Dermatology Innovation Forum
an Advancing Innovation in Dermatology conference

Topical TLR8 Ligands for CTCL

06 March 2025

John P. Vasilakos, PhD

TLR BIOSCIENCES
SMALL MOLECULE INNOVATION

Developing TLR ligand therapeutics to safely and effectively treat cancer

TLR Biosciences

Focus on advancing topical immunotherapy products for the treatment of various cutaneous lesions

Initially, we will develop a topical TLR8 ligand for the treatment of early-stage cutaneous T-cell lymphoma (CTCL)

Team

John Vasilakos, PhD – CEO, 25+ years industry experience developing immunotherapies, including TLR7, 8, 7/8 ligands, for cancer, chronic viral diseases, and vaccine adjuvants. www.linkedin.com/in/jpvasilakos

Alain Rook, MD, Senior Scientific Consultant, Leading expert in CTCL therapy, Directed largest U.S. cutaneous lymphoma referral program for over 34 years, and PI for >20 clinical trials and clinical research & development experience at University of Pennsylvania. www.linkedin.com/in/alain-rook-05a18813

Tillman Pearce, MD, CMO, Key expertise in cancer immunotherapy and drug development of cancer immunotherapeutics, Consulting with immuno-oncology companies with agents such as cancer vaccines, oncolytic viruses, checkpoint inhibitors, bispecific T-cell engagers, cell-derived vesicles, and TLR ligands. Previous roles include CMO at OBI Pharma and Threshold Pharmaceuticals, as well as Biotechnology Strategy Advisor for multiple companies. www.linkedin.com/in/tillman-pearce-2407855

Ted Ringsred, JD, Legal / Business development, 25+ years experience handling pharmaceutical and drug delivery IP strategy at 3M, with particular focus on TLR 7 and 8 agonist technology as well as extensive pharmaceutical and drug delivery business development and transactions experience. www.linkedin.com/in/ted-ringsred-33902349

Louis Schure, TLR Biosciences Founder, Extensive BD experience. He is also the Co-Founder & Chief Executive Officer of Curebiotech, Inc. www.linkedin.com/in/louis-schure-a393

Ian Tong Pan, Business Development Specialist, Independent Contractor. Recent graduate from Vagelos Program in Life Sciences & Management, Wharton, University of Pennsylvania. www.linkedin.com/in/tom-pan

Christopher Powala, Senior Advisor. President & CEO of ARespo BioPharma, Inc. and previously President and CEO of Nflection Therapeutics, Inc. www.linkedin.com/in/christopher-powala-06739215

TLR Biology & Cancer

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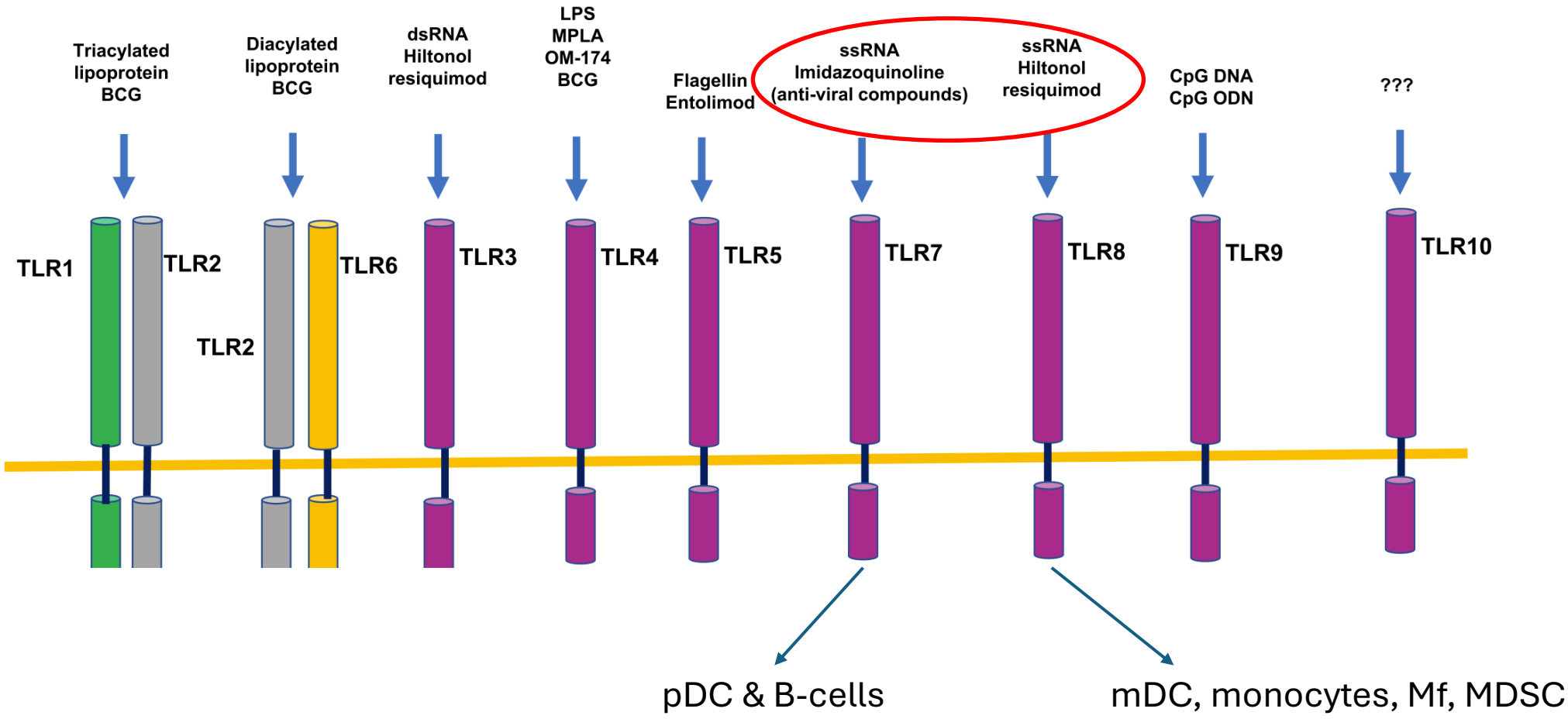
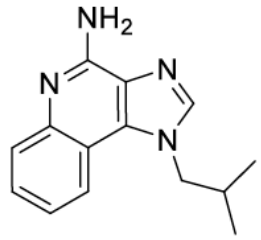
TLRs and TLR Ligands

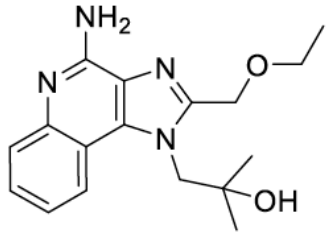


Sun et al,,. 2022. Biomarker Research

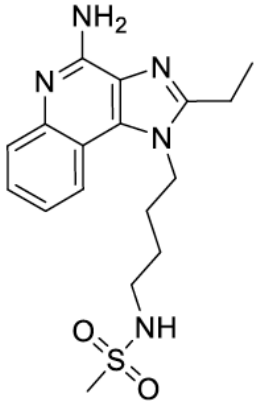
TLRs and TLR Ligands



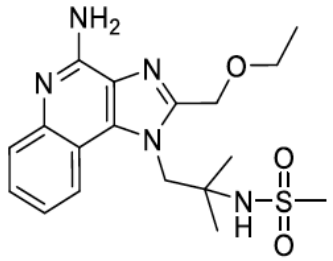
Imiquimod
(TLR 7)



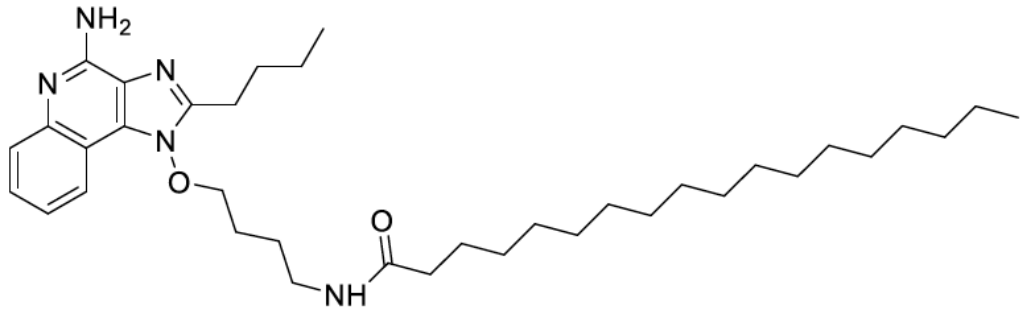
Resiquimod
(TLR 7/8)



3M-001
(852)



3M-011
(854)



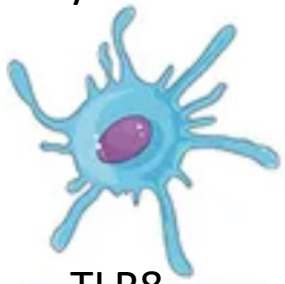
3M-052

Examples of legacy small molecule TLR ligands (3M)

TLR Biology:

TLR7 and TLR8 ligands (agonists) activate innate immunity in a manner that potentiates anti-cancer and anti-viral responses

Myeloid DC



TLR8

↓

+++ Cellular Immunity

Plasmacytoid DC

TLR7

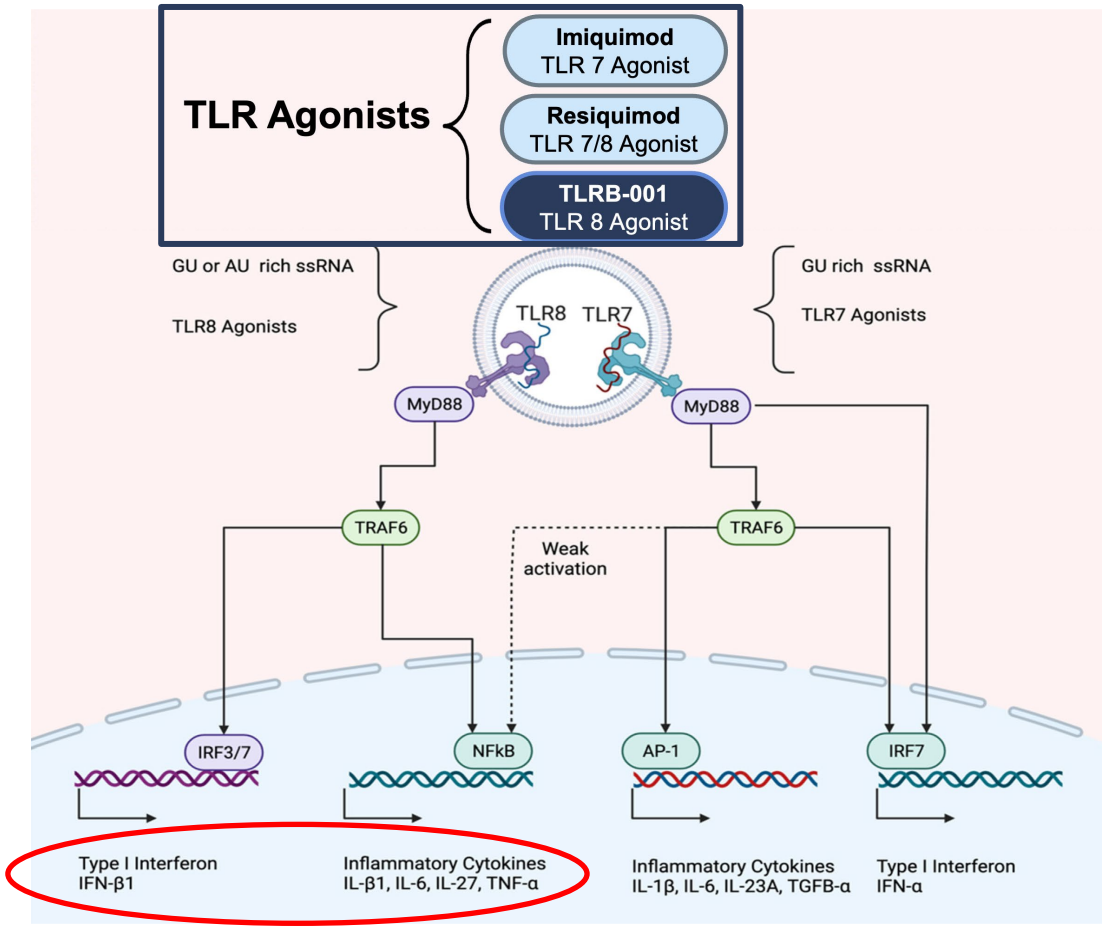
↓

+++ Humoral Immunity

TLR8

↔

Mϕ MDSC



Huen & Rook, 2014

Binding to TLR7/8

↓

Activation of MyD88

↓

Upregulation of NF-κB

↓

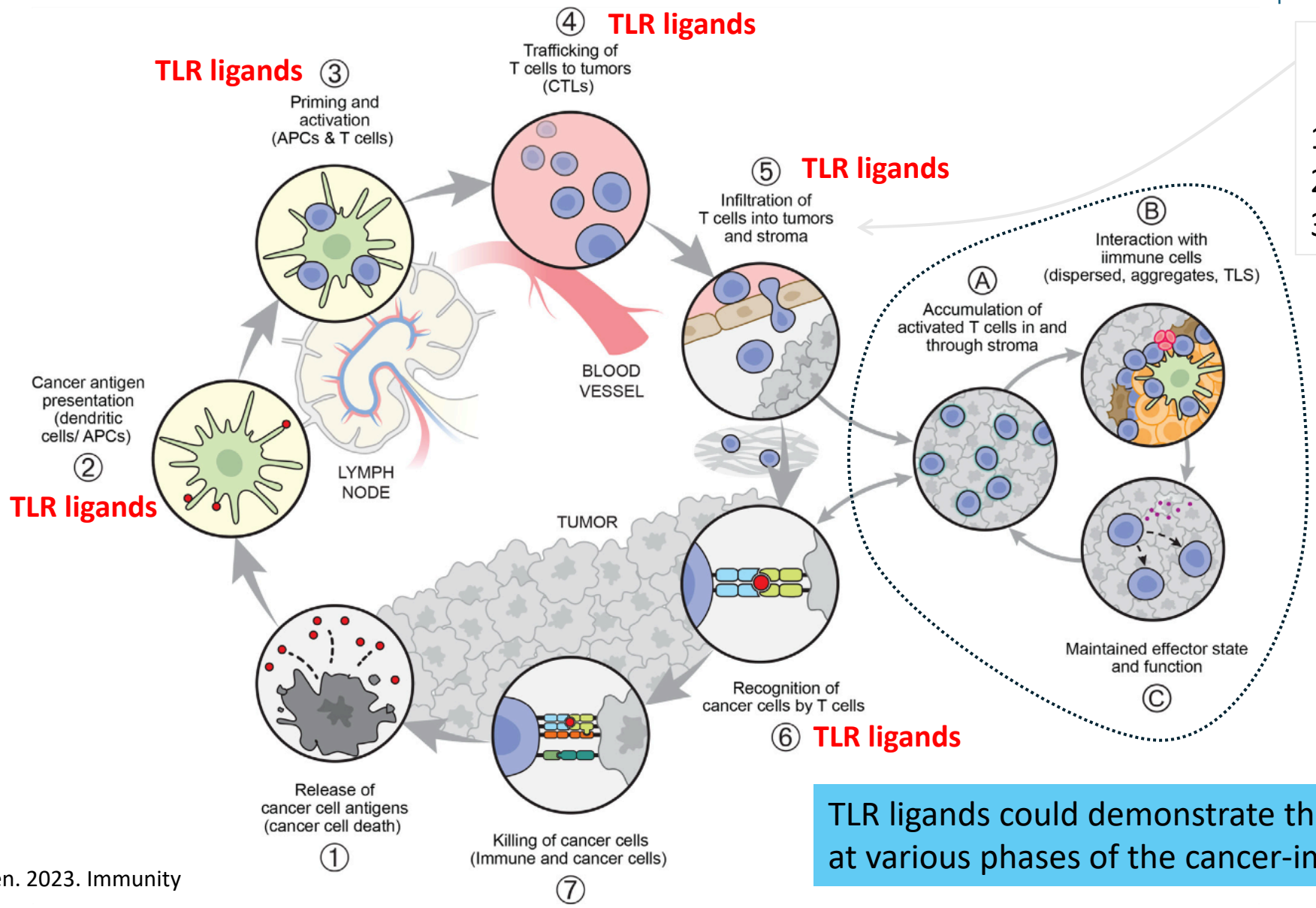
Production of cytokines

↓

Activation of Th1-type CD4 cells, CD8 T- cells, and NK cells

Rationale of TLR7 and TLR8 ligands for the treatment of cancer

Cancer-Immunity Cycle



Primary immune phenotypes

1. Inflamed
2. Immune excluded
3. Immune desert

TLR ligands could demonstrate therapeutic advantages at various phases of the cancer-immunity cycle

Mellman, Chen. 2023. Immunity

Topical TLR ligands for cancer: Clinical Proof-of Concept

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Clinical Evidence of Topical TLR7/8 Ligands Efficacy

Lessons learned from deep experience with imiquimod and resiquimod inform technical and business plan for TLRB-001

Imiquimod (Aldara™) - weak TLR7 agonist approved for the topical treatment of external genital warts, actinic keratosis (AK), and basal cell carcinoma (BCC)

- Although effective for its approved indications and showing promise in certain off-label cancer and pre-cancer treatments, <u>Aldara requires prolonged treatment periods and lacks durable response</u>

Topical Treatment with TLR7/8 Agonists

Topical Treatment with TLR7/8 Agonists can Eradicate Tumors

Proliferating Hemangioma of Infancy

Squamous Cell Carcinoma in Situ

Squamous Cell Carcinoma

- Topical TLR7/8 cream or gel formulations have demonstrated clinical benefit to patients
- The photos above indicate pre and post treatment with TLR7/8 topical formulations

Clinical Benefit Demonstrated Following Treatment with TLR7/8 Agonists (Imiquimod and/or Resiquimod)

- Cutaneous T-Cell Lymphoma
- Cutaneous Metastases of the Breast
- Actinic Keratosis
- Basal Cell Carcinoma
- Bowen's Disease
- Lentigo Maligna Melanoma
- Merkel Cell Carcinoma
- Genital Warts
- Herpes

- Actinic Cheilitis
- Extramammary Paget's Disease
- Paget's Disease of the Breast
- Xeroderma Pigmentosum
- BCC Nevus Syndrome
- Squamous Cell Carcinoma
- Infantile Hemangioma
- Molluscum Contagiosum
- Cervical Intraepithelial Neoplasia
- Verruca Vulgaris (common warts)

Clinical Evidence of Topical TLR7/8 Ligands Efficacy

The 2nd generation TLR agonist, **Resiquimod**, is very potent TLR7/weak TLR8 agonist showing effectiveness in multiple topical indications, including CTCL[1, 2]

- ➢ While the pivotal CTCL study demonstrated promising clinical benefits, it was challenged by a higher-than-expected rate of patient dropouts and potential issues related to insufficient statistical power
- ✓ TLR8 ligand is expected to enhance efficacy and durability more effectively by activating anticancer adaptive immunity

[1] Rook et al, Blood 2015 Vol. 126 Pages 1452-61
[2] Ramelyte et al, Expert Opin Investig Drugs 2019 Vol. 28 Pages 799-809

Cutaneous T-Cell Lymphoma (CTCL) Successfully Treated with Resiquimod, Including Demonstration of Abscopal Effect

- Most patients had a complete or partial response (11/12) of skin lesions
- This benefit was associated with only mild side effects of skin irritation
- Treatment led to improvement of untreated lesions - “abscopal” effect

While neither resiquimod nor imiquimod are approved for CTCL treatment, cases have demonstrated safety and efficacy in treating CTCL off-label

Abscopal effects

Rook et al. Blood 2015;126:1452-61

Topical TLR ligands for CTCL

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Unmet Medical Need

- Rare cancer (0.1-0.2% of all cancers)
- Approximately 25,000 – 50,000 have classic presentation of CTCL known as mycosis fungoides (US)
- US Incidence is 10.2 cases/million
- 6,000 **new** cases in 2021 and expected to rise
- Conservative estimate of **minimum of** 3,000 new cases/year in US
  - ➢ Current therapy is **only modestly** effective

Current Marketed Topical Therapies for CTCL

- Valchlor/Ledaga (Mechlorethamine) Helsinn, small molecule
- Targretin (Bexarotene) Ortho., small molecule

Growing Market

- Global CTCL market is expected to grow at a CAGR of 8.56% from 2020 to reach USD 3.53 billion by 2030 (Globe Newswire, Nov 30, 2021)

TLR Ligands have shown benefit for CTCL patients

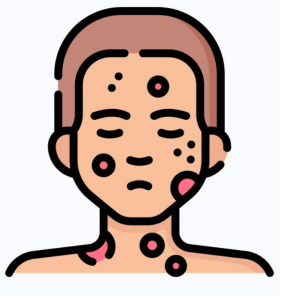
- Topical TLR agonists have demonstrated efficacy in therapy of CTCL
- Topical application of TLR7 agonist imiquimod has been FDA-approved for use in pre-cancerous, cancers, and viral diseases of the skin
- However, the TLR8 ligand TLRB-001 is expected to be more effective and durable for CTCL and other topical cancer and pre-cancer conditions

CTCL Initial Indication Selection

Patients suffer from a ***chronic*** disease with significantly decreased quality of life

Consistent Itching & Pain

Stress From Cancer Progression



Stigma From Appearance

Ineffective Treatments

Molecule Selection
&
Developmental Status

Identification of lead molecule to Phase I

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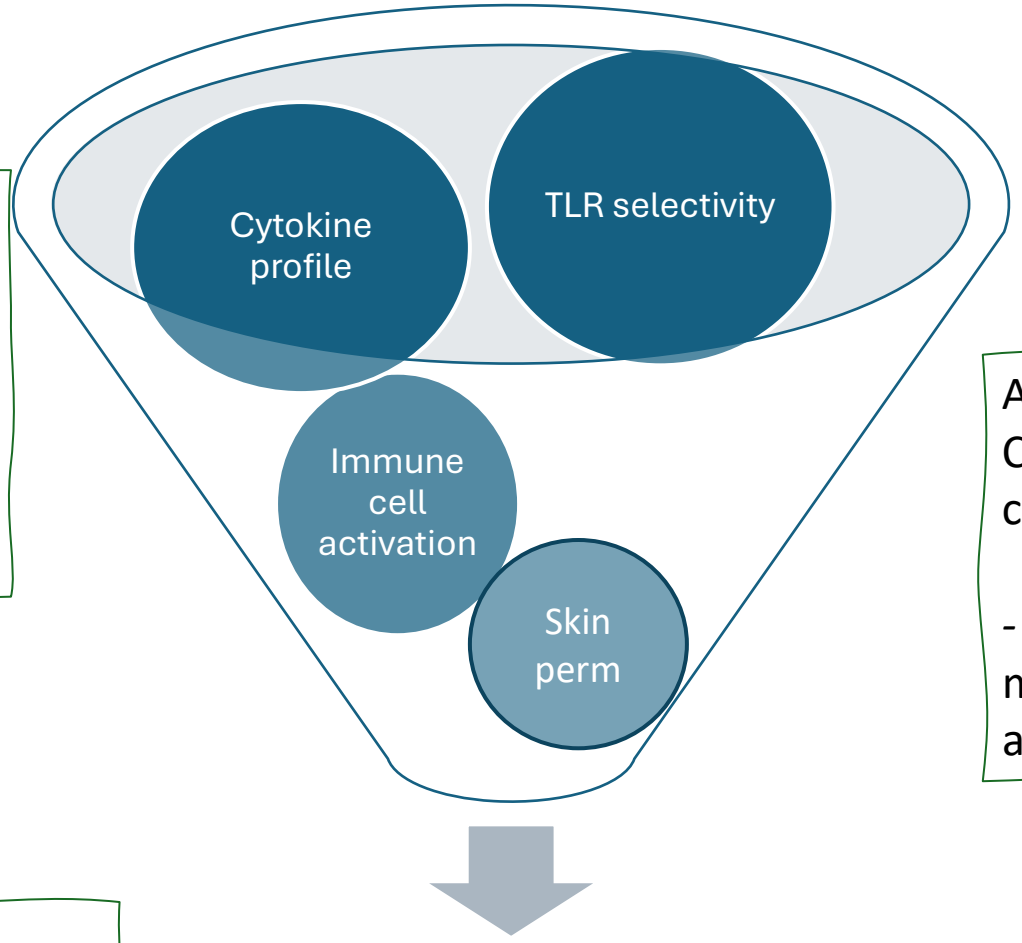
Compound selection rationale
Imidazoquinoline/imidazoquanidine compound screening

1 Selective activation of HEK cells expressing human TLR7 or TLR8

2 Selective induction of IFNγ/IL-12/TNFα secretion from healthy and CTCL patients' PBMC

- *Potency & efficacy*: sub micromolar for IFNγ/IL-12/TNFα and high micromolar for IFNα



3 Activation of healthy donor & CTCL patients PBMC monocytes, cDC, CD4, CD8, & NK cells

- *Potency & efficacy*: sub micromolar for IFNγ/IL-12/TNFα and high micromolar for IFNα

4 Skin permeability
- Pass through stratum corneum & retained in dermis

TLRB-001

Current Status: Preclinical

TLR8-selective lead molecule key characteristics

Synthesis and analytical:

Strait-forward synthetic process, multiple non-GMP lots manufactured, LC-MS analytical method developed

In vitro activity:

Selectively activates TLR8 (TLR7 or TLR8 expressing HEK cells)

- Human TLR8: 0.04μM
- Human TLR7: 30μM

Induces relevant anti-cancer cytokines from human blood cells

- IFNγ & TNFα: 0.04-0.1μM
- IFNα: 30μM

Increases relevant cell surface markers associated with anti-cancer activity from CTCL patients' blood cells

- NK cells: CD69, CD107a
- Monocytes: CD80
- CD11c+ DC: CD80
- CD4 & CD8 T-cells: CD69

Skin permeability:

Lead molecule can penetrate the skin

- In vitro permeability profile demonstrates lead molecule permeation through human stratum corneum, epidermis, and dermis, as well as being retained in the dermis

Formulation:

Cream formulation developed for topical in vivo evaluation

In vivo activity:

Single topical application induces local inflammatory response consistent with TLR activation in swine

Current Status: Preclinical

Next steps

Preclinical
Skin permeation - human and pig
Drug product analytical development (to measure drug in cream formulation)
Species potency comparison - In vitro cytokine secretion from PBMC (human, pig, rat)
Pilot multidose pig study to confirm previous findings

Development
API synthesis – 100g GMP
Develop & manufacture Non-GLP tox formulation
Manufacture GLP tox/clinical formulation
Bioanalytical method development – rat, pig, human
In vivo pharmacology studies to support IND & tox studies
Rat acute tox study
Pig dose-escalation - GLP study with GLP tox formulation
Pig Multi-topical dose Tox - GLP study with GLP tox formulation
Write & Submit IND
Initiate Ph. I Clinical study

Approximate time-line to IND: 1.5-2 yr
Approximate cost: $5 MM