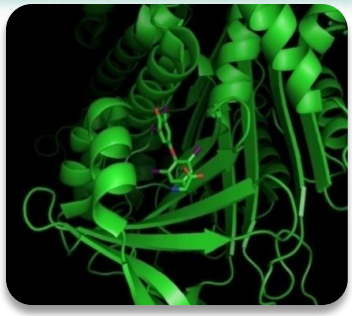
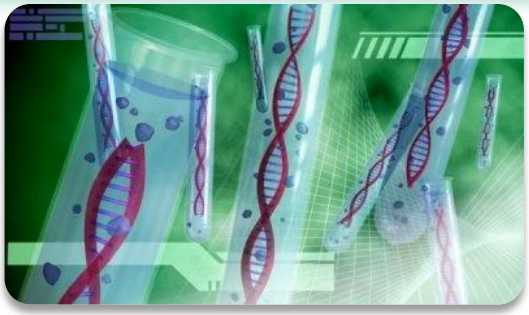




Development of a novel polyherbal product for treatment of Atopic dermatitis & other chronic dermal inflammatory diseases

16th European Dermatology Congress
June 07-08, 2017 Milan, Italy

DABUR RESEARCH FOUNDATION

Dr Anu T. Singh

Vice President (R&D)
Dabur Research Foundation, INDIA

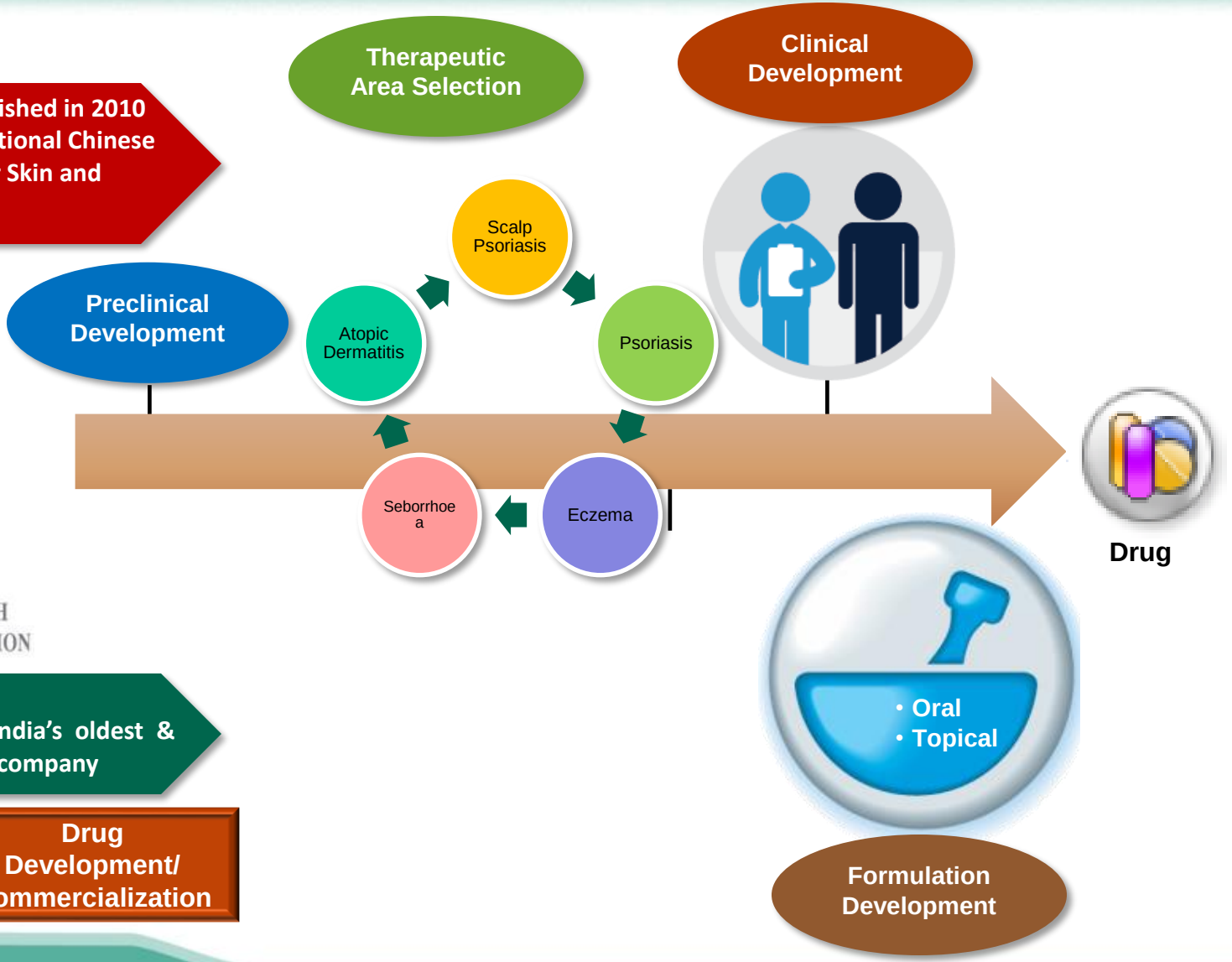
Collaborative Drug Development : Inflammatory Skin Diseases

- Israel based; Established in 2010
- Specialized in Traditional Chinese Medicine (TCM) for Skin and Cancer Treatment

- Established in 1979
- Research arm of India's oldest & largest health care company

Global Collaboration

Drug Development/ Commercialization



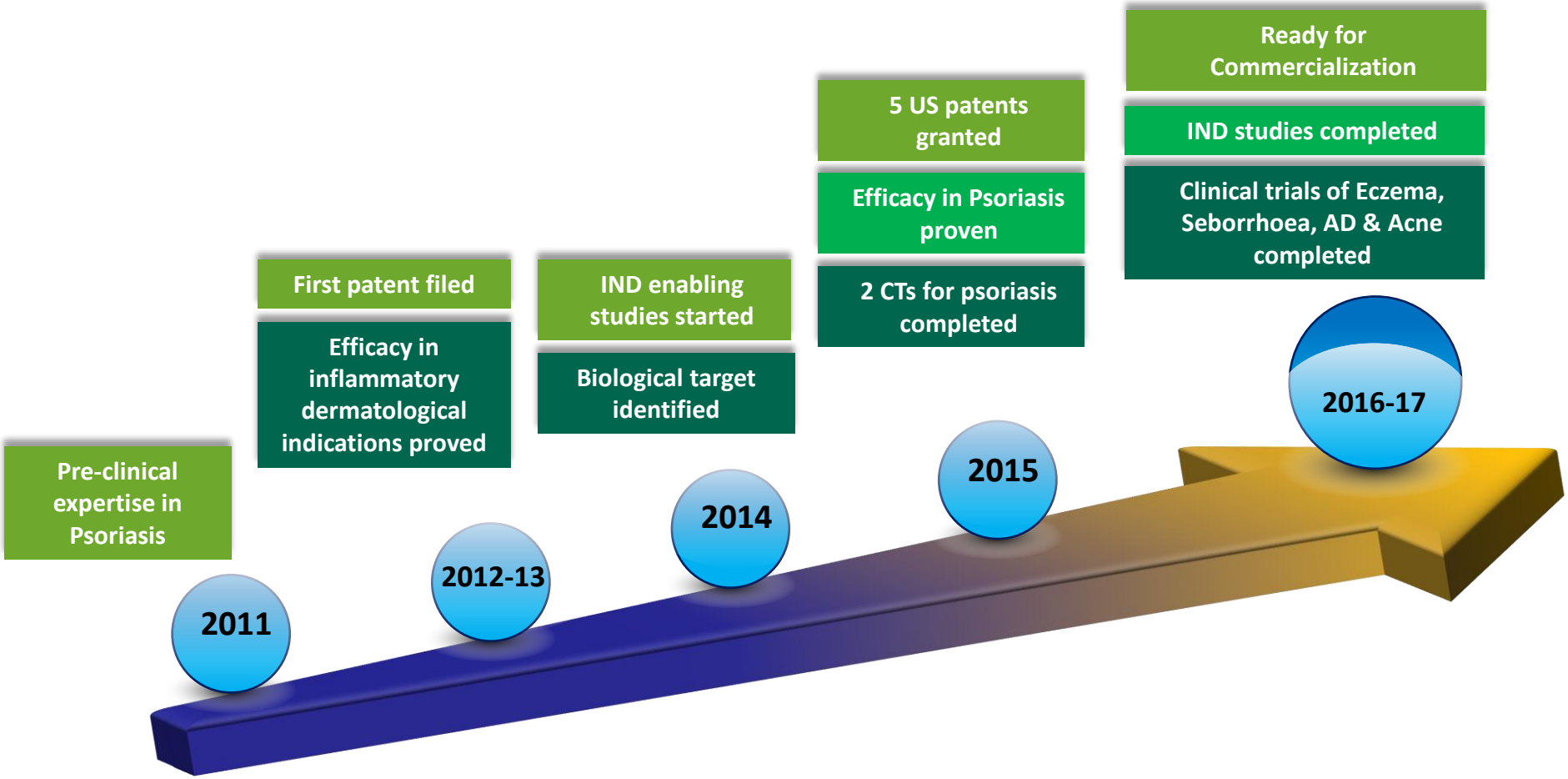
SIRB-001 – Product properties

- A polyherbal product for a wide range of skin diseases
- Fully characterized
- Potent anti-inflammatory
- Clinically validated targets
- Found to be safe for human use
- Tested on over 150 patients
- IP-Over 50 patents filed
- Received provisional clearance for EU commercialization

Scope of SIRB 001

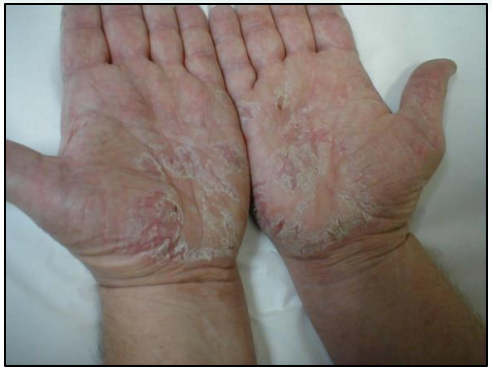
No.	Formulation	Indication
1	Cream	Psoriasis, Eczema, Atopic dermatitis
2	Shampoo - 1	Scalp Psoriasis
3	Hair lotion	Scalp psoriasis
4	Hair Serum / vitalizer	Seborrhoea / Dandruff
5	Shampoo - 2	Seborrhoea / Dandruff
6	Acne Gel	Acne
7	NanoGel	Psoriasis, Eczema, Atopic dermatitis
8	Oral Tablets	Psoriasis, other chronic inflammatory disorders
9	Oral Nanoparticles	Psoriasis, other chronic inflammatory disorders

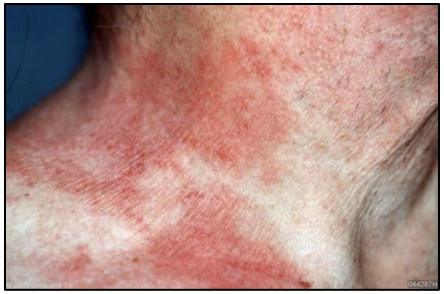
The journey so far…

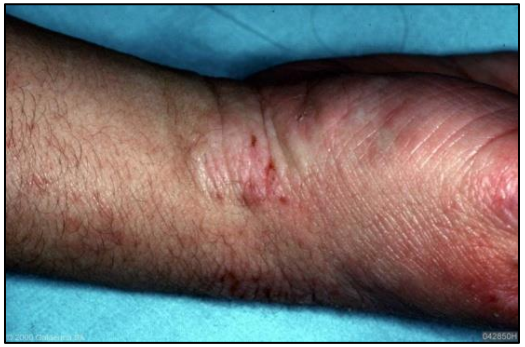


Atopic Dermatitis

- Atopic dermatitis (AD), also known as atopic eczema, is a type of inflammation of the skin (dermatitis).
- It results in itchy, red, swollen, and cracked skin. Clear fluid may come from the affected areas, which often thicken over time.
- In children under one year of age much of the body may be affected. In adults the hands and feet are the most commonly affected areas.
- The cause is unknown but believed to involve genetics, immune system dysfunction, environmental exposures, and difficulties with the permeability of the skin.
- The pathophysiology may involve a mixture of type I and type IV-like hypersensitivity reactions.

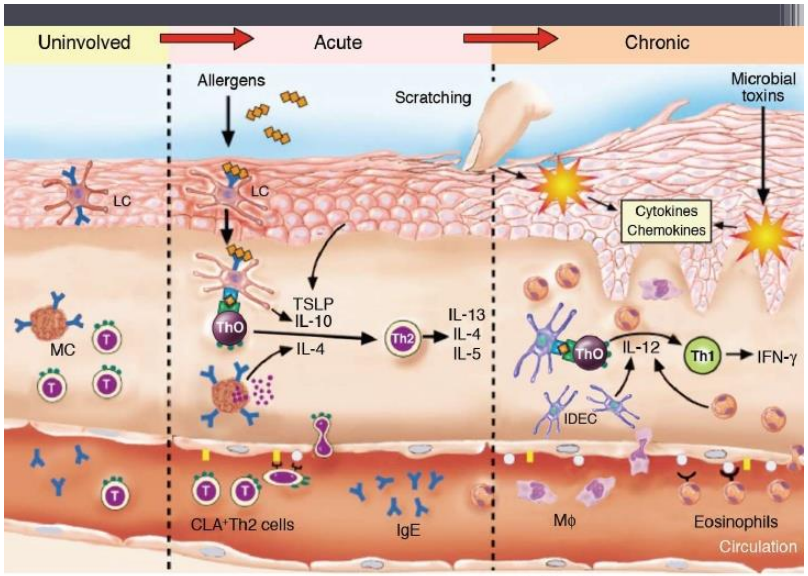






Etiology of AD

- Atopic dermatitis (AD) is a chronic inflammatory disease which results from complex interactions between genetic and environmental mechanisms.
- An altered lipid composition of the stratum corneum is responsible for the xerotic aspect of the skin and determines a higher permeability to allergens and irritants.
- Keratinocytes of AD patients exhibit a propensity to an exaggerated production of cytokines and chemokines, a phenomenon that can have a major role in promoting and maintaining inflammation.
- Dendritic cells expressing membrane IgE receptors play a critical role in the amplification of allergen-specific T cell responses.
- Thymus And Activation Regulated Chemokine (TARC) -CCR4 ligand, overexpressed in eczema lesions and attracts Th2 cells.
- A complex network of cytokines and chemokines contributes to establishing a local milieu that favors the permanence of inflammation in AD skin.

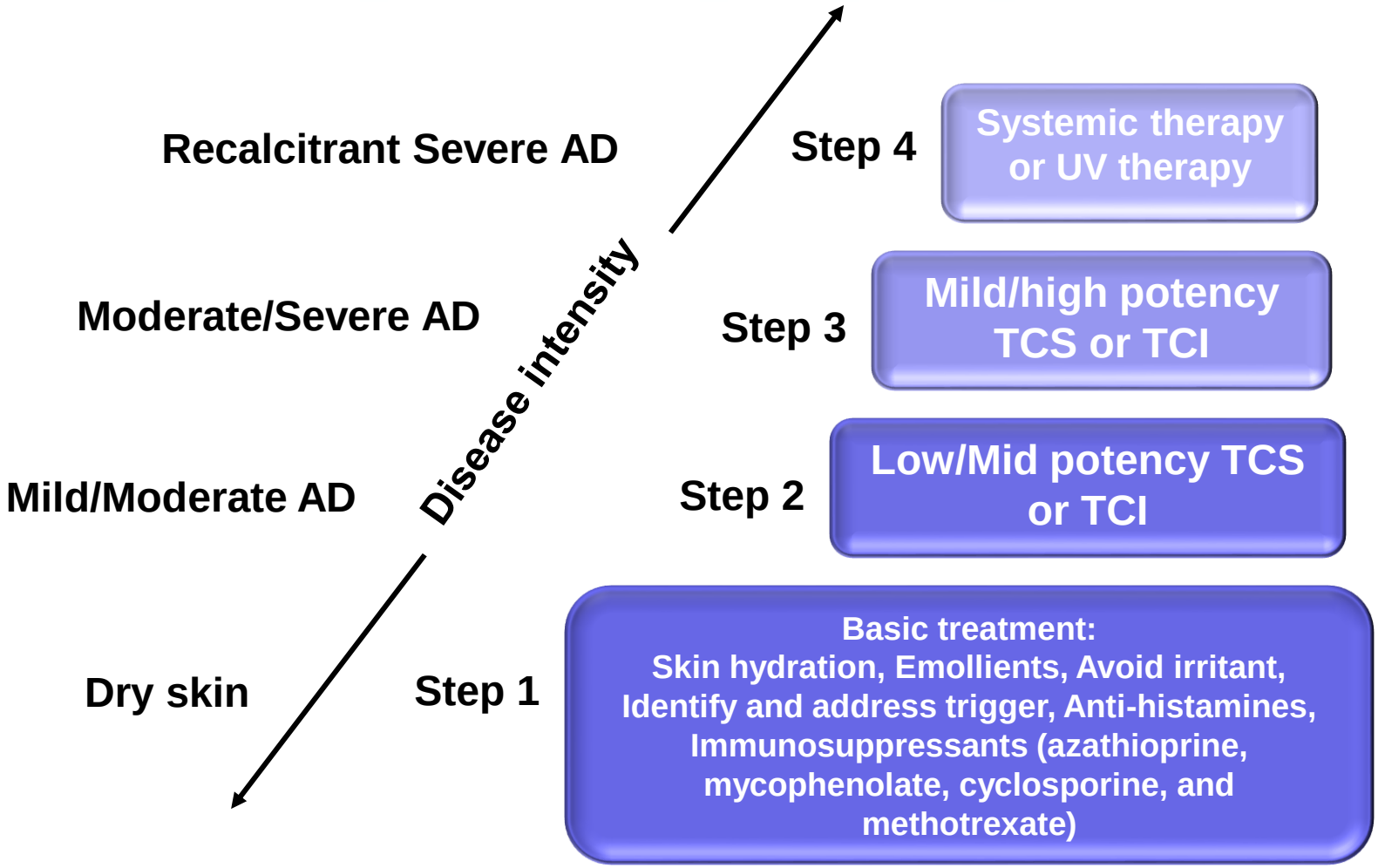


J. Clin. Invest.2004;113:651–657

Atopic dermatitis: mechanism of disease

https://www.slideshare.net/AllergyChula/atopic-dermatitis-mechanism-of-disease

Treatment



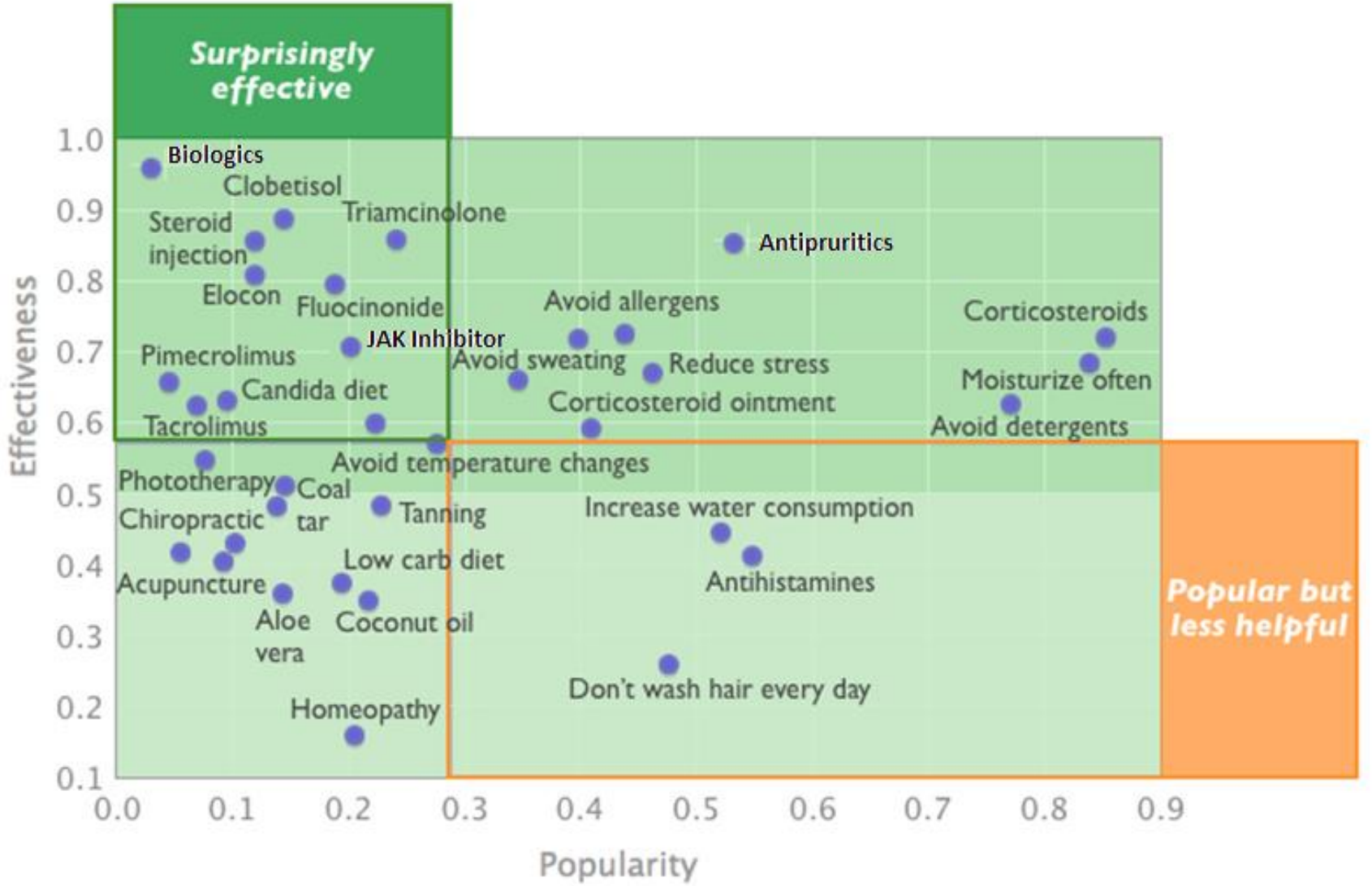
Medscape, 2008

Limitations of current AD treatment options

Treatment	Limitation
Topical corticosteroids	• Long-term use can lead to skin atrophy, spider veins, stretch marks, and pigmentation abnormalities • Rarely in extreme cases, may cause hypothalamic-pituitary-adrenal suppression, leading to Cushing's syndrome
Oral immunosuppressive drugs	• Systemic oral immunosuppressive drugs, such as cyclosporine are often coupled with serious side effects; skin damage, thinned or weakened bones, high blood pressure, high blood sugar, infections etc.
Biologics	• Side effects include flu-like symptoms such as chills, fever, muscle aches, weakness, loss of appetite, nausea, vomiting, and diarrhea • High cost
Phototherapy	• Possible long-term side effects of this treatment include premature skin aging and skin cancer

http://www.medicinenet.com/atopic_dermatitis/page10.htm

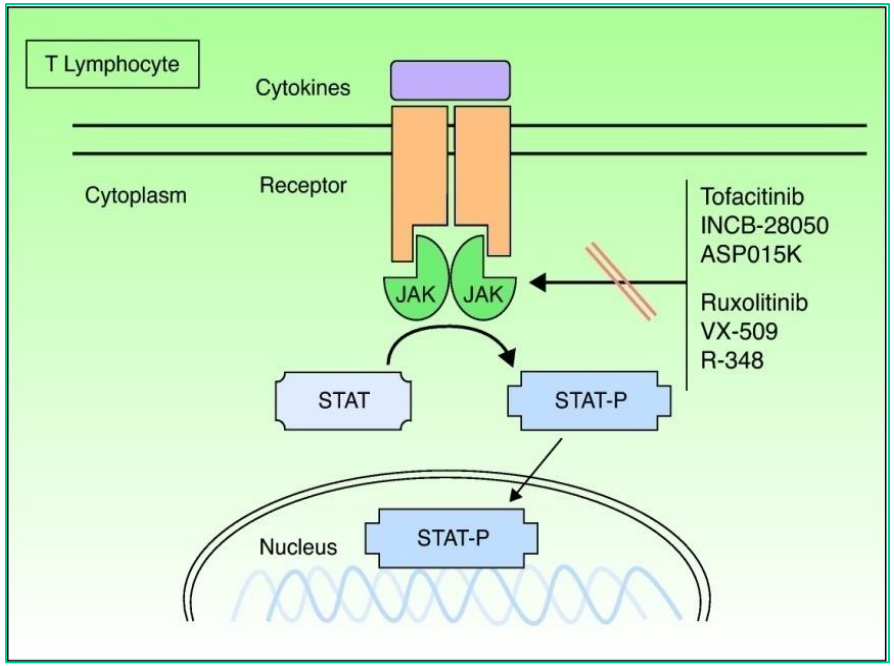
Treatment options



Biologics in Atopic Dermatitis

JAK-kinase inhibitors in AD

- **Janus-Kinases (JAK) are involved in cell signaling pathways activated by cytokines.**
- **Tofacitinib, a JAK kinase inhibitor has emerged as new therapeutics for severe, recalcitrant Atopic Dermatitis.**



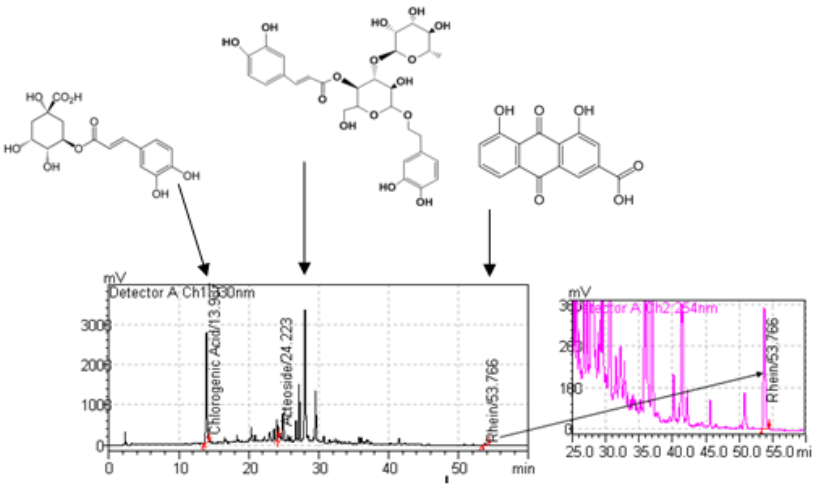
Biologics in AD

Emerging treatments for atopic dermatitis

Therapy	Mechanism of action	Phase of Drug Development
Biologics		
CIM331	Antibody against IL-31 receptor	2
ILV-094	Antibody against IL-22	2
Tralokinumab	Antibody against IL-23	2
Ustekinumab	Antibody against IL-12 & IL-23	2
Dupilumab	Antibody against IL-4 receptor	3
Anti-pruritics		
CT327	Tropomyosin receptor kinase A inhibitor	2
VLY-686	Neurokinin 1 receptor antagonist	2

SIRB 001 - The Product

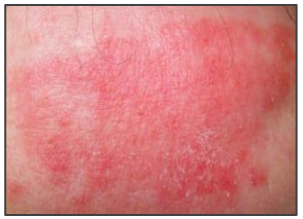
- A novel mixture of 3 herbs; *Rheum palmatum* L. (Da Huang), *Rehmannia glutinosa* Libosch (Sheng di huang) and *Lonicera Japonica* (Jin yin hua) was developed in the ratio 1:1:3.
- Fingerprinting analysis performed by HPLC with 3 marker compounds Chlorogenic acid, Acteoside and Rhein.
- SIRB 001 has been demonstrated to work as anti proliferative immunopotentiating product. It down regulates key proinflammatory cytokines including TNF alpha, IL17/IL23
- SIRB 001 has shown potential for treatment of chronic dermal inflammatory diseases including psoriasis, Eczema & others



Name of marker compound	Herb name
Emodin	
Rhein	HERB-1
Rhapontin	
Carvacrol	
Vanillic acid	HERB-2
Sweroside	
Aucubin	
Digoxin	HERB-3
β-sitosterol	

Anti-AD potential of SIRB 001-Preclinical studies

Atopic dermatitis



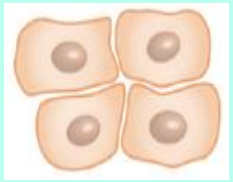
Increased secretion of cytokines by immune cells

Increased production of IgE by lymphocytes

Inflammation in keratinocytes by increased secretion of cytokines

Increased activity of JAK1/JAK3

SIRB-001

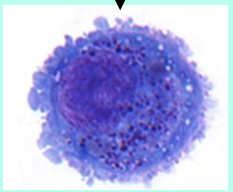


Keratinocytes

Downregulation of TNF-α, IFN-γ, IL-6, TARC and VEGF in keratinocytes (HaCaT)

Macrophages

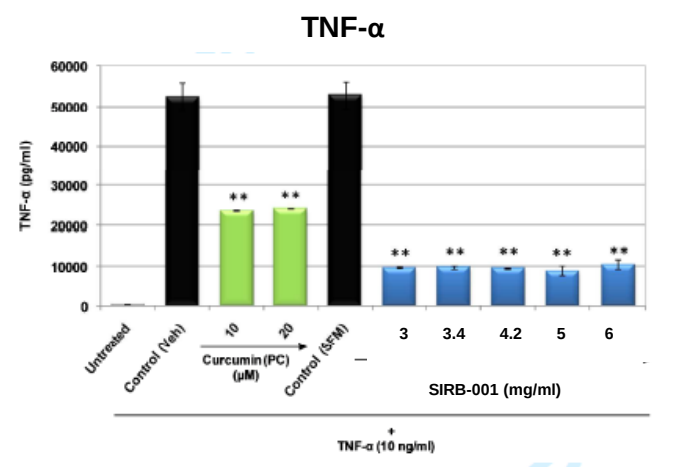
inhibition of IL-6 in immune cells

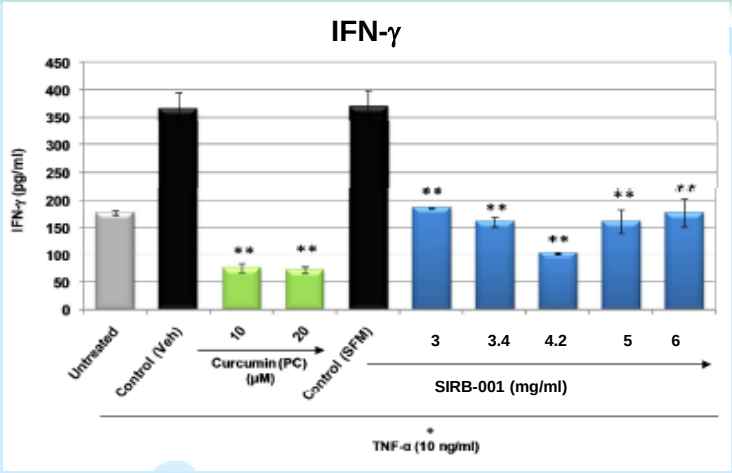


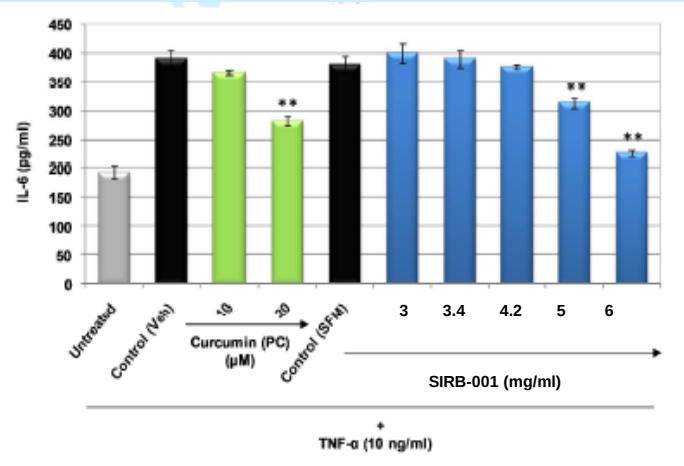
Lymphocytes

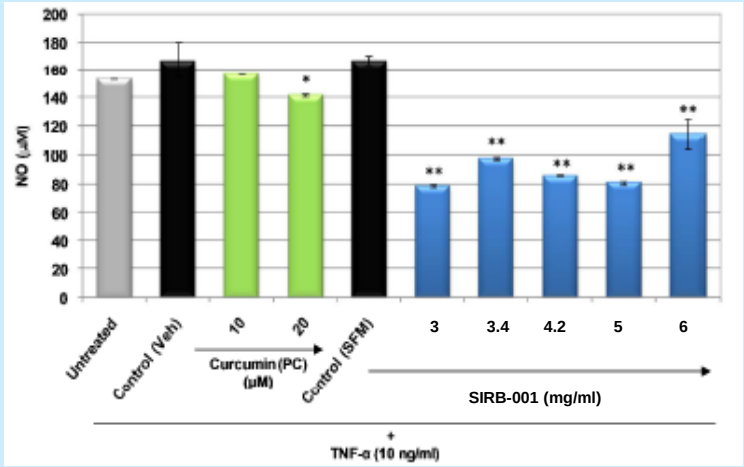
Inhibition of IgE production

In vitro Anti-AD potential of SIRB-001





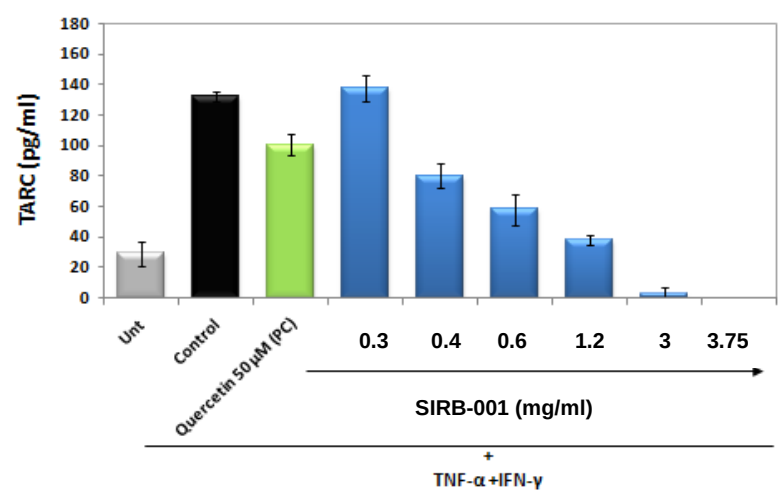




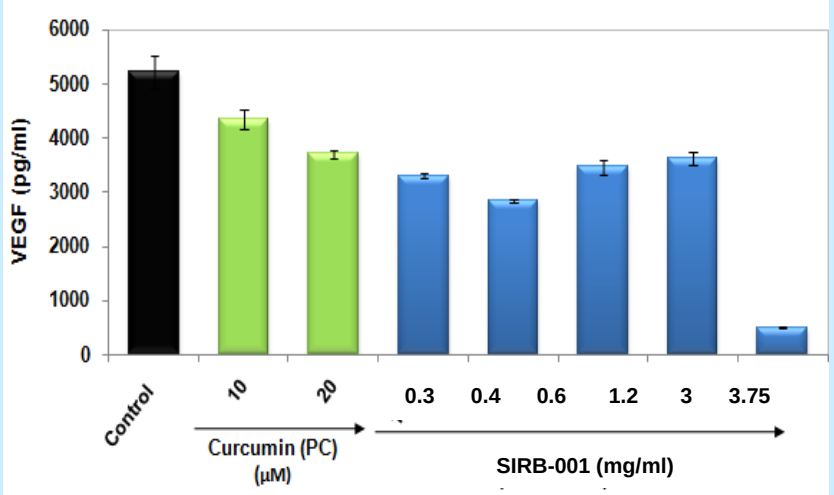
- **Significant downregulation of inflammatory cytokines; TNF-α (80%-85%), IFN-γ (44%-72%), IL-6 (12%-50%) and Nitric Oxide (25%-50%) in keratinocytes (HaCaT)**

In vitro Anti-AD potential of SIRB-001

TARC



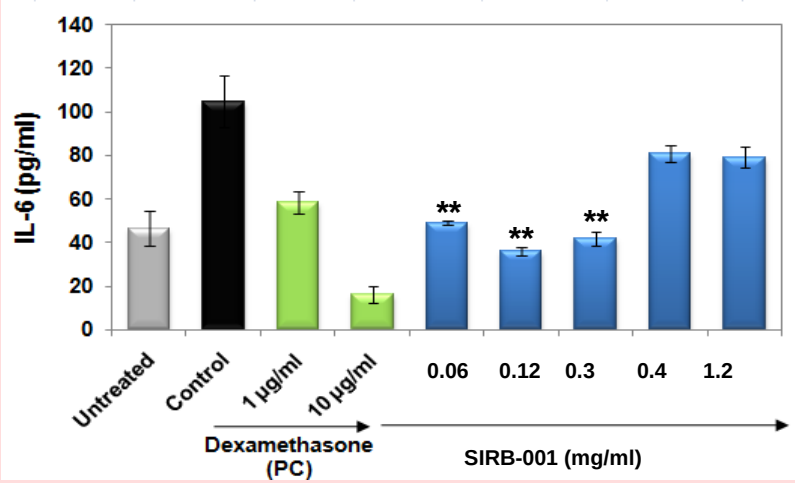
VEGF



- **Significant downregulation of chemokine-TARC (38%-100%) and VEGF (40%-92%) in keratinocytes (HaCaT)**

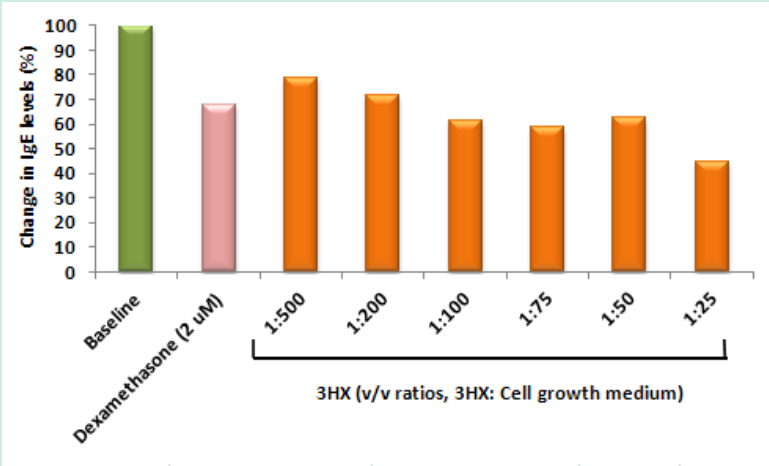
In vitro Anti-AD potential of SIRB-001

IL-6



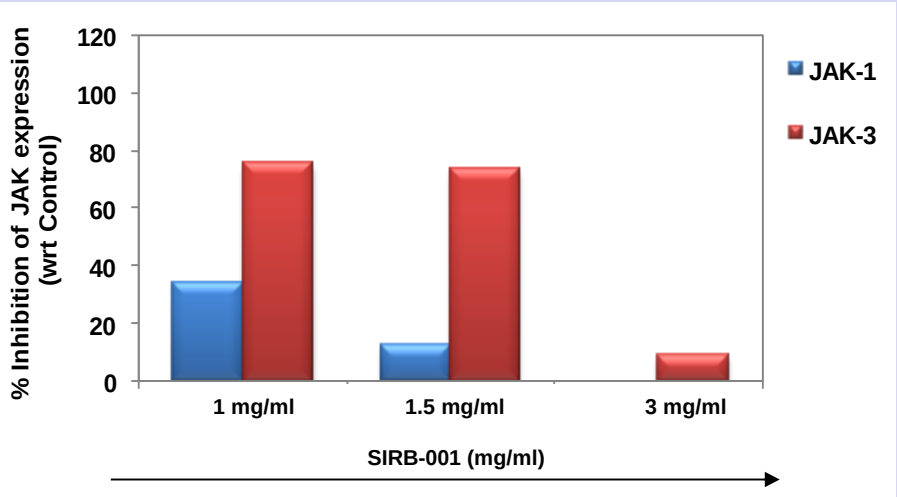
- Significant downregulation of IL-6 (20%-60%) in immune cells (macropahges)

IgE



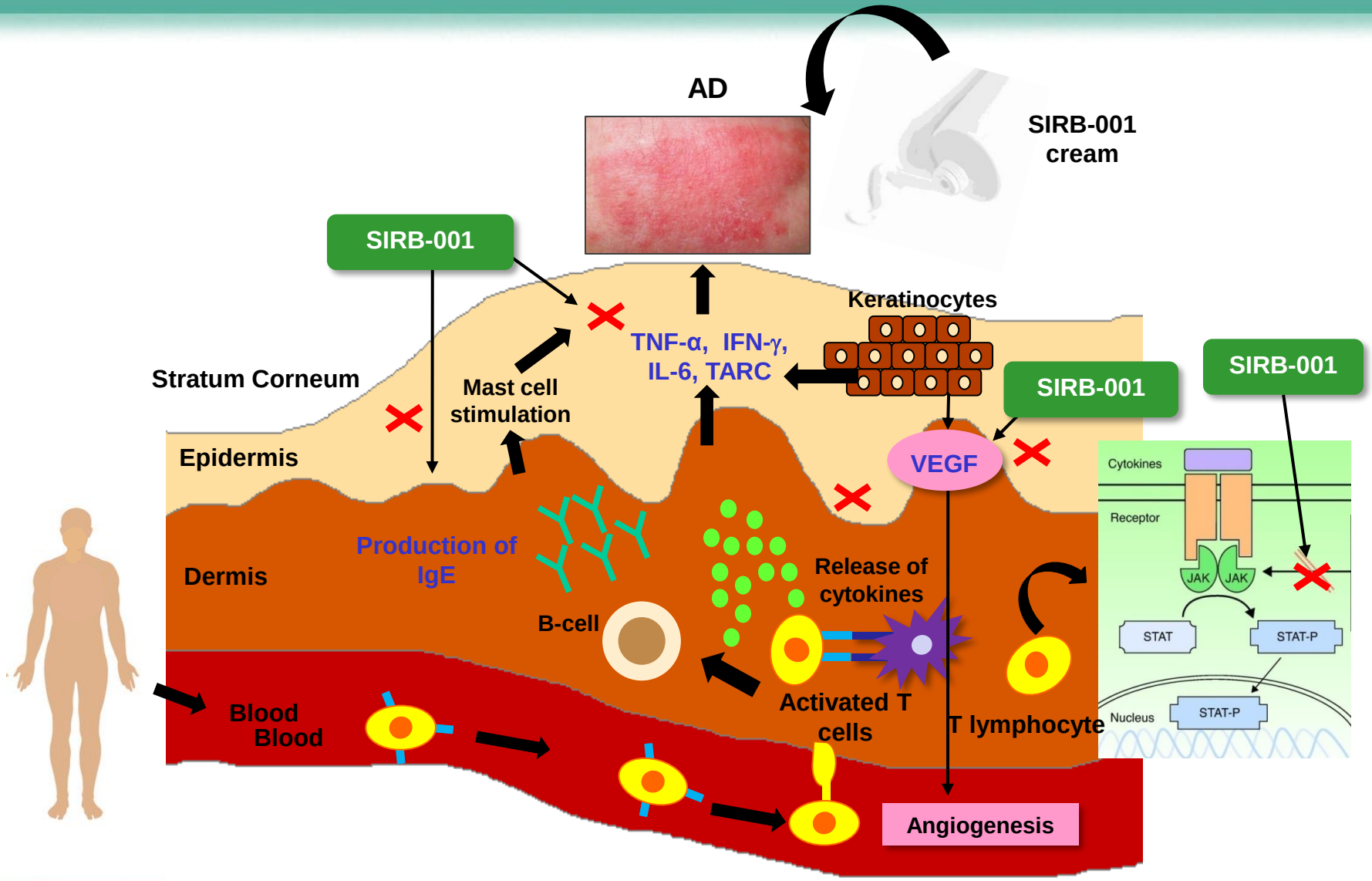
- IgE inhibition (20%-60%) in human myeloma cell line; U-266

In vitro Anti-AD potential of SIRB-001



- **Inhibition of JANUS KINASES - JAK-1/JAK-3 (10%-75%)**

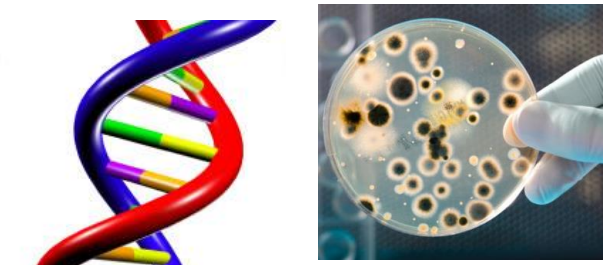
Anti-AD potential of SIRB-001 – Mechanism of action

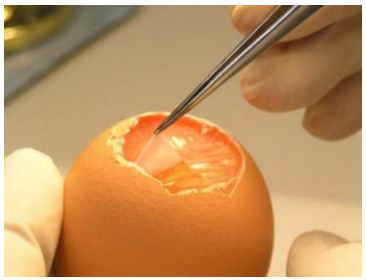


SIRB-001- Safety

Extensive studies carried out in animals have demonstrated SIRB-001 safe for topical and oral administration

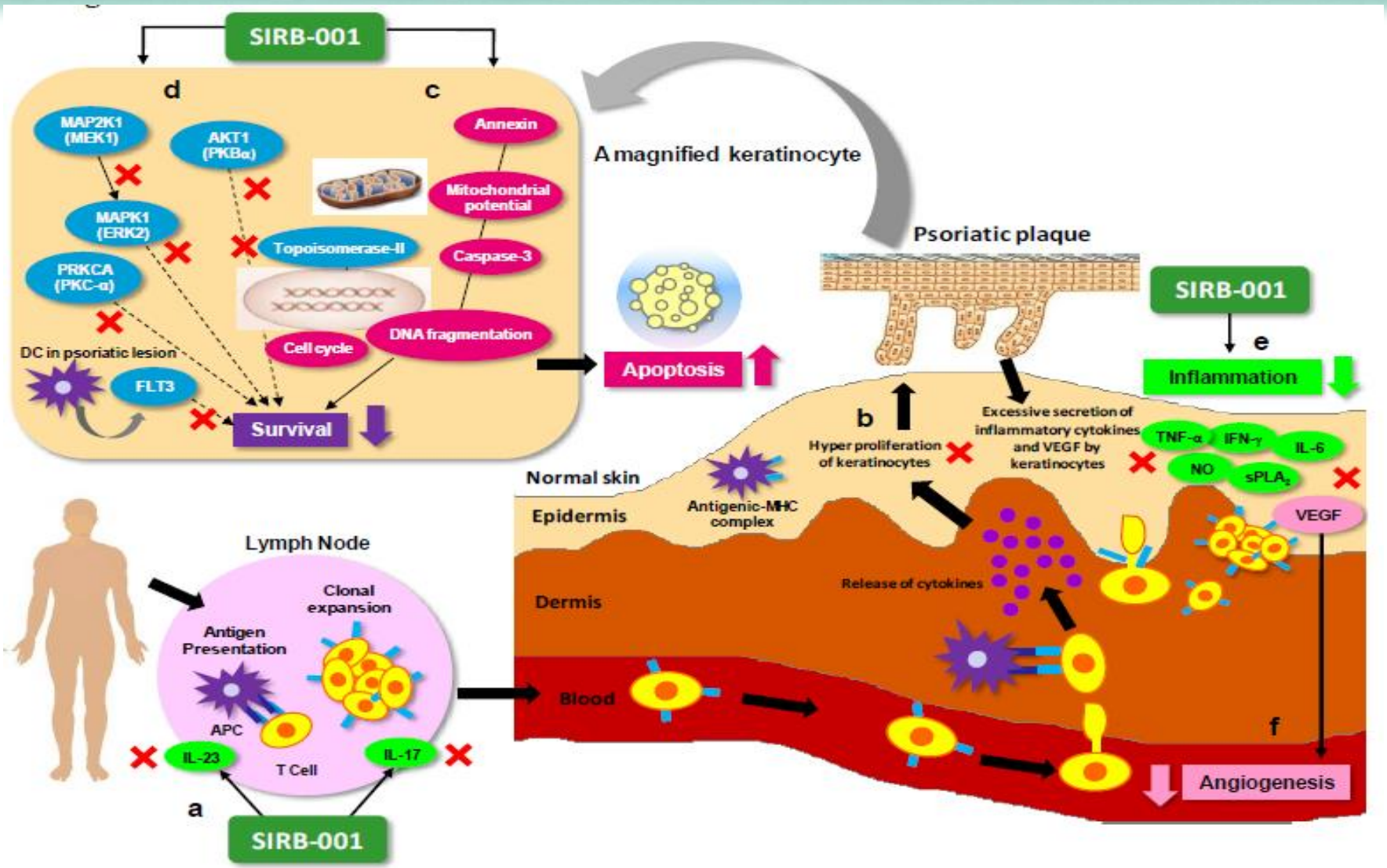
- Acute and sub acute Safety studies
- Chronic safety studies – 6 months
- Mutagenecity
- Reproductive safety
- Skin sensitization
- *In vitro* HetCAM & 3-D skin studies
- Safety pharmacology





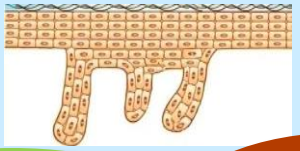
Therapeutic potential of SIRB 001 in other chronic skin inflammatory diseases

Anti psoriatic potential of SIRB 001



SIRB 001 – Unifying MoA in inflammatory skin disorders

PSORIASIS



Inhibitory effect on signaling markers of psoriasis

Anti-inflammatory

Signaling markers

Inflammation – Secretion of cytokines

Anti-proliferative

Hyper-proliferation of keratinocytes

Angiogenesis

Anti-angiogenic

SIRB-001

ATOPIC DERMATITIS

Anti-inflammatory

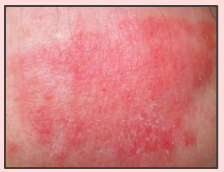
Inflammation – Secretion of cytokines

JAK-1/JAK-3 kinase

Angiogenesis

IgE

Anti-angiogenic



ACNE

Anti-proliferative

Sebum secretion

Sebostatic

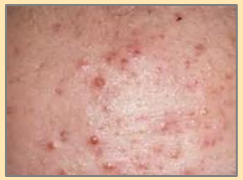
Hyper-proliferation of keratinocytes

Inflammation – Secretion of cytokines

Anti-inflammatory

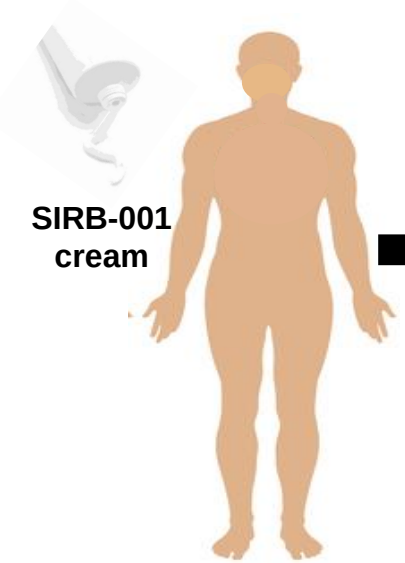
Oxidative stress

Anti-oxidant



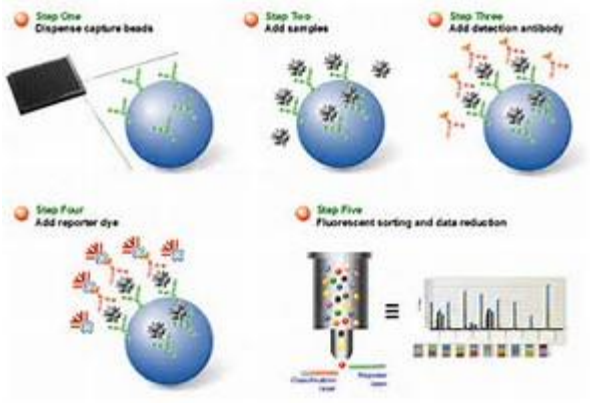
Patient stratification for SIRB-001 - Strategy

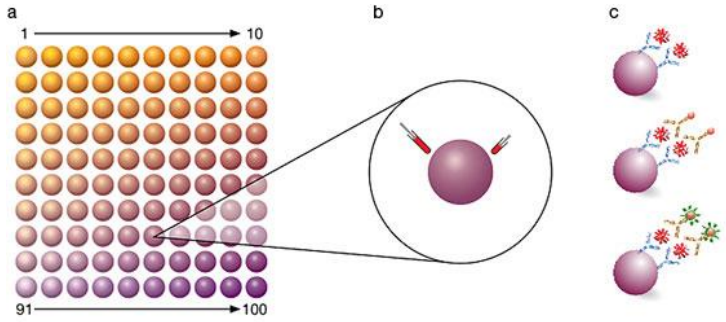
SIRB-001 cream



Psoriasis patients

Blood collection



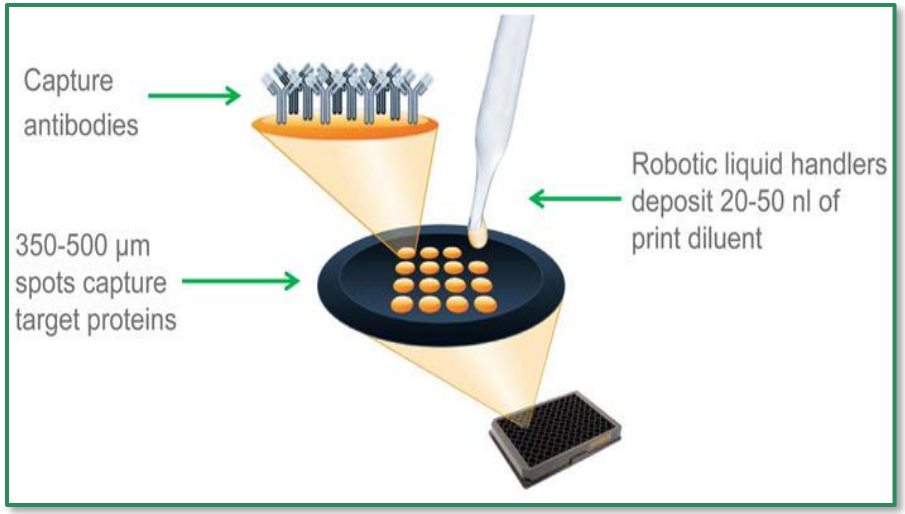


Estimation of inflammatory cytokine panel by Multiplex technology

Identification of biomarkers from psoriasis clinical trial

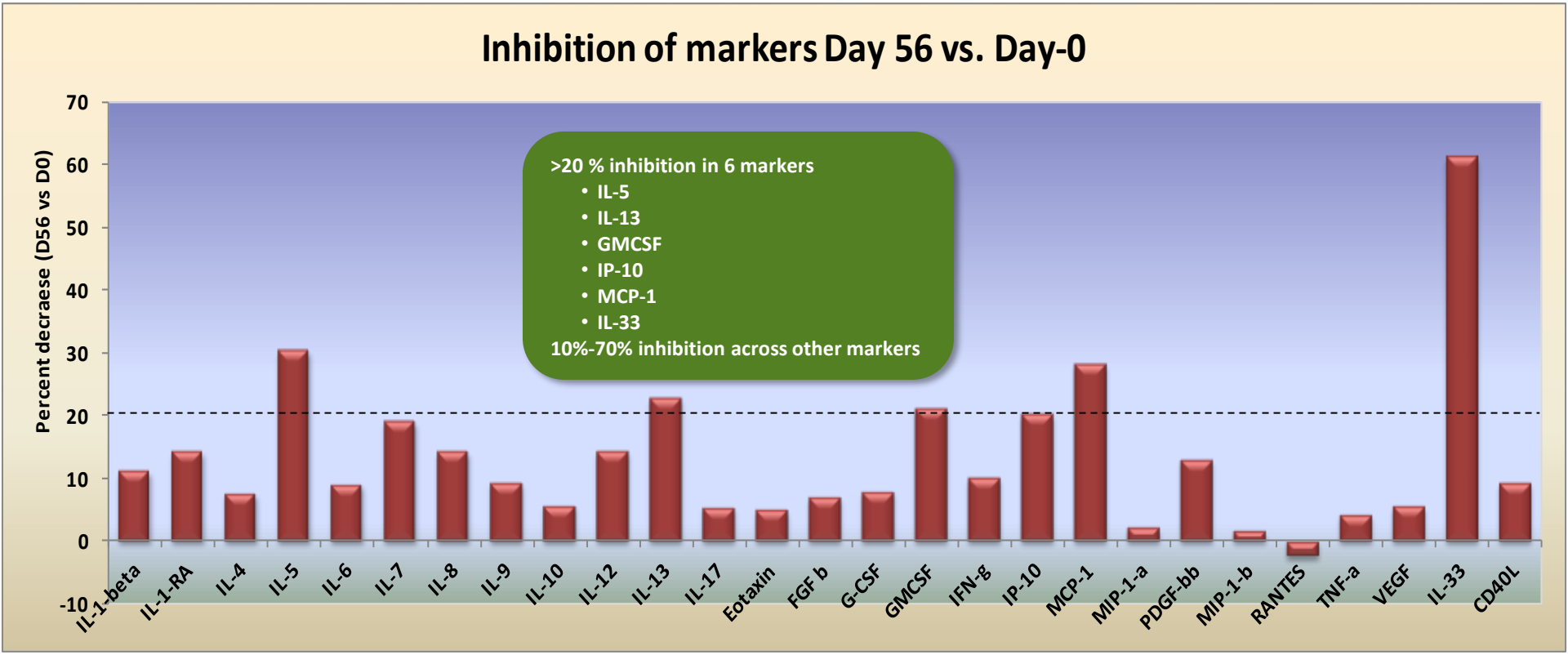
Patient stratification for SIRB-001

- Serum samples collected from 30 patients at 2 time points (baseline and completion of treatment) were analysed for 27 inflammatory markers associated with psoriasis using Multiplex technology.
- Serum samples were also collected from 7 healthy volunteers to evaluate the markers elevated in disease condition.
- Levels of 7 markers was found to be elevated (> 1.5 fold) in disease condition as compared to healthy controls.
- Down regulation (>20%) was observed in 6 markers upon treatment with SIRB-001 cream for 56 weeks.



IL-1-β, IL-1-RA, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-17, Eotaxin, FGF-β, G-CSF, GM-CSF, IFN-γ, IP-10, MCP-1, MIP-1-α, PDGF-bb, MIP-1-β, RANTES, TNF-α, VEGF, IL-33, CD40L

Searching for prognostic markers for SIRB 001….



Biomarkers vs % Inhibition in Biomarker levels in patients after treatment (D56 VS D0)

% Decrease = (Mean value Day 0-Mean value Day 56)x100/Mean value Day 0

Highlights of clinical trial results

Indication	Site	Number of subjects	Evidence of clinical efficacy
Psoriasis	dermatest® RESEARCH INSTITUTE FOR RELIABLE RESULTS *Taking your success personally* Germany	21	
Scalp psoriasis	CIDP CENTRE INTERNATIONAL DE DEVELOPPEMENT PHARMACEUTIQUE India	30	
Eczema	CIDP CENTRE INTERNATIONAL DE DEVELOPPEMENT PHARMACEUTIQUE India	30	
Seborrhoea	CIDP CENTRE INTERNATIONAL DE DEVELOPPEMENT PHARMACEUTIQUE India	30	
Atopic dermatitis	dermatest® RESEARCH INSTITUTE FOR RELIABLE RESULTS *Taking your success personally* Germany	25	
Acne	CIDP CENTRE INTERNATIONAL DE DEVELOPPEMENT PHARMACEUTIQUE India	30	

Recent publications

Evaluation of anti-psoriatic potential of a novel polyherbal formulation by multiparametric analysis

Anti-psoriatic potential and safety of a novel polyherbal formulation

Development of a novel polyherbal topical product for the management of eczema & other chronic dermal inflammatory conditions

Development of a novel polyherbal topical formulation for the management of psoriasis

THANKS