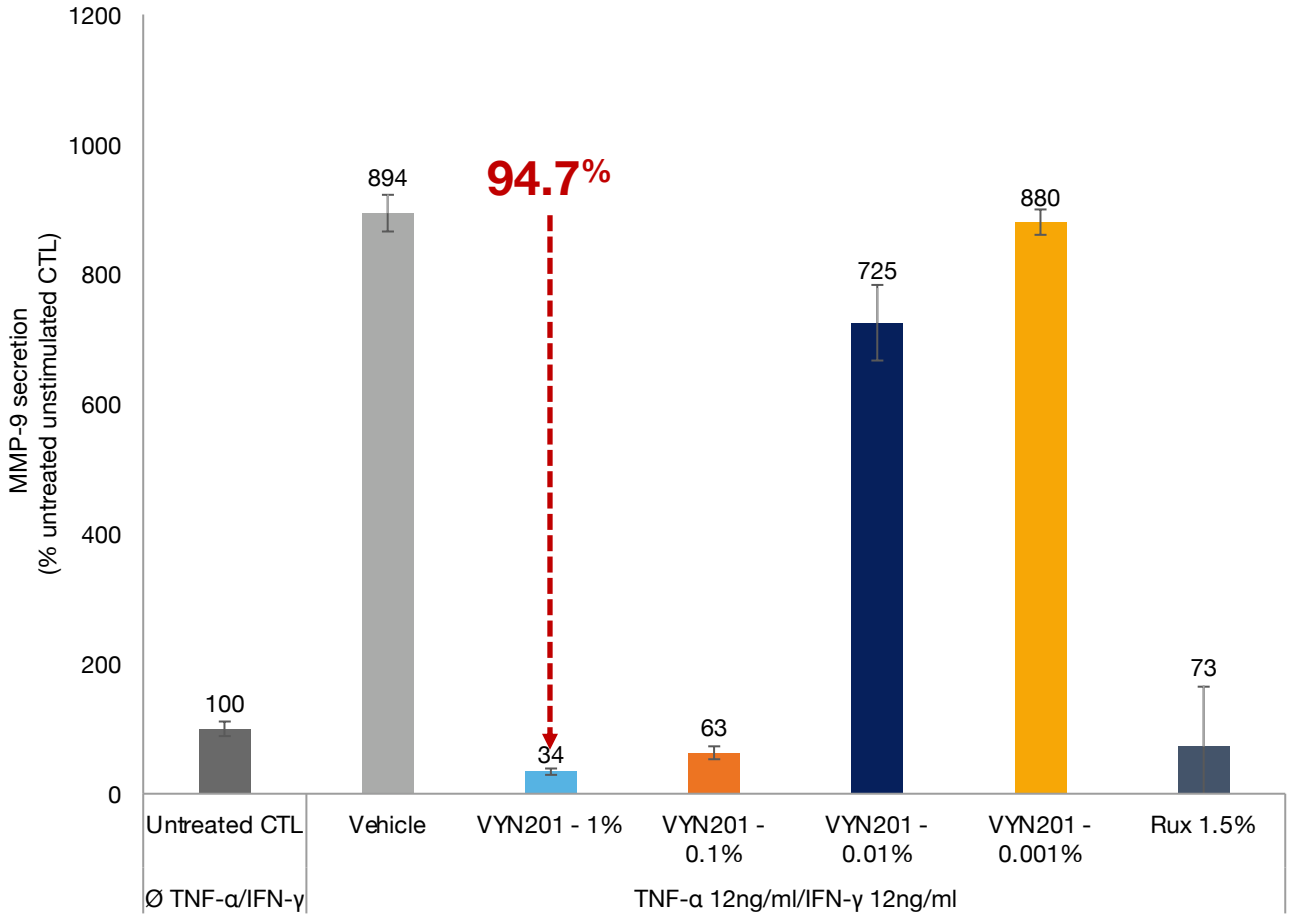
VYN201: Human Tissue Model of Vitiligo – Demonstrated Inhibition of MMP9

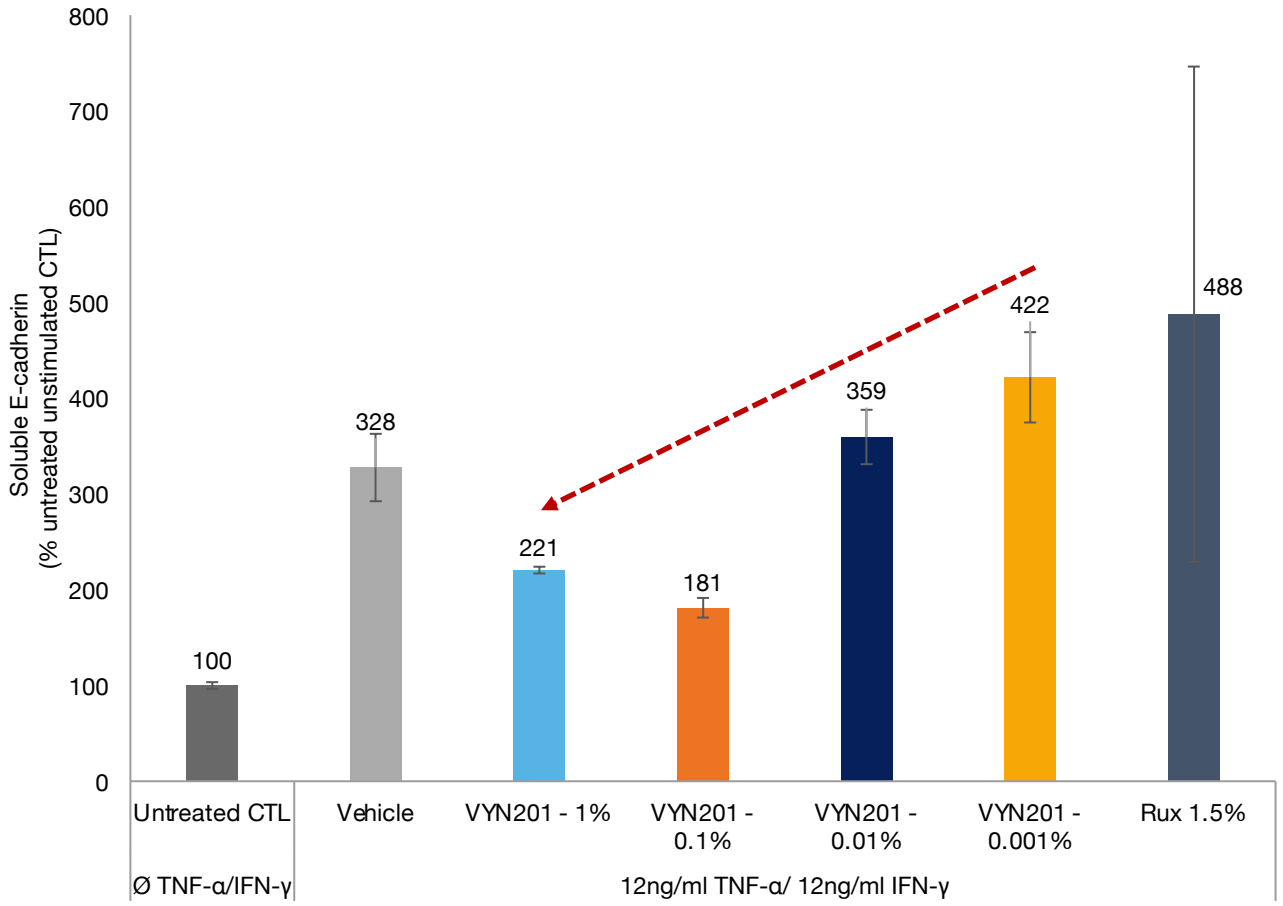
Reconstituted human epithelial (RHE) skin cultures were treated with a TNF-α and IFN-γ cytokine cocktail to induce a vitiligo phenotype (melanocytorrhagy (loss of melanocyte), upregulation of MMP9 and soluble E-cadherin). 24hr prior to stimulation, RHE samples were topically treatment with VYN201 at varying concentrations and topical ruxolitinib 1.5% cream at 3 mg/cm^2



- Stimulated and vehicle treated RHE demonstrated a significant upregulation of MMP9, relative to unstimulated and untreated control
- VYN201 markedly reduced the expression of MMP9 in a dose-dependent manner with a maximal effect at the 1% concentration
- VYN201 1% reduced the secretion of MMP9 by 94.7%, relative to stimulated vehicle, and numerically superior to ruxolitinib 1.5%

VYN201: Human Tissue Model of Vitiligo – Reduction of Soluble E-cadherin

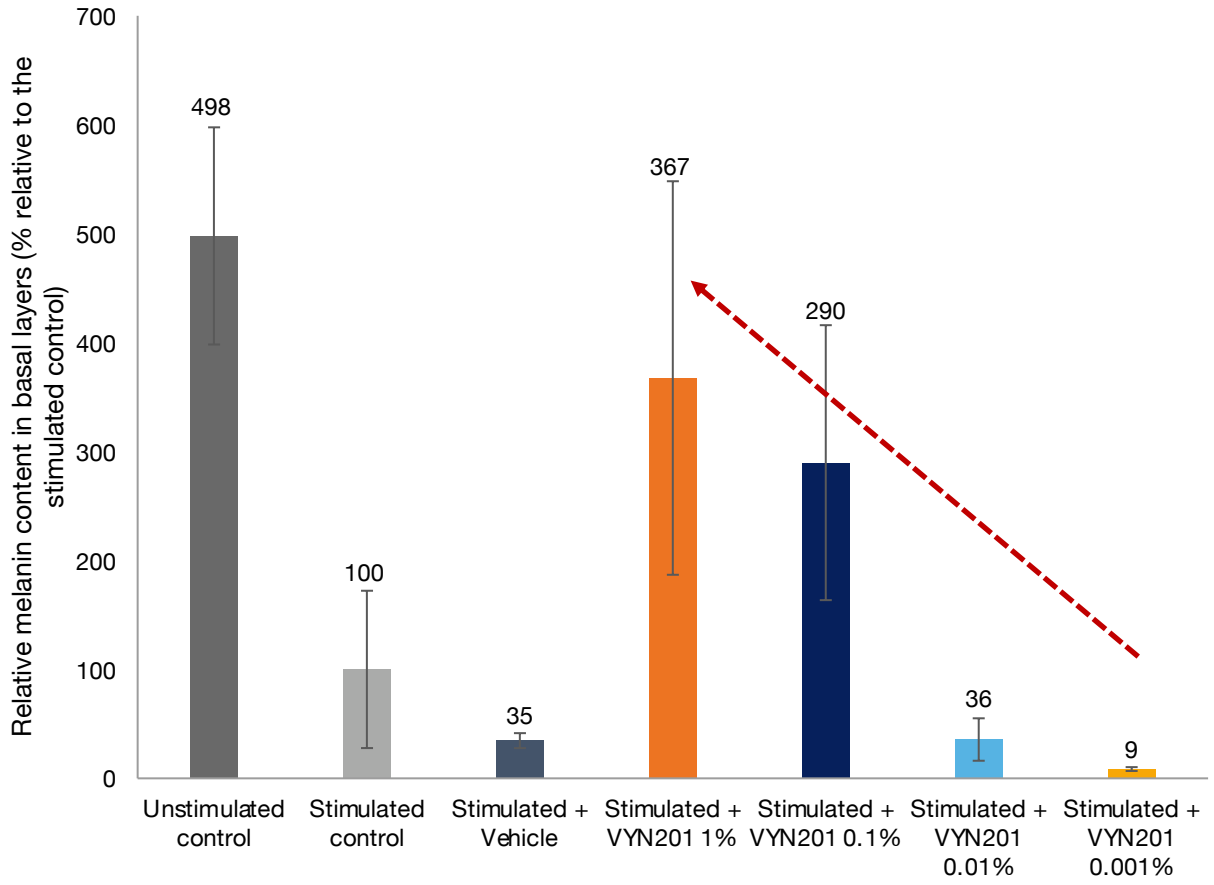
Reconstituted human epithelial (RHE) skin cultures were treated with a TNF-α and IFN-ɣ cytokine cocktail to induce a vitiligo phenotype (melanocytorrhagy (loss of melanocyte), upregulation of MMP9 and soluble E-cadherin). 24hr prior to stimulation, RHE samples were topically treatment with VYN201 at varying concentrations and topical ruxolitinib 1.5% cream at 3 mg/cm^2



- Stimulated and vehicle-treated RHE demonstrated a significant upregulation of soluble E-cadherin, relative to unstimulated control
- **VYN201 affects a dose-dependent reduction in solubilized E-cadherin**
- VYN201 was numerically superior to topical ruxolitinib cream 1.5%

VYN201: Human Tissue Model of Vitiligo – Effect on Melanocyte Retention

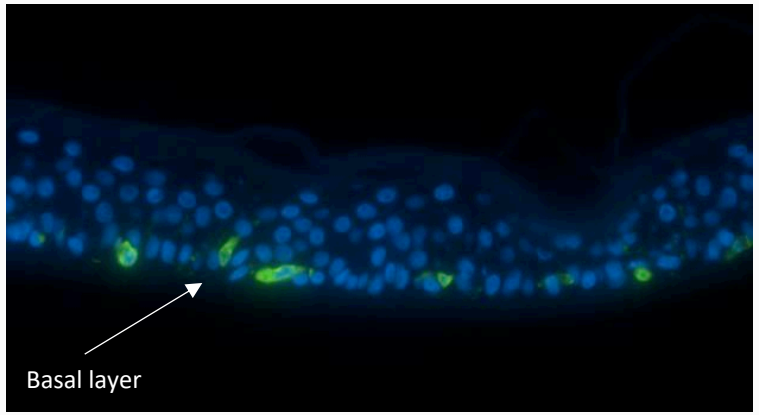
Reconstituted human epithelial (RHE) skin cultures were treated with a TNF-α and IFN-ɣ cytokine cocktail to induce a vitiligo phenotype (melanocytorrhagy (loss of melanocyte), upregulation of MMP9 and soluble E-cadherin). 24hr prior to stimulation, RHE samples were topically treatment with VYN201 at varying concentrations and topical ruxolitinib 1.5% cream at 3 mg/cm^2



- Stimulated and vehicle-treated RHE demonstrated a significant loss in melanin content, relative to unstimulated control
- **VYN201 substantially prevents the loss of melanin pigment in the basal layers of skin in a dose dependent manner**
- Residual melanin levels for VYN201 1% was approximately 10-fold higher than vehicle, retaining approximately 75% of melanin relative to unstimulated control

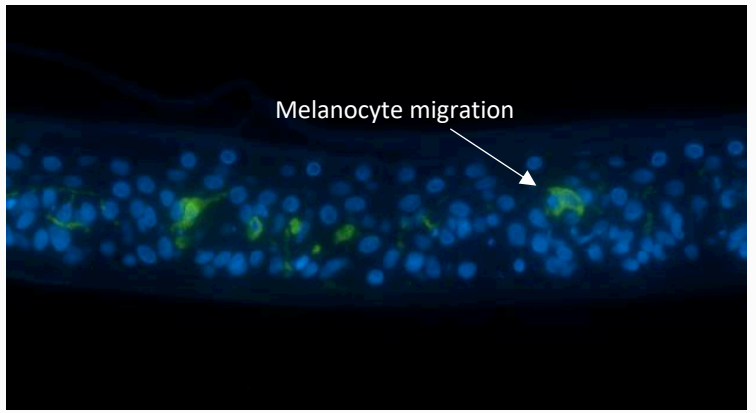
VYN201: Human Tissue Model of Vitiligo - Histology

Micrographic images of TRV immuno-stained induced RHE specimens demonstrating the preservation of melanocytes in the basal layer of samples treated with VYN201 1%



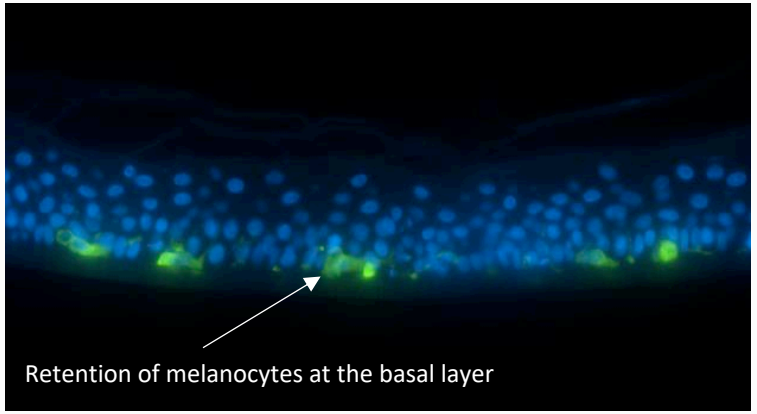
Unstimulated and untreated control

Melanocytes remain at or close to the basal layer implying that E-cadherin adhesion is still functional



Stimulated and Vehicle treated

Clear evidence of melanocyte adhesion disruption, melanocyte detachment and migration through the skin



Stimulated and VYN201 1% treated

VYN201 1% prevents detachment and subsequent loss of melanocytes from the basal layer implying that E-cadherin adhesion is still functional

Keratinocytes (blue), melanocytes (green)

TRV: tyrosinase-related protein 1 (important enabler of melanogenesis)

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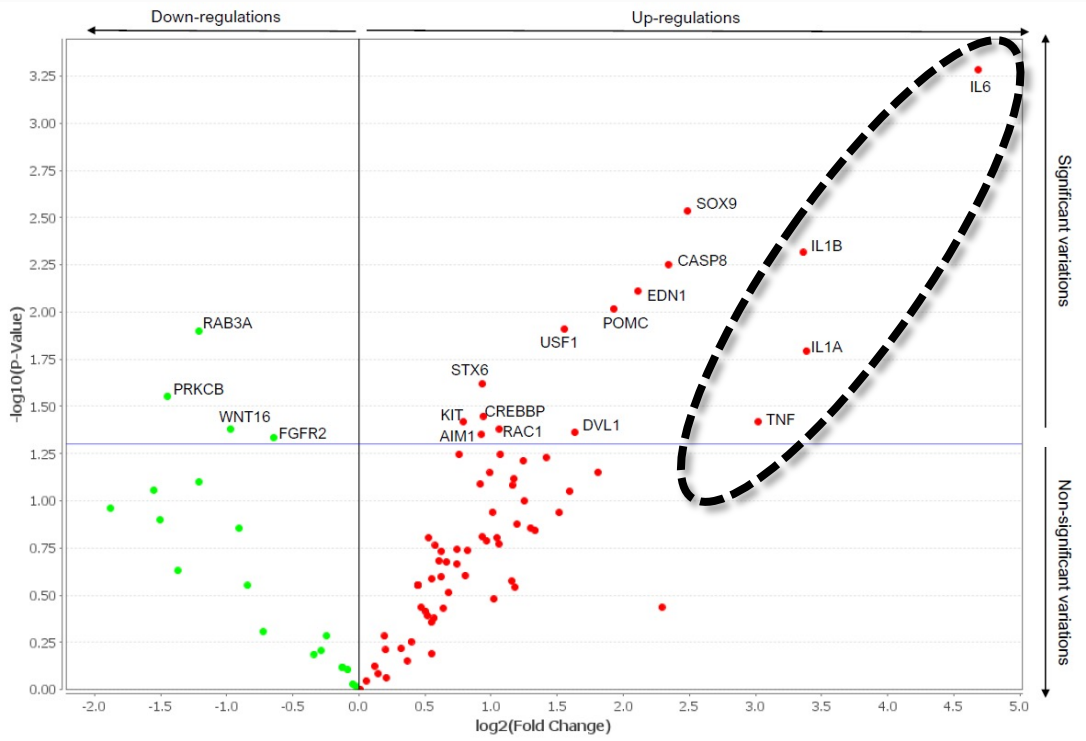
VYN201: Human Tissue Model of Vitiligo – Gene regulation

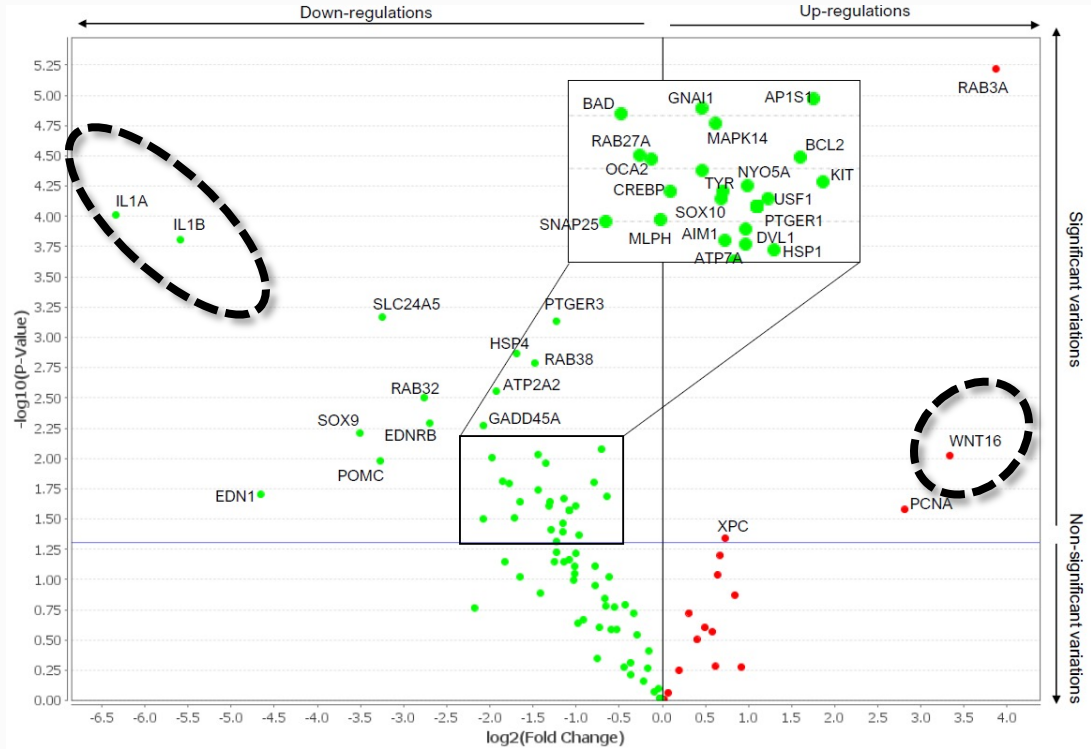
Preliminary data suggest that VYN201 regulates genes relevant to Vitiligo including impacting WNT pathway which is believed to play a key role in melanocyte regeneration

Transcriptome volcano plots of genes relevant to vitiligo (preliminary findings):



Stimulated control

Significant upregulation of cytokines IL6, IL1A and IL1B and TNF



Stimulated and VYN201 1% treated

Significant downregulation of cytokines IL6, IL1A and ILB and TNF and upregulation of the WNT pathway

VYN201: Planned Phase 1 Study Design in Vitiligo

Phase 1a/b initiation planned for 2H 2022

Vitiligo Phase 1a/b design comprising of:

Phase 1a Portion (n=6)

A single ascending / multiple ascending dose cohort in healthy volunteer participants for up to 2 weeks of once-daily treatment.

Primary objective: To identify safe starting doses for vitiligo patients in Phase 1b portion of the study

- Assessments will include TEAEs, pharmacokinetics and local skin tolerance

Phase 1b Portion (n=up to 20)

Treatment on the face and target lesion(s) on trunk of vitiligo patients for 8 weeks of once-daily treatment with planned extension.

Primary objective: Evaluation of the safety and pharmacokinetics of VYN201 in vitiligo patients

- Dose level(s) will be selected based on findings from the Phase 1a portion of the study.
- Assessments will include TEAEs, pharmacokinetics, local skin tolerance, efficacy (F-VASI), biomarkers, photography

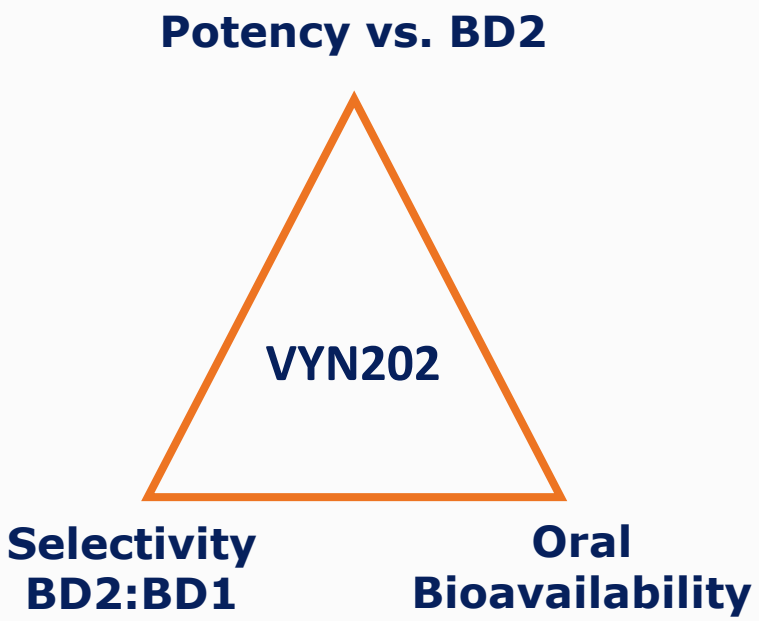
TEAE = Treatment Emergent Adverse Events; F-VASI = Facial Vitiligo Area Scoring Index

VYN202: BD2 selective BET inhibitor

VYNE™ THERAPEUTICS

VYN202 Program Highlights & Molecular Profile

VYN202 is an oral BET inhibitor designed to selectively bind to BD2 and is being developed for major immuno-inflammatory diseases



Potential Target Market[1]:

- Immuno-inflammatory indications such as rheumatoid arthritis, systemic lupus erythematosus, ulcerative colitis/Crohn's and multiple sclerosis; additional potential in myeloproliferative neoplastic disorders[2]

Focused activity:

- Highly selective inhibition of BD2 domain of the BRD4 protein
- Targeting improved safety profile compared to oral pan-BD BET inhibitors

Targeted Near Term Milestones:

- Candidate Selection – 2022

1. Initial indication to be communicated following candidate selection, exercise of option, IND-enabling studies and completion of requisite pre-clinical evaluations
2. List included is not exhaustive of potential indications

How addressing the pathophysiology of vitiligo is providing new therapeutic approaches

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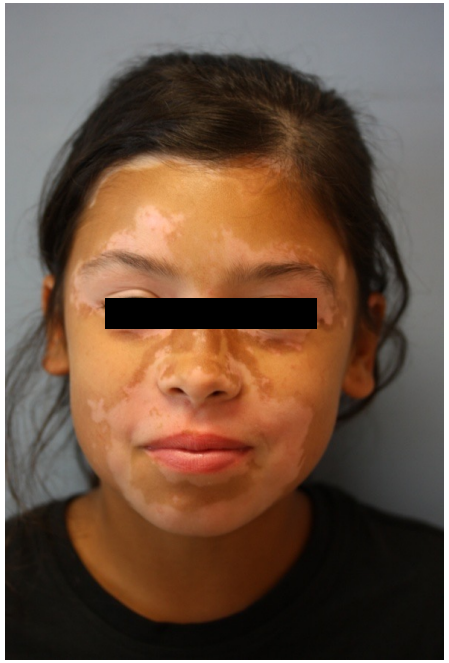
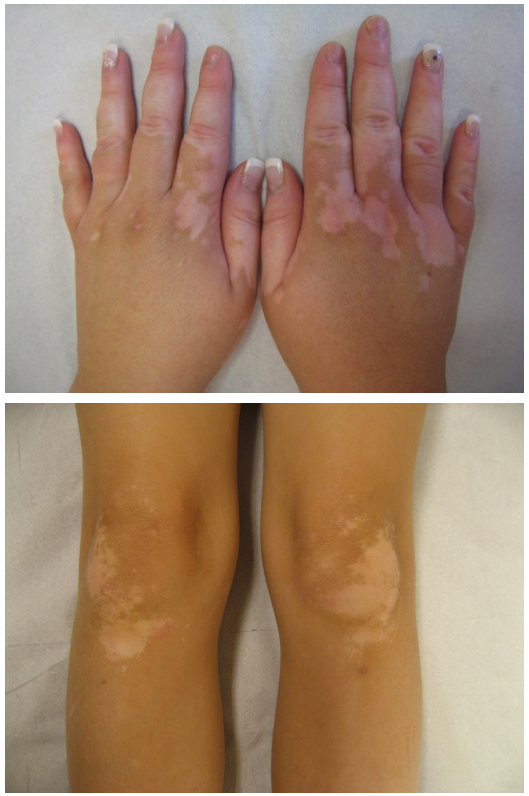
Disclosures

- Almirall
- Abbvie
- Amgen
- Astellas
- BMS
- Celgene
- Galderma
- GSK
- Incyte
- Janssen
- LEO Pharma
- Lilly
- MSD
- Novartis
- Pfizer
- Sanofi-Genzyme
- SUN pharma
- UCB pharma
- Vyne therapeutics

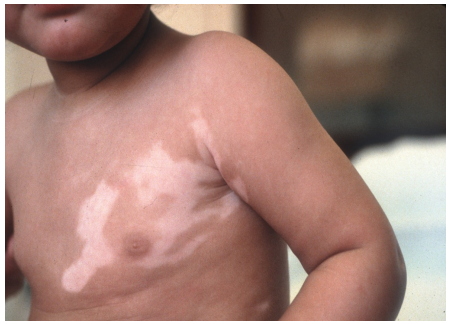
Vitiligo

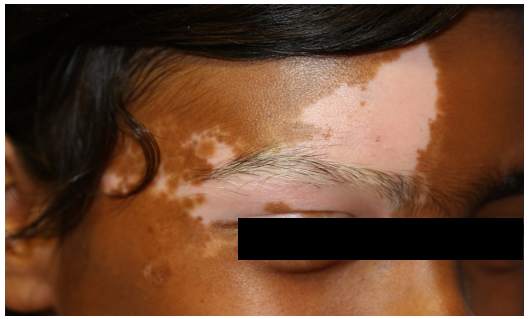
- Acquired depigmentation of the skin and the hair
- Acquired loss of melanocytes
- **0.5 to 2% of worldwide population**
- (Non segmental) vitiligo : 85 to 95% of vitiligo cases



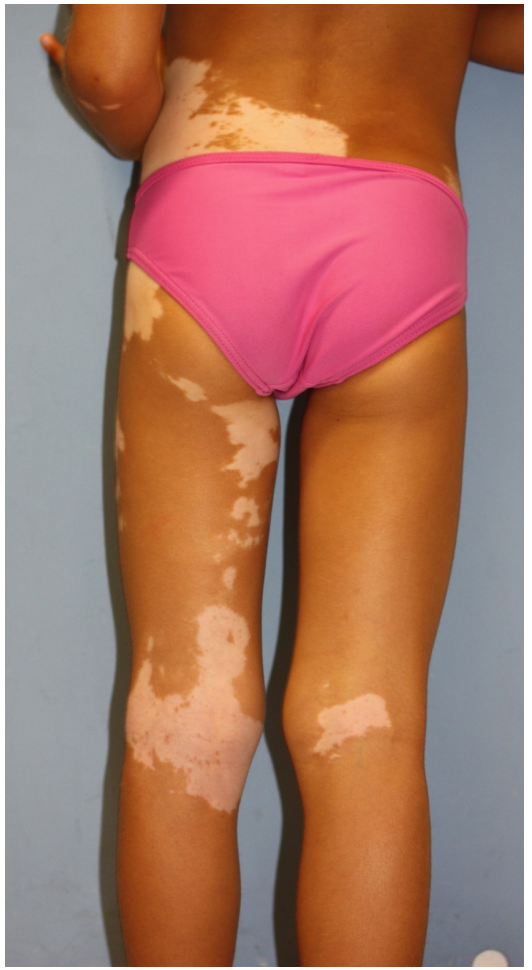


Vitiligo





Segmental vitiligo

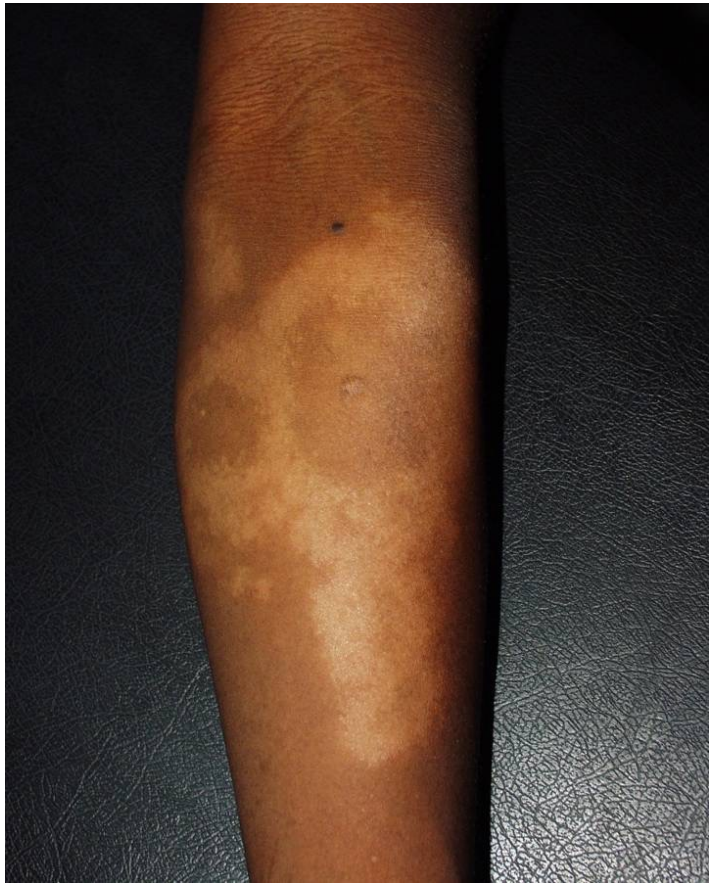


Mixed vitiligo

Image credit T. Passeron.
Bergqvist C, Ezzedine K, 2020;236;571-592.

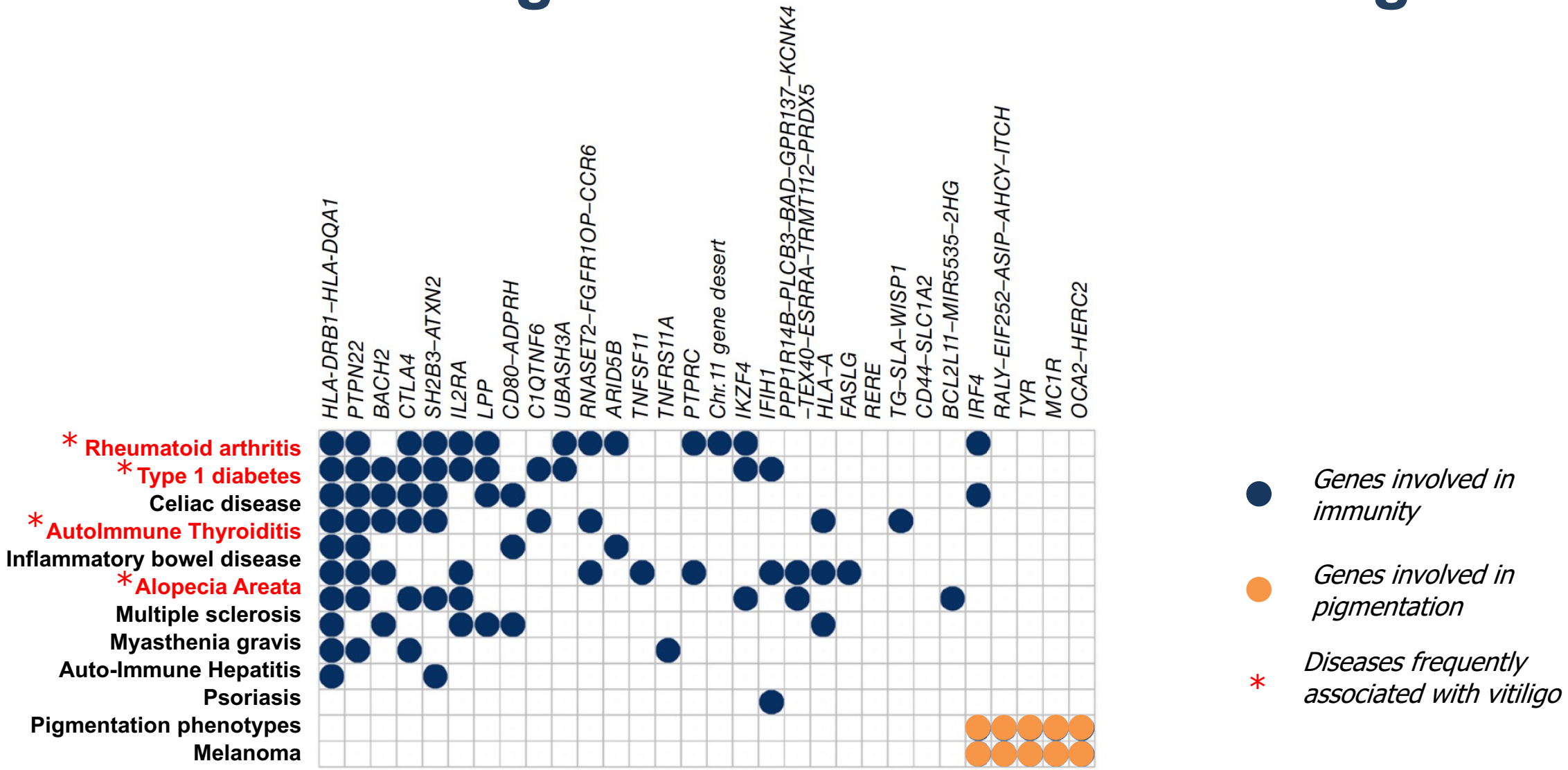
Major impact on affected patients

- Affect social, sexual and professional life (comparable at least to depression or even some cancers)
- Difficulty to find a job
- Major impact in some countries due to resemblance with leprosy
- In Western countries more than half of the affected patients are willing to pay more than 5000 euros to treat their vitiligo



Br J Dermatol. 2009;161:134-9
J Eur Acad Dermatol Venereol. 2022 Apr 2. doi: 10.1111/jdv.18129

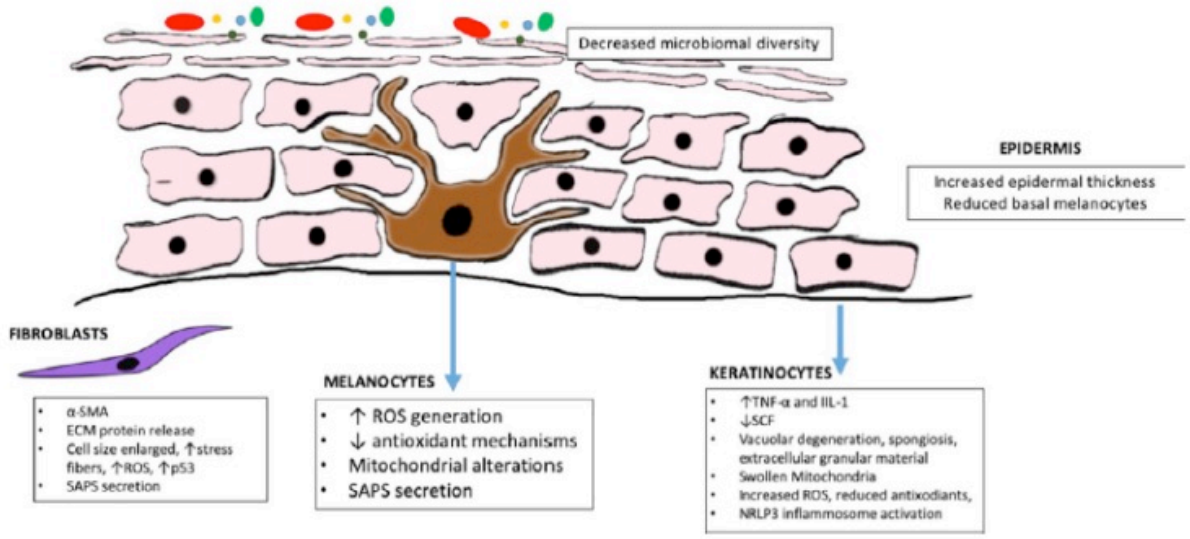
Immune-related genes associated with vitiligo[1–4]



1. Jin Y, al. *Nat Genet*. 2016;48(11):1418-1424; 2. Jin Y, et al. *Genet*. 2012;44(6):676-680; 3. Birlea SA, et al. *J Invest Dermatol*. 2011;131(2):371-381;
4. Jin Y, Birlea SA, et al. *Nat Genet*. 2010;42(7):576-578.

Skin intrinsic abnormalities in vitiligo[1]

- Involvement of melanocytes, keratinocytes and fibroblasts
- Increased susceptibility to oxidative stress
- Increased production of ROS
- SAPS secretion
- Mitochondrial alteration
- Increase ECM protein release

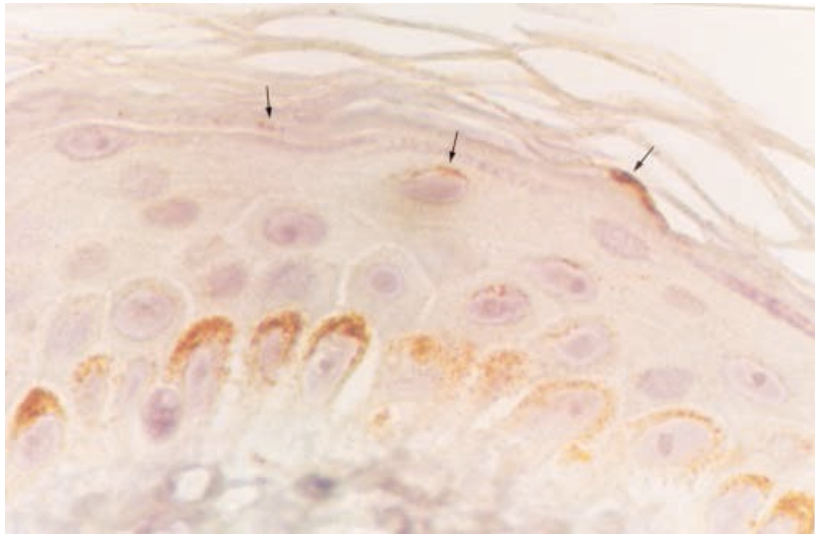


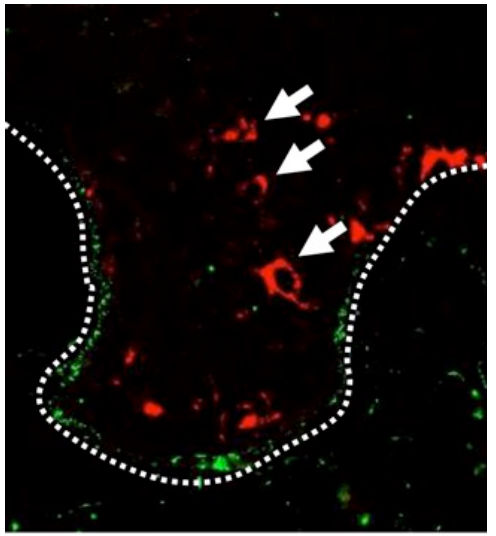
α-SMA, alpha smooth muscle actin; ECM, extracellular matrix; ROS, reactive oxygen species; SAPS, senescence-associated secretory phenotype; SCF, stem cell factor; TNFα, tumour necrosis factor alpha.

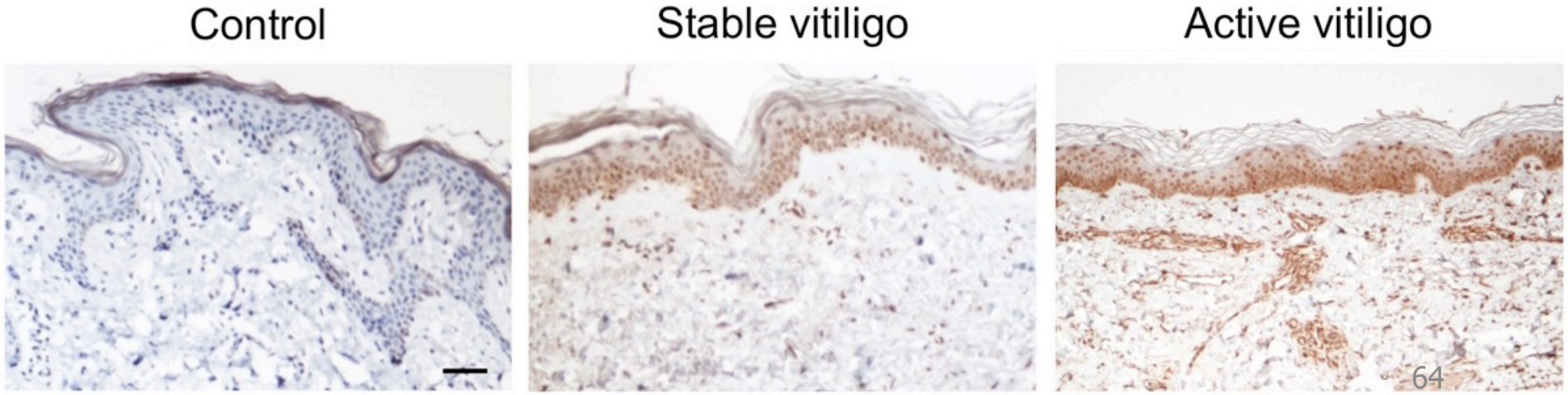
1. Seneschal J, et al. *Pigment Cell Melanoma Res*. 2021;34:236-243.

Melanocytorragy

- Detachment of melanocytes in vitiligo skin[1]
- Altered e-cadherin levels and distribution precede clinical manifestation of vitiligo[2,3]
- IFNγ and TNFα induce melanocyte detachment through E-cadherin disruption by the increase of MMP9[4]







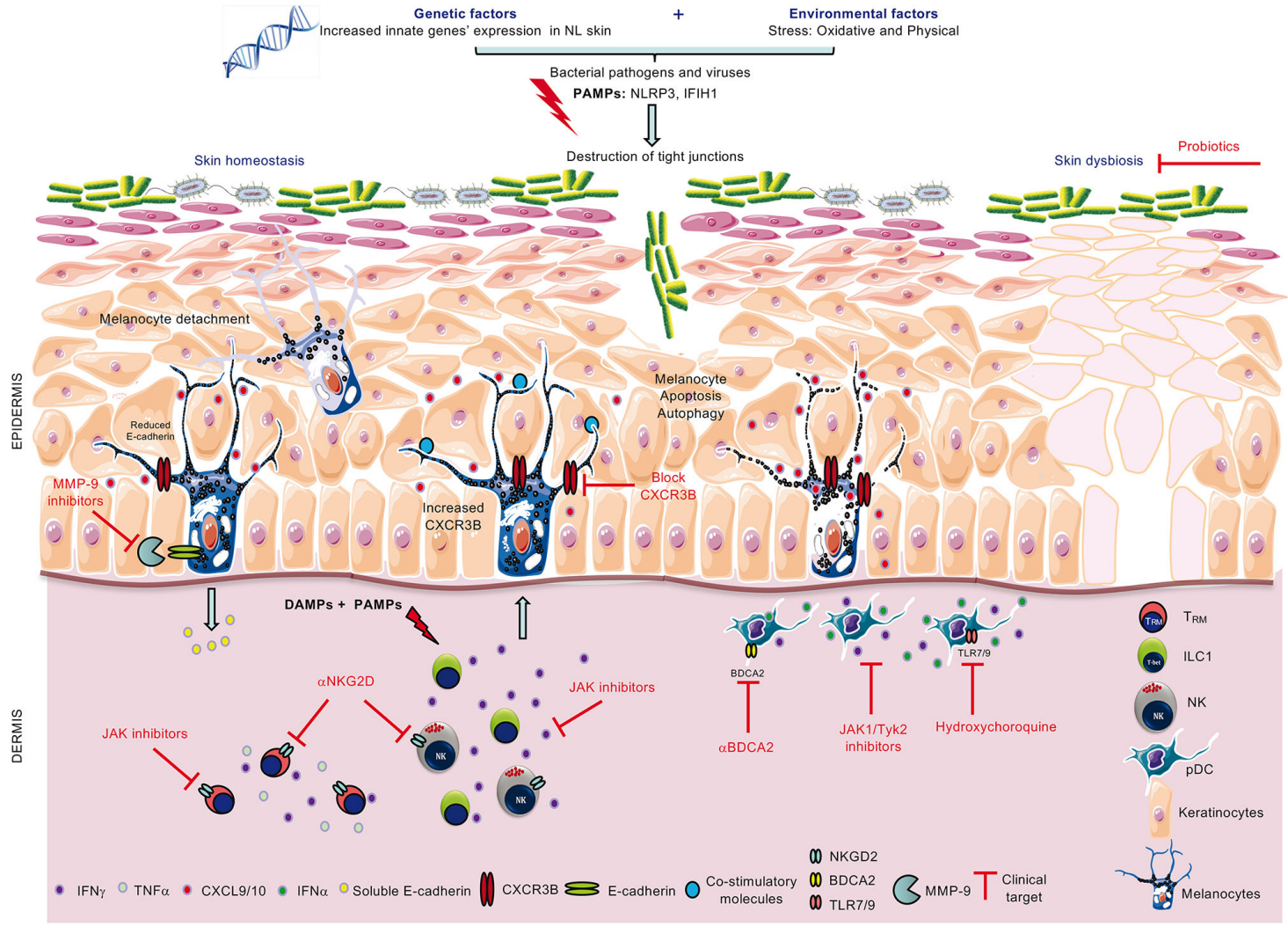
MMP9 immuno-staining

MMP9: metalloproteinase 9

1. Gauthier Y, et al. Pigment Cell Res. 2003;16(4):322-32
2. Wagner RY, et al. J Invest Dermatol. 2015;135(7):1810-1819
3. Grill C, et al. Br J Dermatol. 2018;178(5):1204-1206
4. Boukhedouni N, et al. JCI Insight. 2020;5(11):e133772

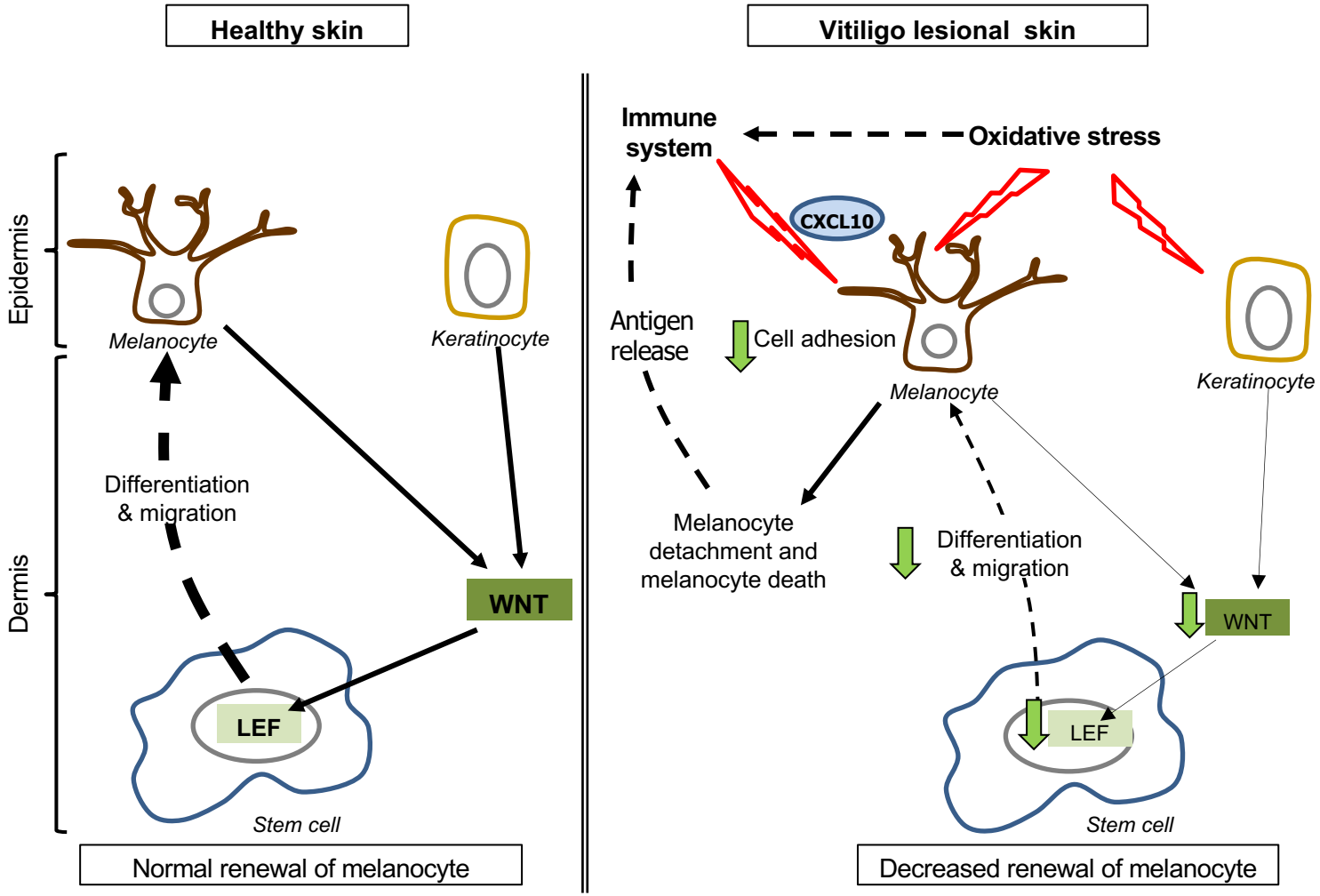
Innate and adaptive immunity

Innate response is the link between stressors and the adaptive anti-melanocytic response



1. Boniface K, et al. Front Immunol. 2021;12:613056.

Melanocyte Regeneration: Key Role of The WNT Pathway



- The WNT pathway has been demonstrated to be important enabler of melanocyte differentiation
- Agonists of the WNT pathway can support melanocyte renewal and melanogenesis

1. Regazzetti C, et al. *J Invest Dermatol.* 2015;135:3105–3114.

Three Objectives in Vitiligo Treatment

To halt the melanocytic loss

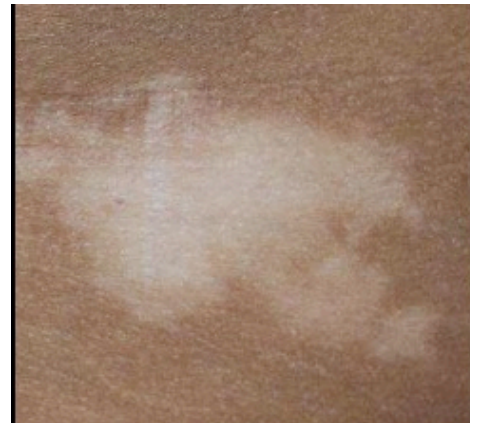
To induce the differentiation and the proliferation of melanocytes
(long process that usually takes 6 to 24 months)

To prevent relapses

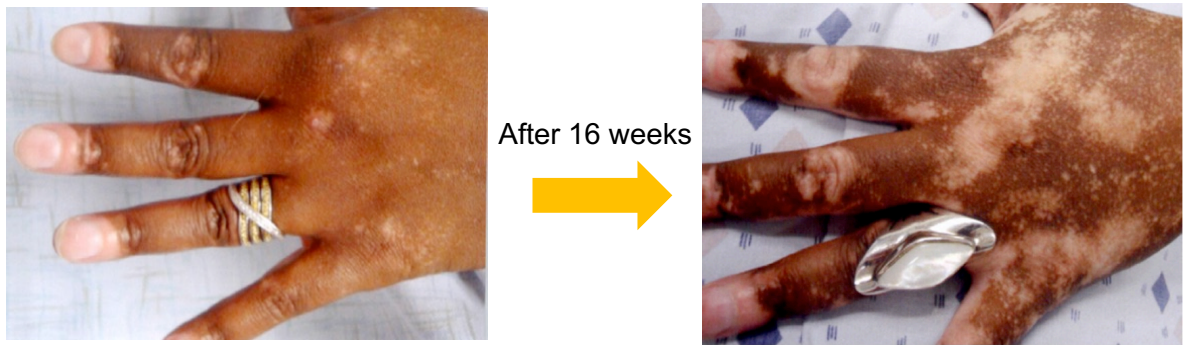
To Halt the Depigmentation

Evolution of Vitiligo

- The course of vitiligo is unpredictable
- Lack of prognosis factors except clinical signs
  - Hypochromic borders under Wood's lamp examination[1,3]
  - Confetti-like depigmentation[2]
  - Development of Vitiligo Signs of Activity Score (VSAS)[3]



When vitiligo is active, it must be treated as a matter of urgency



Top image adapted from van Geel, N et al.;[3] bottom images adapted from Sosa JJ, et al 2015.[2]
VSAS=Vitiligo Signs of Activity Score.

1. Benzekri L, et al. *Brit J Dermatol* 2013; 168:265-71; 2. Sosa JJ, et al. *J Am Acad Dermatol*. 2015;73(2):272-275; 3. Van Geel N, et al. *Br J Dermatol.* 2020;183:801-802.

How To Treat an Active Form of Vitiligo

- Data strongly suggest the usefulness of Oral Mini-Pulse therapy (OMP) for halting vitiligo progression
- MTX, cyclosporine and minocycline also seem to be effective (not indicated for treatment)
- But Nb-UVB appears more important for halting disease progression and has the main advantage of also promoting more efficient repigmentation of vitiligo lesions
- Interest of combining Nb-UVB and OMP in very active forms

MTX=methotrexate; Nb=narrow band; OMP=oral mini-pulse therapy.

1. Kubelis-Lopez DE, et al. *Br J Dermatol. 2019;180:193-194*

To Induce Repigmentation

Combination of Phototherapy and Topical Treatments

- Interest of combining topical calcineurin inhibitors (off-label use) or potent topical steroids with sun exposure or Nb-UVB[1,2]

- Confirmed by meta-analyses

- **Combination approaches are today the gold standard treatment for vitiligo**
- **Better results on the face[3]**
- **Optimal repigmentation requires 6 to 24 months[4]**
- **No FDA or EMA approved treatment for repigmenting vitiligo[5]**
- **High unmet need**

Nb-UVB=narrow band ultraviolet B

1. Dang YP, et al. *Dermatol Ther*. 2016;29(2):126-133; 2. Li R, et al. *Photodermatol Photoimmunol Photomed*. 2017;33(1):22-31; 3. Passeron T, et al. *Lancet*. 2020;396:74-75; 4 Taieb A, al. *BJD*. 2013;168(1):5-19; 5. Rodrigues M, et al. *J Am Acad Dermatol*. 2017;77(1):17-29.

To Prevent The Relapses

Preventing Vitiligo Relapses

- >40% of lesions have new depigmentation in the year following the treatments

- For localized vitiligo:
  - Tacrolimus 0.1% 2/wk
  - Decreases the risk of relapse from 40% to 9.7% [1]
  - Potent topical steroids appears as effective but no demonstration in prospective randomized trials

- For widespread vitiligo:
  - UVB 2 to 4 times / month
  - Expert opinion (no study available)

1 Cavalié, M, *et al. J Invest Dermatol* 2015 ; 135(4):970-4.

Perspectives

	Targets	Compounds	Clinical indications
1st generation	CD4+ & CD8+ T cells	Topical JAK inhibitors (JAK1/2)	Repigmenting localized forms
	CD4+ & CD8+ T cells and NK	Oral JAK inhibitors (JAK1/2; JAK3/TEC)	Repigmenting widespread and/or active forms
	Dendritic cells	Oral JAK inhibitors (JAK1/TYK2)	Early stages / preventing extension
2nd generation	Dendritic cells	Anti-aBCDA2 antibodies	Early stages / preventing extension
	DAMPs	Topical mutant HSP70 gene-gun delivery	Early stages / preventing extension
	DAMPs	New generation of oral or topical antioxidants	Promoting repigmentation / early stages / preventing extension
	PAMPs / Microbiome	Oral or topical probiotics or postbiotics	Early stages / preventing extension
	CD8+ T cells and NK	Anti-NKG2D antibodies	Repigmenting widespread and/or active forms
	TREGS	Low dose of new generation of IL-2	Repigmenting widespread and/or active forms
	TREGS	Anti-CD86-IL-10 antibodies	Repigmenting widespread and/or active forms
	TREGS	Topical CCL22 gene-gun delivery	Repigmenting localized forms
	CD8+ T cells and T resident memory cells	Anti-IL-15 antibodies	Promoting repigmentation / preventing relapses
	Melanocyte detachment	MMP-9 inhibitors	Promoting repigmentation / early stages / preventing extension
	Melanocyte apoptosis	Anti-CXCR3B blocking antibodies	Promoting repigmentation / early stages / preventing extension
	Melanocyte stem cells	WNT agonists / GSK3b inhibitors	Repigmenting resistant areas

NK, Natural Killer; HSP70, Heat shock protein 70; DAMPs, Damage-associated molecular patterns; PAMPs, Pathogen-associated molecular patterns; TREGS, T regulatory cells; MMP9, Matrix metalloproteinase 9.

Adapted from Passeron T. *Lancet* 2020 ; 396(10244):74-5 and *JEADV* 2021, 35, 2305–2307.

What the market needs from new Vitiligo therapies

Treatments today:

- Cumbersome, poly-pharmacy regimen involving both Rx and Dx
- Onset of efficacy can take quite some time to meaningfully develop
- Some new treatments in development e.g. JAK inhibitors, anti-IL15 and WNT agonists (preclinical stage) but many more needed to provide treatment options

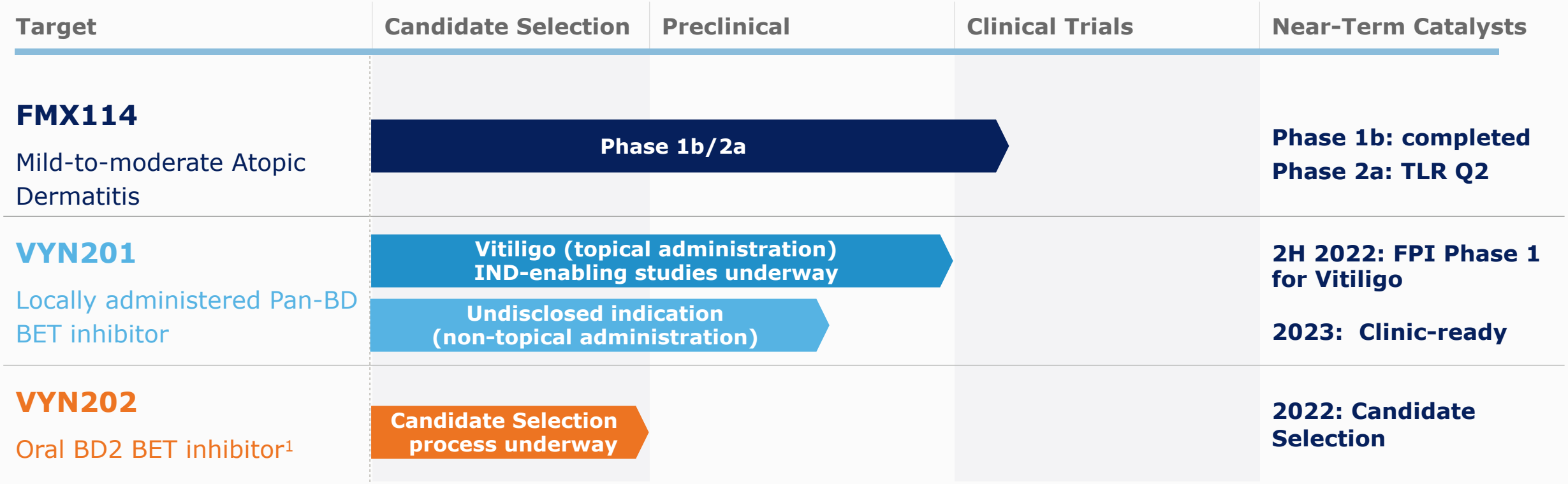
Attributes of a drug to meet the vitiligo market need:

- Works quickly with an enduring effect - greater time to relapse
- No challenging safety signals (“without baggage”)
- Promote melanocyte differentiation/proliferation

Thank you for your attention!

Targeted Clinical Milestones through 2023

Driving Pipeline to Proof-of-Concept



Exclusive Access to Library of NCE BET Inhibitors for Any Indication Worldwide

1. Initial indications for VYN202 to be communicated following completion of requisite pre-clinical evaluations

TLR = Top Line Results; FPI = First Patient In/Enrolled