

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

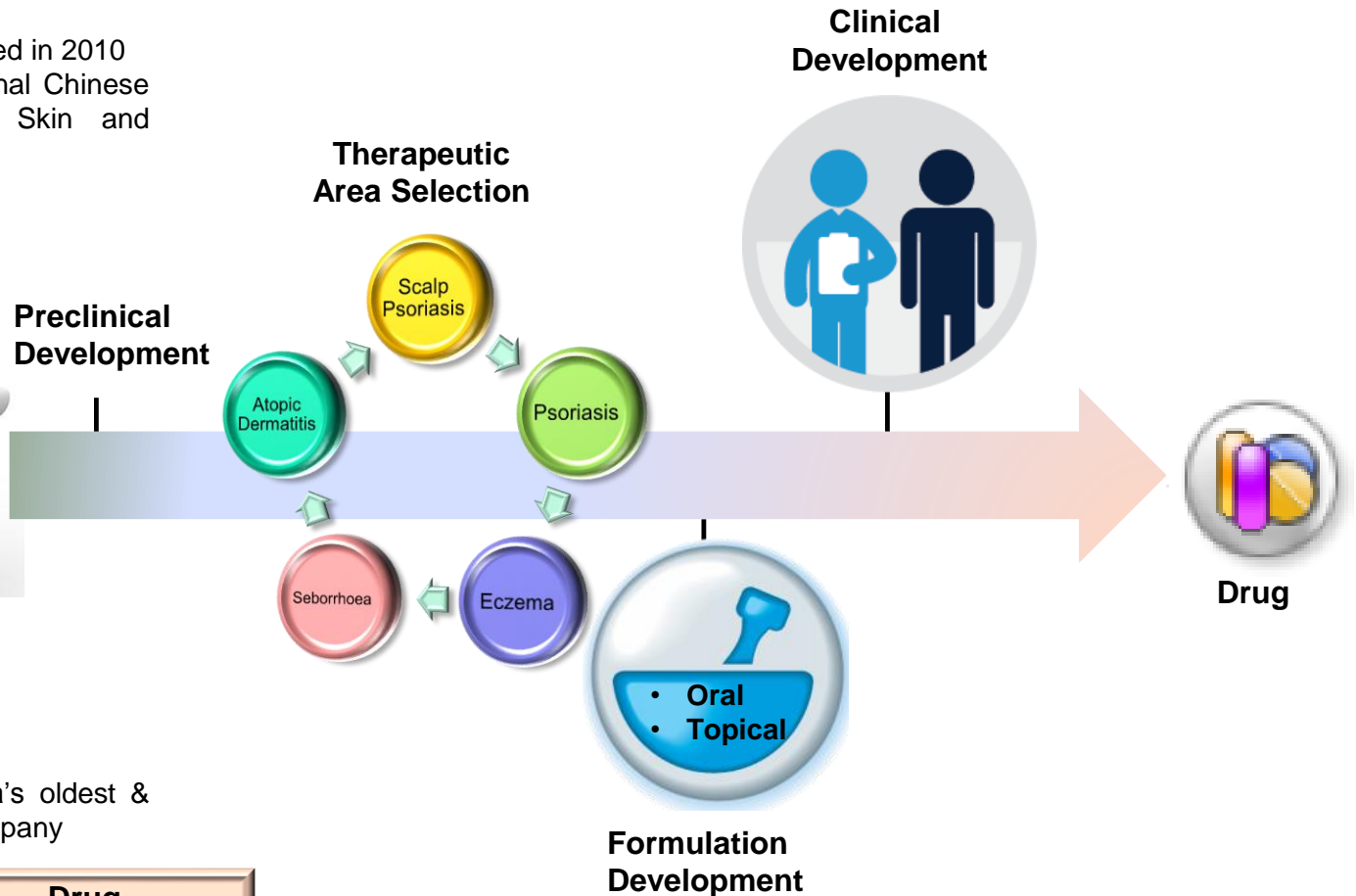
7th European Dermatology Congress
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Alicante, Spain

Dr Anu T. Singh

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



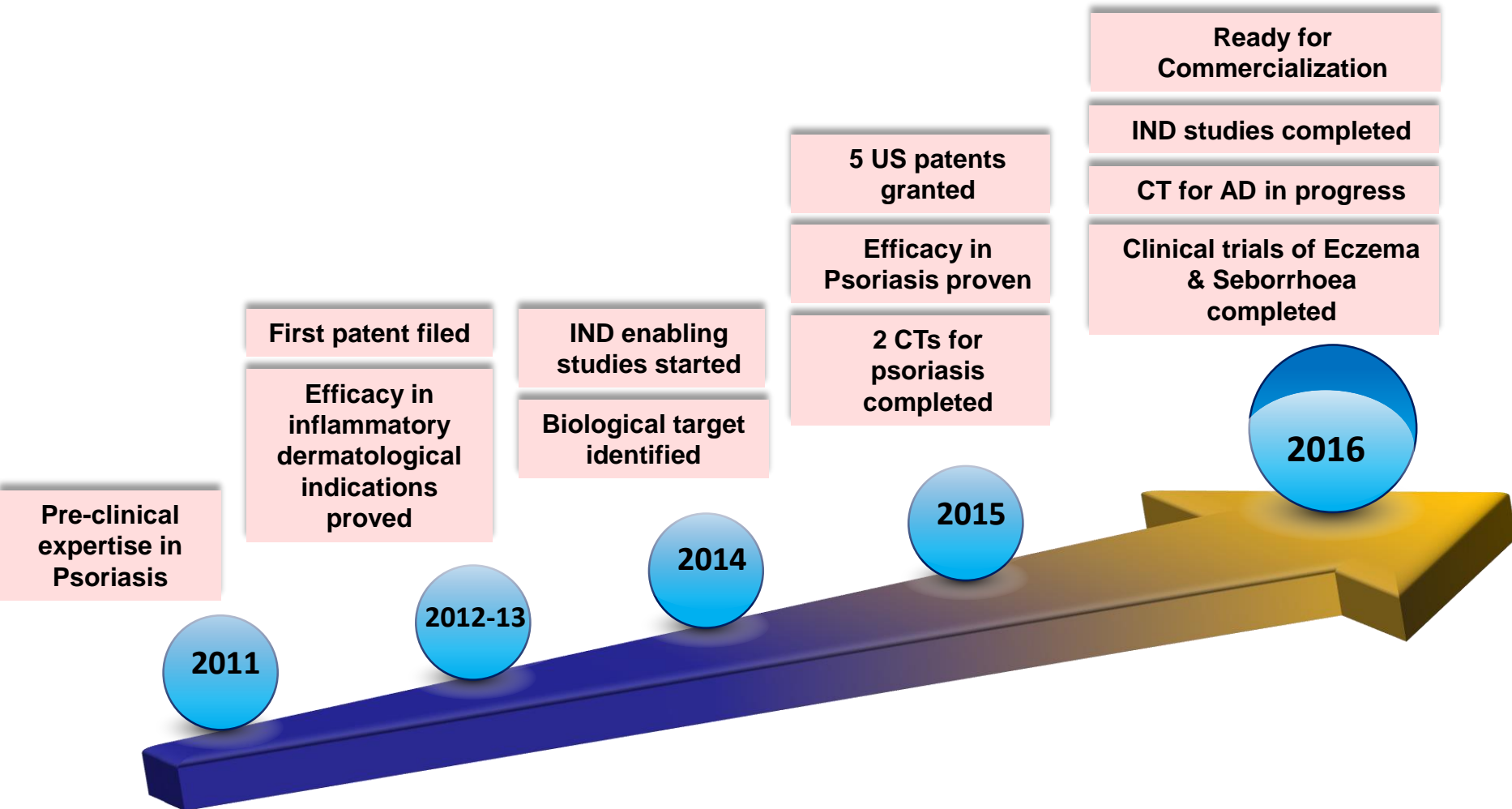
- Israel based; Established in 2010
- Specialized in Traditional Chinese Medicine (TCM) for Skin and Cancer Treatment



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

**Global
Collaboration**

**Drug
Development/
Commercialization**

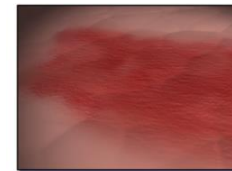


- Eczema or Atopic dermatitis (AD), is a common chronic or recurrent inflammatory skin disease with impaired skin barrier
- Complex interrelationship of genetic, environmental, immunologic, and epidermal factors
- Affects 15-20% of children and 2-10% of adults worldwide
- Characterized by eczematous pruritic lesions and erythematous, vesicular, weeping and crusting patches over dry skin

Eczema



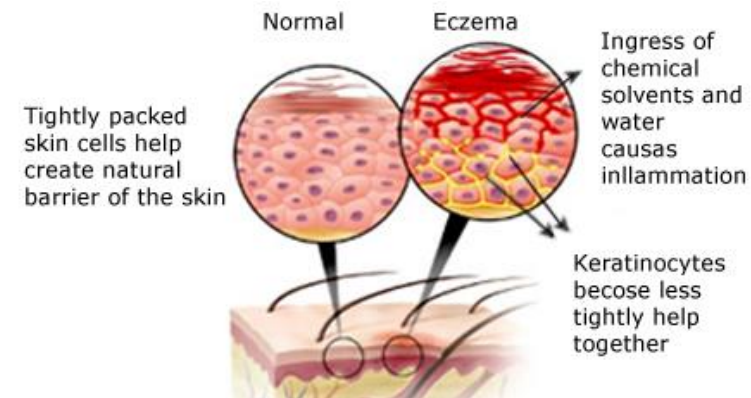
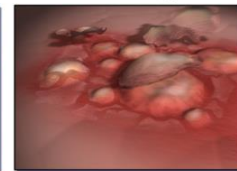
Redness



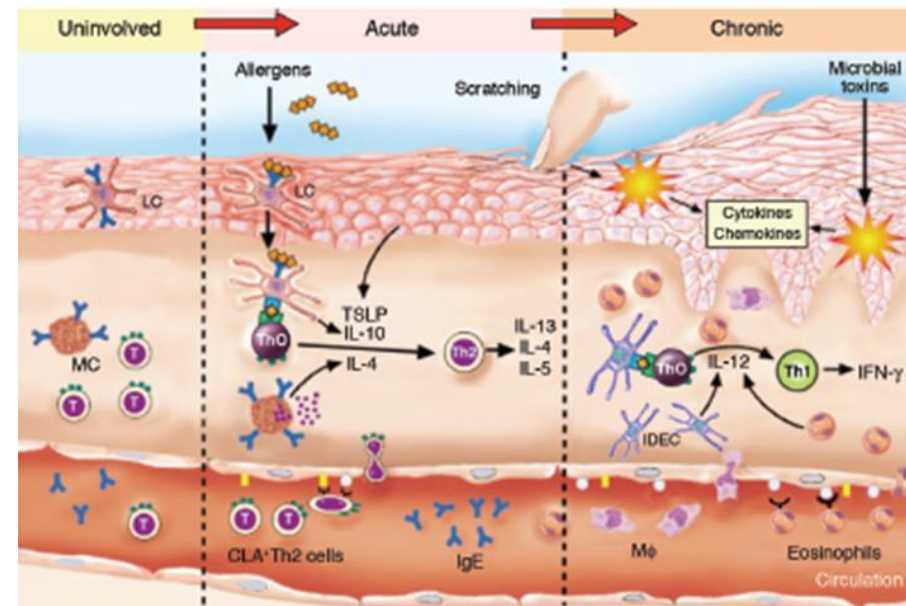
Blisters



Flaking

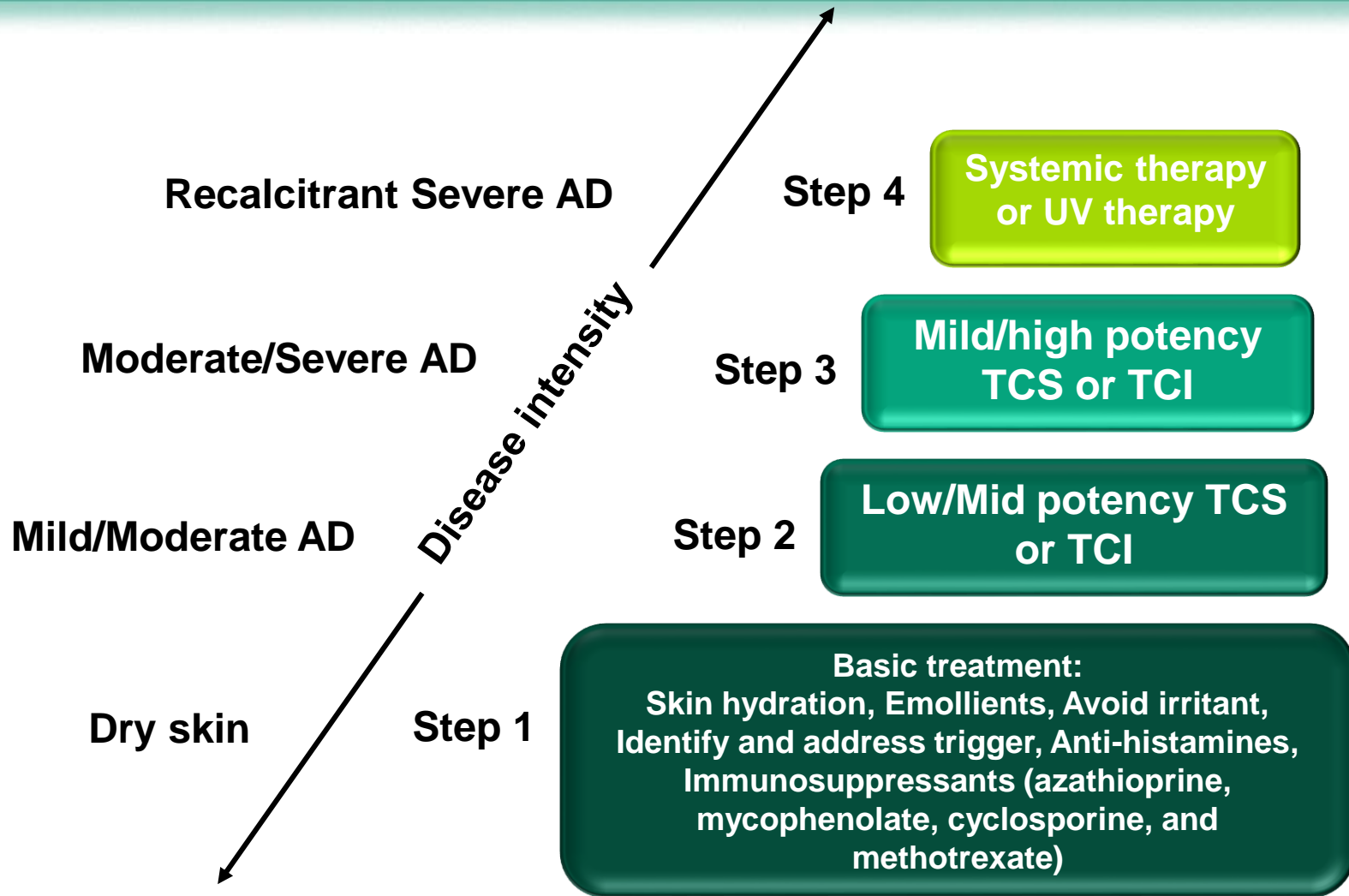


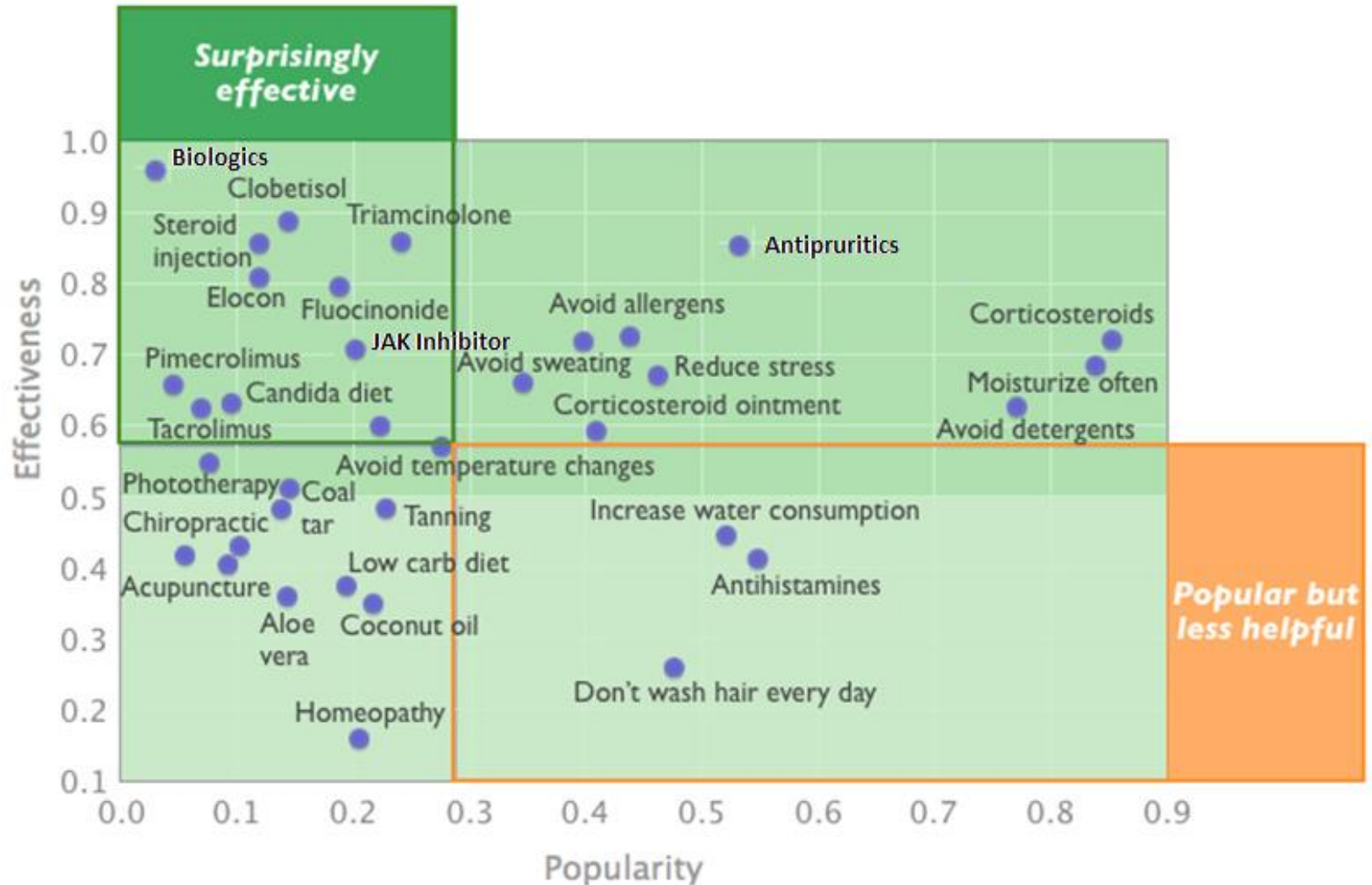
- A defective skin barrier is primary feature of eczema that is aggravated by mechanical injury inflicted by scratching.
- Skin lesions are characterized by infiltrating lymphocytes, monocytes/macrophages, eosinophils and oversecretion of Th2 inflammatory cytokines/chemokines.
- Thymus And Activation Regulated Chemokine (TARC) -CCR4 ligand, overexpressed in eczema lesions and attracts Th2 cells.
- IgE and IgE-mediated mast cell and eosinophil activation contribute to severity of eczema.



Immunologic pathways in Eczema

New insights into atopic dermatitis, Donald Y.M. Leung, 2004



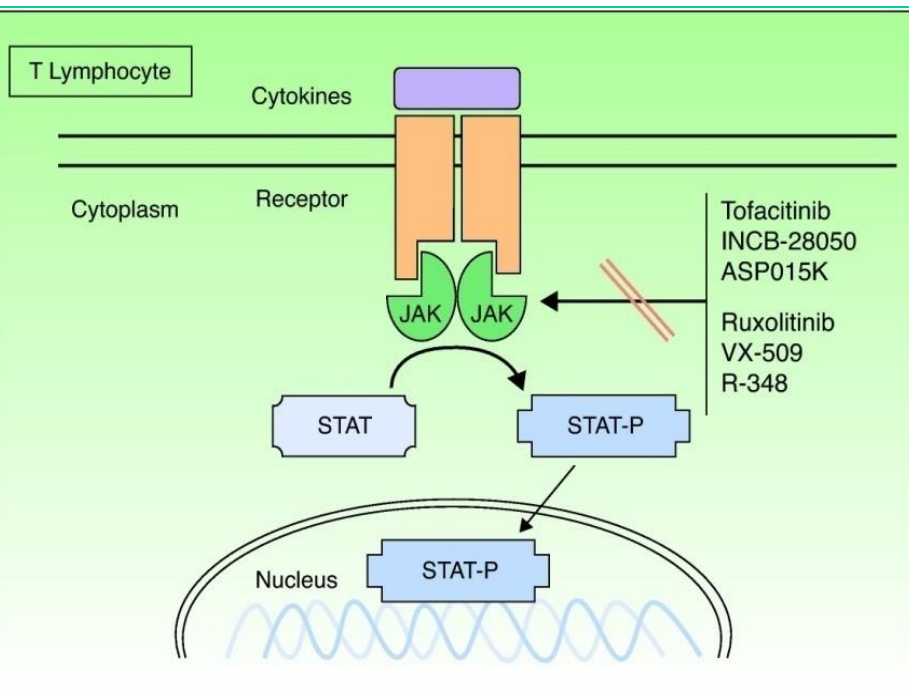


JAK-kinase inhibitors in Eczema

- 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/eczema.

Biologics in Eczema

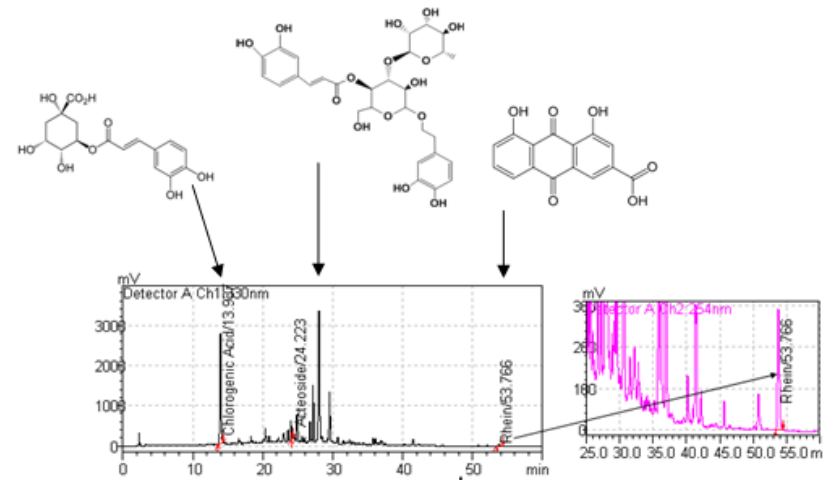
Emerging treatments for atopic dermatitis



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-13	2
Ustekinumab	Antibody against IL-12 & IL-23	2
Dupilumab	Antibody against IL-4 receptor	3
Anti-pruritics		
CT327	Tropomyosin receptor kinase A kinase inhibitor	2
VLY-686	Neurokinin 1 receptor antagonist	2

Adapted from the National Eczema Association's "Eczema Drugs in Development" chart.²⁰

- 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

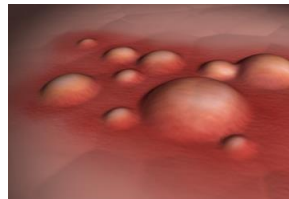


Name of marker compound	Herb name
Emodin	
Rhein	HERB-1
Rhapontin	
Carvacrol	
Vanillic acid	HERB-2
Sweroside	
Aucubin	
Digoxin	HERB-3
β -sitosterol	

Increased secretion of cytokines
by immune cells

Increased production of IgE by
lymphocytes

Eczematous lesion



Inflammation in keratinocytes by
increased secretion of cytokines

Increased activity of JAK1/JAK3

**Anti-eczema
drug**



Macrophages



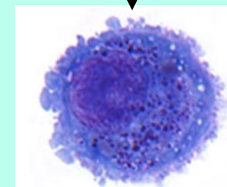
**inhibition of
IL-6 in immune
cells**



Keratinocytes



**Downregulation of
TNF- α ,
TARC and
VEGF in
keratinocytes
(HaCaT)**



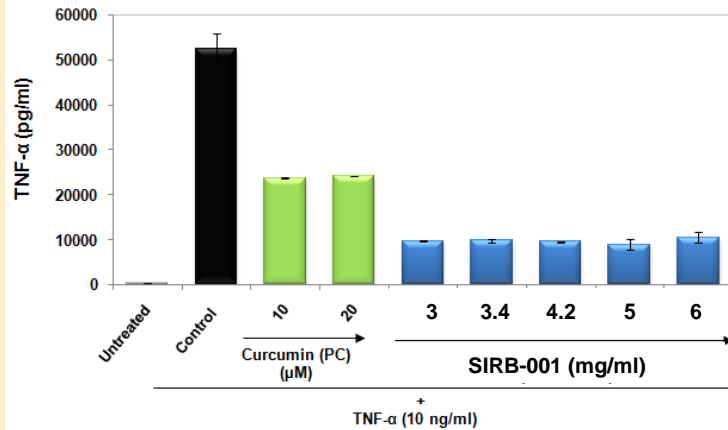
Lymphocytes



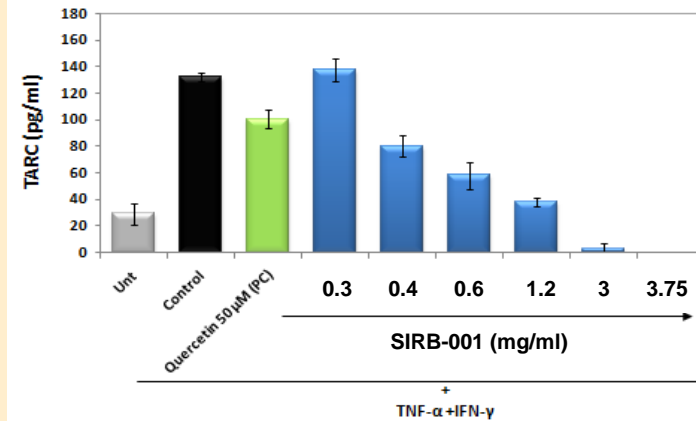
**Inhibition of
IgE production**

- Significant downregulation of TNF- α , TARC and VEGF in keratinocytes (HaCaT)
- Remarkable inhibition of IL-6 in immune cells (RAW264.7)

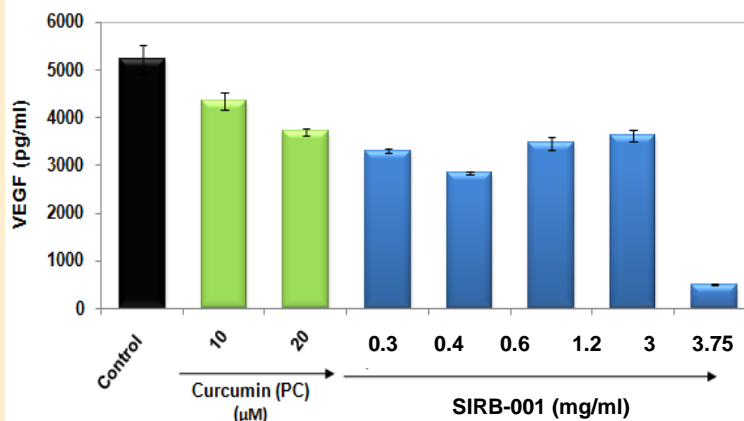
TNF- α



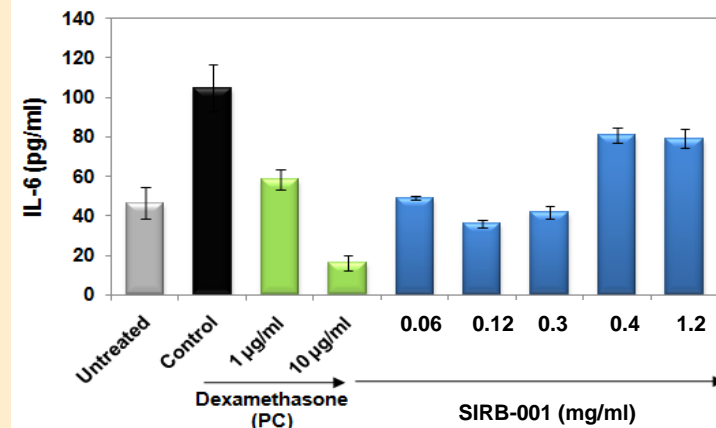
TARC



VEGF

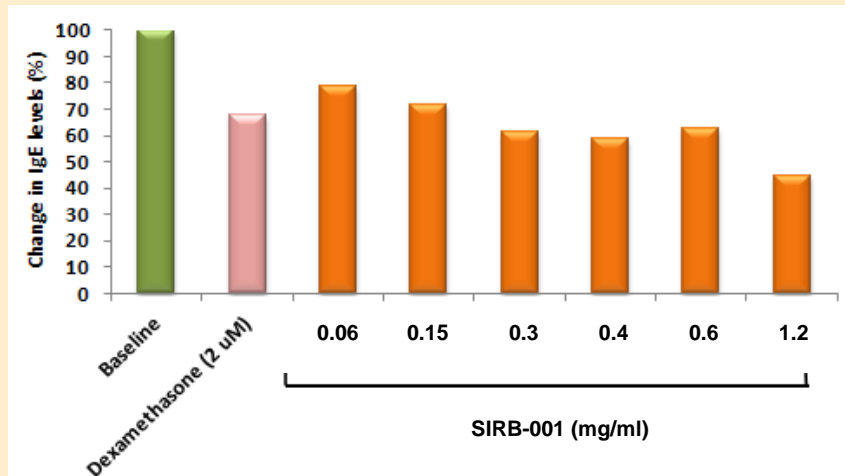


IL-6

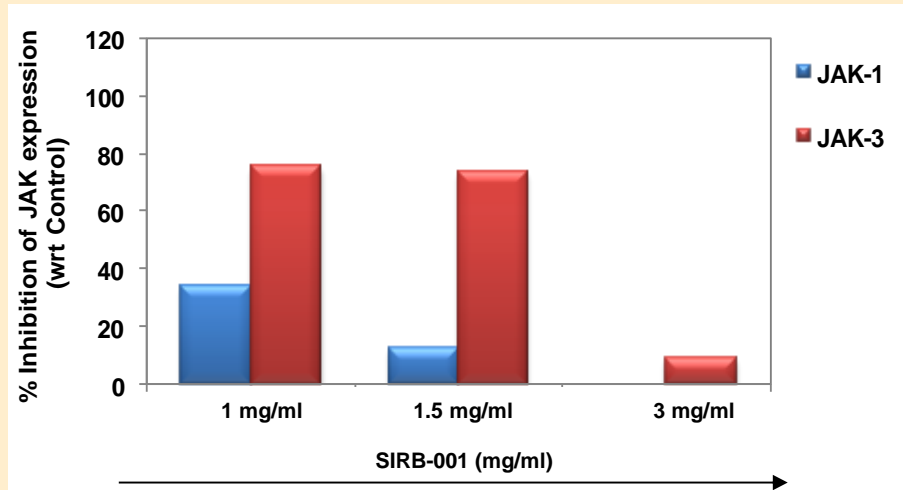


- IgE inhibition in human myeloma cell line; U-266
- Inhibition of JANUS KINASES - JAK-1/JAK-3.

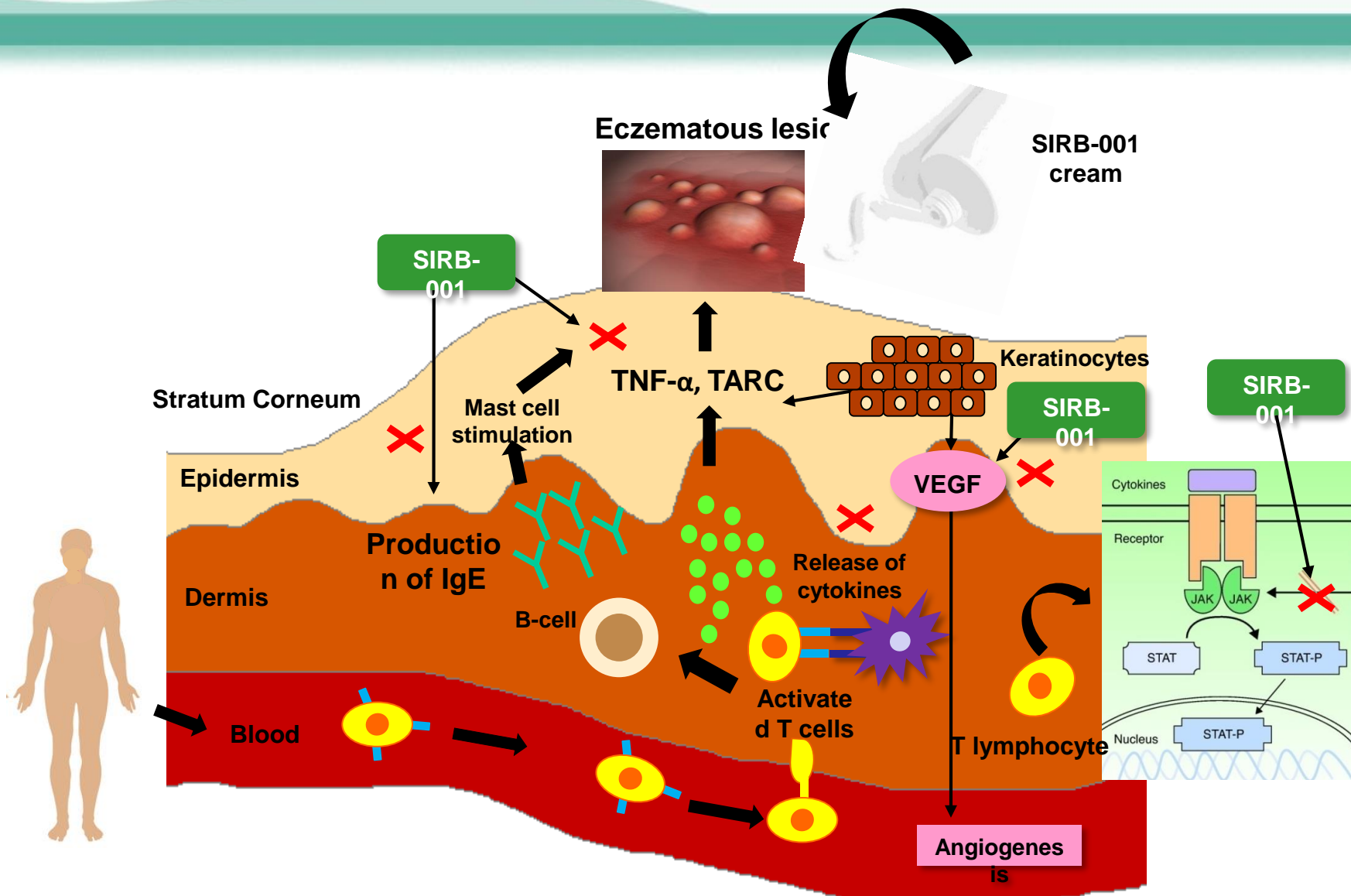
IgE



JAK-1/JAK-3

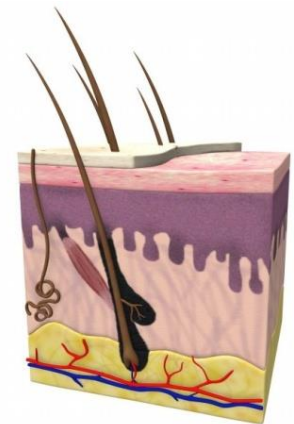
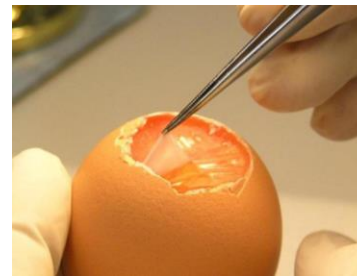


Anti-eczema potential of SIRB-001 – Mechanism of action



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





Preparation of different bases of cream using combination of oil/emulsifiers/water .



Selection of preliminary bases based on its physical appearance and viscosity



Trial Batches



Characterization; Phase Separation; Spread ability; Microbial Analysis etc.



In vitro Drug Release
(using dialysis membrane)



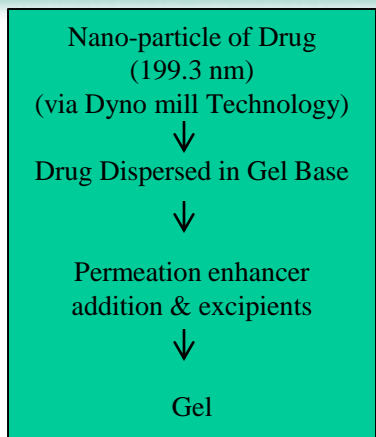
Skin permeation studies
(Diffusion through rat skin)



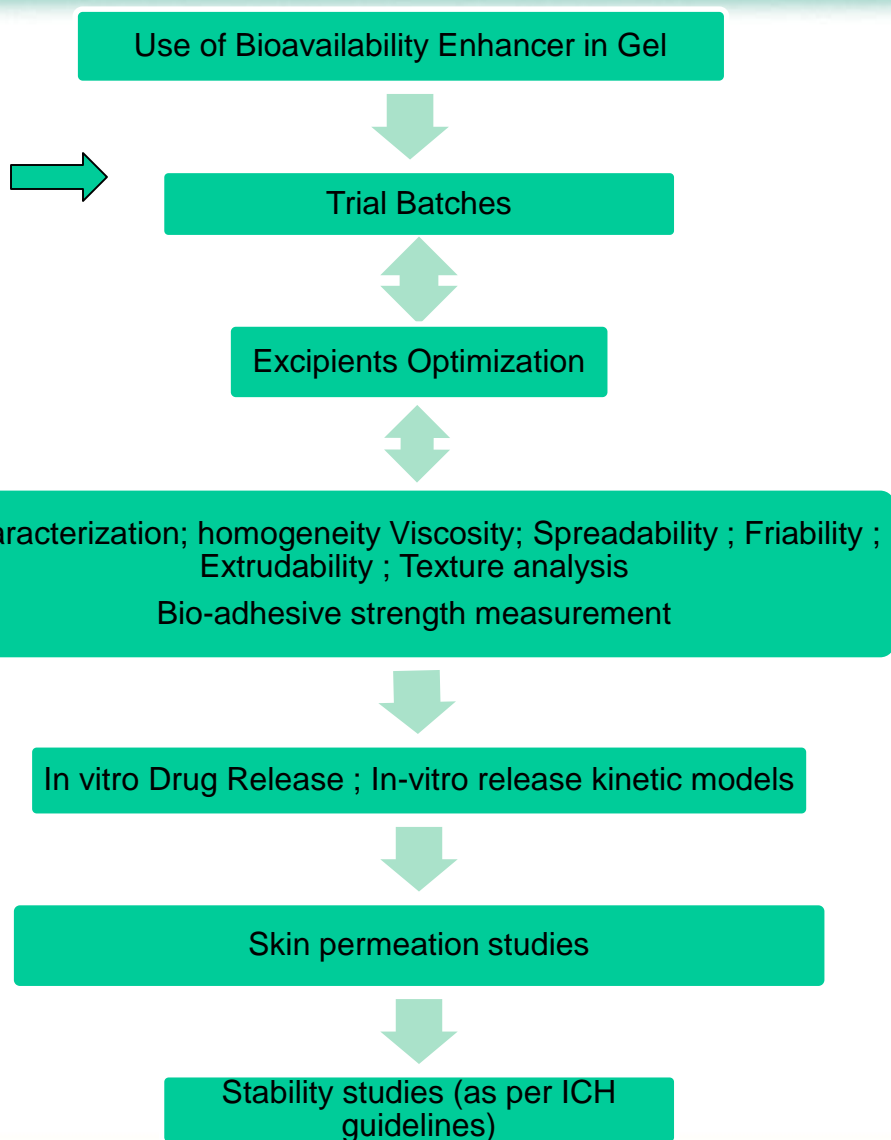
Stability studies (as per ICH guidelines)



Cream Sample



Nanogel Sample



Clinical Development of SIRB 001 as a new treatment modality for Eczema

Basic information on Trial

Disease/Target Area	Eczema	Age group	18-65 Years
Product/Route	Polyherbal, Topical	Male/Female Ratio	Adequate
Type of Trial	Monocentric; Observational	Race	Asian, India
Subjects	30 (25 Completers)	Eczematous Lesion	≤10% (BSA)
Study Duration	4 Weeks	Severity (as per IGAS)	Mild to severe
Region	India		

Evaluation Criteria of the Study

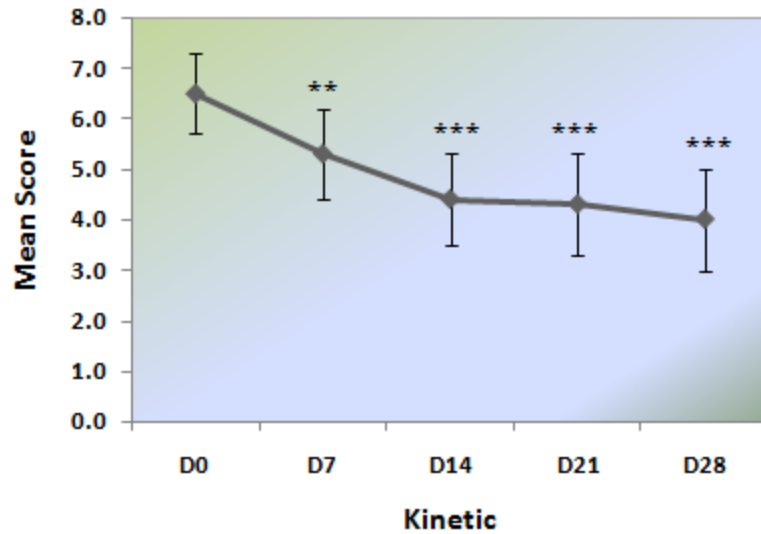
Primary Criteria	Secondary Criteria
<ul style="list-style-type: none"> Clinical Evaluation using ESI Score Clinical Evaluation using IGAS score Reduction of size and area of target lesions 	<ul style="list-style-type: none"> To assess the local skin tolerability and safety of the investigational product in subjects with eczematous lesions Biomarker analysis from serum sample To compare clinical improvement with serum IgE values Self-assessment questionnaire by subjects for assessment of efficacy and product acceptability

Regulatory Activities

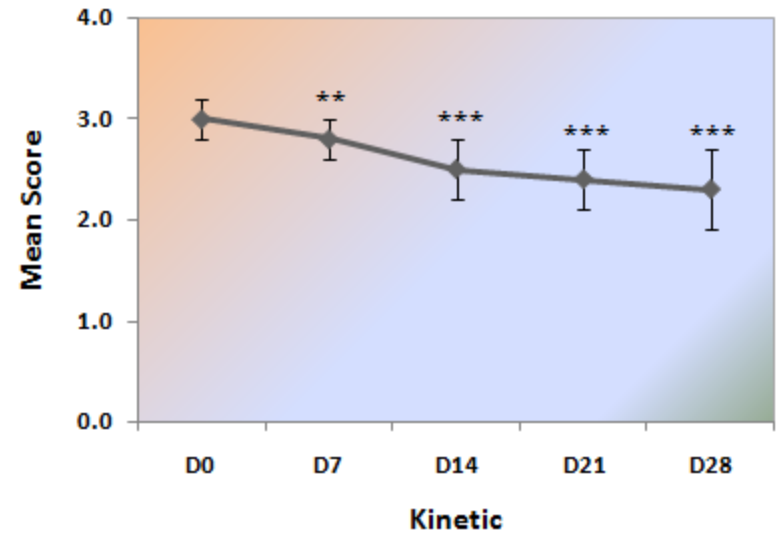
EC Submission	30th Oct. 2015
EC Approval	16th Nov. 2015

IGAS : Investigator Global Assessment Severity Scale

Effect of SIRB-001 on Eczema Severity



Effect of SIRB-001 on Investigator's Global Assessment Severity (IGAS) Scale



Baseline Visit (D0)

Day 7

Day 14

Day 21

Day 28



Subject 1



Subject 2



Subject 3



Subject 4



Baseline
Visit (D0)

Day 28



EFFICACY RESULTS

Eczema Severity Index (ESI): A decrease in the mean score of Eczema Severity Index was observed from D0 to D28. This decrease was found to be statistically significant across all evaluation kinetics when compared to D0.

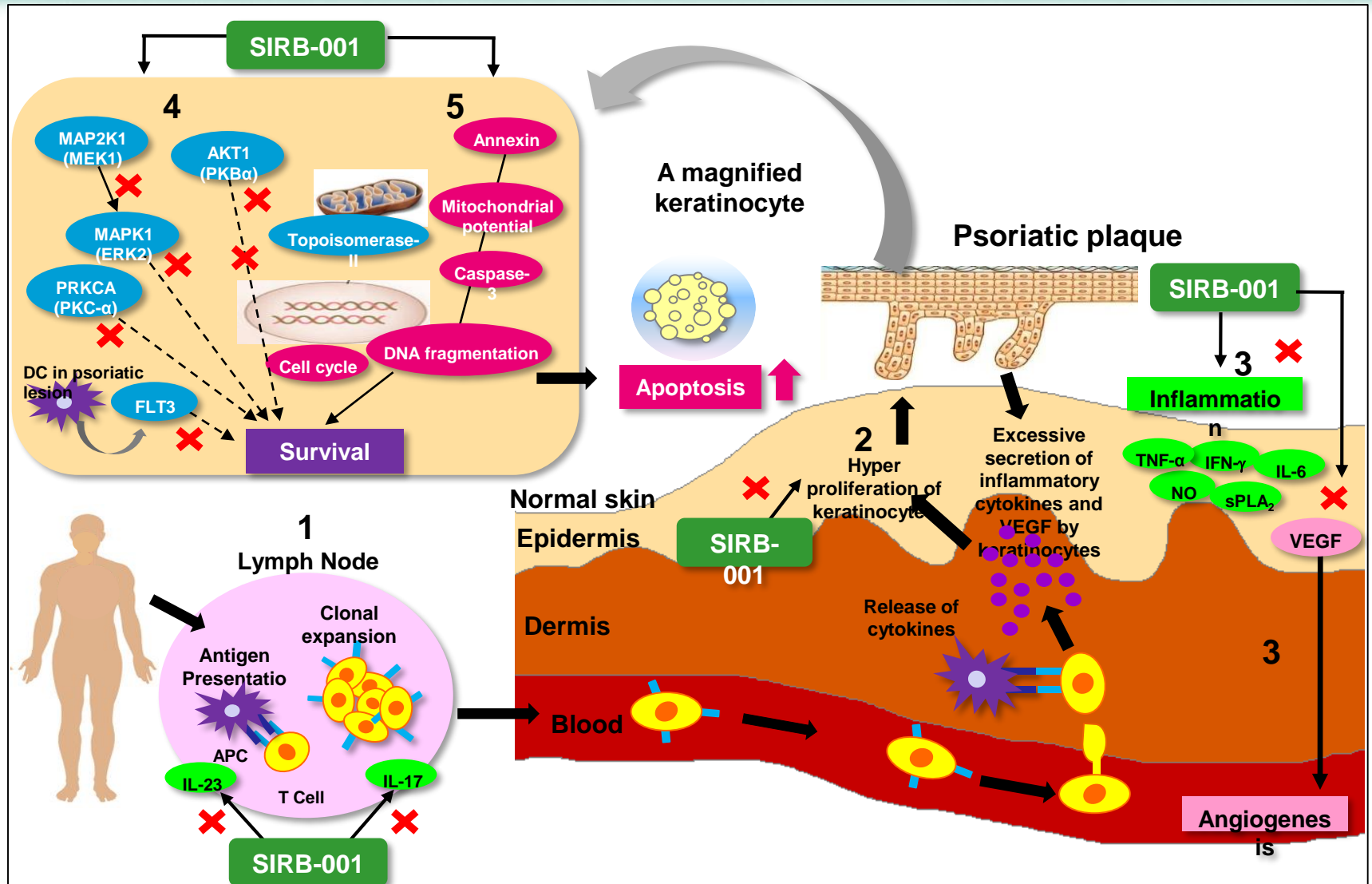
Investigator's Global Assessment Severity (IGAS): The IGAS score also decreased significantly from from D0 to D28. This decrease was found to be statistically significant across all evaluation kinetics when compared to D0.

Immunoglobulin E (IgE) estimation: An increase in the mean value of IgE from D0 to D28 was observed. However, this increase was not found to be statistically significant at D28 when compared to D0.

Self assessment Questionnaire: The self assessment questionnaire analysis done to assess the product acceptability, efficacy and global acceptability also showed significant product acceptability by the subjects in terms of its organoleptic properties and efficacy in reducing the symptoms and size of the eczematous lesion.

Biomarker analysis: Biomarker analysis on serum samples

Therapeutic potential of SIRB 001 in other chronic skin inflammatory diseases



Basic information on Trial

Disease/Target Area	Psoriasis
Product/Route	Polyherbal, Topical
Type of Trial	Observational
Subjects	21
Study Duration	8 Weeks
Primary Endpoint	Tolerability
Region	Germany

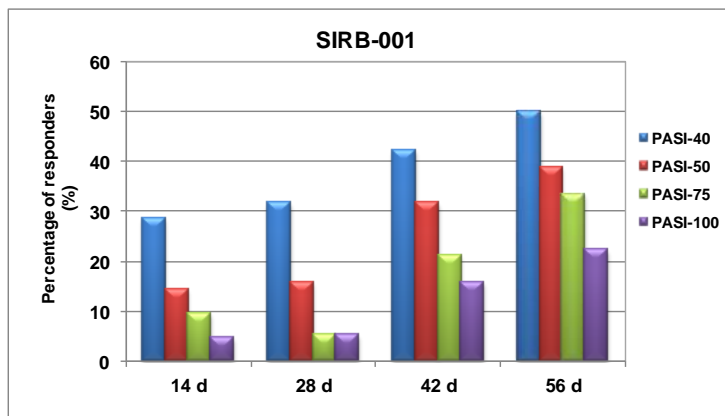
Population Characteristics

Age	18-65 Years
Male/Female Ratio	Adequate
Population	German
Severity	Mild to Moderate

Study Details

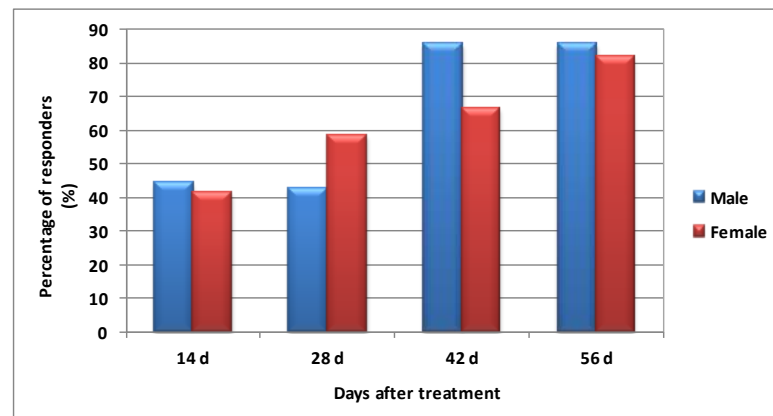
- Each subject attended 5 visits at the study site with 14 day interval
- The objective was to assess the tolerability and safety of investigational product in subjects with psoriatic lesions treated for 4 weeks with twice daily use of investigational products.
- The severity of psoriatic lesion was assessed through PASI score obtained by clinical evaluations of subjects by Dermatologist. Dermatological evaluation criteria involved were, Erythema, Thickness and Scaliness.
- No safety issue was observed during conduct of the study.

Response of SIRB-001 measured by the percentage of patients achieving PASI-40, PASI-50, PASI-75 and PASI-100



- SIRB-001 demonstrated an increase in percentage of patients achieving PASI-40, PASI-50, PASI-75 and PASI-100 after 14 d, 28 d, 42 d and 56 d of treatment.

Response of SIRB-001 in males vs females



- SIRB-001 demonstrated an increase in the no of responders in both male and female patients after 14 d, 28 d, 42 d and 56 d of treatment.

Basic information on Trial

Product/Route	Polyherbal, Topical
Type of Trial	Observational
Subjects	30 (25 Completers)
Study Duration	8 Weeks
Primary Endpoint	Tolerance & Safety
Secondary Endpoint	Efficacy & Product Acceptability
Region	India

Population Characteristics

Age	18-65 Years
Male/Female Ratio	Adequate
Region	Asian, India
Scalp involvement area	10% or greater
Severity (as per IGSS)	At least moderate

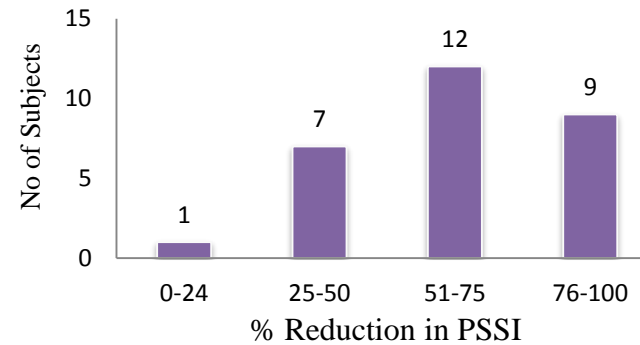
Regulatory Activity

EC Submission	1 st September 2015
EC Approval	21 st September 2015

Results

Based on data, preliminary observation by principal investigator suggest that data suggest that administered IP (Hair Shampoo and Lotion) is highly effective in Scalp Psoriasis. Some highlights of study results shown below:

- 70% of subjects shows improvement of more than 50% in PSSI



- > 56% of subjects shows improvement of more than 51% or more in terms of VSCAPSI
- No serious adverse event was reported in the study
- Overall, maximum reduction as per all three standard scoring system s are:
 - PSSI : Maximum reduction achieved 95%
 - VSCAPSI : Maximum reduction achieved 92%
 - IGSS : Maximum reduction achieved 75%

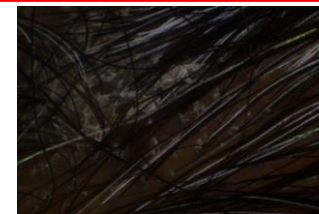
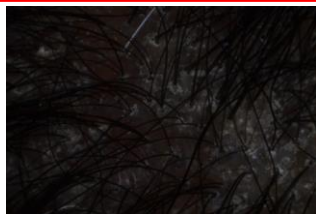
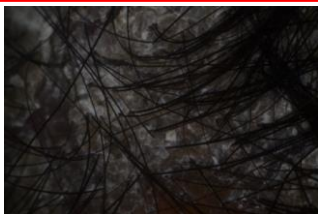
BACK VIEW

FRONT VIEW

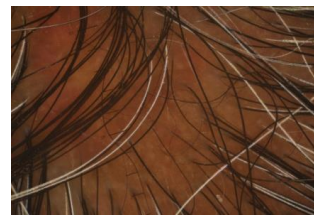
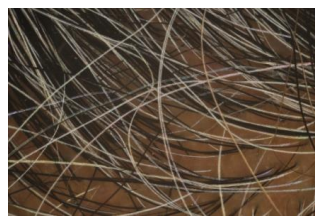
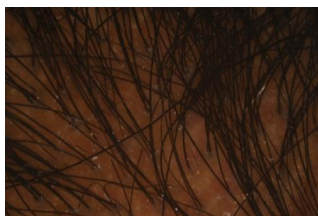
LEFT VIEW

RIGHT VIEW

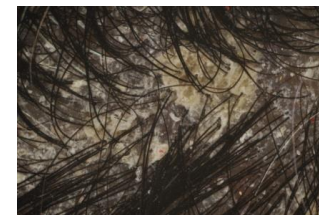
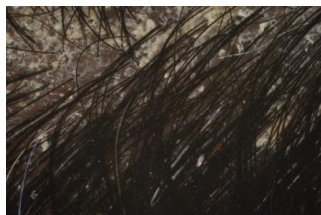
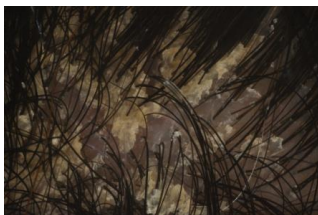
Baseline Visit



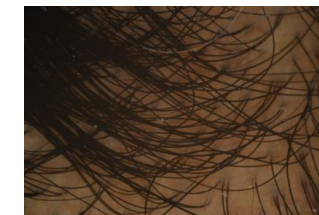
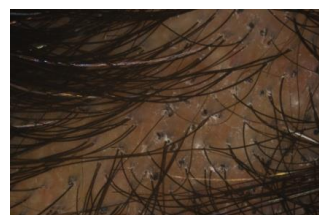
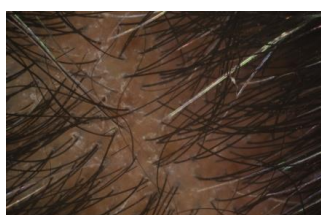
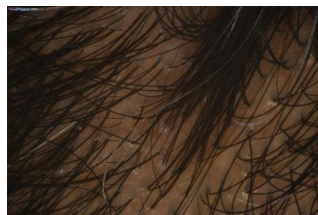
Day-56 Visit



Baseline Visit



Day-56 Visit

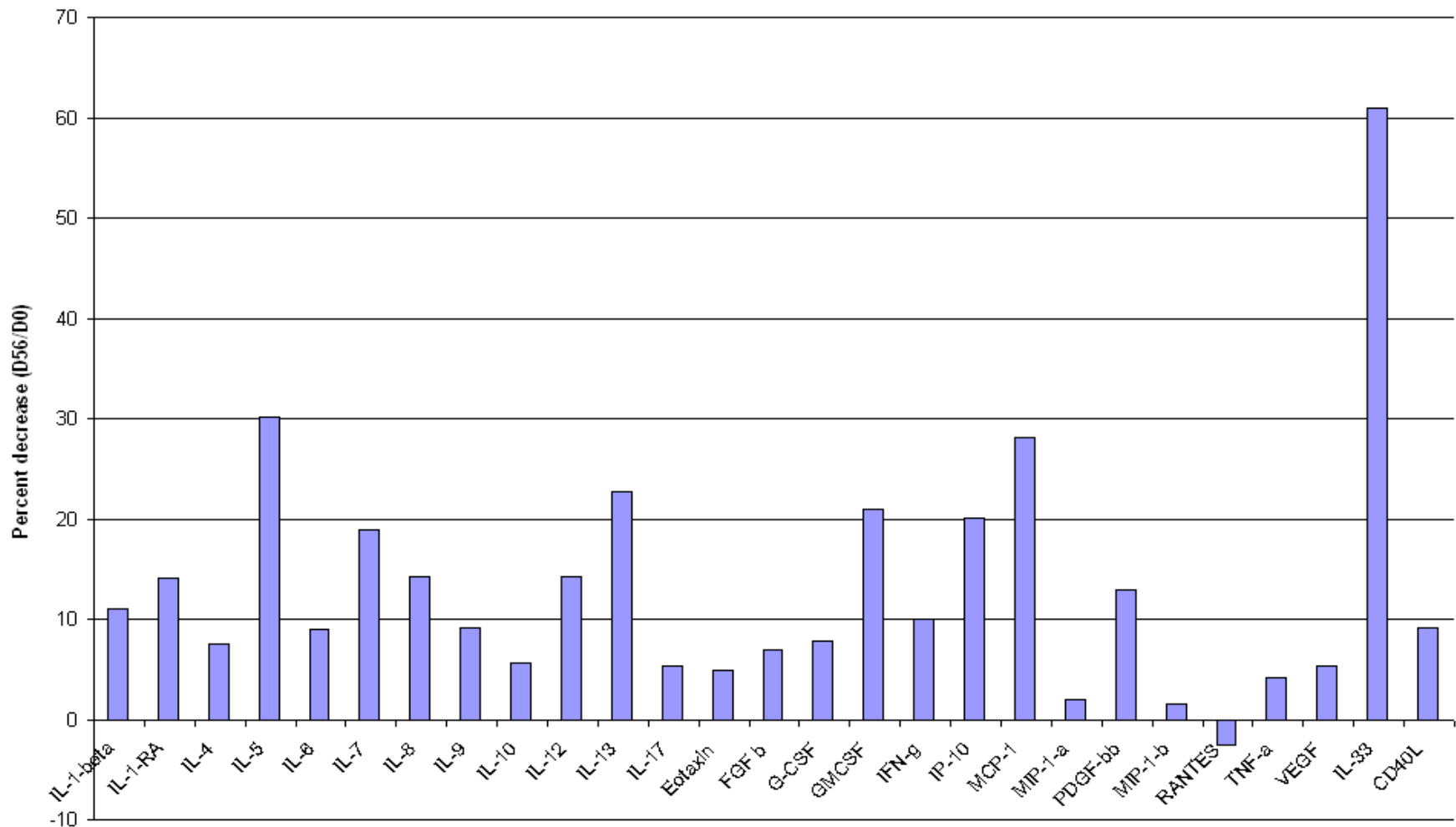


Patient stratification for SIRB 001

Development of a stratification kit to aid patient selection

- 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.

1	IL-1-beta
2	IL-1-RA
3	IL-4
4	IL-5
5	IL-6
6	IL-7
7	IL-8
8	IL-9
9	IL-10
10	IL-12
11	IL-13
12	IL-17
13	Eotaxin
14	FGF b
15	G-CSF
16	GMCSF
17	IFN-g
18	IP-10
19	MCP-1
20	MIP-1-a
21	PDGF-bb
22	MIP-1-b
23	RANTES
24	TNF-a
25	VEGF
26	IL-33
27	CD40L



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

$\% \text{ Decrease} = (\text{Mean value Day 0} - \text{Mean value Day 56}) \times 100 / \text{Mean value Day 0}$

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	NanoGel	Psoriasis, Eczema, Atopic dermatitis
7	Oral Tablets	Psoriasis, other chronic inflammatory disorders
8	Oral Nanoparticles	Psoriasis, other chronic inflammatory disorders





THANKS